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# Diastereoselectivity control in MAC methodology for the preparation of $\alpha$ -hydroxy- $\beta$ -amino acid derivatives

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Xuefeng He. Diastereoselectivity control in MAC methodology for the preparation of  $\alpha$ -hydroxy- $\beta$ -amino acid derivatives. Organic chemistry. Université Paris-Saclay, 2022. English. NNT : 2022UP-ASF095 . tel-04348742

**HAL Id: tel-04348742**

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# Diastereoselectivity control in MAC methodology for the preparation of $\alpha$ -hydroxy- $\beta$ -amino acid derivatives

*Contrôle de la diastéréosélectivité dans la méthodologie MAC pour la  
préparation de dérivés d' $\alpha$ -hydroxy- $\beta$ -aminoacides*

## Thèse de doctorat de l'université Paris-Saclay

École doctorale n°571 : sciences chimiques : molécules, matériaux, instrumentation et  
biosystèmes (2MIB)  
Spécialité de doctorat : Chimie  
Graduate School : Chimie. Référent : Faculté des sciences d'Orsay

Thèse préparée dans l'**Institut de Chimie Moléculaire et des Matériaux d'Orsay**  
(Université Paris-Saclay, CNRS), sous la direction de **David AITKEN**, Professeur  
et le co-encadrement de **Sandrine DELOISY**, Enseignante-Chercheuse

Thèse soutenue à Paris-Saclay, le 15 décembre 2022, par

**Xuefeng HE**

## Composition du Jury

Membres du jury avec voix délibérative

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**Titre :** Contrôle de la diastéréosélectivité dans la méthodologie MAC pour la préparation de dérivés d' $\alpha$ -hydroxy- $\beta$ -aminoacides.

**Mots clés :** molécules bioactives,  $\alpha$ -hydroxy- $\beta$ -aminoacides, réaction multicomposés, oxyhomologation, diastéréosélectivité.

**Résumé :** Cette thèse est consacrée à l'oxyhomologation diastéréosélective d' $\alpha$ -amino aldéhydes *N*-protégés par la méthodologie MAC *one-pot* pour la synthèse d' $\alpha$ -hydroxy- $\beta$ -aminoacides (AHBAs) protégés orthogonalement. Ce motif AHBA est présent dans de nombreux produits naturels et dans des molécules synthétiques biologiquement actives telles que le Taxol ou la (-)-Bestatine.

Nous avons tout d'abord optimisé chacune des trois étapes de la synthèse des réactifs MAC à partir du malononitrile. L'utilisation de triflates de silyle à la place de chlorures de silyle usuellement utilisés dans l'étape de protection du 2-hydroxymalononitrile nous a permis d'établir une synthèse plus efficace et reproductible de trois réactifs MAC silylés : H-MAC-TBS, H-MAC-TIPS et H-MAC-TBDPS.

Trois dérivés *N*-protégés du L-phénylalaninal ont ensuite été étudiés dans des réactions MAC en présence d'alcools. L'emploi du *N*-Boc-L-phénylalaninal a conduit aux  $\alpha$ -hydroxy- $\beta$ -aminoesters correspondants dans un ratio 80:20 en faveur de l'isomère *syn* ; ce qui était conforme avec la littérature. En utilisant le *N*-Boc-*N*-Bn-L-phénylalaninal, le H-MAC-TBS et le méthanol, les esters méthyliques d'oxyhomologation ont été isolés sous forme d'un mélange de deux diastéréoisomères, pour lesquels les configurations n'ont pas pu être attribuées. Enfin, l'oxyhomologation du *N,N*-dibenzyl-L-phénylalaninal en présence de chacun des trois réactifs MAC et de méthanol a conduit aux produits d'oxyhomologation souhaités avec de bons rendements et une haute sélectivité *anti* (ratio *syn/anti*  $\leq 10 : 90$ ) ; la diastéréosélectivité n'ayant pas été influencée par la nature du réactif MAC.

La réaction MAC a ensuite été réalisée en présence du *N,N*-dibenzyl-L-phénylalaninal, du H-MAC-TBS et de divers alcools (11 exemples, rdts jusqu'à 95%). Les alcools primaires ont donné les rendements les plus élevés, tandis que les alcools secondaires ont fourni

les produits de la réaction MAC avec de faibles rendements. Le rapport diastéréoisomérique ( $\leq 10 : 90$ ) est resté constant en faveur du diastéréoisomère *anti* dans tous les cas. Nous avons également réussi à synthétiser efficacement les esters méthylique et éthylique du (2*S*,3*S*)-AHPBA, ainsi que la (-)-allophénylnorstatine.

Le résultat le plus saillant de cette étude est la diastéréosélectivité des réactions d'oxyhomologation du *N,N*-dibenzyl-L-phénylalaninal avec l'ammoniac et les amines. Dans tous les cas, la réaction n'a fourni que le diastéréoisomère *anti*, (10 exemples, rdts jusqu'à 89%, ratio *syn/anti*  $< 2 : 98$ ). Dans le cas de l'ammoniac comme nucléophile, l'excès énantiomérique du produit MAC a également été établi (ee  $> 97\%$ ), confirmant qu'aucune érosion de la pureté énantiomérique inhérente du substrat ne s'est produite au cours de la réaction MAC.

Des  $\alpha$ -amino esters ont également été criblés comme nucléophiles dans la réaction MAC du *N,N*-dibenzyl-L-phénylalaninal avec le H-MAC-TBS. Une bibliothèque de dipeptides contenant les motifs AHPBA *anti* a été efficacement synthétisée (11 exemples, rdts jusqu'à 85 %, 25 : 75  $\leq$  *syn/anti*  $< 2 : 98$ ). Cette méthodologie a également été appliquée avec succès pour la synthèse efficace de la (2*S*,3*S*,5)-épibestatine.

Divers  $\alpha$ -amino aldéhydes *N,N*-dibenzylés ont également été testés dans des réactions MAC en présence du H-MAC-TBS et d'ammoniac ou de la benzylamine. Les  $\alpha$ -hydroxy- $\beta$ -amino amides correspondants ont été obtenus avec des rendements modérés à élevés, et surtout, la très haute diastéréosélectivité *anti* a été maintenue (7 exemples, rdts jusqu'à 92%, *syn/anti*  $< 2 : 98$ ).

Tous ces résultats ont confirmé le contrôle élevé de la diastéréosélectivité *anti* apporté par l'utilisation des groupes protecteurs *N,N*-dibenzyles portés par l' $\alpha$ -aminoaldéhyde.

**Title :** Diastereoselectivity control in MAC methodology for the preparation of  $\alpha$ -hydroxy- $\beta$ -amino acid derivatives.

**Keywords :** biologically active molecules,  $\alpha$ -hydroxy- $\beta$ -amino acids, multicomponent reaction, oxyhomologation, diastereoselectivity.

**Abstract :** This thesis is devoted to the diastereoselective oxyhomologation of *N*-protected  $\alpha$ -amino aldehydes by the one-pot MAC methodology to synthesize orthogonally protected  $\alpha$ -hydroxy- $\beta$ -amino acid (AHBA) derivatives. This AHBA motif is present in many natural products and in synthetic biologically active molecules such as Taxol or (-)-bestatin.

We first optimized each of the three steps in the synthesis of MAC reagents from malononitrile. The use of silyl triflates instead of silyl chlorides in the protection step of the 2-hydroxymalononitrile intermediate allowed us to establish a more efficient and reproducible synthesis of three silylated MAC reagents: H-MAC-TBS, H-MAC-TIPS and H-MAC-TBDPS.

Three *N*-protected derivatives of L-phenylalaninal were further studied in one-pot MAC reactions with these H-MAC-[Si] reagents in the presence of alcohols. The use of *N*-Boc-L-phenylalaninal led to the corresponding AHPBA esters in an expected 80:20 dr in favor of the *syn* isomer; this was consistent with previous results in the literature. Using *N*-Boc-*N*-Bn-L-phenylalaninal, H-MAC-TBS and methanol, the expected oxyhomologated methyl ester products were isolated as a mixture of two diastereomers, for which the configurations could not be assigned. Finally, MAC oxyhomologation of *N,N*-dibenzyl-L-phenylalaninal in the presence of each of the three H-MAC-[Si] reagents and methanol led to the desired oxyhomologated products in good yields and with a high *anti* selectivity (*syn/anti* dr  $\leq$  10:90); whereas the diastereoselectivity was not influenced in any way by the identity of the H-MAC-[Si] reagents.

The *anti* MAC reaction was then performed in the presence of *N,N*-dibenzyl-L-phenylalaninal, H-MAC-TBS and various alcohols (11 examples, yields up to 95%). Primary alcohols gave the highest yields, whereas secondary alcohols represented the limit of the substrate scope by providing the MAC reaction products in low yields. The dr ratio remained constant

at around 10:90 in favor of the *anti* diastereomer in all cases. We also achieved the efficient synthesis of (2*S*,3*S*)-AHPBA methyl and ethyl esters, as well as the parent (2*S*,3*S*)-AHPBA (allophenylnorstatin).

The most salient result in this study was the diastereoselectivity of the oxyhomologation reactions of *N,N*-dibenzyl-L-phenylalaninal with ammonia and amines. In all cases, the reaction effectively provided only the *anti* diastereomer, (10 examples, yields up to 89%, *syn/anti* dr < 2:98). In the case of ammonia as the nucleophilic partner, the high enantiomeric purity was also established (ee > 97%), confirming that no erosion of the inherent enantiomeric composition of the non-racemic substrate occurred in the MAC methodology.

$\alpha$ -Amino esters were also screened as nucleophiles in the one-pot MAC reaction of *N,N*-dibenzyl-L-phenylalaninal and H-MAC-TBS. A library of dipeptides containing *anti*-AHPBA was efficiently synthesized (11 examples, yields up to 85%, 25:75  $\leq$  *syn/anti* dr < 2:98). This methodology was also successfully applied for the efficient synthesis of (2*S*,3*S*,5)-epibestatin.

Various *N,N*-dibenzylated  $\alpha$ -amino aldehydes were also tested in MAC reactions in the presence of H-MAC-TBS and ammonia or benzylamine. The desired  $\alpha$ -hydroxy- $\beta$ -amino amides were obtained in moderate to high yields, and most importantly, the very high *anti* diastereoselectivity was maintained (7 examples, yields up to 92%, *syn/anti* dr < 2:98).

All these results confirmed the high *anti* diastereoselectivity control brought by the use of the *N,N*-dibenzyl protecting group suite of the  $\alpha$ -amino aldehyde; they complement the first one-pot MAC *syn* diastereoselective oxyhomologation of *N*-Cbz-D-phenylalaninal achieved by Nemoto 20 years ago (*syn/anti* dr 80:20).

# Acknowledgments

First of all, I would like to thank Prof. **Brigitte Deguin** from Université Paris-Cité and Prof. **Thierry Constantieux** from Université Aix-Marseille for helping me to review this thesis manuscript. Thanks to Prof. **Sandrine Onger** from Université Paris-Saclay and Dr. **Yvan Six** from CNRS, for being my jury members.

Thanks to Prof. **Marie-Christine Scherrmann** for welcoming me to the team Photochemical Peptidomimetics, Alternative Processes (CP<sup>3</sup>A, ICMMO - UMR8182) and giving me all support for my thesis work.

I want to show my appreciation to my director, Prof. **David Aitken**, for all his support and help. He was involved in every stage of my PhD training to the greatest extent possible, discussing my course selections, developing my presentation skills, and revising all my drafts, which were very touching and impressive. The guidance and advice (which he stressed were only suggestions) he provided me during these four years were also invaluable; when I've been stumped, he's always been able to point out key issues and potential solutions. Aside from that, I'd describe him as a pure scientist. He is curious about all new sparkling in our research, and he was able to sort out which deserves further investigation, which is very inspiring. Being guided by him has been a true honor and a once-in-a-lifetime experience.

Je tiens également à exprimer ma gratitude à ma chef, le Dr **Sandrine Deloisy**. Sur le plan de la vie quotidienne, elle a été ma « *mère française* » depuis le jour de mon arrivée en France. Elle m'a aidé dans toutes les démarches administratives (*ce qui est très utile en France*), m'a accompagné chez mon propriétaire, au supermarché, à la banque pour ouvrir un compte ; et chaque fois que nous écoutions « *Le beau Danube bleu* » dans le laboratoire, elle me poussait à apprendre à danser et à parler aux filles. Lorsqu'il s'agissait de recherche, elle était un vrai patron. Elle m'a appris à travailler comme un véritable chercheur : des manipulations à l'analyse des données, de la recherche bibliographique à la réparation des appareils, en passant par la présentation des résultats, la création de PPT et de posters, la préparation de rapports, etc. Son implication dans le travail est aussi remarquable. Lorsque je me sentais anxieux, le fait de la voir concentrée sur ses missions m'aidait à évacuer le stress et à continuer d'avancer, ce qui est magique. J'aimerais lui exprimer ma profonde reconnaissance pour son accompagnement, ses encouragements et ses conseils au cours des quatre dernières années.

Un grand merci à **Thomas**, qui a pris chaque jour de mes nouvelles et s'est enquis de l'avancement de mes expériences. De temps en temps, nous nous sommes retrouvés autour de quelques verres... - “*We sat and drank with the sun on our shoulders and felt like free men*”. Merci également à **Valérie** pour sa grande gentillesse et son accueil. Mes remerciements à **Sylvie** pour nous avoir aidés à gérer le laboratoire - nous savions que nous pouvions toujours compter sur elle si quelque chose n'allait pas. Merci à **Omar** de m'avoir aidé à préparer mon ppt et à organiser le laboratoire. Merci encore à **Catherine** pour m'avoir aidé avec l'analyse de l'HPLC, à **Florence** pour les instructions de sécurité, et à

**Fatima** pour s'être sentie concernée par l'avancement de ma thèse, ainsi que pour s'être occupée du volume de l'enceinte au Labo 2 pendant presque deux ans.

I obtained a large number of supplies from **Zong** just after I arrived, and his "*impressive quality and quantity*" (Comments from the president of his defense jury) works were also what I wished to produce. **Yong-peng** has been very helpful during my first three years, taking me to the CESFO on my first arrival, to Les Ulis for Carrefour shopping, and to the 13<sup>e</sup> arrondissement for Chinese festivals, etc. His optimistic attitude has also been a great inspiration to me. Merci beaucoup à **Zaynab** for teaching me how to conduct research in France (or how to tolerate French administrations), teaching me safe lab practices (like not turning your back to the fume hood when distilling.), and giving me direct advice on my project, teaching me how to write beautiful handwriting, and so on. And to **Dayi**, a kind, passionate, and reliable young man who is also a strong candidate for the best chef at the Orsay; I'd like to thank him for the many meals he's shared with me over the last three years, especially for all of his support and assistance; I wish him all well for the rest of his life in France (*and he can obtain his residency card soon*). Muchas gracias a **Ivana** for all her help, such as sharing with me how to remove residues with high boiling points (*Ivana's protocol*), how to work with LAH (*Ivana's workup*), and advising me on my project or future career (*Ivana's advice*); Her cakes (*CNRS's pride*) are also noteworthy. Finally, it is difficult to forget those noodles, ròu jiā mó and fried chestnuts from **Xiaodan**, as well as the help on reaction mechanism and translation from Monsieur **Gabriel** (*dit Theon*) - thank you for bringing us a cheerful atmosphere to the lab. I also must warn you that you must wear protective sunglasses well because no doubt your future will be too bright.

Je tiens également à remercier **Marie Buchotte** et **Mathieu Esgulian** pour leur aide dans l'optimisation de la synthèse des réactifs MAC, ainsi que **William** et **Illona** pour leur participation à mon projet. Je tiens encore à remercier **Arthur** et **Slimane**, qui ont travaillé au Labo2: avec le premier, j'ai écouté Erik Satie et Franz List pendant le doux été précédant l'épidémie; avec le second, j'ai été vacciné (et *revacciné*) au cœur de la morosité de la pandémie.

Cette thèse n'aurait pas été possible sans le soutien technique d'autres amis de l'ICMMO. Merci à **Jean-Pierre Baltaze**, **Amandine Dos Santos**, et **Philippe Berdagué** pour leur aide sur l'analyse RMN, et surtout au tout-puissant **Jean-Pierre**, qui est le magicien le plus cool que j'ai jamais rencontré. À **Régis Guillot** pour l'analyse XRD, à **Tanya Inceoglu** et **Hélène Maisonneuve** pour leur aides pour l'analyse MS, ils ont fait un travail formidable. Un merci spécial à **Martial Toffano** (LCM) qui m'a appris en détail comment manipuler l'hydrogénation avec l'autoclave. Enfin, mes remerciements à **Émilie Kolodziej** (LCM), pour son amabilité, son enthousiasme et sa gentillesse incroyables - *nous aimons tous Émilie*.

I will always have a place in my heart for my friends at ICMMO. To **Shengwen Yang** (LCM), who has been one of my best friends for three years, we talk about almost everything, and he's a strong guy with a good heart, and his cooking skills rival Dayi's. To **Chenxiao Qi** (LCM) for taking me to the Stade de France and Paris for the summer music festival; we're more like Parisians because of her. To other friends, including **Yan Chen**, **Donghuang Chen**, and **Hailong Zhang** from LCM, **Shanyu Tang**, **Wei Cao** from MSMT, **Chanjuan Zhang**, **Julien Buendia** from LCI, **Morane Beaumet** from LCBB and **Dan Liu** from SM2B, they have been a great help in my life in ICMMO.

In addition, I'd like to thank **Cong Wang** from LCP, who has been a great help to me since I was enrolled in our university. And **Peng Pan** from ISMO, **Ren Li** from IPN, whose intelligence and open-mindedness always inspired me. I'll never forget our Orsay Salon.

It is also worth mentioning the assistance I received from **Hui-Xuan Chen** since I started my research seven years ago - whenever I see my product precipitated from a column, I'll think of his words: "*You know, sometimes you can see the product directly.*" I'd also like to thank **Hao Liang** for updating our research's progress; and **Xiangmeng Chen** for his help in Guangzhou, Hong Kong, and now Orsay.

And to my best friend, **Zhiqi Liao**, with whom I've shared what I've seen, heard, and thought for the last four years.

Et un autre merci à **Laura**. Tous ces moments que nous avons passés ensemble étaient fantastiques.

I want to thank my parents for their support as I embarked on my academic journey and for allowing me to conduct my research without interruption. (还要感谢我的父母：我的母亲让我对化学产生兴趣，我父亲让我对理想拥有虔诚。感谢他们给我一如既往的支持和鼓励，让我能一路顺利走到现在.)

Finally, I would also like to thank the Guangzhou Elite Program, which financially supported my stay in France.

in Bures

<< Ce qui embellit le désert c'est qu'il cache un puits quelque part...>>

- Antoine de Saint-Exupéry, *Le Petit Prince*

## Abbreviations and Acronyms

Ac	Acetyl
AHBA	$\alpha$ -Hydroxy- $\beta$ -amino acids
AHPBA	3-Amino-2-hydroxy-4-phenylbutyric acid
aq.	Aqueous
ATR	Attenuated Total Reflectance
BINOL	1,1'-bi-2-naphthol
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
Bz	Benzoyl
°C	Celsius centigrade
Calcd.	Calculated
Cat.	Catalyst
Cbz	Benzyloxycarbonyl
<i>conc.</i>	Concentrated
CPA	Chiral phosphoric acid
<i>m</i> -CPBA	<i>meta</i> -Chloroperbenzoic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAM	Di( <i>p</i> -anisyl)methyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMB	2,4-Dimethoxybenzyl
DMF	<i>N,N</i> -Dimethylformamide
DMP	2,2-Dimethoxypropane
DMSO	Dimethyl sulfoxide
dppa	Diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio



E <sup>+</sup>	Electrophile
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EE	Ethoxyethyl
ee	Enantiomeric excess
er	Enantiomeric ratio
eq.	Equivalent
ES	Electrospray ionization
Fmoc	9-Fluorenylmethyloxycarbonyl
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
H-Bond	Hydrogen bond
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
<i>i</i> Bu	Isobutyl
IC <sub>50</sub>	Half maximal inhibitory concentration
Imid.	Imidazole
<i>i</i> Pr	Isopropyl
IR	Infrared
<sup>3</sup> <i>J</i>	Vicinal proton-proton coupling
LAH	Lithium aluminium hydride
K	Kelvin
M	Molar concentration
MAC	Masked Acyl Cyanide
MBA	<i>S</i> -(-)- $\alpha$ -Methylbenzylamine
MOM	Methoxymethyl
Mp	Melting point
Ms	Methanesulfonyl (Mesyl)
NAP	Naphthyl
<i>n</i> -Bu	<i>n</i> -Butyl
n.d.	No data
NMM	<i>N</i> -Methylmorpholine
NMR	Nuclear magnetic resonance
NuH	Nucleophile

OR	Optical rotation
PDC	Pyridinium dichromate
Pf	9-Phenylfluoren-9-yl
Phth	Phthaloyl
PMB	<i>p</i> -Methoxybenzyl
4-PP	4-Pyrrolidinopyridine
ppm	Parts per million
py	Pyridine
PyBoP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
quant.	Quantitative
R <sub>f</sub>	Retardation factor
rt	Room temperature
sat.	Saturated
[Si]	Silyl group
Temp.	Temperature
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -Butyl
TES	Triethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
Tf	Trifluoromethylsulfonyl (Triflyl)
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Ts	Toluenesulfonyl (Tosyl)
XRD	X-ray diffraction

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*Part I:*

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Introduction

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## I. 3-Amino-2-hydroxy-4-phenylbutyric acid (AHPBA) derivatives

### I.1 $\alpha$ -Hydroxy- $\beta$ -amino acids (AHBAs) and their derivatives

$\alpha$ -Hydroxy- $\beta$ -amino acids (AHBAs) are an important subclass of  $\beta$ -amino acids. Inside the molecule, the amino-terminus and carboxyl-terminus are separated by two chiral carbon centers:  $C_\alpha$  and  $C_\beta$ . Thus, all  $\alpha$ -hydroxy- $\beta$ -amino acids have four stereoisomers (Figure 1): (2*S*,3*R*), (2*R*,3*R*), (2*R*,3*S*) and (2*S*,3*S*). The (2*S*,3*R*) and (2*R*,3*S*) are classified as *syn* or *threo* configuration; while (2*R*,3*R*) and (2*S*,3*S*) are classified as *anti* or *erythro* configuration. *Vide infra*.

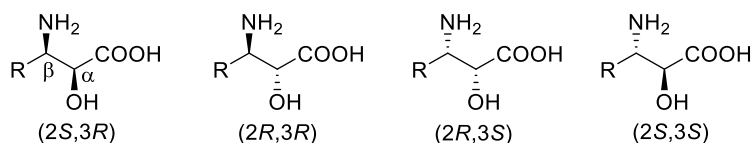


Figure 1, Four stereoisomers of AHBA

The best-known example of AHBA is paclitaxel (Taxol<sup>®</sup>), first isolated in 1971 by Wani *et al.* from *Taxus brevifolia* (pacific yew tree).<sup>1</sup> It contains a 3-amino-2-hydroxy-3-phenylpropanoic acid (phenyl isoserine) residue and a baccatin III tetracyclic system. Other AHBA structures are found in natural products such as amastatin,<sup>2</sup> oscillagins A and B,<sup>3</sup> and some microginins<sup>4</sup> (Figure 2).

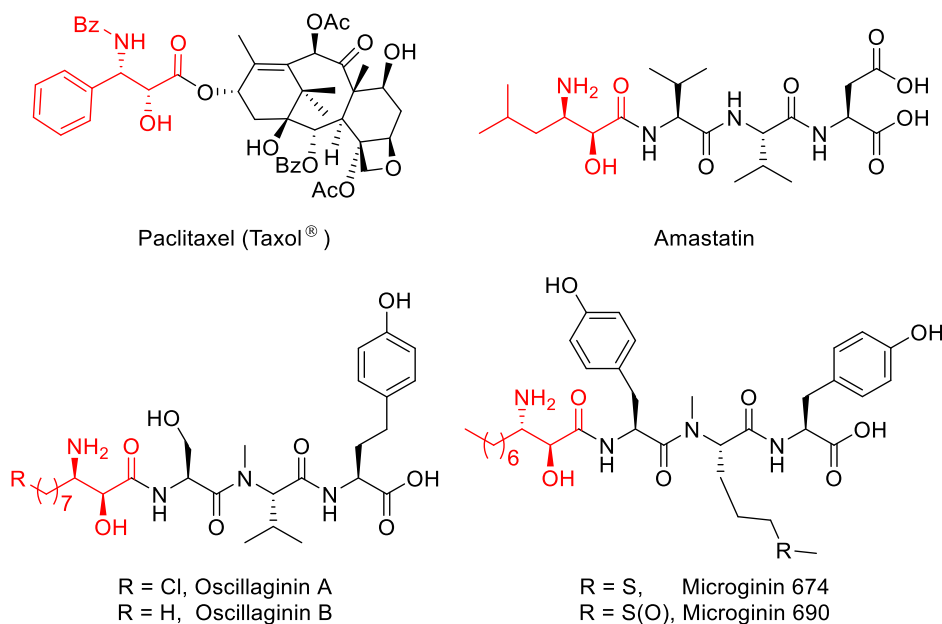
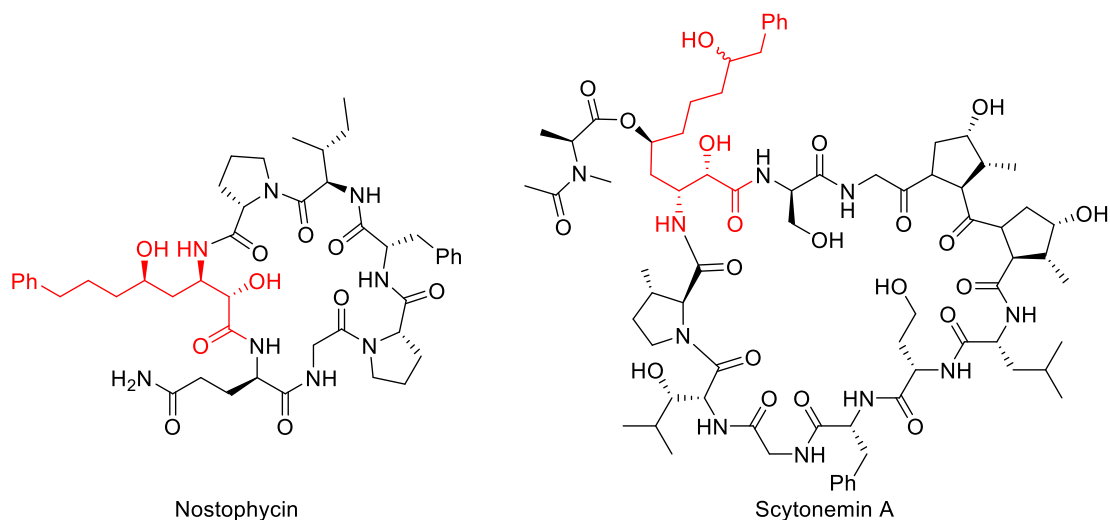
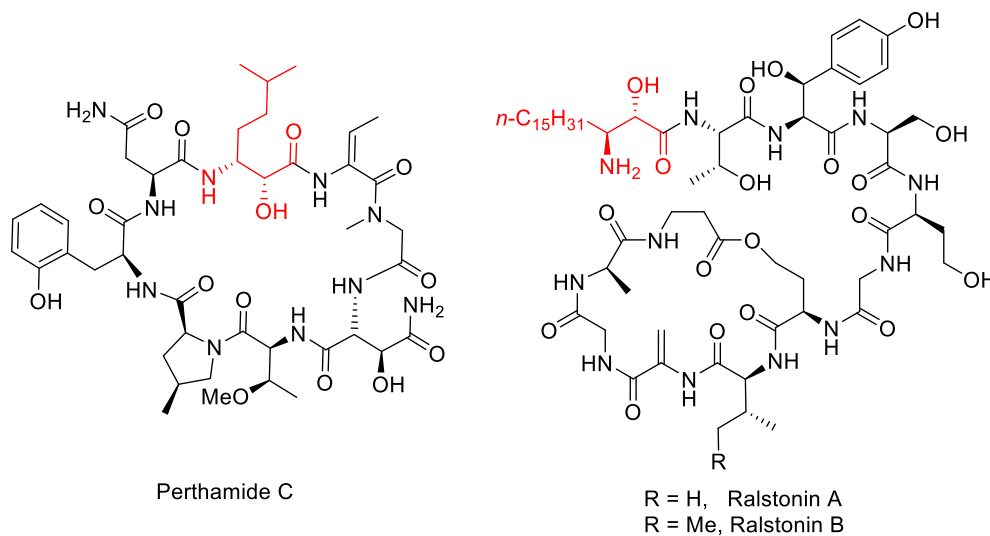


Figure 2, Natural products bearing AHBAs

AHBA residues, in either *syn* or *anti* configuration, are present also as the basic units in many macrocyclic peptides. *Syn*-AHBAs can be found in peptides like nostophycin and scytonemin A (Figure 3). Nostophycin has weak cytotoxic activity against lymphocytic mouse leukemia,<sup>5</sup> and incorporates a (2*S*,3*R*,5*R*)-3-amino-2,5-dihydroxy-8-phenyloctanoic acid residue. Scytonemin A is a calcium antagonist, which contains a (2*S*,3*R*,5*S*)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid moiety.<sup>6</sup>

Figure 3, Macrocyclic peptides containing *syn*-AHPBA

*Anti*-AHPBAs can be found in cyclic peptides like perthamide C and Ralstonins A and B (Figure 4). Perthamide C contains a (2*R*,3*R*)- $\alpha$ -hydroxy- $\beta$ -amino- $\epsilon$ -methylheptanoic acid residue; it displays a potent anti-inflammatory activity.<sup>7</sup> Ralstonins A and B are lipopeptides that contain a (2*S*,3*S*)- $\alpha$ -hydroxy- $\beta$ -aminooctadecanoic acid; they have chlamyospore-inducing activity and phytotoxicity.<sup>8</sup>

Figure 4, Macrocyclic peptides containing *anti*-AHPBA

### 1.2 3-Amino-2-hydroxy-4-phenylbutyric acid (AHPBA) derivatives

Typical  $\beta$ -substituted AHPBAs, 3-amino-2-hydroxy-4-phenylbutyric acid (AHPBA) contains two chiral centers and thus also exists in four stereomeric forms **1a-d** (Figure 5). The *syn* stereomers **1a,c** are also named phenylnorstatin (Pns), while the *anti* stereomers **1b,d** are named allophenylnorstatin (Apsns).

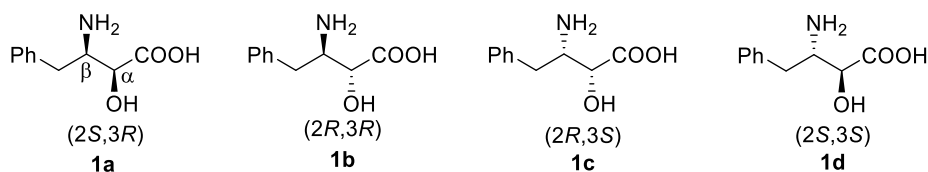


Figure 5, Four stereomers of AHPBA

AHPBA is a constituent of a number of functionalized peptides, the most well-known of which is (–)-bestatin (Ubenimex®). This dipeptide **2a** (Figure 6), containing *syn*-(2*S*,3*R*)-AHPBA and L-leucine,<sup>9</sup> displays broad-specificity aminopeptidases inhibition,<sup>10,11,12,13</sup> and has been widely studied for the treatment of cancer,<sup>14,15,16</sup> leukemia,<sup>12</sup> and lymphedema.<sup>17</sup>

With three chiral centers, (–)-bestatin is one of the eight stereomeric forms. Assuming a constant L-Leu residue, chiral variation of the AHPBA residue gives rise to four stereomers **2a-d** (Figure 6). All these four diastereomers showed inhibition to aminopeptidase B and leucine aminopeptidase.<sup>10</sup> The *anti*-(2*R*,3*R*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **2b** and **2d** differ from (–)-bestatin **2a** at one chiral center. Therefore, they are called epibestatin (*epi* for epimer) and inhibit certain LTA<sub>4</sub> hydrolase<sup>18</sup> and dipeptidyl peptidase 4 (DPP4).<sup>19</sup>

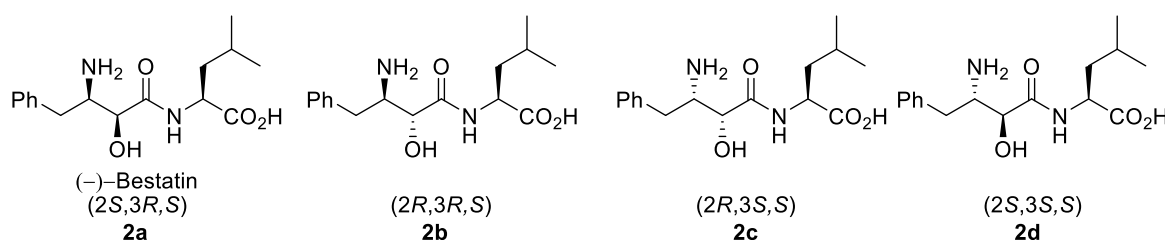


Figure 6, (–)-Bestatin and its three stereomers (based on the AHPBA moiety)

The structure of (–)-bestatin can be found in other peptides, such as probestin **3** and compound **4** (Figure 7). The former is a tetrapeptide that inhibits aminopeptidase M;<sup>20</sup> the latter contains a bestatin-fluorouracil conjugate and is exploited in anti-cancer therapy.<sup>21</sup>

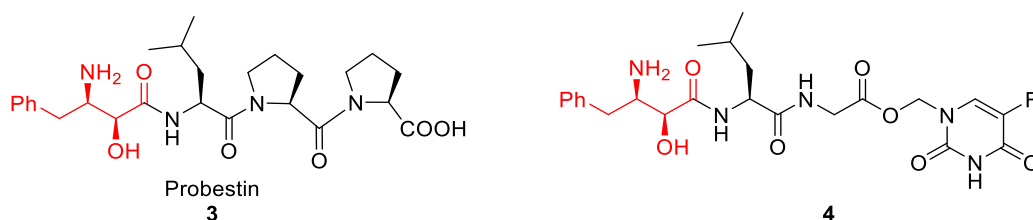


Figure 7, selected examples of Bestatin derivatives

Other examples of *syn*-(2*S*,3*R*)-AHPBA are shown in Figure 8. Phebestin, isolated from *streptomyces* sp. MJ716-M3, was used as an aminopeptidase N inhibitor.<sup>22</sup> Apstatin, a tetrapeptide that acts as an aminopeptidase P inhibitor,<sup>23,24</sup> showed activity in reducing myocardial infarct size.<sup>25</sup> Valistatin is a tripeptide that acts as an aminopeptidase M inhibitor.<sup>26</sup> Tripeptide LYRM03 showed strong inhibition of aminopeptidase N,<sup>27</sup> and could inhibit the metastasis of human breast cancer *in vivo* and *in vitro*.<sup>28</sup>

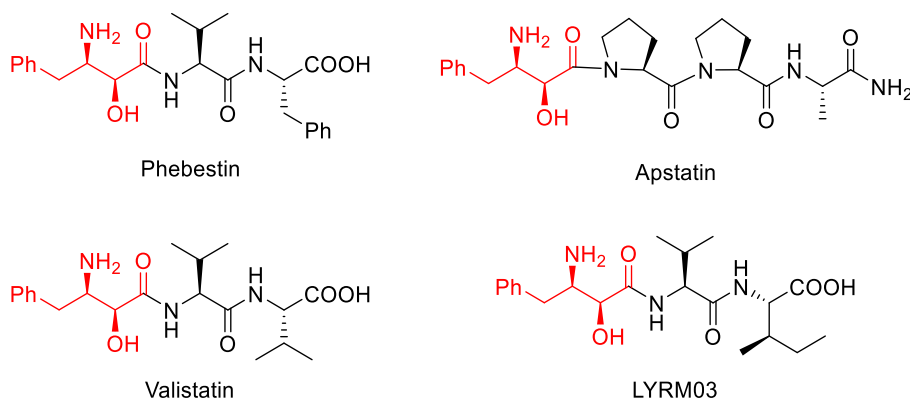


Figure 8, Peptides bearing (2S,3R)-AHPBA

Examples of *anti*-(2S,3S)-AHPBA appear in HIV inhibitors such as R-87366<sup>29</sup> and Pfizer's AG-001859<sup>30</sup> (Figure 9). The former was found to be a potent HIV protease inhibitor; while the latter was in the preclinical phase of development for antiviral activity against HIV,<sup>31</sup> and was recently used for antiviral SARS-CoV-2 (COVID-19) research.<sup>32</sup>

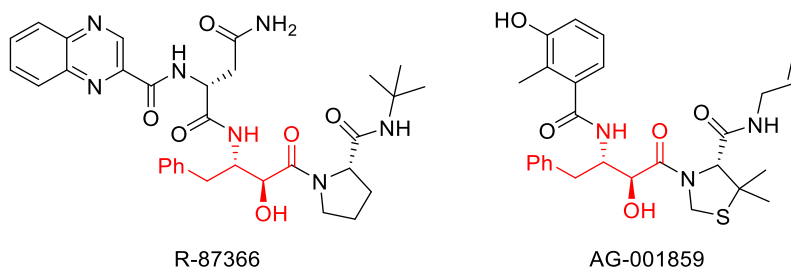


Figure 9, Representative KNI and KMI compounds bearing (2S,3S)-AHPBA

Two other chemical libraries containing *anti*-(2S,3S)-AHPBA are of great interest (Figure 10). The KNI (Kynostatin) family, including KNI-272<sup>33</sup>, are used as HIV-1 protease inhibitors, it also showed activity for HIV-1 protease-induced neurotoxicity.<sup>34</sup> The KMI family, including KMI-1027, act as BACE-1 inhibitors<sup>35</sup> and have potential use in Alzheimer's disease treatment.<sup>36</sup>

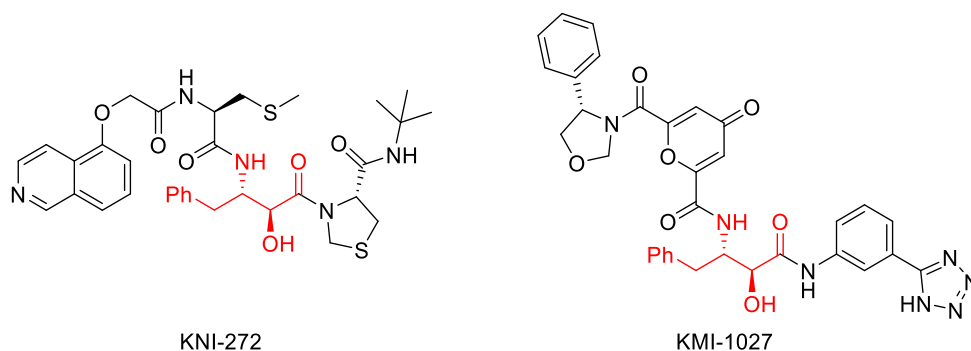


Figure 10, representative KNI and KMI compounds bearing (2S,3S)-AHPBA

### I.3 Synthetic methodology towards AHPBA and Bestatin analogues

The challenges in synthesizing AHPBA and its derivatives are 1) the construction and control of the C<sub>α</sub> and C<sub>β</sub> centers, and 2) the separation of these diastereomeric mixtures. Benefiting from long-standing

research on the synthesis of (–)-bestatin and paclitaxel, synthetic methodology toward AHPBA has been extensively developed over the last four decades.

One approach is to start from chiral substrates, such as amino acids or sugars. Typically, a diastereoselective reaction will be implemented, and the resulting diastereomeric mixture can be separated by standard methods (e.g., chromatography or recrystallization) to give optically pure products. These methodologies can be classified as: 1) homologation from phenylalanine and its derivatives; 2) ring-opening reactions; 3)  $\alpha$ -hydroxylation of  $\beta$ -amino acids.

An alternative approach is to start from achiral materials, which requires enantioselectivity control to obtain a given stereoisomer. Frequently, such reactions are not enantioselective, and a chiral resolution (e.g., preparative HPLC, recrystallization of the diastereomeric derivatives) is necessary. Those methodologies include: 1) diastereoselective hydroxyamination of  $\alpha,\beta$ -unsaturated esters; 2) cross-coupling reactions.

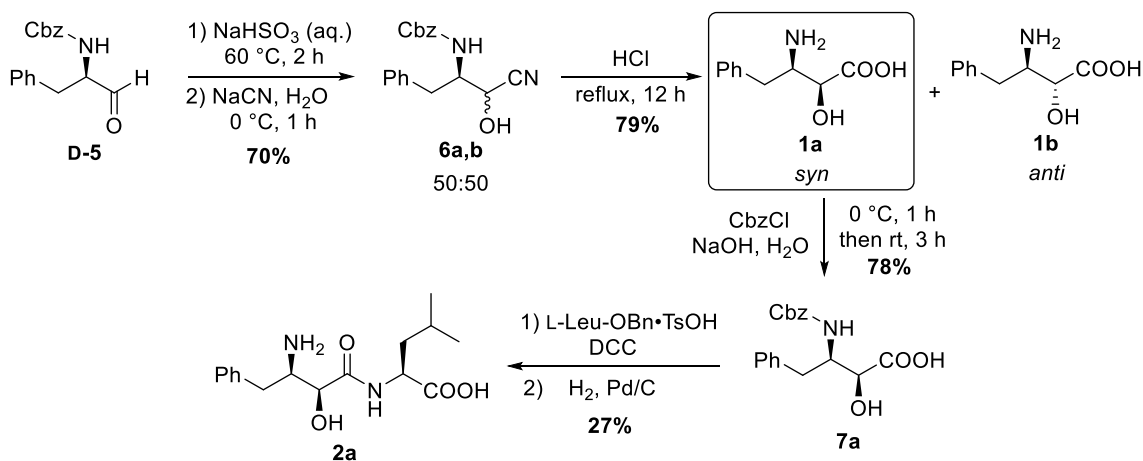
All methods will be presented below.

### 1.3.1 Starting from phenylalaninal

#### 1.3.1.1 through cyanohydrin formation

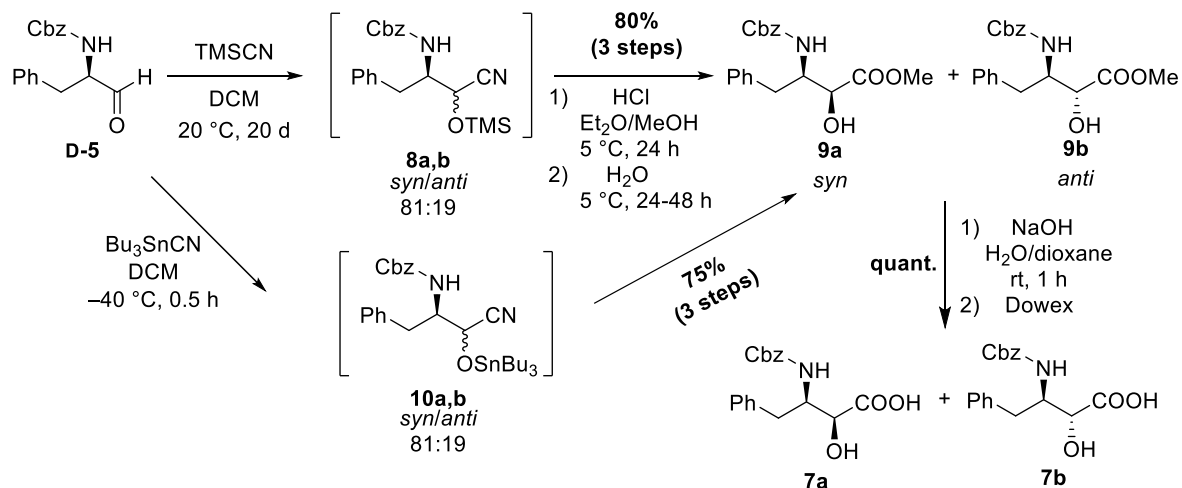
Carbonyl compounds undergo nucleophilic attack by a cyanide anion to give cyanohydrins, which can be hydrolyzed to provide  $\alpha$ -hydroxy acids, including AHPBAs.

Umezawa *et al.* published the first synthesis of optically pure (–)-bestatin in 1976 (Scheme 1).<sup>37</sup> *N*-Cbz-D-phenylalaninal **D-5** was successively treated with sodium hydrogen sulfite and sodium cyanide to generate cyanohydrins **6a,b**. After hydrolysis, (2*S*,3*R*)-AHPBA **1a** and (2*R*,3*R*)-AHPBA **1b** were obtained as a mixture in 79% yield. The author later described the diastereomeric ratio as 50:50.<sup>38</sup> (2*S*,3*R*)-AHPBA **1a** was separated from **1b** using Dowex resin, then coupled to a L-leucine ester to afford (–)-bestatin **2a** after the hydrogenolysis in 27% two steps yield. Although this pathway did not show any diastereoselectivity, it is still widely used for synthesizing (2*S*,3*R*)-AHPBA derivatives.<sup>39,40,41,42,43</sup>



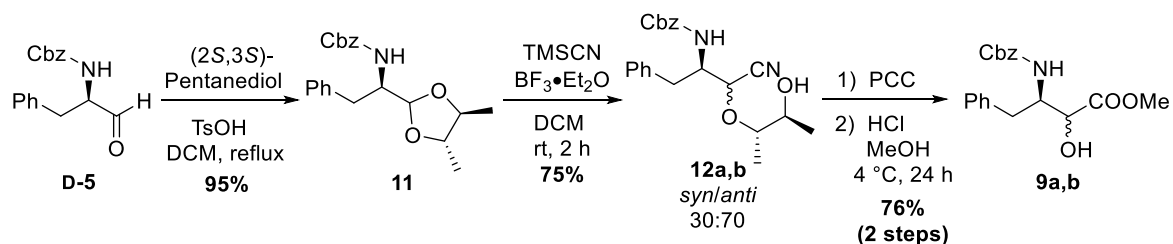
Scheme 1, First synthesis of optically pure (–)-bestatin by Umezawa *et al.*

Later, Herranz *et al.* reported the first diastereoselective preparation of *syn*-AHPBA from *N*-Cbz-*D*-phenylalaninal **D-5** (Scheme 2).<sup>44</sup> The aldehyde **D-5** was treated with trimethylsilyl cyanide for 20 days to give protected cyanohydrins **8a,b** in 81:19 *syn/anti* dr, and the author believed the *syn* diastereoselectivity originated from a chelation-controlled result. The cyanohydrins **8a,b** were transformed into the corresponding (2*S*,3*R*)-AHPBA and (2*R*,3*R*)-AHPBA derivatives **9a,b**. Terashima *et al.* subsequently disclosed that the *in situ* cyanohydrin protection was critical for maintaining the diastereomeric ratio.<sup>45</sup> On the other hand, the use of tributyltin cyanide can shorten the reaction time for the generation of cyanohydrins **10a,b** with identical diastereoselectivity.<sup>46</sup>



Scheme 2, Diastereoselective formation of cyanohydrins investigated by Herranz *et al.*

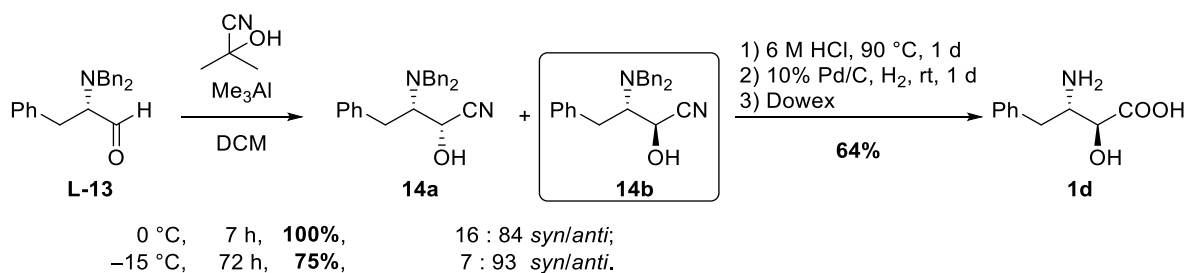
To obtain the *anti*-AHPBA from *N*-Cbz-*D*-phenylalaninal **D-5**, Herranz *et al.* employed a chiral acetal template strategy (Scheme 3).<sup>47</sup> The aldehyde **D-5** was reacted with (2*S*,3*S*)-pentanediol in the presence of *p*-toluenesulfonic acid to give acetal **11**, which was then transformed into cyanohydrins **12a,b** in 75% yield with a 30:70 *syn/anti* dr. Oxidative cleavage of **12a,b** using pyridinium chlorochromate (PCC) followed by an acid treatment gave AHPBA esters **9a,b**. The authors noted that the use of (2*R*,3*R*)-pentanediol for the acetal formation should lead to a reversed diastereoselectivity (70:30 *syn/anti*).



Scheme 3, First synthesis of *anti*-AHPBA using chiral acetal template

In 1988, the direct formation of *anti* cyanohydrin from *N,N*-dibenzyl-*L*-phenylalaninal **L-13** was reported by Reetz *et al.*, and the origin of the selectivity was attributed to the Felkin-Anh model.<sup>48</sup> Later in 1998, Terashima *et al.* exploited this method for the rapid synthesis of *anti*-AHPBA (Scheme 4).<sup>49</sup> Acetone cyanohydrin in the presence of trimethylaluminum generated the cyanohydrins **14a,b** in quantitative yield with a 16:84 *syn/anti* dr. The dr could be improved to 7:93 *syn/anti* by reacting at –

15°C for 72 hours, although with yield loss. After hydrolysis and hydrogenolysis, the *anti*-cyanohydrin **14b** was transformed to (2*S*,3*S*)-AHPBA **1d** in 64% overall yield.

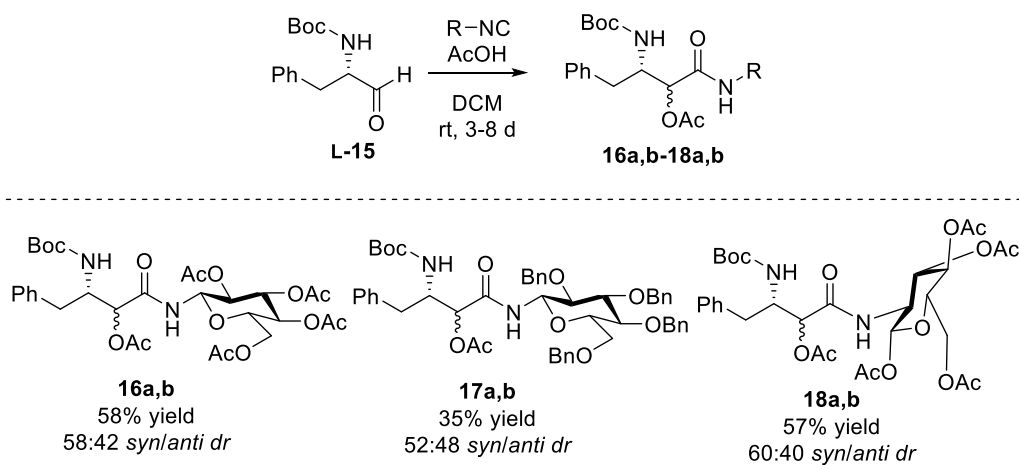


Scheme 4, Synthesis of *anti*-AHPBA using *N,N*-dibenzylphenylalaninal

Related procedures using *N,N*-dibenzyl-L-phenylalaninal **L-13** have been reported by Pedrosa *et al.*<sup>50</sup>, Lei *et al.*<sup>51</sup> and Shibasaki *et al.*<sup>52,53</sup>, all leading to the *anti* diastereoselectivity.

### 1.3.1.2 through Passerini reaction

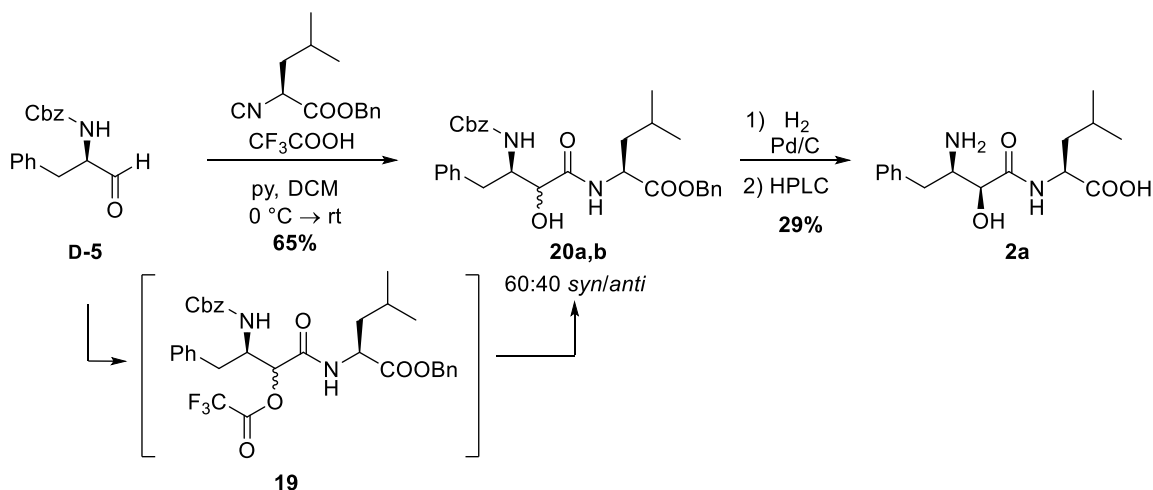
Ziegler *et al.* prepared three sugar-based isocyanoglucoses and examined their performance in the Passerini reaction with *N*-Boc-L-phenylalaninal **L-15** and acetic acid.<sup>54</sup> The corresponding AHPBA amides (**16a,b-18a,b**) were obtained in moderate yields and with slightly favored *syn* diastereoselectivity (Scheme 5).



Scheme 5, Passerini reaction with *N*-Boc-L-phenylalaninal and isocyanoglucoses

In a similar manner but using an L-leucine derived isonitrile as the nucleophile, the first synthesis of (–)-bestatin was completed by Semple *et al.* (Scheme 6).<sup>55</sup> *N*-Cbz-D-phenylalaninal **D-5**, leucine isonitrile derivative, and trifluoroacetic acid were reacted in the presence of pyridine. The trifluoroacetoxy intermediate **19** was initially produced as the Passerini adduct, which was quickly involved in protected bestatin **20a,b** in 65% yield and with 60: 40 dr (without identifying their relative configuration). The hydrogenolysis of **20a,b** followed by HPLC separation of the reaction mixture gave (–)-bestatin **2a** in 29% two steps yield.

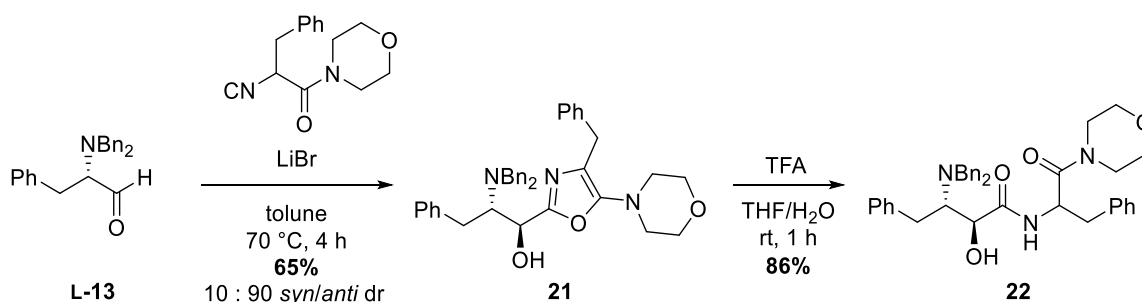




Scheme 6, First synthesis of (-)-Bestatin through the Passerini reaction

Similar methods using simple carboxylic acids were also reported by Banfi *et al.*<sup>56</sup> and Schmidt *et al.*<sup>57,58</sup>. In some cases, the Passerini adducts were hydrolyzed to give the AHPBA in its free amino acid form.<sup>59,60</sup> The use of *N*-mono-protected phenylalaninal always gave the *syn*-favored product. This *syn* diastereoselectivity was later explained as a consequence of the H-bond involved cyclic model.<sup>61</sup> The hydrogen bond between the amine proton and the carbonyl oxygen makes the nucleophilic attack on the *Si* face more favorable than the *Re* face.

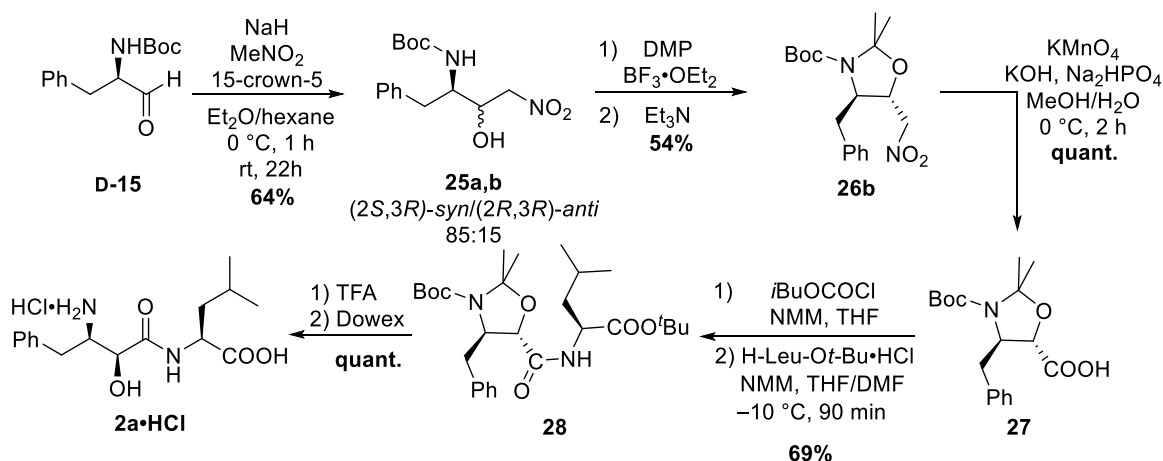
In contrast, reactions using *N,N*-diprotected L-phenylalaninals were characterized as *anti* diastereoselectivity. In the work of Zhu *et al.* (Scheme 7),<sup>62</sup> a truncated two-component Passerini reaction was performed on *N,N*-dibenzyl-L-phenylalaninal **L-13**, phenylalanine derived isonitrile in the presence of lithium bromide, leading to a 10:90 *syn/anti* dr, and *anti* oxazole **21** was isolated in 65% yield. The *anti* diastereoselectivity was explained by the Felkin-Anh model. The subsequent hydrolysis of this oxazole **21** gave *anti*-AHPBA dipeptide **22** in 86% yield.



Scheme 7, Anti diastereoselective Passerini reaction for the synthesis of AHPBA dipeptides

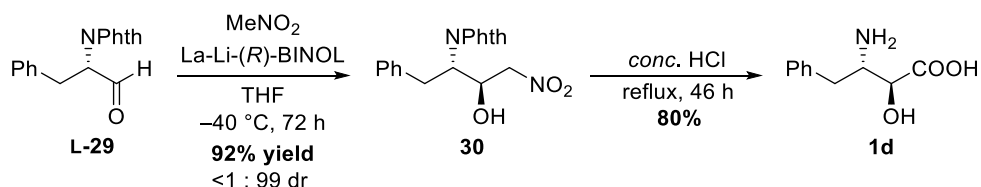
### 1.3.1.3 through Henry (nitroaldol) reaction

In the work of Chauhan *et al.* (Scheme 8),<sup>63</sup> *N*-Boc-D-phenylalaninal **D-15** was reacted with nitromethane anion promoted by sodium hydride and 15-crown-5 to give Henry adducts **25a,b** in 64% yield with 85:15 *syn/anti* dr. Adducts **25a,b** were transformed into *trans* **26b** in 54% yield after chromatography and transformed into acid **27**, which was further coupled with H-Leu-Ot-Bu to furnish (-)-bestatin in its HCl salt form **2a·HCl** after hydrogenolysis.



Scheme 8, Preparation of (-)-bestatin by diastereoselective Henry reaction

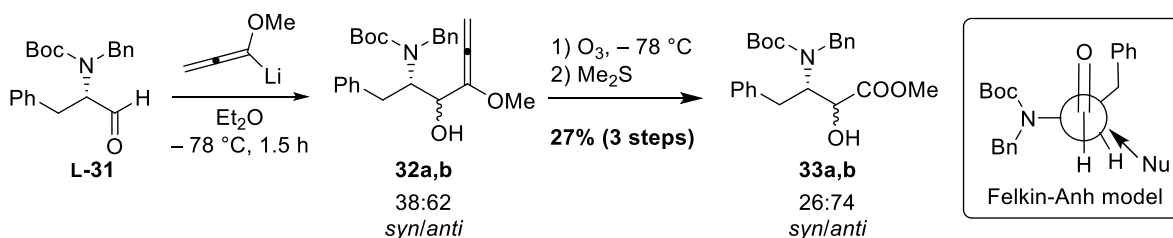
Shibasaki *et al.* reported an *anti* diastereoselective synthesis of AHPBA (Scheme 9).<sup>64</sup> *N*-Phthaloyl-L-phenylalaninal **L-29** was mixed with nitromethane in the presence of La-Li-(*R*)-BINOL complex<sup>65</sup>, and the Henry adduct **30** was obtained in 92% yield with <1: 99 *syn/anti* dr (96% ee). At last, *N*-phthaloyl deprotection and hydrolysis of the nitro alkane gave (2*S*,3*S*)-AHPBA **1d** in 80% yield.



Scheme 9, Preparation of anti-AHPBA by diastereoselective Henry reaction

### 1.3.1.4 through reactions with organometallic reagents

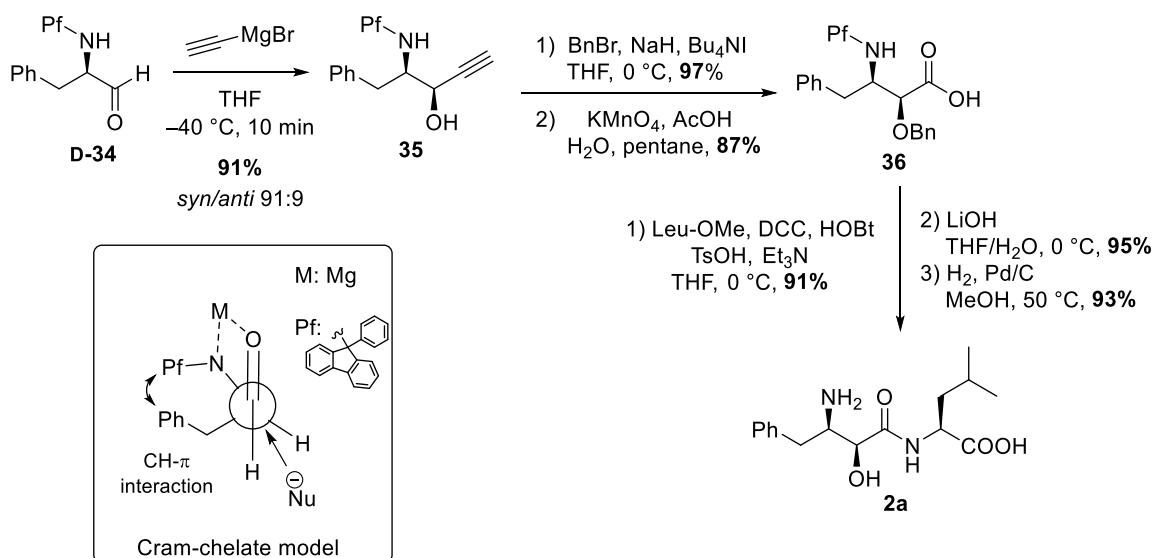
Reißig *et al.* reported the diastereoselective synthesis of (2*S*,3*S*)-AHPBA esters using lithium allene (Scheme 10).<sup>66</sup> *N*-Boc-*N*-Bn-L-phenylalaninal **L-31** was reacted with lithiated methoxyallene to produce allenyl ether alcohols **32a,b** in a 38:62 *syn/anti* ratio. The crude mixture of **32a,b** was treated with ozone at low temperature to give AHPBA methyl esters **33a,b** with 26:74 *syn/anti* dr. The authors rationalized the *anti* diastereoselectivity in terms of a preferred Felkin-Anh model.



Scheme 10, Diastereoselective synthesis of AHPBA using lithium allene reagent

Park *et al.* reported a diastereoselective nucleophilic addition case of Grignard reagent to *N*-Pf-D-phenylalaninal (Scheme 11).<sup>67</sup> Aldehyde **D-34** was treated with ethynylmagnesium bromide to give  $\beta$ -amino alcohol **35** in 91% yield with 91:9 *syn/anti* dr. The *syn* amino alcohol **35** was further transformed

into orthogonally protected AHPBA **36** and (–)-bestatin **2a**. The authors rationalized the high diastereoselectivity on the basis of a chelation-controlled model. A CH- $\pi$  interaction between the *N*-Pf group and the phenyl moiety also contributed to the high diastereoselectivity.

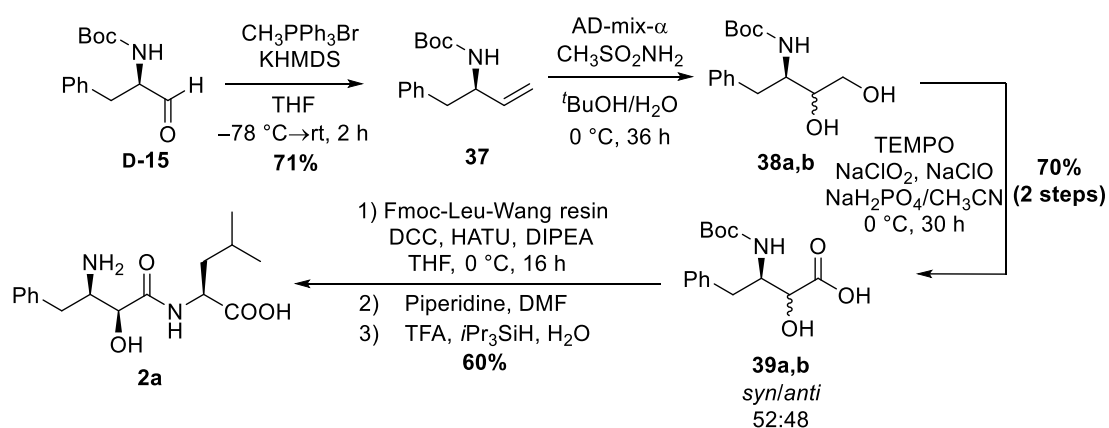


Scheme 11, Diastereoselective synthesis of (–)-bestatin using ethynylmagnesium bromide

Some other examples, such as the work of Sudalai *et al.* on *N*-benzoyl-D-phenylalaninal continued showing *syn* diastereoselectivity,<sup>68</sup> while the work of Ikunaka *et al.* on *N,N*-dibenzyl-L-phenylalaninal showed *anti* diastereoselectivity<sup>69</sup>.

### 1.3.1.5 through Wittig reaction

In 2011, Greenbaum *et al.* published the synthesis of (–)-bestatin from *N*-Boc-D-phenylalaninal starting with a Wittig reaction (Scheme 12).<sup>70,71</sup> Aldehyde **D-15** was reacted with potassium bis(trimethylsilyl) amide (KHMDS) and methyltriphenyl phosphonium bromide to give olefin **37** in 71% yield. This compound underwent a Sharpless dihydroxylation using AD-mix- $\alpha$  to afford diols **38a,b** as a mixture of two diastereomers. Selective oxidation of diol **38a,b** gave *N*-Boc-AHPBAs **39a,b**, and the *syn* diastereomer was transformed into (–)-bestatin **2a**.

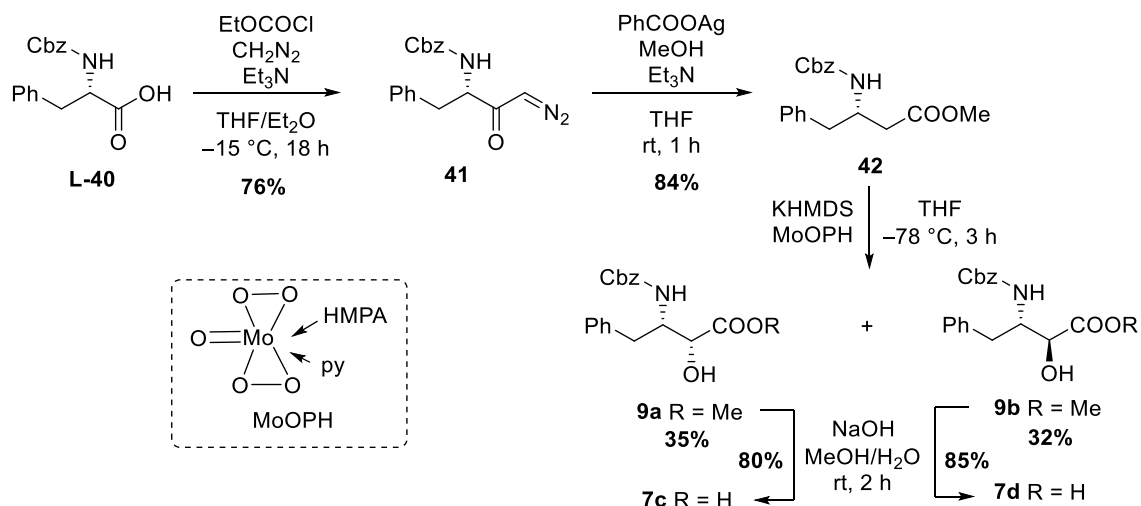


Scheme 12, Diastereoselective synthesis of (–)-bestatin through Wittig reaction

### 1.3.2 Starting from phenylalanine

#### 1.3.2.1 through sequential homologation/hydroxylation

In 1999, Abell *et al.* described a two-stage oxyhomologation of *N*-Cbz-L-phenylalanine **L-40** (Scheme **13**).<sup>72</sup> Methyl  $\beta$ -amino ester **42** was first prepared through Arndt–Eistert reaction. This ester **42** was next treated with potassium hexamethyldisilazide (KHMDS) and Vedejs reagent (MoOPH) to achieve  $\alpha$ -hydroxylation. AHPBA methyl esters **9a** and **9b** were obtained in slight favor of *syn* diastereoselectivity, and final *N*-Cbz-AHPBAs **7a** and **7b** were afforded after saponification.

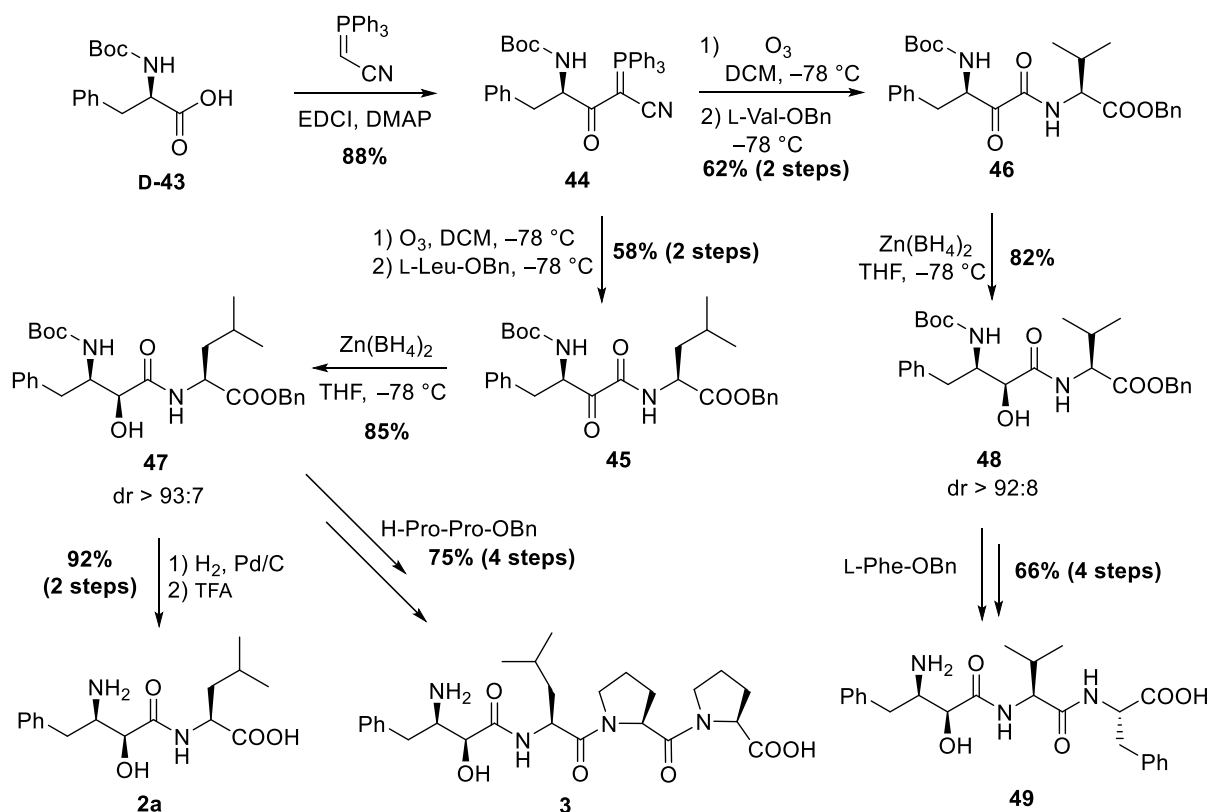


Scheme 13, Oxyhomologation through sequential homologation/hydroxylation

#### 1.3.2.2 through reaction with cyanoylides

Cyano-stabilized phosphorus ylides were employed as acyl equivalents to perform the oxyhomologation of phenylalanine by Wasserman *et al.*<sup>73,74</sup>

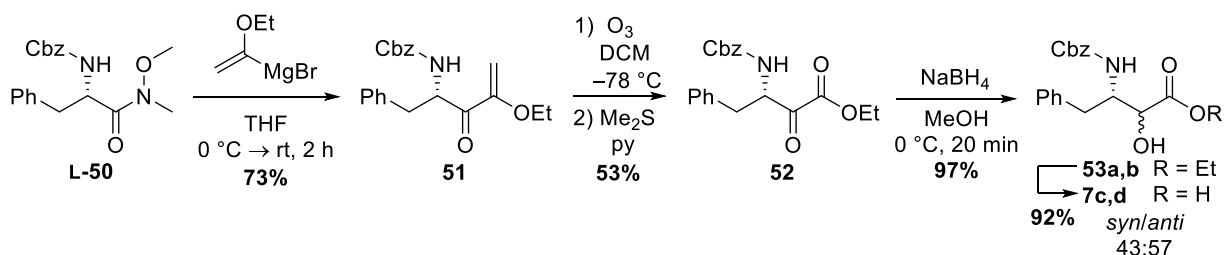
As shown in Scheme **14**, *N*-Boc-D-phenylalanine **D-43** was reacted with phosphorus ylide in the presence of EDCI and DMAP to give acyl cyanophosphorane intermediate **44**. Ozonolysis of this intermediate **44** followed by the coupling with an amino ester gave dipeptidic  $\alpha$ -keto amide **45** or **46**. The subsequent reduction of  $\alpha$ -keto amides using zinc borohydride gave *syn* diastereomer **47** or **48** (*dr* > 92:8 *syn/anti*). This strategy was applied for synthesizing (–)-bestatin **2a**, probestin **3** and phebestin **49**.



Scheme 14, Oxyhomologation using phosphorus ylide

1.3.2.3 through the reduction of  $\alpha$ -keto- $\beta$ -amino acid derivatives

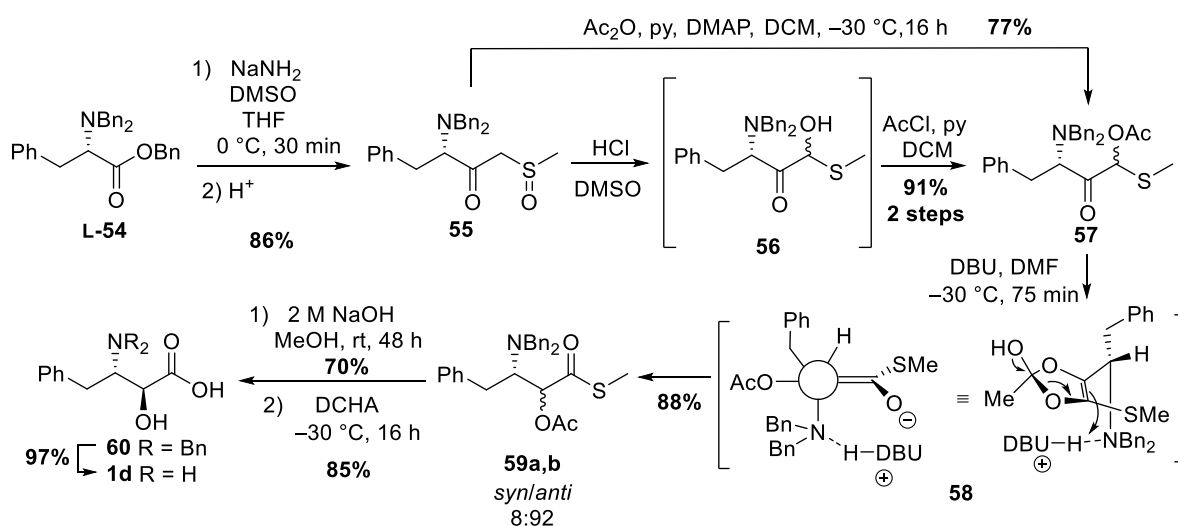
Like the above example, reducing an  $\alpha$ -keto- $\beta$ -amino acid derivative can lead to a chiral  $C_\alpha$  center. The first example of this strategy was presented by Wong *et al.*<sup>75</sup> As shown in Scheme 15, *N*-Cbz-L-phenylalanine Weinreb amide **L-50** was then treated with ( $\alpha$ -ethoxyvinyl)magnesium bromide followed by ozonolysis to give  $\alpha$ -keto ester **52**.<sup>76</sup> Subsequent reduction of this  $\alpha$ -keto ester **52** using sodium borohydride gave AHPBA esters **53a,b** and AHPBAs **7c,d** with a 43:57 *syn/anti* ratio.

Scheme 15, Synthesis of AHPBAs by reduction of an  $\alpha$ -keto- $\beta$ -amino ester by Wong *et al.*

## 1.3.2.4 through Pummerer rearrangement

In 2005, Izawa *et al.* synthesized (2*S*,3*S*)-AHPBA through Pummerer rearrangement and subsequent acyl rearrangement (Scheme 16).<sup>77</sup>  $\beta$ -Ketosulfoxide **55** was prepared from benzyl *N,N*-dibenzyl-L-phenylalaninate **L-54** and underwent a Pummerer rearrangement/acetylation in a sequential or *one-pot* manner to generate  $\alpha$ -acetoxy sulfide **57**. Subsequent  $\alpha,\beta$ -rearrangement of compound **57**

involving acyl migration gave thioesters **59a,b** in 88% yield and 8:92 *syn/anti* dr and finally transformed into free (2*S*,3*S*)-AHPBA **1d**. The authors proposed that the acyl arrangement from compound **57** to **59** might undergo intermediate **58**. The DBU-promoted proton transfer was more favorable and eventually led to an *anti* configuration. The H-bond formed by the *N,N*-diprotected nitrogen with protonated DBU was also attributed to the chiral control. When *N*-Cbz-protected ketosulfoxides were used to participate in the reaction, the dominant configuration of the product was *syn*, and the authors believed that because *N*-Cbz moiety was no longer an effective hydrogen donor.

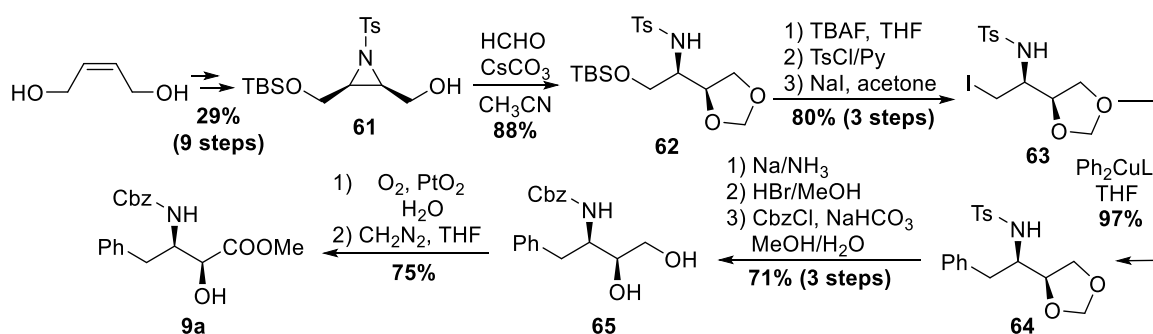


Scheme 16, Preparation of (2*S*,3*S*)-AHPBA through Pummerer rearrangement

### 1.3.3 from ring-opening reactions

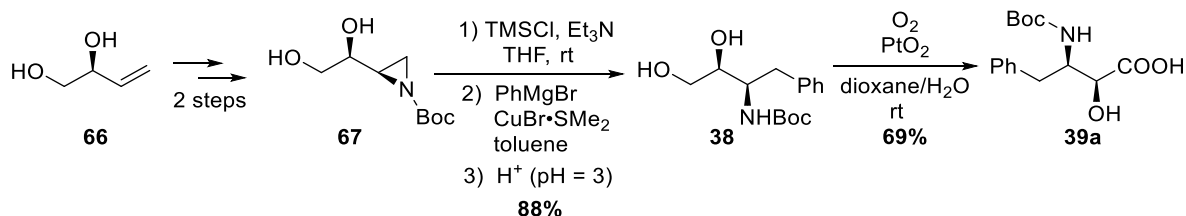
#### 1.3.3.1 Ring opening of aziridines

Ring-opening reactions of activated aziridines have been widely investigated for synthesizing a large panel of  $\beta$ -substituted amino compounds, including AHPBAs.<sup>78</sup> Fuji *et al.* prepared the following optically pure 2,3-disubstituted aziridine **61** from *cis*-but-2-ene-1,4-diol in 9 steps.<sup>79</sup> The regioselective ring-opening of **61** was realized by an  $S_N2$  substitution of the hydroxide anion of the hemiacetal formed with formaldehyde.<sup>80,81</sup> The resulting acetal **62** was transformed into iodide **63**, and the phenyl group was introduced using diphenyl copper lithium. Successive detosylation, acidic hydrolysis, and *N*-Cbz protection gave diol **65**. Finally, the primary alcohol of **65** was selectively oxidized to an acid, which was transformed into (2*S*,3*R*)-AHPBA ester **9a** (Scheme 17).



Scheme 17, Synthesis of *syn*-AHPBA from activated aziridine by Fuji *et al.*

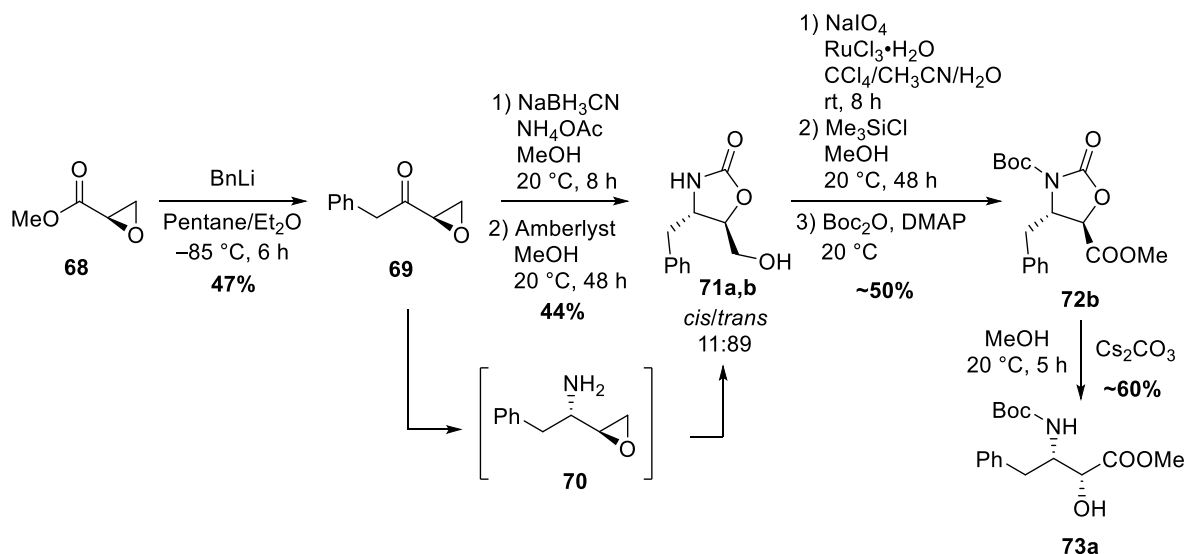
It is possible to directly introduce the phenyl group during the ring-opening step, as shown by Kang *et al.* (Scheme 18).<sup>82</sup> After trimethylsilyl protection of the diol **67**, the ring-opening reaction using phenylmagnesium bromide and cuprous bromide-dimethyl sulfide complex was performed. Diol **38** was obtained after an acidic workup, which was subsequently oxidized to give (2*S*,3*R*)-AHPBA **39a** in 61% overall yield from aziridine **67**.



Scheme 18, Synthesis of *syn*-AHPBA through activated aziridine by Kang *et al.*

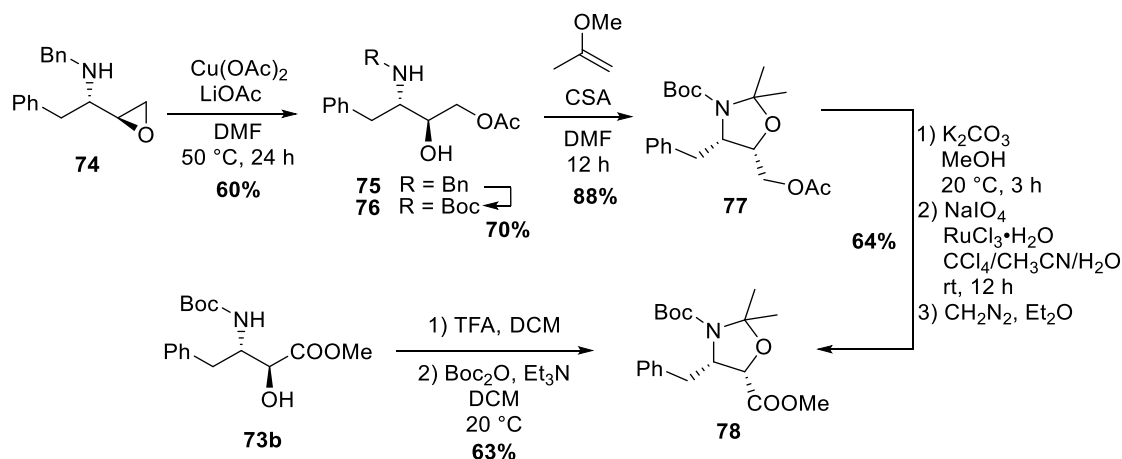
### 1.3.3.2 Ring opening of epoxides

Like aziridine, ring opening of epoxides by the attack of nucleophiles can furnish AHBA. Larchevêque *et al.* first published such an example (Scheme 19).<sup>83</sup> Starting from glycidic ester **68**, the authors prepared  $\alpha,\beta$ -epoxy ketone **69**. Reductive amination of this ketone furnished the aminoepoxide **70**, which was immediately converted into oxazolidinones **71a,b** in a 11:89 *cis/trans* ratio. The *trans* oxazolidinone **71b** was transformed through oxidation/esterification/*N*-Boc protection/basic methanolysis procedures to give (2*R*,3*S*)-AHPBA methyl ester **73a**.



Scheme 19, Synthesis of *syn*-AHPBA from chiral epoxides

Synthesis of *anti*-(2*S*,3*S*) AHPBA was completed through the same strategy (Scheme 20). Nucleophilic addition of the copper acetate to the epoxide **74** in the presence of lithium acetate gave monoprotected diol **75**. After changed the *N*-benzyl group into *N*-Cbz group, the monoprotected diol **76** was then transformed into oxazolidine **77**, and the acetate moiety was oxidized followed by a methylation to produce methyl ester **78**. At last, cleavage of the oxazolidine **78** gave (2*S*,3*S*)-AHPBA **73b**.

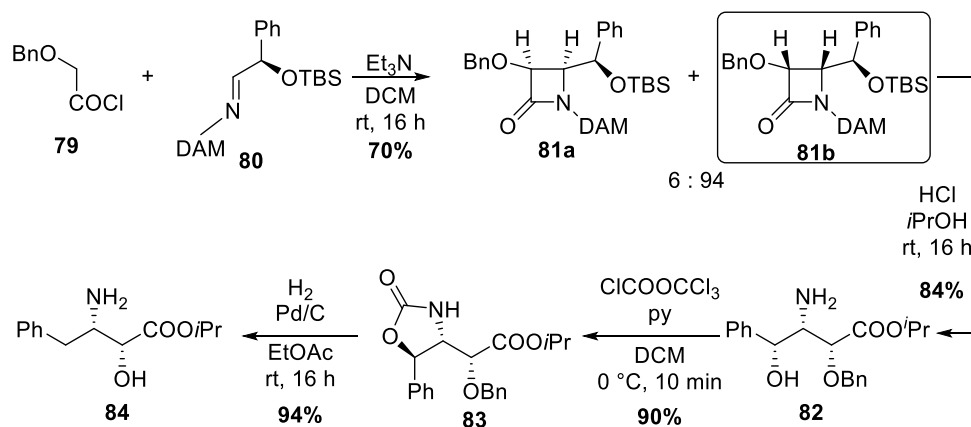


Scheme 20, Synthesis of anti-AHPBA from chiral epoxide

In addition, ring-opening of proper chiral difunctionalized epoxy esters can directly give corresponding AHPBAs: *anti*-AHPBA from *trans* epoxy ester and *syn*-AHPBA from the *cis* epoxy ester.<sup>84,85,86,87</sup>

### 1.3.3.3 Ring opening of $\beta$ -lactams

S. Terashima *et al.* reported the first ring-opening example of *cis*- $\beta$ -lactam for synthesizing *syn*-AHPBA (Scheme 21).<sup>88</sup> [2+2] Cycloaddition of the benzyloxyacetyl chloride **79** and chiral imine **80** gave 3,4-*cis*-2-azetidinone derivatives **81a,b** in 70% yield and 6:94 dr. Ring-opening of  $\beta$ -lactam **81b** was achieved using acidic isopropanol to give fully deprotected isopropyl ester **82**. It was then converted into 2-oxazolidone **83** using trichloromethyl chloroformate and finally transformed into (2*R*,3*S*)-AHPBA isopropyl ester **84**.

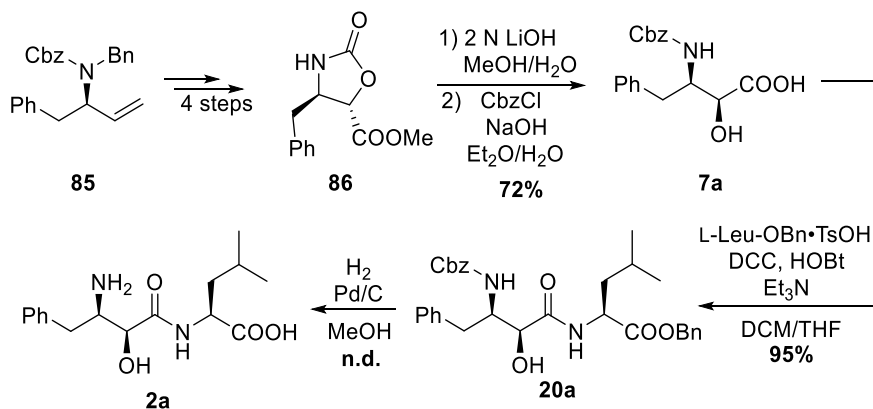
Scheme 21, Synthesis of (2*R*,3*S*)-AHPBA isopropyl ester by Terashima *et al.*

More examples for the synthesis of *syn*-AHPBAs through the ring-opening of *cis*- $\beta$ -lactams were reported by Palomo *et al.*<sup>89,90</sup> and Ha *et al.*<sup>91</sup>, while the synthesis of *anti*-AHPBAs from *trans*- $\beta$ -lactam was reported by Shimizu *et al.*<sup>92</sup>



## 1.3.3.4 Ring opening of oxazolidinones

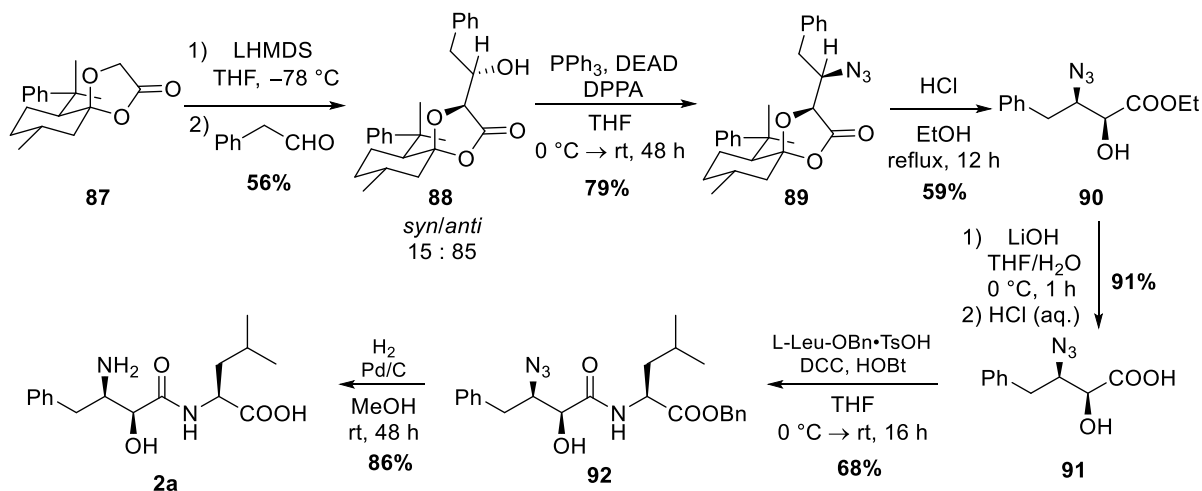
As we introduced, Larchevêque *et al.* synthesized *syn*-AHPBA by converting epoxyketone to *trans*-oxazolidinone followed by ring-opening (see Scheme 19). The opening of proper oxazolidinone substrates can easily give AHPBA derivatives, as shown in the example in Ohno *et al.* (Scheme 22).<sup>93</sup> Chiral allylamine **85** was transformed into *trans* oxazolidinone **86** in four steps, which could transfer into (2*S*,3*R*)-*N*-Cbz-AHPBA **7a** in a 72% yield. (–)-Bestatin **2a** was then synthesized after coupling to a leucine moiety. Similar examples were also reported by Morris *et al.*<sup>94</sup> and Stanchina *et al.*<sup>95</sup>



Scheme 22, Synthesis of *syn*-AHPBA and (–)-bestatin through 2-oxazolidinone by Ohno *et al.*

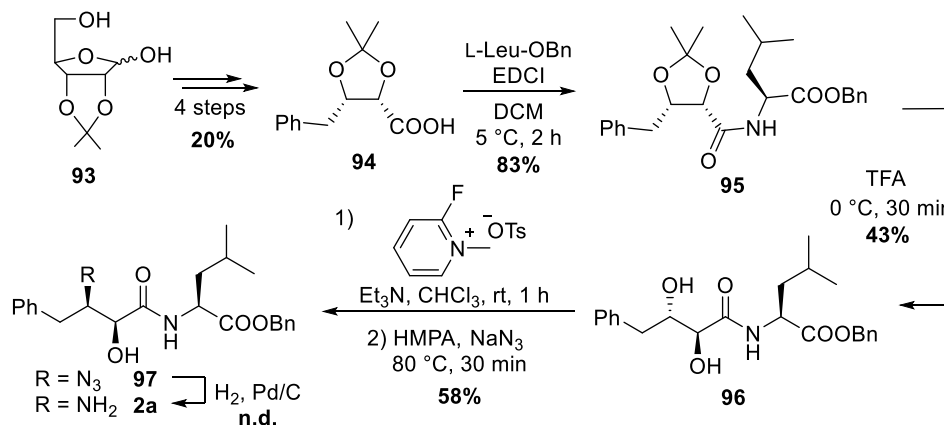
## 1.3.3.5 Other ring opening examples

Ring opening of dioxolanone for the synthesis of AHPBA derivatives was first reported by Pearson *et al.* (Scheme 23).<sup>96,97</sup> 1,4-Dioxolan-2-one **87** bearing chiral glycolic auxiliary was treated with lithium hexamethyldisilazide and phenylacetaldehyde to furnish aldol condensation products **88a,b** in 56% yield with 15:85 *syn/anti* dr. The *anti* diastereomer **88b** was converted to azide **89** by the Mitsunobu reaction. Subsequent ethanolysis led to the ring opening of dioxolanone **89** and gave  $\alpha$ -hydroxy- $\beta$ -azido ester **90**, which was further converted into azido acid **91** and (–)-bestatin **2a**.



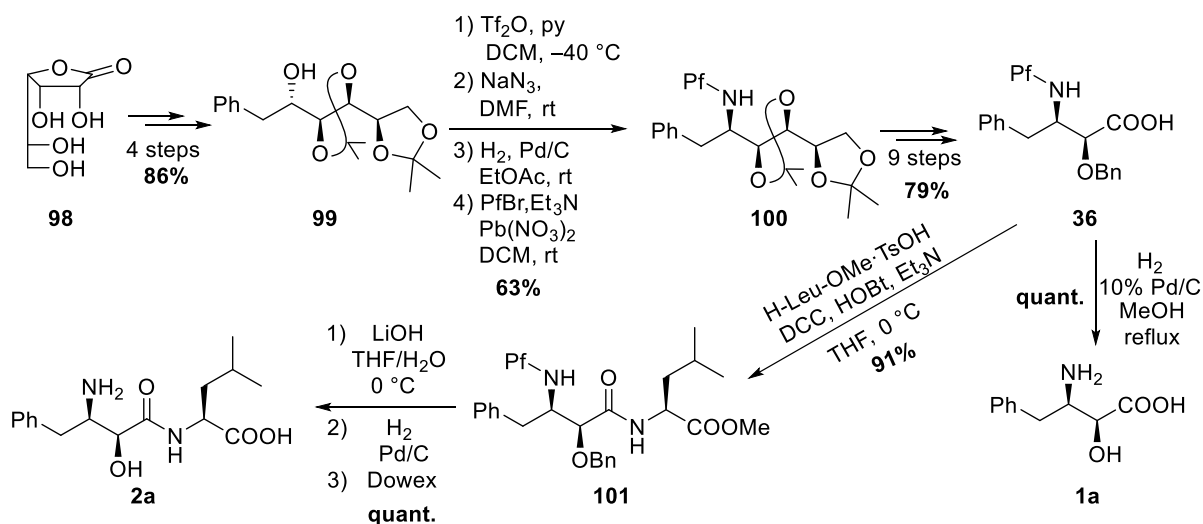
Scheme 23, Synthesis of (–)-bestatin through dioxolanone by Pearson *et al.*

Sugars can also undergo a ring-opening reaction followed by functional group interconversion to afford the AHPBA. In the work of Koseki *et al.* (Scheme 24),<sup>98</sup> 2,3-isopropylidene-D-ribose **93** was transformed into protected  $\alpha,\beta$ -dihydroxy acid **94**, which was coupled with H-Leu-OBn to give **95**, and the dioxolane was cleaved as diol **96**. The C $_{\beta}$ -hydroxy group was selectively activated as fluoride, then transformed into inversed azide **97** through the Mitsunobu reaction. Finally, (-)-bestatin **2a** was afforded after hydrogenolysis.



Scheme 24, Synthesis of (-)-bestatin from D-ribose derivatives

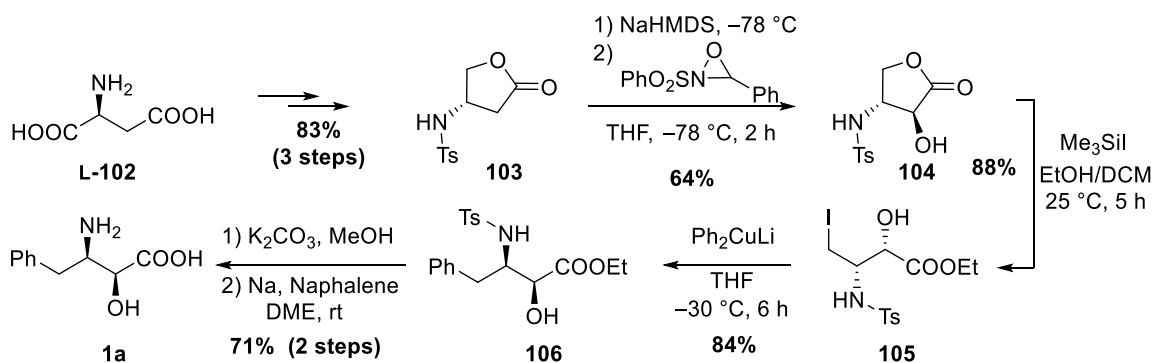
Like ribose, glucose derivatives have been employed to synthesize (2*S*,3*R*)-AHPBA and (-)-bestatin (Scheme 25).<sup>99</sup> D-gulonic acid  $\gamma$ -lactone **98** was transformed into secondary alcohol **99**, and a subsequent triflation/azide substitution/hydrogenation/*N*-Pf protection process gave amine **100**. The two isopropylidene groups were cleaved and transferred into (2*S*,3*R*)-AHPBA **1a** or (-)-Bestatin **2a**. The author also described the synthesis of *anti*-(2*S*,3*S*) AHPBA following the same methodology by adding a C $_{\beta}$ -amino group inversion.



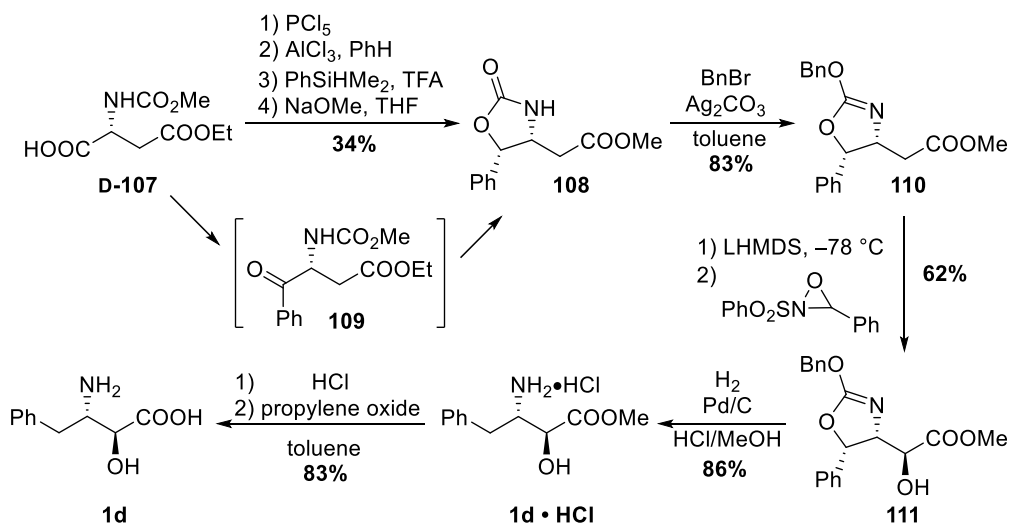
Scheme 25, Synthesis of (2*S*,3*R*)-AHPBA and (-)-bestatin from D-gulonic acid  $\gamma$ -lactone

1.3.4 from  $\beta$ -amino acids derivatives

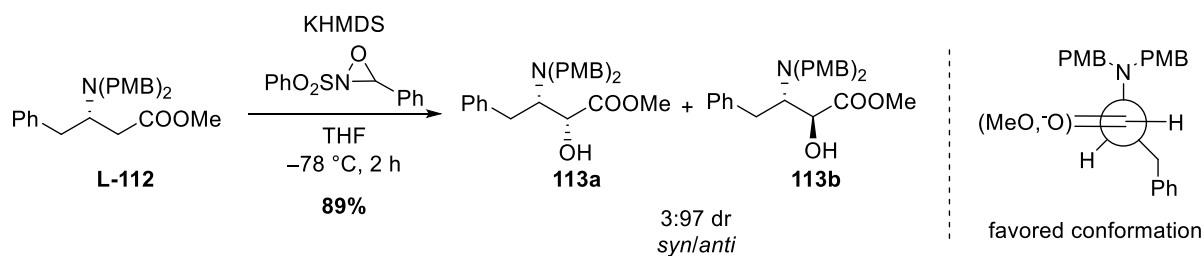
As we showed in the example from Abell *et al.* (see Scheme 13), a  $\beta$ -amino acid was produced from through a homologation of phenylalanine. The new generated  $\beta$ -amino acid could be transformed into an AHPBA motif after an  $\alpha$ -hydroxylation, as shown in the following example from Jefford *et al.* (Scheme 26).<sup>100</sup> L-Aspartic acid **L-102** was converted into  $\gamma$ -lactone **103**, which was successively treated with sodium hexamethyldisilazide (NaHMDS) and 3-phenyl-2-(phenylsulfonyl)oxaziridine to perform diastereoselective  $\alpha$ -hydroxylation. The resulting *trans*  $\alpha$ -hydroxy-*N*-tosylaminobutyrolactone **104** was treated with trimethyl silyl iodide and gave *syn*-AHBA ester **105**. The iodide terminal of **105** was further functionalized into (2*S*,3*R*)-AHPBA ethyl ester **106** and (2*S*,3*R*)-AHPBA **1a**.

Scheme 26, Synthesis of (2*S*,3*R*)-AHPBA from aspartic acid through  $\alpha$ -hydroxylation

*anti*-AHPBA was prepared by Seki *et al.* by changing the *N*-protection suite (Scheme 27).<sup>101</sup> *N*-carbamated D-aspartic acid  $\beta$ -ester **D-107** was transformed into 5-phenyl-2-oxazolidinone-4-acetate **108** through Friedel-Crafts acylation, followed by reduction and transesterification.<sup>102</sup> The acetate **108** was then *O*-benzylated to give oxazoline **110**, which was treated with lithium bis(trimethylsilyl)amide (LHMDS) and 3-phenyl-2-(phenylsulfonyl)oxaziridine to give *anti*- $\alpha$ -hydroxylated compound **111**. Subsequent ring-opening of oxazoline could lead to *anti* (2*S*,3*S*)-AHPBA **1d** as the only product.

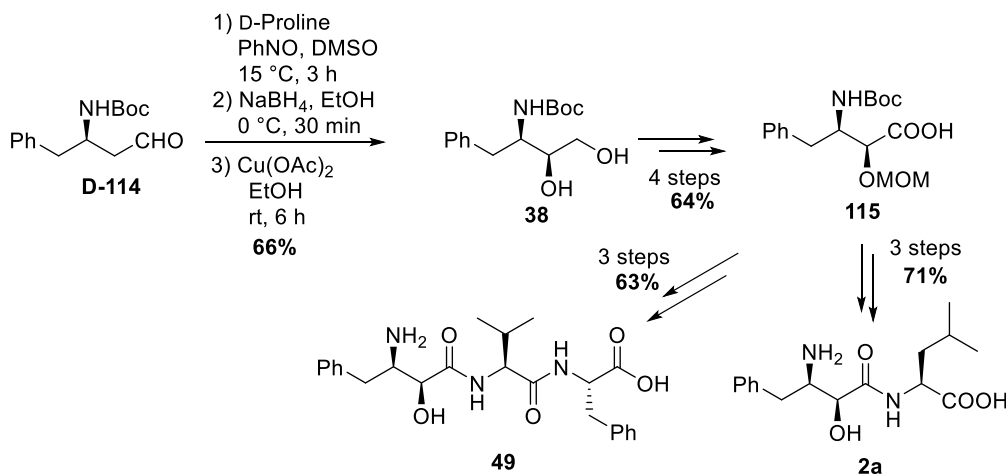
Scheme 27, Synthesis of (2*S*,3*S*)-AHPBA from aspartic ester through  $\alpha$ -hydroxylation

Pedatella *et al.* reported a similar example starting from *N,N*-diprotected  $\beta$ -amino ester **L-112** (Scheme 28). The  $\alpha$ -hydroxylation using potassium bis(trimethylsilyl)amide (KHMDs) and 3-phenyl-2-(phenylsulfonyl)oxaziridine gave AHPBA esters **113a,b** in 89% yield with 3: 97 *syn/anti* dr.<sup>103</sup> The author explained the high selectivity using the following transition state: one of the enolate groups was placed between a hydrogen atom and the protected amino group, and the attack of oxaziridine reagent took place from the lower part of the enolate moiety (the opposite to the bulky nitrogen group), thus gave *anti* compound as the major product.



Scheme 28, Synthesis of (2*S*,3*S*)-AHPBA from  $\beta$ -amino ester through  $\alpha$ -hydroxylation

The diastereoselectivity of  $\alpha$ -hydroxylation can also be controlled by introducing an organocatalyst such as proline. In 2019, Jain *et al.* reported such proline-catalyzed  $\alpha$ -hydroxylation (Scheme 29).<sup>104</sup> The reaction of homo- $\beta$ -D-phenylalaninal **D-114** and nitrosobenzene in the presence of D-proline successfully induced the *S* configuration of  $C_{\alpha}$ , followed by the reduction and *N*-O cleavage steps to give diol **38**. The diol **38** was further functionalized into protected (2*S*,3*R*)-AHPBA **115**, (–)-bestatin **2a**, and phebestin **49**. The introduction of L-proline can lead to the *R* configuration of the  $C_{\alpha}$  center and thus give *anti* (2*R*,3*R*)-AHPBA.<sup>105</sup>



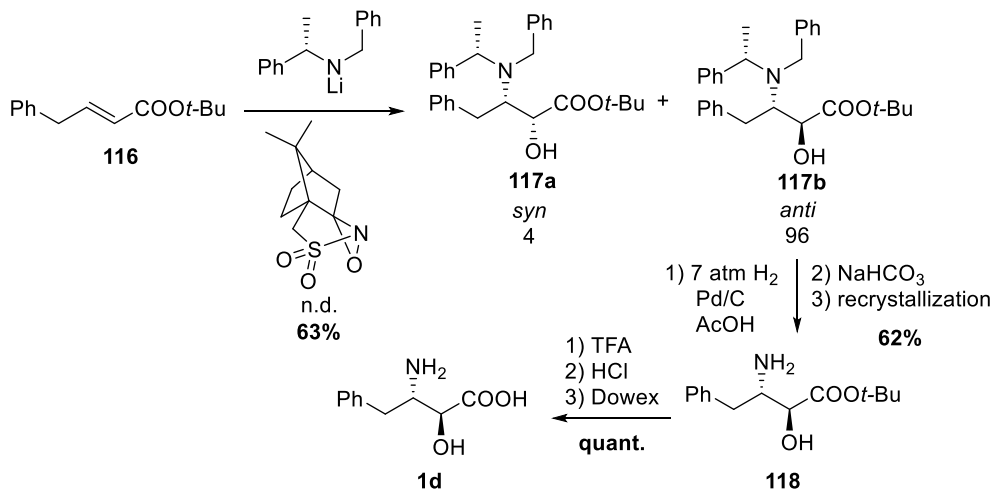
Scheme 29, Organocatalytic  $\alpha$ -hydroxylation of  $\beta$ -amino aldehyde for the synthesis of *syn*-(2*S*,3*R*)-AHPBA

### 1.3.5 from $\alpha,\beta$ -unsaturated esters

#### 1.3.5.1 through sequential aza-Michael addition/hydroxylation

One well-known example of asymmetric conjugate addition on  $\alpha,\beta$ -unsaturated ester was presented by Davies *et al.*<sup>106,107</sup> Butenoate **116** was treated with lithium (*S*)-( $\alpha$ -methylbenzyl)benzylamide to give

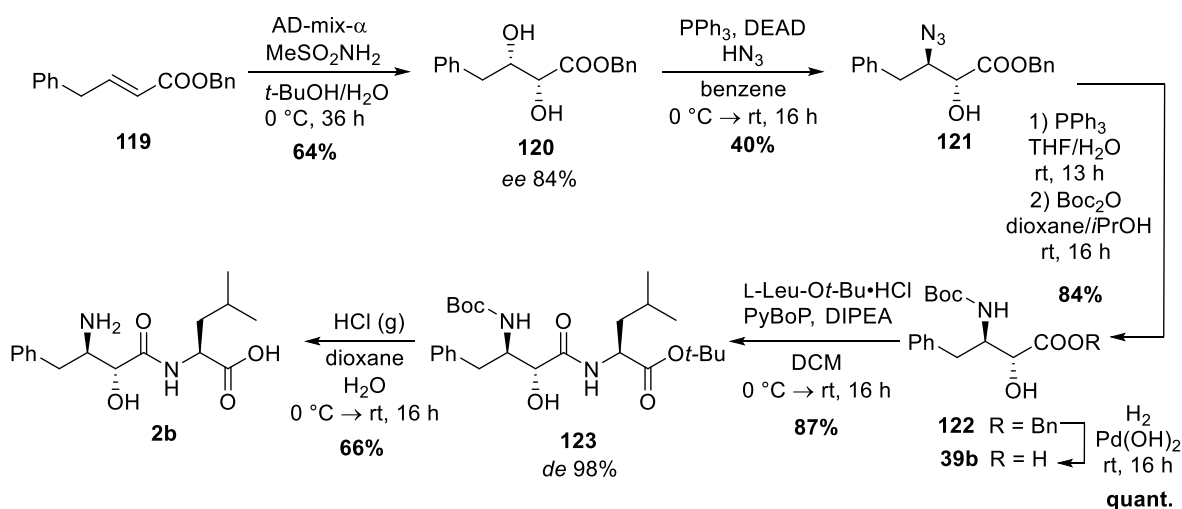
enolate, which was reacted with (+)-(camphorsulphonyl)oxaziridine (Scheme 30). The *in situ* hydroxylation gave AHPBA esters **117a,b** in 63% yield with 4:96 *syn/anti* dr. And the (2*S*,3*S*)-AHPBA **1d** was obtained after the global deprotection of **117b** in 62% yield. Jahn *et al.* later adopted this methodology and achieved the synthesis of *anti*-(2*R*,3*R*)-AHPBA derivatives.<sup>108</sup>



Scheme 30, Synthesis of *anti*-AHPBAs from  $\alpha,\beta$ -unsaturated ester by Davies *et al.*

### 1.3.5.2 through Sharpless dihydroxylation

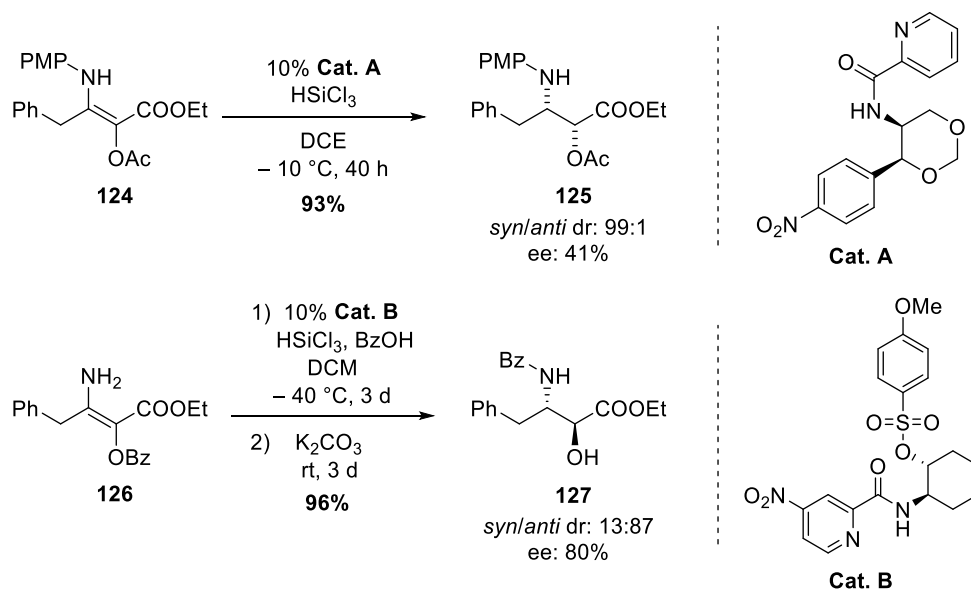
Besides the direct hydroxyamination using lithium amide,  $\alpha,\beta$ -unsaturated ester can also undergo a classical Sharpless dihydroxylation followed by a functional group interconversion to give AHBA derivatives. This strategy was adopted by Hedberg *et al.* for synthesizing (2*R*,3*R*,*S*)-epibestatin in 2010 (Scheme 31).<sup>109</sup> Butenoate **119** was mixed with Sharpless's AD-mix- $\alpha$  in the presence of methanesulfonamide to give (2*R*,3*S*)-diol **120**. The configuration of C $_{\beta}$  of **120** was inverted through the Mitsunobu reaction, and (2*R*,3*R*)- $\alpha$ -hydroxy- $\beta$ -azido ester **121** was obtained in 40% yield. After the Staudinger reaction, *N*-carbamation and hydrogenolysis, *N*-Boc-(2*R*,3*R*)-AHPBA **39b** was afforded in 84% yield. And (2*R*,3*R*,*S*)-epibestatin **2b** was obtained after classical peptide coupling with L-leucine.



Scheme 31, Synthesis of (2*R*,3*R*,*S*)-epibestatin from  $\alpha,\beta$ -unsaturated ester by Hedberg *et al.*

## 1.3.5.3 through asymmetric hydrosilylation

Zhang *et al.* reported the direct synthesis of AHPBAs through Lewis base-catalyzed hydrosilylation and realized a diastereoselectivity control (Scheme 32).<sup>110,111</sup>  $\alpha$ -Acyloxy- $\beta$ -enamino ester **124** was treated with trichlorosilane in the presence of **Cat. A** and *syn*-AHPBA ester **125** was obtained in 93% yield with excellent diastereoselectivity. On the other hand, hydrosilylation of **126** using **Cat. B** followed by a long time basification (3 days) furnished *anti*-AHPBA ester **127** was obtained in 96% yield with good diastereoselectivity and enantioselectivity.

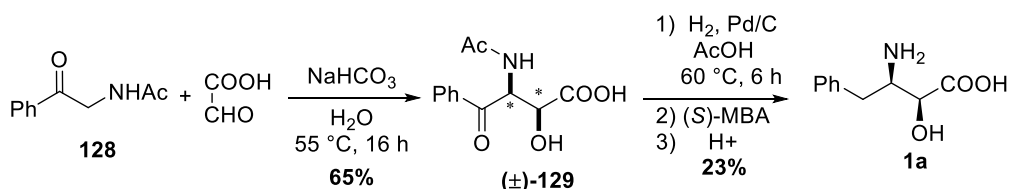


Scheme 32, Synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-AHPBA esters from functionalized  $\alpha,\beta$ -unsaturated esters by Zhang *et al.*

## 1.3.6 from other starting materials

## 1.3.6.1 through coupling reaction

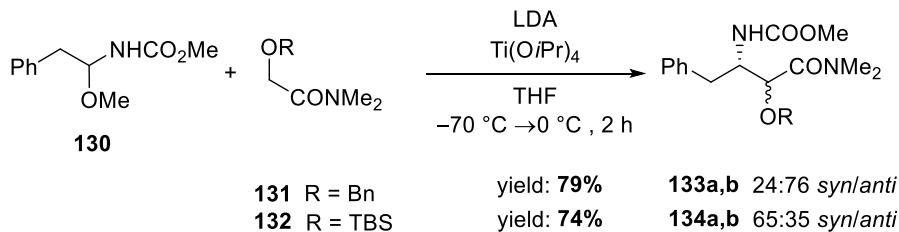
The  $C_\alpha$  and  $C_\beta$  center of the AHPBA molecule can be formed directly through an aldol reaction; Umezawa *et al.* reported such an example (Scheme 33).<sup>112</sup> Aldol reaction of *N*-acyl- $\alpha$ -aminoacetophenone **128** and glyoxylic acid gave *syn*  $\alpha$ -hydroxy- $\beta$ -amino- $\gamma$ -ketone acid derivatives ( $\pm$ )-**129** as a mixture of two racemic diastereomers. After hydrogenolysis, the (2*S*,3*R*)-AHPBA **1a** was isolated by salt formation with *S*-(-)- $\alpha$ -methylbenzylamine (MBA).



Scheme 33, Synthesis of (-)-bestatin from aldol reaction by Umezawa *et al.*

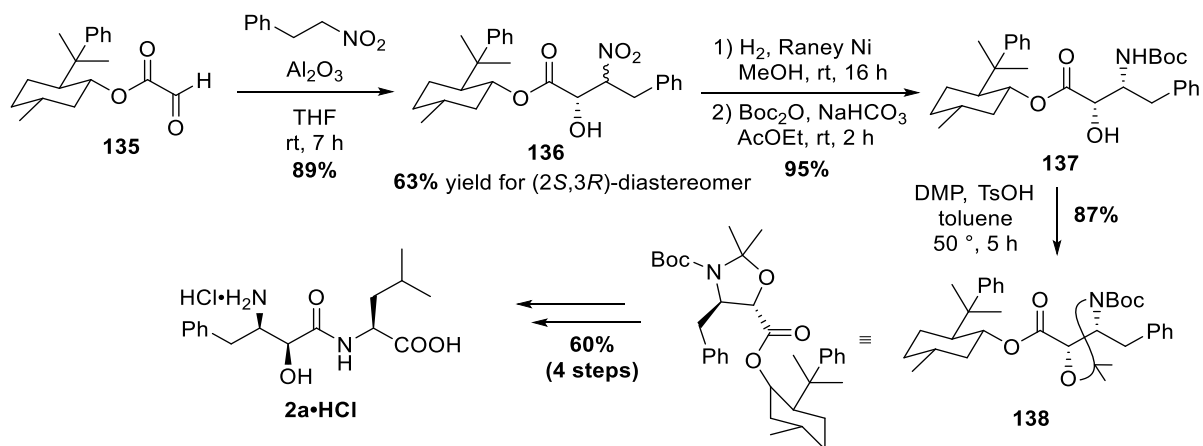
Matsumura *et al.* described a diastereoselective preparation of AHPBA through an aldol reaction (Scheme 34).<sup>113</sup> *N*-methoxycarbonyl-1-methoxyamine **130** was reacted with glycolic acid derivatives to

give a mixture of *syn*-(2*R*,3*S*) and *anti*-(2*S*,3*S*) AHPBA amides **133a,b**-**134a,b**. Using *O*-Benzyl-*N,N*-dimethylglycolamides **131** in the presence of titanium isopropoxide led to *anti*-selectivity. In contrast, the use of *O*-TBS-*N,N*-dimethylglycolamides **132** led to *syn* selectivity. However, the author did not explain the diastereoselectivity difference.



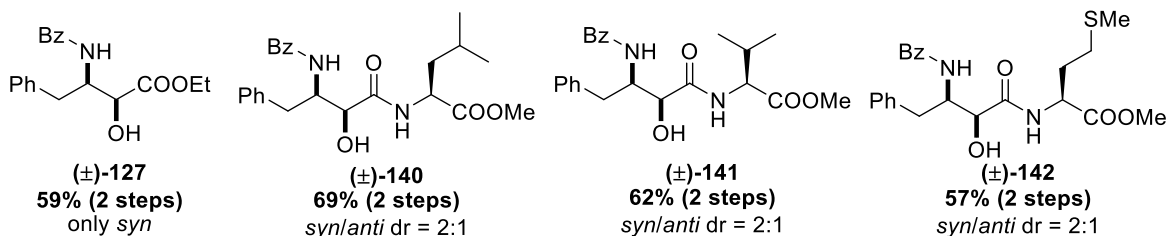
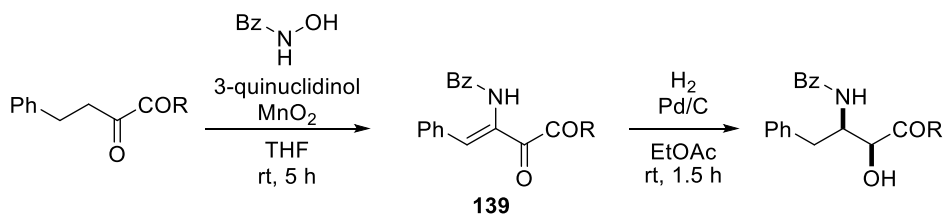
Scheme 34, Diastereoselective aldol reaction in the presence of Lewis acid by Matsumura *et al.*

Henry reaction has been applied to  $\alpha$ -keto aldehydes and gave  $\alpha$ -hydroxy- $\beta$ -nitro carbonyl compound, which was further transformed into an AHPBA molecule. In the example from Jurczak *et al.* (Scheme 35),<sup>114,115</sup> glyoxylate **135** bearing (1*R*)-8-phenylmenthol chiral auxiliary was reacted with 1-nitro-2-phenylethane in the presence of activated aluminum oxide to give compound **136**. Four diastereomers of **136** were produced in 71:19:6:5 [(2*S*,3*R*): (2*S*,3*S*): dia 3: dia 4] ratio, and the major (2*R*,3*R*) diastereomer was isolated in 63% yield from chromatography. The nitro group was hydrogenolyzed, *in situ* carbamated as **137**, and transformed into oxazolidine **138**. Finally, **138** was transformed into (–)-Bestatin **2a**·HCl in four steps. A catalytic version of this methodology using Shibashiki's catalyst was also reported by Barua *et al.*<sup>116</sup>



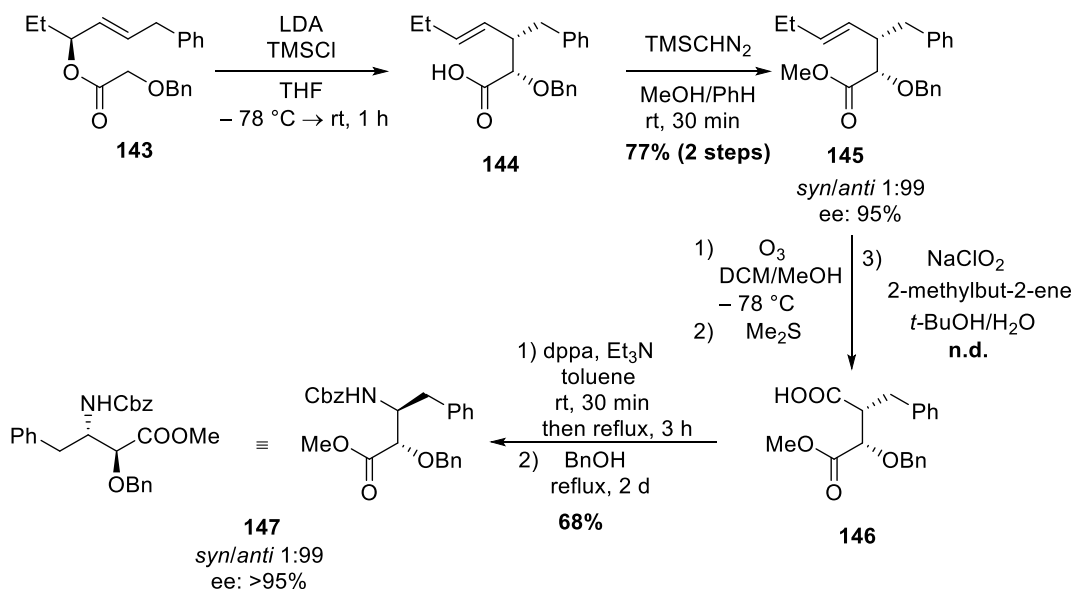
Scheme 35, Synthesis of (–)-bestatin through Henry reaction from glyoxylate

The reduction of  $\beta$ -unsaturated  $\alpha$ -keto carbonyl compounds can also form  $C_\alpha$  and  $C_\beta$  centers in one step. In the example from Baidya *et al.*,<sup>117</sup> a series of enamides **139** were prepared from a nitrosocarbonyl cross-aldol reaction (Scheme 36). Subsequent hydrogenolysis of **139** could give AHPBAs in one step. For simple ester **127**, only *syn* diastereomer was obtained. While for other three dipeptides (**140**, **141**, **142**), the dr was decreased to 2:1 *syn/anti*.

Scheme 36, Synthesis of AHPBA by reduction of  $\alpha$ -keto- $\beta$ -enamides compounds

### 1.3.6.2 through Claisen rearrangement

In the work of Kim *et al.* (Scheme 37),<sup>118</sup> *E*-allylic ester **143** was treated with lithium diisopropylamide and trimethylsilyl chloride to perform Ireland-Claisen rearrangement, and the resulting acid **144** was methylated as  $\alpha$ -hydroxy ester **145** in 77% yield, with 1:99 *syn/anti* dr and 95% ee. The olefin moiety of **145** was cleaved to give acid **146**, which was transformed into acyl azide using diphenylphosphoryl azide and subsequently underwent a Curtius rearrangement to give (2*S*,3*S*)-AHPBA methyl ester **147**. Similarly, (2*R*,3*S*)-AHPBA methyl ester could be synthesized from *Z*-allylic ester.

Scheme 37, Synthesis of (2*S*,3*S*)-AHPBA through Claisen rearrangement

### 1.3.7 Conclusion

Numerous methods have been applied to the synthesis of AHPBA and Bestatins. The diastereoselective approach appears to be more advantageous than the enantioselective approach since it only requires constructing one chiral center. Moreover, separating the resulting diastereomers is much easier than working on those enantiomers.



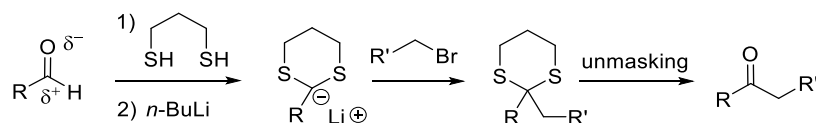
One of the most attractive methods was the oxyhomologation from phenylalanine derivatives, and several diastereoselective examples were reported. However, this approach still has challenges, such as finding more efficient and safer one-carbon synthons, the diastereoselectivity control during the oxyhomologation, and maintaining the original chiral center.

It is worth mentioning that some examples showed the diastereoselectivity embodied in the nucleophilic attack on a  $\alpha$ -amino aldehyde (e.g., cyanohydrin formation from phenylalinal) was related to their *N*-protection suits, and it appeared to be fruitful in controlling the diastereoselectivity by adjusting the protective strategy of the  $\alpha$ -amino group

## II. Masked Acyl Cyanide (MAC) methodology

### II.1 *Umpolung* concept and acyl anion equivalents

The *umpolung* concept was first reported by Corey and Seebach in 1965.<sup>119</sup> They showed that when an aldehyde was transformed into a metalated dithiane, the carbonyl's inherent electrophilic reactivity could be reversed, making the carbon atom nucleophilic, and it could undergo the subsequent nucleophilic addition (Scheme 38). Since the dithiane could be deprotected to provide a carbonyl moiety, it is also referred to as "acyl anion equivalent".<sup>120</sup>



Scheme 38, *Umpolung* reactivity of aldehydes via dithianes

Numerous *umpolung* reagents have been reported that act as acyl anion equivalents. These include metalated dithianes,<sup>121</sup> thiazolium salts,<sup>122</sup> hydrazones,<sup>123</sup> nitronate anions,<sup>124</sup> metallated enol derivatives,<sup>125</sup> metallo aldimines,<sup>126</sup> carbenes,<sup>127</sup> etc. (Figure 11).

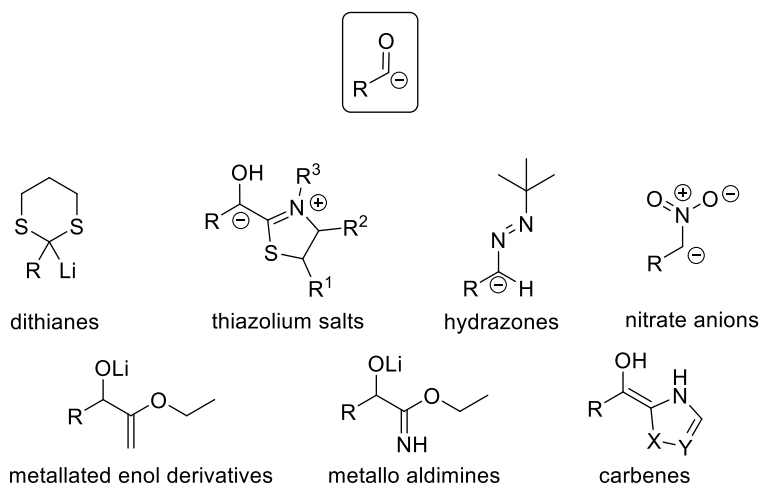


Figure 11, Several adducts of *umpolung* reagents as acyl anion equivalents on a carbonyl

## II.2 Masked Acyl Cyanide (MAC) reagents

In 1990, Nemoto *et al.* reported the following protected 2-hydroxymalononitrile **148** as a new class of *umpolung* reagents.<sup>128</sup> These reagents can formally insert a carbonyl moiety between an electrophile and a nucleophile; therefore, they were considered as acyl anion equivalents (Figure 12).

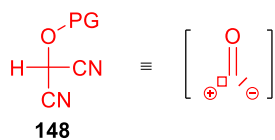
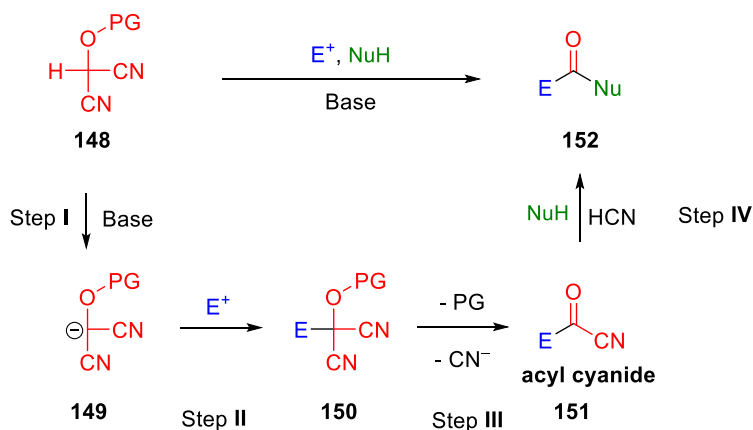


Figure 12, Protected 2-hydroxymalononitrile reagents as acyl anion equivalents

As shown in Scheme 39, protected 2-hydroxymalononitrile **148** can be deprotonated by a base (Step I); the MAC anion **149** will react with an electrophile ( $E^+$ ) to give adduct **150** (Step II). Subsequent elimination of the protecting group (PG) and cyanide anion results in the formation of acyl cyanide **151** (Step III), which is electrophilic, and it can accept a nucleophile to produce MAC product **152** (Step IV).



Scheme 39, Reactivity of MAC (Masked Acyl Cyanide) reagents

As acyl cyanide **151** is generated during the process; therefore, the protected 2-hydroxymalononitrile **148** was named as Masked Acy Cyanide (MAC) reagent, abbreviated as H-MAC-PG, or H-C(CN)<sub>2</sub>O-PG.<sup>129,130</sup>

So far, nine MAC reagents have been reported in the literature (Figure 13): two of them are protected as acetals (H-MAC-EE **148a**, H-MAC-MOM **148b**),<sup>130</sup> and three are protected as esters (H-MAC-Ac **148c**, H-MAC-Bz **148d**, H-MAC-COC<sub>10</sub>H<sub>21</sub> **148e**);<sup>130</sup> the other four are protected as silyl ethers (H-MAC-TES **148f**, H-MAC-TBS **148g**, H-MAC-TIPS **148h**, H-MAC-TBDPS **148i**), they are also labeled as H-MAC-[Si]). Notably, the syntheses of H-MAC-TES **148f**, H-MAC-TIPS **148h** and H-MAC-TBDPS **148i** were first described in the doctoral thesis of Esgulian in the host lab.<sup>131</sup>

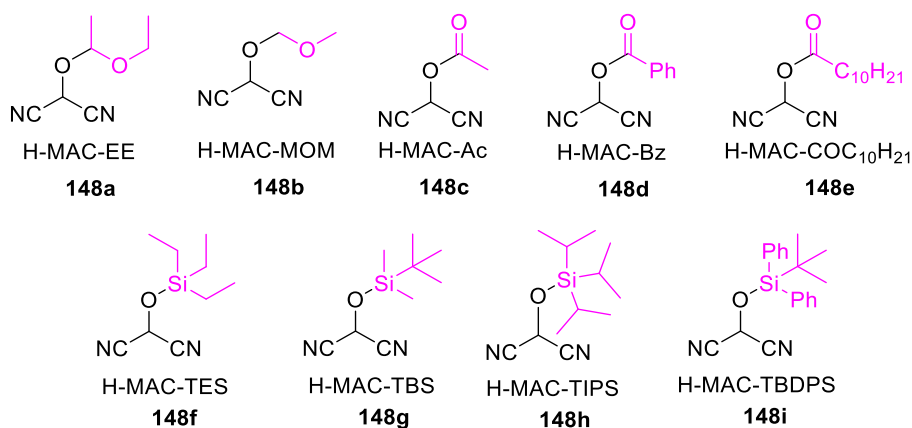


Figure 13, Reported MAC reagents in literature

Only H-MAC-EE **148a**, H-MAC-MOM **148b**, H-MAC-Ac **148c**, and the four silylated MAC reagents **148f-i** have been employed as synthetic acyl anion equivalents. H-MAC-EE **148a** and H-MAC-MOM **148b** have been used in sequential MAC methodology, while H-MAC-Ac **148c** and H-MAC-[Si] **148f-i** were available for both sequential and *one-pot* MAC methodologies.

### II.3 MAC methodology

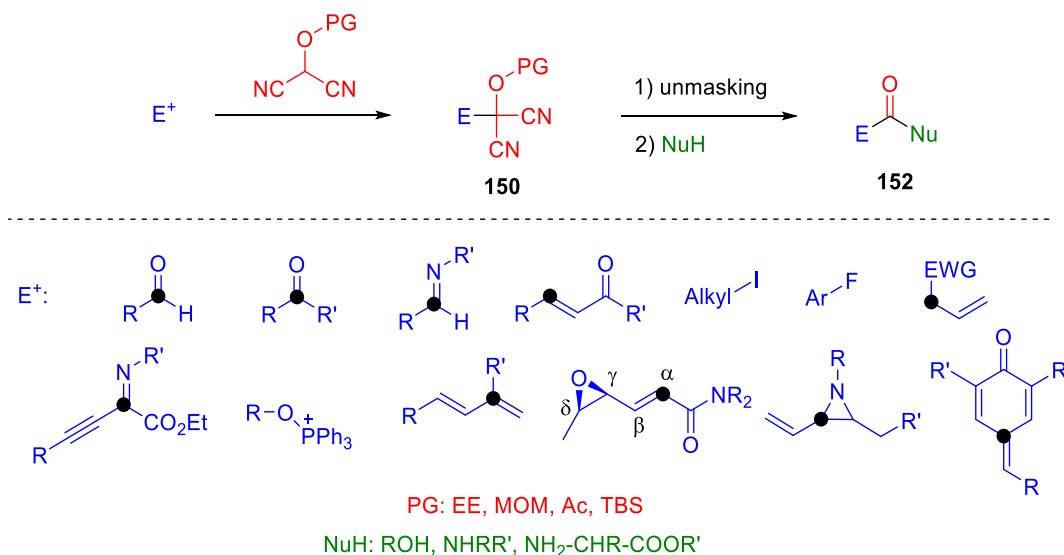
The four-step procedure presented in Scheme 39 is called MAC methodology (in this thesis, we also called it “MAC reaction”). MAC reactions can be manipulated sequentially (steps I/II are independent of steps III/IV) or in a *one-pot* manner (four steps are performed simultaneously).

#### II.3.1 Sequential MAC methodology

If the MAC adduct **150** is stable and can be isolated, then the MAC reaction can be performed sequentially (Scheme 40).

Numerous sequential MAC reactions have been reported over the past three decades. A wide variety of electrophiles have been employed, such as aldehydes,<sup>132,133,134</sup> ketones,<sup>135</sup> imines,<sup>128,136,137,138,139,140,141,142,143,144</sup> enones,<sup>139,145,146,147</sup> alkyl iodides,<sup>128</sup> aryl fluorides,<sup>148</sup> allylic derivatives,<sup>128,149,150,151,152,153</sup> ketimines,<sup>154</sup> Mitsunobu intermediates,<sup>155</sup> dienes,<sup>156</sup>  $\gamma,\delta$ -epoxy- $\alpha,\beta$ -unsaturated carboxamides,<sup>157</sup> vinylaziridines,<sup>158</sup> and *para*-quinone methides (*p*-QMs)<sup>159</sup>.

These reactions towards **150** were mainly promoted by a base, but they could be accomplished using transition metal catalysts<sup>149,150,151,152</sup> or organocatalysts<sup>145,146</sup>.



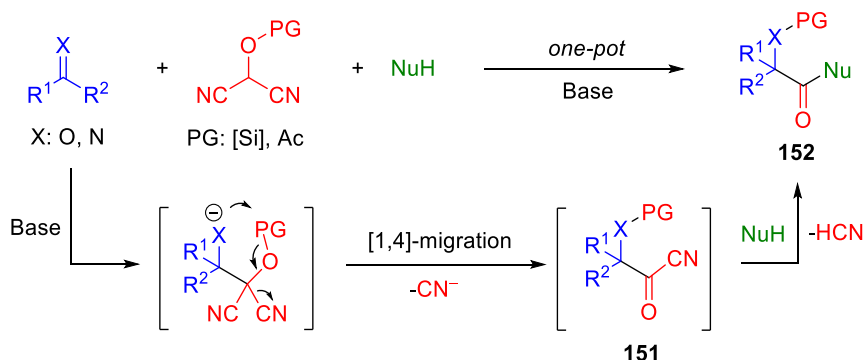
Scheme 40, Sequential MAC methodology and its general substrate scopes

Starting from the MAC adduct **150**, cleavage (*unmasking*) of the alcohol protecting group generates acyl cyanide, which can react with a nucleophile to afford oxyhomologated esters, amides and dipeptides. The unmasking conditions for the MAC adduct **150** are determined by the nature of MAC reagents: H-MAC-EE **148a** and H-MAC-MOM **148b** require acidic conditions, H-MAC-Ac **148c** requires basic conditions, while H-MAC-TBS **148g** need acidic conditions or fluoride reagents.

### II.3.2 One-pot MAC methodology

In the sequential procedure described above, a specific unmasking step is required. However, it is possible to conduct a *one-pot* MAC reaction without recourse to an additional unmasking step.

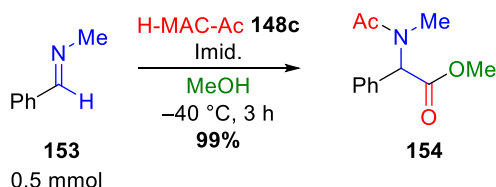
As shown in Scheme **41**, the *one-pot* MAC reaction proceeds through an intramolecular [1,4]-migration of the protecting group to form the acyl cyanide **151**; the subsequent addition of the nucleophile furnishes the oxyhomologated product **152** directly.



Scheme 41, Mechanism for one-pot MAC reactions

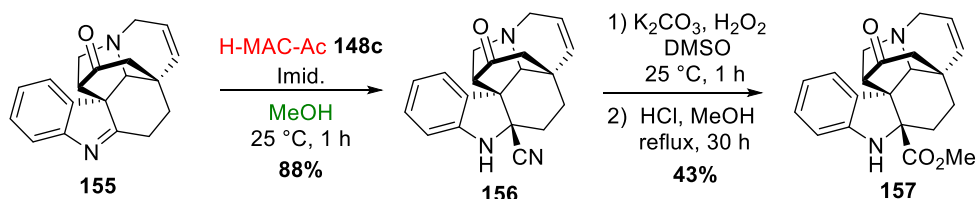
## II.3.2.1 One-pot MAC methodology applied on imines

Nemoto *et al.* reported a *one-pot* MAC reaction using H-MAC-Ac and imines in 2005.<sup>160</sup> *N*-alkylaldimine **153** was mixed with H-MAC-Ac **148c** and imidazole in methanol; reaction for three hours at  $-40\text{ }^{\circ}\text{C}$  gave  $\alpha$ -amino methyl ester **154** in 99% yield (Scheme 42).



Scheme 42, One-pot MAC reaction using H-MAC-Ac and imines

*One-pot* MAC reaction of imines has its limitations. Xia *et al.* reported such an example during the total synthesis of (+)-flavisiamine F (Scheme 43).<sup>161</sup> The constrained imine **155** was reacted with H-MAC-Ac **148c** and methanol, hoping to introduce a methoxycarbonyl moiety in one step. Unfortunately, the MAC reaction did not occur; only the cyanation product **156** was obtained. Although the resulting  $\alpha$ -amino nitrile **156** could be transformed into ester **157** through hydrolysis/esterification, the yield of this two-step process was only 43%.



Scheme 43, H-MAC-Ac for the synthesis of (+)-flavisiamine F

## II.3.2.2 One-pot MAC methodology applied on aldehydes

## II.3.2.2.1 Using H-MAC-Ac as the MAC reagent

Aldehydes **158a-c** were first employed to react with H-MAC-Ac **148c** in a *one-pot* procedure.<sup>162</sup> Using methanol or amines as nucleophiles, the *one-pot* MAC reaction gave the corresponding  $\alpha$ -acetoxy esters or amides in good to excellent yields (Table 1). When aniline was employed as the nucleophile under standard conditions, the MAC reaction didn't yield any MAC product.

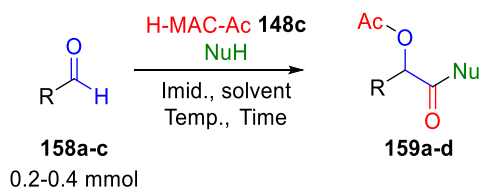


Table 1, One-pot MAC reaction using H-MAC-Ac and aldehydes

Entry	158	R	NuH	Solvent	Temp. (°C)	Time	Yield of 159, (%)
1	a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	MeOH	Et <sub>2</sub> O	rt	3 h	a, 93
2	b	<i>i</i> Pr	MeOH	Et <sub>2</sub> O	-20	24 h	b, 69
3	c	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	BuNH <sub>2</sub>	Acetonitrile	0	15 min	c, 84
4	c	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	PhNH <sub>2</sub>	Acetonitrile	0	2 h	d, 0

### II.3.2.2.2 Using H-MAC-TBS as the MAC reagent

Nemoto *et al.* first applied the *one-pot* MAC reaction on various aldehydes **160a-c** and ketones **160d-f** with H-MAC-TBS **148g** and butylamine (Table 2).<sup>163</sup> The results suggested that the MAC reaction was significantly influenced by the steric bulk of the electrophiles, as well as the polarity of the solvent.

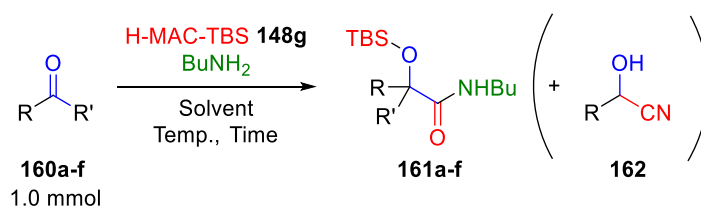


Table 2, One-pot MAC reaction using H-MAC-TBS and aldehydes or ketones

Entry	160	R	R'	Solvent	Temp. (°C)	Time	Yield of 161, (%)
1	a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	H	Acetonitrile	0	5 min	a, 96
2 <sup>a</sup>	b	PhCH <sub>2</sub> CH <sub>2</sub>	H	Acetonitrile	0	5 min	b, 63
4	b	PhCH <sub>2</sub> CH <sub>2</sub>	H	Et <sub>2</sub> O	-25	2 h	b, 85
5	c	<i>t</i> -Bu	H	Et <sub>2</sub> O	-25	20 h	c, 35
6	d	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	Me	Acetonitrile	-25	2 h	d, 98
8	e	Et	Et	Et <sub>2</sub> O	-25	2 h	e, 75
9	f	<i>t</i> -Bu	Me	Et <sub>2</sub> O	-25	20 h	f, 0

<sup>a</sup> cyanohydrin **162** was obtained as a by-product

It is of note that cyanohydrins **162** were observed as side products in the above examples,<sup>163</sup> which originated from the direct cyanation of the starting aldehydes.

In addition to the cyanohydrin formation, another chemoselectivity issue exists between in *one-pot* and sequential MAC reactions, exemplified in the MAC reactions from *N,O*-dimethylhydroxylamine, aldehydes **163a-b** and H-MAC-TBS **148g** in acetonitrile (Table 3).<sup>164</sup> Ideally, this reaction would give Weinreb amides **164a-b**; however, MAC adducts **165a-b** were also isolated from the reaction and even became the major product in some cases. The selectivity was related to the choice of the base: when 4-methylbenzaldehyde **163a** was employed, the use of pyridine gave MAC adduct **165a** as the only product, and the use of DMAP gave MAC product **164a** as the only product. Interestingly, when 4-

(trifluoromethyl)benzaldehyde **163b** was employed, even pyridine gave MAC product **164a** as the major product.

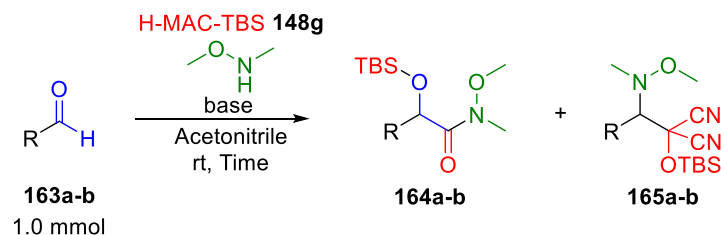
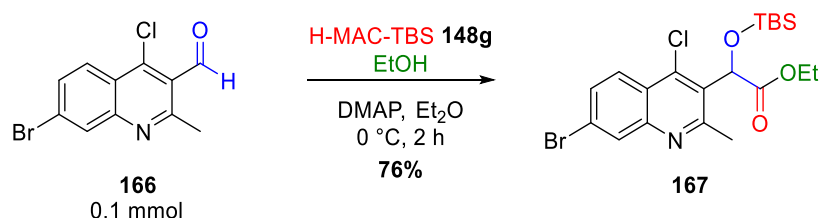


Table 3, Base controlled chemoselective one-pot MAC reactions

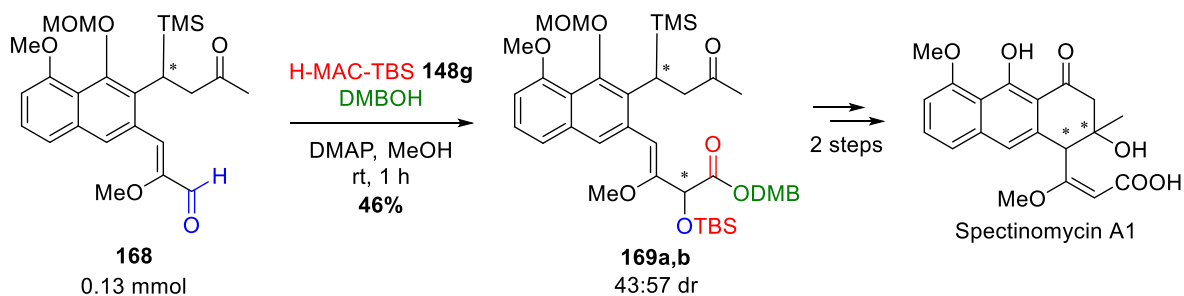
Entry	163	R	Base	Time (h)	Yield of 164, (%)	Yield of 165, (%)
1	a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	py	2	a, 0	a, 88
2	a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	Et <sub>3</sub> N	2	a, 23	a, 57
3	a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	Imid.	5	a, 73	a, 0
4	a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	DMAP	2	a, 91	a, 0
5	b	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	py	60	b, 44	b, 8
6	b	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	DMAP	2	b, 84	b, 0

In 2018, Donahue *et al.* applied a *one-pot* MAC reaction on a formyl quinoline substrate to construct a carboxylate in one step (Scheme 44).<sup>165</sup> The MAC reaction of aldehyde **166**, H-MAC-TBS **148g**, and ethanol gave  $\alpha$ -silyloxy ester **167** in 76% yield. This compound **167** was a precursor of a few potential HIV-1 integrase inhibitors.



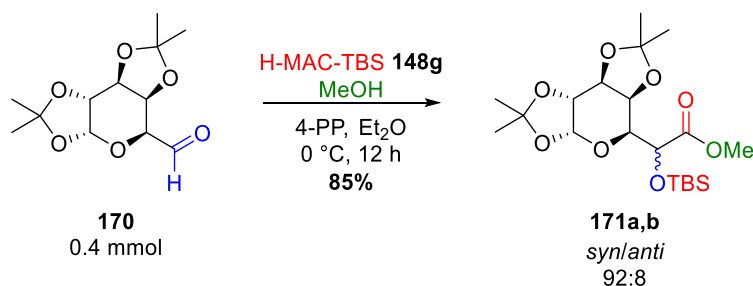
Scheme 44, One-pot MAC reaction using H-MAC-TBS by Donahue *et al.*

Sodeoka *et al.* reported a *one-pot* MAC reaction to synthesize monomeric Spectinomycin A1.<sup>166</sup> MAC reaction with H-MAC-TBS **148g** was applied on functionalized aldehydes **168** and 2,4-dimethoxybenzyl alcohol to give MAC products **169a,b** in 46% yield (Scheme 45). Given that the starting aldehyde has a chiral center (CHTMS), the diastereomeric ratio between the MAC products **169a,b** were checked as 43:57 (without identifying their configuration). The MAC product **169** was further cyclized and deprotected to prepare Spectinomycin A1.

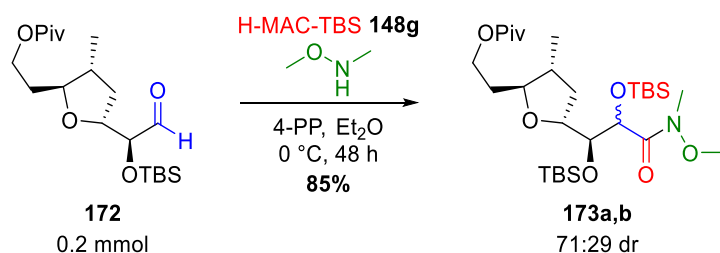


Scheme 45, One-pot MAC reaction for the synthesis of monomeric spectinomycin A1

One interesting *one-pot* MAC reaction using an  $\alpha$ -hydroxy aldehyde as the electrophile was reported by Nemoto *et al.* in 2008.<sup>167</sup> Protected pyranose-derived aldehyde **170** was reacted with H-MAC-TBS **148g** and methanol to give MAC products **171a,b** in 85% yield with 92:8 *syn/anti* dr (Scheme 46).

Scheme 46, One-pot MAC reaction of  $\alpha$ -hydroxy aldehyde and methanol

In 2013, Carter *et al.* described the total synthesis of amphidinolides C and F.<sup>168</sup> In the course of their studies, aldehyde **172** was mixed with H-MAC-TBS **148g** and *N,O*-dimethylhydroxylamine in a *one-pot* procedure for 48 hours at 0 °C to provide the oxyhomologated Weinreb amides **173a,b** in 85% yield (Scheme 47). The diastereomeric ratio of the MAC products **173a,b** was 71:29. The authors assumed that this reaction would give principally the *syn* diastereomer, but they did not determine the configuration of each MAC product. Unfortunately, Weinreb amides **173a,b** did not couple with organolithium reagents as intended, so this MAC protocol was not included in the final synthetic route.

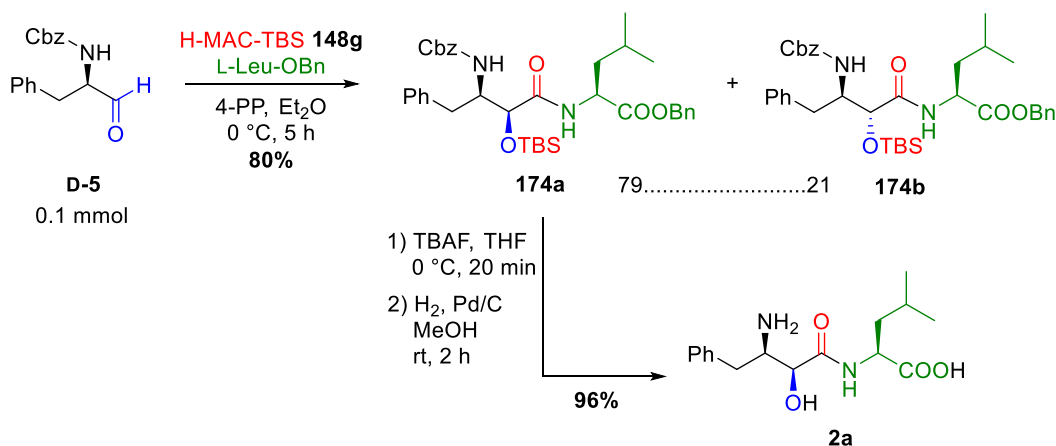
Scheme 47, One-pot MAC reaction of  $\alpha$ -hydroxy aldehyde and *N,O*-dimethylhydroxylamine

### II.3.3 One-pot MAC methodology applied on $\alpha$ -amino aldehydes

In 2000, Nemoto *et al.* described the first application of MAC reaction for synthesizing a peptide: the target was (–)-bestatin (Scheme 48).<sup>163</sup> MAC reaction of *N*-Cbz-D-phenylalaninal **D-5**, benzyl L-leucinate and H-MAC-TBS **148g** successfully furnished **174a,b** in 80% yield with 79:21 *syn/anti* dr. The *syn* diastereomer **174a** was separated from its *anti* diastereomer, and was deprotected in two steps to

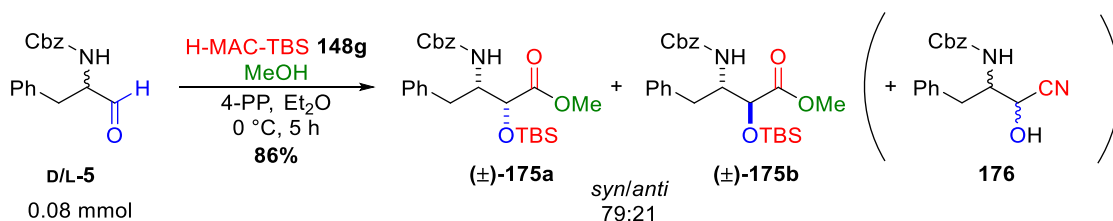


give (–)-bestatin **2a** as a single enantiomer. (–)-Bestatin is a dipeptide containing a 3-amino-2-hydroxy-4-phenylbutyric acid (AHPBA) feature, which is a strong aminopeptidase inhibitor and has been applied for clinical use (see 1.2).



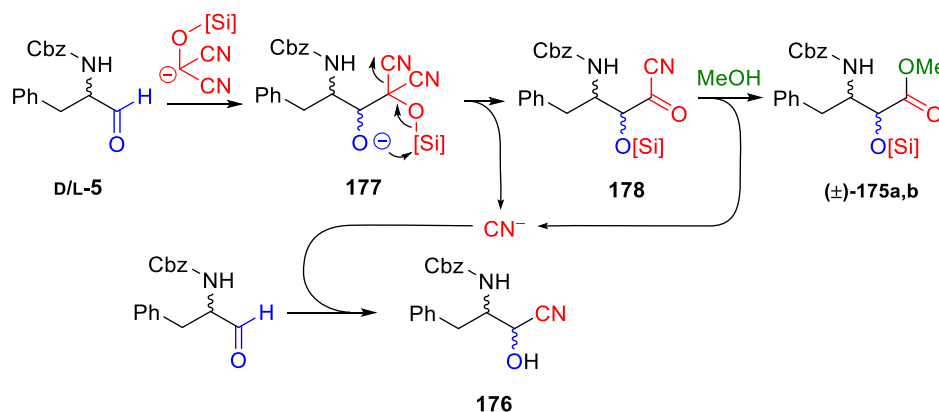
Scheme 48, Synthesis of (–)-bestatin through one-pot MAC reaction by Nemoto *et al.*

A more detailed study about *one-pot* MAC reactions using  $\alpha$ -amino aldehydes as electrophiles were studied next by Nemoto *et al.* in 2001.<sup>169</sup> Racemic *N*-Cbz-D/L-phenylalanyl aldehyde **D/L-5** was mixed with H-MAC-TBS **148g** and methanol in a *one-pot* procedure, and the reaction conditions were screened (Scheme 49). Use of diethyl ether as the solvent can inhibit the formation of cyanohydrin **176**, and delivered MAC products ( $\pm$ )-**175a,b** as the major products. The base and the temperature could also affect the reaction yields. When 4-pyrrolidinopyridine was used, reaction for 5 hours at 0 °C gave MAC products ( $\pm$ )-**175a,b** in 86% yield with 79:21 *syn/anti* dr.



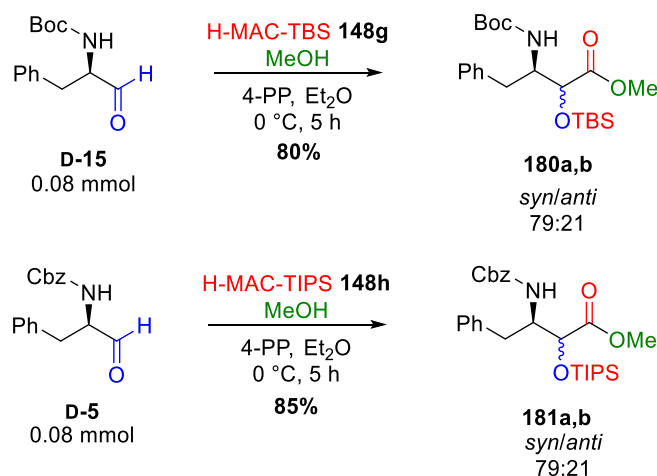
Scheme 49, One-pot MAC reaction applied on racemic *N*-Cbz-phenylalanyl aldehyde by Nemoto *et al.*

The following mechanism was proposed to explain the *one-pot* MAC reaction process and the generation of cyanohydrin **176**. As shown in Scheme 50, the reaction generates two equivalents of cyanide anion, which can react with the starting aldehyde **D/L-5** to give cyanohydrin **176**.

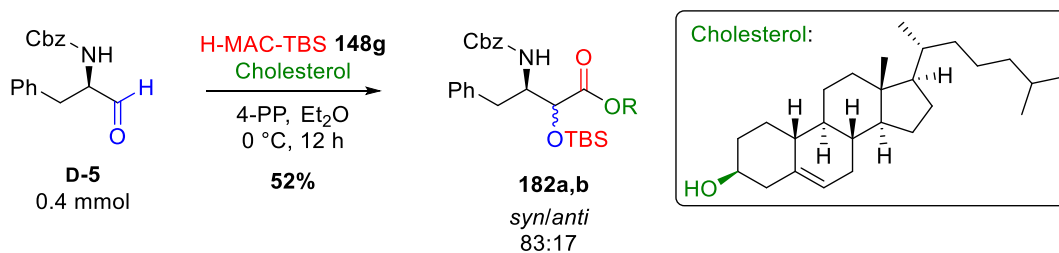


Scheme 50, Mechanism for the one-pot MAC reaction and the generation of cyanohydrin

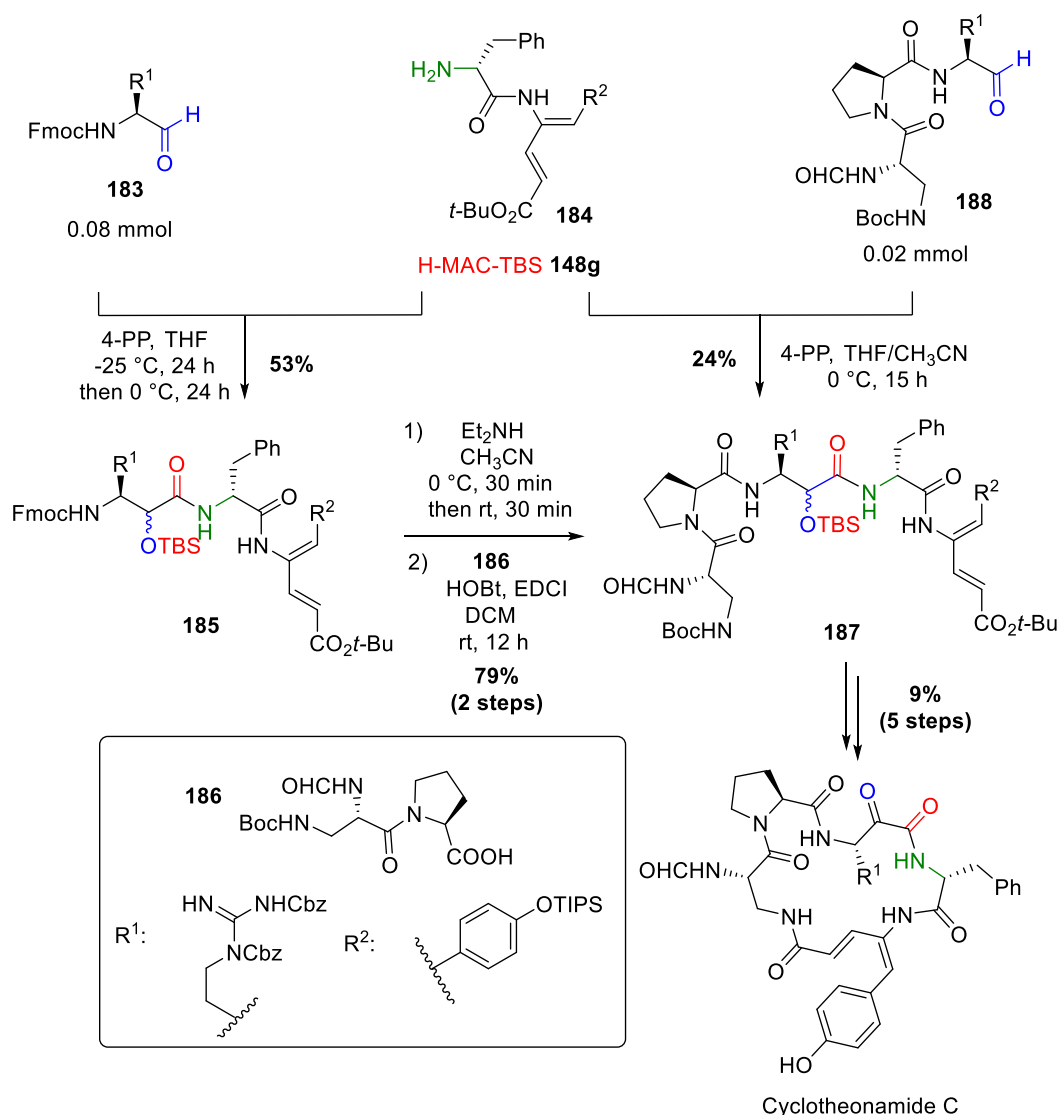
The authors also prepared the two MAC products **180a,b** and **181a,b** from optically pure corresponding *N*-carbamated D-phenylalinals **D-15** and **D-5** (Scheme 51), again with 79:21 *syn/anti* dr. The *syn* diastereoselectivity was rationalized as the result of a non-chelation control. Besides, no chiral erosion at the C $_{\alpha}$  carbon (of the aldehyde) was observed in these experiments.

Scheme 51, One-pot MAC reactions of *N*-protected D-phenylalinal and H-MAC-[Si]

Interestingly, cholesterol was also used as a nucleophile in the *one-pot* MAC reaction in the optimized conditions (Scheme 52).<sup>167</sup> Despite the moderate yield, the diastereoselectivity of this reaction was *syn*, and the ratio between **182a** and **182b** was marginally changed compared to the result of methanol (see Scheme 49).

Scheme 52, One-pot MAC reaction of *N*-Cbz-D-phenylalinal, H-MAC-TBS, and cholesterol

In 2008, Aitken *et al.* described the total synthesis of the macrocyclic pentapeptide Cyclotheonamide C (Scheme 53). First, the author employed protected L-argininal **183** (mono protected  $\alpha$ -amino aldehyde), reacting with dipeptide **184** and H-MAC-TBS **148g** for two days at low temperature, MAC reaction gave tripeptide **185** in 53% yield. Then the tripeptide **185** was coupled with a dipeptide unit **186** to produce pentapeptide **187** in a 79% yield. At the same time, the pentapeptide **187** could be directly obtained by MAC reaction from dipeptide and tripeptide fragments.<sup>170</sup> Using protected L-argininal **188** (tripeptide) as the electrophile, and dipeptide **184** as the nucleophile, reaction with H-MAC-TBS **148g** gave pentapeptide **187** in 24% yield. This MAC reaction successfully coupled a tripeptide with a dipeptide into a pentapeptide, demonstrating the elegant and efficacy use of the *one-pot* MAC methodology for peptide synthesis; it was the most elaborated *one-pot* MAC reaction until today.

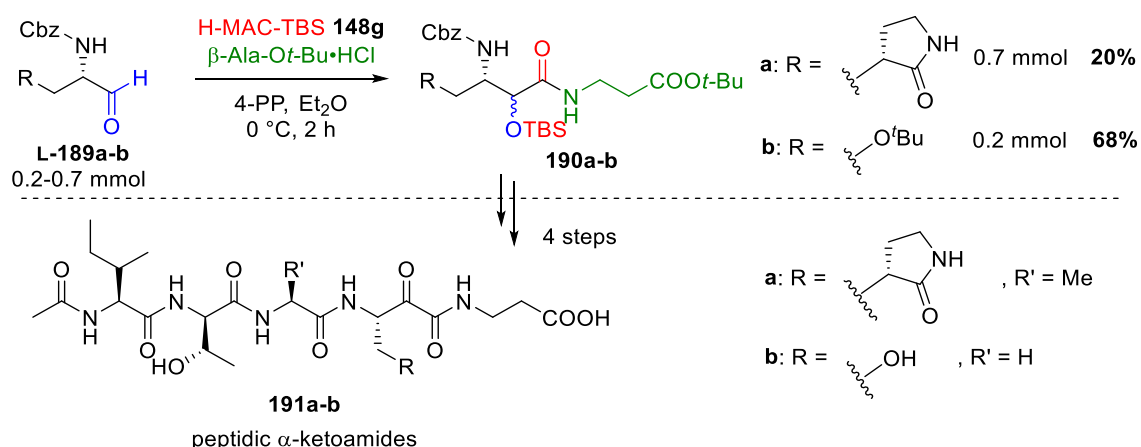


Scheme 53, One-pot MAC reaction towards pentapeptide **187** for the total synthesis of Cyclotheonamide C

The authors did not indicate the diastereoselectivity for both cases because the  $\alpha$ -hydroxy moiety of **187** was oxidized into a  $\alpha$ -ketoamide, and transformed into Cyclotheonamide C in five steps.

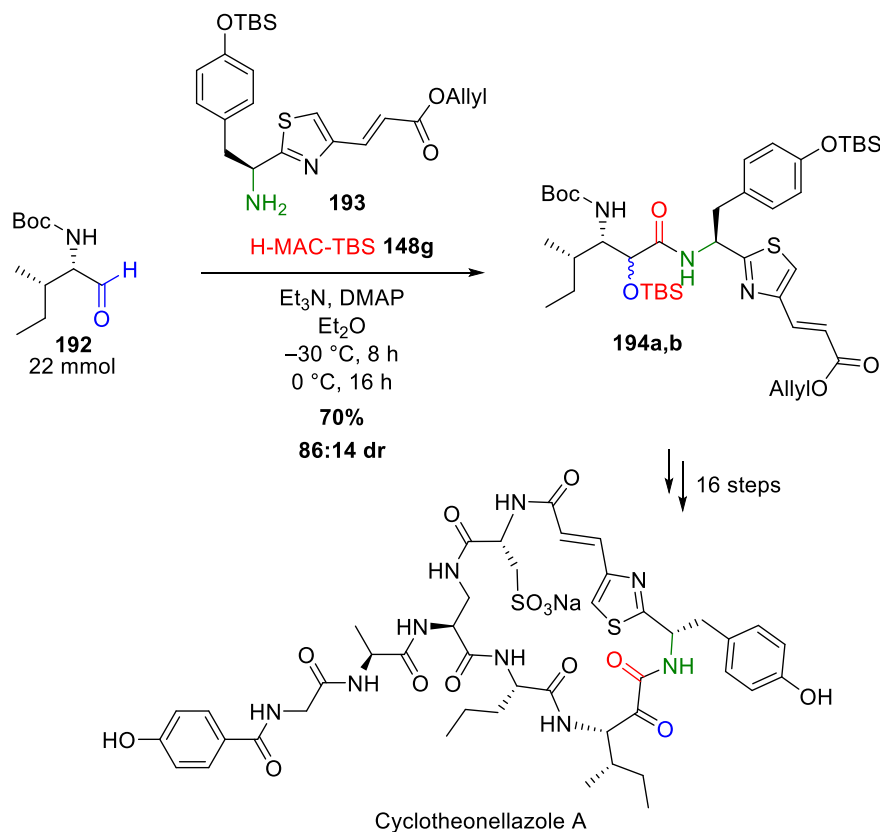
Cyclotheonamide C was isolated from the sponges *Theonella swinhoei*, which showed inhibitory against serine proteases such as thrombin and trypsin.<sup>171</sup>

In 2014, a *one-pot* MAC reaction was employed by Jirgensons *et al.* to synthesize peptidic  $\alpha$ -ketoamides.<sup>172</sup> The authors employed  $\beta$ -Ala-*O**t*-Bu as the nucleophile and reacted it with *N*-Cbz protected aldehydes **L-189a-b** and H-MAC-TBS **148g** in a *one-pot* manner (Scheme 54). The reaction gave dipeptides **190a-b** as mixtures of two diastereomers. The yield of the reactions varied depending on the R group of the  $\alpha$ -amino aldehyde, while the diastereomeric ratio was not given since the products were oxidized into  $\alpha$ -ketoamides. The final peptidic  $\alpha$ -ketoamides **191a-b** showed inhibition of the malarial protease PfSUB1.



Scheme 54, One-pot MAC reactions for the synthesis of peptidic  $\alpha$ -ketoamides

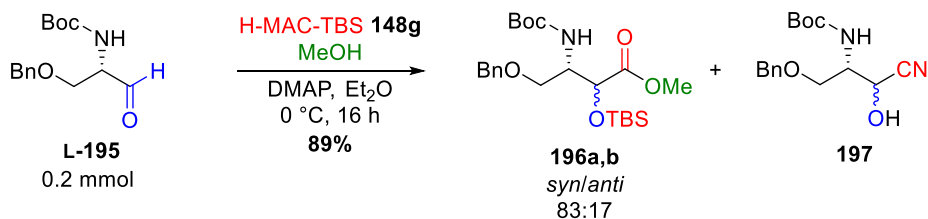
Recently, Chen *et al.* reported the use of a *one-pot* MAC reaction in the total synthesis of Cyclotheonellazole A (Scheme 55).<sup>173</sup> The MAC reaction was performed using *N*-Boc-isoleucinal **192**, amine **193**, and H-MAC-TBS **148g**. MAC products **194a,b** were obtained in 70% yield with a 86:14 ratio (without labeling the configuration). These products **194a,b** were oxidized into  $\alpha$ -ketoamide, which served as a building block for Cyclotheonellazole A, which was first discovered from sponge *Theonella affinis swinhoei* and had potential use in the prevention of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) caused by SARS-COV-2 (COVID-19).



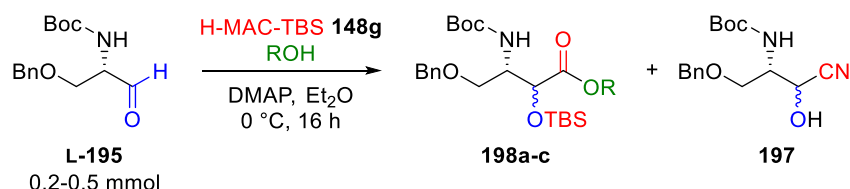
Scheme 55, One-pot MAC reaction in the total synthesis of Cyclotheonellazole A

The PhD thesis of Esgulian, based on work conducted in the host laboratory (2014-2017), focused on the diastereoselectivity control for the *one-pot* MAC reaction of L-serine derived aldehydes.<sup>131</sup>

Esgulian first studied MAC reactions using *N*-Boc-*O*-Bn-L-serinal **L-195** as the electrophile.<sup>174</sup> The aldehyde **L-195**, H-MAC-TBS **148g** and methanol were mixed with DMAP. Reaction for 16 hours at  $0\text{ }^\circ\text{C}$  gave MAC products **196a,b** in 89% yield, with a 83:17 *syn/anti* dr (Scheme 56). Changing the equivalent of H-MAC-TBS **148g**, temperature, reaction time, and even the reaction scale can influence the yield. In some cases, the generation of cyanohydrin **197** was also observed.

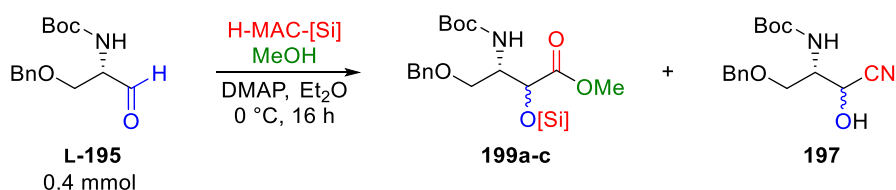
Scheme 56, One-pot MAC reaction of *N*-Boc-*O*-Bn-L-serinal, H-MAC-TBS and methanol

Subsequently, the substrate scope using different alcohols was evaluated (Table 4).<sup>131</sup> The results showed that the MAC reaction yield decreased as the nucleophile's steric bulk increased, albeit maintaining a consistent dr. It should be noted that although Nemoto's use of a secondary alcohol (cholesterol, see Scheme 53) gave a moderate yield, in Esgulian's experiment, only 17% yield was obtained with isopropanol, and a considerable amount of cyanohydrin **197** was isolated from this experiment.

Table 4, One-pot MAC reactions of *N*-Boc-*O*-Bn-*L*-serinal using different alcohols

Entry	R	Yield of 198, (%)	dr ( <i>syn</i> : <i>anti</i> )	Yield of 197 (%)
1	Bn	a, 64	80 : 20	trace
2	<i>i</i> Bu	b, 41	80 : 20	Trace
3	<i>i</i> Pr	c, 17	85 : 15	31

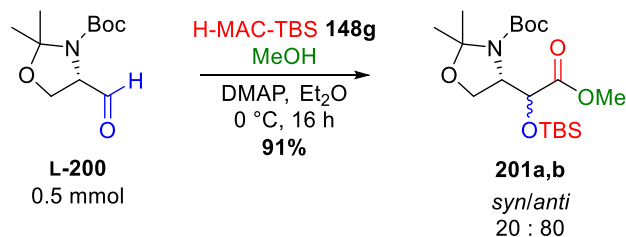
Three other silylated MAC reagents (H-MAC-TES **148f**, H-MAC-TIPS **148h**, and H-MAC-TBDPS **148i**) were tested by Esgulian in the optimized conditions (Table 5).<sup>131</sup> Results suggested that the steric bulk of the silyl group from the MAC reagents could increase the diastereoselectivity of the MAC reaction. When the bulkiest H-MAC-TBDPS **148i** was used, the diastereomeric ratio was increased to 90:10 *syn/anti*. However, the yield of MAC products was decreased to 61%, and a large amount of cyanohydrin **197** was isolated.

Table 5, One-pot MAC reactions of *N*-Boc-*O*-Bn-*L*-serinal using three silylated MAC reagents

Entry	[Si]	Yield of 199, (%)	dr ( <i>syn</i> : <i>anti</i> )	Yield of 197 (%)
1	TES	a, 41	80 : 20	30
2	TIPS	b, 66	85 : 15	26
3	TBDPS	c, 61	90 : 10	30

The MAC products **196a,b** prepared in this work were employed to construct various functionalized small rings, such as  $\gamma$ -lactones, oxazolidinones, oxazolines and aziridines.<sup>131,174</sup>

Esgulian's research then moved to *one-pot* MAC reactions using Garner's aldehyde as the electrophile.<sup>175</sup> The reaction of Garner's aldehyde L-200, H-MAC-TBS **148g** and methanol in a *one-pot* procedure, gave MAC products **201a,b** in 91% yield, with a 20:80 *syn/anti* dr (Scheme 57). The yield of this MAC reaction was significantly influenced by the base species and equivalents, the solvent, the temperature and the equivalent of the MAC reagent. But however, the *anti* MAC product **201b** dominated in all conditions.



Scheme 57, One-pot MAC reaction condition optimizations of Garner's aldehyde by Esgulian

Different MAC reagents and nucleophiles were screened in the subsequent work (Table 6). The results indicated that the yield of the MAC reaction decreased with increasing steric bulk of the nucleophile, but the diastereoselectivity remained constant. Meanwhile, higher diastereoselectivity was obtained by using H-MAC-TBDPS as the MAC reagent.

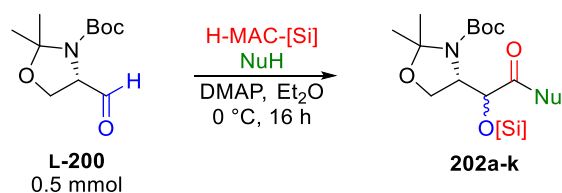
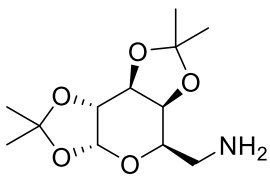


Table 6, One-pot MAC reactions applied on Garner's aldehyde by Esgulian

Entry	[Si]	NuH	Yield of 202, (%)	dr (syn: anti)
1	TBS	EtOH	<b>a</b> , 63	20 : 80
2	TBS	BnOH	<b>b</b> , 64	20 : 80
3	TBS	Allyl-OH	<b>c</b> , 73	20 : 80
4	TBS	<i>i</i> BuOH	<b>d</b> , 55	20 : 80
5	TBS	<i>i</i> PrOH	<b>e</b> , 27	20 : 80
6 <sup>a</sup>	TBS	NH <sub>3</sub>	<b>f</b> , 63	20 : 80
7 <sup>b</sup>	TBS	MeONHMe	<b>g</b> , 90	10 : 90
8	TBS		<b>h</b> , 79	20 : 80
9	TBDPS	MeOH	<b>i</b> , 67	5 : 95
10 <sup>c</sup>	TBDPS	BnOH	<b>j</b> , 87	10 : 90
11	TBDPS	NH <sub>3</sub>	<b>k</b> , 75	15 : 85

<sup>a</sup> reaction time 30 min<sup>b</sup> reaction time 72 h<sup>c</sup> reaction carried out at rt

Until today, this example is the only *anti* diastereoselective *one-pot* MAC reaction in the literature. The MAC products from this work have been employed to synthesize protected *erythro*- $\beta$ -hydroxyaspartic

acids and *erythro*- $\beta$ -hydroxyasparagine derivatives. The latter compound was previously used for the solid-phase synthesis of cyclodepsipeptide stellatolide A.<sup>176</sup>

According to the proposed mechanism (see Scheme 41), the configuration of the newly created chiral center ( $C_\alpha$  of the product) is fixed at the moment by the attack of the MAC anion on the aldehyde carbonyl. Therefore, in the light of Esgulian's work, two following models were proposed to explain the diastereoselectivity (Figure 14).<sup>131</sup>

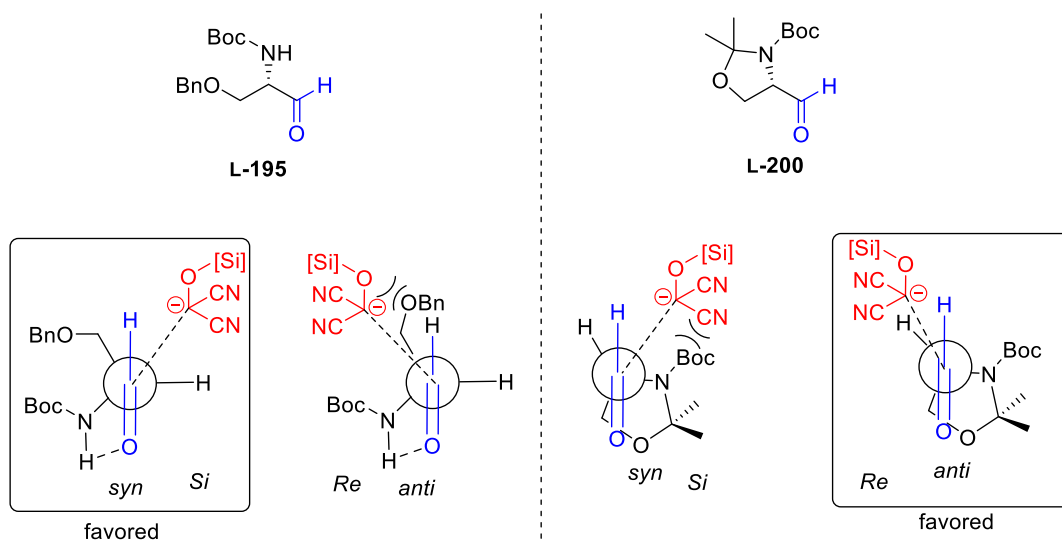


Figure 14, Proposed Hydrogen-bonded model and Felkin-Anh model

The *syn* diastereoselectivity was explained by the hydrogen-bonded model<sup>177</sup>: the hydrogen from the amine group would form a hydrogen bond with the carbonyl oxygen, and the MAC anion would prefer to attack from the *Si* face and give *syn* products. Nevertheless, the existence of this hydrogen bond formation between amine and carbonyl was not proven. While without the hydrogen bond formation between nitrogen and carbonyl oxygen, the attack of the MAC anion on carbonyl will follow the Felkin-Anh model. Thanks to the steric bulk of dimethylloxazolidine moiety, attacking the *Re* face was more favorable than the *Si* face, and gave *anti* diastereoselectivity.

## II.4. Conclusion

MAC reagents are *umpolung* reagents and acyl anion equivalents, that can be used to insert (formally) a carbonyl moiety between an electrophile and a nucleophile. The electrophile and the MAC anion first combine to form a MAC adduct, which can be unmasked and reacted with a nucleophile to produce an oxyhomologated ester, amide, or peptide. These reactions can be performed sequentially or *one-pot*, depending on the nature of electrophiles and MAC reagents.

In sequential MAC reactions, the MAC adduct is stable and can be isolated. Deprotection of the MAC adduct in the presence of a nucleophile gives the final oxyhomologated MAC product. To date, H-MAC-EE **148a**, H-MAC-MOM **148b**, H-MAC-Ac **148c** and H-MAC-TBS **148g** have been used in sequential reactions.



The *one-pot* MAC reaction implicates the MAC reagent/electrophile/nucleophile simultaneously present in the reaction mixture. The acyl cyanide is generated *in situ* and directly reacts with a nucleophile to give oxyhomologated products. In this process, the MAC adduct is not isolated since it undergoes a [1,4]-intramolecular shift to give acyl cyanide. Different electrophiles have been used depending on the nature of MAC reagents:

- For H-MAC-Ac **148c**, aldehydes and imines can be used as electrophiles, though only a few examples have been reported.
- For H-MAC-[Si] **148f-i**, only aldehydes or ketones can be used as electrophiles. The reaction shows diastereoselectivity when  $\alpha$ -chiral aldehydes are employed as electrophiles. For  $\alpha$ -amino aldehydes, yields vary with the steric bulk of the electrophile, the solvent, the temperature, time, and even the reaction scale. Considering the diastereoselectivity, *syn* selectivity has been observed in most cases, regardless of the MAC reagent and the chiral information in the nucleophile. Only reactions of Garner's aldehyde showed *anti* diastereoselectivity, which was likewise unaffected by the nature of the nucleophile or the MAC reagent. This diastereoselectivity may be related to the protection suite of the adjacent amino group, but the evidence is insufficient.

In summary, the *one-pot* MAC reaction can be used to efficiently insert carbonyl groups directly between electrophiles and nucleophiles, which is highly practical and promising for diastereoselective oxyhomologation or rapid construction of peptides.

### III. Objectives of this thesis

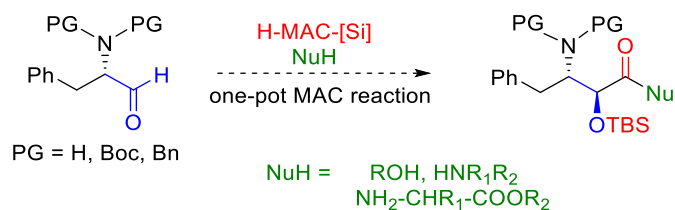
The AHPBA motif exists widely in natural products and bioactive molecules in both *syn* (*threo*) or *anti* (*erythro*) configurations. It has also been used as a building block for peptide synthesis. To date, many methods have been developed for synthesizing AHPBA, and the most used strategy is the diastereoselective oxyhomologation of phenylalanine and its derivatives (e.g., phenylalaninal).

The MAC (Masked Acyl cyanide) methodology allows to create of a carbonyl between an electrophile and a nucleophile using a *umpolung* MAC reagent, and 2-(*tert*-butyldimethylsilyloxy)malononitrile (H-MAC-TBS) is the most studied MAC reagent. In particular, this three-component reaction allows the oxyhomologation of aldehydes with the concomitant creation of a new stereogenic center. When alcohols, amines or amino acids are used as nucleophiles, the MAC reaction will provide oxyhomologated esters, amides or peptides, respectively.

Nemoto *et al.* described four examples of oxyhomologation applied on *N*-carbamate phenylalaninal for the synthesis of AHPBAs using a *one-pot* MAC reaction; those reactions proceeded in high yields and with uniform *syn* diastereoselectivity (*syn/anti* 80:20). The reaction was successfully adopted for the efficient synthesis of (–)-bestatin. Similarly, the host laboratory for this thesis successfully applied the *one-pot* MAC reaction to *N*-Boc protected serinal with *syn* diastereoselectivity (*syn/anti* 80:20). In

contrast, when Garner's aldehyde was used as the electrophile, the diastereoselectivity was predominantly *anti*, and the dr value varied with different MAC reagents. These observations suggest that the diastereoselectivity may be related to the *N*-protecting group.

In this thesis, we will identify the means that allow the *anti* diastereoselective oxyhomologation of phenylalaninal via a multicomponent *one-pot* MAC reaction (Scheme 58). To this end, different *N*-protected phenylalaninals will be employed in the *one-pot* MAC reaction; the diastereoselectivities will be investigated with different H-MAC-[Si] and nucleophiles. Once the control of *anti* diastereoselectivity of the MAC reaction is achieved, we will apply this method to the synthesis of *anti*-AHPBA derivatives, such as (2*S*,3*S*,5*S*)-epibestatin.



Scheme 58, One-pot MAC reaction of the *N*-protected phenylalaninal

We will also investigate *anti* diastereoselective MAC reactions using other  $\alpha$ -amino aldehydes, to obtain a wider library of AHPBA derivatives.

*Part II:*

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## Results and Discussion

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# Chapter 1:

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Synthesis of silylated MAC  
reagents, H-MAC-[Si]

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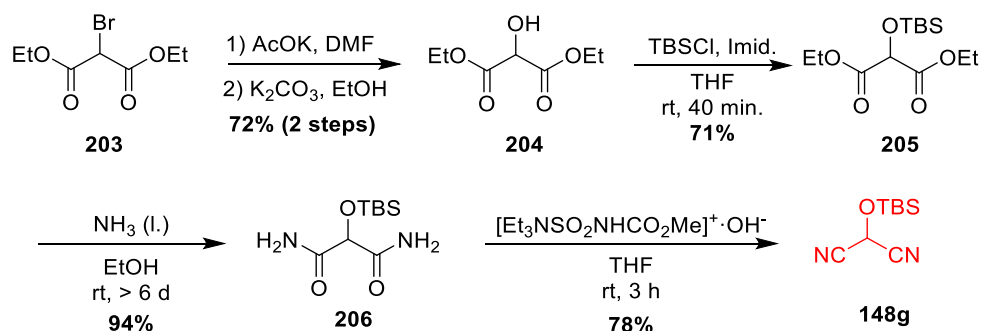
## I. Synthesis of H-MAC-TBS: state of the art

### I.1 Preliminary work of Nemoto

#### II.1.1 From diethyl 2-bromomalonate

2-(*tert*-Butyldimethylsilyloxy)malononitrile, H-MAC-TBS **148g**, was first prepared by Nemoto in 1990 by a five-step sequence starting from diethyl 2-bromomalonate (Scheme 59).<sup>128</sup>

Nucleophilic substitution of diethyl 2-bromomalonate **203** with potassium acetate, followed by ethanolysis of the intermediate diethyl 2-acetoxymalonate under basic conditions, afforded diethyl 2-hydroxymalonate **204** in 72% yield (two steps). *O*-Silylation of alcohol **204** was then carried out with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in tetrahydrofuran to furnish the TBS ether **205** in 71% yield. Subsequent ammonolysis of the *O*-protected malonate **205** with liquid ammonia in ethanol required more than six days at room temperature to give the diamide **206** in 94% yield. Finally, the dehydration of the diamide **206** in the presence of Burgess' reagent afforded H-MAC-TBS **148g** in 78% yield (37% overall yield from diethyl 2-bromomalonate).



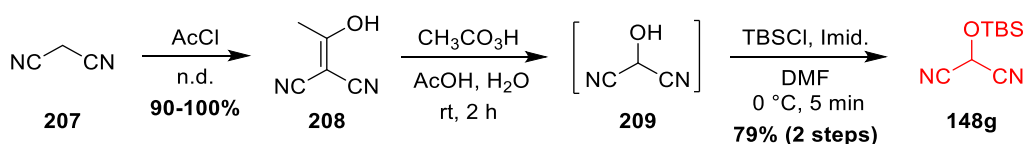
Scheme 59, Synthesis of H-MAC-TBS from diethyl 2-bromomalonate

However, the authors later reported that this synthesis of H-MAC-TBS **148g** had some drawbacks. The yield was less than 10% overall starting from diethyl malonate (six steps), and the ammonolysis step could take up to 10 days.<sup>178</sup> In addition, he indicated that Burgess' reagent was expensive if a large-scale preparation was envisaged.

#### II.1.2 From malononitrile

In 2003, Nemoto described an alternative three-step method for the preparation of various MAC reagents, including H-MAC-TBS, starting from malononitrile (Scheme 60).<sup>178</sup>

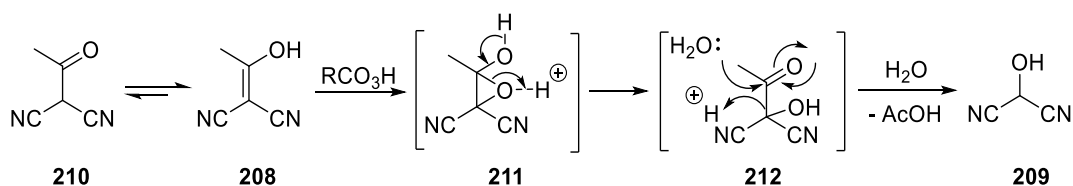
Malononitrile **207** was first treated with acetyl chloride to give 2-(1-hydroxyethylidene)malononitrile **208** in a nearly quantitative yield (although the experimental conditions were not described). Treatment of this enol **208** with peracetic acid in an H<sub>2</sub>O/acetic acid mixture at room temperature for 2 hours provided 2-hydroxymalononitrile **209**. The subsequent *O*-silylation of compound **209** was performed using TBSCl and imidazole in DMF to afford H-MAC-TBS **148g** in 79% yield (two steps) after chromatography.



Scheme 60, Synthesis of H-MAC-TBS from malononitrile by Nemoto

Due to the explosive nature of peracetic acid, the authors recommended using a water bath below 35 °C during the concentration of **209** under reduced pressure and the use of a protective shield. It was also mentioned that 2-hydroxymalononitrile **209** should be directly engaged in the silylation step because it decomposed during attempts to purify it using silica gel column chromatography.

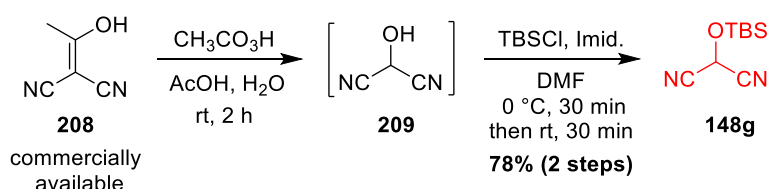
In this work, the authors suggested an epoxidation/ring-opening type mechanism to explain the conversion of enol **208** into the intermediate **212**. Subsequent deacetylation of compound **212** under acidic conditions occurred to give 2-hydroxymalononitrile **209** (Scheme 61).



Scheme 61, Proposed mechanism by Nemoto for the formation of 2-hydroxymalononitrile

## I.2 Complementary work of Rawal

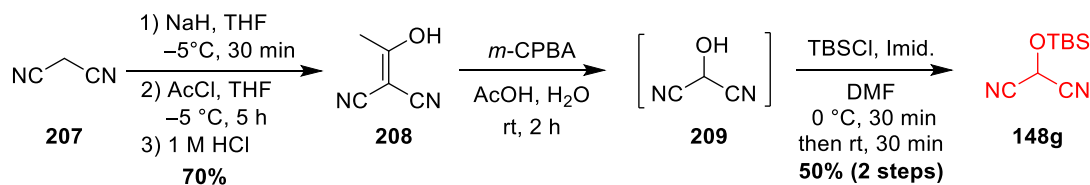
In 2013, Rawal described a more detailed experimental procedure to access H-MAC-TBS **148g** from commercially available 2-(1-hydroxyethylidene)malononitrile **208** (Scheme 62).<sup>179</sup>

Scheme 62, Synthesis of H-MAC-TBS from commercial **208** by Rawal

After the oxidative cleavage of 2-(1-hydroxyethylidene)malononitrile **208** with peracetic acid under Nemoto's conditions, the authors stated that it was important to remove all volatiles from the crude alcohol **209** by carefully concentrating the reaction mixture under vacuum, then high vacuum (< 1 mmHg) for 4 hours. 2-Hydroxymalononitrile **209** was then silylated with TBSCl and imidazole under stirring for 30 minutes at 0 °C and for an additional 30 minutes at room temperature. After workup and purification by silica gel column chromatography (EtOAc/hexanes), H-MAC-TBS **148g** was obtained in a similar yield to that described by Nemoto (78% yield for two steps).

### I.3 Recent work of Chen

Recently in 2022, Chen described a large scale (29 g) synthesis of H-MAC-TBS by an alternative three-step procedure from malononitrile (Scheme 63).<sup>173</sup>



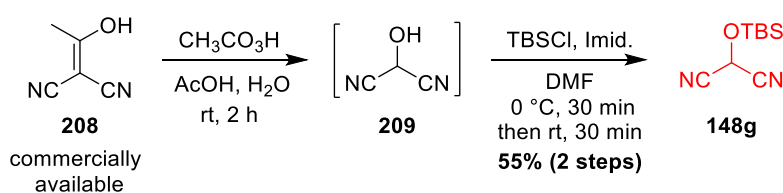
Scheme 63, Synthesis of H-MAC-TBS from malononitrile by Chen

Malononitrile **207** was first deprotonated with sodium hydride in THF at low temperature, and the subsequent acetylation step took place with acetyl chloride. After acidification of the reaction mixture with 1 M HCl, 2-(1-hydroxyethylidene)malononitrile **208** was isolated in 70% yield. The oxidative cleavage of enol **208** was achieved with *m*-chloroperbenzoic acid in an H<sub>2</sub>O/acetic acid mixture at room temperature for two hours afforded 2-hydroxymalononitrile **209**. *O*-silylation of the crude 2-hydroxymalononitrile **209** was then carried out with TBSCl and imidazole in DMF for 30 minutes at 0 °C, and for an additional 30 minutes at room temperature to give H-MAC-TBS **148g** in 50% yield (two steps) after silica gel column chromatography (3-5% EtOAc in petroleum ether).

### I.4 Previous work in the CP3A group

#### I.4.1 From commercially available 2-(1-hydroxyethylidene)malononitrile

When work first began with H-MAC-TBS **148g** in the CP3A research group during the PhD of Esgulian, the reagent was prepared using Rawal's protocol starting from commercial 2-(1-hydroxyethylidene)malononitrile **208** purchased from Aldrich (Scheme 64).<sup>131</sup>

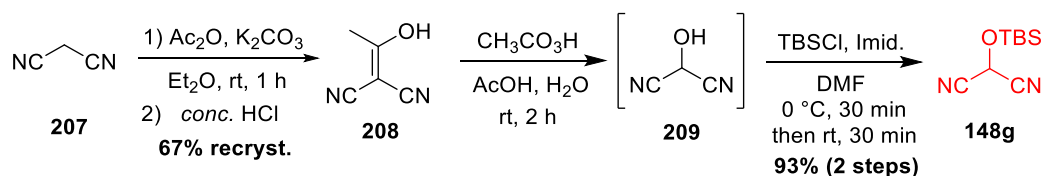


Scheme 64, Synthesis of H-MAC-TBS from commercial **208** by Esgulian

H-MAC-TBS **148g** was obtained in 55% yield by meticulously following Rawal's two-step procedure. In particular, Esgulian found that the yield of the MAC reagent was significantly dependent on the purity of 2-hydroxymalononitrile **209**, and that the latter was most certainly dependent on the quality of the starting enol **208**. The melting point of purchased 2-(1-hydroxyethylidene)malononitrile **208** was measured (Mp = 137-138 °C), and it was concluded that the low yield of H-MAC-TBS might be due to the low purity of our commercial compared to the sample described in the literature<sup>180</sup> (Mp = 140.5 °C).

#### I.4.2 From synthesized 2-(1-hydroxyethylidene)malononitrile

Esgulian then returned to a three-step synthesis beginning with malononitrile (Scheme 65).

Scheme 65, Synthesis of H-MAC-TBS from **207** synthesized by Esgulian

To prepare 2-(1-hydroxyethylidene)malononitrile **208**, Esgulian adapted the procedure of Midorikawa dating from 1962.<sup>180</sup> Malononitrile **207** was first treated with potassium carbonate in diethyl ether, followed by careful addition of acetic anhydride at 0 °C and stirring for one hour at room temperature. Crude enol **208** was afforded after acidification with concentrated HCl. Further recrystallization from toluene allowed to obtain 2-(1-hydroxyethylidene)malononitrile **208** in 67% yield and with high purity (Mp = 140-141 °C).

Recrystallized enol **208** was engaged in the two-step procedure of Rawal to allow the preparation of H-MAC-TBS **148g** in a maximum yield of 93%. However, it was noticed that the procedure was not always reproducible, sometimes leading to lower yields (as low as 36% for two steps).

Esgulian suggested using diethyl ether both for the work-up of the reaction mixture in the silylation step and for the silica gel column chromatography (Et<sub>2</sub>O and pentane mixture) since H-MAC-TBS appeared to be volatile. It was also suggested that the partial pressure should be carefully controlled during all concentration procedures (water bath under 40 °C, until 450 mbar of the pressure).

## II. Synthesis of H-MAC-[Si] reagents

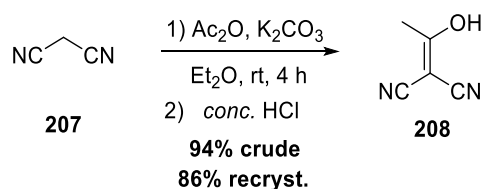
### II.1 Preparation of H-MAC-TBS

We first attempted to synthesize H-MAC-TBS from malononitrile under Esgulian's conditions. Unfortunately, in our hands, these procedures gave no H-MAC-TBS as product. We therefore reexamined each of the three steps in the synthesis from malononitrile.

#### II.1.1 Optimization of the synthesis of 2-(1-hydroxyethylidene)malononitrile

In our hands, acetylation of malononitrile **207** using Esgulian's conditions occurred violently and generated too much foam when acetic anhydride was added. To avoid this, acetic anhydride was introduced in a diethyl ether solution and added dropwise to a malononitrile/potassium carbonate/Et<sub>2</sub>O mixture at 0 °C (Scheme 66). After stirring vigorously for 4 hours at room temperature and acidification with concentrated HCl, 2-(1-hydroxyethylidene)malononitrile **208** was obtained in 94% crude yield (Mp = 141 °C).





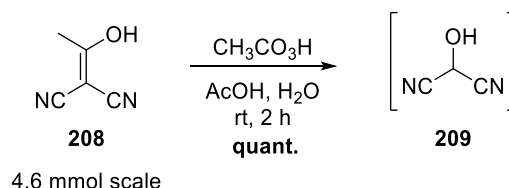
Scheme 66, Optimized synthesis of 2-(1-hydroxyethylidene)malononitrile

Recrystallization of crude **208** from diethyl ether/hexane gave 2-(1-hydroxyethylidene)malononitrile **208** in 86% yield (Mp = 141 °C). Subsequent experiments using enol **208** in either crude or recrystallized form generally gave similar yields, suggesting that the crude compound **208** was pure enough for synthetic purposes.

Following this optimized procedure, 2-(1-hydroxyethylidene)malononitrile **208** was prepared on a multi-gram scale (from 4 g to 10 g). Compound **208** can be stored for several months at -18 °C without any loss of purity. NMR analysis of this compound confirmed that it exists only in its enol form (signals of the carbonyl form **210**, Scheme 61, were never observed).

### II.1.2 Optimization of the oxidative cleavage step

The oxidative cleavage of crude 2-(1-hydroxyethylidene)malononitrile **208** was performed with peracetic acid (35 wt.% in acetic acid) in water at room temperature for 2 hours (Scheme 67).



Scheme 67, Optimized synthesis of 2-hydroxymalononitrile

After many experiments carried out on a 4.6 mmol scale, we concluded that an effective quantitative yield is obtained when the following process is respected:

At the end of the reaction time, the reaction mixture needs to be slowly concentrated on a rotary evaporator (water bath below 35 °C) until the partial pressure was reached 10 mbar. Although we have never observed any complications, a Plexiglas protective shield around the rotary evaporator was used during the concentration of solutions containing peracetic acid.

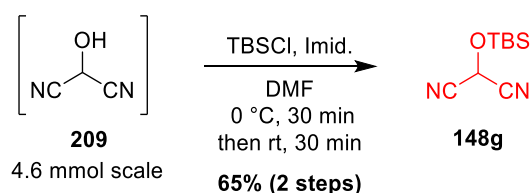
Traces of acetic acid and peracetic acid must be completely removed before 2-hydroxymalononitrile **209** is committed to the silylation step. Three to five co-evaporations with water are necessary. Moreover, the alcohol **209** needs to be dried under a high vacuum (10<sup>-2</sup> mbar) until no more traces of water or acetic acid are observed by <sup>1</sup>H NMR analysis in DMSO-*d*<sub>6</sub>. The presence of acetic acid is noticed by a singlet at 1.91 ppm and that of water at 3.30 ppm. Sometimes, we also observed the presence of hydrogen peroxide by <sup>1</sup>H NMR as a broad singlet at 10.20 ppm, which should be removed by co-evaporations with water.

2-Hydroxymalononitrile **209** obtained in this way is a yellowish oil with fine white solid particles, which provides evidence of the high purity of the sample. It is not stable when left for a long period (16 h) under a high vacuum or for a few hours at room temperature. It turns into a brown oil, and  $^1\text{H}$  NMR confirms its degradation. Therefore, it should be used directly after drying in the subsequent silylation step.

### II.1.3 Optimization of the silylation step

#### II.1.3.1 Silylation of 2-hydroxymalononitrile with *tert*-butyldimethylsilyl chloride (TBSCl)

O-Silylation of crude 2-hydroxymalononitrile **209** was carried out on a 4.6 mmol scale using Rawal's conditions, by reaction with TBSCl and imidazole for 30 minutes at 0 °C and for an additional 30 minutes at room temperature in dry DMF (Scheme 68).



Scheme 68, Protection of 2-hydroxymalononitrile with TBSCl

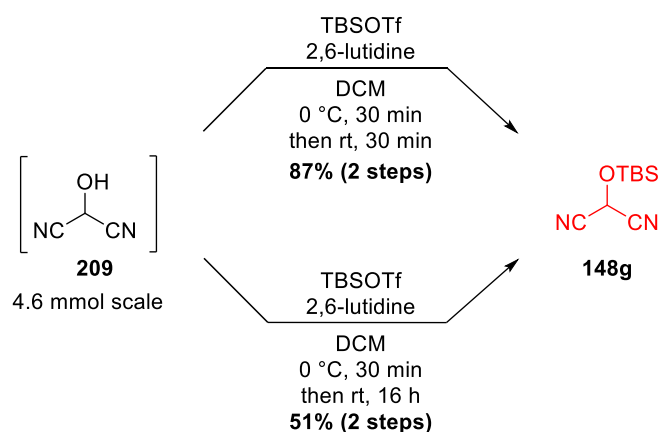
To prevent the decomposition of 2-hydroxymalononitrile **209** under basic conditions, TBSCl was added first, followed by imidazole in several portions at 0 °C. Due to the apparent volatility of H-MAC-TBS **148g**, diethyl ether was used to extract the reaction mixture and to elute the column chromatography. Control of the pressure on the rotary evaporator (water bath under 40 °C, until 450 mbar of pressure) was essential to ensure a good yield.

Under these experimental conditions, H-MAC-TBS **148g** was obtained in a 65% yield from 2-(1-hydroxyethylidene)malononitrile **208** after chromatography.

#### II.1.3.2 Silylation of 2-hydroxymalononitrile with *tert*-butyldimethylsilyl triflate (TBSOTf)

In an effort to improve the yield of the silylation step, *tert*-butyldimethylsilyl triflate (TBSOTf), a more electrophilic reagent,<sup>181</sup> was investigated. Crude 2-hydroxymalononitrile **209** was treated with TBSOTf and 2,6-lutidine in dry dichloromethane at 0 °C for 30 minutes and then at room temperature for an additional 30 minutes or overnight. (Scheme 69).<sup>182</sup>

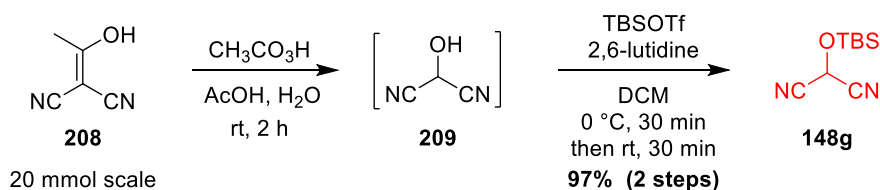
The first experiment was carried out in dichloromethane for 30 minutes at 0 °C and then for an additional 30 minutes at room temperature under argon. Using these conditions, followed by column chromatography, H-MAC-TBS **148g** was obtained a 87% yield (two steps). In a second experiment, extending the reaction time to 16 hours at room temperature led to a decrease in the yield to 51%.



Scheme 69, Protection of 2-hydroxymalononitrile with TBSOTf

### II.1.4 Large-scale preparation of H-MAC-TBS

The synthesis of H-MAC-TBS **148g** from 2-(1-hydroxyethylidene)malononitrile **208** was carried out on a preparative scale using TBSOTf and 2,6-lutidine in dichloromethane using the short reaction time described above. (Scheme 70).



Scheme 70, Large-scale preparation of H-MAC-TBS

Starting from 20 mmol of enol **208**, the isolated yield of **148g** improved to 97 % yield over two steps (3.8 g could be obtained). H-MAC-TBS **148g** obtained in this procedure was a pale yellow liquid, which could be stored under argon for several months at  $-18\text{ }^{\circ}\text{C}$ .

## II.2 Preparation of H-MAC-TIPS and H-MAC-TBDPS

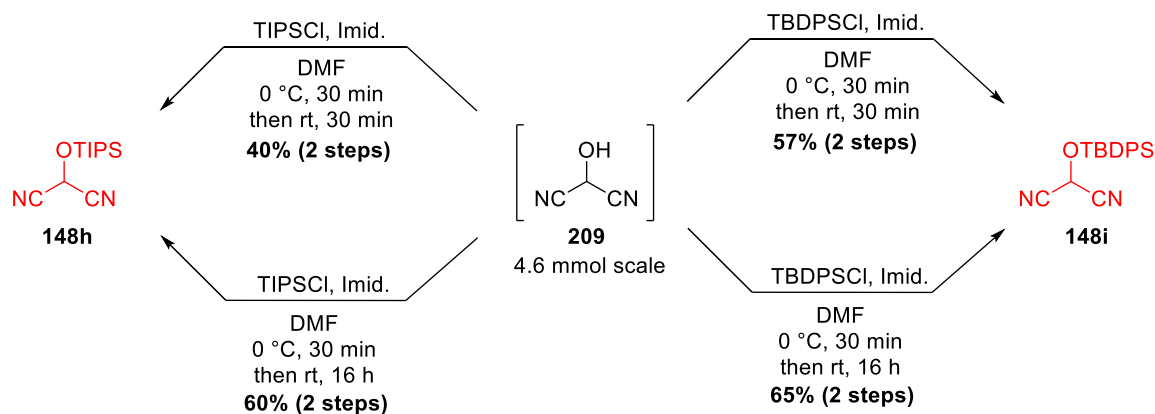
Although most of the MAC reactions described in the literature have employed 2-(*tert*-butyldimethylsilyloxy)malononitrile **148g**, the synthesis of other silylated MAC reagents with a bulky silyl group was of interest since they might have an advantageous impact on the diastereoselectivity of the oxyhomologation reactions envisaged in this work (See table 5).<sup>131</sup> For this reason, we undertook the synthesis of 2-(triisopropoxy)malononitrile (H-MAC-TIPS) **148h** and 2-(*tert*-butyldiphenylsilyloxy)malononitrile (H-MAC-TBDPS) **148i**.

### II.2.1 Silylation of 2-hydroxymalononitrile with silyl chloride reagents

The silylation of 2-hydroxymalononitrile **209** was examined using the corresponding silyl chlorides in the presence of imidazole in dry DMF on a 4.6 mmol scale (Scheme 71).

When triisopropylsilyl chloride (TIPSCl) was used as the silylation reagent, a reaction time of 30 minutes at  $0\text{ }^{\circ}\text{C}$  followed by 30 minutes at room temperature gave H-MAC-TIPS **148h** in 40% yield (two steps),

while 30 minutes at 0 °C followed by 16 hours at room temperature gave H-MAC-TIPS **148h** in 60% yield. Because H-MAC-TIPS is not volatile, pressure control was not required when concentrating the reaction mixture nor chromatographic fractions under reduced pressure. H-MAC-TIPS **148h** was a yellow liquid that could be kept at –18 °C for several months under argon.



Scheme 71, Silylation of 2-hydroxymalononitrile with silyl chloride reagents

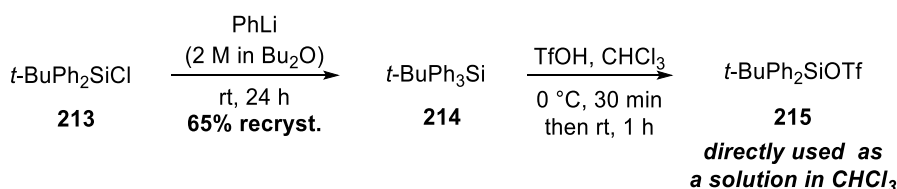
When *tert*-butyldiphenylsilyl chloride (TBDPSCl) was employed for the silylation (Scheme 71), a reaction time of 30 minutes at 0 °C followed by 30 minutes at room temperature yielded H-MAC-TBDPS **148i** in 57 %, while 30 minutes at 0 °C followed by 16 hours at room temperature yielded H-MAC-TBDPS **148i** in 65 %. This MAC reagent **148i** was a white solid that could be kept at –18 °C for several months under argon.

## II.2.2 Silylation of 2-hydroxymalononitrile with silyl triflate reagents

### II.2.2.1 Preparation of *tert*-butyldiphenylsilyl triflate (TBDPSOTf)

Since *tert*-butyldiphenylsilyl triflate (TBDPSOTf) is not commercially available, we prepared it according to the two-step procedure of Hale<sup>183</sup> and Pandit<sup>184</sup> (Scheme 72).

TBDPSCl **213** was reacted for 24 hours with phenyllithium in dibutyl ether to give *tert*-butyltriphenylsilane (*t*-BuPh<sub>3</sub>Si) **214** in 65% yield after recrystallization from ethyl acetate. It was prepared on a large scale (5.2 - 13 g) and could be stored at –18 °C for a long period.



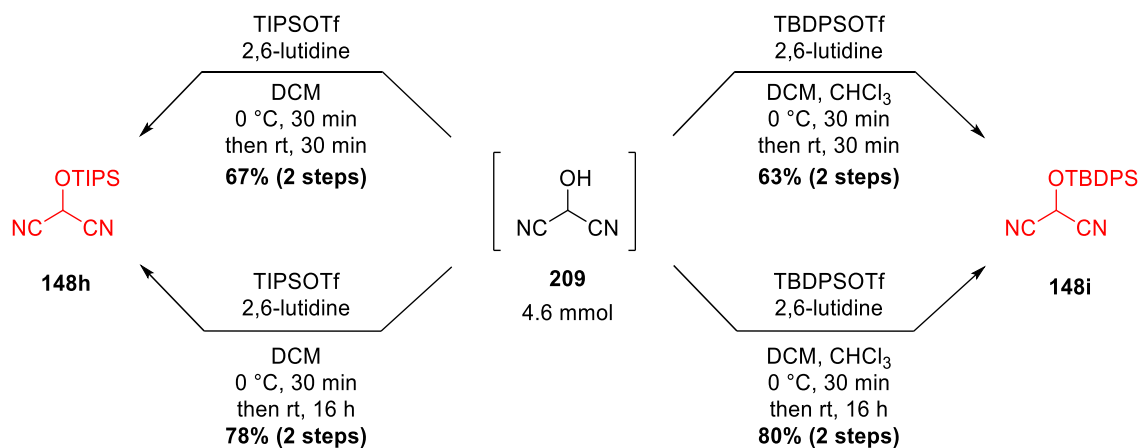
Scheme 72, Synthesis of TBDPSOTf

Dephenylation of this silane **214** with trifluoromethanesulfonic acid (TfOH) in chloroform resulted in its conversion into TBDPSOTf **215**. This reagent was used immediately in chloroform solution in the next step.

## II.2.2.1 Silylation reactions

The silylation of 2-hydroxymalononitrile **209** was examined using silyl triflates in the presence of 2,6-lutidine in dichloromethane (Scheme 73).

When commercial triisopropylsilyl triflate (TIPSOTf) was used, a reaction time of 30 minutes at 0 °C followed by 30 minutes at room temperature gave H-MAC-TIPS **148h** in 67% yield (two steps), while 30 minutes at 0 °C followed by 16 hours at room temperature gave H-MAC-TIPS **148h** in 78% yield (two steps).



Scheme 73, Silylation of 2-hydroxymalononitrile with silyl triflate reagents

When freshly prepared *tert*-butyldiphenylsilyl triflate (TBDSOTf) **215** was used for the silylation, a reaction time of 30 minutes at 0 °C and 30 minutes at room temperature gave H-MAC-TBDPS **148i** in 63% yield (two steps), while 30 minutes at 0 °C and 16 hours at room temperature gave H-MAC-TBDPS **148i** in 80% yield (two steps).

### III. Discussion

We have optimized the three-step synthesis of H-MAC-TBS from malononitrile based on the protocol established by Esgulian.

The main optimization was first focused on the oxidative cleavage of 2-(1-hydroxyethylidene)malononitrile **208**. The major impurities in the crude reaction mixture were excess peracetic acid, water, acetic acid and hydrogen peroxide, which the co-evaporation with water followed by drying under a high vacuum could efficiently remove. The resulting 2-hydroxymalononitrile **209** was highly unstable and therefore needs to be used in the subsequent silylation as soon as possible.

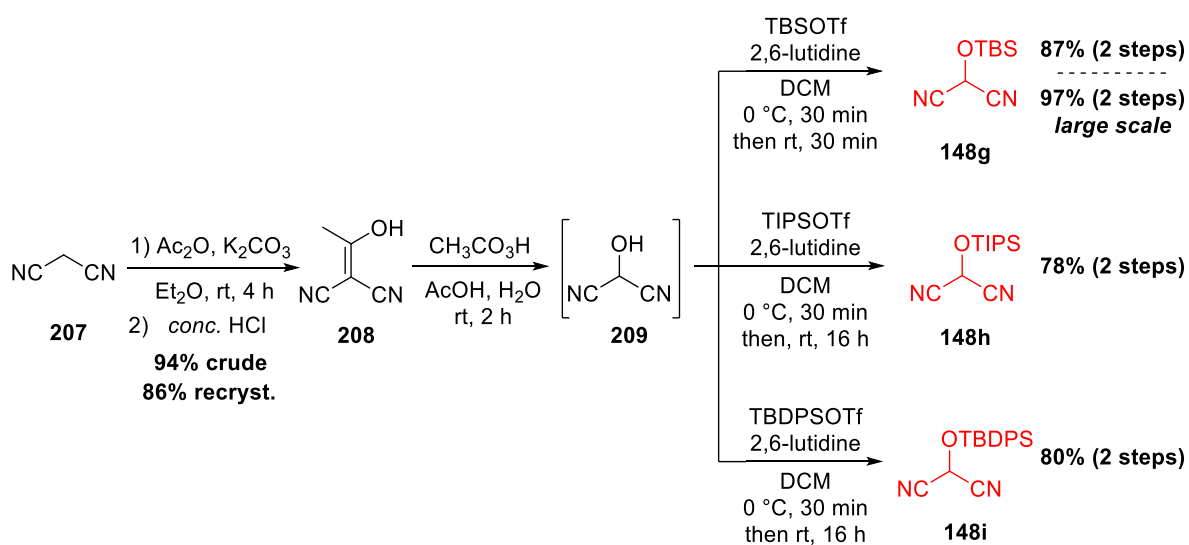
The silylation of 2-hydroxymalononitrile **209** for the synthesis of H-MAC-TBS **148g** was performed using TBSCl and TBSOTf, and TBSOTf seemed to be more efficient than TBSCl. This result is consistent with

the literature that the reactivity of silyl triflate reagents is higher than that of silyl chlorides in protecting secondary alcohol.<sup>181,185</sup>

The same trends were observed in the synthesis of H-MAC-TIPS **148h** and H-MAC-TBDPS **148i**. The use of silyl triflate reagents always gave higher and more reproducible yields than the use of silyl chlorides.

## IV. Conclusion

We have established an efficient and reproducible method for synthesizing H-MAC-[Si] reagents using silyl triflate in the above study. In this new approach, H-MAC-TBS **148g**, H-MAC-TIPS **148h**, and H-MAC-TBDPS **148i** were prepared in very good yields (Scheme 74).



Scheme 74, Optimized synthesis of H-MAC-[Si] reagents from malononitrile

## Chapter 2:

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Diastereoselectivity control in  
MAC reactions of  
*N*-protected L-phenylalaninals

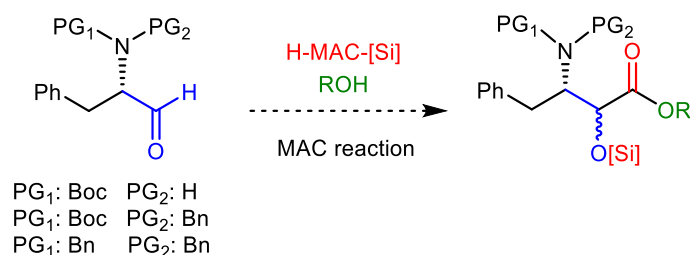
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## I. Introduction

When first employed by Nemoto 20 years ago to carry out the oxyhomologation of *N*-Cbz-D-phenylalaninal, the *one-pot* MAC reaction proceeded with a *syn* diastereoselectivity.<sup>169</sup> The few subsequent applications of this methodology using other *N*-protected amino aldehydes also led mostly to *syn* products (*syn/anti* ratio around 80:20).<sup>163,167,169,174</sup> Recently, however, MAC reactions using Garner's aldehyde gave a high diastereoselectivity in favor of *anti* oxyhomologation adducts.<sup>175</sup> Given the particular constrained structure of Garner's aldehyde, it was established that the attack of the silyloxymalononitrile anion occurred in nonchelating conditions following a Felkin-Anh model.

The objective of the work in this chapter was to investigate the origin of the diastereoselectivity, and hopefully to establish the means to control it, in MAC reactions using a simpler unconstrained *N*-protected amino aldehyde than Garner's aldehyde. In particular, we considered that judiciously selected *N*-protected derivatives of L-phenylalaninal would be appropriate electrophilic substrates, since we would be able to make direct comparisons with Nemoto's observations using *N*-Cbz-D-phenylalaninal. Three complementary *N*-protection suites were selected for study: *N*-Boc, *N*-Boc-*N*-Bn, and *N,N*-dibenzyl protective groups.

We undertook the assessment of the above protected phenylalaninals with each of the three H-MAC-[Si] reagents in MAC reactions using an alcohol as nucleophile. Of particular interest was the evaluation of the diastereoselectivity of the MAC reaction and its rationalization. An overview of the work developed in this chapter is presented in Scheme 75.



Scheme 75, MAC reactions of diversely *N*-protected L-phenylalaninals

## II. MAC reaction of *N*-Boc-L-phenylalaninal

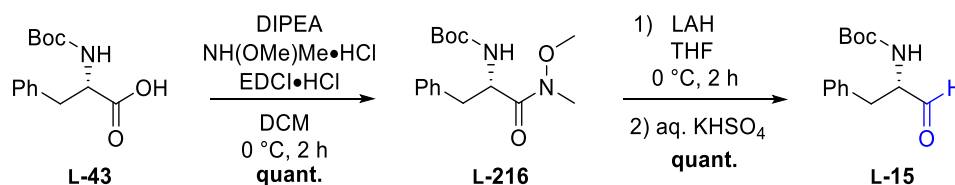
### II.1. Preparation of *N*-Boc-L-phenylalaninal

*N*-Boc-L-phenylalaninal **L-15** was prepared by the following two-step process inspired by the literature (Scheme 76).

Commercially available *N*-Boc-L-phenylalanine **L-43** was activated using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) then coupled with *N,O*-dimethylhydroxylamine to give Weinreb amide **L-216** in quantitative yield.<sup>186</sup> This compound can be stored at  $-18\text{ }^\circ\text{C}$  for several months, and the enantiomeric purity was confirmed by polarimetry: for samples made by this method



$[\alpha]_D^{25} = +21.8$  (*c* 1.0, CHCl<sub>3</sub>), while the literature<sup>187</sup> indicates  $[\alpha]_D^{20} = +21.0$  (*c* 1.0, CHCl<sub>3</sub>), which suggested that the Weinreb amide **L-216** synthesized in this way was optically pure.



Scheme 76, Synthesis of *N*-Boc-*L*-phenylalaninal through Weinreb amide

The aldehyde **L-15** was obtained in quantitative yield by reduction of **L-216** with lithium aluminum hydride (LAH).<sup>131</sup> The crude aldehyde **L-15** was checked by polarimetry:  $[\alpha]_D^{25} = +38.9$  (*c* 1.0, DCM), while the literature<sup>188</sup> suggests  $[\alpha]_D^{n.d.} = +39.3$  (*c* 1.0, DCM). It was used directly in subsequent experiments.

## II.2. MAC reactions of *N*-Boc-*L*-phenylalaninal with H-MAC-[Si] and alcohols

### II.2.1 MAC reactions

Freshly prepared aldehyde **L-15** was employed in MAC reactions using “standard” conditions, which we define as follows: 0.5 mmol of *N*-Boc-*L*-phenylalaninal **L-15** was reacted with 1.2 eq. of an H-MAC-[Si] reagent, 3.0 eq. of an alcohol, and 1.0 eq. of DMAP in Et<sub>2</sub>O at 0 °C for 16 hours to give the corresponding  $\alpha$ -hydroxy- $\beta$ -amino butyric acid ester derivatives **217a,b-222a,b** as chromatographically inseparable mixtures.

The results are collected in Table 7: yields are given for isolated material after column chromatography, and the diastereomeric ratios (dr) were calculated by <sup>1</sup>H NMR analysis of purified MAC products in DMSO-*d*<sub>6</sub> at 360 K (see II.2.2). The major diastereomer in each case was assigned the *syn* configuration by inspection of the vicinal coupling constant between the C <sub>$\alpha$</sub> H and C <sub>$\beta$</sub> H (see II.2.3).

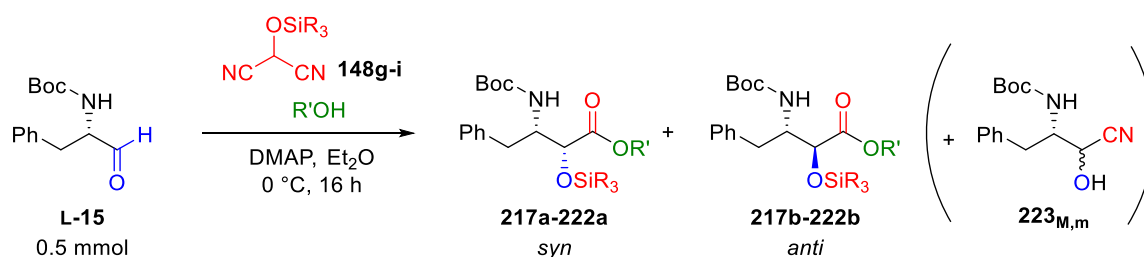


Table 7, MAC reactions of *N*-Boc-*L*-phenylalaninal

Entry	H-MAC-[Si]	R'OH	MAC Products	Yield <sup>a</sup> (%)	dr <sup>b</sup> ( <i>syn/anti</i> )	Yield <sup>a</sup> of 223 <sub>M,m</sub> (%)
1 <sup>c</sup>	H-MAC-TBS	MeOH	<b>217a,b</b>	48	82:18	trace
2 <sup>c</sup>	H-MAC-TBS	BnOH	<b>218a,b</b>	59	83:17	trace
3 <sup>c,d</sup>	H-MAC-TBS	Allyl-OH	<b>219a,b</b>	35	86:14	16

<b>4</b>	H-MAC-TBS	MeOH	<b>217a,b</b>	60	82:18	trace
<b>5</b>	H-MAC-TBS	BnOH	<b>218a,b</b>	63	82:18	trace
<b>6</b>	H-MAC-TIPS	MeOH	<b>220a,b</b>	62	83:17	trace
<b>7</b>	H-MAC-TIPS	BnOH	<b>221a,b</b>	63	84:16	trace
<b>8</b>	H-MAC-TBDPS	MeOH	<b>222a,b</b>	47	81:19	trace

<sup>a</sup> isolated yield of diastereomeric mixture after column chromatography

<sup>b</sup> dr was calculated by <sup>1</sup>H NMR analysis of purified MAC products in DMSO-*d*<sub>6</sub> at 360 K (see II.2.2)

<sup>c</sup> reaction mixture was directly concentrated *in vacuo* and purified

<sup>d</sup> cyanohydrin **223<sub>M,m</sub>** was also isolated as the main side product

In the first experiment, *N*-Boc-*L*-phenylalaninal **L-15** was reacted with H-MAC-TBS **148g** and methanol. The reaction mixture was directly concentrated *in vacuo* prior to chromatography, which gave the MAC product **217a,b** in 48% yield with a dr of 82:18 (entry **1**). In the same condition, benzyl alcohol gave MAC products **218a,b** in a higher yield (59%) with an identical dr (entry **2**). And when allyl alcohol was used (entry **3**), the dr was nearly the same (86:14), but the yield of MAC products **219a,b** was much lower (35%). In this experiment, the cyanohydrin **223<sub>M,m</sub>** was also isolated in 16% yield as a 52:48 mixture of two diastereomers.

When the workup was adapted to include basification with a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution, extraction with diethyl ether, then acidification with 1 M HCl, the isolated yield of MAC products **217a,b** increased to 60% while keeping the similar dr (entry **4**). As a result, this workup was adopted in subsequent experiments.

When H-MAC-TBS **148g** and benzyl alcohol were employed, the yield of MAC products **218a,b** was marginally higher (63%, entry **5**), again with a similar dr.

In a similar manner, *N*-Boc-*L*-phenylalaninal **L-15** was reacted with H-MAC-TIPS **148h** and methanol and benzyl alcohol (entries **6**, **7**). These two experiments gave the MAC products **220a,b** and **221a,b** respectively in nearly the same yields and diastereomeric ratios as the corresponding experiments using H-MAC-TBS **148g**.

Finally, *N*-Boc-*L*-phenylalaninal **L-15** was reacted with H-MAC-TBDPS **148i** and methanol to give MAC products **222a,b** in 47% yield with a 81:19 dr (entry **8**).

Comparison of the reactions employing *N*-Boc-*L*-phenylalaninal **L-15** and methanol (entries **4**, **6** and **8**) revealed that the yields from H-MAC-TBS **148g** and H-MAC-TIPS **148h** were better than the yield from H-MAC-TBDPS **148i**, while the dr values were almost identical *syn/anti* around 80:20. Indeed, this ratio remained constant for all the experiments described in Table **7**, regardless of the identity of the H-MAC-[Si] reagent and the alcohol. The steric hindrance of the silyl protecting group in the MAC reagents had no apparent effect on the diastereoselectivity of the reaction.

### II.2.2 Determination of the diastereomeric ratio

It was not an easy matter to establish the ratio of the two diastereomers using  $^1\text{H}$  NMR spectroscopy at room temperature in either  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  solution. Peaks were poorly resolved, and three sets of peaks were observed for some signals. For example, in each spectrum of all those methoxy esters (**217a,b**, **220a,b**, **222a,b**), three methoxy signals were observed, two of which come from one diastereomer, presumably due to the presence of two rotamers, and the third from the other diastereomer. Higher temperature NMR was used to tackle this problem since rapid interconversion of rotamers was expected to occur at elevated temperatures, simplifying the spectra and facilitating the analysis.<sup>189</sup>

The mixture of MAC products **222a,b** (resulting from the reaction of *N*-Boc-*L*-phenylalaninal **L-15** with H-MAC-TBDPS **148i** and methanol) was examined by  $^1\text{H}$  NMR spectroscopy at 10 K intervals from 295 K (22 °C) to 360 K (87 °C) using  $\text{DMSO}-d_6$  as the solvent. The spectra are superimposed in Figure 15. At 295 K, the three methoxy signals appeared at 3.27 ppm, 3.31 ppm and 3.38 ppm. At 330 K, the two low-field signals coalesced as a new peak at 3.36 ppm. The ratio (81:19) of the two diastereomers **222a** and **222b** was measured at 360 K, which provided a better resolution of the methoxy signals in the range from 3.30 ppm to 3.40 ppm.

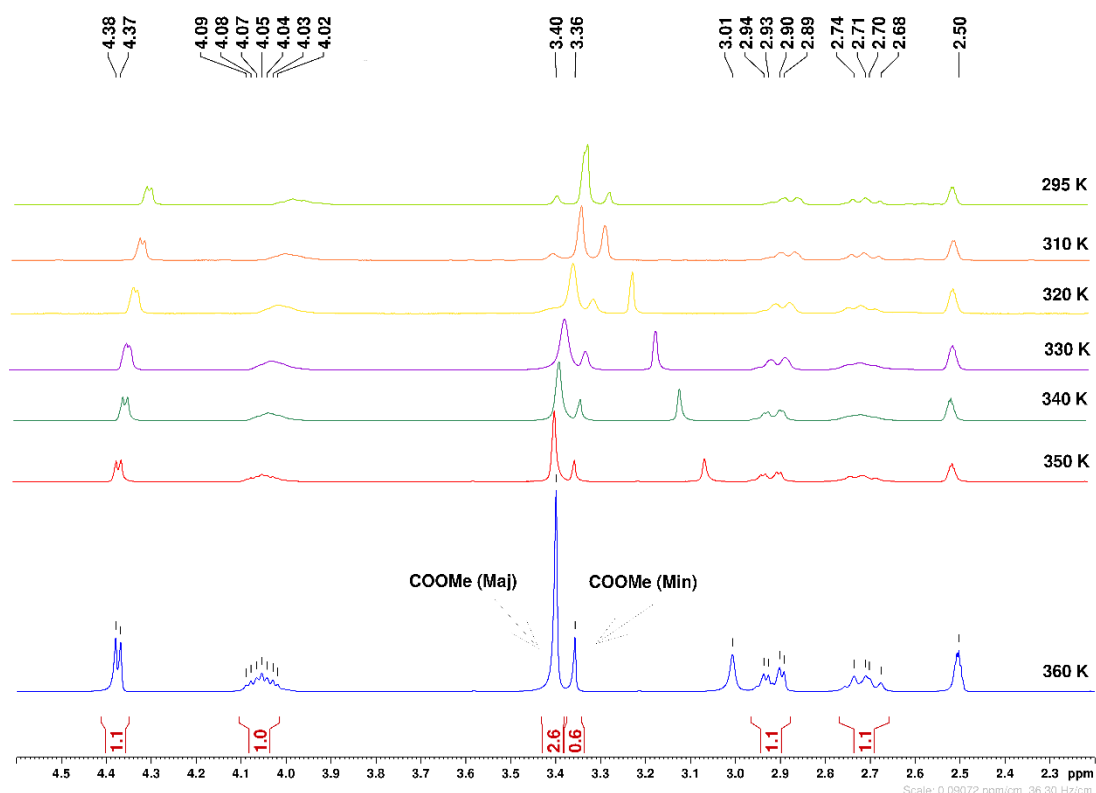


Figure 15,  $^1\text{H}$ -NMR spectra of MAC products **222a,b** at different temperatures (400 MHz,  $\text{DMSO}-d_6$ , from 295 K to 360 K;  $\delta = 2.2$  ppm to 4.6 ppm)

Using the same condition ( $\text{DMSO}-d_6$  at 360 K), all MAC products were analyzed by  $^1\text{H}$  NMR, and their spectra were used for the dr calculation. The singlet of the methoxy group was chosen as the characteristic peak for methyl esters (**217a,b**, **220a,b**, **222a,b**), whereas the doublet signal of  $\text{CHOSiR}_3$

was chosen for benzyl esters (**218a,b**, **221a,b**) and the broad singlet of  $\text{NHCO}_2$  for the allyl esters (**219a,b**).

### II.2.3 Determination of the diastereoselectivity

The NMR spectroscopic data obtained at 360 K in  $\text{DMSO-}d_6$  solution described above were also used to identify the configuration of the two diastereomers obtained in MAC reactions presented in Figure 15.

For any MAC product obtained from an  $\alpha$ -amino aldehyde, H-MAC-TBS **148g** and methanol, a vicinal coupling was observed between its  $\text{C}_\alpha\text{H}$  (yellow) and  $\text{C}_\beta\text{H}$  (blue). In Nemoto's work on N-Cbz-D-phenylalaninal (See Scheme 51), the configuration of each diastereomer was assigned after cleavage of the TBS moiety and then by comparison of the NMR data of the corresponding alcohols with the literature. In Nemoto's MAC compounds ( $\pm$ )-**175a,b**, the  $^3J_{\text{C}_\alpha\text{H-C}_\beta\text{H}}$  in the *syn* compound ( $\pm$ )-**175a** was 1.4 Hz and 3.1 Hz in the *anti* compound ( $\pm$ )-**175b**.<sup>169</sup> In Esgulian's work on N-Boc-O-benzyl-L-serinal, the configuration of each diastereomer was determined by transforming MAC product **196a,b** into the corresponding 4,5-disubstituted oxazolidinones then comparison the vicinal coupling constants ( $^3J_{\text{C}_4\text{H-C}_5\text{H}}$ ) with the literature data. In Esgulian's MAC compounds **196a,b**, the  $^3J_{\text{C}_\alpha\text{H-C}_\beta\text{H}}$  in the *syn* compound **196a** was 2.0 Hz, and in the *anti* compound **196b** was 4.8 Hz (Figure 16).<sup>131</sup>

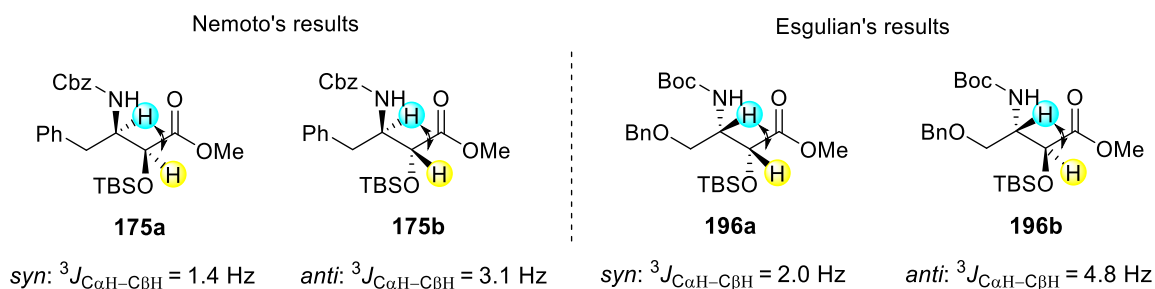
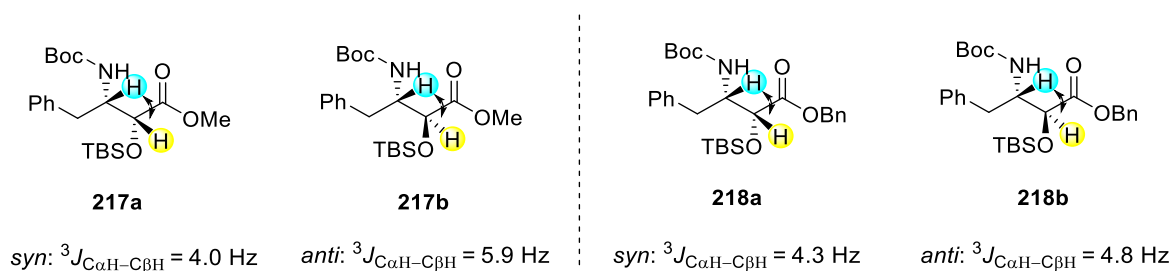


Figure 16, Vicinal coupling constants in MAC products from Nemoto and Esgulian

We examined each of the *syn/anti* MAC product mixtures by  $^1\text{H}$  NMR spectroscopy at 360 K in  $\text{DMSO-}d_6$  and observed different vicinal coupling constants ( $^3J_{\text{C}_\alpha\text{H-C}_\beta\text{H}}$ ) for the major and minor diastereomers. In each case, the  $\text{C}_\alpha\text{H}$  signal appeared as a major doublet and a minor doublet in the range from 4.30 ppm to 4.55 ppm. The major doublet had a smaller  $^3J_{\text{C}_\alpha\text{H-C}_\beta\text{H}}$  coupling constant than the minor doublet, suggesting that the major diastereomer had a *syn* configuration. The integration ratio of the two doublets was approximately 80:20, indicating that they are originated from the same proton ( $\text{C}_\alpha\text{H}$ ) of two diastereomers.

For example, we observed two doublets assigned to the  $\text{C}_\alpha\text{H}$  in the MAC products *syn* **217a** and *anti* **217b** (obtained from the reaction of H-MAC-TBS **148g** and methanol). The major doublet appeared at 4.29 ppm with a coupling constant of 4.0 Hz while the minor doublet appeared at 4.31 ppm with a coupling constant of 5.9 Hz (Figure 17).

Figure 17, Vicinal coupling constants between  $C_{\alpha}H$  and  $C_{\beta}H$  from our MAC reaction products

The MAC products **218a,b** from benzyl alcohol also showed this pattern: the major doublet appeared at 4.36 ppm with a coupling constant of 4.3 Hz while the minor doublet appeared at 4.39 ppm with a coupling constant of 4.8 Hz.

These data suggested that the major diastereomer had a *syn* configuration.

### II.3 Discussion

MAC reactions of *N*-Boc-*L*-phenylalaninal **L-15** with the three H-MAC-[Si] reagents (**148g-i**) and selected alcohols provided mixtures of two diastereomers in good to medium isolated yields. These oxyhomologation products were obtained with a uniform 80:20 *syn/anti* diastereomeric ratio, regardless of the H-MAC-[Si] reagent and the alcohol employed.

The *syn* diastereoselectivity in the MAC reactions of *N*-Boc-*L*-phenylalaninal **L-15** is consistent with Nemoto's results using *N*-Cbz-*D*-phenylalaninal<sup>169</sup> and Esgulian's results<sup>131</sup> using *N*-Boc-*O*-benzyl-*L*-serinal. We proposed that the *syn* diastereoselectivity can be explained by an "H-bonded" or "anti-Felkin-Anh" model (Figure 18). This model involves a preferred conformation of the substrate that is stabilized by an intramolecular hydrogen bond between the NH of the carbamate protected amine and the carbonyl oxygen. Attack of the aldehyde group by the anion of the MAC reagent via the most accessible Bürgi–Dunitz approach would lead preferentially to a *syn* diastereomer.

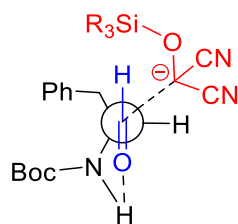


Figure 18, anti-Felkin-Anh model

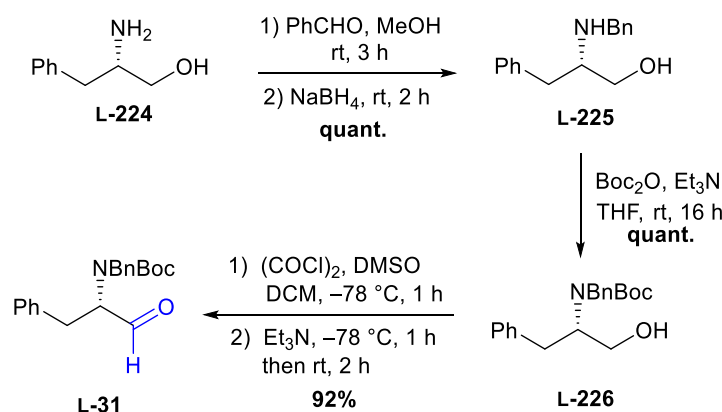
By extension, this model would also explain the preference for a *syn* diastereoselectivity in the MAC reactions described by Nemoto using *N*-Cbz-*D*-phenylalaninal and by Esgulian using *N*-Boc-*O*-benzyl-*L*-serinal.

### III. MAC reaction of *N*-Boc-*N*-Bn-*L*-phenylalaninal

#### III.1 Preparation of *N*-Boc-*N*-Bn-*L*-phenylalaninal

*N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31** was prepared by the following three-step process inspired by the literature<sup>190, 191, 192</sup> (Scheme 77).

Benylation of commercial *L*-phenylalaninol **L-224** was achieved through reductive amination<sup>190</sup> to give *N*-benzyl-*L*-phenylalaninol **L-225** in quantitative yield. The enantiomeric and the chemical purities of this alcohol **L-225** was confirmed by comparing its optical rotation value and its melting point ( $[\alpha]_D^{24} = -9.0$  (*c* 1.2, MeOH), Mp = 55-57 °C) with the literature data<sup>193</sup> ( $[\alpha]_D^{n.d.} = -11.1$  (*c* 1.2, MeOH), Mp = 54-56 °C).



Scheme 77, Preparation of *N*-Boc-*N*-Bn-*L*-phenylalaninal

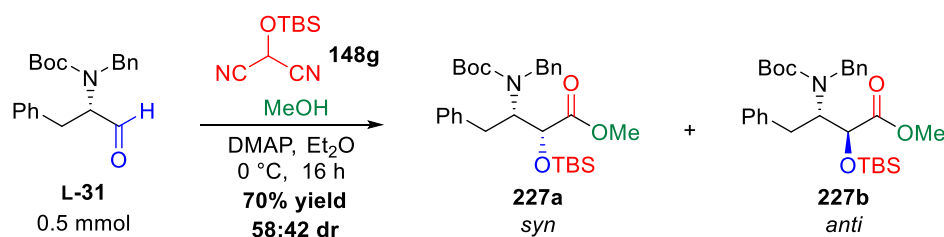
The amine of compound **L-225** was transformed into a *tert*-butyl carbamate by reaction with  $\text{Boc}_2\text{O}$ <sup>191</sup> to provide *N*-Boc-*N*-Bn-*L*-phenylalaninol **L-226** in quantitative yield. The enantiomeric purity of alcohol **L-226** was monitored by comparing its optical rotation value ( $[\alpha]_D^{25} = -41.4$  (*c* 0.8, EtOH)) with the literature data<sup>66</sup> ( $[\alpha]_D^{20} = -57.9$  (*c* 0.8, EtOH)), which suggested that the sample was partially epimerized under basic conditions.

Swern oxidation<sup>192</sup> of compound **L-226** afforded *N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31** in 92% crude yield. The optical rotation was checked ( $[\alpha]_D^{25} = -134.9$  (*c* 1.0,  $\text{CHCl}_3$ )), but the enantiopurity could not be determined because we did not find any comparable literature data. However, as it was irrelevant to the diastereoselectivity study, the following MAC reaction was still conducted. On the other hand, attempted purification of the aldehyde **L-31** by silica gel column chromatography resulted in considerable loss of material, indicating that this aldehyde was unstable on silica gel. Thus, crude aldehyde **L-31** was used directly in the subsequent experiments.

#### III.2 MAC reaction of *N*-Boc-*N*-Bn-*L*-phenylalaninal with H-MAC-TBS and MeOH

##### III.2.1 MAC reaction

Freshly prepared aldehyde **L-31** was used in a MAC reaction employing the same standard conditions as in the previous section (Scheme 78): 0.5 mmol of *N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31** was reacted with 1.2 eq. of H-MAC-TBS **148g**, 3.0 eq. of methanol, and 1.0 eq. of DMAP in  $\text{Et}_2\text{O}$  at 0 °C for 16 hours.



Scheme 78, MAC reaction with MeOH and H-MAC-TBS

After chromatography, the inseparable MAC products **227a,b** were obtained in 70% yield as a 58/42 mixture of two diastereomers. The diastereomeric ratio (dr) was calculated by <sup>1</sup>H NMR analysis of purified MAC products **227a,b** in DMSO-*d*<sub>6</sub> at 360 K (see III.2.2.1).

### III.2.2 Determination of the diastereomeric ratio

#### III.2.2.1 Using NMR spectroscopy

As had been the case for the MAC products obtained from *N*-Boc-*L*-phenylalaninal in the previous section (see II.2), the room temperature <sup>1</sup>H NMR spectrum of the MAC product mixture **227a,b** was also difficult to interpret due to considerable signal broadening, and our suspicion that slowly interconverting rotamers were present.

Using DMSO-*d*<sub>6</sub> as the solvent, <sup>1</sup>H NMR spectra of **227a,b** were recorded at 20 K intervals from 306 K (33 °C) to 360 K (87 °C). The spectra are superimposed in Figure 19.

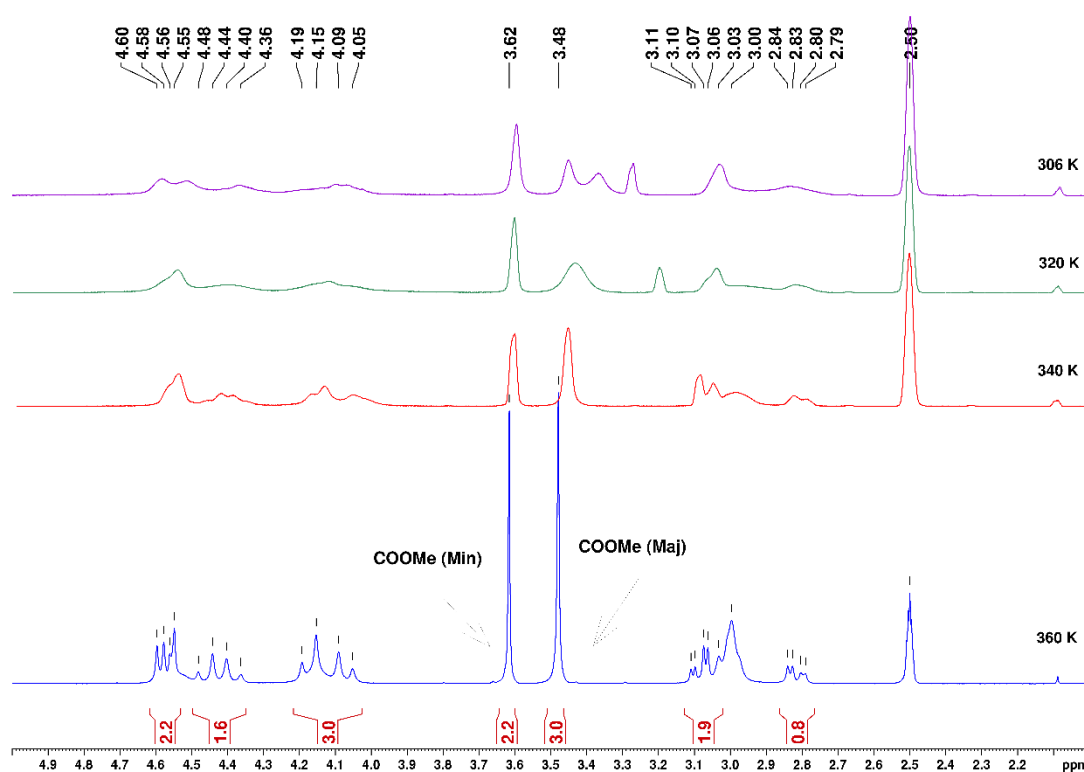


Figure 19, <sup>1</sup>H-NMR spectra of MAC product **227a,b** at different temperatures (400 MHz, DMSO-*d*<sub>6</sub>, from 306 K to 360 K;  $\delta$  = 2.0 ppm to 5.0 ppm)

The methoxy group signal was again used as the benchmark for the analysis. Three methoxy group signals were visible at 306 K, and the two higher-field signals coalesced at 320 K; a better resolution was observed at 360 K, the maximum temperature that can be attained using the 400 MHz spectrometer. Under this condition, two methoxy signals appeared at 3.48 ppm and 3.62 ppm, in a respective ratio of 58:42.

In fact, the  $^1\text{H}$  NMR spectra were not well-resolved even at 360 K. It suggested that the energy barrier of the internal rotation is too high, and it persists even at this temperature. We sought another method for dr determination.

### III.2.2.2 Cleavage of the silyl ether followed by NMR spectroscopy

We considered that NMR spectroscopic analysis of the diastereomeric mixture might be easier after the cleavage of the silyl ether. As Reißig reported the synthesis of the free alcohol of *N*-Boc-*N*-Bn-AHPBA methyl esters **33a,b** (see Scheme 10),<sup>66</sup> and that no rotamers were indicated; which inspired us that if the silyl groups from our MAC products are cleaved, we can compare the resulting alcohol with their results and thus obtain the diastereomeric ratio and the diastereoselectivity.

Removal of the silyl group of the MAC products **227a,b** was investigated using two fluoride reagents (Table 8).

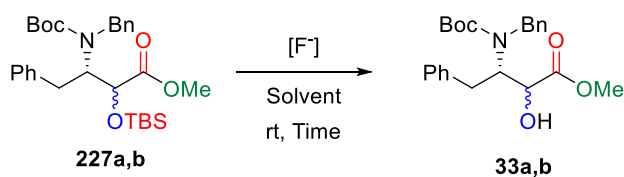


Table 8, Cleavage of silyl ethers **227a,b**

Entry	[F <sup>-</sup> ]	Solvent	Time (h)	Yield <sup>a</sup> (%)	dr <sup>b</sup>
1	TBAF	THF	16	-	-
2	HF·py	THF/pyridine	40	quant.	51:49

<sup>a</sup> isolated yield after column chromatography

<sup>b</sup> dr was calculated by  $^1\text{H}$  NMR analysis of purified alcohols **33a,b** in  $\text{CDCl}_3$  at rt

When 1.5 eq. of tetrabutylammonium fluoride (TBAF) was employed in THF at room temperature for 16 h (entry 1), TLC analysis showed that a large amount of MAC products **227a,b** remained. Better results were obtained using an excess of Olah's reagent (HF·py).<sup>194</sup> After stirring for 40 hours at room temperature (entry 2), TLC analysis showed no remaining MAC products **227a,b**, and the mixture of alcohols **33a,b** was obtained after work-up and chromatography in quantitative yield. The room temperature  $^1\text{H}$  NMR spectrum of alcohols **33a,b** was well refined and showed two sets of signals which we assigned to two diastereomers. As the two methoxy signals of **33a,b** were eclipsed in  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ , rt), the ratio of alcohols **33a,b** was determined by integrating the  $\text{PhCH}_2\text{CH}$  signals, and it was 51:49.



### III.3. Discussion

One representative MAC reaction of *N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31** with H-MAC-TBS **148g** and methanol was carried out and provided the expected oxyhomologation product **227a,b** in reasonable yield. Determination of the diastereomeric ratio proved to be problematic. Like previous results with *N*-Boc-*L*-phenylalaninal **L-15** (see II.2.2), peaks of the <sup>1</sup>H NMR spectra were extremely poorly resolved in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> at room temperature. Similarly, we used higher temperature NMR to deal with this problem. When using DMSO at 360 K, we were able to obtain a 58:42 ratio of the two diastereomers with the integration of methoxy signals.

The determination of the diastereoselectivity was problematic. First, such MAC products of *N*-Boc-*N*-Bn-*L*-phenylalaninal had not been reported, so the reference of <sup>3</sup>*J*<sub>C<sub>α</sub>H-C<sub>β</sub>H</sub> coupling constants for comparison is unavailable; let alone the coupling constants of both C<sub>α</sub>H and C<sub>β</sub>H, because the resolution of those peaks were not ideal even at 360 K.

We also tried cleavage of the TBS ether and compared the deprotected alcohols to the literature data. The deprotection was realized in quantitative yield using hydrogen fluoride but requires 40 hours of reaction time at room temperature. The <sup>1</sup>H NMR spectra of alcohols **33a,b** were well resolved, and the diastereomeric ratio was calculated as 51:49 by integrating the PHCH<sub>2</sub>CH signals. The ratio suggested a racemization of the products in a long time exploring (40 h) of hydrogen fluoride.<sup>195</sup> So, we believe that the alcohols' ratio **33a,b** cannot represent the actual ratio of the MAC products **227a,b**.

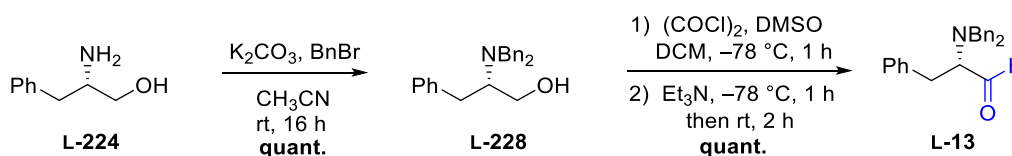
Furthermore, the preparation of *N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31** gave material for which the enantiomeric purity was not confirmed. Although this had no consequence on the diastereoselectivity profile being studied in this chapter, the matter would have to be resolved if applications for the preparation of single stereoisomer molecular targets were to be made.

For these reasons, we did not pursue studies of the MAC reaction of *N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31**, preferring to turn our attention to the third *N*-protection group suite.

## IV. MAC reactions of *N,N*-dibenzyl-*L*-phenylalaninal

### IV.1 Preparation of *N,N*-dibenzyl-*L*-phenylalaninal

*N,N*-Dibenzyl-*L*-phenylalaninal **L-13** was prepared using the following two-step procedure inspired by the literature (Scheme 79).<sup>192,196</sup>



Scheme 79, Preparation of *N,N*-dibenzyl-*L*-phenylalaninal

Commercial *L*-phenylalaninol **L-224** was dibenzylated with a large excess of benzyl bromide under basic conditions to give *N,N*-dibenzyl-*L*-phenylalaninol **L-228** in quantitative yield. The stereochemical purity of this alcohol was confirmed by comparing its optical rotation value ( $[\alpha]_D^{24} = +42.4$  (c 1.0, CHCl<sub>3</sub>)) with the literature value ( $[\alpha]_D^{26} = +46.7$  (c 1.0, CHCl<sub>3</sub>)).<sup>196</sup>

Alcohol **L-228** was subjected to Swern oxidation to afford *N,N*-dibenzyl-*L*-phenylalaninal **L-13**. However, following the workup described in the literature (acidification with 1M HCl, extraction with DCM),<sup>192</sup> the optical rotation of the product varied considerably and sometimes visibly decreased during the measurement ( $-45 < [\alpha]_D^{24} < -83$  (c 1.0, CHCl<sub>3</sub>)), and was in any case lower than the literature value<sup>197</sup> ( $[\alpha]_D^{20} = -90$  (c 1.0, CHCl<sub>3</sub>)). We suspected this may be due to the partial racemization of aldehyde **L-13** during the workup. To alleviate this, instead of using 1M HCl, a saturated ammonium chloride solution was employed in the workup;<sup>198</sup> and the crude aldehyde **L-13** was dissolved in Et<sub>2</sub>O followed by filtration to remove ammonium salts. The product **L-13** obtained in this way had a much better (and stable) optical rotation value ( $[\alpha]_D^{24} = -91$ , (c 1.0, CHCl<sub>3</sub>)), and was used directly in the subsequent MAC reaction experiments.

While the Swern oxidation did finally prove to be satisfactory, we also considered other oxidation methods. When 2-iodoxybenzoic acid (IBX) was used,<sup>199</sup> more than four products were observed on TLC and <sup>1</sup>H NMR analysis, suggesting that the oxidation by IBX was unsuitable for the synthesis.<sup>200</sup> When Dess–Martin periodinane (DMP) was used,<sup>201</sup> the aldehyde **L-13** was detected in the resulting product mixture but could not be isolated due to degradation upon attempted purification by chromatography on silica gel.

## IV.2 MAC reactions of *N,N*-dibenzyl-*L*-phenylalaninal with H-MAC-[Si] and MeOH

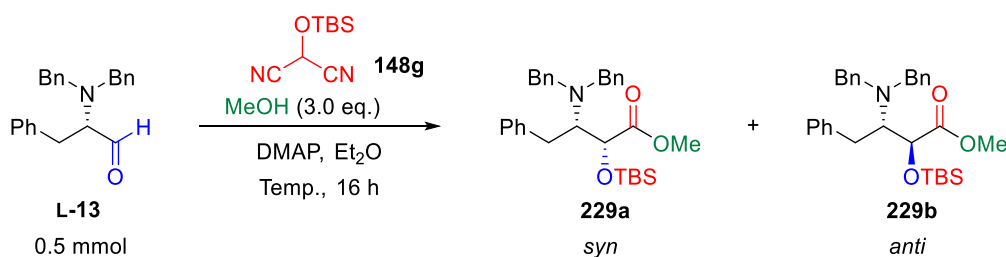
### IV.2.1 Optimization of the reaction conditions

*N,N*-Dibenzyl-*L*-phenylalaninal **L-13** was engaged in MAC reactions with the three different H-MAC-[Si] reagents **148g-i** and methanol to determine the optimal reaction conditions in terms of both yield and diastereoselectivity.

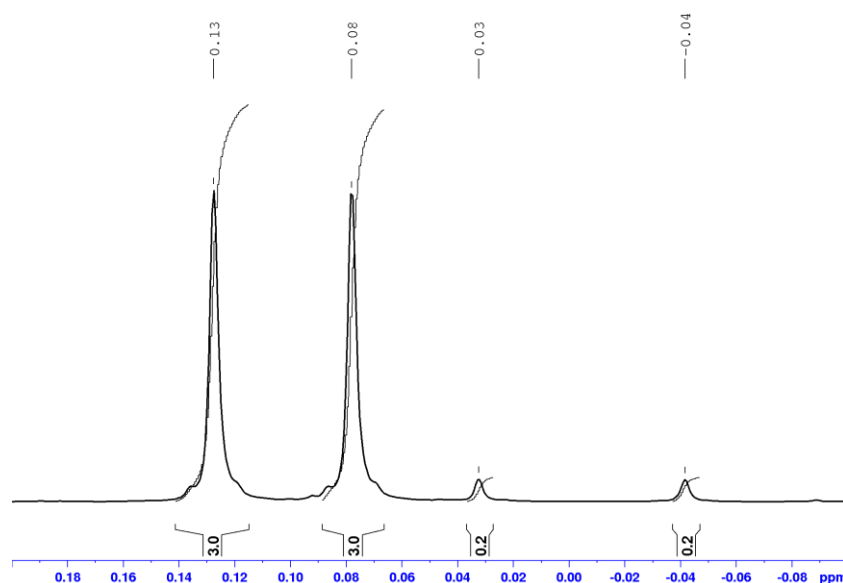
#### IV.2.1.1 MAC reaction with H-MAC-TBS and methanol

*N,N*-dibenzyl-*L*-phenylalaninal **L-13** (0.5 mmol) was reacted with H-MAC-TBS **148g**, DMAP and methanol (3.0 eq.) in Et<sub>2</sub>O for 16 hours, in a series of experiments in which the number of equivalents of the MAC reagent and DMAP were varied, as well as the reaction temperature.

The results are presented in Table 9; yields are given for isolated material after column chromatography. The diastereomeric ratios (dr) were calculated from the <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, rt) of the crude product before chromatography by integrating the Me<sub>2</sub>Si signals of each diastereomer. The major diastereomer **229b** showed two singlets at 0.08 ppm and 0.13 ppm, while the minor diastereomer **229a** showed two singlets at -0.04 ppm and 0.03 ppm (Figure 20). The assignment of an *anti* configuration for the major isomer **229b** was made using <sup>1</sup>H NMR spectroscopic analysis after cleavage of the TBS group (see IV.2.2.1).

Table 9, MAC reaction of *N,N*-dibenzyl-*L*-phenylalaninal, *H*-MAC-TBS and methanol

Entry	<i>H</i> -MAC-TBS (eq.)	DMAP (eq.)	Temp. (°C)	Yield <sup>a</sup> (%)	dr <sup>b</sup> ( <i>syn/anti</i> )
1	1.2	1.0	0	68	6 : 94
2 <sup>c</sup>	1.2	1.0	0	71	7 : 93
3	1.2	2.0	0	77	8 : 92
4	2.4	1.0	0	80	8 : 92
5	2.4	2.0	0	83 <sup>d</sup>	8 : 92
6	2.4	2.0	rt	78	9 : 91

<sup>a</sup> isolated yield after column chromatography<sup>b</sup> dr was calculated by <sup>1</sup>H NMR analysis of crude MAC products in CDCl<sub>3</sub> at rt<sup>c</sup> 3 Å molecular sieves were added<sup>d</sup> 1 eq. of *H*-MAC-TBS was recoveredFigure 20, Me<sub>2</sub>Si singlets from the major and minor diastereomers **229b** and **229a** (entry 1) (360 MHz, CDCl<sub>3</sub>, 300 K; δ = -0.10 ppm to 0.20 ppm)

The first experiment was run using the standard conditions established for the MAC reactions of *N*-Boc-*L*-phenylalaninal (see II.2.1). Freshly prepared aldehyde **L-13** was reacted with methanol, 1.2 eq. of *H*-MAC-TBS, and 1.0 eq. of DMAP at 0 °C (entry 1). The MAC product mixture **229a,b** was isolated in 68% yield and had a 6:94 *syn/anti* dr. A second experiment, conducted in the same way in the presence of 3 Å molecular sieves, gave very similar results (entry 2).

When 2.0 eq. of DMAP and 1.2 eq. of H-MAC-TBS were used, the yield rose to 77% without any erosion of the dr (entry **3**). When 1.0 eq. of DMAP and 2.4 equivalents of H-MAC-TBS were used, the yield was further improved to 80% (entry **4**). Combining these two observations, 2.0 eq. of DMAP and 2.4 eq. of H-MAC-TBS were used and afforded the MAC products **229a,b** in 83% yield with a *syn/anti* dr of 8:92 (entry **5**). In this experiment, approximately 1 eq. of H-MAC-TBS was recovered after the column chromatography. Finally, a slightly lower yield (78%) was observed when the reaction was conducted at room temperature, although the dr was almost the same (entry **6**).

In summary, the best conditions for the MAC reaction of *N,N*-benzyl-*L*-phenylalaninal **L-13** with H-MAC-TBS **148g** and methanol were considered to be those used in entry **5**.

#### IV.2.1.2 MAC reaction with H-MAC-TIPS and methanol

*N,N*-Dibenzyl-*L*-phenylalaninal **L-13** (0.5 mmol) was reacted with H-MAC-TIPS **148h**, DMAP and methanol (3.0 eq.) in Et<sub>2</sub>O for 16 hours, in a series of experiments similar to those described in the previous section.

The results are presented in Table **10**; yields are given for isolated material after column chromatography. The diastereomeric ratios (dr) were calculated from the <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, rt) of the purified product by integration of the CHOTIPS signal of each diastereomer. The signal of the major diastereomer **230b** was a doublet at 4.62 ppm, while that of the minor diastereomer **230a** was a doublet at 4.34 ppm (Figure **21**). The assignment of an *anti* configuration for the major isomer **230b** was made using <sup>1</sup>H NMR spectroscopic analysis after cleavage of the TBS group (see IV.2.2.1).

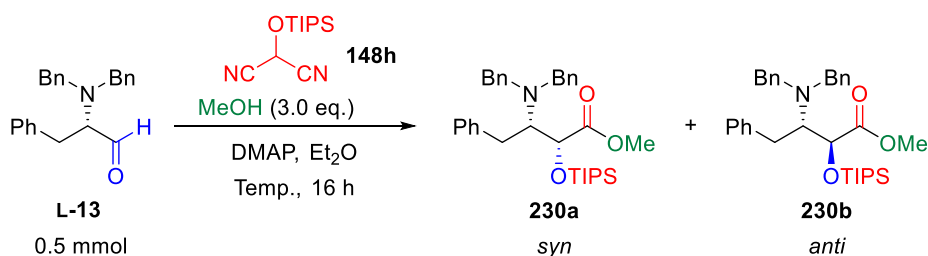


Table **10**, MAC reactions of *N,N*-dibenzyl-*L*-phenylalaninal, H-MAC-TIPS and methanol

Entry	H-MAC-TIPS (eq.)	DMAP (eq.)	Temp. (°C)	Yield <sup>a</sup> (%)	dr <sup>b</sup> ( <i>syn/anti</i> )
<b>1</b>	1.2	1.0	0	56	7 : 93
<b>2</b>	1.2	2.0	0	65	7 : 93
<b>3</b>	1.2	3.0	0	67	9 : 91
<b>4</b>	2.4	1.0	0	71	6 : 94
<b>5</b>	2.4	2.0	0	80 <sup>c</sup>	9 : 91
<b>6</b>	2.4	2.0	rt	70	9 : 91

<sup>a</sup> isolated yield after column chromatography

<sup>b</sup> dr was calculated by <sup>1</sup>H NMR analysis of purified MAC products in CDCl<sub>3</sub> at rt

<sup>c</sup> 0.8 eq. of H-MAC-TBS was recovered

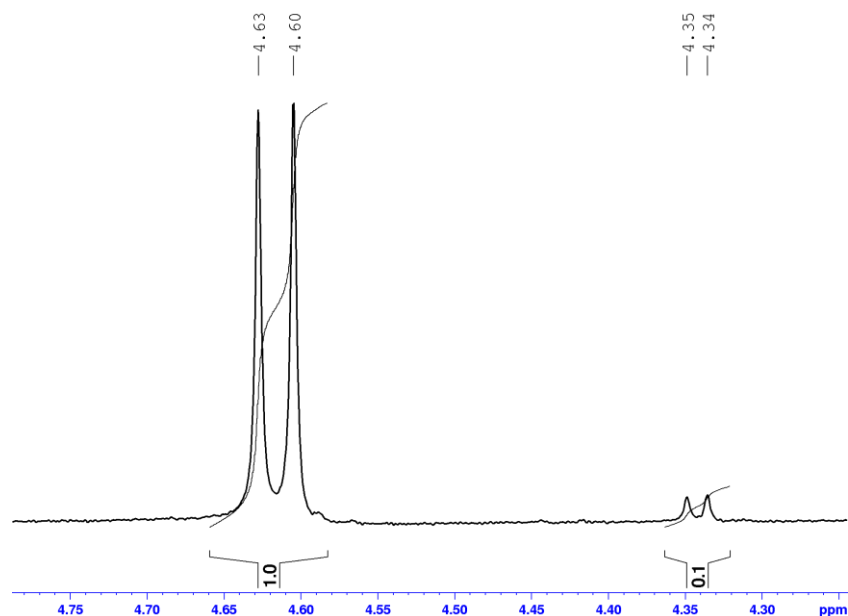


Figure 21, CHOTIPS doublets from the major and minor diastereomers **230b** and **230a** (entry 5) (250 MHz,  $\text{CDCl}_3$ , 300 K;  $\delta = 4.20$  ppm to 4.80 ppm)

In the first experiment, freshly prepared aldehyde **L-13** was reacted with methanol, 1.2 eq. of H-MAC-TBS, and 1.0 eq. of DMAP at 0 °C (entry 1). The MAC product mixture **230a,b** was isolated in 56% yield, with a 7 : 93 *syn/anti* dr. When 2.0 eq. of DMAP was used, the yield improved to 65% without any loss of diastereoselectivity (entry 2). The use of 3.0 eq. of DMAP did not modify the results significantly (entry 3).

When 2.4 eq. of H-MAC-TIPS and 1.0 eq. of DMAP were employed, the yield was 71%, and the *syn/anti* dr was 6 : 94 (entry 4). When 2.4 eq. of H-MAC-TIPS and 2.0 eq. of DMAP were used, the MAC products were obtained in a 80% yield with a similar dr (entry 5). In this experiment, approximately 0.8 eq. of H-MAC-TIPS was recovered after the column chromatography. Finally, conducting the reaction at room temperature decreased the yield to 70% with no change in dr (entry 6).

In summary, the best conditions for the MAC reaction on *N,N*-benzyl-*L*-phenylalaninal **L-13** with H-MAC-TIPS **148h** and methanol were considered to be those used in entry 5.

#### IV.2.1.3 MAC reaction with H-MAC-TBDPS and methanol

*N,N*-Dibenzyl-*L*-phenylalaninal **L-13** (0.5 mmol) was reacted with H-MAC-TBDPS **148i**, DMAP and methanol (3.0 eq.) in  $\text{Et}_2\text{O}$  for 16 hours, in a serie of experiments similar to those described in the two previous sections.

The results are presented in Table 11. Except where indicated, yields are given for isolated material after column chromatography. The diastereomeric ratios (dr) were calculated from the  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ , rt) of the purified product mixture by integration of the COOMe signal of each diastereomer. The signal of the major diastereomer **231b** appeared at 3.19 ppm, while that of the minor diastereomer **231b** appeared at 3.05 ppm (see Figure 22). The assignment of an *anti*

configuration for the major isomer **231b** was made using  $^1\text{H}$  NMR spectroscopic analysis after cleavage of the TBDPS group (see IV.2.2.1), and it was confirmed by single crystal X-ray diffraction (see IV.2.2.2).

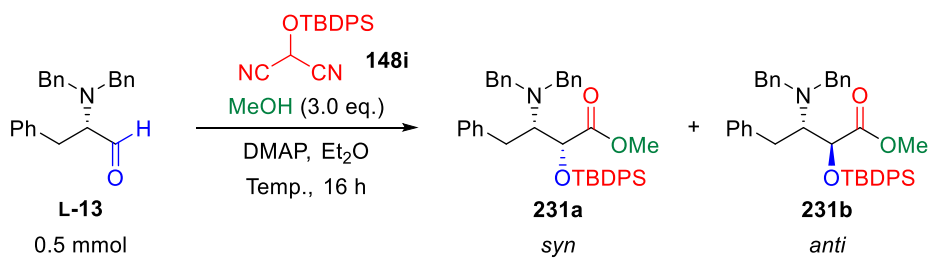


Table 11, MAC reaction of *N,N*-dibenzyl-*L*-phenylalaninal, *H*-MAC-TBDPS and methanol

Entry	H-MAC-TBDPS (eq.)	DMAP (eq.)	Temp. (°C)	Yield <sup>a</sup> (%)	dr <sup>b</sup> ( <i>syn/anti</i> )
1 <sup>c</sup>	1.2	1.0	0	52 <sup>d</sup>	7 : 93
2	1.2	1.0	0	51	8 : 92
3	1.2	2.0	0	51	8 : 92
4	2.4	1.0	0	71	7 : 93
5	2.4	2.0	0	74	7 : 93
6	2.4	2.0	rt	74	9 : 91
7	2.0	2.0	rt	65	10 : 90
8	1.2	2.0	rt	51	10 : 90

<sup>a</sup> isolated yield after column chromatography

<sup>b</sup> dr was calculated by  $^1\text{H}$  NMR analysis of purified MAC products in  $\text{CDCl}_3$  at rt

<sup>c</sup> workup involving extraction/acidification was applied

<sup>d</sup> calculated from  $^1\text{H}$  NMR spectrum of the crude product mixture

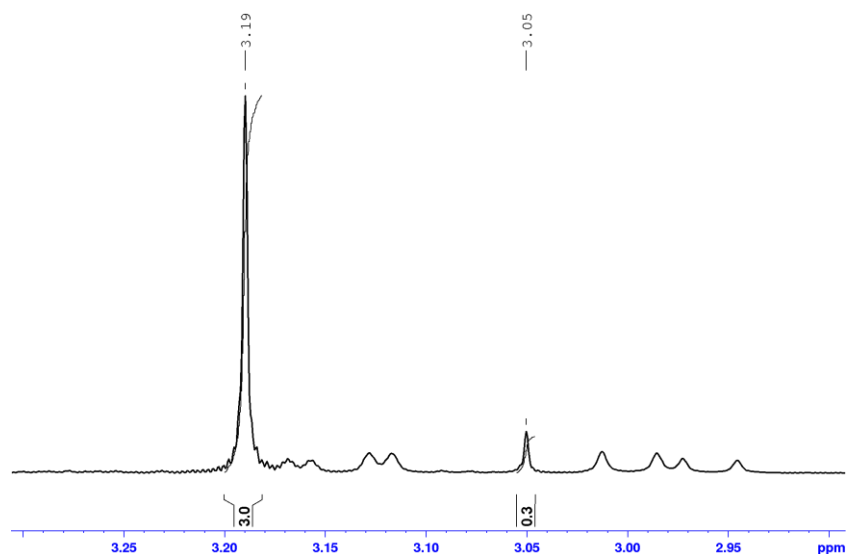


Figure 22, COOMe singlets from the major and minor compounds **231b** and **231a** (entry 6) (360 MHz,  $\text{CDCl}_3$ , 300 K;  $\delta = 2.90$  ppm to 3.30 ppm)

In the first experiment, freshly prepared aldehyde **L-13** was reacted with methanol, 1.2 eq. of H-MAC-TBDPS, and 1.0 eq. of DMAP at 0 °C (entry **1**). The reaction mixture was extracted with Et<sub>2</sub>O and the extracts were washed with 1 M HCl to remove DMAP and then evaporated to give the crude product. However, we were unable to separate the MAC products **231a,b** from the excess of H-MAC-TBDPS **148i** by column chromatography. In consequence, the yield (52%) was estimated by analysis of the <sup>1</sup>H NMR spectrum of the product mixture, and the dr (7:93 *syn/anti*) was evaluated using the same sample.

The second experiment was run under the same conditions, but after the 16 h reaction time, the mixture was evaporated directly under reduced pressure (entry **2**). During this process, the remaining H-MAC-TBDPS **148i** was destroyed, which facilitated the separation of the MAC product mixture **231a,b** by column chromatography. The isolated yield of MAC products was 51% and the dr was 8:92. This experiment showed that evaporation of the reaction mixture greatly facilitated product isolation while it did not affect the yield nor the diastereoselectivity. We therefore applied this simplified procedure in all the subsequent experiments.

When 1.2 eq. of H-MAC-TBDPS and 2.0 eq. of DMAP were used (entry **3**), the results were identical to the previous experiment. When 2.4 eq. of H-MAC-TBDPS and 1.0 eq. of DMAP were employed, the yield rose to 71% and the high dr (7:93) was retained (entry **4**). When 2.4 eq. of H-MAC-TBDPS and 2.0 eq. of DMAP were used, the yield slightly rose to 74% and the dr remained constant (entry **5**).

We wondered whether the reactivity of H-MAC-TBDPS might be lower than its congeners H-MAC-TBS and H-MAC-TIPS, leading to lower yields of MAC oxyhomologation products. We therefore ran the next experiment, using the same reaction mixture as before, at room temperature (entry **6**), but no improvement was observed. Further experiments at room temperature in which the quantity of H-MAC-TBDPS was reduced to 2.0 eq., then to 1.2 eq., resulted in lower product yields and almost no change in the dr values (entries **8** and **9**).

In summary, the best conditions for the MAC reaction on *N,N*-benzyl-*L*-phenylalaninal **L-13** with H-MAC-TBDPS **148i** and methanol were considered to be those used in entry **5**.

## IV.2.2 Determination of the diastereoselectivity

### IV.2.2.1 Cleavage of the silyl ether

The silyl group of each of the three MAC products **229a,b**, **230a,b** and **231a,b** was performed with 1.5 equivalents of TBAF in THF at 0 °C (for **229a,b** and **230a,b**) or room temperature (for **231a,b**). Table **12** summarizes the reaction times and isolated yields of the deprotected compound **232**.

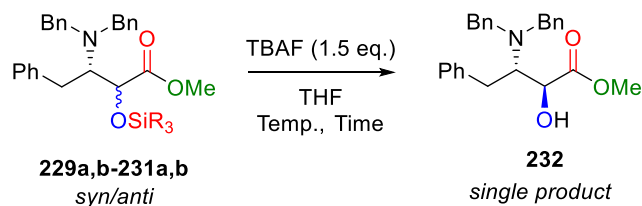


Table 12, Deprotection of silyl ethers with TBAF

Entry	MAC products	SiR <sub>3</sub>	dr of MAC products ( <i>syn/anti</i> )	Temp. (°C)	Time (h)	Yield <sup>a</sup> (%)
1	229a,b	TBS	8 : 92	0	1	80
2	230a,b	TIPS	9 : 91	0	1	86
3	231a,b	TBDPS	7 : 93	rt	16	71

<sup>a</sup> isolated yield after column chromatography

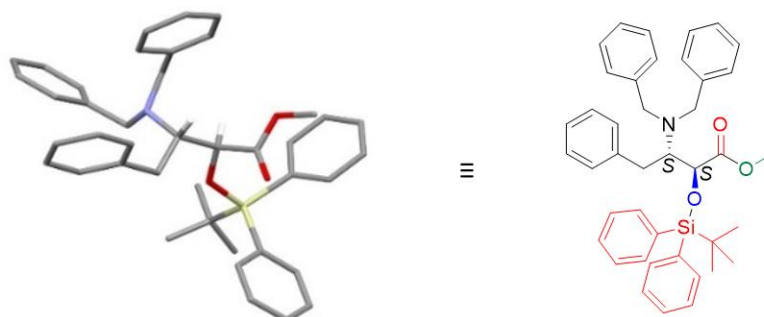
In the <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, rt) of the crude reaction product mixture obtained from each of the three experiments, the signals of the minor silyl ether diastereomer (**229a**, **230a** and **231a**) were visible. This suggested that only the major MAC product diastereomer (**229b**, **230b** and **231b**) had been deprotected under the chosen conditions.

In each case, the deprotected alcohol **232** was isolated as a single stereoisomer in high yield, confirming that it was derived from the major diastereomer of each MAC product mixture. The configuration of **232** was confirmed as *anti* by comparing its <sup>1</sup>H NMR spectral data with those described for this compound in the literature.<sup>202</sup> Its optical rotation value ( $[\alpha]_{\text{D}}^{22} = +35.9$  (c 1.0, CHCl<sub>3</sub>)) was also in agreement with the literature value ( $[\alpha]_{\text{D}}^{20} = +35.8$  (c 1.0, CHCl<sub>3</sub>)).<sup>202</sup>

#### IV.2.2.2 X-ray diffraction analysis

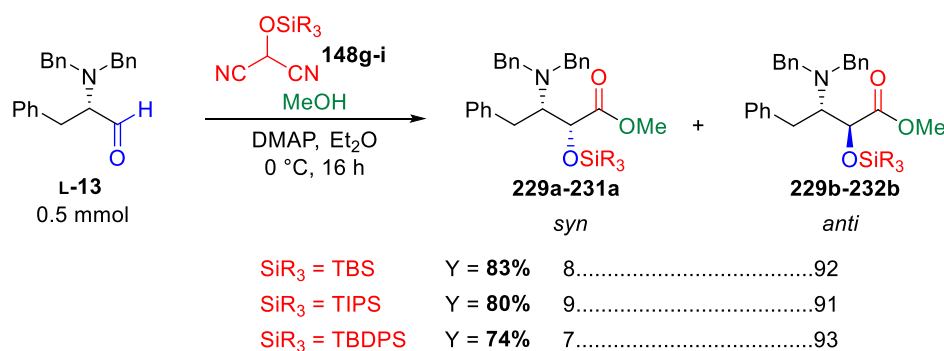
A single crystal of the major MAC product diastereomer **231b** was obtained by slow diffusion of pentane into an Et<sub>2</sub>O solution of compounds **231a,b** at ambient temperature, which is suitable for X-ray diffraction analysis. Result confirmed the *anti*-(2*S*,3*S*) configuration of this diastereomer (Figure 23). Meanwhile, only the major diastereomer was observed in the <sup>1</sup>H NMR spectrum of this crystal (CDCl<sub>3</sub>, rt).



Figure 23, Single crystal X-ray diffraction analysis of compound **231b**

### IV.3 Discussion

The MAC reactions of *N,N*-dibenzyl-*L*-phenylalaninal **L-13** with three different H-MAC-[Si] reagents and methanol as a simple representative nucleophile provided mixtures of two diastereomers in medium-to-good isolated yields when run on a 0.5 mmol scale. The best results obtained for each MAC reagent are summarized in Scheme **80**, which underlines the similar reactivity profiles observed for the trio of H-MAC-[Si] reagents.

Scheme 80, MAC reactions on *N,N*-dibenzyl-*L*-phenylalaninal with H-MAC-[Si] and MeOH

For each H-MAC-[Si] reagent, the best yield was obtained using the following conditions: *N,N*-dibenzyl-*L*-phenylalaninal **L-13** (1.0 eq.), H-MAC-[Si] (2.4 eq.), DMAP (2.0 eq.), methanol (3.0 eq.) in Et<sub>2</sub>O at 0 °C for 16 hours. As had been the case in the study of *N*-Boc-*L*-phenylalaninal **L-15** (see II.2), the yields were marginally better with H-MAC-TBS and H-MAC-TIPS than with H-MAC-TBDPS. These conditions employ an excess of H-MAC-[Si] reagent; in the cases of H-MAC-TBS and H-MAC-TIPS the unreacted reagent could be recovered, whereas the required treatment in the case of H-MAC-TBDPS resulted in the degradation of the unreacted MAC reagent.

In the oxyhomologated product mixtures obtained from these reactions, the dr was uniformly high, ranging  $10:90 \leq \text{dr} \leq 6:94$  over the entire set of experiments. Within the limits of precision of the NMR technique used to determine dr values, all three H-MAC-[Si] reagents performed equally well.

Most significantly, the major diastereomer always had an *anti* configuration. We propose that the *anti* diastereoselectivity of the MAC reactions of *N,N*-dibenzyl-*L*-phenylalaninal **L-13** can be explained by a “Felkin–Anh” model (Figure **24**).<sup>203,204</sup>

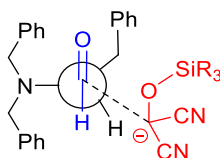


Figure 24, Felkin-Anh model

According to this model, the amino aldehyde substrate adopts a preferred conformation in which the electronegative amine  $\alpha$ -substituent is perpendicular to the plane of the carbonyl group to facilitate  $\sigma^*-\pi^*$  orbital alignment. Attack of such a conformation by the anion of the MAC reagent via the least hindered Bürgi–Dunitz approach would lead preferentially to an *anti* diastereomer.

## V. Comparison of the reactivity profiles

In the above studies, we have examined the MAC oxyhomologation reactions of three different *N*-protected derivatives of *L*-phenylalaninal in combination with three different H-MAC-[Si] reagents and a selected alcohol (methanol in most cases) as a simple representative nucleophile partner. With only marginal variations in efficiency, the optimized reactions proceeded smoothly and in mild conditions and provided the expected oxyhomologation products in satisfying yields, regardless of the *N*-protection suite of *L*-phenylalaninal or the identity of H-MAC-[Si] reagent.

A focal point of these studies was the diastereoselectivity profile of the MAC reactions. While the diastereoselectivity was not influenced in any way by the identity of the H-MAC-[Si] reagents (or the alcohol, within the limited scope that was covered), a dramatic effect was observed depending on the *N*-protecting suite of the *L*-phenylalaninal substrate.

On the one hand, MAC oxyhomologation reactions using *N*-Boc-*L*-phenylalaninal **L-15** as the electrophile proceeded with a clear *syn* selectivity ( $dr \geq 80:20$  *syn/anti*). This can be explained by an “H-bonded” or “anti-Felkin–Anh” model for the first step of the proposed mechanism. Our results are consistent with other examples of MAC reactions using  $\alpha$ -amino aldehyde substrates bearing a single *N*-protecting group (essentially a carbamate), thus retaining one N-H motif. We therefore propose that the “H-bonded” or “anti-Felkin–Anh” model can be used to explain the diastereoselectivity of such systems in general.

On the other hand, MAC oxyhomologation reactions of *N,N*-dibenzyl-*L*-phenylalaninal **L-13** as the electrophile proceeded with a high *anti* selectivity ( $dr \leq 10:90$  *syn/anti*). This remarkable reversal of selectivity can be explained by a Felkin–Anh model for the first step of the proposed mechanism. Indeed, our results are consistent with the high *anti* diastereoselectivity observed in the addition of other types of nucleophiles to *N,N*-dibenzyl  $\alpha$ -amino aldehydes without chelation control.<sup>205</sup>

The limited study carried out on *N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31**, while providing the oxyhomologation products as expected, was inconclusive as regards diastereoselectivity. On the basis of the arguments presented just above, it is tempting to suggest that the absence of an N-H motif

might lead the substrate to adopt a Felkin–Anh conformation, but we were unable to make a reliable assessment of the diastereoselectivity on the single MAC reaction product mixture that was obtained. Further work would be required on this system.

The fact that a panel of different H-MAC-[Si] reagents can be used successfully and with predictable diastereoselectivity in MAC reactions with an *N*-protected phenylalaninal derivative is an advantage in terms of potential synthetic usefulness, since a more-or-less robust silyl ether protecting group can be incorporated in the AHPBA ester MAC product. Indeed, the ease of silyl ether cleavage varies ROTBS > ROTIPS > ROTBDPS, which in general parallels the increase in steric bulk around the silicon atom.<sup>206,207</sup>

## VI. Conclusion

The reactivity profiles of the three H-MAC-[Si] reagents were sufficiently similar to allow us an unrestricted choice. However, given that H-MAC-TIPS and H-MAC-TBDPS offer no advantages over the more commonly used H-MAC-TBS, in terms of either synthetic access or chemical reactivity, we retained H-MAC-TBS for the continuation of our studies.

The *N*-protecting group suite of phenylalaninal is the determining factor for the diastereoselectivity of its oxyhomologation using a MAC reaction. When a single carbamate protecting group is used, a *syn* diastereoselectivity is observed, whereas the use of a *N,N*-dibenzyl protection system leads to predominant *anti* diastereoselectivity. In the continuation of our studies, we wished to develop the synthesis of AHPBA derivatives with an *anti* configuration. For this reason, we decided to retain the *N,N*-dibenzyl protection group in subsequent work.

More specifically, the use of *N,N*-dibenzyl-*L*-phenylalaninal as the electrophilic partner in these studies resulted in the formation of esters of *N,N*-dibenzyl-*O*-silyl protected derivatives of the *anti*-AHPBA, better known as allophenylnorstatin (Apsn). As we indicated in the Introduction, there is considerable interest in derivatives of this  $\alpha$ -hydroxy- $\beta$ -amino acid, and we pursued our studies towards such derivatives, as we will describe in the next chapter.

## Chapter 3:

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MAC reactions for the  
synthesis of *anti*-AHPBA  
derivatives

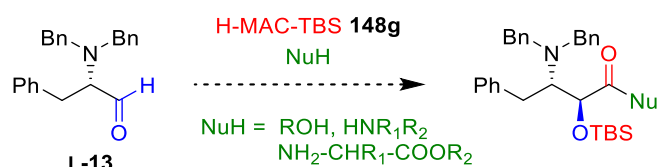
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## I. Introduction

As we saw in the Introduction, many synthetic methodologies have been used to prepare derivatives of the *anti*-AHPBA or allophenylnorstatin. Most of these methodologies implicate the construction of the core *anti*-AHPBA structure before C- or N-terminal derivatization via peptide coupling.

In the preceding chapter, we established optimized MAC reaction conditions for the oxyhomologation of *N,N*-dibenzyl-L-phenylalaninal **L-13** with high *anti* diastereoselectivity, to provide the methyl ester of *N,N*-dibenzyl-*O*-TBS-protected *anti*-AHPBA. We envisaged that this approach could be used to create a wider library of derivatives of stereochemically enriched *anti*-AHPBA, including peptide derivatives, in a *one-pot* procedure.

To evaluate this hypothesis, we proposed to use *N,N*-dibenzyl-L-phenylalaninal **L-13** and H-MAC-TBS **148g** in oxyhomologation reactions in the presence of different nucleophiles. The panel of nucleophiles envisaged included alcohols, amines and  $\alpha$ -amino esters, with the objective of establishing the expedient syntheses of the corresponding esters, amides and dipeptides of *anti*-AHPBA. An overview is presented in Scheme **81**.



Scheme **81**, Synthesis of *anti*-AHPBA derivatives in one-pot MAC reaction

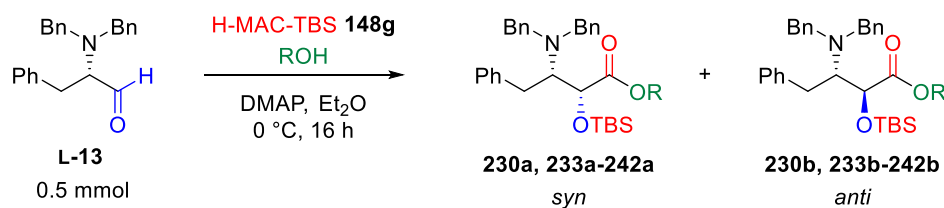
## II. MAC reactions with alcohols

### II.1. Alcohol substrate scope and limitations

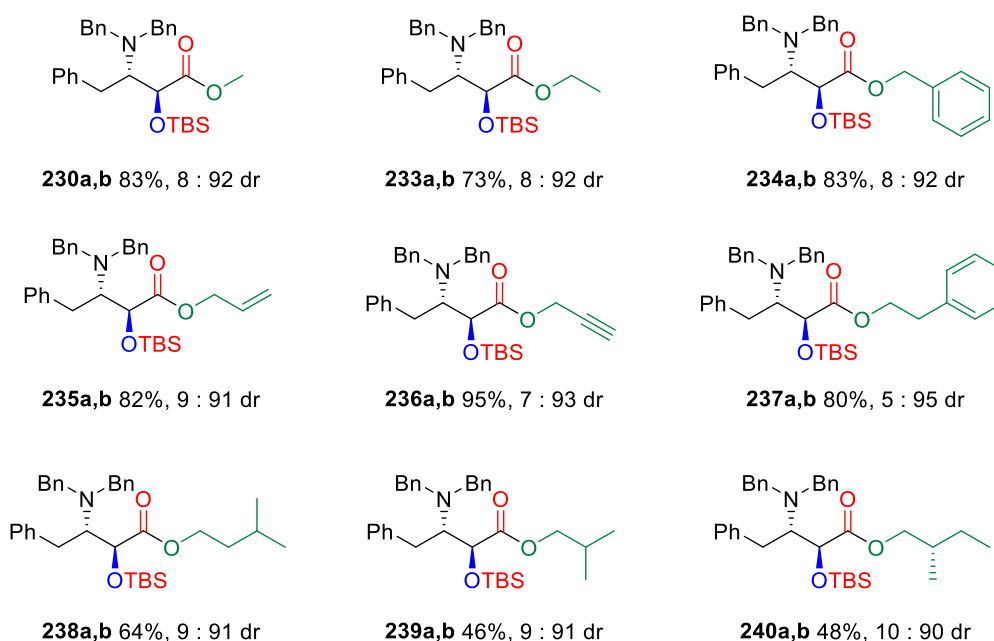
#### II.1.1 Results

Based on the optimized conditions established in the previous chapter, *N,N*-dibenzyl-L-phenylalaninal **L-13** was reacted on a 0.5 mmol scale with 2.4 eq. of H-MAC-TBS **148g**, 2.0 eq. of DMAP and 3.0 eq. of a selected alcohol in Et<sub>2</sub>O at 0 °C for 16 hours. After the standard work-up and column chromatography, an inseparable diastereomeric mixture of the MAC oxyhomologation ester products was obtained (Scheme **82**). Yields are given for isolated material after column chromatography. The diastereomeric ratios (dr) were calculated from the <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, rt) of the crude product mixture by integration of Me<sub>2</sub>Si signals of each diastereomer (except for compounds **241a,b** and **242a,b**, the diastereomeric ratios were calculated from the <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, rt) of the purified product mixture). On the basis of the results obtained in the previous chapter using methanol as the nucleophile (see Chapter 2, IV.2.2), we assumed that the *anti* diastereomer predominated in each case. Support for this contention was provided by the trend observed in the <sup>1</sup>H NMR spectroscopic data for

all samples, which invariably showed the diagnostic TBS methyl groups signals at a lower field for the major diastereomer (*anti*) than for the minor diastereomer (*syn*).



Scheme 82, MAC reaction with various alcohols

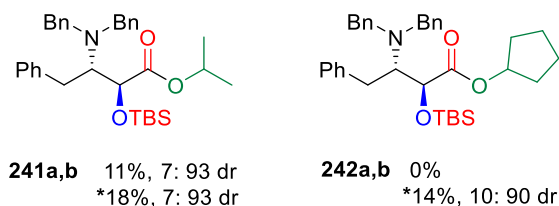


The simple primary alcohols ethanol and benzyl alcohol gave MAC products **233a,b** and **234a,b** in good yields with high diastereoselectivity, similar to methanol as we saw in the previous section. Three other uncongested primary alcohols – allyl alcohol, propargyl alcohol and phenylethanol – gave very good yields of the products (**235a,b-237a,b**) and in high dr, especially for propargyl alcohol (**236a,b**) for which the yield was 95%, and the *syn/anti* dr was 7:93.

When isoamyl alcohol was used, the MAC products **238a,b** were obtained in 64% yield; when isobutanol was used, the MAC products **239a,b** were obtained in a lower 46% yield. Comparable with isobutanol, (*S*)-2-methylbutanol gave a similar yield (48%, **240a,b**). In these three cases, despite the lower yields, the *syn/anti* dr were around 10:90.

Two secondary alcohols were also examined (Scheme 83). Using the above-described conditions, isopropanol gave **241a,b** in only 11% yield, while cyclopentanol did not furnish any MAC reaction products. We modified the reaction conditions, whereby a solution of *N,N*-dibenzyl-L-phenylalaninal **L-13** and H-MAC-TBS **148g** in Et<sub>2</sub>O was treated with DMAP and stirred for 10 minutes at 0 °C, then the alcohol was added and the mixture stirred for 16 hours. Using these modified conditions, **241a,b** was

obtained from isopropanol in 18% yield, while **242a,b** was obtained from cyclopentanol in 14% yield. Again, the *syn/anti* dr of the MAC product mixtures was about 10:90.



Scheme 83, MAC products from isopropanol and cyclopropanol

### II.1.2 Discussion

When linear primary alcohols were employed in the MAC oxyhomologation reaction, they gave good yields of esters with a *syn/anti* dr around 10:90. When branched-chain primary alcohols were used, the yields decreased with increased steric effect while keeping the same diastereoselectivity, notably when the alcohol partner bore a chiral center. The reactivity profile of linear and branched-chain primary alcohols varies only in yield, not in the degree of *anti* diastereoselectivity.

In contrast, the participation of a secondary alcohol was inefficient, and although the dr remained high, the yields of the expected adducts were dramatically decreased.

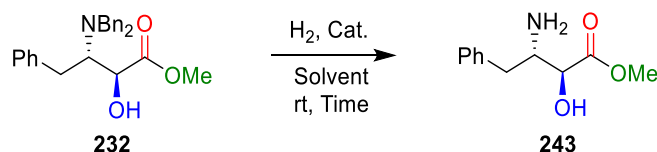
## II.2 Synthesis of (2*S*,3*S*)-AHPBA methyl and ethyl esters

The methyl ester of (2*S*,3*S*)-AHPBA **243** is known to act as a Leukotriene A4 hydrolase (LTA<sub>4</sub>) inhibitor.<sup>208</sup> It has also been used as a building block for the preparation of  $\beta$ -secretase 1 (BACE-1) inhibitors,<sup>35</sup> photobiological switches,<sup>209</sup> and symmetrical peptidomimetic scaffolds.<sup>210</sup> The ethyl ester of (2*S*,3*S*)-AHPBA **244** has been employed as a building block for the synthesis of HIV protease inhibitors<sup>211,212</sup> and cysteine protease inhibitors.<sup>213</sup> It appeared to us that an expedient access to these useful esters might be provided via the MAC oxyhomologation methodology.

### II.2.1 Synthesis of (2*S*,3*S*)-AHPBA methyl ester

We described previously (see Chapter 2, IV.2.2.1) the diastereoselective deprotection of the MAC product mixture **229a,b** using TBAF, to obtain the *anti* free alcohol **232** in 80% yield as a single enantiomer. This alcohol **232** was used as a convenient precursor of (2*S*,3*S*)-AHPBA methyl ester **243**.

Alcohol **232** was submitted to catalytic hydrogenolysis in order to remove the two benzyl groups from the amine. Several conditions were examined, and the results are presented in Table 13. The conversion was calculated from <sup>1</sup>H NMR (CD<sub>3</sub>OD, rt) by comparing the integration of the signal of *CHOH* (in compound **232**,  $\delta$  = 4.53 ppm; while in compound **243**,  $\delta$  = 4.13 ppm). The yield is given for material obtained after filtration through a Celite pad or a PVDF membrane (HPLC filter, 0.22  $\mu$ m pore size).

Table 13, Hydrogenolysis of **232** to provide the (2*S*,3*S*)-AHPBA methyl ester

Entry	Cat.	Equivalent of Cat. <sup>a</sup>	H <sub>2</sub> (bar)	Solvent	Time (h)	Conv. (%)	Yield <sup>b</sup> (%)
1	Pd/C	10%	1	EtOAc	24	0	0
2	Pd/C	100%	1	EtOAc	24	52	-
3	Pd/C	100%	1	EtOAc	48	74	-
4	Pd/C	100%	1	EtOAc	72	84	-
5	Pd/C	100%	1	EtOAc	96	89	-
6	Pd/C	10%	5	EtOAc	24	23	15
7	Pd/C	10%	10	EtOAc	48	100	75
8	Pd(OH) <sub>2</sub> /C	10%	1	EtOAc	24	23	-
9	Pd(OH) <sub>2</sub> /C	10%	1	EtOH	2	100	94 <sup>c</sup>
10	PtO <sub>2</sub>	10%	1	EtOH	16	0	0
11	Pd(OH) <sub>2</sub> /C	10%	1	<i>i</i> PrOH	5	86	-
12	Pd(OH) <sub>2</sub> /C	10%	1	MeOH	1	100	88

<sup>a</sup> wt% to the weight of starting material<sup>b</sup> crude yields after filtration through a Celite pad or a PVDF membrane<sup>c</sup> mixed with ethyl esters

The hydrogenolysis was first examined using palladium on activated carbon (10% wt%) in ethyl acetate under 1 bar hydrogen (balloon). When the 10% of catalyst was used, the starting material was not consumed after stirring for 24 hours (entry **1**). By increasing the use of catalyst to 100%, the conversion was increased to 52% (entry **2**) and rose further with reaction time, reaching 89% (entries **3-5**).

We assessed the effect of increasing the hydrogen pressure using an autoclave reactor. At 5 bars pressure of hydrogen for 24 hours in the presence of 10% Pd/C, a conversion of only 23% was achieved (entry **6**). When the hydrogen pressure was increased to 10 bars, the conversion was complete after 48 hours, and the target methyl ester **243** was obtained in 75% yield (entry **7**).

Other catalysts were screened with a view to achieving hydrogenolysis under only 1 bar hydrogen pressure. Use of 10% Pearlman's catalyst (Pd(OH)<sub>2</sub>/C, 20 wt% on carbon) in ethyl acetate for 24 hours gave only 23% conversion (entry **8**). Remarkably, when the same reaction was performed using ethanol as the solvent, the reaction was finished in 2 hours (entry **9**). However, we also observed the corresponding ethyl ester in the <sup>1</sup>H NMR spectrum of the crude product, which indicated that a transesterification had occurred in this reaction. No conversion was observed using Adams' catalyst (PtO<sub>2</sub>)<sup>214</sup> in ethanol for 16 hours (entry **10**).

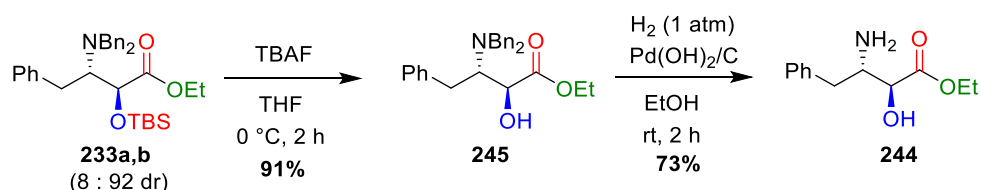


Returning to the promising results obtained using 10% Pearlman's catalyst in ethanol, two other alcohol solvents were examined with the objective of preventing transesterification. When the reaction was carried out in isopropanol, the conversion was 86% after 5 hours. In methanol, complete conversion was achieved in just one hour, and (2*S*,3*S*)-AHPBA methyl ester **243** was obtained in 88% isolated yield.

The (2*S*,3*S*)-AHPBA methyl ester **243** obtained in this manner is a colorless oil that is sensitive to air and should be kept at  $-18\text{ }^{\circ}\text{C}$  under argon.

### II.2.2 Synthesis of (2*S*,3*S*)-AHPBA ethyl ester

Using a similar approach, (2*S*,3*S*)-AHPBA ethyl ester **244** was synthesized in the following two steps (Scheme 84).



Scheme 84, Synthesis of (2*S*,3*S*)-AHPBA ethyl ester

Starting from a MAC diastereomeric mixture **233a,b** (8:92 dr), the diastereoselective cleavage of the TBS ether was achieved by reaction with TBAF in THF at  $0\text{ }^{\circ}\text{C}$  for 2 hours. Column chromatography gave the desired (2*S*,3*S*)-alcohol **245** as a single enantiomer in 91% yield. Catalytic hydrogenolysis in the presence of 10% Pearlman's catalyst in ethanol for 2 hours gave the target (2*S*,3*S*)-AHPBA ethyl ester **244** in 73% yield.

We also assessed the hydrogenolysis in the presence of a 100% of Pd/C in ethyl acetate, which gave only 84% conversion after 48 hours.

The (2*S*,3*S*)-AHPBA ethyl ester **244** obtained in this manner is a colorless oil that is sensitive to air and should be kept at  $-18\text{ }^{\circ}\text{C}$  under argon.

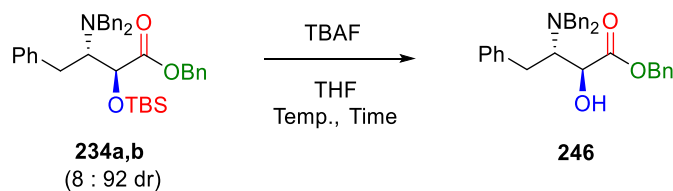
## II.3 Synthesis of (2*S*,3*S*)-AHPBA

To further exploit the availability of esters of *N,O*-protected (2*S*,3*S*)-AHPBA as described above (section II.1), we envisaged the short synthesis of (2*S*,3*S*)-AHPBA **1d** in its free form. The chosen starting material was the MAC product mixture **234a,b** obtained using benzyl alcohol as the nucleophile, since hydrogenolysis of the ester should be achieved at the same time as the removal of the two benzyl groups from the amine.

### II.3.1 Cleavage of the TBS ether

The first step of the synthesis was the cleavage of the TBS ether (Table 14). The MAC product mixture **234a,b** (*syn/anti* 8:92) was treated with 1.5 eq. of TBAF in THF at room temperature for 16 hours, to furnish the alcohol **246** in 74% yield after chromatography (entry 1). Only one stereoisomer was observed in the crude  $^1\text{H}$  NMR spectrum, suggesting the cleavage of TBS was diastereoselective, and

only the *anti* MAC product was deprotected. When the reaction was performed at 0 °C for 50 minutes, the yield improved to 84%, and again only *anti* alcohol was obtained as a single stereoisomer (entry **2**).

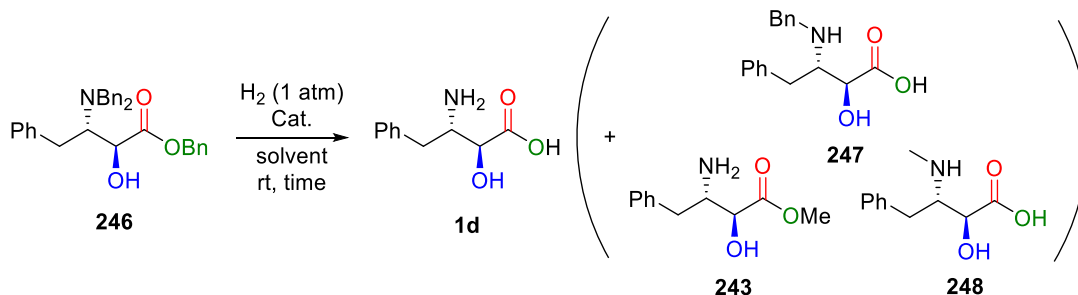
Table 14, Cleavage of TBS ether of **234a,b**

Entry	Temp.	Time	Yield <sup>a</sup>
<b>1</b>	rt	16 h	74%
<b>2</b>	0 °C	50 min	84%

<sup>a</sup> purified yields after column chromatography

### II.3.2 Hydrogenolysis

The alcohol **246** was submitted to catalytic hydrogenolysis in order to remove the three benzyl protection groups in a single reaction. Several conditions were examined, and the results are presented in Table 15. In each case, the yield is given for material obtained after filtration through a Celite pad or a PVDF membrane (HPLC filter, 0.22 μm pore size). The products were characterized by <sup>1</sup>H NMR in CD<sub>3</sub>OD at 293 K combined with HR-MS.

Table 15, Hydrogenolysis for the synthesis of (2*S*,3*S*)-AHPBA

Entry	Cat.	Equivalent of Cat. <sup>a</sup>	Solvent	Time (h)	Yield (%)	Product <sup>b</sup>
<b>1</b>	Pd(OH) <sub>2</sub> /C	10 %	MeOH	16	0	-
<b>2</b>	Pd/C	10 %	MeOH	2	95 <sup>c</sup>	<b>247</b>
<b>3</b>	Pd/C	10%	MeOH	16	n.d.	<b>1d, 243</b>
<b>4<sup>d</sup></b>	Pd/C	10%	MeOH	16	78 <sup>c</sup>	<b>1d, 243</b>
<b>5</b>	Pd/C + Pd(OH) <sub>2</sub> /C	5% + 5%	MeOH	16	81 <sup>c</sup>	<b>1d, 243</b>
<b>6</b>	Pd/C	10%	<i>i</i> PrOH	24	81 <sup>e</sup>	<b>1d, 247</b>
<b>7</b>	Pd/C	10%	EtOAc	24	95 <sup>e</sup>	<b>1d</b>

<sup>a</sup> wt% to the weight of starting material<sup>b</sup> identified by <sup>1</sup>H NMR analysis combined with HR-MS<sup>c</sup> crude yield after filtration through a Celite pad, calculated from the expected mass of **1d**<sup>d</sup> 3 eq. of HCl were added<sup>e</sup> crude yields after filtration through PVDF membrane, calculated from the expected mass of **1d**

The hydrogenolysis of compound **246** was first examined using the optimized conditions developed for the hydrogenolysis of *N,N*-dibenzyl-(2*S*,3*S*)-AHPBA methyl ester **232** (see II.2.1). Alcohol **232** was treated with 10% Pearlman's catalyst and 1 bar hydrogen in methanol for 16 hours. The reactants were completely converted (entry **1**). However, efforts to identify the composition of the complex mixture by <sup>1</sup>H NMR spectroscopy or mass spectrometry were unfruitful.

The hydrogenolysis was then examined using 10% Pd/C palladium on carbon as the catalyst. Reaction in methanol for 2 hours gave principally *N*-Bn-(2*S*,3*S*)-AHPBA **247** in 95% crude yield (entry **2**). Extending the reaction time to 16 hours, (2*S*,3*S*)-AHPBA **1d** and its methyl ester **243** were obtained as a messy mixture (entry **3**). By conducting the reaction in methanol in the presence of 3 eq. of HCl for 16 hours, we obtained the same mixture **1d** and **243** in 78% crude mass yield. The separation of these compounds was not feasible due to their high polarities (entry **4**).

Hydrogenolysis was assessed in the presence of a catalyst mixture,<sup>215</sup> comprising 5% Pd/C and 5% Pd(OH)<sub>2</sub>/C in methanol for 16 hours. Once again, (2*S*,3*S*)-AHPBA **1d** and its methyl ester **243** were obtained as a mixture (entry **5**).

We turned our attention to the use of other solvents in order to avoid the formation of the methyl ester **243**, and possibly other secondary products; indeed, catalytic hydrogenations in methanol have been known to give *N*-methylated products **248**, which we cannot exclude from some of the product mixtures described above.<sup>216</sup> Hydrogenolysis of compound **246** in isopropanol in the presence of 10% Pd/C for 24 hours gave (2*S*,3*S*)-AHPBA **1d** and *N*-Bn-(2*S*,3*S*)-AHPBA **247** as a mixture in 81% crude yield (entry **6**). When the same reaction was carried out in ethyl acetate, (2*S*,3*S*)-AHPBA **1d** was obtained as the only product in 95% yield (entry **7**).

The stereochemical purity of (2*S*,3*S*)-AHPBA **1d** obtained in this way was confirmed by comparing the optical rotation and melting point data ( $[\alpha]_D^{23} = -5.6$  (c 0.1, 1M HCl), Mp = 196 °C (dec.)) with those described in the literature ( $[\alpha]_D^{20} = -5.5$  (c 0.1, 1M HCl), Mp = 195 °C (dec.)).<sup>217</sup>

## II.4 Discussion

A panel of alcohols was employed in the MAC reaction with *N,N*-dibenzyl-L-phenylalaninal **L-13**, and H-MAC-TBS **148g**. Primary alcohols give the highest yields, although the yields decrease considerably with increased steric bulk. Secondary alcohols represent the limit of the substrate scope providing the MAC reaction products in prohibitively poor yields. The dr remains constant at around 10:90 in favor of the *anti* diastereomer in all cases, indicating that diastereoselectivity is independent of the nature of the alcohol; this is in agreement with the proposed MAC reaction mechanism.

These oxyhomologation reactions provide a rapid access to a selection of ester derivatives of *N,O*-orthogonally protected (2*S*,3*S*)-AHPBA; some of which bear reactive motifs (*e.g.*, allyl and propargyl) that appear amenable to subsequent functionalization. We used three of the esters in which the alkyl fragment is considered as a protecting group (*i.e.*, methyl, ethyl and benzyl) to prepare specific (2*S*,3*S*)-AHPBA derivatives in a single enantiomer form. In each case, the selective removal of the silyl ether protecting group turned out to be a key step, since this deprotection appeared to operate only on the

major *anti* component of the MAC product mixture. This unexpected but welcome result efficiently provided the corresponding deprotected alcohol in the *anti* configuration only. The origins of this diastereoselective deprotection are not known; further work would be required to probe its origins.

Starting from the MAC products **229a,b** and **233a,b**, we achieved the efficient synthesis of (2*S*,3*S*)-AHPBA methyl **243** and ethyl esters **244**, respectively. In this way, these derivatives were prepared in only three steps from *N,N*-dibenzyl-L-phenylalaninal **L-13**, in 58% and 48% overall yields, respectively. In the literature,<sup>53, 218, 219</sup> access to these building blocks has generally relied on acid-mediated esterification of (2*S*,3*S*)-AHPBA **1d** itself, which has to be prepared (or purchased commercially). We consider that the present approach may be a useful alternative to the classical access.

Starting from the MAC products **234a,b**, we achieved the efficient synthesis of the parent  $\alpha$ -hydroxy- $\beta$ -amino acid itself, (2*S*,3*S*)-AHPBA **1d**, in a single enantiomer form. This three-step synthesis from *N,N*-dibenzyl-L-phenylalaninal **L-13**, with an overall yield of 66%, constitutes one of the shortest and most efficient to date.

### III. MAC reactions with ammonia and amines

In the previous section, we showed that the MAC oxyhomologation reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** in the presence of alcohols could provide an expedient access to orthogonally protected ester derivatives of (2*S*,3*S*)-AHPBA. In this section, we focus on the corresponding reaction in the presence of nitrogen nucleophiles: firstly, in the form of ammonia, in order to determine the optimized reaction conditions, then using a panel of simple amines in order to evaluate the scope and limitations of the reaction with this category of nucleophile.

#### III.1. MAC reactions with ammonia

##### III.1.1 Optimization of the reaction conditions

*N,N*-Dibenzyl-L-phenylalaninal **L-13** (0.5 mmol) was reacted with H-MAC-TBS **148g** (2.4 eq.), DMAP and ammonia in Et<sub>2</sub>O, in a series of experiments in which the number of equivalents of ammonia and DMAP were varied, as well as the reaction time and temperature. The results are presented in Table **16**; yields are given for isolated material after column chromatography. All *syn/anti* dr were labeled as <2 : 98 according to the following research (see III.1.2) though only one diastereomer was observed in the <sup>1</sup>H NMR spectrum for all entries.

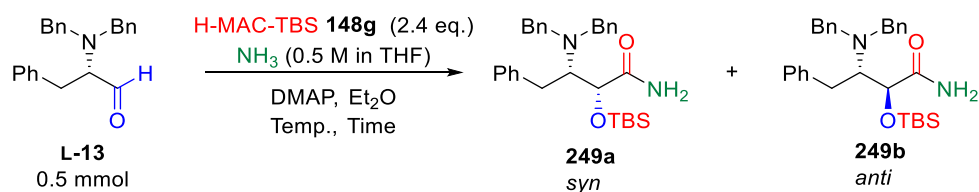


Table 16, MAC reactions with ammonia

Entry	NH <sub>3</sub> (eq.)	DMAP (eq.)	Temp. (°C)	Time (h)	Yield <sup>a</sup> (%)	dr <sup>b</sup> ( <i>syn/anti</i> )
1	3.0	2.0	0	16	86	<2 : 98
2	3.0	0	0	16	76	<2 : 98
3	1.2	2.0	0	16	89	<2 : 98
4	1.2	2.0	rt	1.5	71	<2 : 98

<sup>a</sup> isolated yield after column chromatography

<sup>b</sup> dr was calculated from <sup>1</sup>H-NMR (CDCl<sub>3</sub>, rt) on a concentrated purified sample (see III.1.2)

The first experiment was run under the conditions that had been optimized in the previous section for reactions with an alcohol. Freshly prepared aldehyde **L-13** was reacted with H-MAC-TBS **148g**, 3.0 eq. of ammonia, which was introduced in the form of a 0.5 M solution in THF, and 2.0 eq. of DMAP at 0 °C for 16 h (entry **1**). After work-up, only one MAC product diastereomer **249b** was detected in the crude product mixture and was isolated in 86% yield after chromatography. When the reaction was run in the absence of DMAP, the yield was lowered to 76% (entry **2**), whereas the use of only 1.2 eq. of ammonia gave compound **249b** in an improved yield of 89% (entry **3**). A further experiment was conducted over a shorter period (1.5 hours), during which time all of the aldehyde **L-13** substrate was consumed, according to TLC monitoring; in this case, the MAC product **249b** was isolated in a reduced yield of 71% (entry **4**).

Remarkably, all of these reactions provided a crude product mixture within only one single diastereomer was detected in the <sup>1</sup>H NMR spectrum. The NMR analyses (CDCl<sub>3</sub>, rt) were performed on a 360 MHz instrument, for which we considered at this stage that the detection limit allowed us to deduce a dr <2 : 98 for these reactions (see III.1.2).

By analogy with the *anti* diastereoselectivity observed in MAC reactions of *N,N*-dibenzyl-L-phenylalaninal **L-13** with alcohols (see the previous section), we reasonably assumed that the adduct **249b** also had an *anti* configuration. Support for this was obtained from single crystal X-ray diffraction analysis of **249b**, which confirmed the *anti*-(2*S*,3*S*) configuration of this compound (Figure 25).

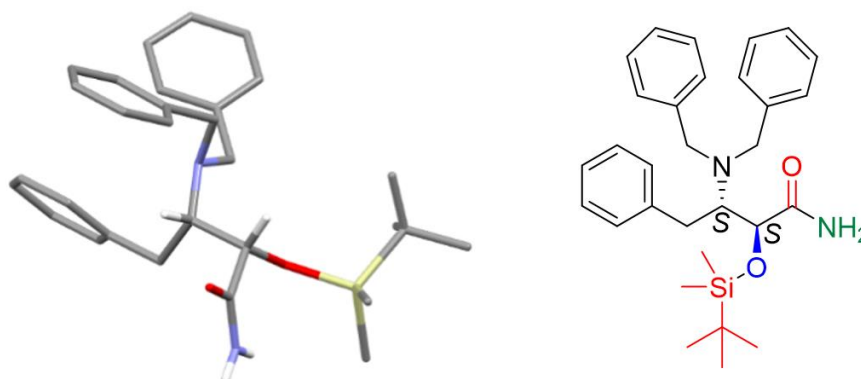
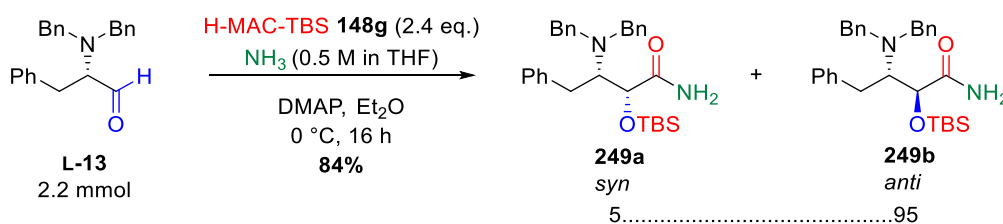


Figure 25, Single crystal X-ray diffraction analysis of compound **249b**

The best yield of the MAC reaction product **249b** was obtained using the conditions of Table 16, entry **3**. We conducted the same reaction on a preparative (gram) scale starting from 2.2 mmol of *N,N*-

dibenzyl-L-phenylalaninal **L-13**. After work-up and chromatography, an inseparable mixture of the MAC product diastereomers **249a,b** was obtained in 84% yield with 5:95 *syn/anti* dr under the best conditions (Scheme 85).



Scheme 85, Larger scale MAC reaction of *N,N*-dibenzyl-L-phenylalaninal and ammonia

### III.1.2 Determination of the diastereoselectivity

The experiments described above provided a high yield of the expected MAC oxyhomologation product **249b** in single diastereomeric form, as far as we could detect from the  $^1\text{H}$  NMR spectra, and we reasonably assumed that its configuration was *anti*. However, we considered it prudent to seek further support for these hypotheses and to permit an assessment of the detection limits of the dr evaluation technique. We therefore considered that it would be useful to obtain an authentic sample of the *syn* diastereomer **249a** either as a single compound or as a mixture of known composition with its *anti* diastereomer **249b**.

#### III.1.2.1 Ammonolysis of esters

In the first instance, we considered that a rapid access to a compound sample containing the *syn* diastereomer **249a** would be to perform the ammonolysis of one of our samples of diastereomeric mixture of esters obtained in the previous section by the oxyhomologation of *N,N*-dibenzyl-phenylalaninal **L-13**, in the presence of an alcohol. While this operation would be expected to give a mixture of diastereomeric amides **249a,b** which may not be separable by chromatography, this matter was of no consequence at this stage, since our requirement was to secure the spectroscopic signature of the *syn* diastereomer, regardless of the presence of the *anti* diastereomer in the sample. For this reason, we attempted the ammonolysis of diastereomeric mixtures of methyl esters **229a,b** and ethyl esters **233a,b** obtained from MAC reactions of methanol and ethanol, respectively. Since the substrates here were mixtures with a dr 8 : 92 (*syn/anti*), we anticipated that the ammonolysis products **249a,b** should have the same dr. Results are presented in Table 17.

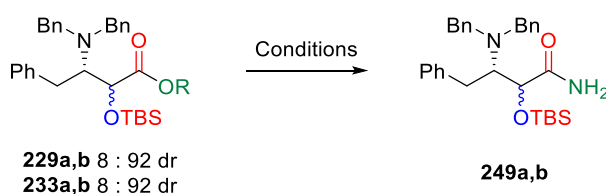


Table 17, Ammonolysis towards the *syn* diastereomer **249a**

Entry	R	Conditions	Yield <sup>a</sup> (%)
1	Et	3.5 eq. HCONH <sub>2</sub> , 1.0 eq. MeONa, DMF, 105 °C, 2 h	5
2	Me	10.0 eq. HCONH <sub>2</sub> , 3.0 eq. MeONa, DMF, 105 °C, 96 h	0
3	Me	NH <sub>3</sub> in MeOH, rt, 48 h	0
4	Me	NH <sub>3</sub> in H <sub>2</sub> O, 65 °C, 24 h	0

<sup>a</sup> isolated yield after column chromatography

The reaction of ethyl esters **233a,b** with 3.5 eq. of formamide and 1.0 eq. of sodium methoxide (5.4 M in MeOH) in DMF<sup>220</sup> at 105 °C for 2 hours gave the corresponding amide mixture **249a,b** in only 5% yield (entry **1**). The *anti* diastereomer **249b** was the main component, as expected, but the *syn* diastereomer **249a** was barely detectable by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub>, rt). We also noticed that the transesterification took place and gave a significant amount of methyl esters as major by-products; therefore, AHPBA methyl esters **229a,b** were used as the starting material in our subsequent experiments.

In the second experiment, methyl esters **229a,b** were reacted with a higher quantity of the reactants (10.0 eq. HCONH<sub>2</sub>, 3.0 eq. MeONa) in a longer reaction time (96 hours, until starting materials were consumed by TLC monitoring), but no desired amide mixture **249a,b** was detected in the <sup>1</sup>H NMR spectrum of the crude mixture (entry **2**).

In the next two experiments, ammonia was employed for the ammonolysis; first as a 7 M solution in methanol at room temperature (entry **3**),<sup>221</sup> then in the form of a 22 wt% ammonium hydroxide solution at 65 °C in a sealed tube (entry **4**).<sup>222</sup> However, no corresponding amide mixture **249a,b** was detected.

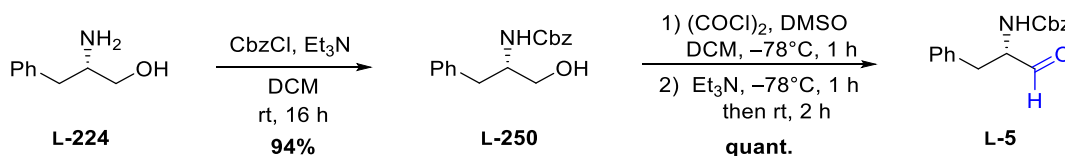
These efforts did not provide the anticipated rapid access to an authentic mixture of *syn* and *anti* amides **249a,b**, so we turned our attention to a longer approach.

### III.1.2.2 MAC oxyhomologation of *N*-Cbz-*L*-phenylalaninal in the presence of ammonia

As we presented in Chapter 2 II.2 as well as Nemoto's results in the Introduction part (See. Scheme **51**, **52**, **53**), the use of mono *N*-carbamate protected  $\alpha$ -amino aldehydes dominantly gave *syn* favored results with approximately 80:20 dr. Therefore, we will use this *syn* selective MAC reaction to obtain an authentic 80:20 *syn/anti* amide mixture, and next transform it into corresponding *N,N*-dibenzyl derivatives. *N*-Cbz-*L*-phenylalaninal **L-5** was chosen instead of *N*-Boc-*L*-phenylalaninal **L-15** for this MAC reaction. Because considering the following *N*-deprotection, the Cbz cleavage condition is milder than Boc, especially in the presence of TBS ether.

#### III.1.2.2.1 Preparation of *N*-Cbz-*L*-phenylalaninal

*N*-Cbz-*L*-phenylalaninal **L-5** was prepared in a two-step procedure (Scheme **86**).

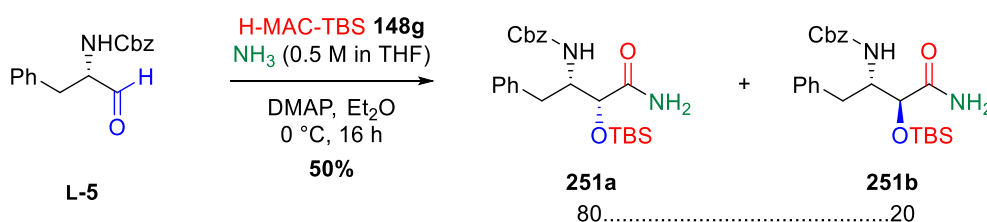
Scheme 86, Synthesis of *N*-Cbz-*L*-phenylalaninal

Commercially available *L*-phenylalaninol **L-224** was reacted with benzyl chloroformate (CbzCl) in the presence of triethylamine<sup>223</sup> to give *N*-Cbz-*L*-phenylalaninol **L-250** in 94% yield. The optical purity of alcohol **L-250** was confirmed by comparison of its optical rotation value ( $[\alpha]_{\text{D}}^{25} = -41.5$  (*c* 1.0, MeOH)) with the literature value<sup>224</sup> ( $[\alpha]_{\text{D}}^{30} = -41.5$  (*c* 1.0, MeOH)).

Swern oxidation of compound **L-250** afforded *N*-Cbz-*L*-phenylalaninal **L-5** in quantitative crude yield. Its low optical rotation value of  $[\alpha]_{\text{D}}^{25} = -3.7$  (*c* 1.0, MeOH) did not compare with the value given in the literature,  $[\alpha]_{\text{D}}^{23} = -52$  (*c* 1.0, MeOH),<sup>225</sup> suggesting extensive racemization.<sup>226</sup> However, considering that the enantiomeric purity of this aldehyde **L-5** is of no consequence for the present objective of conducting a *syn* diastereoselective MAC reaction, the near-racemic aldehyde **L-5** was used in the subsequent experiments.

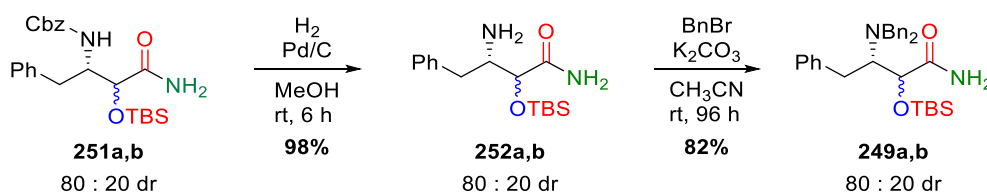
#### III.1.2.2.2 MAC reaction of *N*-Cbz-*L*-phenylalaninal

Freshly prepared *N*-Cbz-*L*-phenylalaninal **L-5** was reacted with 2.4 eq. of H-MAC-TBS **148g**, 1.2 eq of ammonia, and 2.0 eq. of DMAP, using the conditions that had been used for the MAC reaction of *N,N*-dibenzyl-*L*-phenylalaninal **L-13** (see III.1.1). After work-up, a 80:20 *syn/anti* dr was calculated from the <sup>1</sup>H NMR spectrum on the base of the crude product, by integration of PhCH<sub>2</sub>CH signals of each diastereomer; this selectivity was expected based on Nemoto's previous work.<sup>169</sup> Column chromatography gave the desired MAC products **251a,b** in 50% yield (Scheme 87).

Scheme 87, MAC reaction of *N*-Cbz-*L*-phenylalaninal with ammonia

#### III.1.2.2.3 Transformation of the *N*-protecting group suite

The *N*-Cbz-derived MAC product mixture **251a,b** (dr 80:20, *syn/anti*) was transformed into the *N,N*-dibenzyl protected MAC product mixture **249a,b** in two steps (Scheme 88).

Scheme 88, Transformation of the *N*-protective groups



Cleavage of the benzyl carbamate was achieved by hydrogenolysis in the presence of palladium on carbon in methanol at room temperature for 6 hours to give amines **252a,b** in 98% yield. The dr of 80:20 was calculated from the  $^1\text{H}$  NMR spectrum of the crude product by integrating the  $\text{Me}_2\text{Si}$  signals of each diastereomer. The major *syn* compound showed two singlets at 0.17 ppm and 0.19 ppm, while the minor *anti* compound showed two singlets at 0.10 ppm and 0.12 ppm.

The primary amine function in the **252a,b** mixture was dibenzylated using 3.5 equivalents of benzyl bromide and potassium carbonate inspired by the literature.<sup>196</sup> After chromatography, the *N,N*-dibenzyl-*O*-TBS-AHPBA amides **249a,b** mixture was obtained in 82% yield. The *syn/anti* dr of 80:20 was calculated from the  $^1\text{H}$  NMR spectrum of the crude product by integration of *CHN* signal of each diastereomer.

#### III.1.2.2.4 NMR analysis

Two samples of amide mixtures **249a,b** were now in hand: the reference sample with a dr 80:20 (*syn/anti*) obtained starting from *N*-Cbz-phenylalaninal **L-5** according to the sequence of reactions described just above, and the highly stereo-enriched sample obtained by the MAC reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** with ammonia (see III.1.1), for which only the diastereomer **249b** had been detected by  $^1\text{H}$  NMR spectroscopy on a 360 MHz instrument and for which we provisionally suggested as having a dr <2 : 98 (*syn/anti*). These two samples were studied and compared by  $^1\text{H}$  NMR spectroscopy on a Bruker Avance II 600 MHz spectrometer. The superimposed spectra are shown in Figure 26.

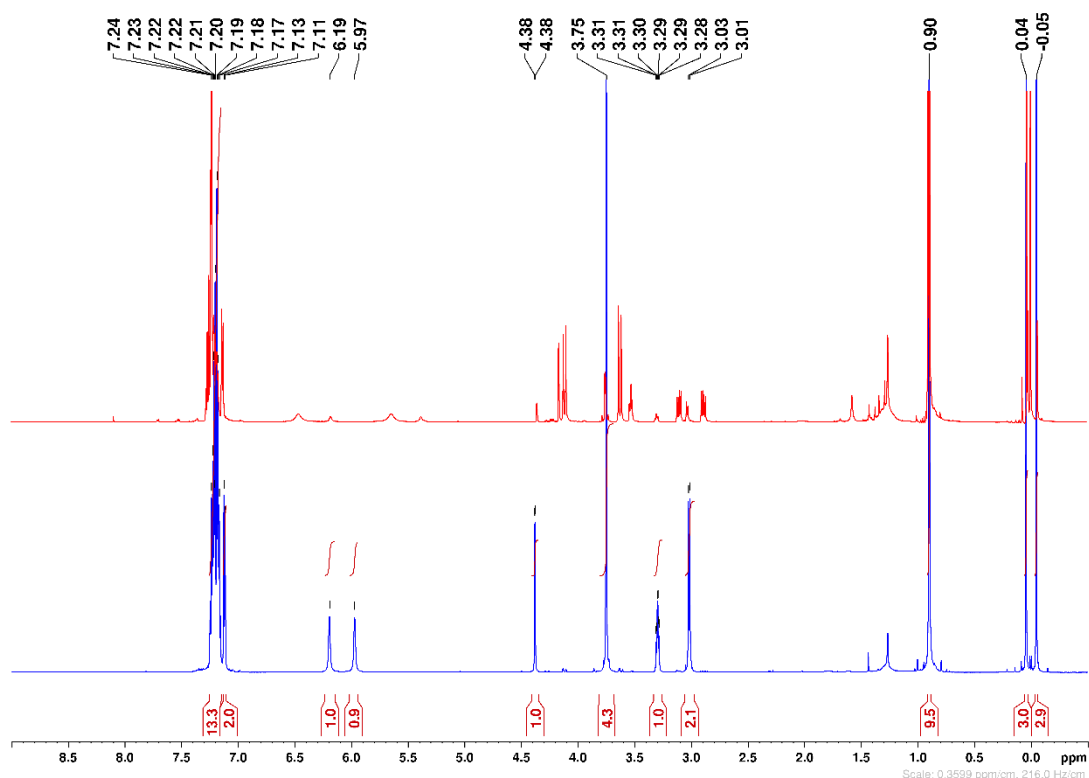


Figure 26,  $^1\text{H}$  NMR spectra comparison. (600 MHz,  $\text{CDCl}_3$ , 300 K;  $\delta = -0.50$  ppm to 8.00 ppm)  
Top: Spectrum of **249a,b** (dr 80 : 20); Bottom: Spectrum of **249a,b** (dr <2 : 98).

The first observation was that the diastereomer **249b** obtained in the MAC reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** with ammonia (see III.1.1) was confirmed as having an *anti* configuration. The second observation was that the minor *syn* diastereomer **249a** was now detected in the sample.

By integration of the CHN signal of each diastereomer, the dr was evaluated as 1:53.2 (Figure 27). Retrospectively, this justifies our proposal that the dr can be considered as <2 : 98 when the minor *syn* diastereomer is not detected in the routine 360 MHz <sup>1</sup>H NMR spectra.

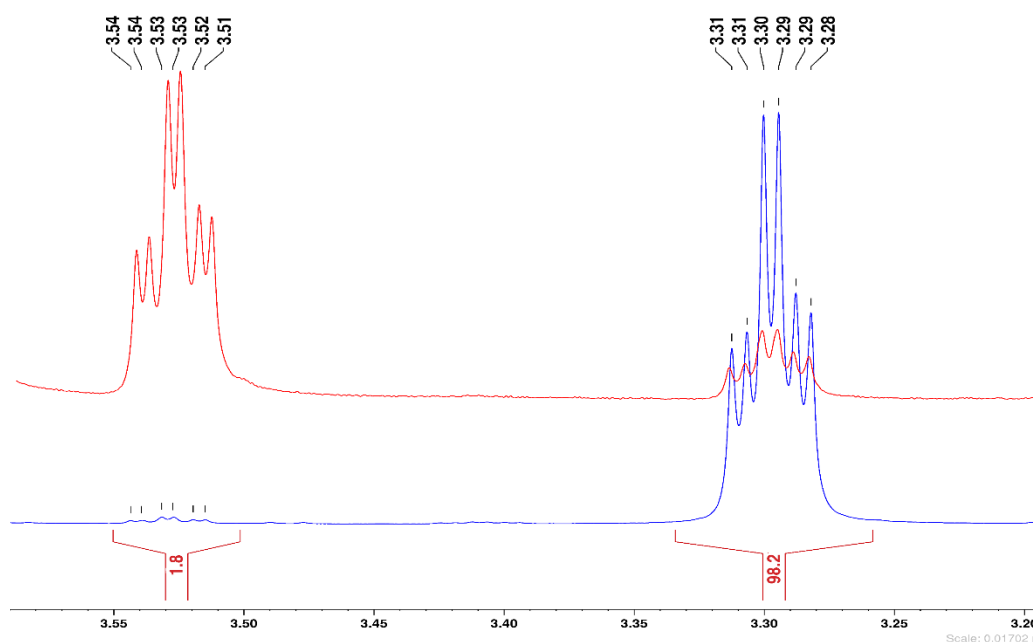


Figure 27, Integration of CHN signals in the <sup>1</sup>H NMR spectrum of **249a,b** (dr <2 : 98)  
(600 MHz, CDCl<sub>3</sub>, 300 K;  $\delta$  = 3.20 ppm to 3.60 ppm)

These analyses confirm the very high *anti* diastereoselectivity of the MAC reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** with ammonia.

### III.1.3 Determination of the enantiomeric purity

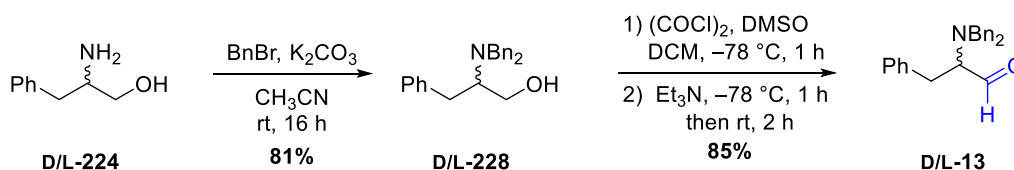
While the above study confirmed the very high *anti* diastereoselectivity of the MAC oxyhomologation of *N,N*-dibenzyl-L-phenylalaninal **L-13** using ammonia as the nucleophile, we wished to verify that no racemization of the  $\alpha$ -amino aldehyde substrate had occurred during the procedure. As we indicated previously, the optical purity of this material was checked carefully immediately before its use (see Chapter 2, IV.1). However, we were mindful of the susceptibility of  $\alpha$ -amino aldehydes to racemization in general,<sup>227</sup> and more particularly, we had indications that at least partial racemization had occurred in the preparation of *N*-Cbz-L-phenylalaninal **L-5** (see III.1.2.2.1) and possibly also in the preparation or use of *N*-Boc-*N*-Bn-L-phenylalaninal **L-31** (see Chapter 2, III.1).

In order to confirm that substrate racemization had not occurred, we decided to repeat the MAC oxyhomologation reaction using the racemic substrate, *N,N*-dibenzyl-D/L-phenylalaninal **D/L-13**, to obtain a reference sample of the racemic mixture of *anti* diastereomer ( $\pm$ )-**249b** (accompanied by

minute amounts of the racemic *syn* diastereomer (**±**)-**249a**) and then conduct a chiral HPLC analysis on the available samples.

### III.1.3.1 Preparation of *N,N*-dibenzyl-*D/L*-phenylalaninal

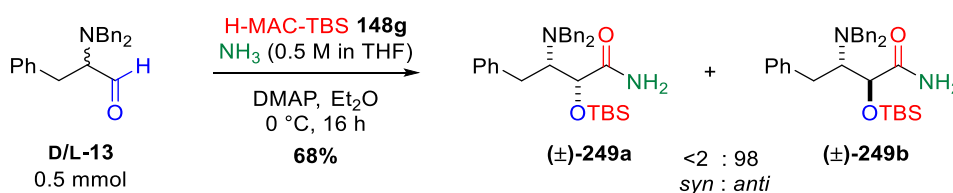
The racemic substrate *N,N*-dibenzyl-*D/L*-phenylalaninal **D/L-13** was prepared using the same procedure as that used to prepare the *N,N*-dibenzyl-*L*-phenylalaninal **L-13** (Scheme **89**). Commercially available *D/L*-phenylalaninol **D/L-224** was treated with benzyl bromide and potassium carbonate to give *N,N*-dibenzyl-*D/L*-phenylalaninol **D/L-228** in 81% yield.<sup>196</sup> Swern oxidation afforded *N,N*-dibenzyl-*D/L*-phenylalaninal **D/L-13** in 85% yield. The crude material was pure enough to be used directly in the subsequent MAC reaction.



Scheme **89**, Synthesis of *N,N*-dibenzyl-*D/L*-phenylalaninal

### III.1.3.2 MAC reaction of *N,N*-dibenzyl-*D/L*-phenylalaninal

The oxyhomologation of *N,N*-dibenzyl-*D/L*-phenylalaninal **D/L-13** was performed using the optimized condition established for the reaction of the enantiomerically pure substrate (see III.1.1). Freshly prepared *N,N*-dibenzyl-*D/L*-phenylalaninal **D/L-13** (0.5 mmol) was reacted with 2.4 eq. of H-MAC-TBS **148g**, 3.0 eq. of ammonia (0.5 M in THF), and 2.0 eq. of DMAP in Et<sub>2</sub>O at 0 °C for 16 hours. After work-up and chromatography, MAC products (**±**)-**249a,b** were obtained in 68% yield (Scheme **90**). As expected, only the *anti* diastereomer was observed in the crude <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, rt), and the *syn/anti* dr was considered as <2 : 98.



Scheme **90**, MAC reaction of *N,N*-dibenzyl-*D/L*-phenylalaninal with ammonia

### III.1.3.3 HPLC analysis

The MAC product mixtures from the reactions of *N,N*-dibenzyl-*L*-phenylalaninal **L-13**, and racemic *N,N*-dibenzyl-*D/L*-phenylalaninal **D/L-13** with ammonia were analyzed using HPLC with a chiral column. The conditions were as follows: Lux Amylose-2 (250 × 4.6 mm) column, hexane-EtOH (70:30, v/v) as the mobile phase, 1.0 mL/min flow rate, column temperature 30 °C, detection wavelength 206 nm.

The HPLC chromatogram of the racemic MAC products (**±**)-**249a,b** from *N,N*-dibenzyl-*D/L*-phenylalaninal **D/L-13** is shown in Figure **28**. One enantiomer appears at an elution time of 3.9 min,

while the other one appears at 4.9 min. These peaks had almost the same integral area, which confirms that the ratio of the two enantiomers [(2*S*,3*S*) and (2*R*,3*R*)] is 50:50 (er).

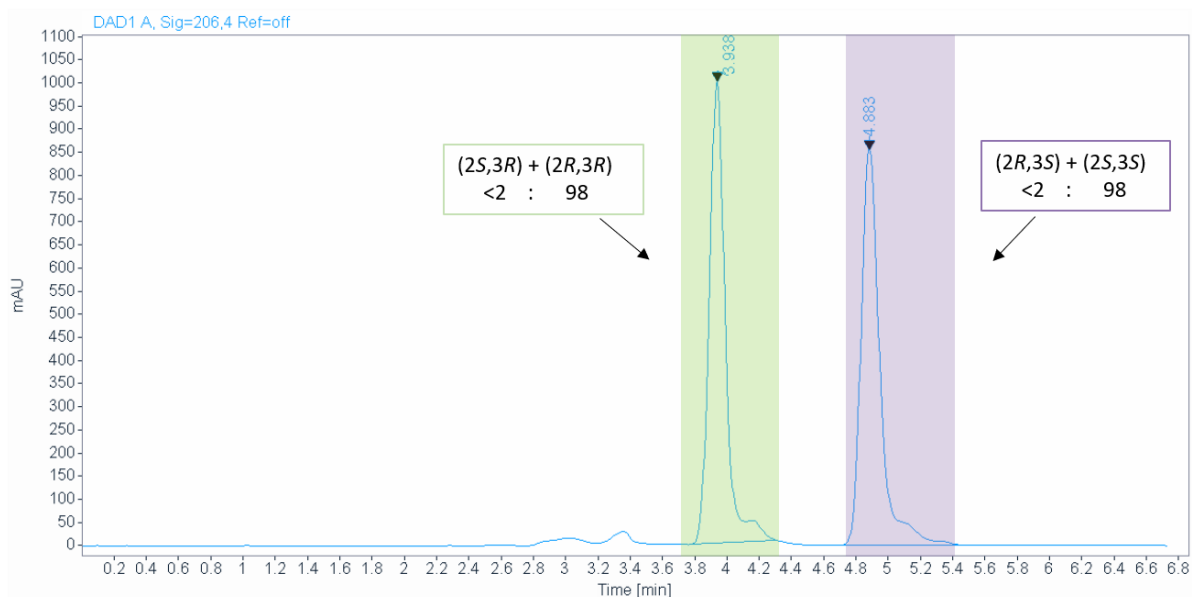


Figure 28, HPLC analysis result of the MAC products ( $\pm$ )-**249a,b** from D/L-phenylalaninal

The HPLC chromatogram of the oxyhomologated amide sample **249a,b** (dr <2 : 98) obtained from *N,N*-dibenzyl-L-phenylalaninal **L-13** is shown in Figure 29.

The main enantiomer appears as a peak at 4.9 min, while the other one shows only a tiny peak at 3.9 min. The two peak areas were 98.6% and 1.4%, respectively.

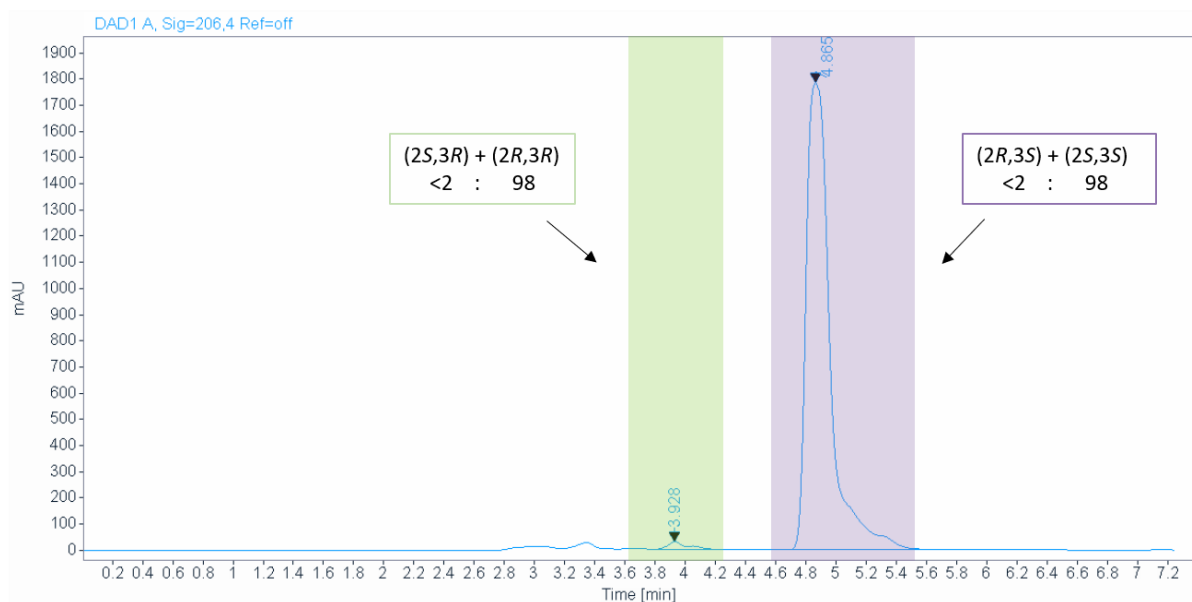


Figure 29, HPLC analysis result of the MAC products **249a,b** from L-phenylalaninal

This analysis indicated that for the MAC products **249a,b** obtained from *N,N*-dibenzyl-L-phenylalaninal **L-13**, the ratio of the two enantiomers [(2*S*,3*S*) and (2*R*,3*R*)] is 98.6 : 1.4. So the enantiomeric excess (ee) of the MAC product **249b** was assigned as 97.2%.

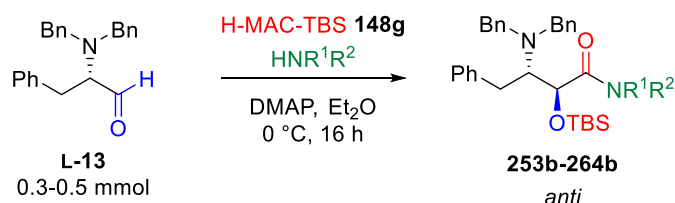
### III.1.4 Discussion

In this section, we examined the prototype MAC oxyhomologation of our selected *anti*-promoting electrophilic substrate with the simplest nitrogen nucleophile. The reaction between *N,N*-dibenzyl-L-phenylalaninal **L-13**, H-MAC-TBS **148g** and ammonia proceeded with very high diastereoselectivity (dr <2 : 98, *syn/anti*) to give the *anti* product **249b** in 89% yield in optimized conditions. The high enantiomeric purity of **249b** was also established (ee > 97%), confirming that no erosion of the inherent enantiomeric composition of the non-racemic substrate had occurred in the MAC methodology, which is consistent with the observations of Nemoto<sup>169</sup> and Aitken<sup>170</sup>. All of these results were encouraging for the pursuit of our studies using other amine nucleophiles.

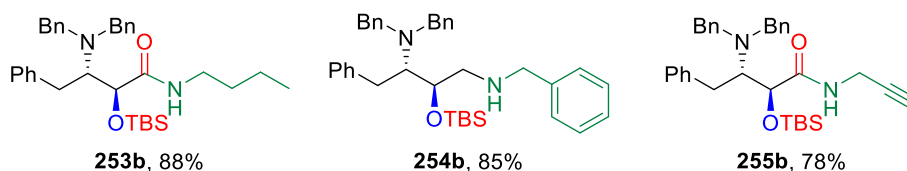
## III.2 Amine substrate scope and limitations

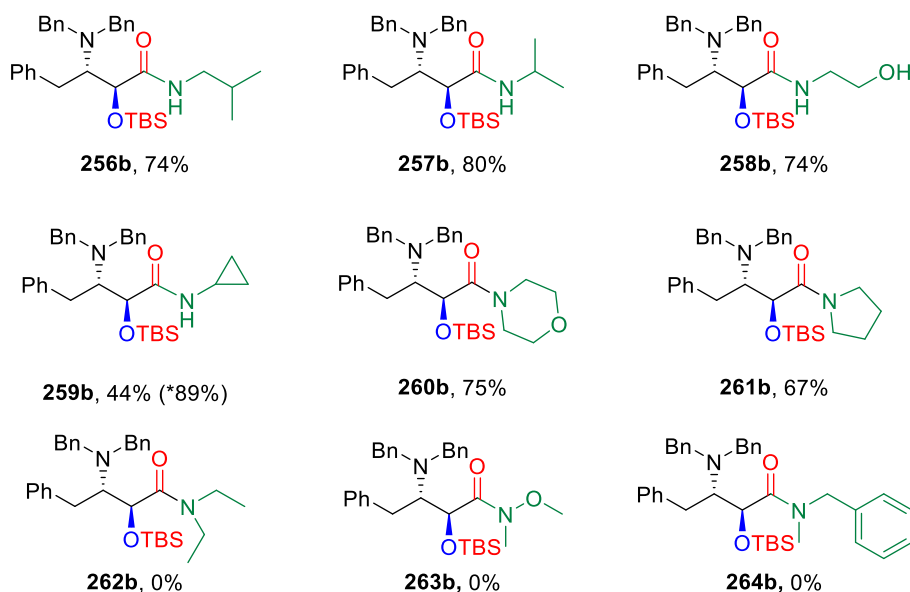
### III.2.1 Aliphatic amines

Based on the optimized conditions established in the previous section, *N,N*-dibenzyl-L-phenylalaninal **L-13** was reacted on a 0.5 mmol scale with 2.4 eq. of H-MAC-TBS **148g**, 2.0 eq. of DMAP and 1.2 eq. of a selected amine in Et<sub>2</sub>O at 0 °C for 16 hours. The MAC oxyhomologation amide products were obtained after the standard work-up and column chromatography; yields are given for isolated material after chromatography (Scheme 91). In each case, we observed only one diastereomer in the 360 MHz <sup>1</sup>H NMR spectrum of the crude product before chromatography; the diastereomeric ratios (dr) were therefore considered to be <2 : 98 (*syn/anti*), in analogy with the results obtained when ammonia had been used as the nucleophile (see III.1.2). It was also reasonably assumed that each of these *anti* diastereomers was of high enantiomeric purity, in analogy with the results obtained when ammonia had been used as the nucleophile (see III.1.3).



Scheme 91, MAC reactions of **L-13** with various amines





The linear primary amines *n*-butylamine, benzylamine, and propargyl amine gave the corresponding MAC amide products (**253b**, **254b** and **255b**) in good to very good yields. When the branched-chain primary amines isobutylamine and isopropylamine were used, the yields for **256b** and **257b** were only slightly lower (74% and 80%, respectively). When 2-aminoethanol was employed as the nucleophile, the reaction gave the amide **258b** in 74% yield, and no evidence for the formation of an ester compound, attesting to the chemoselectivity of the nucleophile (amine > alcohol) as would be expected.

When cyclopropylamine was used as the nucleophile, the reaction was more complicated. Under the standard conditions, the MAC amide product **259b** was isolated in only 44% yield, and many by-products were formed. Based on the HRMS analysis of the crude product mixture, we suspected that one of these by-products might be the  $\alpha$ -amino nitrile **265** (Figure 30), although we could not isolate a sample of this compound. We modified the reaction conditions on the premise that by delaying the addition of cyclopropylamine, we might suppress the formation of the  $\alpha$ -amino nitrile and other unwanted products. A solution of *N,N*-dibenzyl-L-phenylalaninal **L-13** and H-MAC-TBS **148g** in Et<sub>2</sub>O was treated with DMAP and stirred for 15 minutes at 0 °C, then cyclopropylamine was added, and the mixture was stirred for 16 hours at 0 °C. Using these modified conditions, MAC product **259b** was obtained in 89% yield.

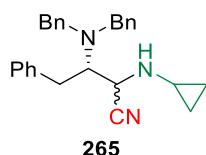


Figure 30,  $\alpha$ -Amino nitrile **265** generated from the MAC reaction with cyclopropylamine

In addition, a single crystal of the MAC product **259b** was obtained by slow diffusion of pentane into an Et<sub>2</sub>O solution of **259b** at ambient temperature, which was suitable for X-ray diffraction analysis. Result confirmed the *anti*-(2*S*,3*S*) configuration of this diastereomer (Figure 31). Meanwhile, the <sup>1</sup>H NMR spectrum of this crystal (CDCl<sub>3</sub>, rt) was consistent, and only one diastereomer was observed.

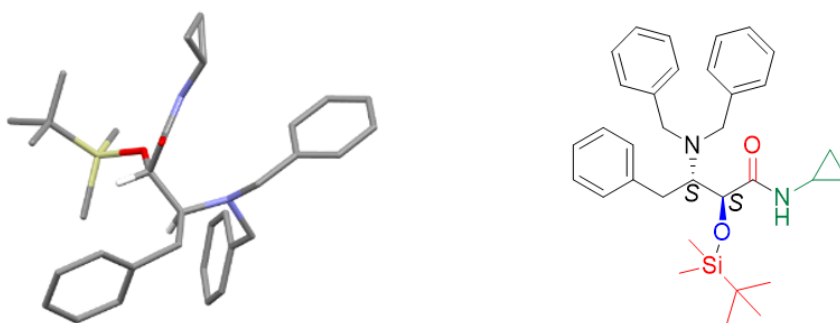


Figure 31, Single crystal X-ray diffraction analysis of compound **259b**

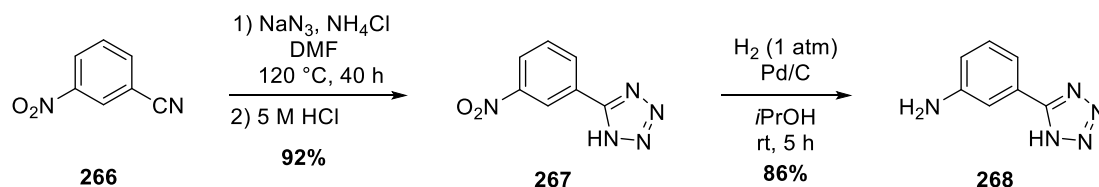
Two cyclic secondary amines, morpholine and pyrrolidine, were examined and the corresponding amides were obtained in good yields (75% for **260b**; 67% for **261b**). The  $^1\text{H}$  NMR spectra of these amides in  $\text{CDCl}_3$  at room temperature were complicated by rotamerism, so the spectra were recorded in  $\text{DMSO-}d_6$  at 360 K in order to confirm the presence of only one diastereomer. Three other unconstrained secondary amines – diethylamine, *N,O*-dimethylhydroxylamine and *N*-methylbenzylamine – were also examined. However, in stark contrast to the success observed with morpholine and pyrrolidine, these reactions failed to produce any of the anticipated MAC amide products **262b-264b**.

### III.2.2 Anilines

As we noted in the Introduction, one therapeutically interesting molecule that includes a (2*S*,3*S*)-AHPBA residue is KMI-1027.<sup>35</sup> We considered that a new, short synthesis of this compound might begin with the oxyhomologation reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** using 3-(1*H*-tetrazol-5-yl)aniline as the nucleophile.

#### III.2.2.1 Synthesis of the 3-(1*H*-tetrazol-5-yl)aniline

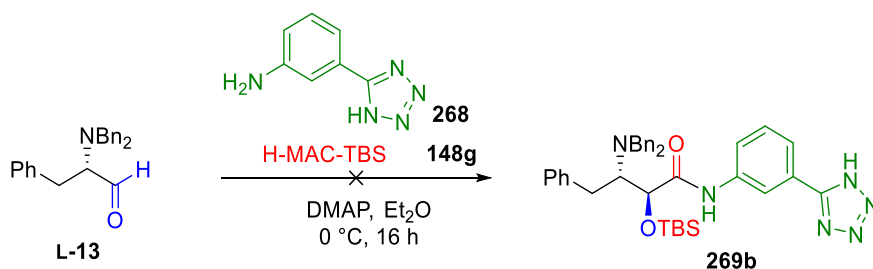
3-(1*H*-Tetrazol-5-yl)aniline **268** was synthesized in two steps, according to the literature.<sup>228</sup> (Scheme 92). Commercially available 3-nitrobenzonitrile **266** was mixed with sodium azide and ammonium chloride in DMF to perform a click azide–nitrile cycloaddition. After acidification, tetrazole **267** was obtained in 92% yield. Hydrogenolysis in the presence of palladium on carbon provided 3-(1*H*-tetrazol-5-yl)aniline **268** in 86% yield. The quality of the title compound **268** was confirmed by comparing its melting point (Mp = 201-203 °C) with the literature data<sup>229</sup> (Mp = 199-200 °C).



Scheme 92, Synthesis of 3-(1*H*-tetrazol-5-yl)aniline **268**

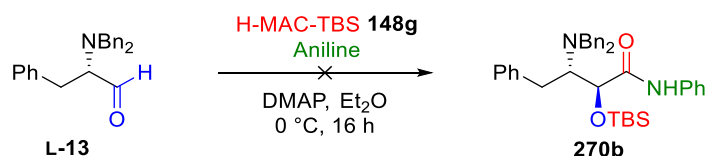
## III.2.2.2 MAC reaction with 3-(1H-tetrazol-5-yl)aniline

Using the optimized conditions for MAC reactions with ammonia and amines, *N,N*-dibenzyl-L-phenylalaninal **L-13** was reacted on a 0.5 mmol scale with 2.4 eq. of H-MAC-TBS **148g**, 2.0 eq. of DMAP and 1.2 eq. of 3-(1H-tetrazol-5-yl)aniline **268** in Et<sub>2</sub>O at 0 °C for 16 hours. However, no trace of the corresponding MAC product **269b** was detected in the <sup>1</sup>H NMR spectrum of the crude product mixture (Scheme 93).

Scheme 93, MAC reaction of **L-13** with 3-(1H-tetrazol-5-yl)aniline

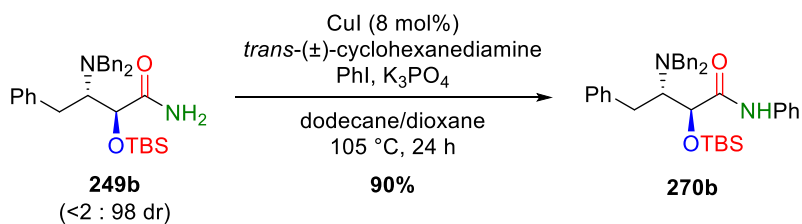
## III.2.2.3 MAC reaction with aniline

In light of the failure of 3-(1H-tetrazol-5-yl)aniline **268** to behave as a nucleophilic partner in a MAC reaction, we examine the reactivity of aniline itself (Scheme 94). Under the usual reaction conditions, neither a MAC anilide product **270b** nor any other identifiable product could be identified in the product mixture.

Scheme 94, MAC reaction of **L-13** with aniline

## III.2.2.4 Indirect access to the anilide

In order to check the chemical stability of the MAC anilide product **270b**, and thus exclude the hypothesis that the compound might have been degraded during its formation, we exploited a MAC reaction to prepare it in an indirect manner. Primary amide **249b** (dr <2 : 98) was obtained as described above in the reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** with ammonia (see III.1.1), and was arylated using the method of Buchwald.<sup>230</sup> The reaction of **249b** (dr <2 : 98) with phenyl iodide in the presence of catalytic copper(I) iodide and *trans*-(±)-cyclohexanediamine as ligand, gave the target anilide **270b** in 90% yield as a single stereomer (Scheme 95). This compound was indeed chemically stable.

Scheme 95, Synthesis of anilide MAC product **270b** through Buchwald arylation



### III.3 Discussion

Generally, the MAC oxyhomologation reaction profile using nitrogen nucleophiles resembled the observations made in the previous section using alcohols, with some notable improvements. In terms of chemical yield, the use of ammonia or unhindered primary amines led to the formation of the corresponding MAC amides efficiently. Secondary amines appeared to be at the limit of the substrate scope, presumably due to steric hindrance, whereby two test cases worked well, but three others failed. It is of note that Nemoto found that both diethylamine and morpholine gave efficient MAC reactions with the less bulky electrophilic partner 4-tolualdehyde.<sup>163</sup> Anilines also seem to be out with the substrate scope here. These results could reasonably be explained by their reduced nucleophilicity compared with amines, although steric effects cannot be excluded. Indeed, Nemoto described a successful MAC reaction using aniline as the nucleophile, again with the less bulky electrophilic partner 4-tolualdehyde.<sup>163</sup>

The most salient result in this study was the diastereoselectivity of the oxyhomologation reactions of *N,N*-dibenzyl-L-phenylalaninal **L-13** with amines. In all cases, the reaction effectively provided only the *anti* diastereomer, and we confirmed spectroscopically that the *syn/anti* dr was <2 : 98. These results confirmed the high diastereoselectivity control brought by the use of the *N,N*-dibenzyl protecting group suite, and is an improvement on the selectivity observed in the previous section for alcohols, for which the *syn/anti* dr was generally around 10:90. This welcome improvement in the *anti* diastereoselectivity (going from alcohol to amine) is not easy to explain; according to the proposed MAC reaction mechanism, the nucleophile should attack the intermediate acyl cyanide in the last step, after the *syn/anti* ratio has been fixed, meaning that no difference in the diastereoselectivity is expected as a function of the type of nucleophile.

Another interesting case was the MAC reaction of cyclopropylamine. Follow the general reaction conditions, the side product  $\alpha$ -amino nitrile **265** was observed by HR-MS in the crude mixture, which could be suppressed by delaying the addition of the nucleophile. A mechanism for the formation of such a side product will be presented subsequently (See IV.3.4).

## IV. MAC reactions with $\alpha$ -amino esters

In the previous section, we showed that the MAC oxyhomologation reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** in the presence of unhindered amines could provide a panel of orthogonally protected amide derivatives of (2*S*,3*S*)-AHPBA with good yields and very high *anti* diastereoselectivity. On this basis, we considered that using an  $\alpha$ -amino ester as a nucleophile should be productive and lead directly to dipeptide derivatives of (2*S*,3*S*)-AHPBA in what would constitute a *one-pot* oxyhomologation/coupling process.

This section reports our findings on this proposition.

IV.1 Preparation of  $\alpha$ -amino methyl esters

A library of  $\alpha$ -amino acid methyl esters was selected for study, featuring various substitution patterns at the  $\alpha$ -carbon (Figure 32). In addition to the unsubstituted methyl glycinate **271**, several mono-substituted esters (**272-279**) bearing alkyl, aryl or benzylic  $\alpha$ -substituents were envisaged, all in single enantiomer form. The cyclic derivative methyl L-prolinate **282** was included, as well as the methyl esters (**280** and **281**) of the  $\alpha,\alpha$ -disubstituted residues 2-aminoisobutyric acid (Aib) and 1-aminocyclopropanecarboxylic acid (Acc).

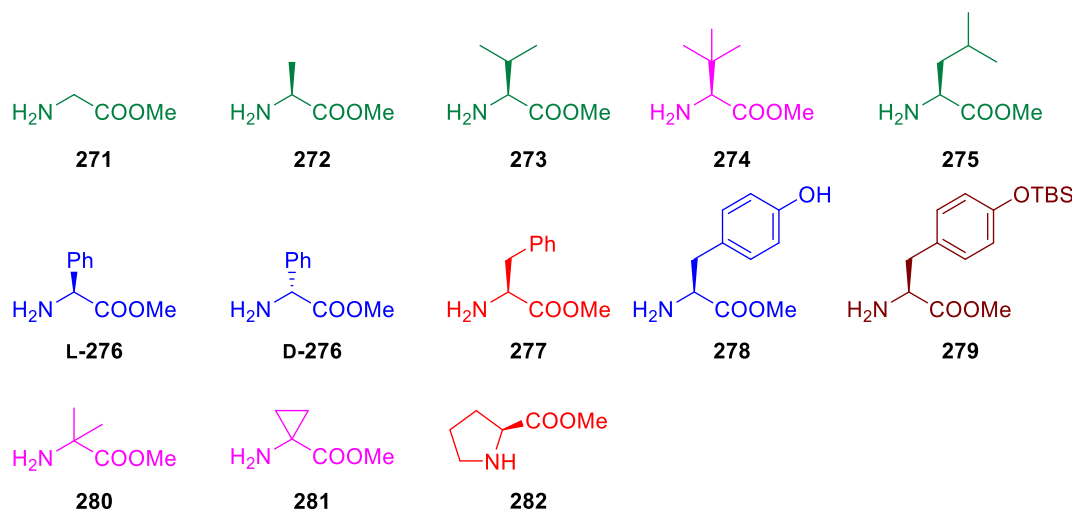
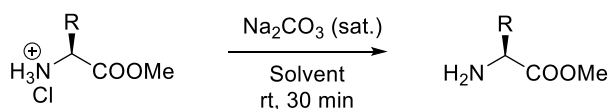


Figure 32. Selected methyl  $\alpha$ -amino esters

The methyl L-phenylglycinate (H-L-Phg-OMe) **L-276**, methyl D-phenylglycinate (H-D-Phg-OMe) **D-276** and methyl tyrosinate (H-Tyr-OMe) **278** were used directly as hydrochloride salts, which were commercially available.

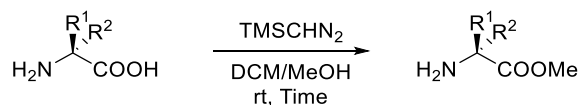
Methyl glycinate (H-Gly-OMe) **271**, methyl L-alaninate (H-Ala-OMe) **272**, methyl L-valinate (H-Val-OMe) **273** and methyl L-leucinate (H-Leu-OMe) **275** were prepared from their commercially available hydrochloride salts inspired by a literature procedure (Table 18).<sup>231</sup> Those hydrochloride salts were treated with a saturated sodium carbonate aqueous solution and dichloromethane (1:1, v/v), stirred for half an hour, then extracted by DCM or diethyl ether, and carefully concentrated under reduced pressure. The  $\alpha$ -amino esters H-Gly-OMe **271**, H-Ala-OMe **272**, H-Val-OMe **273** and H-Leu-OMe **275** were obtained in 20%, 31%, 67%, and 46% yields, respectively. The optical purity of H-Ala-OMe **272** was confirmed by comparing its optical rotation value ( $[\alpha]_D^{28} = +6.1$  ( $c$  1.0,  $\text{CH}_3\text{OH}$ )) with the data described in the literature<sup>232</sup> ( $[\alpha]_D^{20} = +7.0$  ( $c$  1.0,  $\text{CH}_3\text{OH}$ )). The optical rotation of H-Val-OMe **273** was higher than the literature ( $[\alpha]_D^{24} = +31.7$  ( $c$  0.8,  $\text{CHCl}_3$ ), lit.<sup>233</sup>  $[\alpha]_D^{20} = +11.7$  ( $c$  0.8,  $\text{CHCl}_3$ )); and the literature for H-Leu-OMe **275** was not comparable ( $[\alpha]_D^{25} = +13.5$  ( $c$  1.0,  $\text{CHCl}_3$ ), lit.<sup>234</sup>  $[\alpha]_D^{23} = +15.3$  (concentration and solvent not given)). However, we believe this method should not have consequences on the  $\alpha$ -chiral center, and samples of H-Val-OMe **273** and H-Leu-OMe **275** were continued to be used in the next MAC reactions.

Table 18, Preparation of free  $\alpha$ -amino esters from their hydrochlorides

Entry	Product	R	Solvent	Yield <sup>a</sup> (%)
1	H-Gly-OMe <b>271</b>	H	DCM	20
2	H-Ala-OMe <b>272</b>	Me	Et <sub>2</sub> O	31
3	H-Val-OMe <b>273</b>	<i>i</i> Pr	DCM	67
4	H-Leu-OMe <b>275</b>	<i>i</i> Bu	Et <sub>2</sub> O	46

<sup>a</sup> crude yield

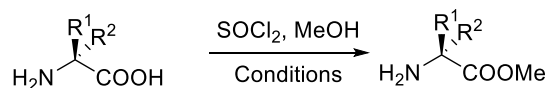
Methyl *L-tert*-leucinate (H-Tle-OMe) **274**, methyl 2-aminoisobutyrate (H-Aib-OMe) **280** and methyl 1-aminocyclopropanecarboxylate methyl ester (H-Acc-OMe) **281** were prepared by treatment of the free  $\alpha$ -amino acid with trimethylsilyldiazomethane (TMSCHN<sub>2</sub>) in a dichloromethane-methanol mixture at room temperature (Table 19).<sup>235</sup> The  $\alpha$ -amino esters H-Tle-OMe **274**, H-Aib-OMe **280** and H-Acc-OMe **281** were obtained in 81%, 64% and 63% yields, respectively. Meanwhile, there is no optical data about H-Tle-OMe **274**.

Table 19, Preparation of  $\alpha$ -amino esters using TMSCHN<sub>2</sub>

Entry	Product	R <sup>1</sup>	R <sup>2</sup>	Time (min)	Yield <sup>a</sup>
1	H-Tle-OMe <b>274</b>	<i>t</i> -Bu	H	15	81%
2	H-Aib-OMe <b>280</b>	Me	Me	60	64%
3	H-Acc-OMe <b>281</b>	CH <sub>2</sub> -CH <sub>2</sub>		20	63%

<sup>a</sup> crude yield

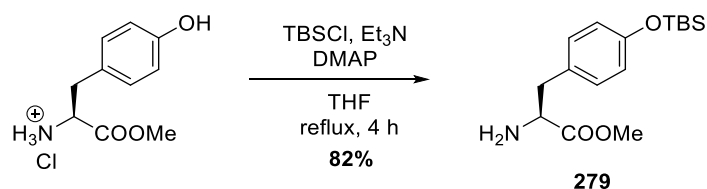
Methyl *L*-phenylalaninate (H-Phe-OMe) **277** and methyl *L*-prolinate (H-Pro-OMe) **282** were prepared using a literature method using thionyl chloride (Table 20).<sup>236</sup> *L*-Phenylalanine was treated with thionyl chloride in methanol at 0 °C, and the reaction was refluxed for 5 hours. After work-up and chromatography, H-Phe-OMe **277** was obtained in quantitative yield. The optical purity of H-Phe-OMe **277** was checked by comparing its optical rotation value ( $[\alpha]_{\text{D}}^{22} = +42.7$  (c 2.0, EtOH)) with the data that data in the literature ( $[\alpha]_{\text{D}}^{20} = +37.5$  (c 2.0, EtOH)). H-Pro-OMe **282** was prepared using a minor adaptation of the literature method.<sup>236</sup> *L*-Proline was treated with thionyl chloride in methanol at 0 °C; two drops of DMF were added,<sup>237</sup> and the reaction was stirred for three days at room temperature. After work-up and chromatography, H-Pro-OMe **282** was obtained in 60% yield. The optical rotation was checked ( $[\alpha]_{\text{D}}^{26} = -25.5$  (c 1.0, CHCl<sub>3</sub>)), which was much lower than those described in the literature ( $[\alpha]_{\text{D}}^{25} = -51.8$  (c 1.0, CHCl<sub>3</sub>)).<sup>238</sup>

Table 20, Preparation of  $\alpha$ -amino esters using thionyl chloride

Entry	Conditions	Product	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>a</sup>
1	Reflux, 5 h	H-Phe-OMe <b>277</b>	Bn	H	quant.
2	DMF (Cat.), rt, 72 h	H-Pro-OMe <b>282</b>	-	-	60%

<sup>a</sup> purified yield after column chromatography

Methyl *O*-TBS-L-tyrosinate (H-Tyr(TBS)-OMe) **279** was prepared by treatment of methyl L-tyrosinate hydrochloride with *tert*-butyldimethylsilyl chloride, triethylamine and a catalytic amount of 4-dimethylaminopyridine under reflux in tetrahydrofuran for 4 hours (Scheme 96).<sup>239</sup> After work-up and chromatography, H-Tyr(TBS)-OMe **279** was obtained in 82% yield. The optical purity was confirmed by comparing its optical rotation ( $[\alpha]_{\text{D}}^{25} = +8.4$  (c 1.0, CHCl<sub>3</sub>)) with those described in the literature ( $[\alpha]_{\text{D}}^{24} = +10.0$  (c 1.0, CHCl<sub>3</sub>)).<sup>240</sup>

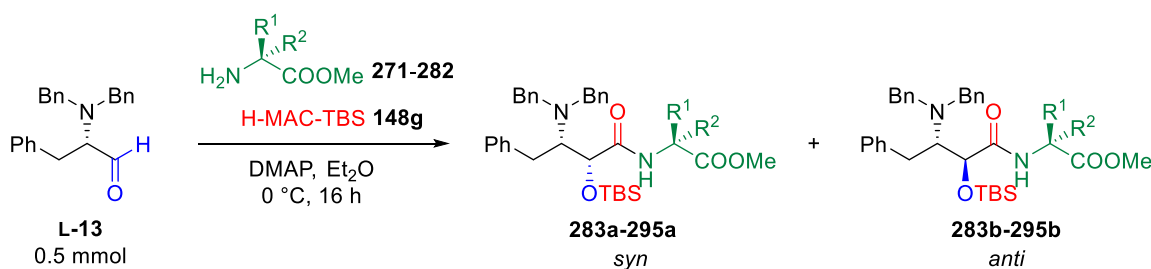
Scheme 96, Preparation of methyl *O*-TBS-L-tyrosinate **279**

## IV.2 Substrate scope and limitations

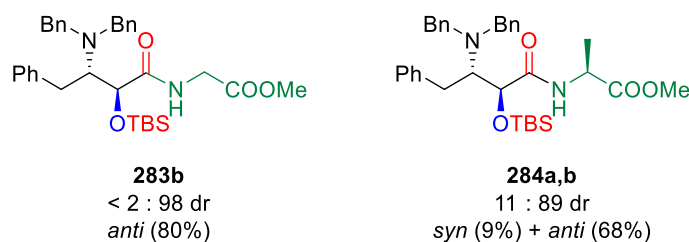
### IV.2.1 Results

Based on the optimized conditions established above (see III.1.1), *N,N*-dibenzyl-L-phenylalaninal **L-13** was reacted on a 0.5 mmol scale with a panel of  $\alpha$ -amino esters as nucleophiles (Scheme 97).

When the nucleophile was employed in free amine form, the mixture of *N,N*-dibenzyl-L-phenylalaninal **L-13** and 2.4 eq. of H-MAC-TBS **148g** in Et<sub>2</sub>O at 0 °C was treated successively with 1.2 eq. of  $\alpha$ -amino ester then 2.0 eq. of DMAP, followed by reaction for 16 hours at this temperature. Yields are given for isolated material after column chromatography. Diastereomeric ratios (dr) were calculated from the <sup>1</sup>H NMR spectra (CDCl<sub>3</sub>, rt) based on crude products (except for the MAC products **285a,b** from H-Val-OMe **273**) by integrating the Me<sub>2</sub>Si signals of each diastereomer. The major diastereomer was assigned an *anti* configuration for the newly formed AHPBA fragment, while the minor diastereomer was assigned a *syn* configuration of the same fragment, as we will explain in the following section (see IV.2.2).

Scheme 97, MAC reactions with various  $\alpha$ -amino esters

Methyl glycinate (H-Gly-OMe) **271** was examined first in the condition described above (Scheme 98). After workup, only one diastereomer was observed in the  $^1\text{H}$  NMR spectrum; the dr was therefore considered in line with the previous amide cases and was labeled as <2 : 98 (*syn/anti*). After chromatography, the MAC dipeptide **283b** was isolated in 80% yield. When methyl L-alaninate (H-Ala-OMe) **272** was used as the nucleophile, the dipeptide mixture **284a,b** was obtained with a *syn/anti* dr of 11:89 observed in the  $^1\text{H}$  NMR spectrum. Following chromatography, the *syn* product **284a** was isolated in 9% yield and the *anti* product **284b** was isolated in 68% yield.



Scheme 98, MAC products from H-Gly-OMe and H-Ala-OMe

When H-Val-OMe **273** was employed as the nucleophile, MAC products **285a,b** were isolated as an inseparable mixture in a 20:80 *syn/anti* dr, and the yield dramatically decreased to 47% (Table 21, entry 1).

We then modified the reaction conditions on the relief that by delaying the addition of  $\alpha$ -amino ester, we might suppress the formation of unwanted byproducts such as  $\alpha$ -amino nitriles (as in the case of cyclopropylamine, See Figure 30). A solution of *N,N*-dibenzyl-L-phenylalanyl-L-alanine **L-13** and H-MAC-TBS **148g** in  $\text{Et}_2\text{O}$  was treated with DMAP and stirred for 15 minutes at  $0\text{ }^\circ\text{C}$ , then H-Val-OMe **273** was added and the mixture was stirred for 16 hours. Under those conditions, **285a,b** was obtained in 74% yield, with an identical 20:80 *syn/anti* dr (entry 2). As a result, the modified reaction condition was adopted in the subsequent experiments for other  $\alpha$ -amino esters.

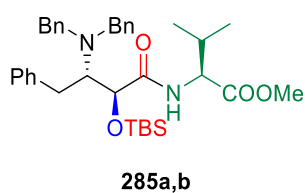


Table 21, MAC products from H-Val-OMe

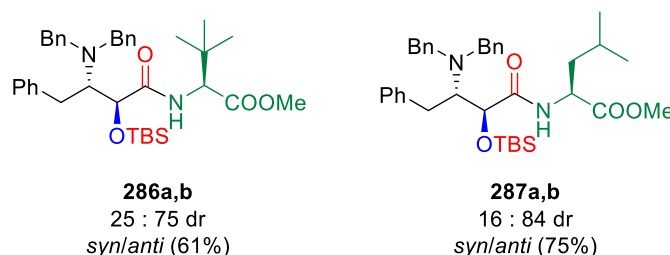
Entry	Conditions	Yield <sup>a</sup> (%)	dr <sup>b</sup> ( <i>syn/anti</i> )
1	General procedure (from H-Gly-OMe <b>271</b> )	47	20 : 80
2	2.0 eq. of DMAP were added first and stirred for 15 minutes at 0 °C, then H-Val-OMe <b>273</b> was added	74	20 : 80
3	3.2 eq. of DMAP were added first and stirred for 15 minutes, then H-Val-OMe·HCl <b>273·HCl</b> was added	72	18 : 82

<sup>a</sup> purified yield after column chromatography

<sup>b</sup> calculated from the <sup>1</sup>H NMR spectrum of the purified product

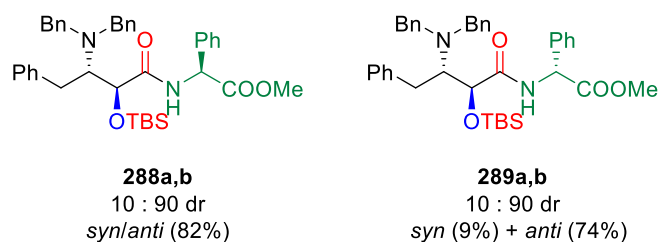
It is worth mentioning that the hydrochloride salt of H-Val-OMe could be directly used in the MAC reaction as the nucleophile. Using the above reaction condition from entry **2**, but employing 3.2 eq. of DMAP. Two diastereomers (dr 21:79) were observed in the crude mixture. Column chromatography provided an inseparable mixture of MAC products **285a,b** in 72% yield, which was similar to those obtained using the free  $\alpha$ -amino ester (74%).

When methyl L-*tert*-leucinate (H-Tle-OMe) **274** was used under the optimized condition cited from above (see Table **21**, entry **2**), an inseparable MAC products mixture **286a,b** was isolated after the column chromatography in 61% yield with a *syn/anti* dr of 25:75. In the same way, methyl L-leucinate (H-Leu-OMe) **275** provided a 16 : 84 mixture of **287a,b** in 75% yield after column chromatography (Scheme **99**).



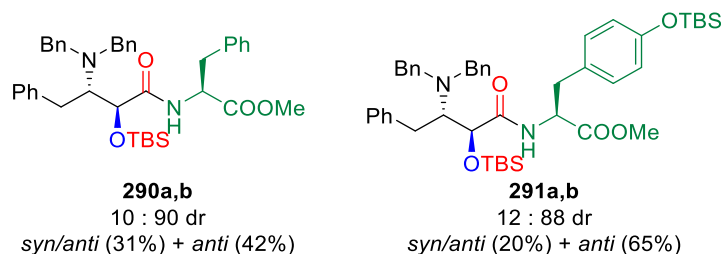
Scheme **99**, MAC products from H-Tle-OMe and H-Leu-OMe

For methyl L- and D- phenylglycinates **L-276** and **D-276**, given their high potential of racemization nature, we directly used their hydrochloride salts as nucleophiles. Under the condition described in Table **21**, entry **3**, the MAC reaction of H-L-Phg-OMe·HCl **L-276** gave dipeptides **288a,b** as an inseparable mixture in 82% yield, with a *syn/anti* 10:90 dr. The analogous MAC reaction conducted on H-D-Phg-OMe·HCl **D-276** gave a mixture of dipeptides **98a,b** with a dr of 10:90 *syn/anti*. After column chromatography, the *syn* product **289a** was isolated in 9% yield, and the *anti* product **289b** was isolated in 74% yield (Scheme **100**).



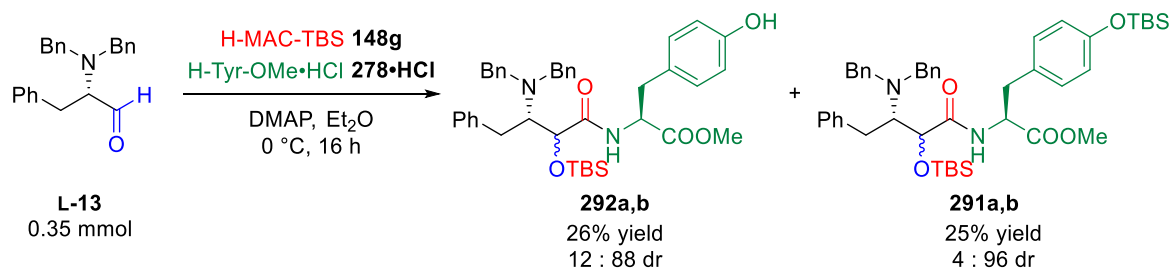
Scheme 100, MAC products from H-L-Phg-OMe and H-D-Phg-OMe

When methyl L-phenylalaninate (H-Phe-OMe) **277** was examined as the nucleophile, the crude dipeptide product mixture **290a,b** showed a *syn/anti* dr of 10:90. After chromatography, one fraction of *anti* diastereomer **290b** was obtained in 42% yield, while 25:75 *syn/anti* mixture **290a,b** was obtained in 31% yield. Using methyl *O*-TBS-L-tyrosinate (H-Tyr(TBS)-OMe) **279** as the nucleophile, MAC reaction gave one pure fraction of *anti* diastereomer **291b** in 65% yield, and 52:48 *syn/anti* mixture of dipetides **291a,b** in 20% yield. The overall *syn/anti* dr of this reaction was 12:88 *syn/anti* (Scheme 101).



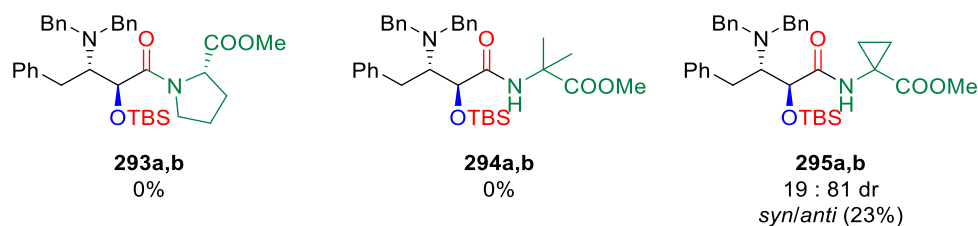
Scheme 101, MAC products from H-Phe-OMe and H-Tyr(TBS)-OMe

In the experiment using methyl L-tyrosinate hydrochloride (H-Tyr-OMe·HCl) **278·HCl**, two pairs of MAC dipeptide products were obtained from the resulting mixture (Scheme 102): in addition to the expected phenolic products **292a,b** obtained as an inseparable mixture in 26% yield with a *syn/anti* dr 12:88, the silyl ether derivatives **291a,b** were also isolated as an inseparable mixture in 25% yield with a *syn/anti* dr of 4:96.



Scheme 102, MAC reaction with H-Tyr-OMe·HCl

Finally, we examined nucleophilic substrates that were more challenging in terms of steric bulk (Scheme 103). In the optimized MAC oxyhomologation conditions described from H-Val-OMe **273** (See Table 21, entry 2), the use of methyl L-prolinate (H-Pro-OMe) **282** provided a complex product mixture in which no MAC products were detected by <sup>1</sup>H NMR spectroscopy and from which no identifiable peptide products could be isolated. Similar observations were made when 2-aminoisobutyric methyl ester (H-Aib-OMe) **280** was employed as the nucleophile.



Scheme 103, MAC products from H-Pro-OMe, H-Aib-OMe and H-Acc-OMe

Only 1-aminocyclopropanecarboxylic acid methyl ester (H-Acc-OMe) **281** provided a MAC product mixture in which two diastereomers were observed in the  $^1\text{H}$  NMR spectrum, with a dr of 19:81. After chromatography, the dipeptides **295a,b** were isolated as an inseparable mixture in a modest 23% yield.

#### IV.2.2 Discussion

The successes observed in the previous sections in MAC reactions of *N,N*-dibenzyl-L-phenylalaninal **L-13** with ammonia and simple amines were repeated here with a panel of  $\alpha$ -amino esters. A small library of fully-protected dipeptide derivatives of general structure *N,N*-dibenzyl-(2*S*,3*S*)-AHPBA(TBS)-Xaa-OMe were obtained in a tandem oxyhomologation/peptide-coupling protocol.

In terms of chemical reactivity, generally good yields of the dipeptide products were obtained, with the scope-limiting factor apparently being the steric hindrance of the nucleophilic partner, as had been observed previously. The  $\alpha$ -unsubstituted and  $\alpha$ -monosubstituted  $\alpha$ -amino esters all performed well, giving the corresponding dipeptides in 61-86% isolated yields, even with the bulkiest of  $\alpha$ -substituents (*t*-butyl).

An exception occurred with H-Tyr-OMe **278**, from which two related product mixtures were obtained in a combined yield of 51%, in which approximately half of the products had been *O*-silylated. This result suggested that H-MAC-TBS might be able to affect the *O*-silylation of a phenol in the MAC reaction conditions, which was never been reported before. It is unclear whether the depletion of the available H-MAC-TBS in the reaction mixture due to the competing *O*-silylation process has a detrimental effect on the efficiency of the MAC oxyhomologation reaction itself. Further work would be required to investigate this hypothesis. However, since tyrosine is most often used in a protected form in peptide synthesis, we were satisfied with the success in the reaction of H-Tyr(TBS)-OMe **279**.

As had already been observed in the studies on alcohols (see II.1) and amines (see III.2), the scope of the reaction appeared to have clear limits in terms of the steric hindrance of the nucleophile. The lack of reactivity of H-Pro-OMe **282** was in this sense not entirely surprising, although it remained rather frustrating given that pyrrolidine had performed in a satisfactory manner in the same conditions (see III.2). The inability of H-Aib-OMe **280** to engage in a productive reaction was likewise unsurprising. Indeed, given the precedents, the isolation of dipeptide mixture **295a,b** from the MAC reaction with H-Acc-OMe **281** could be qualified as an unexpected success, despite the modest yield.

The diastereoselectivity of the oxyhomologation during the formation of the dipeptide adducts was of key importance. With the  $\alpha$ -unsubstituted substrate H-Gly-OMe **271**, the dr was very high, at <2:98



(*syn/anti*). However, with the  $\alpha$ -monosubstituted substrates, the dr was not quite as high, falling in the range  $25:75 \leq dr \leq 10:90$ . Within the  $\alpha$ -monosubstituted substrate panel, the lowest diastereoselectivity (25:75) was observed with the most hindered substituent (*t*-Bu) and the second lowest diastereoselectivity (20:80) was observed with the second most hindered substituent (*i*Pr), while all other dr values were  $\geq 16:84$ . The two cases which gave the least diastereoselectivity were also the two cases that gave the lowest chemical yields, although it is not obvious that there would be a correlation between these two factors.

In terms of diastereoselectivity, the “expected” dipeptide mixture **292a,b** obtained from methyl L-tyrosinate (H-Tyr-OMe) respected the general trend, with a dr of 12:88. The very high dr (4:96) observed for the “unexpected” dipeptide mixture **291a,b** isolated from the same reaction was not easy to explain and is not necessarily the consequence of the MAC oxyhomologation/peptide-coupling process.

Given that the new dipeptide products obtained in the oxyhomologation/coupling process had three stereogenic centers, it was important to verify that the formation of two diastereomers in reactions employing chiral non-racemic  $\alpha$ -monosubstituted  $\alpha$ -amino esters was due to the creation of both *syn* and *anti* forms of the AHPBA core, *i.e.*, with configurations (2*S*,3*S*,*S*) and (2*R*,3*S*,*S*), rather than to partial epimerization of the chiral non-racemic L- $\alpha$ -amino ester partner in the reaction conditions. Indeed, in the latter hypothesis, a fully *anti* diastereoselective oxyhomologation would still lead to the formation of two diastereomers of configurations (2*S*,3*S*,*S*) and (2*S*,3*S*,*R*). To probe this matter, we conducted the reaction using each of the enantiomers of methyl phenylglycinate. Phenylglycine is known to be particularly susceptible to racemization in classical peptide coupling due to the ease of delocalization of an  $\alpha$ -anion onto the phenyl group.<sup>241</sup> In the event, H-L-Phg-OMe **L-276** and H-D-Phg-OMe **D-276** gave almost identical yields (82-83%) and dr values (10:90); the <sup>1</sup>H NMR spectra of the two (and only two) diastereomers obtained from H-L-Phg-OMe were different from the two (and only two) obtained from H-D-Phg-OMe (Table 22).

Table 22, MAC products from H-L-Phg-OMe and H-D-Phg-OMe

From H-L-Phg-OMe <b>L-276</b>	From H-D-Phg-OMe <b>D-276</b>
major (2 <i>S</i> ,3 <i>S</i> , <i>S</i> )	major (2 <i>S</i> ,3 <i>S</i> , <i>R</i> )
minor (2 <i>R</i> ,3 <i>S</i> , <i>S</i> )	minor (2 <i>R</i> ,3 <i>S</i> , <i>R</i> )

This important observation indicated that there had been no erosion of the enantiomeric composition of the phenylglycine partner during the MAC reaction and that the appearance of two diastereoisomers, therefore, had to be attributed to the presence of both *syn* and *anti* configurations of the  $\alpha$ -hydroxy- $\beta$ -amino acid fragment. Since it has already been shown that no racemization of *N,N*-dibenzyl-L-phenylalaninal **L-13** occurs in MAC reaction conditions (see III.1.3), the formation of products **288a,b** from H-L-Phg-OMe **L-276** and of products **289a,b** from H-D-Phg-OMe **D-276** is explained in terms of a “typical” MAC reaction profile with good (but not complete) *anti* diastereoselectivity; neither of the stereogenic centers present in the electrophilic and the nucleophilic

substrates is epimerized. The major diastereomer was reasonably assumed to have an *anti* configuration, by analogy with the *anti* selectivity already observed with simple amine partners (see II.2). By extension, we reasonably assume that all diastereomeric mixtures obtained from  $\alpha$ -monosubstituted L- $\alpha$ -amino ester substrates were composed of a major *anti*-(2*S*,3*S*,*S*) stereoisomer and a minor *syn*-(2*R*,3*S*,*S*) stereoisomer.

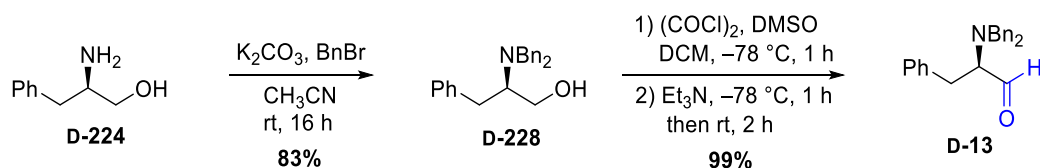
The diastereoselectivity of the MAC reaction with H-Acc-OMe **281** was significant, despite the modest chemical yield (23%). With the exception of H-Gly-OMe **271** – which gave a very high dr (< 2:98) in line with ammonia and simple amines – this  $\alpha,\alpha$ -disubstituted substrate was the only successful member of the substrate panel that was achiral. In the event, the dipeptide product mixture **295a,b** was obtained with a dr of 19:81, entirely in line with the dr values observed with the chiral  $\alpha$ -monosubstituted substrates. This result indicated that the general trend of slight diastereoselectivity erosion in going from a simple amine to an  $\alpha$ -amino ester substrate (other than H-Gly-OMe **271**) is unrelated to the inherent chirality of the  $\alpha$ -amino ester.

### IV.3 Towards the synthesis of (2*R*,3*R*,*S*)-epibestatin

With the above results in hand, we considered that it should be possible to apply the tandem oxyhomologation/peptide coupling protocol to prepare protected derivatives of epibestatin in a *one-pot* reaction. Two diastereomeric forms of this molecule exist that incorporate the leucine residue in its natural L configuration and the AHPBA with an *anti*-relative configuration. The absolute configurations of these epibestatins are (2*R*,3*R*,*S*) and (2*S*,3*S*,*S*). We envisaged the synthesis of each of them using the MAC oxyhomologation/coupling strategy described in the previous section. We began with the former stereoisomer, which implicated *N,N*-dibenzyl-D-phenylalaninal **D-13** as the electrophilic starting material.

#### IV.3.1 Preparation of *N,N*-dibenzyl-D-phenylalaninal

*N,N*-Dibenzyl-D-phenylalaninal **D-13** was synthesized using the same procedure (Scheme **104**) that had been used to prepare its enantiomer (See Chapter 2, IV.I).



Scheme **104**, Synthesis of *N,N*-dibenzyl-D-phenylalaninal

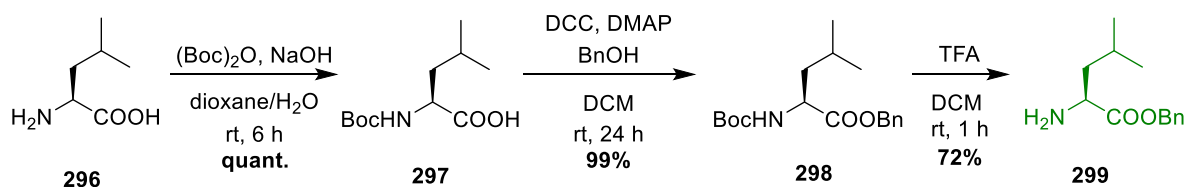
Commercial D-phenylalaninol **D-224** was dibenzylated with benzyl bromide under basic conditions to give *N,N*-dibenzyl-D-phenylalaninol **D-228** in 83% yield.<sup>196</sup> Its optical rotation value was  $[\alpha]_{\text{D}}^{23} = -33.3$  (c 1.0,  $\text{CHCl}_3$ ), compared to a literature value<sup>242</sup>  $[\alpha]_{\text{D}}^{20} = -57.4$  (c 1.0,  $\text{CHCl}_3$ ). The low optical rotation might come from impurities (triethylamine, dichloromethane, etc.) in this sample.

Swern oxidation was performed on the alcohol **D-228** to afford *N,N*-dibenzyl-D-phenylalaninal **D-13** in 99% yield. The purity of the crude aldehyde was monitored by  $^1\text{H}$  NMR spectroscopy, and its

stereochemical purity was checked by polarimetry. Its optical rotation value was  $[\alpha]_D^{23} = +89.2$  ( $c$  1.0,  $\text{CHCl}_3$ ), compared to a literature value<sup>197</sup> for the L enantiomer of  $[\alpha]_D^{20} = -90$  ( $c$  1.00,  $\text{CHCl}_3$ ), which suggested the excellent enantiomeric purity of the sample. The crude aldehyde was used directly in the subsequent MAC reactions.

### IV.3.2 Preparation of benzyl L-leucinate

Benzyl L-leucinate (H-Leu-OBn) **299** was prepared in three steps (Scheme 105). Commercial L-leucine **296** was treated with  $(\text{Boc})_2\text{O}$  in the presence of sodium hydroxide to give *N*-Boc-L-leucine **297** in quantitative yield. This compound was reacted with benzyl alcohol under Steglich conditions inspired by the literature to give *N*-Boc-L-leucine benzyl ester **298** in 99% yield.<sup>243</sup> After cleavage of the *t*-butyl carbamate using trifluoroacetic acid in dichloromethane,<sup>242</sup> H-Leu-OBn **299** was obtained as a colorless oil in 72% yield. The enantiomeric composition of the sample was confirmed by comparing its optical rotation value ( $[\alpha]_D^{20} = +5.7$  ( $c$  1.0,  $\text{CHCl}_3$ )) with that reported in the literature<sup>244</sup> ( $[\alpha]_D^{25} = +5.6$  ( $c$  1.0,  $\text{CHCl}_3$ )). The compound can be kept at  $-18$  °C for several months.

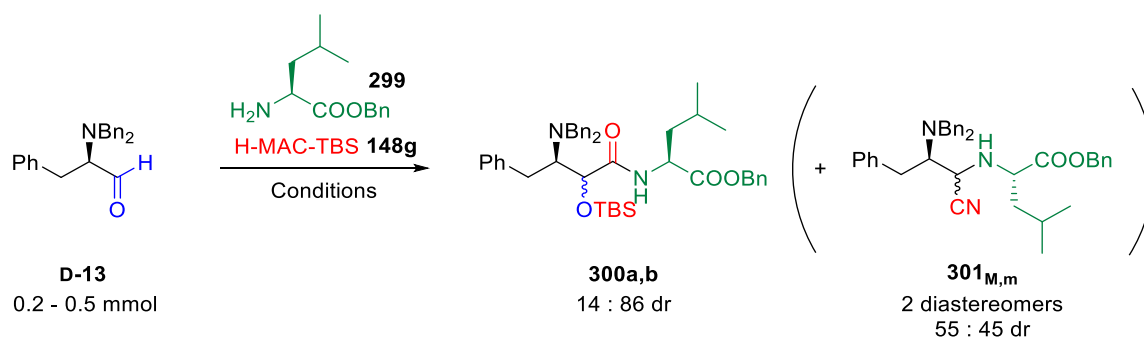


Scheme 105, Preparation of benzyl L-leucinate

### IV.3.3 Optimization of MAC reaction conditions

The MAC reaction was applied to combine *N,N*-dibenzyl-D-phenylalaninal **D-13** with H-MAC-TBS **148g** and H-Leu-OBn **299**. Several conditions were examined, and the results are presented in Table 23.

Two workup procedures were applied: for workup A, the reacting mixture was basified with saturated sodium carbonate aqueous solution, extracted with ether, washed with 1M HCl and brine, and dried in vacuo; for workup B, the reacting mixture was directly dried in vacuo. The yields are given for isolated material after column chromatography. The diastereomeric ratios were calculated from the  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ , rt) of purified products after chromatography by integration of  $\text{Me}_2\text{Si}$  signals of each diastereomer. The ratio (“ratio” in the following texts) of MAC products **300a,b** to side products ( $\alpha$ -amino nitriles) **301<sub>M,m</sub>** was calculated from the  $^1\text{H}$  NMR spectra by comparison of the integration of the *CHOTBS* signals of the MAC products **300a,b** and the signal of the four benzylic protons of the *N,N*-dibenzyl moiety of **301<sub>M,m</sub>** (mixture of two diastereoisomers).

Table 23, MAC reaction of *N,N*-dibenzyl-*D*-phenylalaninal with *H*-MAC-TBS and benzyl *L*-leucinate

Entry	Conditions	Workup	Ratio <sup>a</sup> 300a,b/301 <sub>M,m</sub>	Yield <sup>b</sup> of 300a,b (%)
1	Optimized condition from H-Val-OMe (The addition of H-Leu-OBn was delayed for 15 min)	A	1 : 0.28	36
2	Optimized condition from ammonia	A	1 : 0.45	30 <sup>c</sup>
3	Optimized condition from alcohols	A	1 : 0.86	-
4	Nemoto's procedure for the synthesis of (-)-bestatin	B	1 : 4.9	-
5	Nemoto's procedure for the synthesis of (-)-bestatin	A	1 : 3.3	-
6	Based on entry 1, delaying the addition of H-Leu-OBn to 30 min.	A	- <sup>d, e</sup>	26 <sup>c</sup>
7	Based on entry 1, delaying the addition of H-Leu-OBn to 90 min.	A	- <sup>d, e</sup>	18 <sup>c</sup>

<sup>a</sup> ratio was calculated from the crude <sup>1</sup>H-NMR (CDCl<sub>3</sub>, rt), by integrating the CHOTBS signals of the MAC products **300a,b** and *N,N*-dibenzyl groups of the side product **301<sub>M,m</sub>**

<sup>b</sup> isolated yield of **300a,b** after column chromatography

<sup>c</sup> MAC products were isolated with other impurities

<sup>d</sup> by-compounds **301<sub>M,m</sub>** were not observed

<sup>e</sup> the reaction produces other side products

The MAC reaction was first carried out in the optimized condition from the studies on H-Val-OMe as the nucleophile (See IV.2.1 Table 21, entry 2). In a 0.2 mmol scale, *N,N*-dibenzyl-*D*-phenylalaninal **D-13** was mixed with 2.4 eq. of H-MAC-TBS **148g** in Et<sub>2</sub>O at rt, 2.0 eq. of DMAP was added at 0 °C and stirred for 15 minutes; 1.2 eq. of H-Leu-OBn **299** was finally introduced and reacted for 16 h at 0 °C. After workup, the product "ratio" **300a,b**/**301<sub>M,m</sub>** in the crude mixture was 1 : 0.28 and after chromatography, the MAC dipeptides **300a,b** were obtained in 36% yield and with a *syn/anti* dr of 14:86 (entry 1).

The optimized condition from the studies on ammonia as the nucleophile (see III.1) was then applied in an attempt to improve the yield. *N,N*-Dibenzyl-*D*-phenylalaninal **D-13** (0.5 mmol) and 2.4 eq. of H-MAC-TBS **148g** were mixed in Et<sub>2</sub>O at rt, 1.2 eq. of H-Leu-OBn **299** was introduced at 0 °C, followed by the addition of 2.0 eq. of DMAP, then stirring for 16 h at 0 °C. After the workup, we noticed the crude products were messy with a lot of side products (by <sup>1</sup>H NMR and TLC), and chromatography gave the

MAC dipeptides **300a,b** in 30% yield with the same 14:86 dr. Interestingly, we also isolated the  $\alpha$ -amino nitrile side products **301<sub>M,m</sub>** in 13% yield as a mixture of two diastereomers (dr 55 : 45, although we did not succeed in assigning configurations to these compounds). The “ratio” of MAC dipeptides **300a,b** to side products **301<sub>M,m</sub>** was 1 : 0.45 (entry **2**).

The optimized condition from the studies on methanol as the nucleophile (see Chapter 2, IV.2.1) was also applied; 0.2 mmol of *N,N*-dibenzyl-D-phenylalaninal **D-13**, 2.4 eq. of H-MAC-TBS **148g** and 1.2 eq. of H-Leu-OBn **299** (instead of 3.0 eq.) in Et<sub>2</sub>O were mixed at room temperature, after cooling down to 0 °C, 2.0 eq. of DMAP was introduced and reacting for 16 hours at this temperature. This condition gave more side products: the “ratio” between MAC products **300a,b** and **301<sub>M,m</sub>** was 1 : 0.86 (entry **3**).

The formation of an  $\alpha$ -amino nitrile side product **301<sub>M,m</sub>** was not reported by Nemoto in his synthesis of (–)-bestatin.<sup>163</sup> We repeated the above reaction using 4-pyrrolidinopyridine (4-PP) as the base instead of DMAP and reduced the reaction time to 5 hours in acetonitrile, in accordance with Nemoto’s conditions. The mixture was concentrated directly after the reaction time, and the MAC products/side products “ratio” **300a,b/301<sub>M,m</sub>** was found to be 1 : 4.9 (entry **4**). When the reaction was repeated with an appropriate workup, the resulting MAC products **300a,b**/side product **301<sub>M,m</sub>** “ratio” was 1 : 3.3 (entry **5**). The formation of large amounts of the side products indicated that Nemoto’s conditions were even less suitable for the present MAC reaction than our own conditions.

Noting that the formation of the side product **301<sub>M,m</sub>** had been reduced by delaying the addition of the nucleophile, we repeated the above reaction and increased the waiting time between the addition of DMAP and that of H-Leu-OBn **299** to 30 minutes (entry **6**) and 90 minutes (entry **7**). In these two experiments, no  $\alpha$ -amino nitrile **301<sub>M,m</sub>** was found, but the isolated yields of MAC dipeptides **300a,b** remained modest, at 26% and 18%, respectively. Notably, other unidentified by-products were detected in the <sup>1</sup>H NMR spectra of the crude reaction product mixtures.

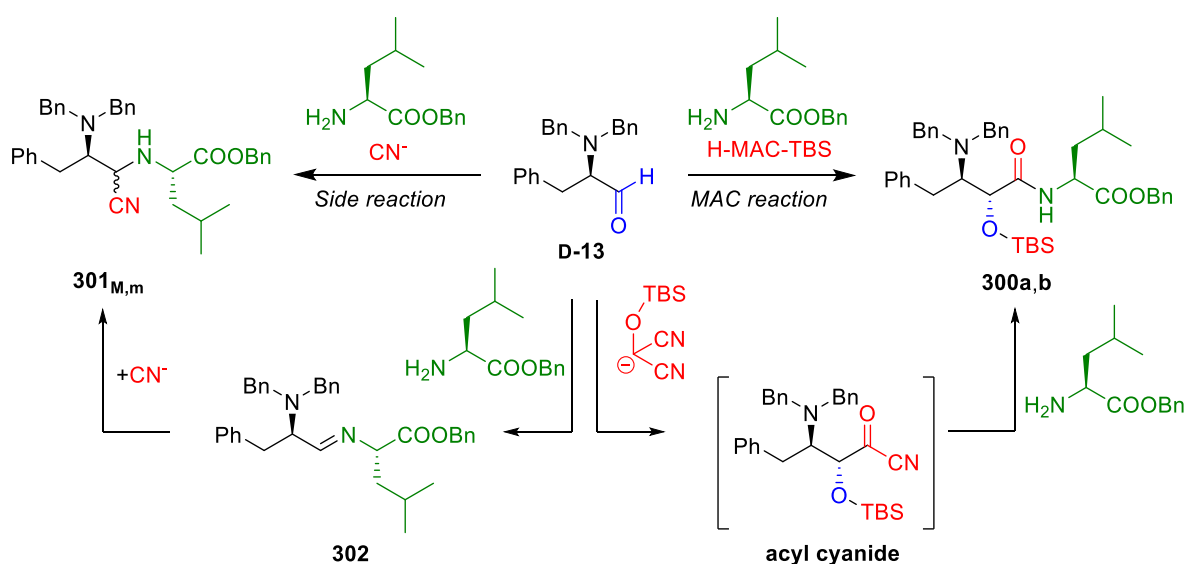
#### IV.3.4 Discussion

The MAC reaction between *N,N*-dibenzyl-D-phenylalaninal **D-13**, H-MAC-TBS **148g**, and H-Leu-OBn **299** did not proceed with the simplicity we had anticipated after the successes observed in the previous section (see IV.2). The reaction protocol which had worked well with various nucleophiles up to this point – ammonia, simple amines or alcohols and  $\alpha$ -amino esters – did not provide a satisfactory access to the target dipeptides **300a,b** despite our considerable efforts to adapt the reaction conditions, notably with respect to the order of introduction of each substrate. In the best case scenario, the dipeptides **300a,b** were obtained in 36% yield and with a dr of 14:86. We assumed that the major diastereomer had the *anti*-(2*R*,3*R*,5) configuration.

The principal problem encountered was the formation of the side product **301<sub>M,m</sub>**. The formation of an  $\alpha$ -amino nitrile was previously detected in the MAC reactions with cyclopropylamine (See III.2.1, Figure **30**) but was not successfully isolated. In the MAC reaction of *N,N*-dibenzyl-D-phenylalaninal **D-13**, H-MAC-TBS **148g** and H-Leu-Bn **299**, the  $\alpha$ -amino nitrile **301<sub>M,m</sub>** was successfully isolated and fully characterized, which confirmed our previous hypothesis.

The formation of an  $\alpha$ -amino nitrile in a *one-pot* MAC reaction of  $\alpha$ -amino aldehyde has never been reported before, to the best of our knowledge. However, some reported examples inspired us to consider this possibility. For instance, in Nemoto's MAC reactions using benzaldehyde, H-MAC-TBS **148g** and *N,O*-dimethylhydroxylamine, the aldehyde might react first with *N,O*-dimethylhydroxylamine to give an imine, and therefore performing a sequential MAC reaction to give compound **165a-b** (See Introduction, Table 3). Another example mentioned that the sterically hindered imine **155** could not perform a *one-pot* MAC reaction with H-MAC-Ac **148c**; thus, only the  $\alpha$ -amino nitrile **156** was obtained as the product (See Introduction, Scheme 43).

On the other hand, given that aldehydes, amines and cyanides were presented simultaneously in our reaction mixture, a *one-pot* Strecker reaction might occur and give  $\alpha$ -amino nitrile via aldimine formation.<sup>245</sup> Therefore, we believed that a similar imine intermediate was generated in situ in our MAC reaction conditions. A mechanism for the formation of  $\alpha$ -amino nitrile **301<sub>M,m</sub>** is proposed in Scheme 106.



Scheme 106, Proposed mechanism for the formation of  $\alpha$ -amino nitrile **301<sub>M,m</sub>** and MAC products **300a,b**

It is suggested that there is a competition between the expected MAC reaction and the reaction of H-Leu-OBn **299** with the cyanide anion and with a part of the aldehyde starting material that had not yet reacted with the anion of the MAC reagent. The imine **302** obtained by a direct combination of *N,N*-dibenzyl-D-phenylalanyl aldehyde **D-13** and H-Leu-OBn **299** could react quickly with cyanide anion present in the mixture, leading to  $\alpha$ -amino nitrile **301<sub>M,m</sub>**. When the MAC reaction was conducted with a waiting time to allow the formation of the acyl cyanide before the addition of H-Leu-OBn **299**, the formation of the  $\alpha$ -amino nitrile **301<sub>M,m</sub>** was suppressed, which is consistent with the proposed mechanism.

The possibility of competitive formation of an  $\alpha$ -amino nitrile exists in any MAC reaction between an  $\alpha$ -amino aldehyde, an amine and an H-MAC-[Si] reagent; although it is one of the attractive features of MAC methodology that it has not been in evidence previously. It is unclear why it should operate in this particular combination of reagents employed here.

The further problem was that the use of longer waiting times, while suppressing the formation of the  $\alpha$ -amino nitrile did not result in improved yields of the target dipeptides **300a,b**. Indeed, other by-products were detected in the crude reaction mixtures, suggesting that other unidentified processes were impeding the expected MAC reaction.

Faced with these difficulties and the modest yield of dipeptides **300a,b**, we did not pursue the intended synthesis of (2*R*,3*R*,*S*)-epibestatin.

#### IV.4 Synthesis of (2*S*,3*S*,*S*)-epibestatin

##### IV.4.1 Optimization of MAC reaction conditions

The MAC reaction was applied to combine *N,N*-dibenzyl-L-phenylalaninal **L-13** with H-MAC-TBS **148g** and H-Leu-OBn **299**. As was the case in the D-phenylalanine serie described in the previous section, several conditions were examined, and the results are presented in Table 24.

In all entries, the reacting mixture was basified with saturated sodium carbonate aqueous solution, extracted with ether, washed with 1M HCl and brine, and finally dried in vacuo. The yields are given for isolated material after column chromatography. The diastereomeric ratios of the MAC products **303a,b** were calculated from the  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ , rt) of the crude sample by integration of  $\text{Me}_2\text{Si}$  signals of each diastereomer. The ratio ("ratio" in the following texts) of MAC products **303a,b** to side products **304<sub>M,m</sub>** was calculated from the  $^1\text{H}$  NMR spectra by comparison of the integration of the CHOTBS signals of the MAC products **303a,b** and the signal of the four benzylic protons of the *N,N*-dibenzyl moiety of **304<sub>M,m</sub>** (mixture of two diastereoisomers).

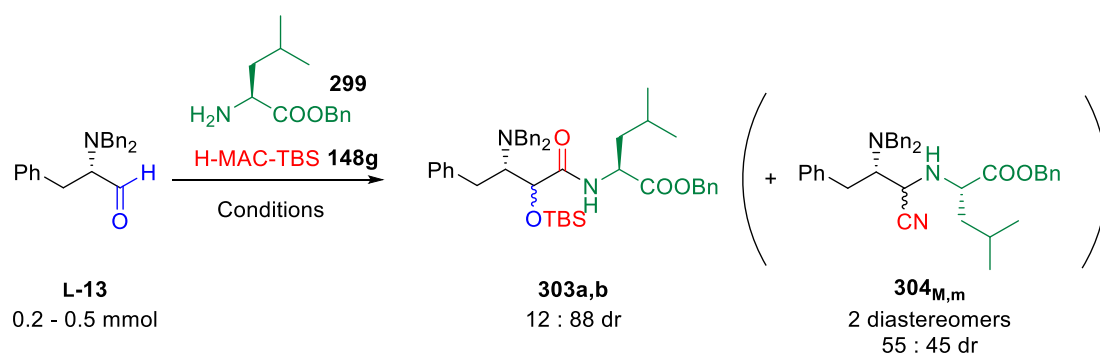


Table 24, MAC reactions of *N,N*-dibenzyl-L-phenylalaninal, H-MAC-TBS, and benzyl L-leucinate

Entry	Conditions	Ratio <sup>a</sup> 303a,b/304 <sub>M,m</sub>	Yield <sup>b</sup> of 303a,b
1	Optimized condition from H-Val-OME (The addition of H-Leu-OBn was delayed for 15 min)	1 : - <sup>c</sup>	85
2	Optimized condition from ammonia	1 : 0.45	36 <sup>d</sup>
3	Optimized condition from alcohols	1 : 1.51	- <sup>e</sup>

<sup>a</sup> ratio was calculated from the crude  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , rt), by integrating the CHOTBS signals of the MAC products **303a,b** and *N,N*-dibenzyl groups of the side product **304<sub>M,m</sub>**

<sup>b</sup> isolated yield after column chromatography

<sup>c</sup>  $\alpha$ -amino nitrile **304<sub>M,m</sub>** was not observed

<sup>d</sup> MAC products were isolated with other impurities

<sup>e</sup> reaction mixture was not purified

The MAC reaction was first carried out in the optimized condition from the studies on H-Leu-OBn **299** as the nucleophile (see IV.3.3, Table 23, entry 1). In a 0.3 mmol scale, *N,N*-dibenzyl-L-phenylalaninal **L-13** was mixed with 2.4 eq. of H-MAC-TBS **148g** in Et<sub>2</sub>O at rt, 2.0 eq. of DMAP was added at 0 °C and stirred for 15 minutes, 1.2 eq. of H-Leu-OBn **299** was finally introduced and reacted for 16 h at 0 °C. After workup, the side product **304<sub>M,m</sub>** was not detected and only MAC products **303a,b** were observed in the <sup>1</sup>H NMR spectra (CDCl<sub>3</sub>, rt) with a *syn/anti* dr of 12 : 88. After chromatography, the desired MAC dipeptides **303a,b** were isolated in 85% yield and with a *syn/anti* dr of 12 : 88 (entry 1).

In the second experiment, the reaction was carried out in the optimized conditions established for ammonia as the nucleophile (see III.1). *N,N*-Dibenzyl-L-phenylalaninal **L-13** (0.5 mmol) and 2.4 eq. of H-MAC-TBS **148g** were mixed in Et<sub>2</sub>O at rt, 1.2 eq. of H-Leu-OBn **299** was introduced at 0 °C followed by the addition of 2.0 eq. of DMAP then stirring for 16 h at 0 °C. After the workup and chromatography, the MAC products **303a,b** were obtained in 36% yield, with a dr of 11:89 (entry 2). Again, an  $\alpha$ -amino nitrile side product **304<sub>M,m</sub>** was isolated as a mixture of two diastereomers, with a dr of 35 : 65, without assignment of their configurations. The “ratio” of MAC dipeptides **303a,b** to side product **304<sub>M,m</sub>** was 1 : 0.45.

In another experiment, 0.2 mmol of *N,N*-dibenzyl-L-phenylalaninal **L-13**, 2.4 eq. of H-MAC-TBS **148g** and 1.2 eq. of H-Leu-OBn **299** in Et<sub>2</sub>O were mixed at room temperature, after cooling down to 0 °C, 2.0 eq. of DMAP was introduced and reacting for 16 hours at this temperature. This condition gave more side product: the “ratio” between MAC products **303a,b** and **304<sub>M,m</sub>** was 1 : 1.51 (entry 3).

As in the previous section, the adaptation of the MAC reaction to include a 15 minutes waiting time to allow the formation of the acyl cyanide before the addition of H-Leu-OBn **299**, resulted in the suppression of the formation of the  $\alpha$ -amino nitrile side product **304<sub>M,m</sub>**. In remarkable contrast with the previous section, this modification resulted in a dramatic increase in the yield of the target MAC dipeptide products **303a,b**.

The successful preparation of the desired peptide mixture in good yield (85%) and with good dr (*syn/anti*, 12 : 88) allowed us to continue with the proposed synthesis of (2*S*,3*S*,5*S*)-epibestatin.

#### IV.4.2 Cleavage of the TBS ether

The silyl ether cleavage was performed using TBAF in THF (Table 25). The MAC dipeptide mixture **303a,b** (*syn/anti*, 12:88) was treated with 1.5 eq. of TBAF in THF for 16 hours at room temperature to give the *anti* alcohol **305** in 61% yield after column chromatography (entry 1).



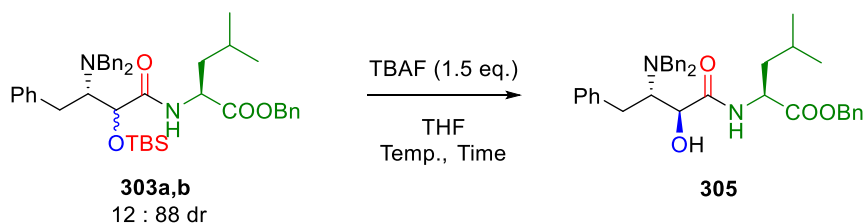


Table 25, Cleavage of TBS ether

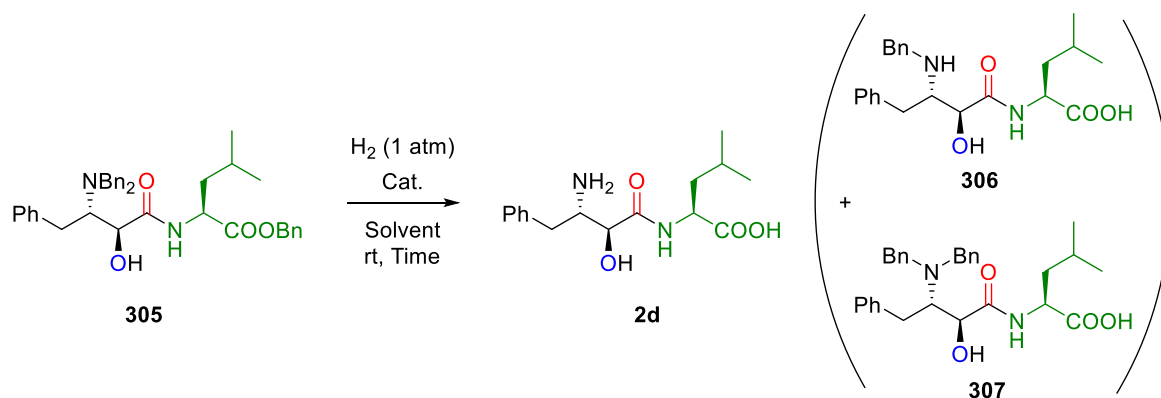
Entry	Temp.	Time	Yield <sup>a</sup>
1	rt	16 h	61%
2	0 °C	4 h	88%

<sup>a</sup> isolated yield after column chromatography

By lowering the reaction temperature to 0 °C and reducing the reaction time to four hours, the yield of *anti* alcohol **305** increased to 88% (entry **2**). Considering that the proportion of *anti* **303b** in the starting material was 88%, the reaction achieved with quantitative conversion. In the <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, rt) of the crude reaction product mixture obtained from entry **2**, the signals of the minor silyl ether diastereomer (**303a**) were visible. It suggested that the TBS cleavage of those MAC product diastereomers (**303a,b**) was diastereoselective under the chosen conditions.

#### IV.4.3 Hydrogenolysis

The alcohol **305** was subjected to catalytic hydrogenolysis to remove all three benzyl protection groups. Several experiments were performed in order to find the most efficient conditions (Table 26). In each case, the yield is given for material obtained after filtration through a Celite pad or a PVDF membrane (HPLC filter, 0.22 μm pore size). And the composition of the resulting product mixture was made by the <sup>1</sup>H NMR and HR-MS.

Table 26, Hydrogenolysis for the synthesis of (2*S*,3*S*,*S*)-epibestatin

Entry	Cat.	Equivalent of catalyst <sup>a</sup>	Solvent	Time (h)	Products <sup>b</sup>	Yield <sup>c</sup> of <b>2d</b> (%)
<b>1</b>	Pd/C	10%	MeOH	3	<b>2d, 306, 307</b>	26
<b>2</b>	Pd/C	10%	<i>i</i> PrOH	24	<b>2d, 306</b>	87 <sup>d</sup>
<b>3</b>	Pd/C	10%	DCM/EtOAc	36	<b>2d, 306, 307</b>	85
<b>4</b>	Pd/C	10%	EtOAc	48	<b>2d</b>	100
<b>5</b>	Pd(OH) <sub>2</sub> /C	10%	MeOH	2	<b>2d</b>	99

<sup>a</sup> wt% to the weight of starting material

<sup>b</sup> product mixture analyzed by HR-MS

<sup>c</sup> isolated yield after column chromatography

<sup>d</sup> compound **2d** mixed with isopropyl esters

The hydrogenolysis of compound **305** was first examined under 1 bar hydrogen pressure using 10% palladium on carbon in methanol for 3 hours (entry **1**). The product mixture contained (2*S*,3*S*,*S*)-epibestatin **2d** and the partially debenzylated compounds **306** and **307**, indicating that the hydrogenolysis was incomplete. When the reaction was repeated using isopropanol as the solvent, and a reaction time of 24 hours, the product still contained the mono-benzyl product **306** (entry **2**). The reaction was repeated again, this time with a mixture of dichloromethane and ethyl acetate (4:1) as the solvent and a reaction time of 36 hours, but once again, the hydrogenolysis was incomplete (entry **3**). When ethyl acetate alone was used as the solvent (in the same conditions employed in the synthesis of (2*S*,3*S*)-AHPBA **1d**, see //3.2) over a reaction time of 48 hours, (2*S*,3*S*,*S*)-epibestatin **2d** was obtained in quantitative yield (entry **4**). Finally, we investigated Pearlman's catalyst for the hydrogenolysis in methanol; after a reaction time of only 2 hours, (2*S*,3*S*,*S*)-epibestatin **2d** was obtained in 99% yield (entry **5**).

The chemical purity of (2*S*,3*S*,*S*)-epibestatin **2d** obtained in this way was confirmed by the <sup>1</sup>H NMR, <sup>13</sup>C NMR and HR-MS (both ES<sup>+</sup> and ES<sup>-</sup>). However, as only a blurry optical rotation value ( $[\alpha]_{578}^{20-25} = -61.3$  (*c* = n.d., AcOH)) was recorded in the literature,<sup>38</sup> the optical rotation value of our sample in acetic acid ( $[\alpha]_{D}^{23} = -29.7$  (*c* 1.0, AcOH)) was measured, and we believe that we obtained the correct compound considering that no differential epimerization could occur during the TBS cleavage and hydrogenation conditions.

## IV.5 Discussion

In this section, we demonstrated that  $\alpha$ -amino methyl esters could be employed as nucleophilic partners in MAC reactions with *N,N*-dibenzyl-L-phenylalaninal **L-13**, providing a *one-pot* tandem oxyhomologation/coupling protocol in which the product dipeptides contain the newly formed AHPBA residue in conveniently protected form. The efficiency of the reactions was dependent on steric factors: while the methyl esters of glycine and  $\alpha$ -monosubstituted  $\alpha$ -amino acids performed well, the methyl esters of proline and of  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids did not.

The diastereoselectivity in successful reactions was generally good, in favor of the formation of the *anti* diastereomer as expected from the results of the previous sections. With the glycine substrate, the dr was < 2:98, while with  $\alpha$ -monosubstituted substrates, the dr fell in the range  $25:75 \leq dr \leq 10:90$ . We found that the greater the steric bulk of the  $\alpha$ -substituent, the lower the yield and the diastereoselectivity.

It was anticipated that the benzyl ester of an  $\alpha$ -monosubstituted  $\alpha$ -amino acid would behave in a similar manner. However, the use of H-Leu-OBn **299** as the nucleophile revealed some surprises. Firstly, an unexpected competing reaction was observed, resulting in the formation of the  $\alpha$ -amino nitrile side products **302<sub>M,m</sub>** and **304<sub>M,m</sub>**, although this could be suppressed by an adaptation of the reaction conditions. Secondly, significant differences were noticed in the reaction of H-Leu-OBn **299** with each of the enantiomers of *N,N*-dibenzylphenylalaninal. In the best reaction conditions, we could find for each case: *N,N*-dibenzyl-L-phenylalaninal **L-13** gave MAC products **303a,b** in a satisfying 85% yield with 12 : 88 *syn/anti* dr, whereas *N,N*-dibenzyl-D-phenylalaninal **D-13** gave MAC products **300a,b** in only 36% yield and 14:86 *syn/anti* dr. It is not obvious why there should be such a significant difference in reactivity, although some sort of “match/mismatch” phenomenon may be operating.

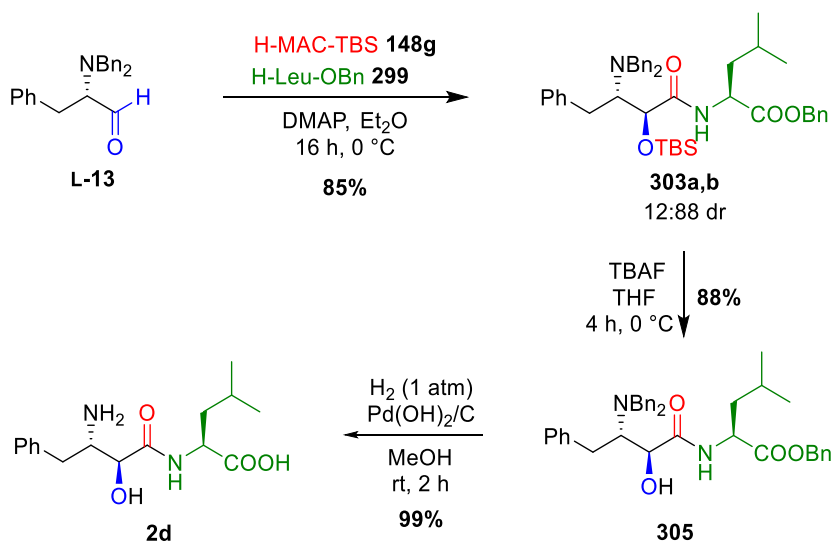
In this section, it was appropriate to check that the formation of two diastereomers was attributable to the formation of *syn* and *anti* configurations during the oxyhomologation, rather than to partial epimerization of the chiral non-racemic  $\alpha$ -amino ester substrate. We confirmed that no such epimerization occurred in the MAC reactions in two independent cases. In the first (described above, see IV.2.2), we showed that the two diastereomers obtained from H-L-Phg-OMe **L-276** were different from the two obtained from H-D-Phg-OMe **D-276**. In the second, which we now describe, we compared the two diastereomers obtained in the reaction of benzyl-L-Leucinate **299** and *N,N*-dibenzyl-L-phenylalaninal **L-13** with those obtained from H-Leu-OBn **299** and *N,N*-dibenzyl-D-phenylalaninal **D-13**. The <sup>1</sup>H NMR spectrum of each sample showed the presence of only one pair of diastereomers, and they were distinct from each other (Table 27). There was no spectral evidence for the presence of an “epimerized” adduct in either case.

Table 27, Possible MAC products from benzyl L-leucinate with D- and L-aldehyde

From <i>N,N</i> -dibenzyl-L-phenylalaninal <b>L-13</b>	From <i>N,N</i> -dibenzyl-D-phenylalaninal <b>D-13</b>
“major” (2 <i>S</i> ,3 <i>S</i> , <i>S</i> )	“major” (2 <i>R</i> ,3 <i>R</i> , <i>S</i> )
“minor” (2 <i>R</i> ,3 <i>S</i> , <i>S</i> )	“minor” (2 <i>S</i> ,3 <i>R</i> , <i>S</i> )
if RCHO epimerized, “major” (2 <i>R</i> ,3 <i>R</i> , <i>S</i> )	if RCHO epimerized, “major” (2 <i>S</i> ,3 <i>S</i> , <i>S</i> )
if RCHO epimerized, “minor” (2 <i>S</i> ,3 <i>R</i> , <i>S</i> )	If RCHO epimerized, “minor” (2 <i>R</i> ,3 <i>S</i> , <i>S</i> )
if H-Leu-OBn epimerized, “major” (2 <i>S</i> ,3 <i>S</i> , <i>R</i> )	if H-Leu-OBn epimerized, “major” (2 <i>R</i> ,3 <i>R</i> , <i>R</i> )
if H-Leu-OBn epimerized, “minor” (2 <i>R</i> ,3 <i>S</i> , <i>R</i> )	If H-Leu-OBn epimerized, “minor” (2 <i>S</i> ,3 <i>R</i> , <i>R</i> )

These observations underline an important feature of the MAC methodology for preparing peptides, wherein epimerization of the substrates is not observed.

While the poor yield of the MAC reaction implicating *N,N*-dibenzyl-D-phenylalaninal **D-13** and H-Leu-OBn **299** discouraged us from pursuing a synthesis of (2*R*,3*R*,*S*)-epibestatin, the synthesis of (2*S*,3*S*,*S*)-epibestatin from *N,N*-dibenzyl-L-phenylalaninal **L-13** was achieved successfully in a three-step procedure (Scheme 107).



Scheme 107, Short synthesis of (2*S*,3*S*,*S*)-epibestatin

The key optimized MAC oxyhomologation/coupling procedure gave the inseparable MAC dipeptide mixture **303a,b** in a highly satisfactory 85% yield and with a 12:88 dr (*syn/anti*). Subsequent TBAF-mediated silyl ether cleavage was performed to provide only the *anti* compound **305** as a single enantiomer in 88% yield (which is quantitative on the basis of the composition of the substrate). Triple debenzylation by catalytic hydrogenolysis was achieved in quantitative yield using Pearlman's catalyst in mild conditions. The overall yield for this synthesis was 74%, which makes it the shortest synthetic route to (2*S*,3*S*,*S*)-epibestatin **2d** known to date. The preparation of (2*S*,3*S*,*S*)-epibestatin **2d** was only previously reported by Umezawa in 1977 via cyanohydrin formation (see Introduction, Scheme 1),<sup>38</sup> and the overall yield was only 4%.

## V. Conclusion

Alcohols, ammonia, amines, and  $\alpha$ -amino esters were examined as nucleophiles for the MAC reactions of *N,N*-dibenzyl-L-phenylalaninal **L-13** with H-MAC-TBS **148g**.

Most of them show good yields, with alcohols up to 96%, ammonia up to 89%, amines up to 89%, and  $\alpha$ -amino esters up to 86%. It should be noted, however, that the steric hindrance of the nucleophile influenced the yield. For example, secondary alcohols, unconstrained secondary amines, and  $\alpha$ -amino esters with a large R group may lead to a dramatic yield loss.

All MAC reactions with *N,N*-dibenzyl-L-phenylalaninal **L-13** show high to very high *anti* diastereoselectivity. All alcohols gave 10:90 *syn/anti* dr, and all amines (including ammonia) gave a dr greater than 2:98 *syn/anti*. The amino esters are slightly different, starting from < 2:98 *syn/anti* dr for

glycinate, and it decreases when R groups become more bulky, the lowest was 25:75 *syn/anti* dr for *tert*-leucinate.

However, the major MAC products above are assigned as *anti*-configuration, which suggests that the *anti* diastereoselectivity came from the *N,N*-diprotected  $\alpha$ -amine moiety. The diastereoselectivity can also be explained with the Felkin-Anh model.

MAC reactions of *N,N*-dibenzyl-L-phenylalaninal **L-13**, H-MAC-TBS **148g**, and various nucleophiles gave MAC products in a good yield and with an *anti* diastereoselectivity. The yield varies depending on the steric effect of the nucleophiles; and the diastereomeric ratio was related to the nature of nucleophiles: amines (including ammonia) gave the best diastereoselectivity, followed by alcohol, and  $\alpha$ -amino ester relied on the bulky R group.

These oxyhomologation reactions provided a rapid access to a library of *N,O*-orthogonally protected (2*S*,3*S*)-AHPBA esters/amides derivatives. It also allows the direct construction of  $\beta$ -dipeptides efficiently.

## Chapter 4:

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MAC reactions of various  
*N,N*-dibenzyl  $\alpha$ -amino  
aldehydes

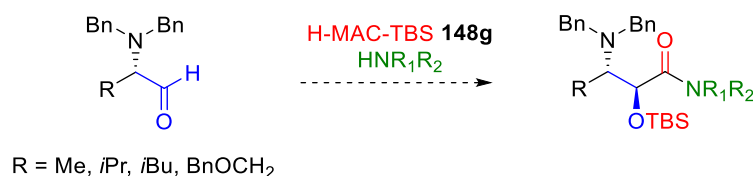
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## I. Introduction

As we mentioned in the introduction part, many of the methodologies used to synthesize AHPBA might be applicable to the synthesis of other AHBA derivatives as well. These include Takita's results using cyanohydrin,<sup>38</sup> Reißig's reaction of lithiated methoxyallene and  $\alpha$ -amino aldehydes,<sup>66</sup> Bode's<sup>246</sup> and Preti's<sup>60</sup> use of Passerini reactions, Vaccaro's ring opening of  $\alpha,\beta$ -epoxycarboxylic acids,<sup>84</sup> Palomo's ring opening of  $\beta$ -lactams,<sup>247</sup> Matsumura's LDA induced coupling between glycolamides derivatives,<sup>113</sup> etc. Other general approaches include Sharpless's catalytic aminohydroxylation,<sup>248</sup> Kobayashi's Mannich reaction of  $\alpha$ -alkoxy enolates with aldimines,<sup>249</sup> Hu's rhodium/CPA co-catalyzed multi-component reactions of diazoacetates, alcohols and imines.<sup>250</sup> In most cases, the diastereoselectivity increases with the steric bulk of the  $\gamma$ -substituent (of the AHBA).

In the preceding chapter, we applied the optimized one-pot MAC reaction for the oxyhomologation of *N,N*-dibenzyl-L-phenylalaninal **L-13** with high *anti* diastereoselectivity, to provide (2*S*,3*S*)-*N,N*-dibenzyl-*O*-TBS-protected AHPBA ester, amide and dipeptides derivatives. We believed that this approach could be used to create a wider library of AHBA derivatives in a one-pot procedure, and we were also interested in the diastereoselectivity of the MAC reaction performed on different aldehydes.

To this end, we proposed to use *N,N*-dibenzyl protected L-alaninal **L-316**, L-valinal **L-313**, L-leucinal **L-310**, and *O*-Bn-L-serinal **L-320** in the one-pot MAC reactions with H-MAC-TBS **148g** and amine nucleophiles (Scheme **108**).



Scheme **108**, Synthesis of other  $\alpha$ -hydroxy- $\beta$ -amino amides in one-pot MAC reaction

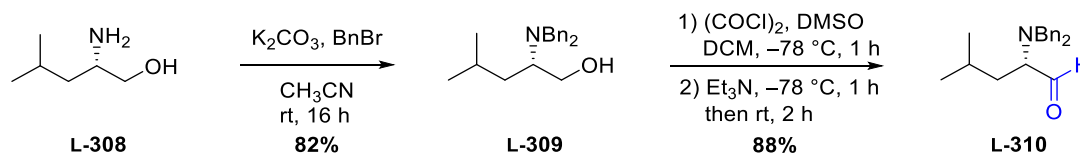
## II. Preparation of *N,N*-dibenzyl $\alpha$ -amino aldehydes

### II.1 from $\alpha$ -amino alcohols

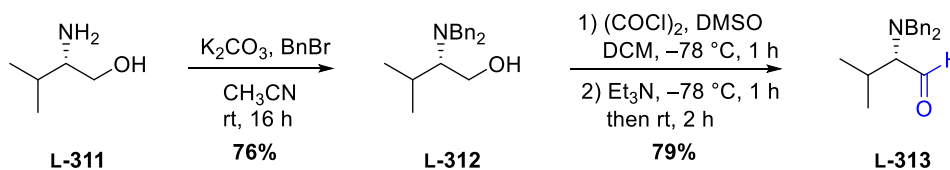
*N,N*-Dibenzyl-L-leucinal **L-310**, *N,N*-dibenzyl-L-valinal **L-313**, and *N,N*-dibenzyl-L-alaninal **L-316** were prepared in two steps from the corresponding amino alcohols using procedures inspired by the literature.<sup>192,196.</sup>

The synthesis of *N,N*-dibenzyl-L-leucinal **L-310** is shown in Scheme **109**. Commercial L-leucinol **L-308** was treated with benzyl bromide in the presence of a large excess of potassium carbonate in CH<sub>3</sub>CN at rt for 16 hours. Workup then column chromatography gave *N,N*-dibenzyl-L-leucinol **L-309** in 82% yield. The optical purity of this compound was checked by comparing its optical rotary value ( $[\alpha]_D^{23} = +79.5$  (*c* 1.0, CHCl<sub>3</sub>)) with that in the literature ( $[\alpha]_D^{20} = +86.4$  (*c* 1.00, CHCl<sub>3</sub>)).<sup>251</sup> The alcohol **L-309** was then

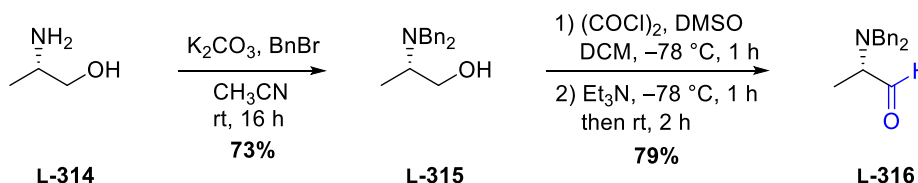
submitted to Swern oxidation to give *N,N*-dibenzyl-L-leucinal **L-310** in 88% yield. The optical rotation of aldehyde **L-310** was checked ( $[\alpha]_D^{24} = -63.6$  (c 1.0, CHCl<sub>3</sub>)), although there is no reported optical rotation value of this compound in the literature. It was used directly without purification in subsequent experiments.

Scheme 109, Synthesis of *N,N*-dibenzyl-L-leucinal

Similarly, commercial L-valinol **L-311** was dibenzylated to give *N,N*-dibenzyl-L-valinol **L-312** in 76% yield (Scheme 110). The optical purity of this compound was confirmed by comparing its optical rotation value ( $[\alpha]_D^{22} = +24.8$  (c 1.0, CHCl<sub>3</sub>)) with that described in the literature ( $[\alpha]_D^{28} = +23.1$  (c 1.00, CHCl<sub>3</sub>)).<sup>252</sup> The subsequent Swern oxidation of alcohol **L-312** was completed in four hours with very careful handling as the aldehyde **L-313** is very unstable. The optical purity of **L-313** was checked ( $[\alpha]_D^{27} = -56.0$  (c 1.0, CHCl<sub>3</sub>)), which was slightly lower than that in the literature ( $[\alpha]_D^{24} = -63.4$  (c 1.00, CHCl<sub>3</sub>)).<sup>252</sup> Due to its instability, aldehyde **L-313** was used directly in the next MAC reaction without purification.

Scheme 110, Synthesis of *N,N*-dibenzyl-L-valinal

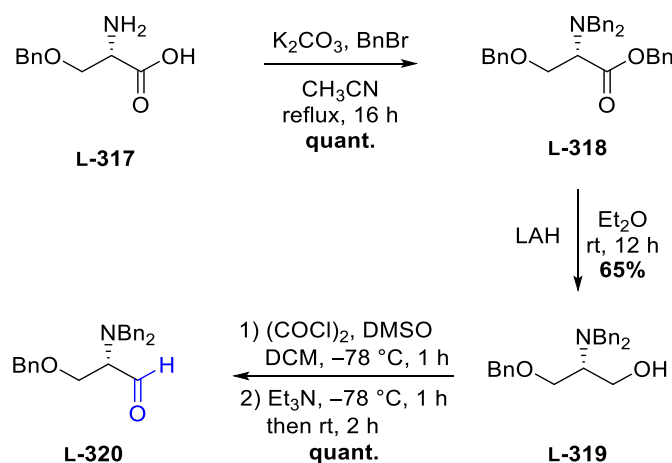
*N,N*-Dibenzyl-L-alaninal **L-316** was prepared from commercially available L-valinol **L-314** (Scheme 111). *N,N*-Dibenzyl-L-alaninol **L-315** was obtained in 73% yield after column chromatography, and its purity was confirmed by comparing the optical rotation and the melting point values ( $[\alpha]_D^{24} = +85.5$  (c 1.0, CHCl<sub>3</sub>), Mp = 42 °C) with those described in the literature ( $[\alpha]_D^{26} = +109.0$  (c 1.0, CHCl<sub>3</sub>)<sup>253</sup>, Mp = 41 °C<sup>254</sup>). Subsequent Swern oxidation of the alcohol **L-315** gave *N,N*-dibenzyl-L-alaninal **L-316** in 79% yield. The enantiomeric purity of the crude aldehyde **L-316** was confirmed by comparing its optical rotation value ( $[\alpha]_D^{27} = -38.7$  (c 1.0, CHCl<sub>3</sub>)) with that described in the literature ( $[\alpha]_D^{20} = -31.9$  (c 1.0, CHCl<sub>3</sub>)).<sup>255</sup> However, we noticed that the optical rotation value decreased quickly during the measurement. The crude aldehyde **L-316** is a colorless oil that turns quickly into a brown syrup; so, the following MAC reaction must be performed immediately and without any purification of the starting aldehyde **L-316**.

Scheme 111, Synthesis of *N,N*-dibenzyl-L-alaninal **L-316**



## II.2 From $\alpha$ -amino acid

*N,N,O*-Tribenzyl-L-serinal **L-320** was prepared following a three-step strategy inspired by the literature (Scheme 112).<sup>254</sup>



Scheme 112, Synthesis of *N,N,O*-tribenzyl-L-serinal

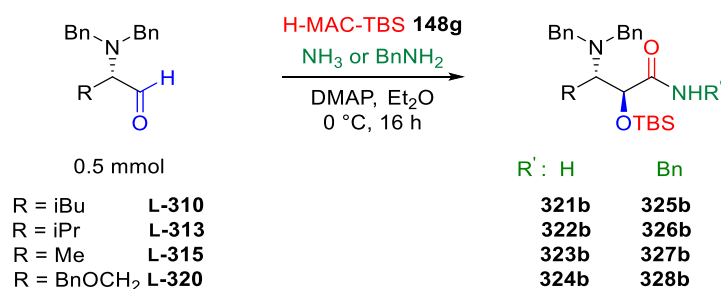
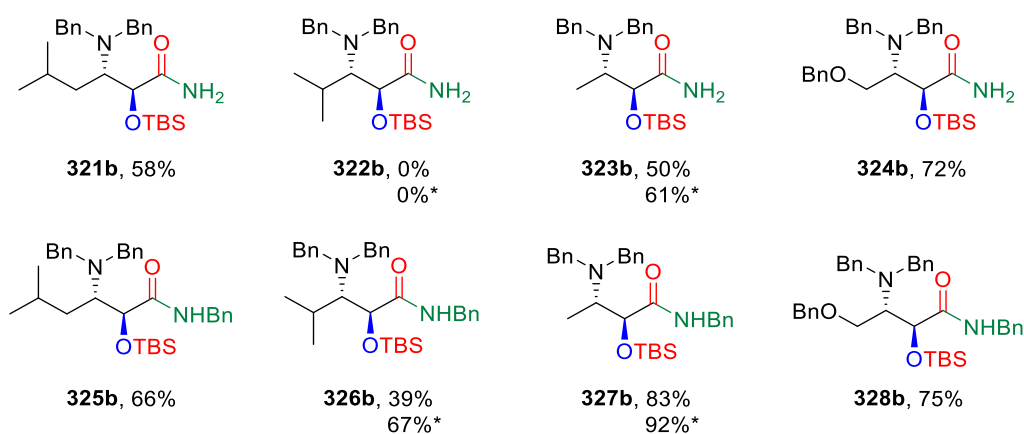
Commercially available *O*-Bn-L-serine **L-317** was reacted with an excess of benzyl bromide and potassium carbonate in acetonitrile for 16 hours under reflux. After workup, crude benzyl *N,N,O*-tribenzyl-L-serinate **L-318** was obtained in quantitative yield.

The reduction of benzyl ester **L-318** was achieved by treatment with lithium aluminum hydride for 12 hours at room temperature. After column chromatography, *N,N,O*-tribenzyl-L-serinol **L-319** was obtained in 65% yield. The optical rotation of alcohol **L-319** was checked ( $[\alpha]_{\text{D}}^{23} = +55.5$  (*c* 1.0, EtOAc)), and it was lower than that described in the literature ( $[\alpha]_{\text{D}}^{20} = +65.4$  (*c* 1.0, EtOAc)).<sup>254</sup>

The subsequent Swern oxidation of alcohol **L-319** gave *N,N,O*-tribenzyl-L-serinal **L-320** in quantitative yield. The optical rotation of aldehyde **L-320** was measured ( $[\alpha]_{\text{D}}^{24} = -7.1$  (*c* 1.0, CHCl<sub>3</sub>)), although there is no reported value for this compound in the literature. It was used directly without purification in subsequent MAC reactions.

## III. MAC reactions with H-MAC-TBS and amines

*N,N*-Dibenzyl  $\alpha$ -amino aldehydes **L-310**, **L-313**, **L-316**, **L-320** were examined in MAC reactions under the optimal conditions established for the reaction of amines (see Chapter 3, III.1.1): 0.5 mmol of aldehyde was mixed with 2.4 eq. of H-MAC-TBS **148g** in Et<sub>2</sub>O at rt, 1.2 eq. of nucleophile (benzylamine or ammonia) was introduced at 0 °C, followed by the addition of 2.0 eq. of DMAP then stirring for 16 hours at 0 °C. Yields of MAC products **321b-328b** are given for isolated material after column chromatography. Results are shown in Scheme 113. In each case, we observed only one diastereomer in the <sup>1</sup>H NMR spectra based on either the crude products or after chromatography. Therefore, the diastereomeric ratios (dr) were considered to be <2:98 *syn/anti* based on the previous study from the MAC reaction of *N,N*-dibenzyl-L-phenylalaninal **L-13** and ammonia (see chapter 3 III.1.2).

Scheme 113, MAC reactions with different  $\alpha$ -amino aldehydes

\* DMAP was first added at 0 °C, followed by the nucleophile 15 minutes later

Ammonia was first employed to react with each of the four aldehydes in the standard reaction conditions. *N,N*-Dibenzyl-L-leucinal **L-310**, *N,N*-dibenzyl-L-alaninal **L-316**, and *N,N,O*-tribenzyl-L-serinal **L-320** gave the corresponding MAC products **321b**, **323b** and **324b** in moderate to good yields (58%, 50% and 72% respectively). However, MAC product **322b** was not obtained from *N,N*-dibenzyl-L-valinal **L-313**.

In further experiments, benzylamine was employed as the nucleophilic partner in MAC reactions with each of the four aldehydes in the standard reaction conditions. When *N,N*-dibenzyl-L-leucinal **L-310** was used, MAC product **325b** was obtained in 66% yield. When *N,N*-dibenzyl-L-valinal **L-313** was used, the yield of **326b** reached 39%. *N,N*-dibenzyl-L-alaninal **L-316** and *N,N,O*-tribenzyl-L-serinal **L-320** gave MAC product **327b** and **328b** in 83% yield and 75%, respectively.

Inspired by the previous MAC reaction results using H-Val-OMe **273** as the nucleophile (see Chapter 3, IV.3.3), we investigated the consequence of delaying the addition of the nucleophilic partner in the case of *N,N*-dibenzyl-L-valinal **L-313** and *N,N*-dibenzyl-L-alaninal **L-316**. On a 0.5 mmol scale, aldehyde and 2.4 eq. of H-MAC-TBS **148g** were mixed in Et<sub>2</sub>O at rt, 2.0 eq. of DMAP was added at 0 °C and stirred for 15 minutes at 0 °C; then the nucleophile was added and the mixture was stirred for another 16 hours at 0 °C. After standard workup, the reaction of *N,N*-dibenzyl-L-alaninal **L-316** and ammonia gave the MAC product **323b** in 61% yield, but *N,N*-dibenzyl-L-valinal **L-313** with ammonia still didn't afford expected MAC product **322b**. With benzylamine, *N,N*-dibenzyl-L-valinal **L-313** gave the MAC product **326b** in a higher yield (67%) than when the standard amine procedure was applied. The yield of the

MAC product **327** from *N,N*-dibenzyl-L-alaninal **L-327** was also improved by delaying the addition of benzylamine and reached 92%. In all cases, only one diastereomer was observed in the crude and purified  $^1\text{H}$  NMR spectra.

#### IV. Discussion

The synthesis of *N,N*-dibenzyl-L-leucinal **L-310**, *N,N*-dibenzyl-L-valinal **L-313**, and *N,N*-dibenzyl-L-alaninal **L-316** was achieved from their corresponding amino alcohols, through a dibenylation and Swern oxidation sequence. *N,N,O*-Tribenzyl-L-serinal **L-320** was prepared from *O*-Bn-L-serine, through a *N,N,O*-tribenylation, LAH reduction and Swern oxidation sequence. All target  $\alpha$ -amino aldehydes were obtained in good yields. Concerning the optical purity of these  $\alpha$ -amino aldehydes, the optical rotation values for *N,N*-dibenzyl-L-leucinal **L-310** and *N,N,O*-tribenzyl-L-serinal **L-320** were not reported in the literature, while the values for *N,N*-dibenzyl-L-valinal **L-313** and *N,N*-dibenzyl-L-alaninal **L-316** were slightly different from the literature. Nevertheless, we decided to use those materials in MAC reactions because the enantiomeric purity has no effect on the diastereoselectivity study of a MAC reaction. However, if applications for the preparation of single stereoisomer molecular targets were to be envisaged, this issue would need to be solved.

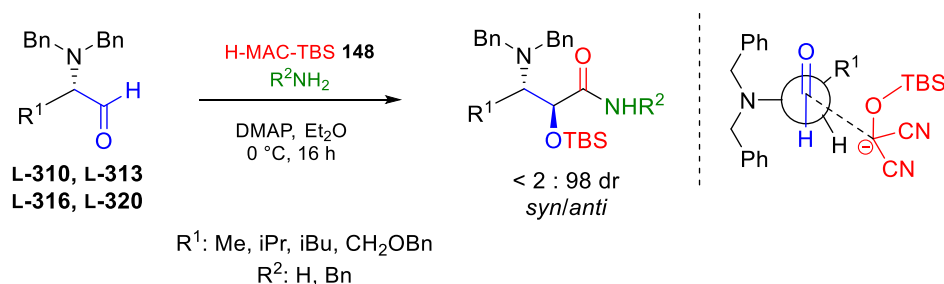
The MAC reactions of those four  $\alpha$ -amino aldehydes were examined first with ammonia and H-MAC-TBS **148g**. The yields of the MAC product appear to be related to the steric bulk of the aldehyde: 58% yield for **321b** from *N,N*-dibenzyl-L-leucinal **L-310**, 50% yield for **323b** from *N,N*-dibenzyl-L-alaninal **L-316** and 72% for **324b** from *N,N,O*-tribenzyl-L-serinal **L-320**. In all experiments, only one diastereomer was observed in  $^1\text{H}$  NMR spectra; therefore the dr values were considered to be <2:98 *syn/anti* based on the previous observation in reactions of *N,N*-dibenzyl-L-phenylalaninal **L-13**, ammonia and H-MAC-TBS **148g**. The use of *N,N*-dibenzyl-L-valinal **L-313** did not yield the desired MAC product nor any other identifiable products.

Using benzylamine as the nucleophile, reactions with H-MAC-TBS **148g** and each of the four aldehydes led to the corresponding MAC products **325b-328b** in moderate to good yields. The yields in this series were highly correlated with the steric bulk of the aldehyde: *N,N*-dibenzyl-L-leucinal **L-310** gave **325b** in a yield of 66%; the yield of **326b** dropped to 39% when *N,N*-dibenzyl-L-valinal **L-313** was used; when *N,N*-dibenzyl-L-alaninal **L-316** was used, the yield of **327b** increases to 83% and finally, the use of *N,N,O*-tribenzyl-L-serinal **L-320** gave **328b** in 75% yield. In all cases, only one diastereomer was observed, suggesting that the high diastereoselectivity was independent of the steric bulk from the aldehyde substrates.

Given the unstable nature of *N,N*-dibenzyl-L-valinal **L-313** and *N,N*-dibenzyl-L-alaninal **L-316**. MAC reactions of those two aldehydes were optimized by delaying the addition of nucleophiles. Results showed that this modification could indeed improve the yields: for the MAC reaction of *N,N*-dibenzyl-L-alaninal **L-316** and ammonia, the yield of **323b** increased to 61%; for the MAC reaction of *N,N*-dibenzyl-L-valinal **313** and benzylamine, the yield of **326b** increased to 67%; for the MAC reaction of *N,N*-dibenzyl-L-alaninal **L-316** and benzylamine, the yield of **327b** increased to 92%. In all cases, only

one diastereomer was observed, suggesting an excellent *anti* diastereoselectivity was maintained under these conditions. Again, the use of *N,N*-dibenzyl-L-valinal **L-313** and ammonia did not yield the desired MAC product.

With the exception of *N,N*-dibenzyl-L-valinal **L-313** with ammonia, all the MAC reactions studied gave the corresponding MAC products in moderate to very good yields. Most significantly, the excellent *anti* diastereoselectivity was in evidence in all cases. These results indicated that the substituent at the  $\beta$ -position of the *N,N*-dibenzyl  $\alpha$ -amino aldehyde does not affect the diastereoselectivity of the MAC reaction. In other words, the *N,N*-di-substituted  $\alpha$ -amino group always plays a determining role in controlling the diastereoselectivity of this MAC reaction, which can be explained by the following Felkin-Anh model (Scheme 114).



Scheme 114, *Anti* diastereoselectivity of MAC reactions with *N,N*-dibenzyl  $\alpha$ -amino aldehydes

As mentioned earlier, the diastereoselectivity in reported examples for synthesizing AHBA changed with the starting substrate. However, in the one-pot MAC methodology, the high *anti* diastereoselectivity is maintained for different *N,N*-dibenzyl  $\alpha$ -amino aldehydes. Therefore, this methodology might be applicable to the efficient construction of other *anti*-AHBA skeletons (for example, epiamastatin<sup>256</sup>).

It is worth mentioning that following Esgulian's MAC reaction using Garner's aldehyde, H-MAC-TBDPS and ammonia (See Introduction, Table 6, entry 9), a *N,O*-acetonide hydrolysis of the *anti* MAC product into to release the free  $\gamma$ -hydroxy group was described. The product was then transformed into Fmoc-protected *erythro*- $\beta$ -hydroxyasparagine (*eHyAsn*),<sup>175</sup> which was previously used for the solid-phase synthesis of cyclodepsipeptide stellatolide A.<sup>257</sup> In our research, the MAC reaction of *N,N,O*-tribenzyl-L-serinal **L-320**, H-MAC-TBS **148g** and ammonia indeed gave the key *anti*-AHBA feature **324b** as the only MAC product. Compared with Esgulian's results, our work gave the *anti* AHBA **324b** in a higher diastereoselectivity, and might provide an easier access to an intermediate in the synthesis of *eHyAsn*.

## V. Conclusion

When different *N,N*-dibenzyl  $\alpha$ -amino aldehydes were employed in the one-pot MAC reaction with H-MAC-TBS and amine, the yield decreased with increased steric bulk of the starting aldehyde. However, in all cases, the diastereoselectivity of the MAC reaction was very high (<math>< 2 : 98 \text{ syn/anti}</math>), suggesting that the *anti* diastereoselectivity depends only on the protective group suite of the  $\alpha$ -amino groups.

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# General Conclusion & Perspectives

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## I. General Conclusion

The main objective of this thesis was to investigate the diastereoselectivity control of one-pot MAC oxyhomologation methodology, with the aim of opening new pathways for the diastereoselective synthesis of orthogonally protected AHPBA derivatives (esters, amides and dipeptides). The successful achievement of this goal also allowed us to conduct the synthesis of a wider library of other AHBA scaffolds.

We first optimized the three-step synthesis of H-MAC-[Si] reagents from malononitrile, using silyl triflates instead of silyl chlorides to establish a more efficient and reproducible synthesis of three silylated MAC reagents: H-MAC-TBS, H-MAC-TIPS and H-MAC-TBDPS.

Next, *N*-protected L-phenylalaninal, H-MAC-[Si], and alcohols were employed as MAC reaction partners, and we discovered that the diastereoselectivity of the MAC reaction was affected by the *N*-protection suite. Using *N*-Boc-L-phenylalaninal, H-MAC-[Si] and alcohols,  $\alpha$ -(*tert*-butyldimethylsilyloxy)- $\beta$ -(*tert*-butyloxycarbonylamino)-AHPBA esters were obtained in a universal 80:20 *syn/anti* dr, which was in line with previous results from Nemoto and Esgulian. The use of *N*-Boc-*N*-Bn-L-phenylalaninal, H-MAC-TBS and methanol gave oxyhomologated esters as a mixture of two diastereomers, but it was not possible to assign the configuration. When *N,N*-dibenzyl-L-phenylalaninal was employed to react with H-MAC-[Si] and methanol, the diastereoselectivity was reversed to *anti*, with a 10:90 *syn/anti* dr; the *anti* diastereoselectivity was independent to the nature of MAC reagents, and can be explained by a Felkin-Anh model.

Subsequently, we used *N,N*-dibenzyl-L-phenylalaninal with H-MAC-TBS and alcohols to investigate the scope and limitations of this MAC reaction. The yield varied with the steric hindrance of the alcohol, but all alcohols (including one which was chiral) gave a consistent 10/90 *syn/anti* dr, suggesting that the diastereoselectivity is independent of the nature of alcohol. Moreover, the yields from secondary alcohols were very low, although the dr was still maintained. Through this strategy, we realized the efficient synthesis of (2*S*,3*S*)-AHPBA methyl and ethyl ester, as well as (2*S*,3*S*)-AHPBA (allophenylnorstatin) itself, which is by far one of the most efficient methods to obtain (2*S*,3*S*)-AHPBA from L-phenylalaninal.

Ammonia and amines were also employed in the MAC reaction with *N,N*-dibenzyl-L-phenylalaninal and H-MAC-TBS. All MAC reactions gave homologated AHPBA amides in good to very good yields, and most importantly, the *syn/anti* dr was improved to <2 : 98. We also proved that the chiral center of the aldehyde was well maintained, which won't racemize in the MAC reaction conditions.

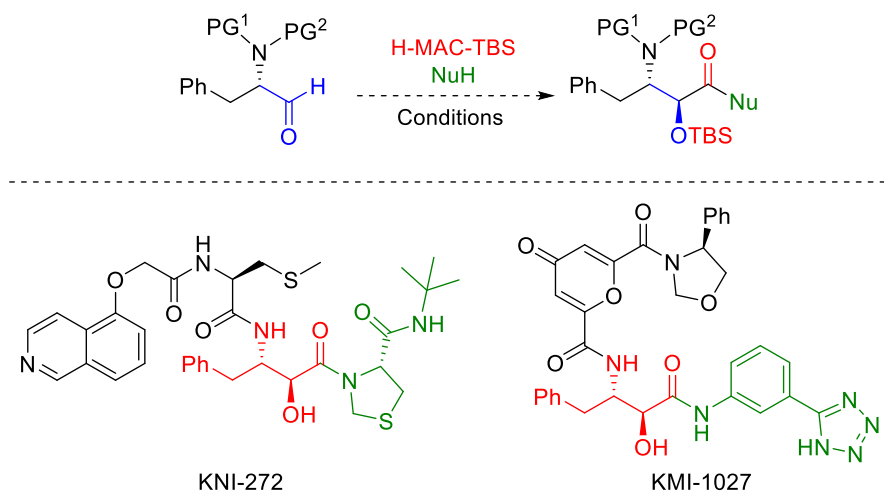
Different  $\alpha$ -amino esters were also screened as nucleophiles in the one-pot MAC reaction with *N,N*-dibenzyl-L-phenylalaninal and H-MAC-TBS, and a library of dipeptides containing *anti*-AHPBA was synthesized in high yields and diastereoselectivity. With this strategy, we achieved the efficient synthesis of (2*S*,3*S*,5)-epibestatin, an analog of biologically active (-)-bestatin.

Finally, MAC reactions of different *N,N*-dibenzyl  $\alpha$ -amino aldehydes (Leu, Ala, Val, Ser), amines (ammonia and benzylamine) and H-MAC-TBS were investigated, and the yields of these MAC reactions varied with the steric bulky size of the  $\alpha$ -side chain; but the dr were maintained as <2 : 98 *syn/anti* for all cases. These results suggested that the MAC methodology was applicable to the efficient construction of other *anti*-AHPBA features.

## II. Perspectives

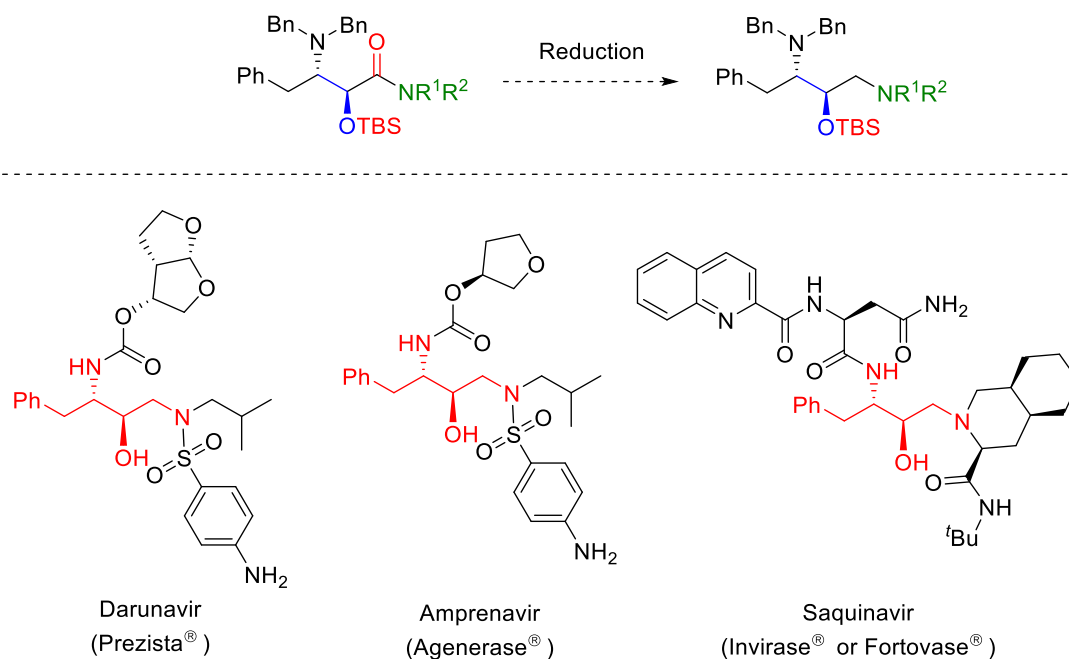
To date, few groups are studying MAC reagents and subsequent diastereoselective MAC reactions. Our findings could provide a strong tool for the *anti* oxyhomologation of  $\alpha$ -amino aldehydes.

1. It would be interesting to optimize the MAC reaction conditions for synthesizing *anti*-AHPBAs with large steric bulk or weak nucleophiles. Some nucleophiles, such as aniline or H-Pro-OMe, could not yield any oxyhomologated products in our MAC reaction conditions. These results proposed the challenge of synthesizing bioactive molecules such as KNI-272 or KMI-1027 (Scheme 115). We may need to continue to optimize the reaction conditions or change the steric bulk of the  $\alpha$ -amino protection groups.



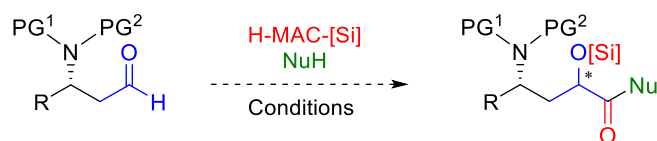
Scheme 115, Synthesis of KNI-272 and KMI-1027 by one-pot MAC reactions

2. The MAC reaction in the thesis allows us for the rapid synthesis of *anti*-AHPBA amides with very high diastereoselectivity. In fact, these amides could be reduced to hydroxylamine derivatives, which is the core structure of a series of clinical medicines such as Darunavir (Prezista® from Janssen, antiretroviral medication)<sup>258</sup>, Amprenavir (Agenerase® from GSK, HIV infection treatment)<sup>259</sup> and Saquinavir (Invirase® or Fortovase® from Roche, HIV-1 treatment)<sup>260</sup>. It is of great interest to investigate the effective reduction process to transform those *anti*-AHPBA amides into amines while maintaining the C $\alpha$  and C $\beta$  amide chiral centers (Scheme 116).



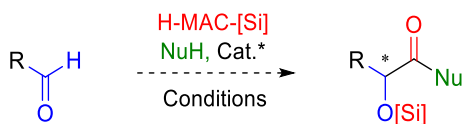
Scheme 116, Reduction of MAC products for the synthesis of clinical medicines

3. The synthesis of  $\alpha,\beta$ - or  $\beta,\gamma$ -disubstituted  $\gamma$ -amino acids derivatives is one of the main topics of the host lab. It would be interesting to investigate the diastereoselective oxyhomologation of  $\beta$ -amino aldehydes by a *one-pot* MAC reaction (Scheme 117).



Scheme 117, One-pot MAC reaction for the synthesis of  $\alpha$ -hydroxy- $\gamma$ -amino acid derivatives

4. Given that all enantioselective MAC reactions have so far been reported only using a sequential manner, it is of interest to perform the enantioselectivity control during a *one-pot* MAC reaction using non-chiral substrates (Scheme 118). This process may be achieved by using organocatalysts (such as proline derivatives), chiral amines as bases (thioureas, squaramides) or chiral phosphoric acids.



Scheme 118, Enantioselective one-pot MAC reactions



*Part III:*

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Experimental Part

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## General experimental information

Peracetic acid solution (35 wt.% in acetic acid) and ammonia (0.5 M in THF) were purchased from Acros. Solvents and reagents were purified under argon as follows: Et<sub>2</sub>O and THF were distilled from Na/benzophenone; DMF, 1,4-dioxane, acetonitrile, DMSO and 2,6-lutidine were distilled from CaH<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub> was passed through an activated alumina column immediately before use; methanol and ethanol were distilled from Mg/I<sub>2</sub>; benzyl alcohol, isopropanol, isobutanol, isoamyl alcohol and (*S*)-2-methylbutan-1-ol were distilled from CaO; allyl alcohol, propargyl alcohol and phenylethyl alcohol were dried over CaSO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub> and Na<sub>2</sub>SO<sub>4</sub> respectively, followed by distillation; benzylamine, morpholine and pyrrolidine were distilled from KOH; *n*-butylamine was distilled from CaH<sub>2</sub>; isobutylamine and cyclopropylamine were distilled from Na<sub>2</sub>SO<sub>4</sub>; propargylamine, isopropylamine and 2-aminoethanol were dried over 4 Å MS and subsequently distilled. All other reagents were obtained commercially and were used directly as supplied.

Preparative flash column chromatography was performed using columns packed with SDS (35-70 μm) or Macherey–Nagel (40-63 μm) silica gel. Preparative TLC was carried out on commercial 20 cm x 20 cm x 2 mm silica gel plates (Merck 60F-254). Analytical thin-layer chromatography, used to monitor preparative column chromatography and to provide characteristic retention factors (*R<sub>f</sub>*), was performed on 0.25 mm commercial coated silica gel plates (Merck 60F-254). TLC plates were visualized by UV fluorescence at 254 nm, then revealed by heating after dipping in a phosphomolybdic acid solution (6% in EtOH), or a ninhydrin solution (1.5% in *n*-BuOH) or a potassium permanganate solution (7.5% in water).

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker DPX 250 (250 and 62.9 MHz, respectively), Bruker AV 300 (300 and 75.5 MHz, respectively), Bruker AV 360 (360 and 90.6 MHz, respectively), Bruker AV 400 (400 and 100.6 MHz, respectively) or Bruker AVII 600 (600 MHz) spectrometers. Chemical shifts (δ) are given in parts per million, using solvent signals as internal standards (CDCl<sub>3</sub>: δ<sub>H</sub> = 7.26 ppm, δ<sub>C</sub> = 77.0 ppm; DMSO-*d*<sub>6</sub>: δ<sub>H</sub> = 2.50 ppm, δ<sub>C</sub> = 39.5 ppm; CD<sub>3</sub>OD: δ<sub>H</sub> = 3.31 ppm, δ<sub>C</sub> = 49.0 ppm; D<sub>2</sub>O: δ<sub>H</sub> = 4.79 ppm). Assignments were aided by JMOD pulse sequences and 2D experiments (HSQC, HMBC, COSY). Splitting patterns for <sup>1</sup>H NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (*J*) are reported in hertz (Hz).

Positive and negative electrospray (ES<sup>+</sup>, ES<sup>-</sup>) high resolution mass spectra (HRMS) were recorded with a Bruker Daltonics micrOTOF-Q instrument.

Melting points (Mp) were obtained in open capillary tubes using a Büchi M-560 melting point apparatus and are uncorrected.

Infrared spectroscopy (IR) analyses were recorded on a FT-IR Perkin-Elmer Spectrum Two spectrophotometer; maximum absorbances (ν) are given in cm<sup>-1</sup>. Spectra of neat samples were recorded using an ATR diamond accessory. For compound **L-5**, the solution state spectrum was

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recorded as a 5 mM CHCl<sub>3</sub> solution in an Omni-cell Specac 1 mm path-length NaCl solution cell, with background solvent subtraction.

Optical rotations (OR) were measured on a Jasco P-1010 polarimeter using a 10 cm quartz cell; values for  $[\alpha]_D^T$  were obtained with the D-line of sodium at the indicated temperature  $T$ , using solutions of concentration ( $c$ ) in units of g.100 mL<sup>-1</sup>.

Elemental analyses were performed by the Microanalysis Service of the I.C.S.N. (Gif-sur-Yvette, France).

Single crystals suitable for X-ray diffraction were obtained by slow diffusion of pentane into a Et<sub>2</sub>O solution of **231b**, **249b** and **259b** at ambient temperature. For compounds **231b** and **249b**, X-ray diffraction data were collected by using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus I $\mu$ S source CuK $\alpha$  radiation. For compound **259b**, X-ray diffraction data were collected by using a Kappa X8 APPEX II Bruker diffractometer with graphite-monochromated MoK $\alpha$  radiation ( $\lambda = 0.71073$  Å). In all cases, the crystal was mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flash-frozen in a nitrogen-gas stream at 100 K. The temperature of the crystal was maintained at the selected value by means of a 700 series Cryostream cooling device to within an accuracy of  $\pm 1$  K. The data were corrected for Lorentz polarization and absorption effects. The structures were solved by direct methods using SHELXS-97<sup>[1]</sup> and refined against  $F^2$  by full-matrix least-squares techniques using SHELXL-2018<sup>[2]</sup> with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. Calculations were performed by using the Crystal Structure crystallographic software package WINGX.<sup>[3]</sup> The absolute configuration was determined by refining the Flack parameters<sup>[4]</sup> using a large number of Friedel's pairs.

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<sup>[1]</sup> Sheldrick, G. M. SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, **1997**.

<sup>[2]</sup> Sheldrick, G. M. *Acta Cryst. A* **2008**, *64*, 112-122.

<sup>[3]</sup> Farrugia, L. J. *J. Appl. Cryst.*, **1999**, *32*, 837-838.

<sup>[4]</sup> Parsons, S.; Flack, H. D.; Wagner, T. *Acta Cryst. B* **2013**, *69*, 249–259.

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## General procedures

### General procedure for the *N,N*-dibenylation of $\alpha$ -amino alcohols.<sup>196</sup>

To a solution of  $\alpha$ -amino alcohol (c. 0.2 mmol, 1 equiv.) in CH<sub>3</sub>CN was added K<sub>2</sub>CO<sub>3</sub> (2.4 equiv.) and the mixture was cooled down until 0 °C. BnBr (2.4 equiv.) was added dropwise, and the reaction mixture was stirred overnight under argon at room temperature. NEt<sub>3</sub> (10 mL) was added, and the mixture was stirred for an additional 30 minutes. Then, EtOAc (20 mL) and water (20 mL) were added, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Flash column chromatography gave the *N,N*-dibenzylated  $\alpha$ -amino alcohol.

### General procedure for the Swern oxidation of $\alpha$ -amino alcohols.<sup>192</sup>

To dry DMSO (2.6 equiv.), dry DCM (10 mL) was added, and the solution was cooled down to -78 °C by a dry ice/acetone bath. Oxalyl chloride (1.3 equiv.) was added dropwise, and the reaction mixture was stirred at -78 °C for 1 hour. Then, the  $\alpha$ -amino alcohol (c. 1.6 mmol, 1 equiv.) was added as a solid or as a solution in DCM (2 mL). After stirring for 1 hour at -78 °C, NEt<sub>3</sub> (2.6 equiv.) was introduced in one portion and the reaction mixture was stirred for 1 hour at -78 °C followed by 2 hours at room temperature. After addition of DCM (20 mL) and water (20 mL), the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were washed successively with a saturated aqueous NH<sub>4</sub>Cl solution (50 mL) and brine (50 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The resulting turbid liquid was diluted with Et<sub>2</sub>O (5 mL), filtered over cotton and the filtrate was concentrated under high vacuum to give crude  $\alpha$ -amino aldehyde. It was used without any purification in the next step.

### General procedures for the MAC reactions.

**Method A (alcohol procedure).** To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** (c. 0.5 mmol, 1 equiv.) and H-MAC-[Si] **148g-i** (2.4 equiv.) under argon, were added dry Et<sub>2</sub>O (5 mL) followed by the alcohol (3 equiv.). After cooling at 0 °C, DMAP (2 equiv.) was added in one portion and the reaction mixture was stirred overnight under argon at this temperature. A saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (10 mL) was introduced at 0 °C. After addition of water (10 mL) to dissolve the salts, the aqueous phase was extracted with Et<sub>2</sub>O (6 x 10 mL). The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash chromatography to give the corresponding ester MAC reaction products.

**Method B (amine procedure).** To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** or *N*-Cbz-L-phenylalaninal **L-5** or *N,N*-dibenzyl  $\alpha$ -amino aldehyde **L-310**, **L-313**, **L-316**, **L-320** (c. 0.5 mmol, 1 equiv.) and H-MAC-TBS **148g** (2.4 equiv.) under argon, was added dry Et<sub>2</sub>O (5 mL). After cooling at 0 °C, the amine (1.2 equiv.) or the  $\alpha$ -amino acid ester (1.2 equiv.) was introduced, followed by DMAP (2 equiv.) in one portion. The reaction mixture was stirred overnight under argon at 0 °C, then a saturated

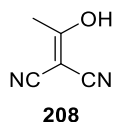
aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) was added. After addition of water (20 mL) to dissolve the salts, the aqueous phase was extracted with Et<sub>2</sub>O (6 × 10 mL). The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash chromatography to give the corresponding amide MAC reaction products.

**Method C (*epi*-bestatin procedure).** To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** or *N,N*-dibenzyl-D-phenylalaninal **D-13** or *N,N*-dibenzyl α-amino aldehyde **L-310**, **L-313**, **L-316**, **L-320** (c. 0.5 mmol, 1 equiv.) and H-MAC-TBS **148g** (2.4 equiv.) under argon, was added dry Et<sub>2</sub>O (5 mL). After cooling at 0 °C, DMAP (2 equiv.) was added in one portion, followed 15 minutes later by the alcohol (3 equiv.), or amine (1.2 equiv.) or the α-amino acid ester (1.2 equiv.). The reaction mixture was stirred overnight under argon at 0 °C, then a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) was added. After addition of water (20 mL) to dissolve the salts, the aqueous phase was extracted with Et<sub>2</sub>O (6 × 10 mL). The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash chromatography to give the corresponding amide MAC reaction products.

**Method D (from the hydrochloride salt of the α-amino acid ester).** To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** (c. 0.5 mmol, 1 equiv.) and H-MAC-TBS **148g** (2.4 equiv.) under argon, was added dry Et<sub>2</sub>O (5 mL). After cooling at 0 °C, DMAP (3.2 equiv.) was added in one portion, followed 15 minutes later by the amine (1.2 equiv.) or the α-amino acid methyl ester hydrochloride (1.2 equiv.). The reaction mixture was stirred overnight under argon at 0 °C, then a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) was added. After addition of water (20 mL) to dissolve the salts, the aqueous phase was extracted with Et<sub>2</sub>O (6 × 10 mL). The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash chromatography to give the corresponding amide MAC reaction products.

## Chapter 1: Synthesis of silylated MAC reagents, H-MAC-[Si]

### 2-(1-Hydroxyethylidene)malononitrile (**208**).



C<sub>5</sub>H<sub>4</sub>N<sub>2</sub>O  
108 g/mol

Commercially available malononitrile (3.00 g, 45.4 mmol) was dissolved in ether (50 mL). Potassium carbonate (7.50 g, 54.3 mmol) was added in one portion and the reaction mixture was stirred vigorously for 1 hour at room temperature under argon. After cooling at 0 °C, acetic anhydride (6.9 mL, 73.0 mmol) diluted in Et<sub>2</sub>O (25 mL) was added dropwise over 20 min and the reaction mixture was stirred for 4 hours at room temperature. Water (30 mL) was introduced, and the mixture was acidified at 0 °C with concentrated HCl until pH ~ 1. The aqueous phase was extracted with Et<sub>2</sub>O (3 x 20 mL) and the combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give 2-(1-hydroxyethylidene)malononitrile **208** (4.60 g, 94%) as a yellow-orange solid (Mp = 141 °C). Crude 2-(1-hydroxyethylidene)malononitrile **208** obtained in this way showed a very satisfactory <sup>1</sup>H NMR spectrum and could be used in the subsequent reaction without further purification. An analytically pure sample was obtained by recrystallization from Et<sub>2</sub>O/*n*-hexane to furnish **208** (4.22 g, 86%) as a light yellow-orange solid.

**Mp** = 141 °C (lit.<sup>180</sup> 141 °C)

**TLC** R<sub>f</sub> = 0.25 (EtOAc/MeOH, 9:1)

**IR** (ATR), ν (cm<sup>-1</sup>): 3045, 2610, 2238, 2225, 1600, 1574, 1507, 1402, 1359, 1227

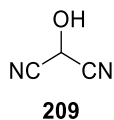
**HRMS** (ES<sup>-</sup>): calcd. for C<sub>5</sub>H<sub>3</sub>N<sub>2</sub>O [M-H]<sup>-</sup> 107.0251; found 107.0250

**<sup>1</sup>H NMR** (360 MHz, DMSO-*d*<sub>6</sub>), δ (ppm): 2.21 (s, 3H, =C-CH<sub>3</sub>), 12.1 (br s, 1H, =C-OH)

**<sup>13</sup>C NMR** (62.9 MHz, DMSO-*d*<sub>6</sub>), δ (ppm): 21.2 (=C-CH<sub>3</sub>), 59.2 (C(CN)<sub>2</sub>), 113.8 (C(CN)CN), 115.7 (C(CN)CN), 189.3 (=C-OH)

**Anal.** calcd. for C<sub>5</sub>H<sub>4</sub>N<sub>2</sub>O: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.54; H, 3.53; N, 25.97

### 2-Hydroxymalononitrile (**209**).



C<sub>3</sub>H<sub>2</sub>N<sub>2</sub>O  
82 g/mol

To a solution of crude 2-(1-hydroxyethylidene)malononitrile **208** (1.00 g, 9.26 mmol) in water (24 mL) was added dropwise over 10 min at 0 °C a peracetic acid solution (35 wt.% in acetic acid, 6.2 mL, 32.3 mmol) diluted with glacial acetic acid (20 mL). After complete addition, the resulting clear yellow solution was stirred at room temperature for 2 hours. The reaction mixture was gradually concentrated on a rotary evaporator (water bath below 35 °C) until 10 mbar and traces of acetic acid were removed by three co-evaporations with water. (NOTE: Although we have never observed any complications, a

Plexiglas protective shield around the rotary evaporator was used during concentration of peracetic acid). The residual yellowish oil was dried under high vacuum ( $10^{-2}$  mbar) until no more traces of water or acetic acid were observed by  $^1\text{H}$  NMR (around 2 h). Unstable 2-hydroxymalononitrile **209** (~760 mg, 9.26 mmol, quant.), isolated as a milky yellowish oil, was quickly analyzed by NMR. It was then engaged directly in the next reaction without any purification.

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ),  $\delta$  (ppm): 6.08 (s, 1H,  $\text{CH}(\text{CN})_2$ ), 8.22 (br s, 1H, OH)

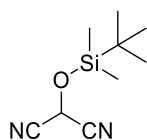
$^{13}\text{C}$  NMR (62.9 MHz,  $\text{DMSO}-d_6$ ),  $\delta$  (ppm): 49.9 ( $\text{CH}(\text{CN})_2$ ), 114.6 ( $\text{CH}(\text{CN})_2$ )

### General procedures for 2-hydroxymalononitrile silylation

**Method E (using a silyl chloride).** Crude 2-hydroxymalononitrile **209** (4.63 mmol, 1 equiv.) was dissolved in DMF (10 mL) under argon and the solution was cooled at 0 °C. Silyl chloride reagent (1.5 equiv.) was added in one portion, followed by imidazole (2.0 equiv.) in several portions. The reaction mixture was then stirred for the specified time and at the indicated temperature (see below). After addition of a saturated aqueous  $\text{Na}_2\text{CO}_3$  solution (10 mL), the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (6 x 10 mL). The combined organic layers were washed with 1 M HCl (50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated on a rotary evaporator (water bath at 40 °C) until the appropriate pressure depending of the nature of the H-MAC-[Si]. The crude residue was then purified by flash silica gel column chromatography to afford pure *O*-silylated hydroxymalononitrile.

**Method F (using a silyl triflate).** To an ice-cooled mixture of crude 2-hydroxymalononitrile **209** (4.63 mmol, 1 equiv.) in  $\text{CH}_2\text{Cl}_2$  (5 mL) under argon was added the silyl triflate reagent (1.5 equiv.) in a single portion followed by dropwise addition of 2,6-lutidine (2.0 equiv.) and the reaction mixture was then stirred for the specified time and at the indicated temperature (see below). After addition of a saturated aqueous  $\text{Na}_2\text{CO}_3$  solution (10 mL), the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (6 x 10 mL) and the combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated on a rotary evaporator (water bath at 40 °C) until the appropriate pressure depending on the nature of the H-MAC-[Si]. The crude residue was then purified by flash silica gel column chromatography to afford pure *O*-silylated hydroxymalononitrile.

#### 2-(*tert*-Butyldimethylsilyloxy)malononitrile, H-MAC-TBS (148g).



$\text{C}_9\text{H}_{16}\text{N}_2\text{OSi}$

196 g/mol

148g

According to method E: silylation of 2-hydroxymalononitrile **209** (380 mg, 4.63 mmol) was performed with *tert*-butyldimethylsilyl chloride (1.05 g, 7.00 mmol) and imidazole (630 mg, 9.26 mmol,) in DMF for 30 min at 0 °C followed by 30 min at room temperature. After work-up and concentration under reduced pressure (until 450 mbar), the brown liquid residue was purified by flash silica gel column

chromatography (pentane then pentane/Et<sub>2</sub>O, 20:1; then concentration of fractions on a rotary evaporator with a water bath at 40 °C until 450 mbar) to give H-MAC-TBS **148g** (583 mg, 65% over 2 steps) as a colorless liquid.

*According to method F:* silylation of 2-hydroxymalononitrile **209** (380 mg, 4.63 mmol) was carried out with *tert*-butyldimethylsilyl triflate (1.6 mL, 6.97 mmol) and 2,6-lutidine (1.08 mL, 9.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> for 30 min at 0 °C followed by 30 min at room temperature. After work-up and concentration under reduced pressure (until 450 mbar), the pale brown liquid residue was purified by flash silica gel column chromatography (pentane then pentane/Et<sub>2</sub>O, 20:1; then concentration of fractions on a rotary evaporator with a water bath under 40 °C until 450 mbar) to furnish H-MAC-TBS **148g** (790 mg, 87% over 2 steps) as a colorless liquid.

H-MAC-TBS **148g** can be stored under argon for several months at -18 °C.

TLC  $R_f$  = 0.18 (pentane/Et<sub>2</sub>O, 20:1)

IR (ATR),  $\nu$  (cm<sup>-1</sup>): 2957, 2934, 2862, 2252, 1473, 1259, 1115

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.28 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.94 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 5.33 (s, 1H, CH(CN)<sub>2</sub>)

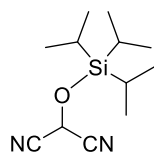
<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -5.5 (Si(CH<sub>3</sub>)<sub>2</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 50.8 (CH(CN)<sub>2</sub>), 112.3 (CH(CN)<sub>2</sub>)

**Anal.** calcd. for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>OSi: C, 55.06; H, 8.21; N, 14.27. Found: C, 54.81; H, 8.12; N, 14.13.

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>128</sup>

**Larger scale synthesis of H-MAC-TBS (148g).** To a solution of crude 2-(1-hydroxyethylidene)malononitrile **208** (2.15 g, 19.9 mmol) in water (25 mL) was added dropwise over 20 min at 0 °C a peracetic acid solution (35 wt.% in acetic acid, 13.4 mL, 69.8 mmol) diluted with glacial acetic acid (42 mL). After complete addition, the resulting clear yellow solution was stirred at room temperature for 2 hours. The reaction mixture was gradually concentrated on a rotary evaporator (water bath below 35 °C) until 10 mbar and traces of acetic acid were removed by three co-evaporations with water. (NOTE: Although we have never observed any complications, a Plexiglas protective shield around the rotary evaporator was used during concentration of peracetic acid). The residual yellowish oil was dried under high vacuum (10<sup>-2</sup> mbar) until no more trace of water and acetic acid was observed by <sup>1</sup>H NMR (around 2 h). To the crude 2-hydroxymalononitrile **209** (1.66 g, 19.9 mmol) in solution in CH<sub>2</sub>Cl<sub>2</sub> (8 mL), were slowly introduced *tert*-butyldimethylsilyl triflate (7.1 mL, 31.0 mmol), followed by 2,6-lutidine (4.8 mL, 41.5 mmol). The resulting solution was stirred for 30 min at 0 °C and for an additional 30 min at room temperature. After addition of a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (40 mL), the aqueous layer was extracted with Et<sub>2</sub>O (6 x 20 mL) and the combined organic phases were washed with 1 M HCl (100 mL), brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated on a rotary evaporator (water bath at 40 °C) until 450 mbar. The crude residue was then purified by flash silica gel column chromatography (pentane then pentane/Et<sub>2</sub>O, 20:1; then concentration of fractions on a rotary evaporator with a water bath under 40 °C until 450 mbar) to furnish compound **148g** (3.79 g, 97% over 2 steps) as a colorless liquid.



**2-(Triisopropylsilyloxy)malononitrile, H-MAC-TIPS (148h).**C<sub>12</sub>H<sub>22</sub>N<sub>2</sub>OSi

238 g/mol

**148h**

According to method E: silylation of 2-hydroxymalononitrile **209** (380 mg, 4.63 mmol) was performed with triisopropylsilyl chloride (1.5 mL, 7.01 mmol) and imidazole (630 mg, 9.26 mmol) in DMF overnight from 0 °C to room temperature. After work-up and concentration under reduced pressure, the brown liquid residue was purified by two successive silica gel column chromatographies (pentane then pentane/Et<sub>2</sub>O, 50:1; pentane then pentane/Et<sub>2</sub>O, 20:1) to separate H-MAC-TIPS from triisopropylsilanol. H-MAC-TIPS **148h** (665 mg, 60% over 2 steps) was isolated as a colorless viscous liquid.

According to method F: silylation of 2-hydroxymalononitrile **209** (380 mg, 4.63 mmol) was carried out with triisopropylsilyl triflate (1.9 mL, 7.05 mmol) and 2,6-lutidine (1.08 mL, 9.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> overnight from 0 °C to room temperature. After work-up and concentration under reduced pressure, the brown liquid residue was purified by two successive silica gel column chromatographies (pentane then pentane/Et<sub>2</sub>O, 50:1; pentane then pentane/Et<sub>2</sub>O, 20:1) to separate H-MAC-TIPS from triisopropylsilanol. H-MAC-TIPS **148h** (862 mg, 78% over 2 steps) was obtained as a colorless liquid.

H-MAC-TIPS **148h** can be stored under argon for several months at -18 °C.

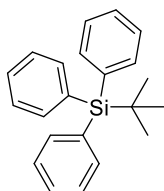
**TLC** *R<sub>f</sub>* = 0.23 (pentane/Et<sub>2</sub>O, 20:1)

**IR** (ATR), ν (cm<sup>-1</sup>): 2948, 2870, 2252, 1463, 1114

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>), δ (ppm): 1.07-1.14 (m, 18H, SiCH(CH<sub>3</sub>)<sub>2</sub>), 1.16-1.24 (m, 3H, SiCH(CH<sub>3</sub>)<sub>2</sub>), 5.40 (s, 1H, CH(CN)<sub>2</sub>)

**<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>), δ (ppm): 11.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 17.3 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 51.3 (CH(CN)<sub>2</sub>), 112.3 (CH(CN)<sub>2</sub>)

**Anal.** calcd. for C<sub>12</sub>H<sub>22</sub>N<sub>2</sub>OSi: C, 60.46; H, 9.30; N, 11.75. Found: C, 60.20; H, 9.08; N, 11.67.

***tert*-Butyltriphenylsilane (214).**C<sub>22</sub>H<sub>24</sub>Si

316 g/mol

**214**

According to literature procedures,<sup>184,261</sup> *tert*-butyldiphenylsilyl chloride **213** (6.4 mL, 25.0 mmol) was added dropwise over 10 minutes to a stirred solution of phenyllithium (2 M in dibutylether, 15.0 mL,

30.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 hours, then cooled to 0 °C. Undried Et<sub>2</sub>O (8 mL) was added in one portion, followed by water (16 mL) drop by drop. The resulting solid was filtered off under suction, washed with water (20 mL) and dried under high vacuum. The crude white solid (6.1 g) was recrystallized from EtOAc to afford *tert*-butyltriphenylsilane **214** (5.17 g, 16.3 mmol, 65%) as colorless crystals.

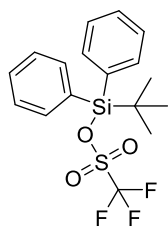
**Mp** = 158 °C (lit.<sup>261</sup> 158-159 °C)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>), δ (ppm): 1.25 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 7.37-7.46 (m, 9H, SiPh), 7.64-7.67 (m, 6H, SiPh)

**<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>), δ (ppm): 18.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 28.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 127.6 (CH<sub>Ph</sub>), 129.1 (CH<sub>Ph</sub>), 134.8 (C<sub>Ph</sub>), 136.5 (CH<sub>Ph</sub>)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>261</sup>

#### ***tert*-Butyldiphenylsilyl triflate (**215**).**



**215**

C<sub>17</sub>H<sub>19</sub>F<sub>3</sub>O<sub>3</sub>SSi

388 g/mol

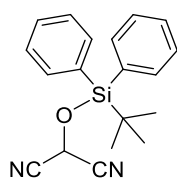
According to literature procedures,<sup>184,261</sup> trifluoromethanesulfonic acid (1.25 mL, 14.0 mmol) was added dropwise over 30 minutes to a cooled solution of recrystallized *t*-BuSiPh<sub>3</sub> **214** (4.43 g, 14.0 mmol) in anhydrous CHCl<sub>3</sub> (6 mL) cooled at -10 °C. The reaction mixture was stirred under argon for 30 minutes at 0 °C, and then allowed to warm to room temperature over 1 hour. TBDSOTf **215** was used immediately as a 1.43 M solution in CHCl<sub>3</sub> (total volume of the solution: 9.8 mL). An analytically pure sample could be obtained by distillation under reduced pressure (Kugelrohr, ~150 °C/0.075 mbar). It was isolated as a pale pink oil.

**IR** (ATR), ν (cm<sup>-1</sup>): 2936, 2863, 1689, 1473, 1429, 1395, 1187, 1118, 1019

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>), δ (ppm): 1.22 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 7.43-7.48 (m, 4H, SiPh), 7.52-7.57 (m, 2H, SiPh), 7.70-7.73 (m, 4H, SiPh)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>), δ (ppm): 19.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 26.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 128.2 (CH<sub>Ph</sub>), 131.5 (CH<sub>Ph</sub>), 134.0 (C<sub>Ph</sub>), 135.5 (CH<sub>Ph</sub>)

The boiling point and <sup>1</sup>H NMR data were in agreement with those described in literature.<sup>261,262</sup>

**2-(*tert*-Butyldiphenylsilyloxy)malononitrile, H-MAC-TBDPS (148i).**C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>OSi

320 g/mol

**148i**

According to method E: silylation of 2-hydroxymalononitrile **209** (380 mg, 4.63 mmol) was performed with *tert*-butyldiphenylsilyl chloride (1.8 mL, 7.03 mmol) and imidazole (630 mg, 9.26 mmol,) in DMF for 30 min at 0 °C followed by 30 min at room temperature. After work-up and concentration under reduced pressure, the orange viscous oil was purified by flash silica gel column chromatography (pentane/Et<sub>2</sub>O, 9:1) to give H-MAC-TBDPS **148i** (965 mg, 65% over 2 steps) as a colorless viscous oil, which crystallized as a white solid after standing for 24 hours at –18 °C.

According to method F: silylation of 2-hydroxymalononitrile **209** (380 mg, 4.63 mmol) was carried out with *tert*-butyldiphenylsilyl triflate (1.43 M in CHCl<sub>3</sub>, 5.0 mL, 7.15 mmol) and 2,6-lutidine (1.08 mL, 9.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> overnight from 0 °C to room temperature. After work-up and concentration under reduced pressure, the brown liquid residue was purified by flash silica gel column chromatography (pentane, then pentane/Et<sub>2</sub>O: 20:1) to furnish H-MAC-TBDPS **148i** (1.18 g, 80% over 2 steps) as a colorless viscous oil, which crystallized as a white solid after standing for 16 hours under high vacuum (10<sup>-2</sup> mbar).

H-MAC-TBDPS **148i** can be stored under argon for several months at –18 °C.

**Mp** = 48 °C

**TLC** *R<sub>f</sub>* = 0.25 (pentane/Et<sub>2</sub>O, 20:1).

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3074, 2962, 2933, 2890, 2860, 2253, 1590, 1472, 1428, 1112

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>NaOSi [M+Na]<sup>+</sup> 343.1237; found 343.1228

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 1.15 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 5.08 (s, 1H, CH(CN)<sub>2</sub>), 7.46-7.59 (m, 6H, SiPh), 7.69-7.73 (m, 4H, SiPh)

**<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 19.3 (SiC(CH<sub>3</sub>)<sub>3</sub>), 26.3 (SiC(CH<sub>3</sub>)<sub>3</sub>), 51.5 (CH(CN)<sub>2</sub>), 111.9 (CH(CN)<sub>2</sub>), 128.5 (CH<sub>Ph</sub>), 129.3 (C<sub>Ph</sub>), 131.2 (CH<sub>Ph</sub>), 135.5 (CH<sub>Ph</sub>)

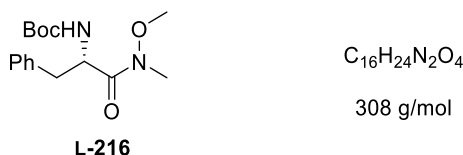
**Anal.** calcd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>OSi: C, 71.21; H, 6.29; N, 8.74. Found: C, 71.22; H, 6.33; N, 8.55.

## Chapter 2: Diastereoselectivity control in MAC reactions of *N*-protected L-phenylalaninals

### MAC reaction of *N*-Boc-L-phenylalaninal

#### *N*-Boc-L-phenylalaninal's synthesis.

#### *N*-tert-Butoxy-L-phenylalanine Weinreb amide (**L-216**).



Commercially available *N*-Boc-L-phenylalanine **L-43** (1.33 g, 5.0 mmol) was dissolved in dry DCM (65 mL) under argon. Distilled DIPEA (1.0 mL, 5.7 mmol) was then added and the flask was cooled down to 0 °C. *N,O*-Dimethylhydroxylamine hydrochloride (0.55 g, 5.6 mmol) was introduced, followed by the addition of EDCI•HCl (1.05 g, 5.5 mmol) in 5 portions. The reaction mixture was stirred for 2 hours at 0 °C and then poured into 1 M HCl (100 mL) with ice. The aqueous phase was extracted with Et<sub>2</sub>O (3 x 20 mL) and the combined organic layers were washed with brine (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (pentane/EtOAc, 2:1) to afford Weinreb amide **L-216** (1.53 g, quant.) as a white solid.

TLC  $R_f$  = 0.67 (pentane/EtOAc, 5:1)

OR  $[\alpha]_D^{24} = +21.8$  (c 1.0, CHCl<sub>3</sub>), lit.<sup>263</sup>  $[\alpha]_D^{22} = +21.0$  (c 1.0, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 1.34 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.82 (dd,  $J = 13.8, 7.3$  Hz, 1H) and 3.00 (dd,  $J = 13.8, 6.3$  Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.12 (s, 3H, NCH<sub>3</sub>), 3.61 (s, 3H, NOCH<sub>3</sub>), 4.84-4.95 (m, 1H, CHN), 5.13 (br d,  $J = 9.0$  Hz, 1H, NHCO<sub>2</sub>), 7.08-7.16 (m, 2H, Ph), 7.16-7.29 (m, 3H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 28.1 (OC(CH<sub>3</sub>)<sub>3</sub>), 31.8 (NCH<sub>3</sub>), 38.6 (PhCH<sub>2</sub>CH), 51.3 (CHN), 61.3 (NOCH<sub>3</sub>), 79.3 (OC(CH<sub>3</sub>)<sub>3</sub>), 126.5 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 129.2 (CH<sub>Ph</sub>), 136.4 (C<sub>Ph</sub>), 155.0 (NHCO<sub>2</sub>), 172.1 (CONCH<sub>3</sub>)

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>263</sup>

#### *N*-Boc-L-phenylalaninal (**L-15**).



*N*-tert-Butoxy-L-phenylalanine Weinreb amide **L-216** (308 mg, 1.0 mmol) was dissolved in dry THF (10 mL) at 0 °C under argon. Lithium aluminum hydride (78 mg, 2.1 mmol) was then introduced in small portions and the reaction mixture was stirred for 2 hours at 0 °C. 1 M KHSO<sub>4</sub> (15 mL) was added dropwise at 0 °C, and the reaction mixture was allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with 1 M

HCl (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Crude aldehyde **L-15** (248 mg, quant.) was obtained as a white solid and was pure enough to be used in the MAC reaction without any purification.

**Mp** = 81 °C (lit.<sup>264</sup> 80-84 °C)

**TLC** *R<sub>f</sub>* = 0.50 (pentane/Et<sub>2</sub>O, 7:3)

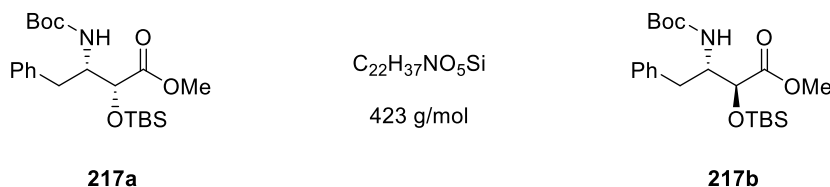
**OR** [α]<sub>D</sub><sup>24</sup> = +38.9 (c 1.0, DCM), lit.<sup>264</sup> [α]<sub>D</sub><sup>23</sup> = +39.3 (c 1.0, DCM)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>), δ (ppm): 1.45 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 3.13 (d, *J* = 6.8 Hz, 2H, PhCH<sub>2</sub>CH), 4.44 (t, *J* = 6.8 Hz, 1H, CHN), 5.07 (br s, 1H, NHCO<sub>2</sub>), 7.08-7.16 (m, 2H, Ph), 7.16-7.29 (m, 3H, Ph)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>264</sup>

### MAC reactions.

**Methyl (2*R*,3*S*)- and (2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanoate (**217a** and **217b**).**



To freshly prepared *N*-Boc-L-phenylalaninal **L-15** (126 mg, 0.51 mmol) mixed with H-MAC-TBS **148g** (120 mg, 0.61 mmol) under argon, was added dry Et<sub>2</sub>O (5 mL) followed by methanol (62 μL, 1.53 mmol). After cooling at 0 °C, DMAP (62 mg, 0.51 mmol) was added in one portion and the reaction mixture was stirred overnight at this temperature. A saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (15 mL) was introduced at 0 °C, and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phases were washed with 1 M HCl (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. A 84:16 ratio of the *syn/anti* diastereomers **217a/217b** was determined by <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> at 360 K) by integration of the OMe signals. Flash column chromatography (pentane/Et<sub>2</sub>O, 4:1 then 8:3) gave inseparable MAC reaction products **217a,b** (dr 82:18, 130 mg, 60%), as a colorless oil.

**TLC** *R<sub>f</sub>* = 0.55 (pentane/Et<sub>2</sub>O/DCM, 10:1:5), 0.33 (pentane/Et<sub>2</sub>O, 7:3)

**IR** (ATR), ν (cm<sup>-1</sup>): 3449, 3029, 2952, 2929, 2858, 1759, 1715, 1603, 1493, 1455, 1365, 1251, 1165

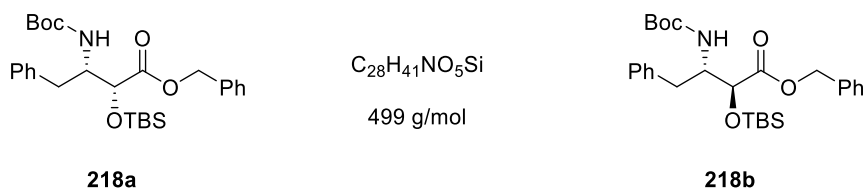
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>22</sub>H<sub>37</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup> 446.2333; found 446.2317

*Spectroscopic data for the major syn (2*R*,3*S*)-diastereomer (**217a**):*

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 360 K), δ (ppm): 0.08 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.93 (s, 9H, Si(CH<sub>3</sub>)<sub>3</sub>), 1.28 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.67 (br dd, *J* = 12.8, 10.4 Hz, 1H) and 2.81 (dd, *J* = 12.8, 4.0 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.65 (s, 3H, OCH<sub>3</sub>), 3.99 (dddd, *J* = 10.4, 8.4, 4.0, 4.0 Hz, 1H, CHN), 4.29 (d, *J* = 4.0 Hz, 1H, CHOTBS), 6.11 (br s, 1H, NHCO<sub>2</sub>), 7.14-7.30 (m, 5H, Ph)

$^{13}\text{C}$  NMR (100.6 MHz, DMSO- $d_6$ , 360 K),  $\delta$  (ppm): -5.8 (SiCH<sub>3</sub>), -5.4 (SiCH<sub>3</sub>), 17.5 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 27.7 (OC(CH<sub>3</sub>)<sub>3</sub>), 35.9 (PhCH<sub>2</sub>CH), 51.0 (OCH<sub>3</sub>), 54.9 (CHN), 73.2 (CHOTBS), 77.4 (OC(CH<sub>3</sub>)<sub>3</sub>), 125.5 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 138.3 (C<sub>Ph</sub>), 154.4 (NHCO<sub>2</sub>), 171.1 (COOCH<sub>3</sub>)

**Benzyl (2*R*,3*S*)- and (2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanoate (218a and 218b).**



To freshly prepared *N*-Boc-L-phenylalaninal **L-15** (113 mg, 0.42 mmol) mixed with H-MAC-TBS **148g** (106 mg, 0.54 mmol) under argon, was added dry Et<sub>2</sub>O (5 mL) followed by benzyl alcohol (140  $\mu\text{L}$ , 1.35 mmol). After cooling at 0 °C, DMAP (55 mg, 0.45 mmol) was added in one portion and the reaction mixture was stirred overnight at this temperature. A saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (10 mL) was introduced at 0 °C, and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phases were washed with 1 M HCl (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Flash column chromatography (cyclohexane/DCM, 2:1) gave inseparable MAC reaction products **218a,b** (dr 82:18, 149 mg, 63%), as a light-yellow oil. The 82:18 ratio of the *syn/anti* diastereomers **218a/218b** was determined by  $^1\text{H}$  NMR (DMSO- $d_6$  at 360 K) by integration of the CHOTBS signals.

**TLC**  $R_f$  = 0.62 (pentane/Et<sub>2</sub>O, 7:3), 0.12 (cyclohexane/DCM, 2:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3445, 3030, 2955, 2930, 2858, 1754, 1714, 1603, 1494, 1455, 1365, 1252, 1165

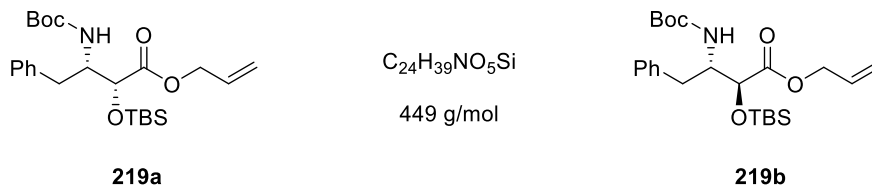
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>28</sub>H<sub>41</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup> 522.2646; found 522.2627

*Spectroscopic data for the major syn (2*R*,3*S*)-diastereomer (217a):*

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ , 360 K),  $\delta$  (ppm) : 0.05 (s, 3H, SiCH<sub>3</sub>), 0.07 (s, 3H, SiCH<sub>3</sub>), 0.91 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.27 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.68 (dd,  $J$  = 14.0, 10.2 Hz, 1H) and 2.82 (dd,  $J$  = 14.0, 4.3 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.99-4.07 (m, 1H, CHN), 4.36 (d,  $J$  = 4.3 Hz, 1H, CHOTBS), 5.10 (d,  $J$  = 12.4 Hz, 1H) and 5.18 (d,  $J$  = 12.4 Hz, 1H) (AB syst., OCH<sub>2</sub>Ph), 6.12 (br s, 1H, NHCO<sub>2</sub>), 7.11-7.22 (m, 4H, Ph), 7.22-7.28 (m, 2H, Ph), 7.32-7.42 (m, 4H, Ph)

$^{13}\text{C}$  NMR (100.6 MHz, DMSO- $d_6$ , 360 K),  $\delta$  (ppm): -5.7 (SiCH<sub>3</sub>), -5.5 (SiCH<sub>3</sub>), 17.4 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 27.7 (OC(CH<sub>3</sub>)<sub>3</sub>), 35.8 (PhCH<sub>2</sub>CH), 55.0 (CHN), 65.7 (OCH<sub>2</sub>Ph), 73.3 (CHOTBS), 77.4 (OC(CH<sub>3</sub>)<sub>3</sub>), 125.5 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 127.8 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 135.4 (C<sub>Ph</sub>), 138.3 (C<sub>Ph</sub>), 154.4 (NHCO<sub>2</sub>), 170.6 (COOCH<sub>2</sub>Ph)

**Allyl (2*R*,3*S*)- and (2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanoate (219a and 219b).**



To freshly prepared *N*-Boc-L-phenylalaninal **L-15** (120 mg, 0.48 mmol) mixed with H-MAC-TBS **148g** (114 mg, 0.58 mmol) under argon, was added dry Et<sub>2</sub>O (5 mL) followed by allyl alcohol (100 μL, 1.47 mmol). After cooling at 0 °C, DMAP (58 mg, 0.48 mmol) was added in one portion and the reaction mixture was stirred overnight at 0 °C. Reaction mixture was concentrated under reduced pressure. Normal pressure column chromatography (pentane/Et<sub>2</sub>O, 9:1 then 7:3 then 6:4) gave inseparable MAC reaction products **219a,b** (dr 86:14, 76 mg, 35%), as a colorless oil. The 86:14 ratio of the *syn/anti* diastereomers **219a/219b** was determined by <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> at 360 K) by integration of the NHCO<sub>2</sub> signals.

**TLC** *R<sub>f</sub>* = 0.69 (pentane/Et<sub>2</sub>O, 7:3)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3447, 3029, 2976, 2956, 2931, 2858, 1756, 1714, 1650, 1493, 1472, 1391, 1366, 1251, 1166, 1147, 1121

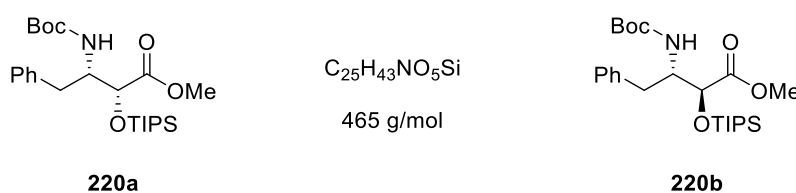
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>24</sub>H<sub>39</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup> 450.2670; found 450.2648

*Spectroscopic data for the major syn (2*R*,3*S*)-diastereomer (219a):*

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 360 K),  $\delta$  (ppm): -0.08 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.93 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.28 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.60-2.74 (m, 1H) and 2.82 (dd, *J* = 13.9, 4.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.91-4.05 (m, 1H, CHN), 4.33 (d, *J* = 4.0 Hz, 1H, CHOTBS), 4.49-4.66 (m, 2H, OCH<sub>2</sub>CH=CH<sub>2</sub>), 5.23 (dd, *J* = 10.6, 1.6 Hz, 1H, OCH<sub>2</sub>CH=CH<sub>*cis*</sub>), 5.34 (dd, *J* = 17.2, 1.6 Hz, 1H, OCH<sub>2</sub>CH=CH<sub>*trans*</sub>), 5.86-5.99 (m, 1H, OCH<sub>2</sub>CH=CH<sub>2</sub>), 6.18 (br s, 1H, NHCO<sub>2</sub>), 7.12-7.31 (m, 5H, Ph)

<sup>13</sup>C NMR (100.6 MHz, DMSO-*d*<sub>6</sub>, 360 K),  $\delta$  (ppm): -5.7 (SiCH<sub>3</sub>), -5.3 (SiCH<sub>3</sub>), 17.5 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.3 (SiC(CH<sub>3</sub>)<sub>3</sub>), 27.7 (OC(CH<sub>3</sub>)<sub>3</sub>), 35.9 (PhCH<sub>2</sub>CH), 54.8 (CHN), 65.7 (OCH<sub>2</sub>CH=CH<sub>2</sub>), 73.3 (CHOTBS), 77.4 (OC(CH<sub>3</sub>)<sub>3</sub>), 117.6 (OCH<sub>2</sub>CH=CH<sub>2</sub>), 125.6 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 132.0 (OCH<sub>2</sub>CH=CH<sub>2</sub>), 138.4 (C<sub>Ph</sub>), 154.5 (NHCO<sub>2</sub>), 170.4 (COOAlI)

**Methyl (2*R*,3*S*)- and (2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-4-phenyl-2-((triisopropylsilyl)oxy)-butanoate (220a and 220b).**



To freshly prepared *N*-Boc-L-phenylalaninal **L-15** (109 mg, 0.44 mmol) mixed with H-MAC-TIPS **148h** (127 mg, 0.53 mmol) under argon, was added dry Et<sub>2</sub>O (5 mL) followed by methanol (54 μL, 1.33 mmol).

After cooling at 0 °C, DMAP (54 mg, 0.44 mmol) was added in one portion and the reaction mixture was stirred overnight at this temperature. A saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (15 mL) was introduced at 0 °C, and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with 1 M HCl (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. A 84:16 ratio of the *syn/anti* diastereomers **220a/220b** was determined by <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> at 360 K) by integration of the OMe signals. Flash column chromatography (pentane/Et<sub>2</sub>O/DCM, 20:1:5 then 10:1:5) gave three fractions of inseparable MAC reaction products **220a,b** (dr 18:82, 12 mg, 6%) and (dr 70:30, 33 mg, 16%) and (dr 98:2, 82.4 mg, 40%), as colorless oils.

TLC *R*<sub>f</sub> = 0.40 (pentane/Et<sub>2</sub>O/DCM, 10:1:5)

IR (ATR),  $\nu$  (cm<sup>-1</sup>): 3446, 3029, 2964, 2943, 2868, 1759, 1713, 1603, 1493, 1454, 1390, 1366, 1246, 1151

HRMS (ES<sup>+</sup>): calcd. for C<sub>25</sub>H<sub>43</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup> 488.2803; found 488.2778

*Spectroscopic data for the major syn (2R,3S)-diastereomer (220a):*

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 360 K),  $\delta$  (ppm): 1.05-1.15 (m, 21H, Si(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>), 1.29 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.63 (br dd, *J* = 13.6, 11.2 Hz, 1H) and 2.94 (dd, *J* = 13.6, 3.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.68 (s, 3H, OCH<sub>3</sub>), 3.89-3.99 (m, 1H, CHN), 4.47 (d, *J* = 4.4 Hz, 1H, CHOTIPS), 6.20 (br s, 1H, NHCO<sub>2</sub>), 7.12-7.28 (m, 5H, Ph)

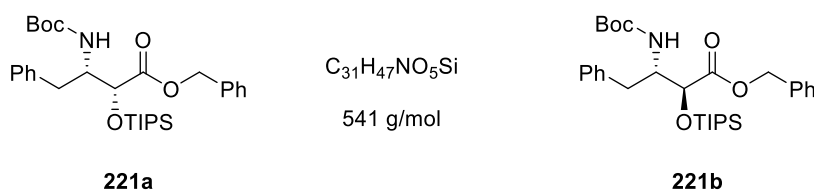
<sup>13</sup>C NMR (100.6 MHz, DMSO-*d*<sub>6</sub>, 360 K),  $\delta$  (ppm): 11.5 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 17.3 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 27.7 (OC(CH<sub>3</sub>)<sub>3</sub>), 34.5 (PhCH<sub>2</sub>CH), 50.9 (OCH<sub>3</sub>), 55.6 (CHN), 73.3 (CHOTIPS), 77.5 (OC(CH<sub>3</sub>)<sub>3</sub>), 125.5 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 138.6 (C<sub>Ph</sub>), 154.4 (NHCO<sub>2</sub>), 171.0 (COOCH<sub>3</sub>)

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>, 293 K), mixture of 2 rotamers (A:B = 2:1),  $\delta$  (ppm) : 1.05-1.13 (m, 21H, Si(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>), 1.34 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.76 (dd, *J* = 13.7, 8.5 Hz, 1H) and 2.98 (dd, *J* = 13.7, 6.1 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.69 (s, 2H, OCH<sub>3</sub>, rot. A), 3.73 (s, 1H, OCH<sub>3</sub>, rot. B), 4.21-4.34 (m, 1H, CHN), 4.41 (d, *J* = 2.2 Hz, 1H, CHOTIPS), 4.91 (br d, *J* = 10.1 Hz, 1H, NHCO<sub>2</sub>), 7.15-7.37 (m, 5H, Ph)

*Spectroscopic data for the minor anti (2S,3S)-diastereomer (220b):*

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 293 K),  $\delta$  (ppm): 1.02-1.09 (m, 21H, Si(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>), 1.37 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.78 (br d, *J* = 7.3 Hz, 2H, PhCH<sub>2</sub>CH), 3.63 (s, 3H, OCH<sub>3</sub>), 4.20-4.35 (m, 1H, CHN), 4.57 (d, *J* = 3.0 Hz, 1H, CHOTIPS), 4.82 (br d, *J* = 8.5 Hz, 1H, NHCO<sub>2</sub>), 7.14-7.32 (m, 5H, Ph)

**Benzyl (2R,3S)- and (2S,3S)-3-((tert-butoxycarbonyl)amino)-4-phenyl-2-((triisopropylsilyl)oxy)-butanoate (221a and 221b).**





To freshly prepared *N*-Boc-L-phenylalaninal **L-15** (109 mg, 0.44 mmol) mixed with H-MAC-TIPS **148h** (126 mg, 0.53 mmol) under argon, was added dry Et<sub>2</sub>O (5 mL) followed by benzyl alcohol (140 μL, 1.35 mmol). After cooling at 0 °C, DMAP (54 mg, 0.44 mmol) was added in one portion and the reaction mixture was stirred overnight at this temperature. A saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (15 mL) was introduced at 0 °C, and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with 1 M HCl (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. A 83:17 ratio of the *syn/anti* diastereomers **221a/221b** was determined by <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> at 360 K) by integration of the CHOTIPS signals. Flash column chromatography (pentane/Et<sub>2</sub>O/DCM, 20:1:5 then 10:1:5) gave MAC reaction products **221a,b** (dr 84:16, 149 mg, 63%), as a colorless oil.

TLC *R*<sub>f</sub> = 0.55 (pentane/Et<sub>2</sub>O/DCM, 10:1:5)

IR (ATR), ν (cm<sup>-1</sup>): 3445, 3030, 2962, 2943, 2867, 1755, 1716, 1604, 1494, 1455, 1391, 1366, 1246, 1146

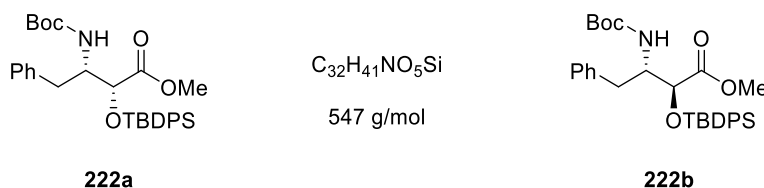
HRMS (ES<sup>+</sup>): calcd. for C<sub>31</sub>H<sub>47</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup> 564.3115; found 564.3091

*Spectroscopic data for the major syn (2R,3S)-diastereomer (221a):*

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 360 K), δ (ppm): 0.99-1.13 (m, 21H, Si(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>), 1.28 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.63 (dd, *J* = 14.0, 11.0 Hz, 1H) and 2.95 (dd, *J* = 14.0, 3.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.91-4.01 (m, 1H, CHN), 4.52 (d, *J* = 4.8 Hz, 1H, CHOTIPS), 5.11 (d, *J* = 12.4 Hz, 1H) and 5.21 (d, *J* = 12.4 Hz, 1H) (AB syst., OCH<sub>2</sub>Ph), 6.24 (br s, 1H, NHCO<sub>2</sub>), 7.12-7.30 (m, 5H, Ph), 7.32-7.45 (m, 5H, Ph)

<sup>13</sup>C NMR (100.6 MHz, DMSO-*d*<sub>6</sub>, 360 K), δ (ppm): 11.4 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 17.2 (SiCH(CH<sub>3</sub>)<sub>2</sub>), 27.6 (OC(CH<sub>3</sub>)<sub>3</sub>), 34.3 (PhCH<sub>2</sub>CH), 55.6 (CHN), 65.7 (OCH<sub>2</sub>Ph), 73.2 (CHOTIPS), 77.5 (OC(CH<sub>3</sub>)<sub>3</sub>), 125.5 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 127.8 (CH<sub>Ph</sub>), 127.8 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 135.3 (C<sub>Ph</sub>), 138.6 (C<sub>Ph</sub>), 154.2 (NHCO<sub>2</sub>), 170.4 (COOCH<sub>2</sub>Ph)

**Methyl (2R,3S)- and (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-((tert-butyldiphenylsilyl)oxy)-4-phenylbutanoate (222a and 222b).**



To freshly prepared *N*-Boc-L-phenylalaninal **L-15** (125 mg, 0.50 mmol) mixed with H-MAC-TBDPS **148i** (197 mg, 0.62 mmol) under argon, was added dry Et<sub>2</sub>O (5 mL) followed by methanol (62 μL, 1.50 mmol). After cooling at 0 °C, DMAP (62 mg, 0.50 mmol) was added in one portion and the reaction mixture was stirred overnight at this temperature. A saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (15 mL) was introduced at 0 °C, and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with 1 M HCl (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. A 83:17 ratio of the *syn/anti* diastereomers **222a/222b** was determined by <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> at 360 K) by

integration of the OMe signals. Flash column chromatography (pentane/Et<sub>2</sub>O/DCM, 20:1:5 then 10:1:5) gave MAC reaction products **222a,b** (dr 81:19, 128 mg, 47%), as a colorless oil.

**TLC**  $R_f$  = 0.40 (pentane/Et<sub>2</sub>O/DCM, 10:1:5)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3447, 3266, 3071, 2952, 2931, 2858, 1757, 1708, 1603, 1495, 1454, 1428, 1391, 1365, 1250, 1167

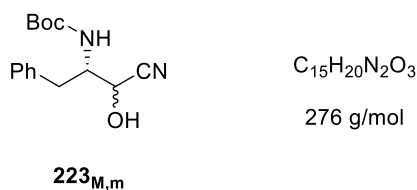
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>32</sub>H<sub>41</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup> 570.2646; found 570.2623

*Spectroscopic data for the major syn (2R,3S)-diastereomer (222a):*

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 360 K),  $\delta$  (ppm): 1.11 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.28 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.64-2.78 (dd,  $J$  = 14.0, 10.0 Hz, 1H) and 2.91 (dd,  $J$  = 14.0, 4.0 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.40 (s, 3H, OCH<sub>3</sub>), 3.98-4.11 (m, 1H, CHN), 4.37 (d,  $J$  = 4.8 Hz, 1H, CHOTBDPS), 6.23 (br s, 1H, NHCO<sub>2</sub>), 7.12-7.21 (m, 3H, Ph), 7.21-7.29 (m, 2H, Ph), 7.36-7.50 (m, 6H, Ph), 7.60-7.75 (m, 4H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, DMSO-*d*<sub>6</sub>, 360 K),  $\delta$  (ppm): 18.6 (SiC(CH<sub>3</sub>)<sub>3</sub>), 26.4 (SiC(CH<sub>3</sub>)<sub>3</sub>), 27.6 (OC(CH<sub>3</sub>)<sub>3</sub>), 35.3 (PhCH<sub>2</sub>CH), 50.6 (OCH<sub>3</sub>), 55.2 (CHN), 73.9 (CHOTBDPS), 77.4 (OC(CH<sub>3</sub>)<sub>3</sub>), 125.4 (CH<sub>Ph</sub>), 126.9 (CH<sub>Ph</sub>), 127.1 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 129.2 (CH<sub>Ph</sub>), 129.3 (CH<sub>Ph</sub>), 132.4 (C<sub>Ph</sub>), 134.9 (CH<sub>Ph</sub>), 135.0 (CH<sub>Ph</sub>), 138.3 (C<sub>Ph</sub>), 154.3 (NHCO<sub>2</sub>), 173.4 (COOCH<sub>3</sub>)

**tert-Butyl ((1S,2S)- and (1R,2S)-1-cyano-1-hydroxy-3-phenylpropan-2-yl)carbamate (223<sub>M,m</sub>).**



C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>

276 g/mol

Cyanohydrin **223<sub>M,m</sub>** was observed in the MAC reaction of *N*-Boc-L-phenylalaninal **L-15** (120 mg, 0.48 mmol) with H-MAC-TBS **148g** (114 mg, 0.58 mmol) and allyl alcohol (100  $\mu$ L, 1.47 mmol). It was isolated as a light yellow oil (dr 52:48, 21 mg, 16%) during the column chromatography (pentane/Et<sub>2</sub>O, 9:1 then 7:3 then 6:4). Identification of the Major (M) and minor (m) diastereomers was not performed.

**TLC**  $R_f$  = 0.10 (pentane/Et<sub>2</sub>O, 7:3)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3355, 3029, 2977, 2931, 2862, 1684, 1604, 1509, 1497, 1455, 1391, 1367, 1271, 1249, 1161

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup> 299.1366; found 299.1364

*Spectroscopic data for the 52/48 mixture of diastereomers 223<sub>M,m</sub>:*

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 360 K),  $\delta$  (ppm): 1.29 (s, 4.3H, (OC(CH<sub>3</sub>)<sub>3</sub>)<sub>m</sub>), 1.32 (s, 4.7H, (OC(CH<sub>3</sub>)<sub>3</sub>)<sub>M</sub>), 2.58-2.68 (m, 0.52H) and 2.73 (dd,  $J$  = 14.0, 10.4 Hz, 0.52H) (AB part of ABX syst., (PhCH<sub>2</sub>CH)<sub>M</sub>), 2.96 (dd,  $J$  = 19.6, 4.0 Hz, 0.48H) and 2.96 (dd,  $J$  = 19.6, 3.2 Hz, 0.48H) (AB part of ABX syst., (PhCH<sub>2</sub>CH)<sub>m</sub>), 3.82-3.92 (m, 1H, (CHN)<sub>M+m</sub>), 4.38 (d,  $J$  = 7.0 Hz, 0.48H, (CHOH)<sub>m</sub>), 4.55 (d,  $J$  = 5.8 Hz, 0.52H, (CHOH)<sub>M</sub>), 6.49 (d,  $J$  = 5.8 Hz, 0.52H, (OH)<sub>M</sub>), 6.57 (d,  $J$  = 7.0 Hz, 0.48H, (OH)<sub>m</sub>), 6.72 (br s, 1H, (NHCO<sub>2</sub>)<sub>M+m</sub>), 7.16-7.31 (m, 5H, (Ph)<sub>M+m</sub>)

## MAC reaction of *N*-Boc-*N*-Bn-*L*-phenylalaninal

### *N*-Boc-*N*-Bn-*L*-phenylalaninal's synthesis.

#### *N*-Benzyl-*L*-phenylalaninol (L-225).



According to a literature procedure,<sup>190</sup> commercially available *L*-phenylalaninol **L-224** (1.01 g, 7.3 mmol) was dissolved in dry MeOH (13 mL). Distilled benzaldehyde (745  $\mu$ L, 7.3 mmol) was added, and the reaction mixture was stirred under argon for 3 hours at room temperature until TLC indicates no more starting material. Then, the mixture was cooled down to 0 °C and NaBH<sub>4</sub> (488 mg, 12.9 mmol) was added in one portion. After stirring for 2 hours at room temperature, acetic acid (1.0 mL, 17.5 mmol) was added dropwise to quench the reaction, and the reaction mixture was stirred for 10 minutes at room temperature. Saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (10 mL) was slowly introduced (until no more gas release was observed), and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give **L-225** (2.63 g, quant.) as a pale-yellow oil, which turned into a solid after standing for 16 hours under high vacuum. It was then engaged directly in the next reaction without any purification.

**Mp** = 56-57 °C (lit.<sup>265</sup> 54-56 °C)

**TLC** *R<sub>f</sub>* = 0.07 (pentane/EtOAc, 3:1)

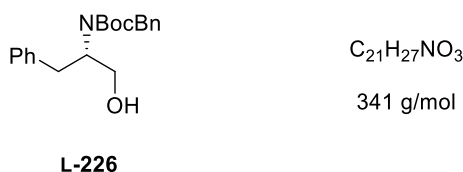
**OR** [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -9.0 (*c* 1.2, MeOH), lit.<sup>265</sup> [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -11.1 (*c* 1.2, MeOH)

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 2.52 (br s, 2H, OH+NH), 2.79 (dd, *J* = 13.7, 7.1 Hz, 1H) and 2.86 (dd, *J* = 13.7, 7.1 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 2.92-3.04 (m, 1H, CHN), 3.39 (dd, *J* = 10.9, 5.4 Hz, 1H) and 3.67 (dd, *J* = 10.9, 3.8 Hz, 1H) (AB part of ABX syst., CHCH<sub>2</sub>OH), 3.80 (s, 2H, NCH<sub>2</sub>Ph), 7.17-7.39 (m, 10H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 37.9 (PhCH<sub>2</sub>CH), 51.0 (NCH<sub>2</sub>Ph), 59.3 (CHN), 62.4 (CH<sub>2</sub>OH), 126.4 (CH<sub>Ph</sub>), 127.1 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 129.1 (CH<sub>Ph</sub>), 138.3 (C<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>)

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>265</sup>

#### *N*-Boc-*N*-Bn-*L*-phenylalaninol (L-226).



According to a literature procedure,<sup>266</sup> *N*-benzyl-*L*-phenylalaninol **L-225** (1.86 g, 7.7 mmol) was dissolved in dry THF (26 mL) under argon. Et<sub>3</sub>N (1.2 mL, 8.6 mmol) and Boc<sub>2</sub>O (1.89 g, 8.7 mmol) were

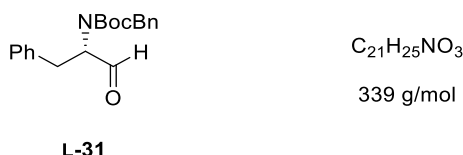
added successively, and the reaction mixture was stirred for 16 hours at room temperature. 1 M HCl was added until pH = 1, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/EtOAc, 5:1 then 3:1) to give the *N,N*-diprotected alcohol **L-226** (2.79 g, quant.), as a sticky colorless oil.

**TLC** R<sub>f</sub> = 0.46 (pentane/EtOAc, 3:1)

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 350 K), δ (ppm): 1.32 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.80 (dd, *J* = 13.6, 8.8 Hz, 1H) and 2.87 (dd, *J* = 13.6, 6.0 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.42-3.59 (m, 2H, CHCH<sub>2</sub>OH), 3.96-4.10 (m, 1H, CHN), 4.22 (d, *J* = 16.0 Hz, 1H) and 4.33 (d, *J* = 16.0 Hz, 1H) (AB syst., NCH<sub>2</sub>Ph), 4.48 (t, *J* = 4.0 Hz, 1H, OH), 7.09-7.15 (m, 2H, Ph), 7.15-7.29 (m, 8H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, DMSO-*d*<sub>6</sub>, 350 K), δ (ppm): 27.6 (OC(CH<sub>3</sub>)<sub>3</sub>), 35.3 (PhCH<sub>2</sub>CH), 48.4 (NCH<sub>2</sub>Ph), 60.6 (CHN), 61.8 (CH<sub>2</sub>OH), 78.3 (OC(CH<sub>3</sub>)<sub>3</sub>), 125.4 (CH<sub>Ph</sub>), 126.0 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 127.7 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 138.9 (C<sub>Ph</sub>), 139.5 (C<sub>Ph</sub>), 154.8 (NHCO<sub>2</sub>)

#### ***N*-Boc-*N*-Bn-L-phenylalaninal (**L-31**).**



According to the general procedure, Swern oxidation of *N*-Boc-*N*-Bn-L-phenylalaninol **L-226** (300 mg, 0.88 mmol) was performed with DMSO (120 μL, 1.70 mmol), oxalyl chloride (100 μL, 1.17 mmol) in DCM (4 mL), followed by the addition of NEt<sub>3</sub> (320 μL, 2.30 mmol). Crude *N*-Boc-*N*-Bn-L-phenylalaninal **L-31** (274 mg, 92%) was isolated as a viscous yellow oil. It was engaged in the MAC reaction without any purification. Attempt of purification by flash column chromatography (pentane/EtOAc, 10:1) led to partial decomposition of aldehyde **L-31**.

**TLC** R<sub>f</sub> = 0.28 (pentane/EtOAc, 10:1)

**OR** [α]<sub>D</sub><sup>25</sup> = -134.9 (c 1.0, CHCl<sub>3</sub>)

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 360 K), δ (ppm): 1.40 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.96 (dd, *J* = 13.9, 9.0 Hz, 1H) and 3.27 (dd, *J* = 13.9, 5.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.71 (d, *J* = 15.2 Hz, 1H) and 4.46 (d, *J* = 15.2 Hz, 1H) (AB syst., NCH<sub>2</sub>Ph), 4.04 (dd, *J* = 9.0, 5.2 Hz, 1H, CHN), 7.16-7.20 (m, 4H, Ph), 7.20-7.32 (m, 6H, Ph), 9.46 (s, 1H, CHO)

**<sup>13</sup>C NMR** (100.6 MHz, DMSO-*d*<sub>6</sub>, 360 K), δ (ppm): 27.5 (OC(CH<sub>3</sub>)<sub>3</sub>), 35.6 (PhCH<sub>2</sub>CH), 51.4 (NCH<sub>2</sub>Ph), 67.0 (CHN), 80.0 (OC(CH<sub>3</sub>)<sub>3</sub>), 125.8 (CH<sub>Ph</sub>)<sub>M</sub>, 126.1 (CH<sub>Ph</sub>)<sub>m</sub>, 126.7 (CH<sub>Ph</sub>)<sub>M</sub>, 126.9 (CH<sub>Ph</sub>)<sub>m</sub>, 127.2 (CH<sub>Ph</sub>)<sub>M</sub>, 127.3 (CH<sub>Ph</sub>)<sub>m</sub>, 127.8 (CH<sub>Ph</sub>)<sub>M</sub>, 127.9 (CH<sub>Ph</sub>)<sub>m</sub>, 128.0 (CH<sub>Ph</sub>)<sub>M</sub>, 128.0 (CH<sub>Ph</sub>)<sub>m</sub>, 128.7 (CH<sub>Ph</sub>)<sub>M</sub>, 128.8 (CH<sub>Ph</sub>)<sub>m</sub>, 135.8 (C<sub>Ph</sub>), 136.3 (C<sub>Ph</sub>), 136.6 (C<sub>Ph</sub>), 137.6 (C<sub>Ph</sub>), 154.2 (NHCO<sub>2</sub>), 198.1 (CHO)

<sup>1</sup>H NMR data in DMSO-*d*<sub>6</sub> at 360 K were in agreement with those described in literature.<sup>267</sup>

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>, 300 K), mixture of 2 rotamers (A:B = 60:40), δ (ppm): 1.45 and 1.47 (2s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>, rot A+B), 2.87 and 2.91 (2d, *J* = 14.4 Hz, 0.8H, PhCH<sub>2</sub>CH, rot B), 3.02 and 3.08 (2d, *J* = 14.4 Hz, 1H, NCH<sub>2</sub>Ph, rot A+B), 3.19 and 3.26 (2d, *J* = 14.4 Hz, 1.2H, PhCH<sub>2</sub>CH, rot A), 3.44-3.52 (m, 0.6H, CHN,

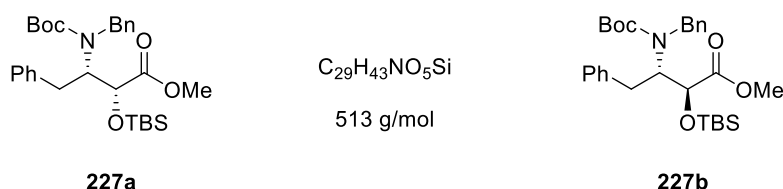
rot A), 3.52-3.60 (m, 0.4H, CHN, rot B), 4.53 (d,  $J = 14.4$  Hz, 0.4H, NCHHPh, rot B), 4.82 (d,  $J = 14.4$  Hz, 0.6H, NCHHPh, rot A), 6.99-7.05 (m, 2H, Ph), 7.05-7.31 (m, 4H, Ph), 9.30 (s, 0.6H, CHO, rot A), 9.40 (s, 0.4H, CHO, rot B)

$^{13}\text{C}$  NMR (90.6 MHz,  $\text{CDCl}_3$ , 300 K), mixture of 2 rotamers (A:B = 60:40),  $\delta$  (ppm): 27.3 ( $\text{OC}(\text{CH}_3)_3$ ), 33.1 (PhCH<sub>2</sub>CH, rot B), 33.2 (PhCH<sub>2</sub>CH, rot A), 51.8 (NCH<sub>2</sub>Ph, rot A), 52.3 (NCH<sub>2</sub>Ph, rot B), 67.1 (CHN, rot A), 67.5 (CHN, rot B), 81.1 ( $\text{OC}(\text{CH}_3)_3$ , rot B), 81.8 ( $\text{OC}(\text{CH}_3)_3$ , rot A), 126.5 ( $\text{CH}_{\text{Ph}}$ , rot B), 126.7 ( $\text{CH}_{\text{Ph}}$ , rot A), 127.6 ( $\text{CH}_{\text{Ph}}$ ), 127.7 ( $\text{CH}_{\text{Ph}}$ ), 128.3 ( $\text{CH}_{\text{Ph}}$ ), 128.6 ( $\text{CH}_{\text{Ph}}$ ), 128.7 ( $\text{CH}_{\text{Ph}}$ ), 129.2 ( $\text{CH}_{\text{Ph}}$ ), 137.3 ( $\text{C}_{\text{Ph}}$ , rot A), 137.5 ( $\text{C}_{\text{Ph}}$ , rot B), 137.9 ( $\text{C}_{\text{Ph}}$ , rot A), 138.2 ( $\text{C}_{\text{Ph}}$ , rot B), 154.8 ( $\text{NHCO}_2$ , rot A), 155.3 ( $\text{NHCO}_2$ , rot B), 198.4 (CHO, rot A), 198.6 (CHO, rot B)

$^1\text{H}$  and  $^{13}\text{C}$  NMR data in  $\text{CDCl}_3$  at 300 K were in agreement with those described in literature.<sup>266</sup>

### MAC reaction with MeOH.

#### Methyl (2*R*,3*S*)- and (2*S*,3*S*)-3-(benzyl(*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanoate (**227a** and **227b**).



Freshly prepared *N*-Boc-*N*-Bn-*L*-phenylalaninal **L-31** (170 mg, 0.50 mmol) was mixed with H-MAC-TBS **148g** (118 mg, 0.60 mmol) under argon. Dry  $\text{Et}_2\text{O}$  (5 mL) was added, followed by methanol (61  $\mu\text{L}$ , 1.50 mmol). After cooling at 0 °C, DMAP (61 mg, 0.50 mmol) was added in one portion and the reaction mixture was stirred overnight at this temperature. A saturated aqueous  $\text{Na}_2\text{CO}_3$  solution (20 mL) followed by water (20 mL) to dissolve the salts were successively introduced at 0 °C, and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with  $\text{EtOAc}$  (3 x 20 mL) and the combined organic phases were washed with 1 M HCl (20 mL), brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ /DCM, 20:1:4) gave inseparable MAC reaction products **227a,b** (181 mg, 70%), as a colorless oil. A 58:42 ratio of two diastereomers was determined by  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$  at 360 K) by integration of the OMe signals. Identification of the major (M) and the minor (m) diastereomers could be not achieved.

TLC  $R_f = 0.30$  (pentane/ $\text{Et}_2\text{O}$ /DCM, 20:1:4)

IR (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3386, 3064, 3028, 2951, 2930, 2856, 1754, 1738, 1694, 1650, 1495, 1454, 1391, 1366, 1253, 1164, 1122, 1023, 993

HRMS ( $\text{ES}^+$ ): calcd. for  $\text{C}_{29}\text{H}_{44}\text{NO}_5\text{Si}$  [ $\text{M}+\text{H}$ ]<sup>+</sup> 514.2983; found 514.2960

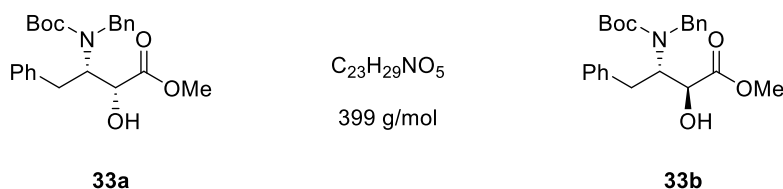
Spectroscopic data for the 58/42 mixture of diastereomers **227<sub>M,m</sub>**:

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ , 360 K),  $\delta$  (ppm): 0.04 (s, 1.3H, ( $\text{SiCH}_3$ )<sub>m</sub>), 0.05 (s, 1.3H, ( $\text{SiCH}_3$ )<sub>m</sub>), 0.05 (s, 1.7H, ( $\text{SiCH}_3$ )<sub>M</sub>), 0.07 (s, 1.7H, ( $\text{SiCH}_3$ )<sub>M</sub>), 0.91 (s, 9H, ( $\text{SiC}(\text{CH}_3)_3$ )<sub>M+m</sub>), 1.29 (s, 3.8H, ( $\text{OC}(\text{CH}_3)_3$ )<sub>m</sub>), 1.36 (s,

5.2H, (OC(CH<sub>3</sub>)<sub>3</sub>)<sub>M</sub>), 2.82 (dd, *J* = 14.4, 5.2 Hz, 0.42H) and 2.95-3.05 (m, 0.42H) (AB part of ABX syst., (PhCH<sub>2</sub>CH)<sub>M</sub>), 2.95-3.05 (m, 0.58H) and 3.09 (dd, *J* = 14.0, 4.8 Hz, 0.58H) (AB part of ABX syst., (PhCH<sub>2</sub>CH)<sub>M</sub>), 3.48 (s, 1.7H, (OCH<sub>3</sub>)<sub>M</sub>), 3.62 (s, 1.3H, (OCH<sub>3</sub>)<sub>M</sub>), 4.03-4.24 (m, 0.58H, (CHN)<sub>M</sub>), 4.07 (d, *J* = 15.6 Hz, 0.58H) and 4.17 (d, *J* = 15.6 Hz, 0.58H) (AB syst., (NCH<sub>2</sub>Ph)<sub>M</sub>), 4.38 (d, *J* = 16.0 Hz, 0.42H) and 4.46 (d, *J* = 16.0 Hz, 0.42H) (AB syst., (NCH<sub>2</sub>Ph)<sub>M</sub>), 4.51-4.61 (m, 1.42H, (CHOTBS)<sub>M+m</sub>+(CHN)<sub>M</sub>), 6.95-7.24 (m, 10H, Ph<sub>M+m</sub>)

<sup>13</sup>C NMR (100.6 MHz, DMSO-*d*<sub>6</sub>, 360K), δ(ppm): -5.9 (SiCH<sub>3</sub>)<sub>M</sub>, -5.8 (SiCH<sub>3</sub>)<sub>M</sub>, -5.8 (SiCH<sub>3</sub>)<sub>M</sub>, -5.7 (SiCH<sub>3</sub>)<sub>M</sub>, 17.3 (SiC(CH<sub>3</sub>)<sub>3</sub>)<sub>M+m</sub>, 25.1 (SiC(CH<sub>3</sub>)<sub>3</sub>)<sub>M+m</sub>, 27.4 (OC(CH<sub>3</sub>)<sub>3</sub>)<sub>M</sub>, 27.4 (OC(CH<sub>3</sub>)<sub>3</sub>)<sub>M</sub>, 34.1 (PhCH<sub>2</sub>CH)<sub>M</sub>, 34.7 (PhCH<sub>2</sub>CH)<sub>M</sub>, 49.6 (NCH<sub>2</sub>Ph)<sub>M</sub>, 50.5 (NCH<sub>2</sub>Ph)<sub>M</sub>, 50.7 (OCH<sub>3</sub>)<sub>M</sub>, 50.9 (OCH<sub>3</sub>)<sub>M</sub>, 60.1 (CHN)<sub>M</sub>, 60.1 (CHN)<sub>M</sub>, 73.0 (CHOTBS)<sub>M</sub>, 73.8 (CHOTBS)<sub>M</sub>, 78.6 (OC(CH<sub>3</sub>)<sub>3</sub>)<sub>M</sub>, 78.9 (OC(CH<sub>3</sub>)<sub>3</sub>)<sub>M</sub>, 125.5 (CH<sub>Ph</sub>), 125.6 (CH<sub>Ph</sub>), 125.6 (CH<sub>Ph</sub>), 125.9 (CH<sub>Ph</sub>), 126.6 (CH<sub>Ph</sub>), 126.8 (CH<sub>Ph</sub>), 127.2 (CH<sub>Ph</sub>), 127.2 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 128.3 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 137.5 (C<sub>Ph</sub>), 138.0 (C<sub>Ph</sub>), 138.3 (C<sub>Ph</sub>), 139.0 (C<sub>Ph</sub>), 154.4 (NHCO<sub>2</sub>)<sub>M</sub>, 154.6 (NHCO<sub>2</sub>)<sub>M</sub>, 170.9 (COOCH<sub>3</sub>)<sub>M</sub>, 171.2 (COOCH<sub>3</sub>)<sub>M</sub>

**Methyl (2*R*,3*S*)- and (2*S*,3*S*)-3-(benzyl(*tert*-butoxycarbonyl)amino)-2-hydroxy-4-phenylbutanoate (33a and 33b).**



Inspired by the literature,<sup>268</sup> hydrogen fluoride (70 wt.% in pyridine, 0.6 mL, 23.0 mmol) was added dropwise to a stirred solution of MAC products **227a,b** (34.1 mg, 0.66 mmol) in a 1:1 (v/v) dry pyridine/THF (1.8 mL). After stirring for 40 hours at room temperature (until no more starting material was observed), EtOAc (5 mL) was introduced followed by the addition of solid NaHCO<sub>3</sub> (~2 g) until no more gas is released. The mixture was stirred for 15 minutes at room temperature, and then filtered through cotton which was washed through with EtOAc. The combined filtrates and washings were concentrated under reduced pressure. Flash column chromatography (pentane/Et<sub>2</sub>O, 2:1) gave (2*R*,3*S*) *syn*-alcohol **33a** (6 mg, 21%), and a mixture of *syn* and *anti* alcohols **33a,b** (dr 38:62, 22 mg, 79%) as a colorless oil.

*Data for syn (2R,3S)-diastereomer (33a), a colorless oil:*

**TLC** *R<sub>f</sub>* = 0.21 (pentane/EtOAc, 7:3)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ (ppm): 1.48 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.72 (dd, *J* = 13.3, 5.9 Hz, 1H) and 3.23-3.39 (m, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.58 (s, 3H, OCH<sub>3</sub>), 3.80-3.92 (m, 1H, CHN), 4.02 (d, *J* = 15.4 Hz, 1H) and 4.42 (d, *J* = 15.4 Hz, 1H) (AB syst., NCH<sub>2</sub>Ph), 4.16 (dd, *J* = 9.6, 4.1 Hz, 1H, CHOH), 5.83 (br s, 1H, OH), 7.02-7.39 (m, 10H, Ph)

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>), δ (ppm): 28.3 (OC(CH<sub>3</sub>)<sub>3</sub>), 35.1 (PhCH<sub>2</sub>CH), 51.9 (OCH<sub>3</sub>), 54.1 (NCH<sub>2</sub>Ph), 64.0 (CHN), 72.4 (CHOH), 81.2 (OC(CH<sub>3</sub>)<sub>3</sub>), 126.6 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 129.4 (CH<sub>Ph</sub>), 137.9 (C<sub>Ph</sub>), 157.2 (NHCO<sub>2</sub>), 173.6 (COOCH<sub>3</sub>)

<sup>1</sup>H and <sup>13</sup>C NMR were in agreement with those described in literature.<sup>66</sup>

Data for *anti* (2*S*,3*S*)-diastereomer (**33b**):

TLC  $R_f$  = 0.15 (pentane/Et<sub>2</sub>O, 7:3)

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 1.42 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 2.92 (dd,  $J$  = 13.7, 6.5 Hz, 1H) and 3.09-3.20 (m, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.56 (s, 3H, OCH<sub>3</sub>), 4.03 (d,  $J$  = 15.1 Hz, 1H) and 4.38-4.47 (m, 2H) (AB syst., NCH<sub>2</sub>Ph+CHOH), 4.24-4.31 (m, 1H, CHN), 4.78 (br s, 1H, OH), 7.02-7.39 (m, 10H, Ph)

<sup>1</sup>H NMR were in agreement with those described in literature.<sup>66</sup>

## MAC reaction of *N,N*-dibenzyl-L-phenylalaninal

### *N,N*-Dibenzyl-L-phenylalaninal's synthesis.

#### *N,N*-Dibenzyl-L-phenylalaninol (L-228).



According to the general procedure, commercially available L-phenylalaninol **L-224** (3.00 g, 19.8 mmol) was *N,N*-dibenzylated with K<sub>2</sub>CO<sub>3</sub> (6.58 g, 47.6 mmol), benzyl bromide (5.7 mL, 48.0 mmol) in CH<sub>3</sub>CN (100 mL). The crude residue was purified by flash column chromatography (pentane/EtOAc, 5:1) to give *N,N*-dibenzyl-L-phenylalaninol **L-228** (6.63 g, quant.), as a white solid.

**Mp** = 72 °C (lit.<sup>269</sup> 71-73 °C)

TLC  $R_f$  = 0.48 (pentane/EtOAc, 5:1)

**OR**  $[\alpha]_D^{24}$  = +41.5 (*c* 1.0, DCM) and +42.4 (*c* 1.0, CHCl<sub>3</sub>), lit.<sup>196</sup>  $[\alpha]_D^{26}$  = +46.7 (*c* 1.0, CHCl<sub>3</sub>)

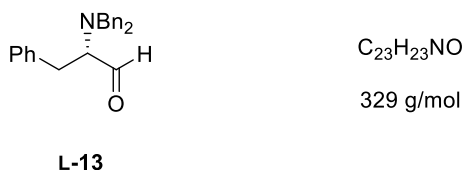
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3397, 3066, 3024, 2921, 2870, 1599, 1496, 1454, 1067

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 2.44 (dd,  $J$  = 13.0, 9.4 Hz, 1H) and 3.01-3.17 (m, 3H) (AB part of ABX syst., PhCH<sub>2</sub>CH, CHN, OH), 3.33 (br dd,  $J$  = 10.4, 3.6 Hz, 1H) and 3.52 (t,  $J$  = 10.4 Hz, 1H) (AB syst., CHCH<sub>2</sub>OH), 3.49 (d,  $J$  = 13.5 Hz, 2H) and 3.93 (d,  $J$  = 13.5 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 7.07-7.13 (m, 2H, Ph), 7.24-7.34 (m, 13H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 31.7 (PhCH<sub>2</sub>CH), 53.2 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 60.3 (CH<sub>2</sub>OH), 60.8 (CHN), 126.2 (CH<sub>Ph</sub>), 127.3 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.9 (CH<sub>Ph</sub>), 139.0 (C<sub>Ph</sub>), 139.1 (C<sub>Ph</sub>)

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>269</sup>

#### *N,N*-Dibenzyl-L-phenylalaninal (L-13).



According to the general procedure, Swern oxidation of *N,N*-dibenzyl-L-phenylalaninol **L-228** (1.00 g, 3.02 mmol) was performed with DMSO (560  $\mu$ L, 7.84 mmol), oxalyl chloride (360  $\mu$ L, 3.92 mmol) in

DCM (15 mL), followed by the addition of  $\text{NEt}_3$  (1.1 mL, 7.84 mmol). Crude *N,N*-dibenzyl-L-phenylalaninal **L-13** (994 mg, quant.) was isolated as a light yellow oil. It was used without any purification in the MAC reaction.

TLC  $R_f = 0.63$  (pentane/EtOAc, 10:1)

OR  $[\alpha]_D^{24} = -91.2$  ( $c$  1.0,  $\text{CHCl}_3$ ), lit.<sup>197</sup>  $[\alpha]_D^{20} = -90.0$  ( $c$  1.0,  $\text{CHCl}_3$ )

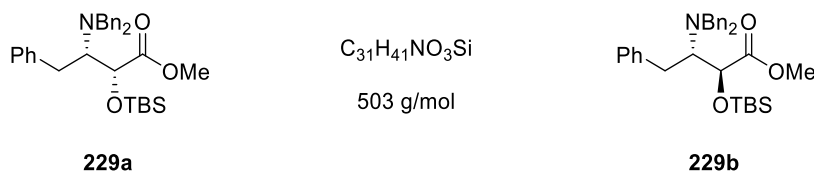
$^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 3.02 (dd,  $J = 13.9, 6.1$  Hz, 1H) and 3.23 (dd,  $J = 13.9, 7.2$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.64 (dd,  $J = 7.2, 6.1$  Hz, 1H, CHN), 3.75 (d,  $J = 13.7$  Hz, 2H) and 3.91 (d,  $J = 13.7$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 7.21-7.28 (m, 2H, Ph), 7.30-7.39 (m, 13H, Ph), 9.80 (s, 1H, CHO)

$^{13}\text{C NMR}$  (90.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 30.2 ( $\text{PhCH}_2\text{CH}$ ), 54.9 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 68.6 (CHN), 126.3 ( $\text{CH}_{\text{Ph}}$ ), 127.4 ( $\text{CH}_{\text{Ph}}$ ), 128.5 ( $\text{CH}_{\text{Ph}}$ ), 128.9 ( $\text{CH}_{\text{Ph}}$ ), 129.5 ( $\text{CH}_{\text{Ph}}$ ), 139.0 ( $\text{C}_{\text{Ph}}$ ), 139.2 ( $\text{C}_{\text{Ph}}$ ), 202.2 (CHO)

$^1\text{H NMR}$  data were in agreement with those described in the literature.<sup>192</sup>

### MAC reactions with H-MAC-[Si] and MeOH.

Methyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (**229a** and **229b**).



To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** (155 mg, 0.47 mmol) and H-MAC-TBS **148g** (223 mg, 1.14 mmol) under argon, were added dry  $\text{Et}_2\text{O}$  (5 mL) followed by methanol (58  $\mu\text{L}$ , 1.43 mmol). After cooling at 0  $^\circ\text{C}$ , DMAP (115 mg, 0.94 mmol) was added in one portion and the reaction mixture was stirred overnight under argon at this temperature. A saturated aqueous  $\text{Na}_2\text{CO}_3$  solution (10 mL) followed by water (10 mL) to dissolve the salts were successively introduced at 0  $^\circ\text{C}$ , and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (6 x 10 mL) and the combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. A 8:92 ratio of *syn/anti* diastereomers **229a/229b** was determined by  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ , 20:1) gave inseparable MAC reaction products **229a,b** (dr 8:92, 196 mg, 83%), as a colorless oil.

TLC  $R_f = 0.39$  (pentane/ $\text{Et}_2\text{O}$ , 20:1)

IR (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3022, 2951, 2925, 2858, 1752, 1738, 1605, 1494, 1454, 1250, 1125

HRMS ( $\text{ES}^+$ ): calcd. for  $\text{C}_{31}\text{H}_{42}\text{NO}_3\text{Si}$   $[\text{M}+\text{H}]^+$  504.2928; found 504.2904

Spectroscopic data for the major *anti* (2*S*,3*S*)-diastereomer (**229b**):

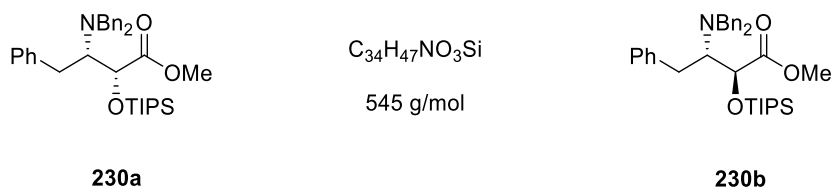
$^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 0.08 (s, 3H,  $\text{SiCH}_3$ ), 0.13 (s, 3H,  $\text{SiCH}_3$ ), 0.96 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ), 2.91-3.05 (m, 2H,  $\text{PhCH}_2\text{CH}$ ), 3.37-3.44 (m, 1H, CHN), 3.53 (s, 3H,  $\text{OCH}_3$ ), 3.61 (d,  $J = 13.9$  Hz, 2H) and 3.78 (d,



$J = 13.9$  Hz, 2H) (AB syst.,  $N(\text{CH}_2\text{Ph})_2$ ), 4.60 (d,  $J = 4.3$  Hz, 1H, CHOTBS), 7.08-7.14 (m, 6H, Ph), 7.17-7.31 (m, 9H, Ph)

$^{13}\text{C}$  NMR (90.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): -4.8 ( $\text{Si}(\text{CH}_3)_2$ ), 18.2 ( $\text{Si}(\text{C}(\text{CH}_3)_3$ ), 25.8 ( $\text{Si}(\text{C}(\text{CH}_3)_3$ ), 32.6 ( $\text{PhCH}_2\text{CH}$ ), 51.5 ( $\text{OCH}_3$ ), 54.4 ( $N(\text{CH}_2\text{Ph})_2$ ), 62.7 (CHN), 71.9 (CHOTBS), 125.8 ( $\text{CH}_{\text{Ph}}$ ), 126.7 ( $\text{CH}_{\text{Ph}}$ ), 127.9 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.7 ( $\text{CH}_{\text{Ph}}$ ), 129.6 ( $\text{CH}_{\text{Ph}}$ ), 139.5 ( $\text{C}_{\text{Ph}}$ ), 140.3 ( $\text{C}_{\text{Ph}}$ ), 173.4 ( $\text{COOCH}_3$ )

**Methyl (2*R*,3*S*)- and (2*S*,3*S*)-3-(dibenzylamino)-2-(triisopropylsilyloxy)-4-phenylbutanoate (230a and 230b).**



To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** (164 mg, 0.50 mmol) and H-MAC-TIPS **148h** (290 mg, 1.22 mmol) under argon, were added dry  $\text{Et}_2\text{O}$  (5 mL) followed by methanol (62  $\mu\text{L}$ , 1.53 mmol). After cooling at 0 °C, DMAP (122 mg, 1.00 mmol) was added in one portion and the reaction mixture was stirred overnight under argon at this temperature. A saturated aqueous  $\text{Na}_2\text{CO}_3$  solution (10 mL) followed by water (10 mL) to dissolve the salts were successively introduced at 0 °C, and the stirring was continued for 20 minutes at room temperature. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (6 x 10 mL). The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ , 20:1) gave inseparable MAC reaction products **230a,b** (dr 9:91, 217 mg, 80%), as a colorless oil. The 9:91 ratio of *syn/anti* diastereomers **230a/230b** was determined by  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 293 K) by integration of the CHOTIPS signals.

TLC  $R_f = 0.36$  (pentane/ $\text{Et}_2\text{O}$ , 20:1)

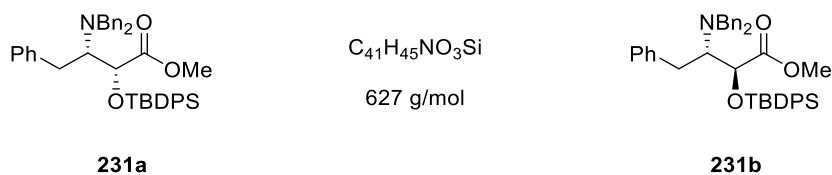
IR (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3028, 2946, 2864, 2804, 1755, 1738, 1604, 1495, 1455, 1256, 1122

HRMS ( $\text{ES}^+$ ): calcd. for  $\text{C}_{34}\text{H}_{48}\text{NO}_3\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  546.3398; found 546.3375

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (230b):*

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 0.96-1.10 (m, 21H,  $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$ ), 2.99 (dd,  $J = 14.8, 9.5$  Hz, 1H) and 3.08 (dd,  $J = 14.8, 5.0$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.35-3.44 (m, 1H, CHN), 3.55 (s, 3H,  $\text{OCH}_3$ ), 3.60 (d,  $J = 13.8$  Hz, 2H) and 3.69 (d,  $J = 13.8$  Hz, 2H) (AB syst.,  $N(\text{CH}_2\text{Ph})_2$ ), 4.62 (d,  $J = 5.8$  Hz, 1H, CHOTIPS), 7.04-7.10 (m, 4H, Ph), 7.14-7.29 (m, 11H, Ph)

$^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 12.7 ( $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$ ), 18.1 ( $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$ ), 32.8 ( $\text{PhCH}_2\text{CH}$ ), 51.4 ( $\text{OCH}_3$ ), 54.6 ( $N(\text{CH}_2\text{Ph})_2$ ), 63.8 (CHN), 73.2 (CHOTIPS), 125.9 ( $\text{CH}_{\text{Ph}}$ ), 126.7 ( $\text{CH}_{\text{Ph}}$ ), 127.9 ( $\text{CH}_{\text{Ph}}$ ), 128.1 ( $\text{CH}_{\text{Ph}}$ ), 128.9 ( $\text{CH}_{\text{Ph}}$ ), 129.6 ( $\text{CH}_{\text{Ph}}$ ), 139.5 ( $\text{C}_{\text{Ph}}$ ), 140.8 ( $\text{C}_{\text{Ph}}$ ), 173.4 ( $\text{COOCH}_3$ )

**Methyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldiphenylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (231a and 231b).**


To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** (146 mg, 0.44 mmol) and H-MAC-TBDPS **148i** (340 mg, 1.06 mmol) under argon, were added dry Et<sub>2</sub>O (5 mL) followed by methanol (54 μL, 1.33 mmol). After cooling at 0 °C, DMAP (108 mg, 0.88 mmol) was added in one portion and the reaction mixture was stirred overnight under argon at this temperature. The resulting reaction mixture was concentrated under reduced pressure to destroy excess of H-MAC-TBDPS and purified directly. Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **231a,b** (dr 7:93, 203 mg, 74%) as a colorless oil, which changed into a foam after standing for 16 h under high vacuum. The 7:93 ratio of *syn/anti* diastereomers **231a/231b** was determined by <sup>1</sup>H NMR (CDCl<sub>3</sub>, 293 K) by integration of the OMe signals.

**TLC** *R<sub>f</sub>* = 0.20 (pentane/Et<sub>2</sub>O, 20:1)

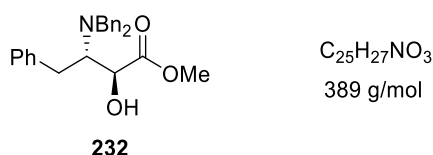
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3027, 2950, 2929, 2855, 2800, 1748, 1601, 1496, 1451, 1428, 1360, 1257, 1106

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>41</sub>H<sub>46</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 628.3241; found 628.3210

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (231b):*

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 1.09 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.98 (dd, *J* = 14.8, 9.7 Hz, 1H) and 3.14 (dd, *J* = 14.8, 4.0 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.19 (s, 3H, OCH<sub>3</sub>), 3.38-3.44 (m, 1H, CHN), 3.45 (d, *J* = 13.7 Hz, 2H) and 3.62 (d, *J* = 13.7 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.54 (d, *J* = 5.4 Hz, 1H, CHOTBDPS), 6.96-7.02 (m, 4H, Ph), 7.11-7.17 (m, 7H, Ph), 7.20-7.27 (m, 4H, Ph), 7.32-7.43 (m, 6H, Ph), 7.62-7.67 (m, 4H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 19.5 (SiC(CH<sub>3</sub>)<sub>3</sub>), 27.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 33.1 (PhCH<sub>2</sub>CH), 51.1 (OCH<sub>3</sub>), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 63.4 (CHN), 73.2 (CHOTBDPS), 125.9 (CH<sub>Ph</sub>), 126.6 (CH<sub>Ph</sub>), 127.4 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 127.8 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 129.8 (CH<sub>Ph</sub>), 132.9 (C<sub>Ph</sub>), 133.0 (C<sub>Ph</sub>), 136.0 (CH<sub>Ph</sub>), 136.1 (CH<sub>Ph</sub>), 139.4 (C<sub>Ph</sub>), 140.6 (C<sub>Ph</sub>), 172.5 (COOCH<sub>3</sub>)

**Methyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate (232).**


*From methyl (2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (229a,b):*

To a stirred solution of MAC reaction products **229a,b** (dr 8:92, 161 mg, 0.32 mmol) in dry THF (10 mL) at 0 °C under argon, was added dropwise TBAF (1 M in THF, 480 μL, 0.48 mmol). After stirring for 1 hour at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20

mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/EtOAc, 5:1) to give the *anti*-alcohol **232** (100 mg, 80%), as a colorless oil.

*From methyl (2RS,3S)-3-(dibenzylamino)-2-(triisopropylsilyloxy)-4-phenylbutanoate (230a,b):* Following the above procedure using MAC reaction products **230a,b** (dr 9:91, 169 mg, 0.31 mmol) in dry THF (10 mL) and TBAF (1 M in THF, 470 μL, 0.47 mmol), *anti*-alcohol **232** (104 mg, 86%) was obtained as a colorless oil after flash column chromatography (pentane/EtOAc, 3:1).

*From methyl (2RS,3S)-2-(tert-butylidiphenylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (231a,b):* To a stirred solution of MAC reaction products **231a,b** (dr 7:93, 200 mg, 0.32 mmol) in dry THF (10 mL) at 0 °C under argon, was added dropwise TBAF (1 M in THF, 480 μL, 0.48 mmol). After stirring for 16 hours at room temperature, the reaction mixture was quenched by addition of a saturated aqueous NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/EtOAc, 5:1) to give the *anti*-alcohol **232** (88 mg, 71%), as a colorless oil.

**TLC**  $R_f$  = 0.20 (pentane/EtOAc, 5:1)

**OR**  $[\alpha]_D^{22} = +35.9$  (c 1.0, CHCl<sub>3</sub>), lit.<sup>270</sup>  $[\alpha]_D^{20} = +35.8$  (c 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3513, 3062, 3026, 2952, 2803, 1729, 1602, 1494, 1453, 1369, 1252, 1220, 1105

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>25</sub>H<sub>28</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 390.2064; found 390.2051

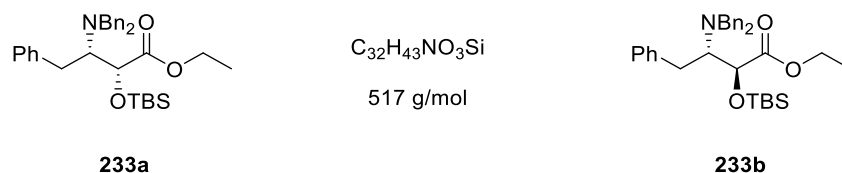
**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 2.82 (dd,  $J = 14.0, 7.6$  Hz, 1H) and 3.04 (dd,  $J = 14.0, 7.2$  Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.14 (br s, 1H, CHOH), 3.43 (ddd,  $J = 7.6, 7.2, 1.8$  Hz, 1H, CHN), 3.53 (s, 3H, OCH<sub>3</sub>), 3.67 (d,  $J = 13.7$  Hz, 2H) and 3.83 (d,  $J = 13.7$  Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.50 (br s, 1H, CHOH), 7.04-7.10 (m, 2H, Ph), 7.19-7.32 (m, 13H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 31.9 (PhCH<sub>2</sub>CH), 52.3 (OCH<sub>3</sub>), 54.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 62.1 (CHN), 69.6 (CHOH), 126.1 (CH<sub>Ph</sub>), 126.9 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 129.5 (CH<sub>Ph</sub>), 139.0 (C<sub>Ph</sub>), 139.5 (C<sub>Ph</sub>), 174.9 (COOCH<sub>3</sub>)

## Chapter 3: MAC reactions for the synthesis of *anti*-AHPBA derivatives

### MAC reactions of *N,N*-dibenzyl-L-phenylalaninal with alcohols as nucleophiles

**Ethyl (2*R*,3*S*)- and (2*S*,3*S*)- 2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (233a and 233b).**



According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (151 mg, 0.46 mmol), H-MAC-TBS **148g** (215 mg, 1.10 mmol), ethanol (82  $\mu$ L, 1.40 mmol) and DMAP (112 mg, 0.92 mmol) in Et<sub>2</sub>O (5 mL). A 9:91 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **233a** and **233b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **233a,b** (dr 9:91, 174 mg, 73%), as a viscous colorless oil.

TLC *R*<sub>f</sub> = 0.29 (pentane/Et<sub>2</sub>O, 20:1)

IR (ATR),  $\nu$  (cm<sup>-1</sup>): 3027, 2956, 2929, 2854, 2796, 1747, 1730, 1601, 1494, 1454, 1365, 1254, 1130

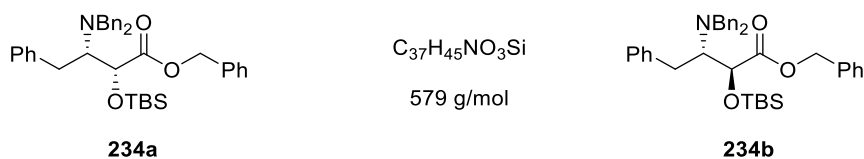
HRMS (ES<sup>+</sup>): calcd. for C<sub>32</sub>H<sub>44</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 518.3085; found 518.3062

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (233b):*

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.09 (s, 3H, SiCH<sub>3</sub>), 0.13 (s, 3H, SiCH<sub>3</sub>), 0.96 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.10 (t, *J* = 7.0 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.90 (dd, *J* = 14.4, 5.0 Hz, 1H) and 2.98 (dd, *J* = 14.4, 8.8 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.34-3.41 (m, 1H, CHN), 3.57 (d, *J* = 13.7 Hz, 2H) and 3.83 (d, *J* = 13.7 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.87-4.05 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.62 (d, *J* = 3.6 Hz, 1H, CHOTBS), 7.02-7.07 (m, 2H, Ph), 7.08-7.13 (m, 4H, Ph), 7.15-7.23 (m, 9H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>),  $\delta$ (ppm): -4.7 (SiCH<sub>3</sub>), -4.6 (SiCH<sub>3</sub>), 14.0 (OCH<sub>2</sub>CH<sub>3</sub>), 18.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.6 (PhCH<sub>2</sub>CH), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 60.6 (OCH<sub>2</sub>CH<sub>3</sub>), 62.7 (CHN), 71.4 (CHOTBS), 125.7 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 140.2 (C<sub>Ph</sub>), 173.1 (COOEt)

**Benzyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (234a and 234b).**



According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (147 mg, 0.45 mmol), H-MAC-TBS **148g** (212 mg, 1.08 mmol), benzyl alcohol (140  $\mu$ L, 1.35 mmol) and DMAP (110 mg, 0.90 mmol) in Et<sub>2</sub>O (5 mL). A 8:92 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-

diastereomers **234a** and **234b** was determined by  $^1\text{H}$  NMR analysis ( $\text{CDCl}_3$  at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ , 20:1) gave inseparable MAC reaction products **234a,b** (dr 8:92, 215 mg, 83%), as a colorless oil.

**TLC**  $R_f$  = 0.34 (pentane/ $\text{Et}_2\text{O}$ , 20:1)

**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3031, 2956, 2929, 2858, 2801, 1752, 1730, 1601, 1494, 1454, 1363, 1253, 1123

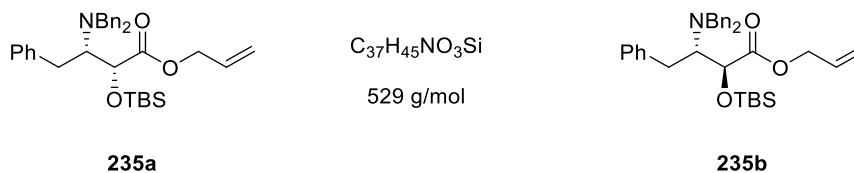
**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{37}\text{H}_{46}\text{NO}_3\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  580.3241; found 580.3217

*Spectroscopic data for the major anti (2S,3S)-diastereomer (234b):*

$^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 0.05 (s, 3H,  $\text{SiCH}_3$ ), 0.13 (s, 3H,  $\text{SiCH}_3$ ), 0.95 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 2.80 (dd,  $J$  = 14.4, 4.3 Hz, 1H) and 2.95 (dd,  $J$  = 14.4, 9.7 Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.31-3.38 (m, 1H, CHN), 3.55 (d,  $J$  = 14.6 Hz, 2H) and 3.87 (d,  $J$  = 14.6 Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 4.71 (d,  $J$  = 2.9 Hz, 1H, CHOTBS), 4.85 (d,  $J$  = 12.2 Hz, 1H) and 5.03 (d,  $J$  = 12.2 Hz, 1H) (AB syst.,  $\text{OCH}_2\text{Ph}$ ), 6.82-6.91 (m, 2H, Ph), 7.03-7.11 (m, 6H, Ph), 7.12-7.19 (m, 9H, Ph), 7.27-7.31 (m, 3H, Ph)

$^{13}\text{C}$  NMR (90.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): -4.7 ( $\text{SiCH}_3$ ), -4.6 ( $\text{SiCH}_3$ ), 18.2 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.8 ( $\text{SiC}(\text{CH}_3)_3$ ), 32.4 ( $\text{PhCH}_2\text{CH}$ ), 54.4 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 62.6 (CHN), 66.3 ( $\text{OCH}_2\text{Ph}$ ), 70.9 (CHOTBS), 125.7 ( $\text{CH}_{\text{Ph}}$ ), 126.6 ( $\text{CH}_{\text{Ph}}$ ), 127.8 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.1 ( $\text{CH}_{\text{Ph}}$ ), 128.4 ( $\text{CH}_{\text{Ph}}$ ), 128.6 ( $\text{CH}_{\text{Ph}}$ ), 129.7 ( $\text{CH}_{\text{Ph}}$ ), 135.4 ( $\text{C}_{\text{Ph}}$ ), 139.6 ( $\text{C}_{\text{Ph}}$ ), 140.1 ( $\text{C}_{\text{Ph}}$ ), 172.9 ( $\text{COOBn}$ )

**Allyl (2R,3S)- and (2S,3S)-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (235a and 235b).**



According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (143 mg, 0.43 mmol), H-MAC-TBS **148g** (203 mg, 1.03 mmol), allyl alcohol (88  $\mu\text{L}$ , 1.29 mmol) and DMAP (105 mg, 0.86 mmol) in  $\text{Et}_2\text{O}$  (5 mL). A 9:91 ratio of the (2R,3S)- and (2S,3S)-diastereomers **235a** and **235b** was determined by  $^1\text{H}$  NMR analysis ( $\text{CDCl}_3$  at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ , 20:1) gave inseparable MAC reaction products **235a,b** (dr 9:91, 188 mg, 82%), as a colorless oil.

**TLC**  $R_f$  = 0.35 (pentane/ $\text{Et}_2\text{O}$ , 20:1)

**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3027, 2956, 2929, 2858, 2800, 1751, 1730, 1602, 1494 1453, 1362, 1252, 1126

**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{33}\text{H}_{44}\text{NO}_3\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  530.3085; found 530.3060

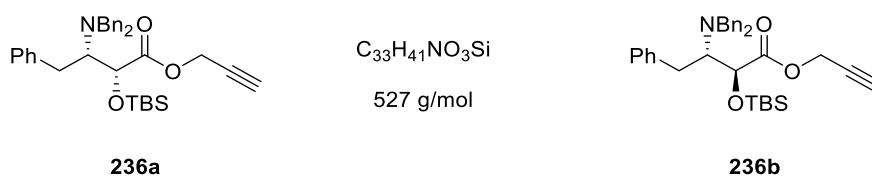
*Spectroscopic data for the major anti (2S,3S)-diastereomer (235b):*

$^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 0.08 (s, 3H,  $\text{SiCH}_3$ ), 0.13 (s, 3H,  $\text{SiCH}_3$ ), 0.96 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 2.91 (dd,  $J$  = 14.4, 5.0 Hz, 1H) and 2.99 (dd,  $J$  = 14.4, 9.0 Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.37-3.45 (m, 1H, CHN), 3.58 (d,  $J$  = 14.0 Hz, 2H) and 3.83 (d,  $J$  = 14.0 Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 4.35 (ddt,  $J$  =

13.0, 5.8, 1.1 Hz, 1H) and 4.43 (ddt,  $J = 13.0, 6.1, 1.1$  Hz, 1H) (AB part of ABXM syst.,  $\text{OCH}_2\text{CH}=\text{CH}_2$ ), 4.66 (d,  $J = 3.6$  Hz, 1H, CHOTBS), 5.11-5.21 (m, 2H,  $\text{OCH}_2\text{CH}=\text{CH}_2$ ), 5.74 (dddd,  $J = 16.9, 10.4, 6.1, 5.8$  Hz, 1H,  $\text{OCH}_2\text{CH}=\text{CH}_2$ ), 7.01-7.08 (m, 2H, Ph), 7.08-7.13 (m, 4H, Ph), 7.15-7.23 (m, 9H, Ph)

$^{13}\text{C}$  NMR (90.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): -4.7 ( $\text{SiCH}_3$ ), -4.6 ( $\text{SiCH}_3$ ), 18.2 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.9 ( $\text{SiC}(\text{CH}_3)_3$ ), 32.5 ( $\text{PhCH}_2\text{CH}$ ), 54.5 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 62.7 (CHN), 65.3 ( $\text{OCH}_2\text{CH}=\text{CH}_2$ ), 71.4 (CHOTBS), 118.6 ( $\text{OCH}_2\text{CH}=\text{CH}_2$ ), 125.8 ( $\text{CH}_{\text{Ph}}$ ), 126.7 ( $\text{CH}_{\text{Ph}}$ ), 127.9 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.7 ( $\text{CH}_{\text{Ph}}$ ), 129.7 ( $\text{CH}_{\text{Ph}}$ ), 131.7 ( $\text{OCH}_2\text{CH}=\text{CH}_2$ ), 139.5 ( $\text{C}_{\text{Ph}}$ ), 140.1 ( $\text{C}_{\text{Ph}}$ ), 172.7 (COOAll)

**Propargyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (236a and 236b).**



According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (143 mg, 0.43 mmol), H-MAC-TBS **148g** (202 mg, 1.03 mmol), propargyl alcohol (80  $\mu\text{L}$ , 1.29 mmol) and DMAP (105 mg, 0.86 mmol) in  $\text{Et}_2\text{O}$  (5 mL). A 7:93 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **236a** and **236b** was determined by  $^1\text{H}$  NMR analysis ( $\text{CDCl}_3$  at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ , 20:1) gave inseparable MAC reaction products **236a,b** (dr 7:93, 217 mg, 95%), as a colorless oil.

**TLC**  $R_f = 0.15$  (pentane/ $\text{Et}_2\text{O}$ , 20:1)

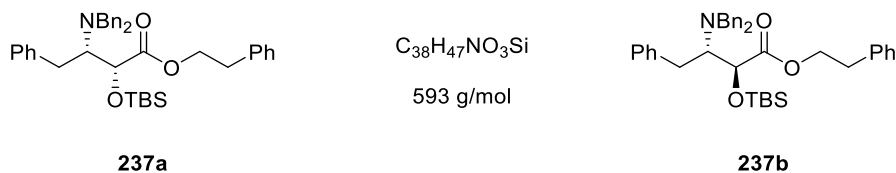
**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3311, 3027, 2951, 2929, 2856, 2802, 2134, 1757, 1740, 1602, 1493, 1452, 1363, 1250, 1124

**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{33}\text{H}_{42}\text{NO}_3\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  528.2928; found 528.2906

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (236b):*

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 0.09 (s, 3H,  $\text{SiCH}_3$ ), 0.13 (s, 3H,  $\text{SiCH}_3$ ), 0.95 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 2.42 (t,  $J = 2.7$  Hz, 1H,  $\text{OCH}_2\text{C}\equiv\text{CH}$ ), 2.89-3.03 (m, 2H,  $\text{PhCH}_2\text{CH}$ ), 3.36-3.45 (m, 1H, CHN), 3.58 (d,  $J = 14.0$  Hz, 2H) and 3.79 (d,  $J = 14.0$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 4.40 (dd,  $J = 15.6, 2.7$  Hz, 1H) and 4.56 (dd,  $J = 15.6, 2.7$  Hz, 1H) (AB syst.,  $\text{OCH}_2\text{C}\equiv\text{CH}$ ), 4.63 (d,  $J = 3.9$  Hz, 1H, CHOTBS), 7.05-7.13 (m, 6H, Ph), 7.16-7.25 (m, 9H, Ph)

$^{13}\text{C}$  NMR (90.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): -4.8 ( $\text{SiCH}_3$ ), -4.7 ( $\text{SiCH}_3$ ), 18.1 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.8 ( $\text{SiC}(\text{CH}_3)_3$ ), 32.6 ( $\text{PhCH}_2\text{CH}$ ), 51.9 ( $\text{OCH}_2\text{C}\equiv\text{CH}$ ), 54.4 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 62.6 (CHN), 71.5 (CHOTBS), 75.0 ( $\text{OCH}_2\text{C}\equiv\text{CH}$ ), 77.3 ( $\text{OCH}_2\text{C}\equiv\text{CH}$ ), 125.8 ( $\text{CH}_{\text{Ph}}$ ), 126.7 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.8 ( $\text{CH}_{\text{Ph}}$ ), 129.6 ( $\text{CH}_{\text{Ph}}$ ), 139.4 ( $\text{C}_{\text{Ph}}$ ), 140.1 ( $\text{C}_{\text{Ph}}$ ), 172.2 ( $\text{COOCH}_2\text{C}\equiv\text{CH}$ )

**2-Phenylethyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (237a and 237b).**


According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (145 mg, 0.44 mmol), H-MAC-TBS **148g** (208 mg, 1.06 mmol), 2-phenylethanol (160  $\mu$ L, 1.33 mmol) and DMAP (108 mg, 0.88 mmol) in Et<sub>2</sub>O (5 mL). A 5:95 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **237a** and **237b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **237a,b** (dr 5:95, 210 mg, 80%), as a colorless oil.

**TLC** *R<sub>f</sub>* = 0.05 (pentane/Et<sub>2</sub>O, 20:1)

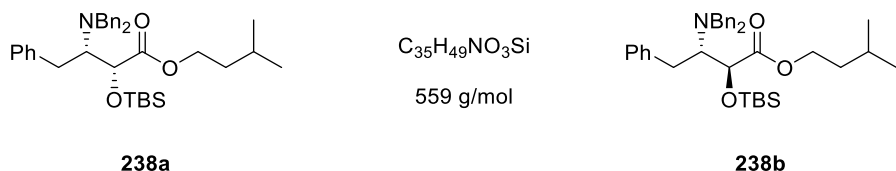
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3027, 2953, 2929, 2857, 2801, 1751, 1729, 1601, 1495, 1453, 1361, 1254, 1130

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>38</sub>H<sub>48</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 594.3398; found 594.3372

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (237b):*

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.05 (s, 3H, SiCH<sub>3</sub>), 0.11 (s, 3H, SiCH<sub>3</sub>), 0.95 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.75 (t, *J* = 7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>Ph), 2.84 (dd, *J* = 14.4, 4.8 Hz, 1H) and 2.98 (dd, *J* = 14.4, 9.0 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.32-3.43 (m, 1H, CHN), 3.57 (d, *J* = 14.2 Hz, 2H) and 3.83 (d, *J* = 14.2 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.12 (t, *J* = 7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>Ph), 4.63 (d, *J* = 3.3 Hz, 1H, CHOTBS), 6.97-7.04 (m, 2H, Ph), 7.06-7.13 (m, 6H, Ph), 7.16-7.35 (m, 12H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -4.8 (SiCH<sub>3</sub>), -4.6 (SiCH<sub>3</sub>), 18.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.5 (PhCH<sub>2</sub>CH), 34.8 (OCH<sub>2</sub>CH<sub>2</sub>Ph), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 62.5 (CHN), 65.1 (OCH<sub>2</sub>CH<sub>2</sub>Ph), 71.3 (CHOTBS), 125.7 (CH<sub>Ph</sub>), 126.5 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 137.4 (C<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 173.0 (COOCH<sub>2</sub>CH<sub>2</sub>Ph)

**3-Methylbutyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (238a and 238b).**


According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (141 mg, 0.43 mmol), H-MAC-TBS **148g** (202 mg, 1.03 mmol), isoamyl alcohol (140  $\mu$ L, 1.29 mmol) and DMAP (105 mg, 0.86 mmol) in Et<sub>2</sub>O (5 mL). A 9:91 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **238a** and **238b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of

the Me groups of the TBS signals. Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **238a,b** (dr 9:91, 154 mg, 64%), as a colorless oil.

**TLC**  $R_f$  = 0.44 (pentane/Et<sub>2</sub>O, 20:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3031, 2956, 2928, 2857, 2801, 1750, 1726, 1603, 1494, 1455, 1362, 1253, 1126

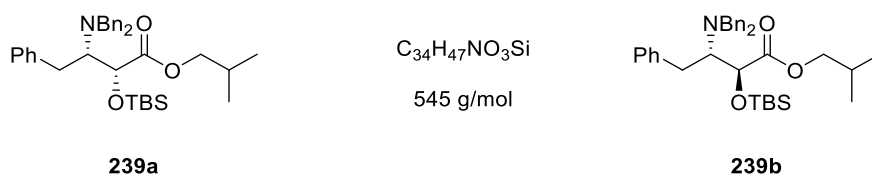
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>35</sub>H<sub>50</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 560.3554; found 560.3531

*Spectroscopic data for the major anti (2S,3S)-diastereomer (238b):*

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.10 (s, 3H, SiCH<sub>3</sub>), 0.14 (s, 3H, SiCH<sub>3</sub>), 0.83 (d,  $J$  = 6.8 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.97 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.34 (q,  $J$  = 6.8 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.44-1.52 (m, 1H, OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2.88 (dd,  $J$  = 14.8, 4.8 Hz, 1H) and 3.00 (dd,  $J$  = 14.8, 9.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.34-3.41 (m, 1H, CHN), 3.57 (d,  $J$  = 13.6 Hz, 2H) and 3.87 (d,  $J$  = 13.6 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.90-4.02 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 4.66 (d,  $J$  = 2.8 Hz, 1H, CHOTBS), 7.01-7.05 (m, 2H, Ph), 7.06-7.11 (m, 4H, Ph), 7.14-7.23 (m, 9H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -4.6 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 18.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.3 (OCH<sub>2</sub>CH<sub>2</sub>CHCH<sub>3</sub>), 22.4 (OCH<sub>2</sub>CH<sub>2</sub>CHCH<sub>3</sub>), 24.7 (OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.5 (PhCH<sub>2</sub>CH), 37.1 (OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 62.6 (CHN), 63.2 (OCH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 71.1 (CHOTBS), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 140.1 (C<sub>Ph</sub>), 173.2 (COOCH<sub>2</sub>)

**Isobutyl (2R,3S)- and (2S,3S)-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (239a and 239b).**



According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (138 mg, 0.42 mmol), H-MAC-TBS **148g** (196 mg, 1.00 mmol), isobutanol (118  $\mu$ L, 1.27 mmol) and DMAP (103 mg, 0.84 mmol) in Et<sub>2</sub>O (5 mL). A 9:91 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **239a** and **239b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **239a,b** (dr 9:91, 105 mg, 46%), as a colorless oil.

**TLC**  $R_f$  = 0.39 (pentane/Et<sub>2</sub>O, 20:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3026, 2957, 2931, 2857, 2800, 1750, 1730, 1603, 1495, 1453, 1363, 1251, 1129

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>34</sub>H<sub>48</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 546.3398, found 546.3375

*Spectroscopic data for the major anti (2S,3S)-diastereomer (239b):*

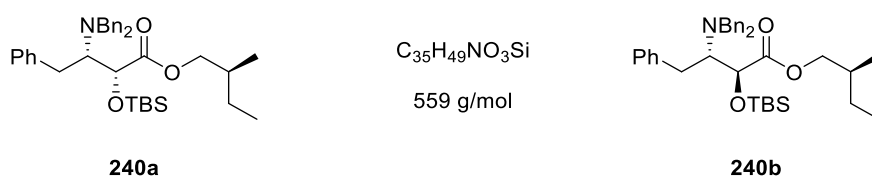
**<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.10 (s, 3H, SiCH<sub>3</sub>), 0.15 (s, 3H, SiCH<sub>3</sub>), 0.76 (d,  $J$  = 6.7 Hz, 3H, OCH<sub>2</sub>CHCH<sub>3</sub>), 0.79 (d,  $J$  = 6.7 Hz, 3H, OCH<sub>2</sub>CHCH<sub>3</sub>), 0.98 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.73 (nonuplet,  $J$  = 6.7 Hz, 1H, OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2.87 (dd,  $J$  = 14.5, 5.0 Hz, 1H) and 3.01 (dd,  $J$  = 14.5, 9.0 Hz, 1H) (AB part of ABX syst.,



PhCH<sub>2</sub>CH), 3.34-3.44 (m, 1H, CHN), 3.57 (d, *J* = 14.0 Hz, 2H) and 3.89 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.65 (dd, *J* = 10.5, 6.7 Hz, 1H) and 3.70 (dd, *J* = 10.5, 6.7 Hz, 1H) (AB part of ABX syst., OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 4.70 (d, *J* = 2.8 Hz, 1H, CHOTBS), 6.97-7.06 (m, 2H, Ph), 7.06-7.12 (m, 4H, Ph), 7.14-7.24 (m, 9H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -4.6 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 18.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 19.1 (OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 27.5 (OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 32.4 (PhCH<sub>2</sub>CH), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 62.5 (CHN), 70.9 (OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 71.0 (CHOTBS), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 173.2 (COO*i*Bu)

**(S)-2-Methylbutyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (**240a** and **240b**).**



According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (131 mg, 0.40 mmol), H-MAC-TBS **148g** (188 mg, 0.96 mmol), (*S*)-2-methylbutan-1-ol (135  $\mu$ L, 1.20 mmol) and DMAP (98 mg, 0.80 mmol) in Et<sub>2</sub>O (4 mL). A 10:90 ratio of the (*2R,3S*)- and (*2S,3S*)-diastereomers **240a** and **240b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **240a,b** (dr 10:90, 107 mg, 48%), as a colorless oil.

**TLC** *R<sub>f</sub>* = 0.27 (pentane/Et<sub>2</sub>O, 20:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3027, 2957, 2929, 2858, 2800, 1747, 1726, 1603, 1496, 1453, 1361, 1254, 1128

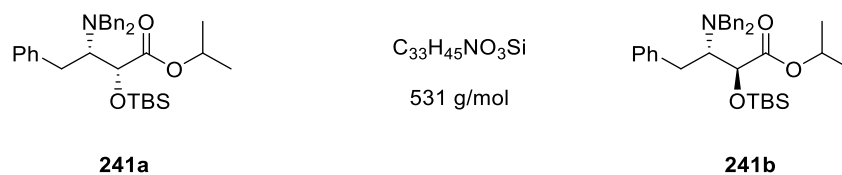
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>35</sub>H<sub>50</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 560.3554; found 560.3534

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (**240b**):*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.10 (s, 3H, SiCH<sub>3</sub>), 0.14 (s, 3H, SiCH<sub>3</sub>), 0.74 (d, *J* = 6.8 Hz, 3H, OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 0.81 (t, *J* = 7.4 Hz, 3H, OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 0.97 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.18-1.28 (m, 2H, OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 1.46-1.56 (m, 1H, OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 2.86 (dd, *J* = 14.6, 4.8 Hz, 1H) and 3.01 (dd, *J* = 14.6, 9.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.35-3.42 (m, 1H, CHN), 3.57 (d, *J* = 14.0 Hz, 2H) and 3.90 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.69 (dd, *J* = 10.6, 6.6 Hz, 1H) and 3.78 (dd, *J* = 10.6, 6.2 Hz, 1H) (AB part of ABX syst., OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 4.69 (d, *J* = 2.4 Hz, 1H, CHOTBS), 7.00-7.04 (m, 2H, Ph), 7.06-7.11 (m, 4H, Ph), 7.13-7.24 (m, 9H, Ph)

<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -4.6 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 11.1 (OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 16.2 (OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 18.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.4 (PhCH<sub>2</sub>CH), 33.9 (OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 62.5 (CHN), 69.4 (OCH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), 70.9 (CHOTBS), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 173.3 (COOCH<sub>2</sub>)

**Isopropyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (241a and 241b).**



According to the general procedure A, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (121 mg, 0.37 mmol), H-MAC-TBS **148g** (175 mg, 0.89 mmol), isopropanol (85  $\mu$ L, 1.11 mmol) and DMAP (90 mg, 0.74 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **241a,b** (dr 7:93, 21 mg, 11%), as a colorless oil. The 7:93 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **241a** and **241b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (172 mg, 0.52 mmol), H-MAC-TBS **148g** (245 mg, 1.25 mmol), DMAP (127 mg, 1.04 mmol) and isopropanol (120  $\mu$ L, 1.56 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 20:1) gave inseparable MAC reaction products **241a,b** (dr 10:90, 48 mg, 18%), as a viscous colorless oil. The 10:90 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **241a** and **241b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

**TLC**  $R_f$  = 0.40 (pentane/Et<sub>2</sub>O, 20:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3028, 2952, 2930, 2855, 2800, 1749, 1721, 1604, 1495, 1454, 1373, 1258, 1141, 1105

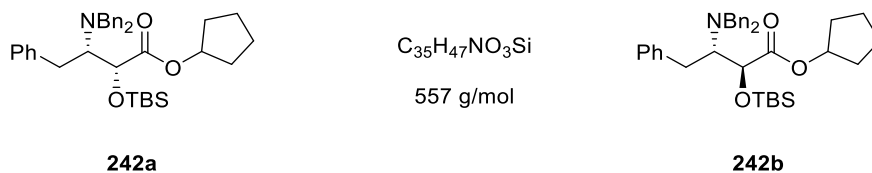
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>33</sub>H<sub>46</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 532.3241; found 532.3217

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (241b):*

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.12 (s, 3H, SiCH<sub>3</sub>), 0.16 (s, 3H, SiCH<sub>3</sub>), 0.99 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.03 (d,  $J$  = 6.3 Hz, 3H, OCHCH<sub>3</sub>), 1.18 (d,  $J$  = 6.3 Hz, 3H, OCHCH<sub>3</sub>), 2.82 (dd,  $J$  = 14.8, 4.7 Hz, 1H) and 2.98 (dd,  $J$  = 14.8, 9.7 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.32 (ddd,  $J$  = 6.8, 4.7, 2.5 Hz, 1H, CHN), 3.52 (d,  $J$  = 14.0 Hz, 2H) and 3.93 (d,  $J$  = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.68 (d,  $J$  = 2.5 Hz, 1H, CHOTBS), 4.86 (septuplet,  $J$  = 6.3 Hz, 1H, OCH(CH<sub>3</sub>)<sub>2</sub>), 6.94-7.02 (m, 2H, Ph), 7.05-7.12 (m, 4H, Ph), 7.15-7.23 (m, 9H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -4.6 (SiCH<sub>3</sub>), -4.4 (SiCH<sub>3</sub>), 18.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 21.5 (OCHCH<sub>3</sub>), 21.8 (OCHCH<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.4 (PhCH<sub>2</sub>CH), 54.3 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 62.4 (CHN), 68.2 (OCH(CH<sub>3</sub>)<sub>2</sub>), 70.4 (CHOTBS), 125.7 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.8 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 140.1 (C<sub>Ph</sub>), 172.9 (COO*i*Pr)

**Cyclopentyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (242a and 242b).**



According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (161 mg, 0.49 mmol), H-MAC-TBS **148g** (231 mg, 1.18 mmol), DMAP (120 mg, 0.98 mmol) and cyclopentanol (95  $\mu$ L, 1.47 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 30:1) gave inseparable MAC reaction products **242a,b** (dr 10:90, 38 mg, 14%), as a viscous colorless oil. The 10:90 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **242a** and **242b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

**TLC** *R<sub>f</sub>* = 0.43 (pentane/Et<sub>2</sub>O, 10:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3025, 2956, 2929, 2860, 2800, 1758, 1728, 1604, 1494, 1462, 1379, 1268, 1121

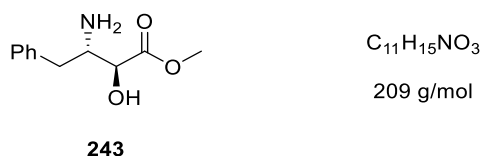
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>35</sub>H<sub>48</sub>NO<sub>3</sub>Si [M+H]<sup>+</sup> 558.3398; found 558.3371

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (242b):*

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.13 (s, 3H, SiCH<sub>3</sub>), 0.16 (s, 3H, SiCH<sub>3</sub>), 1.00 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.39-1.53 (m, 4H, OCH(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 1.56-1.71 (m, 4H, OCH(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 2.84 (dd, *J* = 14.7, 4.8 Hz, 1H) and 3.00 (dd, *J* = 14.7, 9.3 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.35 (ddd, *J* = 9.3, 4.8, 2.4 Hz 1H, CHN), 3.55 (d, *J* = 14.0 Hz, 2H) and 3.93 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.68 (d, *J* = 2.4 Hz, 1H, CHOTBS), 4.96-5.03 (m, 1H, OCH(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 6.95-7.03 (m, 2H, Ph), 7.07-7.13 (m, 4H, Ph), 7.15-7.25 (m, 9H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -4.6 (SiCH<sub>3</sub>), -4.4 (SiCH<sub>3</sub>), 18.2 (SiC(CH<sub>3</sub>)<sub>3</sub>), 23.5 (OCHCH<sub>2</sub>CH<sub>2</sub>), 23.6 (OCHCH<sub>2</sub>CH<sub>2</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.3 (PhCH<sub>2</sub>CH), 32.5 (OCH(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 62.4 (CHN), 70.6 (CHOTBS), 77.6 (OCH(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 125.7 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 173.1 (COOCH)

**Methyl (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate (243).**



Palladium hydroxide (20 wt.%) on activated carbon (7.2 mg) was added to a solution of methyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **232** (55 mg, 0.14 mmol) in MeOH (10 mL). The resulting mixture was stirred under H<sub>2</sub> (1 atm pressure) for 1 hour at room temperature and then filtered through a pad of Celite which was washed through with MeOH. The combined filtrate and washings were concentrated under reduced pressure. The residual pale yellow oil was taken up in Et<sub>2</sub>O, filtered through a PVDF membrane (0.22  $\mu$ m pore size) and the filtrate was evaporated under reduced pressure to furnish (2*S*,3*S*)-allophenylnorstatin methyl ester **243** (26 mg, 88%), as a colorless oil.

TLC  $R_f$  = 0.50 (MeOH)

OR  $[\alpha]_D^{22} = +24.1$  (c 1.0, CH<sub>3</sub>OH)

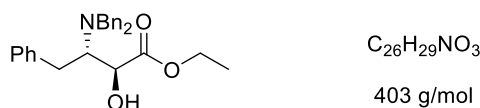
IR (ATR),  $\nu$  (cm<sup>-1</sup>): 3474, 3357, 3297, 3028, 2953, 2922, 2853, 1732, 1601, 1583, 1496, 1452, 1438, 1207

HRMS (ES<sup>+</sup>): calcd. for C<sub>11</sub>H<sub>16</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 210.1125; found 210.1119

<sup>1</sup>H NMR (360 MHz, CD<sub>3</sub>OD),  $\delta$  (ppm): 2.63 (dd,  $J$  = 13.7, 8.6 Hz, 1H) and 2.86 (dd,  $J$  = 13.7, 6.0 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.27-3.36 (m, 1H, CHN), 3.67 (s, 3H, OCH<sub>3</sub>), 4.14 (d,  $J$  = 4.0 Hz, 1H, CHOH), 7.18-7.25 (m, 3H, Ph), 7.26-7.33 (m, 2H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CD<sub>3</sub>OD),  $\delta$  (ppm): 39.5 (PhCH<sub>2</sub>CH), 52.4 (OCH<sub>3</sub>), 57.0 (CHN), 74.8 (CHOH), 127.5 (CH<sub>Ph</sub>), 129.5 (CH<sub>Ph</sub>), 130.5 (CH<sub>Ph</sub>), 139.8 (C<sub>Ph</sub>), 174.6 (COOMe)

### Ethyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate (**245**).



**245**

Tetrabutylammonium fluoride (1 M in THF, 930  $\mu$ L, 0.93 mmol) was added dropwise to a stirred solution of ethyl (2*RS*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **233a,b** (dr 8:92, 322 mg, 0.62 mmol) in dry THF (15 mL) at 0 °C. After stirring for 2 hours at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous NH<sub>4</sub>Cl solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 10:1:1 then pentane/EtOAc, 5:1) to furnish the *anti*-alcohol **245** (229 mg, 91%), as a colorless oil.

TLC  $R_f$  = 0.34 (pentane/EtOAc, 5:1)

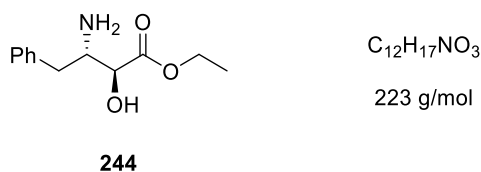
OR  $[\alpha]_D^{19} = +70.4$  (c 1.0, CHCl<sub>3</sub>)

IR (ATR),  $\nu$  (cm<sup>-1</sup>): 3499, 3062, 3025, 2974, 2804, 1724, 1603, 1495, 1452, 1368, 1249, 1215, 1105

HRMS (ES<sup>+</sup>): calcd. for C<sub>26</sub>H<sub>30</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 404.2220; found 404.2204

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 1.11 (t,  $J$  = 7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.78 (dd,  $J$  = 14.0, 7.2 Hz, 1H) and 3.00 (dd,  $J$  = 14.0, 7.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.12 (d,  $J$  = 6.1 Hz, 1H, CHOH), 3.44 (ddd,  $J$  = 7.2, 7.2, 2.1 Hz, 1H, CHN), 3.64 (d,  $J$  = 14.0 Hz, 2H) and 3.86 (d,  $J$  = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.89-4.05 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.52 (dd,  $J$  = 6.1, 2.1 Hz, 1H, CHOH), 7.00-7.05 (m, 2H, Ph), 7.19-7.28 (m, 13H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 13.8 (OCH<sub>2</sub>CH<sub>3</sub>), 31.9 (PhCH<sub>2</sub>CH), 54.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.6 (OCH<sub>2</sub>CH<sub>3</sub>), 61.9 (CHN), 69.4 (CHOH), 126.0 (CH<sub>Ph</sub>), 126.8 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 129.5 (CH<sub>Ph</sub>), 139.0 (C<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 174.6 (COOEt)

**Ethyl (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate (244).**

$C_{12}H_{17}NO_3$   
223 g/mol

Palladium hydroxide (20 wt.%) on activated carbon (4 mg) was added to a solution of ethyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **245** (37 mg, 0.09 mmol) in EtOH (10 mL). The resulting mixture was stirred under  $H_2$  (1 atm pressure) for 2 hours at room temperature and then filtered through a pad of Celite which was washed with EtOH. The combined filtrate and washings were concentrated under reduced pressure. The residual pale yellow oil was taken up in Et<sub>2</sub>O, filtered through a PVDF membrane (0.22  $\mu$ m pore size) and the filtrate was evaporated under reduced pressure to furnish (2*S*,3*S*)-allophenylnorstatin ethyl ester **244** (15 mg, 73%), as a colorless oil.

**TLC**  $R_f$  = 0.57 (MeOH)

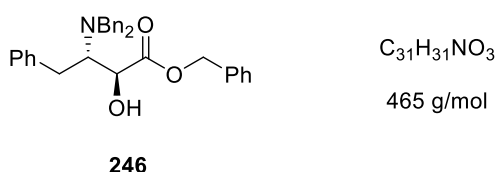
**OR**  $[\alpha]_D^{24} = +20.0$  (c 1.0, CH<sub>3</sub>OH) and  $[\alpha]_D^{23} = +10.1$  (c 1.0, CH<sub>3</sub>CN)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3478, 3362, 3287, 3064, 2924, 2859, 1731, 1602, 1496, 1454, 1368, 1202

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>12</sub>H<sub>18</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 224.1281; found 224.1274

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$  (ppm): 1.21 (t,  $J$  = 7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.36 (br s, 2H, NH<sub>2</sub>), 2.46 (dd,  $J$  = 13.2, 8.8 Hz, 1H) and 2.76 (dd,  $J$  = 13.2, 4.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.01-3.10 (m, 1H, CHN), 3.85 (br d,  $J$  = 4.8 Hz, 1H, CHOH), 4.02-4.12 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.52 (br s, 1H, CHOH), 7.15-7.23 (m, 3H, Ph), 7.24-7.31 (m, 2H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, DMSO-*d*<sub>6</sub>),  $\delta$  (ppm): 14.1 (OCH<sub>2</sub>CH<sub>3</sub>), 38.8 (PhCH<sub>2</sub>CH), 56.0 (CHN), 59.8 (OCH<sub>2</sub>CH<sub>3</sub>), 74.5 (CHOH), 125.8 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 129.3 (CH<sub>Ph</sub>), 139.5 (C<sub>Ph</sub>), 172.7 (COOEt)

**Benzyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate (246).**

$C_{31}H_{31}NO_3$   
465 g/mol

To a stirred solution of benzyl (2*RS*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **234a,b** (dr 8:92; 173 mg, 0.30 mmol) in dry THF (4 mL) at 0 °C under argon, was added dropwise TBAF (1 M in THF, 450  $\mu$ L, 0.45 mmol). After stirring for 50 minutes at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous NH<sub>4</sub>Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/EtOAc, 10:1) to furnish the *anti*-alcohol **246** (117 mg, 84%), as a colorless oil.

**TLC**  $R_f$  = 0.32 (pentane/EtOAc, 5:1)

**OR**  $[\alpha]_{\text{D}}^{22} = +28.7$  (*c* 1.0,  $\text{CHCl}_3$ )

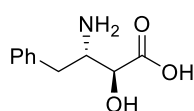
**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3514, 3066, 3028, 2926, 2804, 1730, 1599, 1496, 1452, 1258, 1211, 1104

**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{31}\text{H}_{32}\text{NO}_3$   $[\text{M}+\text{H}]^+$  466.2376; found 466.2365

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.68 (dd,  $J = 14.1, 6.9$  Hz, 1H) and 2.96 (dd,  $J = 14.1, 7.8$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.09 (d,  $J = 6.0$  Hz, 1H,  $\text{CHOH}$ ), 3.44 (ddd,  $J = 7.8, 6.9, 1.8$  Hz, 1H, CHN), 3.61 (d,  $J = 14.0$  Hz, 2H) and 3.86 (d,  $J = 14.0$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 4.60 (dd,  $J = 6.0, 1.8$  Hz, 1H,  $\text{CHOH}$ ), 4.88 (d,  $J = 12.3$  Hz, 1H) and 4.92 (d,  $J = 12.3$  Hz, 1H) (AB syst.,  $\text{OCH}_2\text{Ph}$ ), 6.85-6.90 (m, 2H, Ph), 7.04-7.09 (m, 2H, Ph), 7.11-7.16 (m, 3H, Ph), 7.18-7.24 (m, 10H, Ph), 7.26-7.32 (m, 3H, Ph)

**$^{13}\text{C}$  NMR** (75.5 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 31.9 ( $\text{PhCH}_2\text{CH}$ ), 54.5 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 61.9 (CHN), 67.2 ( $\text{OCH}_2\text{Ph}$ ), 69.4 ( $\text{CHOH}$ ), 126.0 ( $\text{CH}_{\text{Ph}}$ ), 126.8 ( $\text{CH}_{\text{Ph}}$ ), 127.9 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.1 ( $\text{CH}_{\text{Ph}}$ ), 128.3 ( $\text{CH}_{\text{Ph}}$ ), 128.5 ( $\text{CH}_{\text{Ph}}$ ), 128.7 ( $\text{CH}_{\text{Ph}}$ ), 129.6 ( $\text{CH}_{\text{Ph}}$ ), 134.8 ( $\text{C}_{\text{Ph}}$ ), 138.9 ( $\text{C}_{\text{Ph}}$ ), 139.6 ( $\text{C}_{\text{Ph}}$ ), 174.5 ( $\text{COOBn}$ )

**(2S,3S)-3-Amino-2-hydroxy-4-phenylbutanoic acid, (–)-allophenylnorstatin (1d).**



$\text{C}_{10}\text{H}_{13}\text{NO}_3$

195 g/mol

**1d**

Palladium (10 wt.%) on activated carbon (6 mg) was added to a solution of benzyl (2S,3S)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **246** (50 mg, 0.10 mmol) in EtOAc (8 mL). The resulting mixture was stirred under  $\text{H}_2$  (1 atm pressure) for 24 hours at room temperature and then filtered through a short pad of Celite which was washed through with further EtOAc. Water (3 x 5 mL) was then allowed to percolate through the solid material that remained on the Celite pad. The combined aqueous extracts were concentrated under reduced pressure and dried under high vacuum to furnish (2S,3S)-allophenylnorstatin **1d** (20 mg, 95%), as a white powder.

**Mp** = 196 °C (dec.), lit.<sup>271</sup> 195 °C (dec.)

**TLC**  $R_f = 0.53$  (MeOH)

**OR**  $[\alpha]_{\text{D}}^{23} = -5.6$  (*c* 0.1, 1 M HCl), lit.<sup>272</sup>  $[\alpha]_{\text{D}}^{20} = -5.5$  (*c* 0.1, 1 M HCl)

**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3369, 3024, 1599, 1549, 1417, 1342, 1301, 1062

**HRMS** ( $\text{ES}^-$ ): calcd. for  $\text{C}_{10}\text{H}_{12}\text{NO}_3$   $[\text{M}-\text{H}]^-$  194.0822; found 194.0819

**$^1\text{H}$  NMR** (300 MHz,  $\text{D}_2\text{O}$ ),  $\delta$  (ppm): 2.91 (dd,  $J = 14.4, 10.5$  Hz, 1H) and 3.02 (dd,  $J = 14.4, 3.9$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.89 (ddd,  $J = 10.5, 3.9, 3.3$  Hz, 1H,  $\text{CHNH}_2$ ), 4.33 (d,  $J = 3.3$  Hz, 1H,  $\text{CHOH}$ ), 7.33-7.52 (m, 5H, Ph)

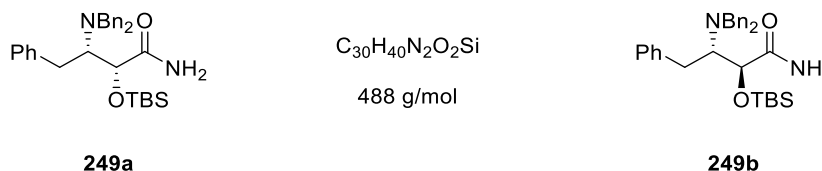
**$^{13}\text{C}$  NMR** (75.5 MHz,  $\text{D}_2\text{O}$ ),  $\delta$  (ppm): 33.1 ( $\text{PhCH}_2\text{CH}$ ), 55.7 ( $\text{CHNH}_2$ ), 71.4 ( $\text{CHOH}$ ), 127.6 ( $\text{CH}_{\text{Ph}}$ ), 129.2 ( $\text{CH}_{\text{Ph}}$ ), 129.4 ( $\text{CH}_{\text{Ph}}$ ), 135.4 ( $\text{C}_{\text{Ph}}$ ), 176.4 ( $\text{COOH}$ )

$^1\text{H}$  and  $^{13}\text{C}$  NMR data were in agreement with those described in literature.<sup>271,272</sup>

## MAC reaction of *N*-protected-L-phenylalaninal derivatives with ammonia

### MAC reaction of *N,N*-dibenzyl-L-phenylalaninal

**(2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (249a and 249b).**



According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (144 mg, 0.44 mmol), H-MAC-TBS **148g** (207 mg, 1.06 mmol), ammonia (0.5 M in THF, 1.1 mL, 0.55 mmol) and DMAP (108 mg, 0.88 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 2:1) gave inseparable MAC reaction products **249a,b** (dr 2:98, 191 mg, 89%), as a pale yellow solid. The 2:98 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **249a/249b** was determined by <sup>1</sup>H NMR analysis (600 MHz, CDCl<sub>3</sub> at 293 K) by integration of the CHNBn<sub>2</sub> signals. Chiral analytical HPLC (lux-amylose-2, hexane/EtOH: 70/30, 1 mL/min) realized on a sample of **249b** (1 mg in 1 mL of *i*PrOH) furnished an enantiomeric excess of 97%. A single crystal suitable for X-ray diffraction was obtained by slow diffusion of pentane into a Et<sub>2</sub>O solution of **249b** at room temperature.

*Preparative scale according to the procedure B:* To freshly prepared *N,N*-dibenzyl-L-phenylalaninal **L-13** (724 mg, 2.2 mmol) were added H-MAC-TBS **148g** (1.014 g, 5.2 mmol) and Et<sub>2</sub>O (20 mL) under argon. After cooling at 0 °C, ammonia (0.5 M in THF, 5.2 mL, 2.6 mmol) was introduced, followed by DMAP (537 mg, 4.4 mmol) in one portion and the reaction mixture was stirred overnight under argon at 0 °C. A saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and water (20 mL) were added, and the aqueous phase was extracted with Et<sub>2</sub>O (6 x 20 mL). The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Flash column chromatography (pentane/EtOAc, 5:1) gave recovered H-MAC-TBS **148g** (350 mg, 1.8 mmol, 0.8 eq.) and inseparable MAC reaction products **249a,b** (dr 5:95, 898 mg, 84%), as a pale-yellow solid.

*Data for the major anti (2*S*,3*S*)-diastereomer (249b), a pale-yellow solid:*

**Mp** = 107 °C

**TLC** *R<sub>f</sub>* = 0.10 (pentane/Et<sub>2</sub>O, 2:1)

**OR** [ $\alpha$ ]<sub>D</sub><sup>26</sup> = -15.8 (*c* 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3480, 3279, 3211, 3063, 3027, 2954, 2929, 2857, 2804, 1688, 1602, 1495, 1454, 1361, 1255, 1098

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>30</sub>H<sub>41</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 489.2932; found 489.2010

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -0.04 (s, 3H, SiCH<sub>3</sub>), 0.05 (s, 3H, SiCH<sub>3</sub>), 0.90 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 3.00 (dd, *J* = 14.0, 7.2 Hz, 1H) and 3.04 (dd, *J* = 14.0, 7.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.30 (ddd, *J* = 7.6, 7.2, 3.2 Hz, 1H, CHNBn<sub>2</sub>), 3.73 (d, *J* = 14.4 Hz, 2H) and 3.77 (d, *J* = 14.4 Hz, 2H) (AB syst.,

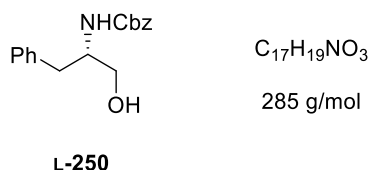
$N(\text{CH}_2\text{Ph})_2$ , 4.39 (d,  $J = 3.2$  Hz, 1H,  $\text{CHOTBS}$ ), 6.19 (br s, 2H,  $\text{CONH}_2$ ), 7.09-7.14 (m, 2H, Ph), 7.14-7.34 (m, 13H, Ph)

$^{13}\text{C}$  NMR (90.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -5.1 ( $\text{SiCH}_3$ ), -4.7 ( $\text{SiCH}_3$ ), 18.0 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.8 ( $\text{SiC}(\text{CH}_3)_3$ ), 32.6 ( $\text{PhCH}_2\text{CH}$ ), 54.3 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 64.0 ( $\text{CHNBN}_2$ ), 73.0 ( $\text{CHOTBS}$ ), 125.8 ( $\text{CH}_{\text{Ph}}$ ), 126.6 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.1 ( $\text{CH}_{\text{Ph}}$ ), 128.8 ( $\text{CH}_{\text{Ph}}$ ), 129.7 ( $\text{CH}_{\text{Ph}}$ ), 139.6 ( $\text{C}_{\text{Ph}}$ ), 140.0 ( $\text{C}_{\text{Ph}}$ ), 176.4 ( $\text{CONH}_2$ )

### MAC Reaction of *N*-Cbz-L-phenylalaninal

#### *N*-Cbz-L-phenylalaninal's synthesis.

#### *N*-Cbz-L-phenylalaninol (L-250).



According to a literature procedure,<sup>273</sup> commercial L-phenylalaninol **L-224** (1.00 g, 6.6 mmol) was dissolved in dry DCM (22 mL) and cooled to 0 °C. Benzyl chloroformate (1.2 mL, 8.6 mmol) was added dropwise at 0 °C, followed by  $\text{NEt}_3$  (4.6 mL, 33.0 mmol) and the reaction mixture was stirred at room temperature overnight. After washings with brine (3 x 20 mL), the organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford *N*-Cbz-L-phenylalaninol **L-250** (1.77 g, 94%), as a viscous colorless oil. It was engaged directly in the next reaction without any purification.

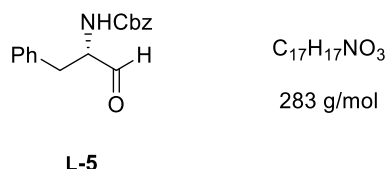
TLC  $R_f = 0.38$  (DCM/MeOH, 20:1)

OR  $[\alpha]_{\text{D}}^{25} = -41.5$  (c 1.0, MeOH), lit.<sup>274</sup>  $[\alpha]_{\text{D}}^{30} = -41.5$  (c 1.0, MeOH)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 2.20 (br s, 1H, OH), 2.87 (d,  $J = 6.9$  Hz, 2H,  $\text{PhCH}_2\text{CH}$ ), 3.58 (m, 1 H) and 3.69 (m, 1 H) (AB syst.,  $\text{CH}_2\text{OH}$ ), 3.89-4.00 (m, 1H,  $\text{CHNCbz}$ ), 5.02 (br d,  $J = 8.4$  Hz, 1H, NH), 5.08 (s, 2H,  $\text{PhCH}_2\text{O}$ ), 7.15-7.43 (m, 10 H, Ph)

$^1\text{H}$  NMR data were in agreement with those described in literature.<sup>274</sup>

#### *N*-Cbz-L-phenylalaninal (L-5).



According to the general procedure, Swern oxidation of *N*-Cbz-L-phenylalaninol **L-5** (500 mg, 1.75 mmol) was performed with DMSO (325  $\mu\text{L}$ , 4.56 mmol), oxalyl chloride (195  $\mu\text{L}$ , 2.28 mmol) in DCM (10 mL), followed by the addition of  $\text{NEt}_3$  (1.1 mL, 7.84 mmol). Crude *N*-Cbz-L-phenylalaninal **L-5** (495 mg, quant.) was isolated as a viscous yellow oil. It was engaged in the MAC reaction without any purification.

TLC  $R_f = 0.23$  (pentane/ $\text{Et}_2\text{O}$ , 1:1)



OR  $[\alpha]_D^{25} = -3.7$  (c 1.0, MeOH), lit.<sup>275</sup>  $[\alpha]_D^{23} = -52$  (c 1, MeOH) and  $[\alpha]_D^{25} = -0.9$  (c 0.1, DCM), lit.<sup>276</sup>  $[\alpha]_D = +29$  (c 0.1, DCM)

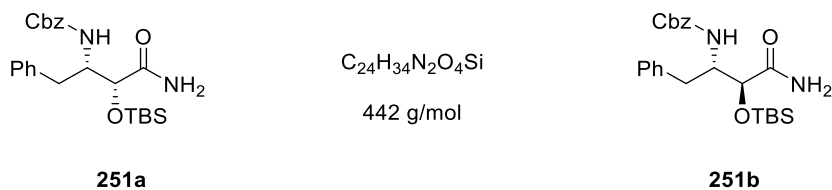
IR (5 mM in  $\text{CHCl}_3$ ),  $\nu$  ( $\text{cm}^{-1}$ ): 3428, 3019, 1715

$^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 3.15 (br d,  $J = 6.3$  Hz, 2H,  $\text{PhCH}_2\text{CH}$ ), 4.52 (q,  $J = 6.7$  Hz, 1H,  $\text{CHNCbz}$ ), 5.11 (s, 2H,  $\text{PhCH}_2\text{O}$ ), 5.30 (br s, 1H, NH), 7.06-7.43 (m, 10H, Ph), 9.64 (s, 1H, CHO).

$^1\text{H NMR}$  data were in agreement with those described in literature.<sup>275</sup>

### MAC Reaction.

**(2R,3S)- and (2S,3S)-3-(Benzyloxycarbonylamino)-2-(tert-butyldimethylsilyloxy)-4-phenylbutanamide (251a and 251b).**



According to the general procedure B, the MAC reaction was performed with *N*-Cbz-L-phenylalaninal **L-13** (142 mg, 0.50 mmol), H-MAC-TBS **148g** (236 mg, 1.20 mmol), ammonia (0.5 M in THF, 1.2 mL, 0.60 mmol) and DMAP (122 mg, 1.00 mmol) in  $\text{Et}_2\text{O}$  (5 mL). A 80:20 ratio of the (2R,3S)- and (2S,3S)-diastereomers **251a/251b** was determined by  $^1\text{H NMR}$  analysis ( $\text{CDCl}_3$  at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/ $\text{EtOAc}$ , 2:1) gave inseparable MAC reaction products **251a,b** (dr 80:20, 110 mg, 50%), as a pale yellow oil.

TLC  $R_f = 0.36$  (pentane/ $\text{EtOAc}$ , 2:1)

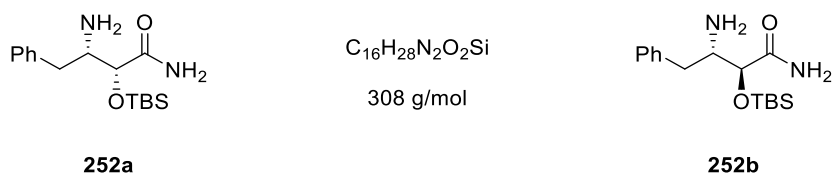
IR (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3480, 3304, 3199, 3064, 3029, 2954, 2929, 2857, 1709, 1682, 1603, 1498, 1455, 1402, 1340, 1254, 1218, 1107, 1042

HRMS ( $\text{ES}^+$ ): calcd. for  $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_4\text{Si}$   $[\text{M}+\text{H}]^+$  443.2361; found 443.2346

*Spectroscopic data for the major syn (2R,3S)-diastereomer (251a):*

$^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 0.16 (s, 3H,  $\text{SiCH}_3$ ), 0.22 (s, 3H,  $\text{SiCH}_3$ ), 0.97 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 2.55 (dd,  $J = 14.0, 10.4$  Hz, 1H) and 3.01 (dd,  $J = 14.0, 3.6$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 4.15-4.23 (m, 1H,  $\text{CHNCbz}$ ), 4.26 (d,  $J = 3.6$  Hz, 1H,  $\text{CHOTBS}$ ), 4.92 (d,  $J = 12.2$  Hz, 1H) and 5.04 (d,  $J = 12.2$  Hz, 1H) (AB syst.,  $\text{OCH}_2\text{Ph}$ ), 5.61 (d,  $J = 9.7$  Hz, 1H,  $\text{NHCbz}$ ), 5.91 (br s, 1H, CONH), 6.58 (br s, 1H, CONH), 7.13-7.34 (m, 10H, Ph)

$^{13}\text{C NMR}$  (75.5 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -5.3 ( $\text{SiCH}_3$ ), -4.7 ( $\text{SiCH}_3$ ), 18.0 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.7 ( $\text{SiC}(\text{CH}_3)_3$ ), 36.0 ( $\text{PhCH}_2\text{CH}$ ), 55.4 ( $\text{CHNCbz}$ ), 66.5 ( $\text{OCH}_2\text{Ph}$ ), 74.0 ( $\text{CHOTBS}$ ), 126.4 ( $\text{CH}_{\text{Ph}}$ ), 127.9 ( $\text{CH}_{\text{Ph}}$ ), 128.4 ( $\text{CH}_{\text{Ph}}$ ), 129.1 ( $\text{CH}_{\text{Ph}}$ ), 136.6 ( $\text{C}_{\text{Ph}}$ ), 137.8 ( $\text{C}_{\text{Ph}}$ ), 155.7 ( $\text{NCOO}$ ), 175.1 ( $\text{CONH}_2$ )

**(2*R*,3*S*)- and (2*S*,3*S*)-3-Amino-2-(*tert*-butyldimethylsilyloxy)-4-phenylbutanamide (252a and 252b).**

Palladium (10 wt.%) on activated carbon (4 mg) was added to a solution of *N*-Cbz protected MAC products **251a,b** (dr 80:20, 41 mg, 0.09 mmol) in MeOH (6 mL). The resulting mixture was stirred under H<sub>2</sub> (1 atm pressure) for 6 hours at room temperature and then filtered through a short pad of Celite which was washed through with further MeOH. The combined filtrates were concentrated under reduced pressure and dried under high vacuum to furnish *N*-deprotected MAC products **252a,b** (dr 80:20, 27 mg, 98%), as a colorless oil. The 80:20 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **252a/252b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

**TLC** *R*<sub>f</sub> = 0.10 (pentane/EtOAc, 1:5)

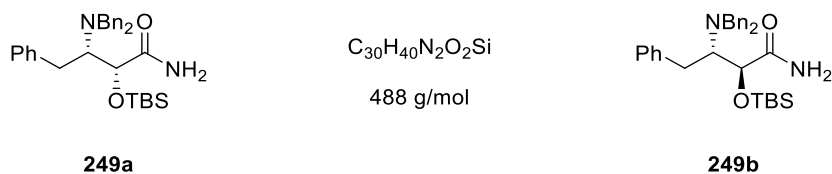
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3479, 3288, 3027, 2954, 2928, 2856, 1683, 1602, 1583, 1495, 1472, 1389, 1254, 1091

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>16</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 309.1993; found 309.1987

*Spectroscopic data for the major syn (2*R*,3*S*)-diastereomer (252a):*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.17 (s, 3H, SiCH<sub>3</sub>), 0.19 (s, 3H, SiCH<sub>3</sub>), 1.01 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.22 (br s, 2H, CHNH<sub>2</sub>), 2.48 (dd, *J* = 13.6, 10.6 Hz, 1H) and 2.96 (dd, *J* = 13.6, 3.4 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.24-3.32 (m, 1H, CHNH<sub>2</sub>), 4.19 (d, *J* = 2.8 Hz, 1H, CHOTBS), 6.11 (br s, 1H, CONH), 6.60 (br s, 1H, CONH), 7.18-7.28 (m, 3H, Ph), 7.28-7.36 (m, 2H, Ph)

<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.0 (SiCH<sub>3</sub>), -4.9 (SiCH<sub>3</sub>), 18.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 41.0 (PhCH<sub>2</sub>CH), 56.4 (CHNH<sub>2</sub>), 76.7 (CHOTBS), 126.4 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 129.2 (CH<sub>Ph</sub>), 139.0 (C<sub>Ph</sub>), 175.7 (CONH<sub>2</sub>)

**(2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (249a and 249b, dr 80:20).**

To a solution of *N*-deprotected MAC products **252a,b** (dr 80:20, 43 mg, 0.14 mmol) in CH<sub>3</sub>CN (5 mL) was added K<sub>2</sub>CO<sub>3</sub> (97 mg, 0.70 mmol) and the mixture was cooled down until 0 °C. BnBr (60  $\mu$ L, 0.49 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 4 days. Then, EtOAc (20 mL) and brine (20 mL) were added, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with 1 M HCl (50 mL) and brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Flash column chromatography (pentane/EtOAc, 5:1 then 2:1) gave *N,N*-dibenzylated MAC products **249a,b** (dr 80:20, 56 mg, 82%), as

a beige solid. The 80:20 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **249a/249b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

**TLC** *R<sub>f</sub>* = 0.08 (pentane/Et<sub>2</sub>O, 2:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3482, 3277, 3156, 3062, 3027, 2953, 2928, 2857, 2801, 1690, 1602, 1585, 1495, 1453, 1362, 1254, 1098

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>30</sub>H<sub>41</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 489.2932; found 489.2908

*Spectroscopic data for the major syn (2*R*,3*S*)-diastereomer (249a):*

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.02 (s, 3H, SiCH<sub>3</sub>), 0.06 (s, 3H, SiCH<sub>3</sub>), 0.93 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.90 (dd, *J* = 14.4, 7.5 Hz, 1H) and 3.13 (dd, *J* = 14.4, 6.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.55 (ddd, *J* = 7.5, 6.6, 2.7 Hz, 1H, CHNBn<sub>2</sub>), 3.64 (d, *J* = 13.8 Hz, 2H) and 4.14 (d, *J* = 13.8 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.17 (d, *J* = 2.7 Hz, 1H, CHOTBS), 5.83 (br s, 1H, CONH), 6.52 (br s, 1H, CONH), 7.13-7.19 (m, 2H, Ph), 7.19-7.341 (m, 13H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.0 (SiCH<sub>3</sub>), -5.0 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.3 (PhCH<sub>2</sub>CH), 55.3 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.1 (CHNBn<sub>2</sub>), 76.9 (CHOTBS), 126.2 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 129.3 (CH<sub>Ph</sub>), 139.5 (C<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>), 175.6 (CONH<sub>2</sub>)

## MAC Reactions on *N,N*-dibenzyl-D/L-phenylalaninal

### *N,N*-Dibenzyl-D/L-phenylalaninal's synthesis.

#### *N,N*-Dibenzyl-D/L-phenylalaninol (D/L-228).



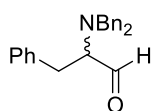
**D/L-228**

According to the general method, commercially available D/L-phenylalaninol **D/L-224** (2.00 g, 13.23 mmol) was *N,N*-dibenzylated with K<sub>2</sub>CO<sub>3</sub> (4.39 g, 31.77 mmol), BnBr (3.7 mL, 31.75 mmol) in CH<sub>3</sub>CN (50 mL). The crude residue was purified by silica gel column chromatography (pentane/EtOAc, 5:1) to give *N,N*-dibenzyl-D/L-phenylalaninol **D/L-228** (3.55 g, 81%), as a white solid.

**TLC** *R<sub>f</sub>* = 0.40 (pentane/EtOAc, 5:1)

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 2.44 (dd, *J* = 13.0, 9.4 Hz, 1H) and 2.99-3.17 (m, 3H) (AB part of ABX syst., PhCH<sub>2</sub>CH, CHN+OH), 3.30-3.39 (m, 1H) and 3.52 (t, *J* = 10.4 Hz, 1H) (AB part of ABX syst., CH<sub>2</sub>OH), 3.49 (d, *J* = 13.3 Hz, 2H) and 3.93 (d, *J* = 13.3 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 7.07-7.14 (m, 2H, Ph), 7.17-7.37 (m, 13H, Ph)

<sup>1</sup>H NMR data were in agreement with those described in literature<sup>269</sup> and with those of *N,N*-dibenzyl-L-phenylalaninol **L-228**.

***N,N*-Dibenzyl-D/L-phenylalaninal (D/L-13).**C<sub>23</sub>H<sub>23</sub>NO

329 g/mol

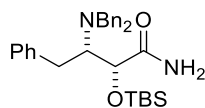
**D/L-13**

According to the general procedure, Swern oxidation of *N,N*-dibenzyl-D/L-phenylalaninol **D/L-13** (500 mg, 1.50 mmol) was performed with DMSO (280  $\mu$ L, 3.95 mmol), oxalyl chloride (180  $\mu$ L, 2.09 mmol) in DCM (7 mL), followed by the addition of NEt<sub>3</sub> (0.6 mL, 4.32 mmol). Crude *N,N*-dibenzyl-D/L-phenylalaninal **D/L-13** (419 mg, 85%) was isolated as a viscous yellow oil. It was used without any purification in the MAC reaction.

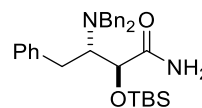
**TLC**  $R_f$  = 0.75 (pentane/EtOAc, 5:1)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 2.89-3.00 (m, 1H) and 3.16 (dd,  $J$  = 14.1, 7.5 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.53-3.61 (m, 1H, CHNBn<sub>2</sub>), 3.68 (d,  $J$  = 13.7 Hz, 2H) and 3.83 (d,  $J$  = 13.7 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 7.12-7.19 (m, 2H, Ph), 7.20-7.36 (m, 13H, Ph), 9.72 (s, 1H, CHO)

<sup>1</sup>H NMR data were in agreement with those described for *N,N*-dibenzyl-L-phenylalaninal **L-13**.

**MAC Reaction.*****syn*- and *anti*-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide ( $\pm$ )-249a and ( $\pm$ )-249b).****( $\pm$ )-249a**C<sub>30</sub>H<sub>40</sub>N<sub>2</sub>O<sub>2</sub>Si

488 g/mol

**( $\pm$ )-249b**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-D/L-phenylalaninal **D/L-249** (115 mg, 0.35 mmol), H-MAC-TBS **148g** (165 mg, 0.84 mmol), ammonia (0.5 M in THF, 0.84 mL, 0.42 mmol) and DMAP (86 mg, 0.70 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/EtOAc, 5:1) gave racemic MAC reaction products **( $\pm$ )-249a/( $\pm$ )-249b** (dr <2:98, 116 mg, 68%), as a pale yellow solid.

**TLC**  $R_f$  = 0.15 (pentane/Et<sub>2</sub>O, 2:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3479, 3274, 3062, 3027, 2954, 2929, 2857, 2803, 1687, 1602, 1583, 1494, 1453, 1361, 1254, 1097

**Spectroscopic data for the major *anti* diastereomer (**( $\pm$ )-249b**):**

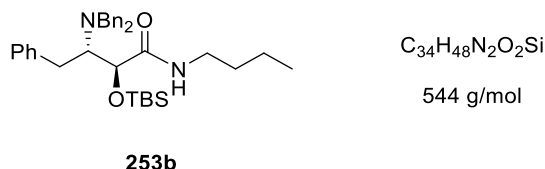
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.06 (s, 3H, SiCH<sub>3</sub>), 0.04 (s, 3H, SiCH<sub>3</sub>), 0.89 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 3.01 (br d,  $J$  = 6.9 Hz, 2H, PhCH<sub>2</sub>CH), 3.29 (td,  $J$  = 7.5, 3.3 Hz, 1H, CHNBn<sub>2</sub>), 3.74 (s, 4H, N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.38 (d,  $J$  = 3.3 Hz, 1H, CHOTBS), 6.07 (br s, 1H, CONH), 6.19 (br s, 1H, CONH), 7.08-7.14 (m, 2H, Ph), 7.15-7.28 (m, 13H, Ph)

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -5.1 ( $\text{SiCH}_3$ ), -4.7 ( $\text{SiCH}_3$ ), 18.0 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.8 ( $\text{SiC}(\text{CH}_3)_3$ ), 32.5 ( $\text{PhCH}_2\text{CH}$ ), 54.3 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 64.0 ( $\text{CHNBn}_2$ ), 73.0 ( $\text{CHOTBS}$ ), 125.9 ( $\text{CH}_{\text{Ph}}$ ), 126.6 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.1 ( $\text{CH}_{\text{Ph}}$ ), 128.8 ( $\text{CH}_{\text{Ph}}$ ), 129.7 ( $\text{CH}_{\text{Ph}}$ ), 139.6 ( $\text{C}_{\text{Ph}}$ ), 140.0 ( $\text{C}_{\text{Ph}}$ ), 176.3 ( $\text{CONH}_2$ )

Data were in agreement with those described for the MAC reaction products **249a,b** of the L-serie.

### MAC reactions of *N,N*-dibenzyl-L-phenylalaninal with amines as nucleophiles

#### (2*S*,3*S*)-*N*-Butyl-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (**253b**).



According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (137 mg, 0.42 mmol), H-MAC-TBS **148g** (198 mg, 1.01 mmol), *n*-butylamine (148  $\mu\text{L}$ , 0.50 mmol) and DMAP (102 mg, 0.84 mmol) in  $\text{Et}_2\text{O}$  (5 mL). Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ / $\text{EtOH}$ , 10:2:0.1) gave the MAC reaction product **253b** (dr <2:98, 202 mg, 88%), as a yellow viscous oil.

TLC  $R_f$  = 0.35 (pentane/ $\text{Et}_2\text{O}$ / $\text{EtOH}$ , 10:2:0.1), 0.10 (pentane/ $\text{Et}_2\text{O}$ , 10:1)

OR  $[\alpha]_D^{24} = -32.1$  ( $c$  1.0,  $\text{CHCl}_3$ )

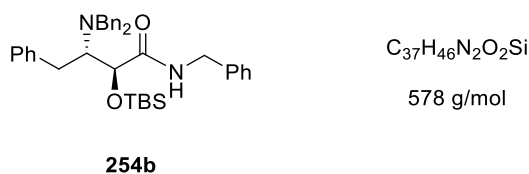
IR (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3431, 3063, 3027, 2956, 2929, 2854, 2801, 1672, 1603, 1521, 1492, 1456, 1362, 1254, 1088

HRMS ( $\text{ES}^+$ ): calcd. for  $\text{C}_{34}\text{H}_{49}\text{N}_2\text{O}_2\text{Si}$   $[\text{M}+\text{H}]^+$  545.3558; found 545.3535

$^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -0.14 (s, 3H,  $\text{SiCH}_3$ ), -0.03 (s, 3H,  $\text{SiCH}_3$ ), 0.86 (t,  $J = 7.2$  Hz, 3H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 1.20-1.37 (m, 4H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.78-2.90 (m, 1H) and 3.17-3.26 (m, 1H) (AB syst.,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.99 (dd,  $J = 14.4, 7.9$  Hz, 1H) and 3.02 (dd,  $J = 14.4, 7.2$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.29 (ddd,  $J = 7.9, 7.2, 2.9$  Hz, 1H,  $\text{CHNBn}_2$ ), 3.75 (s, 4H,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 4.34 (d,  $J = 2.9$  Hz, 1H,  $\text{CHOTBS}$ ), 6.35 (br t,  $J = 5.8$  Hz, 1H, CONH), 7.11-7.16 (m, 2H, Ph), 7.16-7.28 (m, 13H, Ph)

$^{13}\text{C}$  NMR (90.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -5.2 ( $\text{SiCH}_3$ ), -4.7 ( $\text{SiCH}_3$ ), 13.6 ( $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 18.0 ( $\text{SiC}(\text{CH}_3)_3$ ), 20.2 ( $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 25.9 ( $\text{SiC}(\text{CH}_3)_3$ ), 31.3 ( $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 32.1 ( $\text{PhCH}_2\text{C}$ ), 38.6 ( $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 54.6 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 64.1 ( $\text{CHNBn}_2$ ), 72.5 ( $\text{CHOTBS}$ ), 125.8 ( $\text{CH}_{\text{Ph}}$ ), 126.7 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.1 ( $\text{CH}_{\text{Ph}}$ ), 128.6 ( $\text{CH}_{\text{Ph}}$ ), 129.7 ( $\text{CH}_{\text{Ph}}$ ), 139.8 ( $\text{C}_{\text{Ph}}$ ), 140.0 ( $\text{C}_{\text{Ph}}$ ), 172.9 (CONH)

#### (2*S*,3*S*)-*N*-Benzyl-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (**254b**).



According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (138 mg, 0.42 mmol), H-MAC-TBS **148g** (198 mg, 1.01 mmol), benzylamine (55  $\mu$ L, 0.50 mmol) and DMAP (103 mg, 0.84 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 5:1) gave the MAC reaction product **254b** (dr <2:98, 206 mg, 85%), as a viscous colorless oil.

**TLC**  $R_f$  = 0.27 (pentane/Et<sub>2</sub>O, 5:1)

**OR**  $[\alpha]_D^{25}$  = -32.1 (c 1.0, CHCl<sub>3</sub>)

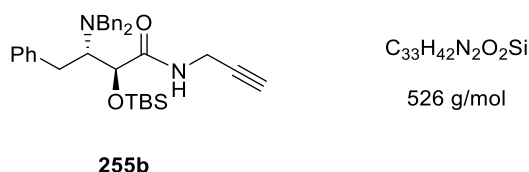
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3427, 3062, 3027, 2952, 2928, 2855, 2801, 1672, 1602, 1512, 1494, 1454, 1365, 1256, 1098

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>37</sub>H<sub>47</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 579.3401; found 579.3381

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.27 (s, 3H, SiCH<sub>3</sub>), -0.08 (s, 3H, SiCH<sub>3</sub>), 0.75 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.99 (dd,  $J$  = 14.0, 7.9 Hz, 1H) and 3.04 (dd,  $J$  = 14.0, 7.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.31 (ddd,  $J$  = 7.9, 7.2, 3.2 Hz, 1H, CHNBN<sub>2</sub>), 3.73 (d,  $J$  = 14.4 Hz, 2H) and 3.78 (d,  $J$  = 14.4 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.85 (dd,  $J$  = 14.0, 4.3 Hz, 1H) and 4.49 (dd,  $J$  = 14.0, 7.2 Hz, 1H) (AB part of ABX syst., NHCH<sub>2</sub>Ph), 4.37 (d,  $J$  = 3.2 Hz, 1H, CHOTBS), 6.56 (br dd,  $J$  = 6.8, 4.3 Hz, 1H, CONH), 7.11-7.17 (m, 4H, Ph), 7.17-7.31 (m, 16H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -5.3 (SiCH<sub>3</sub>), -4.7 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.1 (PhCH<sub>2</sub>C), 43.3 (NHCH<sub>2</sub>Ph), 54.6 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.3 (CHNBN<sub>2</sub>), 72.7 (CHOTBS), 125.9 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 137.5 (C<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 172.7 (CONH)

**(2S,3S)-N-(Prop-2-yn-1-yl)-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (255b).**



C<sub>33</sub>H<sub>42</sub>N<sub>2</sub>O<sub>2</sub>Si  
526 g/mol

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (115 mg, 0.35 mmol), H-MAC-TBS **148g** (165 mg, 0.84 mmol), propargylamine (34  $\mu$ L, 0.42 mmol) and DMAP (86 mg, 0.70 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/Et<sub>2</sub>O/DCM, 10:1:2) gave the MAC reaction product **255b** (dr <2:98, 144 mg, 78%), as a pale yellow oil.

**TLC**  $R_f$  = 0.27 (pentane/Et<sub>2</sub>O/DCM, 10:1:2)

**OR**  $[\alpha]_D^{25}$  = -32.9 (c 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3434, 3308, 3063, 3029, 2952, 2928, 2856, 2804, 2248, 1675, 1602, 1494, 1453, 1361, 1257, 1128, 1088

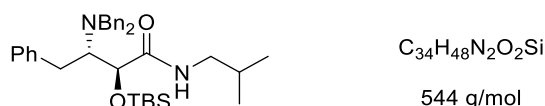
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>33</sub>H<sub>43</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 527.3088; found 527.3062

**<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.10 (s, 3H, SiCH<sub>3</sub>), 0.00 (s, 3H, SiCH<sub>3</sub>), 0.89 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.14 (t,  $J$  = 2.5 Hz, 1H, NCH<sub>2</sub>C $\equiv$ CH), 3.01 (br d,  $J$  = 7.5 Hz, 2H, PhCH<sub>2</sub>CH), 3.24 (td,  $J$  = 7.5, 3.3 Hz, 1H,

CHNBn<sub>2</sub>), 3.54 (ddd, *J* = 17.2, 4.2, 2.5 Hz, 1H) and 4.08 (ddd, *J* = 17.2, 6.5, 2.5 Hz, 1H) (AB syst., NCH<sub>2</sub>C≡CH), 3.73 (s, 4H, N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.37 (d, *J* = 3.3 Hz, 1H, CHOTBS), 6.43 (br dd, *J* = 6.5, 4.2 Hz, 1H, CONH), 7.09-7.15 (m, 2H, Ph), 7.17-7.31 (m, 13H, Ph)

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.1 (SiCH<sub>3</sub>), -4.7 (SiCH<sub>3</sub>), 18.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 28.5 (NCH<sub>2</sub>C≡CH), 32.4 (PhCH<sub>2</sub>CH), 54.6 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.1 (CHNBn<sub>2</sub>), 71.7 (NCH<sub>2</sub>C≡CH), 73.0 (CHOTBS), 78.9 (NCH<sub>2</sub>C≡CH), 126.0 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 172.7 (CONH)

**(2S,3S)-N-Isobutyl-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (256b).**



**256b**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (115 mg, 0.35 mmol), H-MAC-TBS **148g** (165 mg, 0.84 mmol), isobutylamine (42 μL, 0.42 mmol) and DMAP (86 mg, 0.70 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/Et<sub>2</sub>O/DCM, 10:1:2) gave the MAC reaction product **256b** (dr <2:98, 141 mg, 74%), as a pale yellow oil.

TLC *R<sub>f</sub>* = 0.29 (pentane/Et<sub>2</sub>O/DCM, 10:1:2)

OR [α]<sub>D</sub><sup>26</sup> = -35.5 (c 1.0, CHCl<sub>3</sub>)

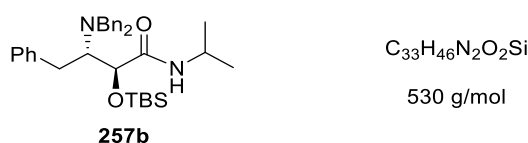
IR (ATR), ν (cm<sup>-1</sup>): 3428, 3062, 3028, 2956, 2928, 2856, 2801, 1669, 1602, 1518, 1494, 1454, 1368, 1253, 1089

HRMS (ES<sup>+</sup>): calcd. for C<sub>34</sub>H<sub>49</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 545.3558; found 546.3534

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>), δ (ppm) : -0.13 (s, 3H, SiCH<sub>3</sub>), -0.03 (s, 3H, SiCH<sub>3</sub>), 0.84 (d, *J* = 6.8 Hz, 3H, NCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.86 (d, *J* = 6.8 Hz, 3H, NCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.61 (nonuplet, *J* = 6.8 Hz, 1H, NCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2.70 (ddd, *J* = 13.5, 6.5, 5.8 Hz, 1H) and 3.05 (ddd, *J* = 13.5, 6.8, 6.5 Hz, 1H) (AB syst., NCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 3.01 (br d, *J* = 7.6 Hz, 2H, PhCH<sub>2</sub>CH), 3.31 (td, *J* = 7.6, 2.9 Hz, 1H, CHNBn<sub>2</sub>), 3.73 (d, *J* = 14.8 Hz, 2H) and 3.77 (d, *J* = 14.8 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.37 (d, *J* = 2.9 Hz, 1H, CHOTBS), 6.47 (br t, *J* = 5.8 Hz, CONH), 7.10-7.15 (m, 2H, Ph), 7.15-7.26 (m, 13H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.1 (SiCH<sub>3</sub>), -4.7 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 20.3 (NCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 28.3 (NCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 32.1 (PhCH<sub>2</sub>CH), 46.3 (NCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 54.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.2 (CHNBn<sub>2</sub>), 72.5 (CHOTBS), 125.9 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 173.0 (CONH)

**(2S,3S)-N-Isopropyl-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (257b).**



**257b**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (140 mg, 0.42 mmol), H-MAC-TBS **148g** (198 mg, 1.01 mmol), isopropylamine (43  $\mu$ L, 0.50 mmol) and DMAP (103 mg, 0.84 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/EtOAc/DCM/NEt<sub>3</sub>, 10:0.5:3:0.1) gave the MAC reaction product **257b** (dr <2:98, 178 mg, 80%), as a pale yellow oil.

**TLC**  $R_f$  = 0.41 (pentane/EtOAc/DCM/NEt<sub>3</sub>, 10:0.5:3:0.1)

**OR**  $[\alpha]_D^{26} = -28.8$  (*c* 1.0 in CHCl<sub>3</sub>)

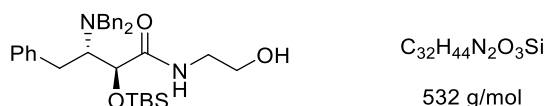
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3420, 3062, 3028, 2957, 2930, 2858, 2800, 1664, 1603, 1514, 1494, 1455, 1365, 1255, 1126, 1090, 1071.

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>33</sub>H<sub>47</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 531.3401; found 531.3376

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.10 (s, 3H, SiCH<sub>3</sub>), 0.01 (s, 3H, SiCH<sub>3</sub>), 0.91 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.92 (d, *J* = 6.5 Hz, 3H, NCHCH<sub>3</sub>), 1.12 (d, *J* = 6.5 Hz, 3H, NCHCH<sub>3</sub>), 2.96 (dd, *J* = 14.2, 7.6 Hz, 1H) and 3.01 (dd, *J* = 14.2, 7.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.32 (ddd, *J* = 7.6, 7.6, 2.9 Hz, 1H, CHNBn<sub>2</sub>), 3.72 (d, *J* = 14.0 Hz, 2H) and 3.79 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.94 (octuplet, *J* = 6.5 Hz, 1H, NCH(CH<sub>3</sub>)<sub>2</sub>), 4.37 (d, *J* = 2.9 Hz, 1H, CHOTBS), 6.27 (br d, *J* = 7.9 Hz, 1H, CONH), 7.06-7.13 (m, 2H, Ph), 7.14-7.27 (m, 13H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.1 (SiCH<sub>3</sub>), -4.6 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.2 (NCHCH<sub>3</sub>), 22.5 (NCHCH<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.0 (PhCH<sub>2</sub>CH), 40.9 (NCH(CH<sub>3</sub>)<sub>2</sub>), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 63.8 (CHNBn<sub>2</sub>), 72.2 (CHOTBS), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.8 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 172.1 (CONH)

**(2*S*,3*S*)-*N*-(2-Hydroxyethyl)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (258b).**



**258b**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (130 mg, 0.40 mmol), H-MAC-TBS **148g** (195 mg, 0.98 mmol), 2-aminoethanol (30  $\mu$ L, 0.48 mmol) and DMAP (98 mg, 0.80 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 2:1 then Et<sub>2</sub>O) gave the MAC reaction product **258b** (dr <2:98, 158 mg, 74%), as a yellow oil.

**TLC**  $R_f$  = 0.37 (DCM/MeOH, 20:1), 0.38 (Et<sub>2</sub>O)

**OR**  $[\alpha]_D^{27} = -33.6$  (*c* 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3422, 3061, 3026, 2952, 2929, 2857, 2800, 1655, 1601, 1524, 1494, 1453, 1362, 1254, 1094, 1072

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>32</sub>H<sub>45</sub>N<sub>2</sub>O<sub>3</sub>Si, [M+H]<sup>+</sup> 533.3194; found 533.3182

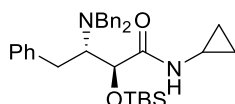
**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.15 (s, 3H, SiCH<sub>3</sub>), -0.02 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.45 (br s, 1H, NCH<sub>2</sub>CH<sub>2</sub>OH), 3.03 (br d, *J* = 7.6 Hz, 2H, PhCH<sub>2</sub>CH), 3.05-3.13 (m, 1H) and 3.24-3.35 (m,



1H) (AB syst., NCH<sub>2</sub>CH<sub>2</sub>OH), 3.24-3.35 (m, 1H, CHNBn<sub>2</sub>), 3.44-3.58 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>OH), 3.72 (d, *J* = 14.4 Hz, 2H) and 3.77 (d, *J* = 14.4 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.35 (d, *J* = 3.2 Hz, 1H, CHOTBS), 6.78 (br t, *J* = 5.6 Hz, 1H, CONH), 7.13-7.23 (m, 6H, Ph), 7.24-7.29 (m, 9H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.3 (SiCH<sub>3</sub>), -4.8 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 31.9 (PhCH<sub>2</sub>CH), 41.8 (NCH<sub>2</sub>CH<sub>2</sub>OH), 54.6 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.9 (NCH<sub>2</sub>CH<sub>2</sub>OH), 64.2 (CHNBn<sub>2</sub>), 72.6 (CHOTBS), 125.9 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 174.2 (CONH)

**(2S,3S)-N-Cyclopropyl-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (259b).**



C<sub>33</sub>H<sub>44</sub>N<sub>2</sub>O<sub>2</sub>Si

528 g/mol

**259b**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (130 mg, 0.40 mmol), H-MAC-TBS **148g** (192 mg, 0.98 mmol), cyclopropylamine (35 μL, 0.48 mmol) and DMAP (98 mg, 0.80 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 5:1) gave the MAC reaction product **259b** (dr <2:98, 93 mg, 44%), as a yellow oil. A single crystal suitable for X-ray diffraction was obtained by slow diffusion of pentane into a Et<sub>2</sub>O solution of **259b** at room temperature.

According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (148 mg, 0.45 mmol), H-MAC-TBS **148g** (212 mg, 1.08 mmol), DMAP (110 mg, 0.90 mmol) and cyclopropylamine (37 μL, 0.54 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 5:1) gave the MAC reaction product **259b** (dr <2:98, 211 mg, 89%), as a yellow oil.

TLC *R<sub>f</sub>* = 0.15 (pentane/Et<sub>2</sub>O, 5:1)

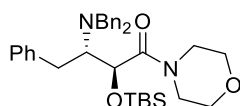
OR [α]<sub>D</sub><sup>26</sup> = -39.2 (*c* 1.0, CHCl<sub>3</sub>)

IR (ATR), ν (cm<sup>-1</sup>): 3423, 3087, 3063, 3026, 2953, 2928, 2856, 2798, 1672, 1601, 1508, 1494, 1454, 1365, 1254, 1091, 1074

HRMS (ES<sup>+</sup>): calcd. for C<sub>33</sub>H<sub>45</sub>N<sub>2</sub>O<sub>2</sub>Si, [M+H]<sup>+</sup> 529.3245; found 529.3220

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>), δ (ppm) : -0.14 (s, 3H, SiCH<sub>3</sub>), 0.01 (s, 3H, SiCH<sub>3</sub>), 0.22-0.30 (m, 1H) and 0.36-0.44 (m, 1H) (AB syst., NCHCH<sub>2</sub>), 0.61-0.69 (m, 1H) and 0.71-0.79 (m, 1H) (AB syst., NCHCH<sub>2</sub>), 0.91 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.48-2.57 (m, 1H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.04 (dd, *J* = 14.0, 7.6 Hz, 1H) and 3.09 (dd, *J* = 14.0, 7.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.35 (ddd, *J* = 7.6, 7.6, 2.9 Hz, 1H, CHNBn<sub>2</sub>), 3.78 (d, *J* = 14.4 Hz, 2H) and 3.82 (d, *J* = 14.4 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.36 (d, *J* = 2.9 Hz, 1H, CHOTBS), 6.45 (br d, *J* = 2.2 Hz, 1H, CONH), 7.17-7.22 (m, 2H, Ph), 7.23-7.28 (m, 4H, Ph), 7.29-7.34 (m, 9H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.3 (SiCH<sub>3</sub>), -4.8 (SiCH<sub>3</sub>), 5.7 (NCHCH<sub>2</sub>), 6.3 (NCHCH<sub>2</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 21.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.0 (PhCH<sub>2</sub>CH), 54.6 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.1 (CHNBn<sub>2</sub>), 72.5 (CHOTBS), 125.9 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 174.5 (CONH)

**(2S,3S)-2-(tert-Butyldimethylsilyloxy)-3-(dibenzylamino)-1-morpholino-4-phenylbutan-1-one (260b).**C<sub>34</sub>H<sub>46</sub>N<sub>2</sub>O<sub>3</sub>Si

558 g/mol

**260b**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (151 mg, 0.46 mmol), H-MAC-TBS **148g** (216 mg, 1.10 mmol), morpholine (50  $\mu$ L, 0.55 mmol) and DMAP (112 mg, 0.92 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 5:1) gave the MAC reaction product **260b** (dr <2:98, 192 mg, 75%), as a viscous pale yellow oil.

**TLC**  $R_f$  = 0.36 (pentane/Et<sub>2</sub>O, 5:1)

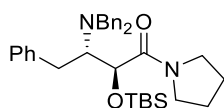
**OR**  $[\alpha]_D^{21} = +6.9$  (*c* 1.1, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3062, 3025, 2956, 2928, 2855, 2801, 1664, 1643, 1602, 1494, 1454, 1433, 1362, 1253, 1116

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>34</sub>H<sub>47</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup> 559.3350; found 559.3325

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub> at 360 K),  $\delta$  (ppm) : 0.09 (s, 3H, SiCH<sub>3</sub>), 0.11 (s, 3H, SiCH<sub>3</sub>), 0.92 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 3.00 (br d, *J* = 6.0 Hz, 2H, PhCH<sub>2</sub>CH), 3.10-3.38 (m, 9H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O, CHNBn<sub>2</sub>), 3.67 (d, *J* = 14.4 Hz, 2H) and 3.76 (d, *J* = 14.4 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.83 (br d, *J* = 5.2 Hz, 1H, CHOTBS), 7.07-7.15 (m, 4H, Ph), 7.16-7.27 (m, 9H, Ph), 7.28-7.35 (m, 2H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, DMSO-*d*<sub>6</sub> at 360 K),  $\delta$  (ppm) : -5.4 (SiCH<sub>3</sub>), -4.9 (SiCH<sub>3</sub>), 17.4 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.3 (SiC(CH<sub>3</sub>)<sub>3</sub>), 31.3 (PhCH<sub>2</sub>CH), 42.9 (N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 53.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.5 (CHNBn<sub>2</sub>), 65.2 (N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 73.1 (CHOTBS), 125.1 (C<sub>Ph</sub>), 126.1 (C<sub>Ph</sub>), 127.4 (C<sub>Ph</sub>), 127.5 (C<sub>Ph</sub>), 127.9 (C<sub>Ph</sub>), 128.8 (C<sub>Ph</sub>), 139.2 (C<sub>Ph</sub>), 140.7 (C<sub>Ph</sub>), 169.6 (CONH)

**(2S,3S)-2-(tert-Butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (261b).**C<sub>34</sub>H<sub>46</sub>N<sub>2</sub>O<sub>2</sub>Si

542 g/mol

**261b**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (134 mg, 0.41 mmol), H-MAC-TBS **148g** (192 mg, 0.98 mmol), pyrrolidine (40  $\mu$ L, 0.49 mmol) and DMAP (100 mg, 0.82 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/EtOAc/DCM, 10:1:1) gave the MAC reaction product **261b** (dr <2:98, 149 mg, 67%), as a viscous pale yellow oil.

**TLC**  $R_f$  = 0.10 (pentane/Et<sub>2</sub>O, 5:1)

**OR**  $[\alpha]_D^{21} = -4.8$  (*c* 1.0, CHCl<sub>3</sub>)

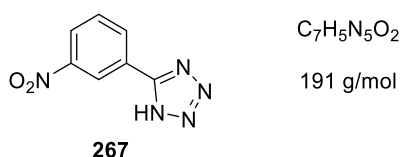
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3060, 3027, 2954, 2929, 2858, 2800, 1655, 1635, 1495, 1451, 1362, 1254, 1123, 1094

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>34</sub>H<sub>47</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 543.3401; found 543.3378

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub> at 360 K),  $\delta$  (ppm) : 0.04 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.89 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.62 (m, 4H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 0.04 (s, 3H, SiCH<sub>3</sub>), 0.08 (s, 3H, SiCH<sub>3</sub>), 0.89 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.55-1.68 (m, 4H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 3.00 (dd, *J* = 14.4, 8.0 Hz, 1H) and 3.08 (dd, *J* = 14.4, 3.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.22-3.34 (m, 5H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>, CHNBn<sub>2</sub>), 3.64 (d, *J* = 14.0 Hz, 2H) and 3.73 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.61 (br d, *J* = 6.0 Hz, 1H, CHOTBS), 7.08-7.14 (m, 4H, Ph), 7.14-7.26 (m, 9H, Ph), 7.26-7.33 (m, 2H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, DMSO-*d*<sub>6</sub> at 360 K),  $\delta$  (ppm): -5.5 (SiCH<sub>3</sub>), -5.2 (SiCH<sub>3</sub>), 17.4 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.4 (N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>), 25.3 (SiC(CH<sub>3</sub>)<sub>3</sub>), 31.6 (PhCH<sub>2</sub>CH), 44.3 (NCH<sub>2</sub>CH<sub>2</sub>), 45.4 (NCH<sub>2</sub>CH<sub>2</sub>), 53.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.3 (CHNBn<sub>2</sub>), 74.6 (CHOTBS), 125.2 (CH<sub>Ph</sub>), 126.1 (CH<sub>Ph</sub>), 127.3 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 139.2 (C<sub>Ph</sub>), 141.1 (C<sub>Ph</sub>), 169.0 (CONH)

### 5-(3-Nitrophenyl)-1H-tetrazole (267).



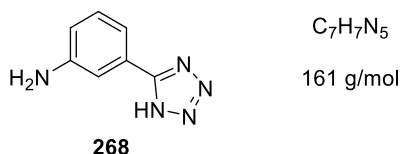
According to a literature procedure,<sup>277</sup> 3-nitrobenzonitrile **266** (700 mg, 4.7 mmol) was mixed with sodium azide (917 mg, 14.1 mmol) and ammonium chloride (754 mg, 14.1 mmol) under argon. DMF (10 mL) was introduced, the vessel was sealed and the reaction mixture was stirred at 120 °C for 40 hours. Water (10 mL) was introduced followed by 5 M HCl (10 mL) until pH = 2.<sup>278</sup> The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give 5-(3-nitrophenyl)-1H-tetrazole **267** (822 mg, 92%), as a white solid. The crude product was directly used in the next step without any purification.

**Mp** = 153-155 °C, lit.<sup>279</sup> 153-157 °C

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 7.75 (t, *J* = 8.2 Hz, 1H, Ar), 8.38 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H, Ar), 8.60-8.52 (m, 1H, Ar), 9.07-9.01 (m, 1H, Ar)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>280</sup>

### 3-(1H-tetrazol-5-yl)aniline (268).



According to a literature procedure,<sup>277</sup> palladium (10 wt.%) on activated carbon (72 mg) was added to a solution of 5-(3-nitrophenyl)-1H-tetrazole **267** (364 mg, 1.9 mmol) in isopropanol (15 mL). The resulting mixture was stirred under H<sub>2</sub> (1 atm pressure) for 5 hours at room temperature and then filtered through a short plug of dicalite which was washed through with further isopropanol. The combined filtrates and washings were concentrated under reduced pressure and dried under high

vacuum to furnish 3-(1*H*-tetrazol-5-yl)aniline **268** (263 mg, 86%), as a beige solid. The crude product was directly used in the next step without any purification.

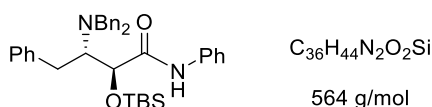
**TLC**  $R_f$  = 0.13 (pentane/EtOAc, 1:1)

**Mp** = 201-203 °C, lit.<sup>281</sup> 199-200 °C

**<sup>1</sup>H NMR** (300 MHz, CD<sub>3</sub>OD),  $\delta$  (ppm): 6.87-6.92 (m, 1H, Ar), 7.26 (dd,  $J$  = 2.1, 1.4 Hz, 1H, Ar), 7.28 (d,  $J$  = 0.5 Hz, 1H, Ar), 7.33 (ddd,  $J$  = 2.1, 1.4, 0.5 Hz, 1H, Ar)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>277</sup>

**(2*S*,3*S*)-*N*-Phenyl-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide (270b).**



**270b**

According to a literature procedure,<sup>282</sup> (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamide **249b** (58 mg, 0.12 mmol), CuI (2 mg, 0.01 mmol) and K<sub>3</sub>PO<sub>4</sub> (51 mg, 0.24 mmol) were introduced into a sealed vessel. *trans*-Cyclohexane-1,2-diamine (13 mg, 0.11 mmol), dodecane (240  $\mu$ L) and PhI (15  $\mu$ L, 0.13 mmol) were successively added. After introduction of dry dioxane (2 mL), the reaction mixture was stirred under argon at 105 °C for 24 hours. EtOAc (10 mL) and water (10 mL) were introduced, and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with 1 M HCl (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et<sub>2</sub>O, 4:1) to give *N*-phenylbutanamide **270b** (61 mg, 90%), as a colorless oil.

**TLC**  $R_f$  = 0.37 (pentane/Et<sub>2</sub>O, 10:1)

**OR**  $[\alpha]_D^{25} = -54.4$  ( $c$  1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3400, 3084, 3061, 3026, 2952, 2928, 2856, 2800, 1687, 1601, 1522, 1494, 1441, 1362, 1312, 1254, 1090, 1074

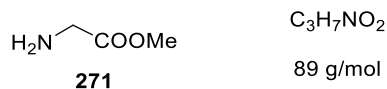
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>36</sub>H<sub>45</sub>N<sub>2</sub>O<sub>2</sub>Si, [M+H]<sup>+</sup> 565.3245; found 565.3226

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.07 (s, 3H, SiCH<sub>3</sub>), 0.04 (s, 3H, SiCH<sub>3</sub>), 0.94 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 3.08 (d,  $J$  = 7.6 Hz, 2H, PhCH<sub>2</sub>CH), 3.40 (td,  $J$  = 7.6, 4.0 Hz, 1H, CHNBn<sub>2</sub>), 3.75 (d,  $J$  = 14.2 Hz, 2H) and 3.81 (d,  $J$  = 14.2 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.44 (d,  $J$  = 4.0 Hz, 1H, CHOTBS), 7.05-7.10 (m, 1H, Ph), 7.11-7.31 (m, 17H, Ph), 7.39-7.44 (m, 2H, Ph), 8.06 (br s, 1H, CONH)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.2 (SiCH<sub>3</sub>), -4.7 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.8 (PhCH<sub>2</sub>CH), 54.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.3 (CHNBn<sub>2</sub>), 73.9 (CHOTBS), 119.3 (CH<sub>Ph</sub>), 124.2 (CH<sub>Ph</sub>), 126.0 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 128.9 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 137.2 (C<sub>Ph</sub>), 139.5 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 171.0 (CONH)

## MAC reactions of *N,N*-dibenzyl-L-phenylalaninal with $\alpha$ -amino esters as nucleophiles

### Methyl glycinate (**271**).

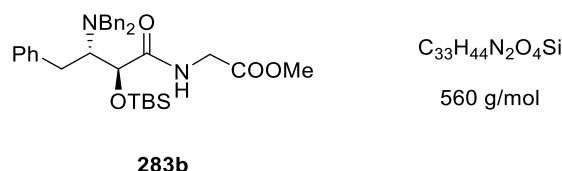


According to a literature procedure,<sup>231</sup> glycine methyl ester hydrochloride **271**·HCl (1.00 g, 4.00 mmol) was mixed with a saturated aqueous  $Na_2CO_3$  solution (20 mL) and DCM (20 mL). The biphasic mixture was stirred for 30 minutes at room temperature, and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were dried over  $Na_2SO_4$  and concentrated under reduced pressure to give methyl glycinate **271** (68 mg, 20 %), as a colorless oil.

$^1H$  NMR (250 MHz,  $CDCl_3$ ),  $\delta$  (ppm): 1.45 (br s, 2H,  $NH_2$ ), 3.43 (s, 2H,  $CH_2$ ), 3.72 (s, 3H,  $OCH_3$ )

$^1H$  NMR data were in agreement with those described in literature.<sup>283</sup>

### Methyl ((2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)glycinate (**283b**).



According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (165 mg, 0.50 mmol), H-MAC-TBS **148g** (236 mg, 1.20 mmol), previously prepared glycine methyl ester **271** (54 mg, 0.60 mmol) and DMAP (122 mg, 1.00 mmol) in  $Et_2O$  (5 mL). Flash column chromatography (pentane/ $EtOAc$ , 5:1) gave the MAC reaction product **283b** (dr <2:98, 224 mg, 80%), as a yellow oil.

TLC  $R_f$  = 0.26 (pentane/ $EtOAc$ , 5:1)

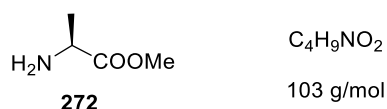
OR  $[\alpha]_D^{23} = -26.0$  (c 1.0,  $CHCl_3$ )

IR (ATR),  $\nu$  ( $cm^{-1}$ ): 3423, 3063, 3029, 2953, 2930, 2858, 2803, 1748, 1672, 1601, 1515, 1495, 1454, 1437, 1365, 1253, 1208, 1094

HRMS ( $ES^+$ ): calcd. for  $C_{33}H_{45}N_2O_4Si$   $[M+H]^+$  561.3143; found 561.3119

$^1H$  NMR (360 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : -0.09 (s, 3H,  $SiCH_3$ ), -0.01 (s, 3H,  $SiCH_3$ ), 0.91 (s, 9H,  $Si(CH_3)_3$ ), 3.00 (dd,  $J = 14.0, 7.6$  Hz, 1H) and 3.06 (dd,  $J = 14.0, 7.4$  Hz, 1H) (AB part of ABX syst.,  $PhCH_2CH$ ), 3.34 (ddd,  $J = 7.6, 7.4, 2.5$  Hz, 1H,  $CHNBn_2$ ), 3.50 (dd,  $J = 18.7, 4.1$  Hz, 1H) and 4.01 (dd,  $J = 18.7, 6.1$  Hz, 1H) (AB part of ABX syst.,  $NCH_2CO_2CH_3$ ), 3.69 (s, 3H,  $OCH_3$ ), 3.74 (s, 4H,  $N(CH_2Ph)_2$ ), 4.40 (d,  $J = 2.5$  Hz, 1H,  $CHOTBS$ ), 6.85 (br t,  $J = 5.0$  Hz, 1H,  $CONH$ ), 7.09-7.28 (m, 15H, Ph)

$^{13}C$  NMR (90.6 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : -5.2 ( $SiCH_3$ ), -4.8 ( $SiCH_3$ ), 18.0 ( $SiC(CH_3)_3$ ), 25.8 ( $SiC(CH_3)_3$ ), 32.1 ( $PhCH_2CH$ ), 40.6 ( $NCH_2CO_2Me$ ), 52.1 ( $OCH_3$ ), 54.6 ( $N(CH_2Ph)_2$ ), 64.1 ( $CHNBn_2$ ), 72.7 ( $CHOTBS$ ), 125.8 ( $CH_{Ph}$ ), 126.7 ( $CH_{Ph}$ ), 128.0 ( $CH_{Ph}$ ), 128.1 ( $CH_{Ph}$ ), 128.6 ( $CH_{Ph}$ ), 129.6 ( $CH_{Ph}$ ), 139.6 ( $C_{Ph}$ ), 139.9 ( $C_{Ph}$ ), 169.7 ( $CO_2CH_3$ ), 173.1 ( $CONH$ )

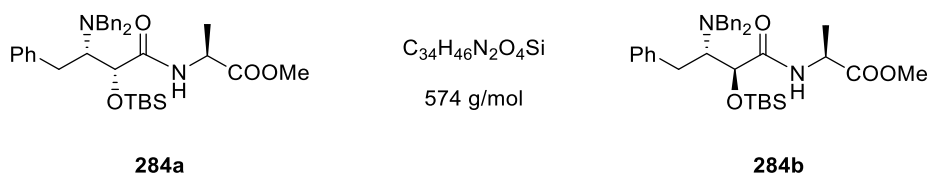
**Methyl L-alaninate (272).**

According to a literature procedure,<sup>231</sup> L-alanine methyl ester hydrochloride **272·HCl** (713 mg, 5.1 mmol) was mixed with a saturated aqueous  $Na_2CO_3$  solution (20 mL) and  $Et_2O$  (20 mL). The biphasic mixture was stirred for 30 minutes at room temperature, and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were dried over  $Na_2SO_4$  and concentrated under reduced pressure to give methyl L-alaninate **272** (162 mg, 31%), as a colorless oil.

OR  $[\alpha]_D^{28} = +6.1$  (*c* 1.0,  $CH_3OH$ ), lit.<sup>232</sup>  $[\alpha]_D^{20} = +7.0$  (*c* 1.0,  $CH_3OH$ )

<sup>1</sup>H NMR (360 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : 1.33 (d, *J* = 7.2 Hz, 3H,  $NCH(CH_3)$ ), 1.58 (br s, 2H,  $NH_2$ ), 3.55 (q, *J* = 7.2 Hz, 1H,  $NCH(CH_3)$ ), 3.72 (s, 3H,  $OCH_3$ )

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>232</sup>

**Methyl ((2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-L-alaninate (284a and 284b).**

According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (92 mg, 0.28 mmol), H-MAC-TBS **148g** (132 mg, 0.67 mmol), previously prepared L-alanine methyl ester **272** (35 mg, 0.34 mmol) dissolved in  $Et_2O$  (0.5 mL), DMAP (74 mg, 0.61 mmol), in  $Et_2O$  (3 mL). A 10:90 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **284a** and **284b** was determined by <sup>1</sup>H NMR analysis ( $CDCl_3$  at 293 K) by integration of the  $CHOTBS$  signal of **284a** and the  $CHNBn_2$  signal of **284b**. Flash column chromatography (pentane/ $EtOAc$ , 10:1 then 5:1) gave *anti* diastereomer **284b** (109 mg, 68%) and *syn* diastereomer **284a** (15 mg, 9%).

Data for the major *anti* (2*S*,3*S*,*S*)-diastereomer (**284b**), a viscous yellow oil:

TLC  $R_f = 0.13$  (pentane/ $EtOAc$ , 5:1)

OR  $[\alpha]_D^{27} = -28.3$  (*c* 1.0,  $CHCl_3$ )

IR (ATR),  $\nu$  ( $cm^{-1}$ ): 3419, 3062, 3026, 2953, 2930, 2856, 2801, 1744, 1671, 1603, 1507, 1495, 1452, 1362, 1254, 1208, 1157, 1094

HRMS ( $ES^+$ ): calcd. for  $C_{34}H_{47}N_2O_4Si$   $[M+H]^+$  575.3299; found 575.3274

<sup>1</sup>H NMR (360 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : -0.07 (s, 3H,  $SiCH_3$ ), 0.00 (s, 3H,  $SiCH_3$ ), 0.93 (s, 9H,  $SiC(CH_3)_3$ ), 1.13 (d, *J* = 7.2 Hz, 3H,  $NCH(CH_3)$ ), 3.02 (br d, *J* = 7.6 Hz, 2H,  $PhCH_2CH$ ), 3.34 (td, *J* = 7.6, 2.9 Hz, 1H,  $CHNBn_2$ ), 3.72 (s, 3H,  $OCH_3$ ), 3.75 (d, *J* = 14.4 Hz, 2H) and 3.80 (d, *J* = 14.4 Hz, 2H) (AB syst.,  $N(CH_2Ph)_2$ ), 4.35-4.45 (m, 2H,  $CHOTBS$ ,  $NCH(CH_3)$ ), 6.98 (br d, *J* = 7.2 Hz, 1H,  $CONH$ ), 7.10-7.16 (m, 2H,  $Ph$ ), 7.16-7.30 (m, 13H,  $Ph$ )

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.3 (SiCH<sub>3</sub>), -4.7 (SiCH<sub>3</sub>), 17.8 (NCH(CH<sub>3</sub>)), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 31.8 (PhCH<sub>2</sub>CH), 47.6 (NCH(CH<sub>3</sub>)), 52.2 (OCH<sub>3</sub>), 54.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.1 (CHNBn<sub>2</sub>), 72.1 (CHOTBS), 125.9 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 172.7 and 172.8 (CO<sub>2</sub>CH<sub>3</sub>, CONH)

Data for the minor syn (2R,3S,S)-diastereomer (**284a**), a viscous yellow oil:

**TLC** *R<sub>f</sub>* = 0.09 (pentane/EtOAc, 5:1)

**OR** [α]<sub>D</sub><sup>27</sup> = +7.0 (c 1.0, CHCl<sub>3</sub>)

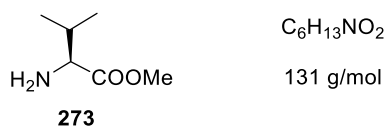
**IR** (ATR), ν (cm<sup>-1</sup>): 3425, 3063, 3027, 2953, 2928, 2857, 1744, 1680, 1603, 1507, 1496, 1452, 1362, 1254, 1208, 1156, 1098

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>34</sub>H<sub>47</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 575.2299; found 575.3279

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>), δ (ppm) : 0.00 (s, 3H, SiCH<sub>3</sub>), 0.01 (s, 3H, SiCH<sub>3</sub>), 0.93 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.42 (d, *J* = 7.2 Hz, 3H, NCH(CH<sub>3</sub>)), 2.85 (dd, *J* = 14.4, 7.2 Hz, 1H) and 3.09 (dd, *J* = 14.4, 7.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.55 (ddd, *J* = 7.2, 7.2, 2.5 Hz, 1H, CHNBn<sub>2</sub>), 3.61 (d, *J* = 14.0 Hz, 2H) and 4.00 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 4.18 (d, *J* = 2.5 Hz, 1H, CHOTBS), 4.58 (quintet, *J* = 7.2 Hz, 1H, NCH(CH<sub>3</sub>)), 7.11-7.33 (m, 16H, Ph, CONH)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.0 (SiCH<sub>3</sub>), -4.9 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 18.8 (NCH(CH<sub>3</sub>)), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 33.1 (PhCH<sub>2</sub>CH), 47.9 (NCH(CH<sub>3</sub>)), 52.4 (OCH<sub>3</sub>), 55.1 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.2 (CHNBn<sub>2</sub>), 76.8 (CHOTBS), 126.1 (CH<sub>Ph</sub>), 126.6 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.3 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 129.3 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 172.0 and 173.0 (CO<sub>2</sub>CH<sub>3</sub>, CONH)

### Methyl L-valinate (**273**).



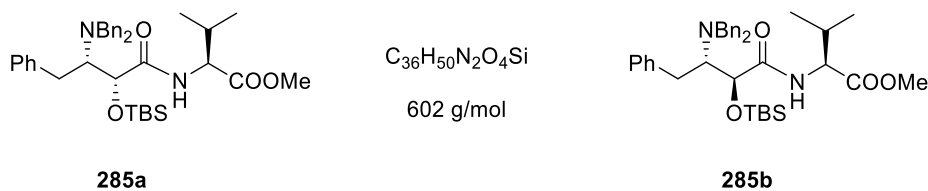
According to a literature procedure, <sup>231</sup> valine methyl ester hydrochloride **273**·HCl (1.0 g, 6.0 mmol) was mixed with a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and DCM (20 mL). The biphasic mixture was stirred for 30 minutes at room temperature, and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give methyl L-valinate **273** (530 mg, 67%), as a colorless oil.

**OR** [α]<sub>D</sub><sup>24</sup> = +31.7 (c 0.8, CHCl<sub>3</sub>), lit.<sup>233</sup> [α]<sub>D</sub><sup>20</sup> = +11.7 (c 0.8, CHCl<sub>3</sub>); [α]<sub>D</sub><sup>24</sup> = +127.4 (c 3.2, MeOH), lit.<sup>233</sup> [α]<sub>D</sub><sup>20</sup> = +38.0 (c 3.2, MeOH)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>), δ (ppm) : 0.89 (d, *J* = 6.6 Hz, 3H, NCH(CH(CH<sub>3</sub>))), 0.96 (d, *J* = 6.9 Hz, 3H, NCH(CH(CH<sub>3</sub>))), 1.46 (br s, 2H, NH<sub>2</sub>), 1.95-2.06 (m, 1H, NCH(CH(CH<sub>3</sub>)<sub>2</sub>)), 3.29 (d, *J* = 4.8 Hz, 1H, NCH(CH(CH<sub>3</sub>)<sub>2</sub>)), 3.71 (s, 3H, OCH<sub>3</sub>)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>233</sup>

**Methyl ((2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-L-valinate (**285a** and **285b**).**



According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (70 mg, 0.21 mmol), H-MAC-TBS **148g** (100 mg, 0.51 mmol), previously prepared L-valine methyl ester **273** (33 mg, 0.25 mmol), DMAP (52 mg, 0.42 mmol) in Et<sub>2</sub>O (2 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 5:1) gave inseparable MAC reaction products **285a,b** (dr 20:80, 59 mg, 47%), as a yellow oil. The 20:80 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **285a** and **285b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (70 mg, 0.21 mmol), H-MAC-TBS **148g** (100 mg, 0.51 mmol), DMAP (52 mg, 0.42 mmol) and previously prepared L-valine methyl ester **273** (33 mg, 0.25 mmol), in Et<sub>2</sub>O (2 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 5:1) gave inseparable MAC reaction products **285a,b** (dr 20:80, 93 mg, 74%), as a yellow oil. The 20:80 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **285a** and **285b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

According to the general procedure D, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (63 mg, 0.19 mmol), H-MAC-TBS **148g** (90 mg, 0.46 mmol), DMAP (75 mg, 0.61 mmol) and L-valine methyl ester hydrochloride **273·HCl** (38 mg, 0.23 mmol) in Et<sub>2</sub>O (2 mL). A 21:79 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **285a** and **285b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/EtOAc, 10:1 then 5:1) gave inseparable MAC reaction products **285a,b** (dr 18:82, 82 mg, 72%), as a yellow oil.

**TLC** *R<sub>f</sub>* = 0.55 (pentane/EtOAc, 5:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3423, 3064, 3027, 2955, 2930, 2858, 2801, 1742, 1677, 1603, 1496, 1454, 1364, 1256, 1207, 1097

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>36</sub>H<sub>51</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 603.3613; found 603.3594

*Spectroscopic data for the major anti (2*S*,3*S*,*S*)-diastereomer (**285b**):*

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.06 (s, 3H, SiCH<sub>3</sub>), 0.13 (s, 3H, SiCH<sub>3</sub>), 0.84 (d, *J* = 6.8 Hz, 3H, NCH(CHCH<sub>3</sub>)), 0.89 (d, *J* = 6.8 Hz, 3H, NCH(CHCH<sub>3</sub>)), 1.01 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.95-2.06 (m, 1H, NCH(CH(CH<sub>3</sub>)<sub>2</sub>)), 2.93 (dd, *J* = 14.2, 5.6 Hz, 1H) and 3.06 (dd, *J* = 14.2, 9.2 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.43 (ddd, *J* = 9.2, 5.6, 2.4 Hz, 1H, CHNBn<sub>2</sub>), 3.68 (d, *J* = 14.4 Hz, 2H) and 3.88 (d, *J* = 14.4 Hz,





**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3421, 3062, 3028, 2954, 2931, 2858, 1738, 1678, 1603, 1495, 1454, 1368, 1347, 1254, 1215, 1164, 1096

**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{37}\text{H}_{53}\text{N}_2\text{O}_4\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  617.3769; found 617.3740

*Spectroscopic data for the major anti (2S,3S,S)-diastereomer (286b):*

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 0.06 (s, 3H,  $\text{SiCH}_3$ ), 0.20 (s, 3H,  $\text{SiCH}_3$ ), 0.93 (s, 9H,  $\text{NCH}(\text{C}(\text{CH}_3)_3)$ ), 1.04 (s, 9H,  $\text{Si}(\text{C}(\text{CH}_3)_3)$ ), 2.88 (dd,  $J = 14.4, 5.1$  Hz, 1H) and 3.07 (br dd,  $J = 14.4, 10.2$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.44 (br ddd,  $J = 10.2, 5.1, 1.8$  Hz, 1H,  $\text{CHNBn}_2$ ), 3.64 (d,  $J = 14.1$  Hz, 2H) and 3.91 (d,  $J = 14.1$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 3.71 (s, 3H,  $\text{OCH}_3$ ), 4.39 (d,  $J = 9.0$  Hz, 1H,  $\text{NCH}(\text{C}(\text{CH}_3)_3)$ ), 4.66 (d,  $J = 1.8$  Hz, 1H,  $\text{CHOTBS}$ ), 6.95-7.03 (m, 3H,  $\text{CONH}$ , Ph), 7.04-7.09 (m, 3H, Ph), 7.14-7.25 (m, 10H, Ph)

**$^{13}\text{C}$  NMR** (75.5 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -4.9 ( $\text{SiCH}_3$ ), -4.1 ( $\text{SiCH}_3$ ), 18.0 ( $\text{Si}(\text{C}(\text{CH}_3)_3)$ ), 25.9 ( $\text{Si}(\text{C}(\text{CH}_3)_3)$ ), 26.5 ( $\text{NCH}(\text{C}(\text{CH}_3)_3)$ ), 32.5 ( $\text{PhCH}_2\text{CH}$ ), 34.2 ( $\text{NCH}(\text{C}(\text{CH}_3)_3)$ ), 51.6 ( $\text{OCH}_3$ ), 53.9 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 59.9 ( $\text{NCH}(\text{C}(\text{CH}_3)_3)$ ), 63.1 ( $\text{CHNBn}_2$ ), 72.2 ( $\text{CHOTBS}$ ), 125.8 ( $\text{C}_{\text{Ph}}$ ), 126.6 ( $\text{C}_{\text{Ph}}$ ), 128.0 ( $\text{C}_{\text{Ph}}$ ), 128.6 ( $\text{C}_{\text{Ph}}$ ), 129.6 ( $\text{C}_{\text{Ph}}$ ), 139.4 ( $\text{C}_{\text{Ph}}$ ), 139.5 ( $\text{C}_{\text{Ph}}$ ), 171.4 ( $\text{CO}_2\text{CH}_3$ ), 173.2 ( $\text{CONH}$ )

#### Methyl L-leucinate (275).



**275**

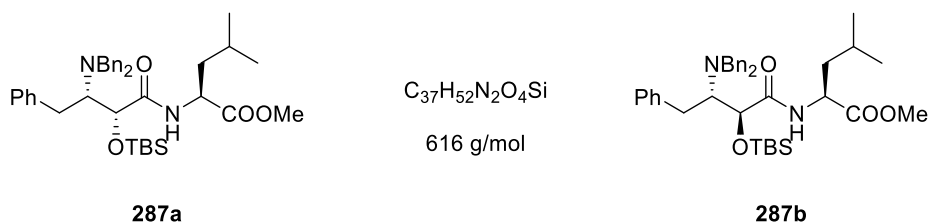
According to a literature procedure,<sup>231</sup> L-leucine methyl ester hydrochloride **275·HCl** (1.0 g, 5.0 mmol) was mixed with a 1:1 (v/v, 40 mL) mixture of saturated aqueous  $\text{Na}_2\text{CO}_3$  and  $\text{Et}_2\text{O}$ , and the reaction mixture was stirred for 30 minutes at room temperature. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 20 mL), the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give methyl L-leucinate **275** (368 mg, 46%), as a colorless oil.

**OR**  $[\alpha]_{\text{D}}^{25} = +13.5$  (c 1.0,  $\text{CHCl}_3$ ), lit.<sup>284</sup>  $[\alpha]_{\text{D}}^{23} = +15.3$  (concentration and solvent not given)

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 0.91 (d,  $J = 4.8$  Hz, 3H,  $\text{CH}_2\text{CHCH}_3$ ), 0.93 (d,  $J = 5.1$  Hz, 3H,  $\text{CH}_2\text{CHCH}_3$ ), 1.36-1.47 (m, 1H) and 1.50-1.61 (m, 1H) (AB syst.,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.69-1.84 (m, 1H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 3.42-3.51 (m, 1H,  $\text{CHN}$ ), 3.71 (s, 3H,  $\text{OCH}_3$ )

$^1\text{H}$  NMR data were in agreement with those described in literature.<sup>285</sup>

#### Methyl ((2R,3S)- and (2S,3S)- 2-(tert-butyltrimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-L-leucinate (287a and 287b).



According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (87 mg, 0.26 mmol), H-MAC-TBS **148g** (125 mg, 0.64 mmol), DMAP (65 mg, 0.53

mmol) and previously prepared L-leucine methyl ester **275** (46 mg, 0.32 mmol) dissolved in Et<sub>2</sub>O (0.5 mL), in Et<sub>2</sub>O (3 mL). A 16:84 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **287a/287b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/EtOAc, 20:1 then 10:1) gave inseparable MAC reaction products **287a,b** (dr 16:84, 121 mg, 75%), as a yellow oil.

TLC *R<sub>f</sub>* = 0.63 (pentane/EtOAc, 5:1)

IR (ATR),  $\nu$  (cm<sup>-1</sup>): 3424, 3063, 3027, 2953, 2929, 2857, 2802, 1745, 1674, 1602, 1495, 1453, 1365, 1254, 1201, 1153, 1092

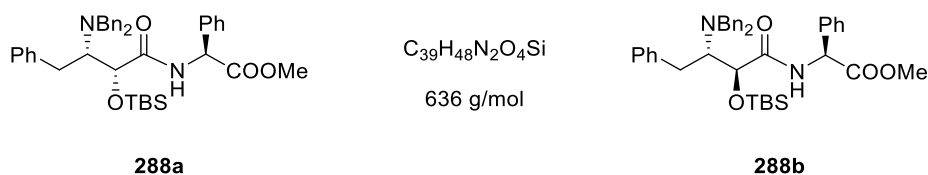
HRMS (ES<sup>+</sup>): calcd. for C<sub>37</sub>H<sub>53</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 617.3769; found 617.3749

Spectroscopic data for the major anti (2*S*,3*S*,*S*)-diastereomer (**287b**):

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.03 (s, 3H, SiCH<sub>3</sub>), 0.02 (s, 3H, SiCH<sub>3</sub>), 0.79 (d, *J* = 5.8 Hz, 3H, NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 0.80 (d, *J* = 5.8 Hz, 3H, NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 0.94 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.27-1.34 (m, 1H) and 1.42-1.50 (m, 1H) (AB syst., NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 1.42-1.50 (m, 1H, NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 2.94 (dd, *J* = 13.7, 7.2 Hz, 1H) and 3.02 (dd, *J* = 13.7, 7.9 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.34 (ddd, *J* = 7.9, 7.2, 2.5 Hz, 1H, CHNBn<sub>2</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 3.71 (d, *J* = 14.0 Hz, 2H) and 3.81 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.36-4.42 (m, 1H, NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 4.43 (d, *J* = 2.5 Hz, 1H, CHOTBS), 6.80 (br d, *J* = 7.6 Hz, 1H, CONH), 7.06-7.11 (m, 2H, Ph), 7.13-7.24 (m, 13H, Ph)

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.2 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.1 (NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 22.3 (NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 24.8 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 31.9 (PhCH<sub>2</sub>CH), 41.3 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 50.5 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 52.0 (OCH<sub>3</sub>), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.0 (CHNBn<sub>2</sub>), 72.0 (CHOTBS), 125.9 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 139.8 (C<sub>Ph</sub>), 172.7 and 172.9 (CO<sub>2</sub>CH<sub>3</sub>, CONH)

**Methyl ((2*R*,3*S*)- and (2*S*,3*S*)- 2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-L-phenylglycinate (**288a** and **288b**).**



According to the general procedure D, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (63 mg, 0.19 mmol), H-MAC-TBS **148g** (90 mg, 0.46 mmol), DMAP (74 mg, 0.61 mmol) and L-phenylglycine methyl ester hydrochloride **L-276-HCl** (46 mg, 0.23 mmol), in Et<sub>2</sub>O (2 mL). A 10:90 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **288a/288b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the CHOTBS signals. Flash column chromatography (pentane/EtOAc, 10:1 then 5:1 then 2:1) gave inseparable MAC reaction products **288a,b** (dr 9:91, 99 mg, 82%), as a yellow oil.

TLC *R<sub>f</sub>* = 0.41 (pentane/EtOAc, 5:1)

**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3425, 3063, 3027, 2952, 2929, 2857, 2801, 1743, 1673, 1603, 1494, 1454, 1330, 1255, 1211, 1171, 1094

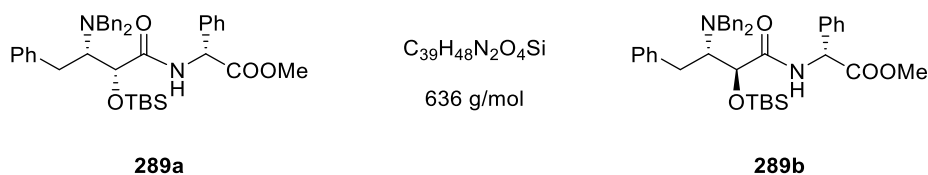
**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{39}\text{H}_{49}\text{N}_2\text{O}_4\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  637.3456; found 637.3426

*Spectroscopic data for the major anti (2S,3S,S)-diastereomer (288b):*

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 0.04 (s, 3H,  $\text{SiCH}_3$ ), 0.05 (s, 3H,  $\text{SiCH}_3$ ), 0.96 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 2.89 (dd,  $J = 13.8, 7.2$  Hz, 1H) and 2.98 (dd,  $J = 13.8, 7.8$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.29 (ddd,  $J = 7.8, 7.2, 2.7$  Hz, 1H,  $\text{CHNBn}_2$ ), 3.68 (d,  $J = 14.7$  Hz, 2H) and 3.78 (d,  $J = 14.7$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 3.71 (s, 3H,  $\text{OCH}_3$ ), 4.48 (d,  $J = 2.7$  Hz, 1H,  $\text{CHOTBS}$ ), 5.38 (d,  $J = 6.6$  Hz, 1H,  $\text{NCH}(\text{Ph})$ ), 6.99-7.06 (m, 2H, Ph), 7.08-7.29 (m, 18H, Ph), 7.33-7.40 (m, 1H, CONH)

$^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -5.1 ( $\text{SiCH}_3$ ), -4.7 ( $\text{SiCH}_3$ ), 18.0 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.9 ( $\text{SiC}(\text{CH}_3)_3$ ), 32.3 ( $\text{PhCH}_2\text{CH}$ ), 52.6 ( $\text{OCH}_3$ ), 54.3 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 56.4 ( $\text{NCH}(\text{Ph})$ ), 64.3 ( $\text{CHNBn}_2$ ), 72.2 ( $\text{CHOTBS}$ ), 125.8 ( $\text{CH}_{\text{Ph}}$ ), 126.6 ( $\text{CH}_{\text{Ph}}$ ), 127.3 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.5 ( $\text{CH}_{\text{Ph}}$ ), 128.6 ( $\text{CH}_{\text{Ph}}$ ), 128.9 ( $\text{CH}_{\text{Ph}}$ ), 129.6 ( $\text{CH}_{\text{Ph}}$ ), 139.5 ( $\text{C}_{\text{Ph}}$ ), 139.7 ( $\text{C}_{\text{Ph}}$ ), 170.8 ( $\text{CO}_2\text{CH}_3$ ), 172.7 (CONH)

**Methyl ((2R,3S)- and (2S,3S)-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-D-phenylglycinate (289a and 289b).**



According to the general procedure D, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (63 mg, 0.19 mmol), H-MAC-TBS **148g** (90 mg, 0.46 mmol), DMAP (74 mg, 0.61 mmol) and D-phenylglycine methyl ester hydrochloride **D-276·HCl** (46 mg, 0.23 mmol), in  $\text{Et}_2\text{O}$  (2 mL). A 10:90 ratio of the (2R,3S,R)- and (2S,3S,R)-diastereomers **289a/289b** was determined by  $^1\text{H}$  NMR analysis ( $\text{CDCl}_3$  at 293 K) by integration of the  $\text{CHOTBS}$  signals. Flash column chromatography (pentane/ $\text{EtOAc}$ , 10:1 then 7:1 then 5:1) gave the *anti* (2S,3S,R)-MAC product **289b** (90 mg, 74%) and the *syn* (2R,3S,R)-MAC product **289a** (11 mg, 9%).

*Data for the major anti (2S,3S,R)-diastereomer (289b), a pale yellow oil:*

**TLC**  $R_f = 0.48$  (pentane/ $\text{EtOAc}$ , 5:1)

**OR**  $[\alpha]_{\text{D}}^{27} = -76.9$  (c 1.0,  $\text{CHCl}_3$ )

**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3413, 3062, 3026, 2953, 2929, 2857, 2801, 1743, 1673, 1602, 1494, 1455, 1330, 1256, 1217, 1172, 1094

**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{39}\text{H}_{49}\text{N}_2\text{O}_4\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  637.3456; found 637.3425

$^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -0.27 (s, 3H,  $\text{SiCH}_3$ ), -0.05 (s, 3H,  $\text{SiCH}_3$ ), 0.88 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 3.03 (dd,  $J = 13.3, 7.9$  Hz, 1H) and 3.09 (dd,  $J = 13.3, 7.2$  Hz, 1H) (AB part of ABX syst.,  $\text{PhCH}_2\text{CH}$ ), 3.37 (ddd,  $J = 7.9, 7.2, 2.2$  Hz, 1H,  $\text{CHNBn}_2$ ), 3.64 (s, 3H,  $\text{OCH}_3$ ), 3.74 (d,  $J = 14.4$  Hz, 2H) and 3.81 (d,  $J = 14.4$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 4.43 (d,  $J = 2.2$  Hz, 1H,  $\text{CHOTBS}$ ), 5.26 (d,  $J = 6.8$  Hz, 1H,  $\text{NCH}(\text{Ph})$ ), 7.08-7.14 (m, 2H, Ph), 7.15-7.27 (m, 13H, Ph), 7.27-7.33 (m, 5H, Ph), 7.47 (d,  $J = 6.8$  Hz, 1H, CONH)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.1 (SiCH<sub>3</sub>), -4.6 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.0 (PhCH<sub>2</sub>CH), 52.7 (OCH<sub>3</sub>), 54.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 56.2 (NCH(Ph)), 64.0 (CHNBn<sub>2</sub>), 72.2 (CHOTBS), 125.8 (CH<sub>Ph</sub>), 126.6 (CH<sub>Ph</sub>), 127.4 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 128.9 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 136.5 (C<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 170.7 (CO<sub>2</sub>CH<sub>3</sub>), 172.4 (CONH)

Data for the minor syn (2*R*,3*S*,*R*)-diastereomer (**289a**), a viscous colorless oil:

**TLC** *R<sub>f</sub>* = 0.41 (pentane/EtOAc, 5:1)

**IR** (ATR), ν (cm<sup>-1</sup>): 3424, 3063, 3028, 2953, 2929, 2856, 1744, 1682, 1603, 1495, 1454, 1330, 1259, 1212, 1173, 1097

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>39</sub>H<sub>49</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 637.3456; found 637.3429

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>), δ (ppm) : 0.04 (s, 3H, SiCH<sub>3</sub>), 0.14 (s, 3H, SiCH<sub>3</sub>), 0.94 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.77 (dd, *J* = 14.1, 6.8 Hz, 1H) and 2.94 (dd, *J* = 14.1, 8.7 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.52 (d, *J* = 13.7 Hz, 3H) and 3.81 (d, *J* = 13.7 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>, CHNBn<sub>2</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 4.22 (d, *J* = 2.7 Hz, 1H, CHOTBS), 5.57 (d, *J* = 7.2 Hz, 1H, NCH(Ph)), 6.96-7.06 (m, 5H, Ph), 7.06-7.15 (m, 5H, Ph), 7.18-7.24 (m, 3H, Ph), 7.33-7.46 (m, 7H, Ph), 7.55 (d, *J* = 7.5 Hz, 1H, CONH)

**<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.2 (SiCH<sub>3</sub>), -4.8 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 33.6 (PhCH<sub>2</sub>CH), 52.7 (OCH<sub>3</sub>), 54.9 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 56.4 (NCH(Ph)), 61.2 (CHNBn<sub>2</sub>), 76.9 (CHOTBS), 126.0 (CH<sub>Ph</sub>), 126.5 (CH<sub>Ph</sub>), 127.7 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 129.1 (CH<sub>Ph</sub>), 129.3 (CH<sub>Ph</sub>), 136.3 (C<sub>Ph</sub>), 139.5 (C<sub>Ph</sub>), 139.8 (C<sub>Ph</sub>), 171.0 (CO<sub>2</sub>CH<sub>3</sub>), 172.2 (CONH)

### Methyl L-phenylalaninate (**277**).



C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub>

179 g/mol

**277**

According to a literature procedure,<sup>286</sup> L-phenylalanine (826 mg, 5.0 mmol) was dissolved in MeOH (20 mL) and the solution was cooled down to 0 °C. Thionyl chloride (5.0 mL, 27.1 mmol) was introduced dropwise, and the reaction mixture was stirred under reflux for 5 hours. The mixture was concentrated under vacuum and a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution was introduced until pH = 9. The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed by brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give methyl L-phenylalaninate **277** (938 mg, quant.), as a colorless oil. It was pure enough to be used directly in the following reaction.

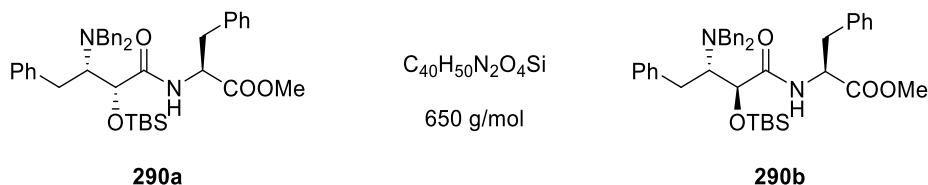
**TLC** *R<sub>f</sub>* = 0.60 (DCM/MeOH, 5:1)

**OR** [α]<sub>D</sub><sup>22</sup> = +42.7 (c 2.0, EtOH), lit.<sup>287</sup> [α]<sub>D</sub><sup>20</sup> = +37.5 (c 2.0, EtOH)

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>), δ (ppm): 1.54-1.64 (m, 2H, NH<sub>2</sub>), 2.86 (dd, *J* = 13.2, 8.1 Hz, 1H) and 3.10 (dd, *J* = 13.2, 5.4 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.72 (s, 3H, OMe), 3.72-3.78 (m, 1H, PhCH<sub>2</sub>CH), 7.15-7.22 (m, 2H, Ph), 7.23-7.35 (m, 3H, Ph)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>286</sup>

**Methyl ((2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-L-phenylalaninate (**290a** and **290b**).**



According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (165 mg, 0.50 mmol), H-MAC-TBS **148g** (236 mg, 1.20 mmol), DMAP (122 mg, 1.00 mmol) and previously prepared L-phenylalanine methyl ester **277** (53 mg, 0.60 mmol), in Et<sub>2</sub>O (5 mL). A 10:90 ratio of the (2*R*,3*S,S*)- and (2*S*,3*S,S*)-diastereomers **290a/290b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/EtOAc, 10:1) gave the (2*S*,3*S,S*)-MAC product **290b** (135 mg, 42%) and a mixture of **290a,b** (dr 25:75, 101 mg, 31%).

According to the general procedure D, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (63 mg, 0.19 mmol), H-MAC-TBS **148g** (90 mg, 0.46 mmol), DMAP (75 mg, 0.61 mmol) and L-phenylalanine methyl ester hydrochloride (49 mg, 0.23 mmol), in Et<sub>2</sub>O (2 mL). A 17:83 ratio of the (2*R*,3*S,S*)- and (2*S*,3*S,S*)-diastereomers **290a/290b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/EtOAc, 10:1 then 5:1) gave the (2*R*,3*S,S*)-MAC product **290a** (3 mg, 2%) and a mixture of **290a,b** (dr 13:87, 59 mg, 48%).

*Data for the major anti (2*S*,3*S,S*)-diastereomer (**290b**), a yellow oil:*

**TLC** *R*<sub>f</sub> = 0.09 (pentane/EtOAc, 10:1)

**OR** [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +5.5 (*c* 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3416, 3061, 3025, 2953, 2930, 2856, 1743, 1673, 1602, 1495, 1453, 1363, 1254, 1203, 1094

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>40</sub>H<sub>51</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 651.3613; found 651.3581

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.10 (s, 3H, SiCH<sub>3</sub>), 0.03 (s, 3H, SiCH<sub>3</sub>), 0.84 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.71 (dd, *J* = 14.4, 6.5 Hz, 1H) and 2.91 (dd, *J* = 14.4, 8.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CHNBn<sub>2</sub>), 2.79 (dd, *J* = 14.0, 6.5 Hz, 1H) and 2.96 (dd, *J* = 14.0, 6.5 Hz, 1H) (AB part of ABX syst., NCH(CH<sub>2</sub>Ph)), 3.32 (ddd, *J* = 8.6, 6.5, 2.5 Hz, 1H, CHNBn<sub>2</sub>), 3.64 (s, 3H, OCH<sub>3</sub>), 3.67 (d, *J* = 14.0, 2H) and 3.79 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.46 (d, *J* = 2.5 Hz, 1H, CHOTBS), 4.69 (dt, *J* = 7.6, 6.5 Hz, 1H, NCH(CH<sub>2</sub>Ph)), 6.82 (d, *J* = 7.6 Hz, 1H, CONH), 7.00-7.05 (m, 4H, Ph), 7.10-7.26 (m, 16H, Ph).

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.2 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.1 (PhCH<sub>2</sub>CH), 37.6 (NCH(CH<sub>2</sub>Ph)), 52.0 (OCH<sub>3</sub>), 52.7 (NCH(CH<sub>2</sub>Ph)), 54.2 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 63.5 (CHNBn<sub>2</sub>), 72.1 (CHOTBS), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 127.2 (CH<sub>Ph</sub>), 127.9 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 128.9 (CH<sub>Ph</sub>), 129.6 (CH<sub>Ph</sub>), 135.4 (C<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>), 171.5 (CO<sub>2</sub>CH<sub>3</sub>), 172.9 (CONH).

*Data for the minor (2*R*,3*S,S*)-diastereomer (**290a**), a yellow oil:*



*O*-TBS-*L*-tyrosine methyl ester **279** (149 mg, 0.48 mmol) and DMAP (98 mg, 0.80 mmol) in Et<sub>2</sub>O (4 mL). A 13:87 ratio of the (*2R,3S,S*)- and (*2S,3S,S*)-diastereomers **291a/291b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/EtOAc, 10:1 then 5:1) gave inseparable MAC reaction products **291a,b** (dr 12:88, 270 mg, 86%), as a colorless viscous oil.

According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-*L*-phenylalaninal **L-13** (70 mg, 0.21 mmol), H-MAC-TBS **148g** (100 mg, 0.51 mmol), DMAP (52 mg, 0.42 mmol) and previously prepared *O*-TBS-*L*-tyrosine methyl ester **279** (79 mg, 0.25 mmol), in Et<sub>2</sub>O (2 mL). Flash column chromatography (pentane/EtOAc, 10:1) gave the *anti* diastereomer **291b** (107 mg, 65%), and a mixture of *syn* and *anti* diastereomers **291a,b** (dr 48:52, 32 mg, 20%) as a colorless viscous oil. The 48:52 ratio of the (*2R,3S,S*)- and (*2S,3S,S*)-diastereomers **291a/291b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals.

*Data for the major anti (2S,3S,S)-diastereomer (291b), a colorless viscous oil:*

**TLC** *R<sub>f</sub>* = 0.11 (pentane/EtOAc, 10:1) and 0.48 (pentane/EtOAc, 5:1)

**OR** [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +14.2 (*c* 1.0, CHCl<sub>3</sub>)

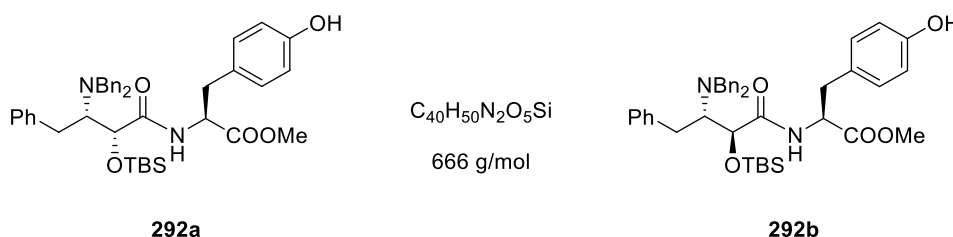
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3420, 3061, 3027, 2952, 2930, 2857, 2803, 1746, 1675, 1608, 1508, 1496, 1472, 1361, 1254, 1203, 1099

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>46</sub>H<sub>65</sub>N<sub>2</sub>O<sub>5</sub>Si<sub>2</sub> [M+H]<sup>+</sup> 781.4427; found 781.4391

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -0.08 (s, 3H, SiCH<sub>3</sub>), 0.04 (s, 3H, SiCH<sub>3</sub>), 0.12 (s, 6H, OSi(CH<sub>3</sub>)<sub>2</sub>), 0.86 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.95 (s, 9H, OSiC(CH<sub>3</sub>)<sub>3</sub>), 2.71 (dd, *J* = 13.6, 6.8 Hz, 1H) and 2.92 (dd, *J* = 13.6, 5.6 Hz, 1H) (AB part of ABX syst., NCH(CH<sub>2</sub>Ar)), 2.83 (dd, *J* = 14.4, 6.8 Hz, 1H) and 2.96 (dd, *J* = 14.4, 8.4 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.36 (ddd, *J* = 8.4, 6.8, 2.8 Hz, 1H, CHNBn<sub>2</sub>), 3.64 (s, 3H, OCH<sub>3</sub>), 3.69 (d, *J* = 14.0 Hz, 2H) and 3.81 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.48 (d, *J* = 2.8 Hz, 1H, CHOTBS), 4.64 (dt, *J* = 6.8, 5.6 Hz, 1H, NCH(CH<sub>2</sub>Ar)), 6.66 (d, *J* = 8.4 Hz, 2H, Ar), 6.83 (d, *J* = 7.6 Hz, 1H, CONH), 6.87 (d, *J* = 8.4 Hz, 2H, Ar), 7.03-7.07 (m, 2H, Ph), 7.14-7.26 (m, 13H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): -5.1 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), -4.5 (OSi(CH<sub>3</sub>)<sub>2</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 18.0 (OSiC(CH<sub>3</sub>)<sub>3</sub>), 25.6 (OSiC(CH<sub>3</sub>)<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.2 (PhCH<sub>2</sub>CH), 36.9 (NCH(CH<sub>2</sub>Ar)), 51.9 (OCH<sub>3</sub>), 52.9 (NCH(CH<sub>2</sub>Ar)), 54.3 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 63.6 (CHNBn<sub>2</sub>), 72.3 (CHOTBS), 120.2 (CH<sub>Ar</sub>), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 130.0 (CH<sub>Ar</sub>), 139.6 (C<sub>Ph</sub>, C<sub>Ar</sub>), 139.7 (C<sub>Ph</sub>), 154.8 (C<sub>Ar</sub>), 171.7 (CO<sub>2</sub>CH<sub>3</sub>), 173.0 (CONH)

**Methyl ((2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-*L*-tyrosinate (**292a** and **292b**).**





According to the general procedure D, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (115 mg, 0.35 mmol), H-MAC-TBS **148g** (165 mg, 0.84 mmol), L-tyrosine methyl ester hydrochloride **178·HCl** (97 mg, 0.42 mmol) and DMAP (137 mg, 1.12 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/EtOAc, 10:1 then 5:1) gave an inseparable mixture of MAC products **292a,b** (dr 12:88, 60 mg, 26%) as a colorless oil, and an inseparable mixture of *O*-TBS protected MAC products **291a/291b** (dr 4:96, 68 mg, 25%), as a colorless oil. The 4:96 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **291a/291b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals, and the 12:88 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **292a/292b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the CHOTBS signals.

TLC *R<sub>f</sub>* = 0.13 (pentane/EtOAc, 5:1)

IR (ATR), ν (cm<sup>-1</sup>): 3406, 3317 (br), 3062, 3028, 2952, 2928, 2856, 1743, 1657, 1614, 1514, 1496, 1453, 1442, 1363, 1255, 1208, 1100

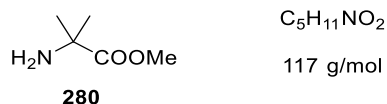
HRMS (ES<sup>+</sup>): calcd. for C<sub>40</sub>H<sub>51</sub>N<sub>2</sub>O<sub>5</sub>Si [M+H]<sup>+</sup> 667.3562; found 667.3529

*Spectroscopic data for the major anti (2*S*,3*S*,*S*)-diastereomer (292b):*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ (ppm): -0.07 (s, 3H, SiCH<sub>3</sub>), 0.06 (s, 3H, SiCH<sub>3</sub>), 0.88 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 2.74 (dd, *J* = 14.2, 6.6 Hz, 1H) and 2.89 (dd, *J* = 14.2, 6.4 Hz, 1H) (AB part of ABX. syst., NCH(CH<sub>2</sub>Ar)), 2.74 (dd, *J* = 14.4, 6.4 Hz, 1H) and 2.95 (dd, *J* = 14.4, 8.8 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.36 (ddd, *J* = 8.8, 6.4, 2.4 Hz, 1H, CHNBn<sub>2</sub>), 3.65 (s, 3H, OCH<sub>3</sub>), 3.69 (d, *J* = 14.0 Hz, 2H) and 3.82 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.50 (d, *J* = 2.4 Hz, 1H, CHOTBS), 4.66 (dt, *J* = 6.6, 6.4 Hz, 1H, NCH(CH<sub>2</sub>Ar)), 6.64 (d, *J* = 8.4 Hz, 2H, Ar), 6.86 (d, *J* = 6.4 Hz, 1H, CONH), 6.88 (d, *J* = 8.4 Hz, 2H, Ar), 7.01-7.06 (m, 2H, Ph), 7.14-7.42 (m, 13H, Ph)

<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>), δ (ppm): -5.2 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.1 (PhCH<sub>2</sub>CH), 36.9 (NCH(CH<sub>2</sub>Ar)), 52.0 (OCH<sub>3</sub>), 52.9 (NCH(CH<sub>2</sub>Ar)), 54.2 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 63.5 (CHNBn<sub>2</sub>), 72.2 (CHOTBS), 115.8 (CH<sub>Ar</sub>), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 126.9 (CH<sub>Ph</sub>), 127.7 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 128.9 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 130.0 (CH<sub>Ph</sub>), 130.0 (CH<sub>Ar</sub>), 139.6 (C<sub>Ph</sub>, C<sub>Ar</sub>), 139.7 (C<sub>Ph</sub>), 155.3 (C<sub>Ar</sub>), 171.7 (CO<sub>2</sub>CH<sub>3</sub>), 173.2 (CONH)

### Methyl 2-aminoisobutyrate (Aib-OMe) (**280**).

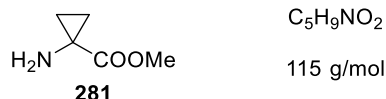


Inspired by a literature procedure,<sup>235</sup> to 2-aminoisobutyric acid (1.0 g, 9.7 mmol) was introduced a 1:1 (v/v, 10 mL) mixture of MeOH and DCM. After cooling to 0 °C, TMSCHN<sub>2</sub> (2 M in Et<sub>2</sub>O, 5.9 mL, 11.7 mmol) was added slowly and the reaction mixture was stirred for 1 hour at room temperature until the yellow color disappeared. 5 drops of acetic acid were then added and the mixture was stirred for 10 minutes, filtrated through cotton and washed with DCM. The filtrates and washings were concentrated under reduced pressure to afford methyl 2-aminoisobutyrate **280** (726 mg, 64%), as a pale-yellow viscous oil. It was pure enough to be used directly in the following reaction.

TLC  $R_f$  = 0.62 (DCM/MeOH, 5:1)

$^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 1.34 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 1.72 (br s, 2H,  $\text{NH}_2$ ), 3.71 (s, 3H,  $\text{OCH}_3$ )

**Methyl 1-aminocyclopropanecarboxylate (Acc•OMe) (281).**

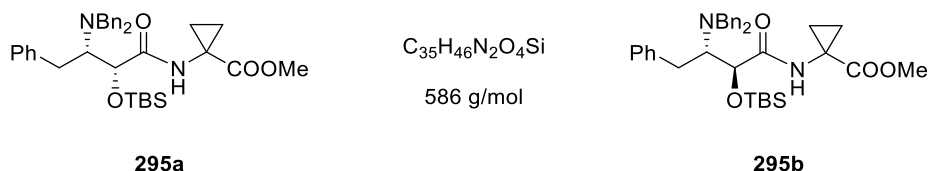


Inspired by a literature procedure,<sup>235</sup> to 1-aminocyclopropanecarboxylic acid (300 mg, 2.97 mmol) was introduced a 1:1 (v/v, 10 mL) mixture of MeOH and DCM. After cooling to 0 °C,  $\text{TMSCHN}_2$  (2 M in  $\text{Et}_2\text{O}$ , 1.8 mL, 3.6 mmol) was added slowly and the reaction mixture was stirred for 20 minutes at room temperature until the yellow color disappeared. 5 drops of acetic acid were then added and the mixture was stirred for 10 minutes, filtrated through cotton and washed with DCM. All the filtrates were concentrated under reduced pressure to afford methyl 1-aminocyclopropanecarboxylate **281** (217 mg, 63%), as a pale-yellow viscous oil. It was pure enough to be used directly in the following reaction.

TLC  $R_f$  = 0.57 (DCM/MeOH, 5:1)

$^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 1.01-1.07 (m, 2H,  $\text{NCCH}_2$ ), 1.27-1.32 (m, 2H,  $\text{NCCH}_2$ ), 2.04-2.09 (m, 2H,  $\text{NH}_2$ ), 3.69 (s, 3H,  $\text{OCH}_3$ )

**Methyl 1-((2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanamido)cyclopropanecarboxylate (295a and 295b).**



According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-*L*-phenylalaninal **L-13** (90 mg, 0.27 mmol), H-MAC-TBS **148g** (129 mg, 0.66 mmol), DMAP (67 mg, 0.55 mmol) and previously prepared 1-aminocyclopropanecarboxylic acid methyl ester **281** (38 mg, 0.33 mmol) dissolved in  $\text{Et}_2\text{O}$  (0.5 mL), in  $\text{Et}_2\text{O}$  (3 mL). A 19:81 ratio of the (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers **295a/295b** was determined by  $^1\text{H NMR}$  analysis ( $\text{CDCl}_3$  at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/ $\text{EtOAc}$ , 10:1 then 5:1) gave inseparable MAC reaction products **295a,b** (dr 15:85, 37 mg, 23%), as a viscous yellow oil.

TLC  $R_f$  = 0.32 (pentane/ $\text{EtOAc}$ , 5:1)

IR (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3423, 3063, 3027, 2953, 2927, 2855, 2802, 1735, 1686, 1602, 1494, 1453, 1335, 1254, 1198, 1162, 1094

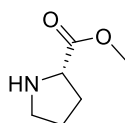
HRMS ( $\text{ES}^+$ ): calcd. for  $\text{C}_{35}\text{H}_{47}\text{N}_2\text{O}_4\text{Si}$  [ $\text{M}+\text{H}$ ]<sup>+</sup> 587.3299; found 587.3270

*Spectroscopic data for the major anti (2*S*,3*S*)-diastereomer (295b):*

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>), δ (ppm) : -0.09 (s, 3H, SiCH<sub>3</sub>), 0.05 (s, 3H, SiCH<sub>3</sub>), 0.82-0.91 (m, 2H) and 1.42-1.51 (m, 2H) (AB syst., NC(CH<sub>2</sub>)<sub>2</sub>), 0.93 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 3.01 (dd, *J* = 13.8, 8.4 Hz, 1H) and 3.09 (dd, *J* = 13.8, 6.9 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.34 (ddd, *J* = 8.4, 6.9, 2.1 Hz, 1H, CHNBn<sub>2</sub>), 3.55 (s, 3H, OCH<sub>3</sub>), 3.67 (d, *J* = 14.4 Hz, 2H) and 3.82 (d, *J* = 14.4 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.46 (br d, *J* = 2.1 Hz, 1H, CHOTBS), 6.92 (br s, 1H, CONH), 7.10-7.14 (m, 2H, Ph), 7.14-7.32 (m, 13H, Ph)

**<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.2 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 17.2 (NCCH<sub>2</sub>), 17.4 (NCCH<sub>2</sub>), 18.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 31.5 (PhCH<sub>2</sub>CH), 32.8 (NC(CH<sub>2</sub>)<sub>2</sub>), 52.4 (OCH<sub>3</sub>), 54.5 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 63.9 (CHNBn<sub>2</sub>), 72.1 (CHOTBS), 125.8 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 172.3 (CO<sub>2</sub>CH<sub>3</sub>), 174.1 (CONH)

### Methyl L-prolinate (**282**).



C<sub>6</sub>H<sub>11</sub>NO<sub>2</sub>

129 g/mol

**282**

L-proline (1.0 g, 8.7 mmol) was dissolved in MeOH (15 mL) and the solution was cooled down to 0 °C. Thionyl chloride (0.7 mL, 9.5 mmol) was introduced dropwise, followed by the addition of DMF (2 drops), and the reaction mixture was stirred for 3 days at room temperature (no more starting material). The mixture was concentrated under vacuum (with co-evaporations of excess of thionyl chloride with toluene) and a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) was introduced. The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed by brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give methyl L-prolinate **282** (668 mg, 60%), as a colorless oil. It was pure enough to be used directly in the MAC reaction.

TLC *R<sub>f</sub>* = 0.20 (DCM/MeOH, 20:1)

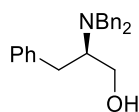
OR [α]<sub>D</sub><sup>26</sup> = -25.5 (c 1.0, CHCl<sub>3</sub>), (lit.<sup>238</sup> [α]<sub>D</sub><sup>25</sup> = -51.8 (c 1.0, CHCl<sub>3</sub>))

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>), δ (ppm) : 1.69-1.80 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>N), 1.80-1.90 (m, 1H) and 2.09-2.19 (m, 1H) (AB syst., CH<sub>2</sub>CHN), 2.06 (br s, 1H, NH), 2.91 (td, *J* = 10.1, 6.6 Hz, 1H) and 3.07 (td, *J* = 10.1, 6.6 Hz, 1H) (AB syst., CH<sub>2</sub>N), 3.73 (s, 3H, OCH<sub>3</sub>), 3.77 (dd, *J* = 8.7, 5.8 Hz, 1H, CHN)

## Towards the synthesis of (2*R*,3*R*,5*S*)-epibestatin

### *N,N*-Dibenzyl-D-phenylalaninal's synthesis.

#### *N,N*-Dibenzyl-D-phenylalaninol (**D-228**).



C<sub>23</sub>H<sub>25</sub>NO

332 g/mol

**D-228**

According to the general method, commercially available D-phenylalaninol **D-224** (2.0 g, 13.23 mmol) was *N,N*-dibenzylated with K<sub>2</sub>CO<sub>3</sub> (4.39 g, 31.77 mmol), BnBr (3.7 mL, 31.75 mmol) in CH<sub>3</sub>CN (90 mL).

The crude residue was purified by column chromatography (pentane/EtOAc, 5:1) to give *N,N*-dibenzyl-D-phenylalaninol **D-228** (3.62 g, 83%), as a light yellow solid.

**Mp** = 71-72 °C (lit.<sup>288</sup> 67-70 °C)

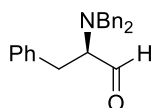
**TLC**  $R_f$  = 0.58 (pentane/EtOAc, 2:1)

**OR**  $[\alpha]_D^{24} = -33.3$  ( $c$  1.0,  $\text{CHCl}_3$ ), lit.<sup>288</sup>  $[\alpha]_D^{20} = -57.4$  ( $c$  1.0,  $\text{CHCl}_3$ )

**<sup>1</sup>H NMR** (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.44 (dd,  $J = 13.0, 9.4$  Hz, 1 H) and 3.01-3.17 (m, 3 H) (AB part of ABX syst.,  $\text{PhCH}_2\text{C}$ , and CHN, OH), 3.33 (dd,  $J = 10.4, 3.6$  Hz, 1 H) and 3.52 (dd,  $J = 10.4, 10.4$  Hz, 1 H) (AB part of ABX syst.,  $\text{CHCH}_2\text{OH}$ ), 3.49 (d,  $J = 13.5$  Hz, 2 H) and 3.93 (d,  $J = 13.5$  Hz, 2 H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 7.07-7.13 (m, 2H, Ph), 7.24-7.34 (m, 13H, Ph)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>288</sup>

### *N,N*-Dibenzyl-D-phenylalaninal (**D-13**).



$\text{C}_{23}\text{H}_{23}\text{NO}$

329 g/mol

**D-13**

According to the general procedure, Swern oxidation of *N,N*-dibenzyl-L-phenylalaninol **D-228** (500 mg, 1.50 mmol) was performed with DMSO (280  $\mu\text{L}$ , 3.90 mmol), oxalyl chloride (180  $\mu\text{L}$ , 2.0 mmol) in DCM (7 mL), followed by the addition of  $\text{NEt}_3$  (0.6 mL, 4.32 mmol). Crude *N,N*-dibenzyl-D-phenylalaninal **D-13** (494 mg, 99%) was isolated as a viscous yellow oil. It was used without any purification in the next step.

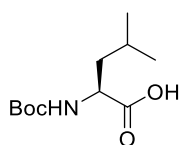
**TLC**  $R_f$  = 0.68 (pentane/EtOAc, 5:1)

**OR**  $[\alpha]_D^{23} = +89.2$  ( $c$  1.0,  $\text{CHCl}_3$ )

**<sup>1</sup>H NMR** (360 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.96 (dd,  $J = 14.0, 5.7$  Hz, 1H) and 3.16 (dd,  $J = 14.0, 7.2$  Hz, 1H) (ABX syst.,  $\text{PhCH}_2\text{C}$ ), 3.58 (br dd,  $J = 6.8, 6.5$  Hz, 1H, CHN), 3.69 (d,  $J = 13.7$  Hz, 2H) and 3.84 (d,  $J = 13.7$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 7.12-7.23 (m, 2H, Ph), 7.23-35 (m, 13H, Ph), 9.74 (s, 1H, CHO)

### Benzyl L-leucinate's synthesis.

#### *N*-(*tert*-Butoxycarbonyl)-L-leucine, *N*-Boc-L-leucine (**297**).



$\text{C}_{11}\text{H}_{21}\text{NO}_4$

231 g/mol

**297**

According to a literature procedure,<sup>289</sup> commercially available L-Leucine **296** (1.0 g, 7.6 mmol) was mixed with 1,4-dioxane (40 mL) and water (20 mL). A 1 M solution of NaOH (17.0 mL, 17.0 mmol) was added dropwise at 0 °C. After total addition,  $\text{Boc}_2\text{O}$  (1.83 g, 8.4 mmol) was added at 0 °C, and the reaction mixture was slowly warmed to room temperature and stirred for 6 hours. The mixture was

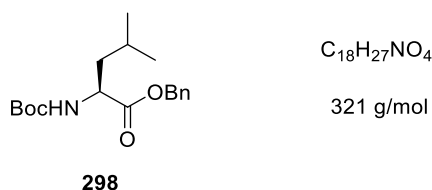
diluted with EtOAc (30 mL), then cooled at 0 °C and acidified with 1 M HCl until pH = 3. The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dry over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give crude *N*-Boc-L-leucine **297** (1.75 g, quant.). It was used in the next step without any purification.

**TLC**  $R_f$  = 0.44 (DCM/MeOH/AcOH, 10:1:0.3)

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.95 (d,  $J$  = 6.3 Hz, 6H, (CH<sub>3</sub>)<sub>2</sub>CH), 1.44 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 1.48-1.82 (m, 3H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>), 4.25-4.36 (m, 1H, CHNH<sub>2</sub>Boc), 4.87 (br d,  $J$  = 8.1 Hz, CHNH<sub>2</sub>Boc)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>289</sup>

### Benzyl *N*-(*tert*-butoxycarbonyl)-L-leucinate, benzyl *N*-Boc-L-leucinate (**298**).



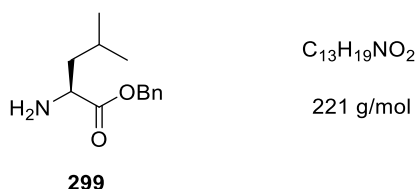
According to a literature procedure,<sup>290</sup> *N*-Boc-L-leucine **297** (1.0 g, 5.9 mmol) was dissolved in dry DCM (100 mL). After cooling at 0 °C, benzyl alcohol (1.5 mL, 14.4 mmol), DMAP (56 mg, 0.5 mmol) and DCC (1.14 g, 5.5 mmol) were successively added. The mixture was stirred under argon for 1 hour at 0 °C, then for 24 hours at room temperature. After filtration of DCU and evaporation of the filtrate, EtOAc (30 mL) was added and the organic phase was washed successively with brine (20 mL), 1 M HCl (20 mL), brine (20 mL), 5 % aqueous NaHCO<sub>3</sub> (20 mL) and brine (20 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Flash column chromatography (pentane/EtOAc, 8:1) gave benzyl *N*-Boc-L-leucinate **298** (1.37 g, 99%), as a colorless oil.

**TLC**  $R_f$  = 0.40 (pentane/EtOAc, 5 :1)

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.91 (d,  $J$  = 6.4 Hz, 3H, CH<sub>3</sub>CH), 0.93 (d,  $J$  = 6.4 Hz, 3H, CH<sub>3</sub>CH), 1.43 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 1.45-1.74 (m, 3H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>), 4.28-4.41 (m, 1H, CHNH<sub>2</sub>Boc), 4.89 (d,  $J$  = 9.2 Hz, 1H, CHNH<sub>2</sub>Boc), 5.12 (d,  $J$  = 12.4 Hz, 1H) and 5.19 (d,  $J$  = 12.4 Hz, 1H) (AB syst., OCH<sub>2</sub>Ph), 7.27-7.48 (m, 5H, Ph)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>291</sup>

### Benzyl L-leucinate, H-Leu-OBn (**299**).



Benzyl *N*-Boc-L-leucinate **298** (1.37 g, 4.3 mmol) was dissolved in DCM (10 mL) and the solution was cooled down to 0 °C. TFA (6.5 mL, 85.6 mmol) was added, and the reaction mixture was stirred for 1 hour at room temperature. After concentration under reduced pressure, traces of TFA were co-evaporated with DCM (3 x 20 mL). The resulting crude product was dissolved in DCM (30 mL) and NEt<sub>3</sub>

(5.6 mL, 41.0 mmol) was added, and the reaction mixture was stirred for 1 hour at room temperature. After addition of water (10 mL), the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (pentane/EtOAc, 7:1 then 5:1) to give benzyl L-leucinate **299** (682 mg, 72%), as a yellow oil.

**TLC**  $R_f$  = 0.10 (pentane/EtOAc, 5 :1)

**OR**  $[\alpha]_D^{20}$  = +5.7 (*c* 1.0, CHCl<sub>3</sub>), lit.<sup>292</sup>  $[\alpha]_D^{25}$  = +5.6 (*c* 1.0, CHCl<sub>3</sub>)

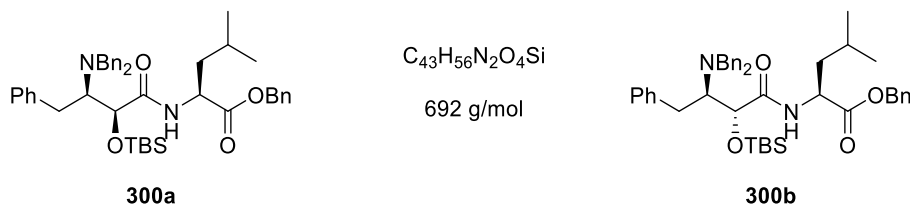
**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 0.90 (d, *J* = 6.9 Hz, 3H, CH<sub>2</sub>CHCH<sub>3</sub>), 0.92 (d, *J* = 6.4 Hz, 3H, CH<sub>2</sub>CHCH<sub>3</sub>), 1.39-1.50 (m, 1H) and 1.51-1.64 (m, 1H) (AB syst., CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.70-1.84 (m, 1H, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.92 (br s, 2H, NH<sub>2</sub>), 3.52 (dd, *J* = 8.7, 5.5 Hz, 1H, CHNH<sub>2</sub>), 5.15 (s, 2H, OCH<sub>2</sub>Ph), 7.31-7.38 (m, 5H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 21.7 (CH<sub>2</sub>CHCH<sub>3</sub>), 22.9 (CH<sub>2</sub>CHCH<sub>3</sub>), 24.6 (CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 43.9 (CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 52.8 (CHNH<sub>2</sub>), 66.4 (OCH<sub>2</sub>Ph), 128.1 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 135.7 (C<sub>Ph</sub>), 176.4 (CO<sub>2</sub>Bn)

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>242</sup>

#### MAC reaction.

**Benzyl ((2*S*,3*R*)- and (2*R*,3*R*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-L-leucinate (**300a** and **300b**).**



According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-D-phenylalaninal **D-13** (71 mg, 0.21 mol), H-MAC-TBS **148g** (98 mg, 0.50 mmol), DMAP (51 mg, 0.42 mmol) and previously prepared benzyl-L-Leucinate **299** (557 mg, 0.26 mmol), in Et<sub>2</sub>O (2 mL). A 14:86 ratio of the (2*S*,3*R*,*S*)- and (2*R*,3*R*,*S*)-diastereomers **300a/300b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/Et<sub>2</sub>O, 10:1) gave inseparable MAC reaction products **300a,b** (dr 14:86, 52 mg, 36%).

**TLC**  $R_f$  = 0.27 (pentane/Et<sub>2</sub>O, 10:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3413, 3063, 3028, 2955, 2928, 2857, 1739, 1673, 1603, 1507, 1495, 1454, 1365, 1254, 1184, 1152, 1094

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>43</sub>H<sub>57</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 693.4082; found 693.4051

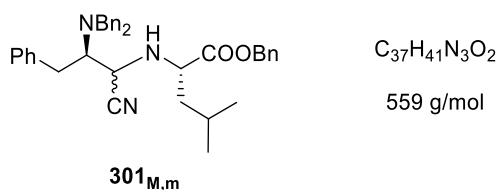
*Spectroscopic data for the major anti (2*R*,3*R*,*S*)-diastereomer (**300b**):*

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.04 (s, 3H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.07 (s, 3H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.90 (dd, *J* = 9.0, 5.8 Hz, 6H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.94 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.24-1.36 (m, 1H) and 1.40-1.52 (m, 1H) (AB part of ABX syst., CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.40-1.52 (m, 1H, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2.95 (dd, *J* = 14.0, 6.8 Hz, 1H) and 3.01 (dd, *J* = 14.0, 8.3 Hz, 1H)(AB part of ABX syst., PhCH<sub>2</sub>CH), 3.36 (ddd, *J* = 8.3, 6.8, 2.2 Hz, 1H, CHNBn<sub>2</sub>), 3.68 (d, *J* = 14.0 Hz,

2H) and 3.83 (d,  $J = 14.0$  Hz, 2H)(AB syst.,  $N(CH_2Ph)_2$ ), 4.47 – 4.61 (m, 1H,  $NHCHCH_2$ ), 4.54 (d,  $J = 2.2$  Hz, 1H,  $CHOTBS$ ), 5.03 (d,  $J = 12.2$  Hz, 2H) and 5.07 (d,  $J = 12.2$  Hz, 2H)(AB part of ABX syst.,  $OCH_2Ph$ ), 6.94 (d,  $J = 8.3$  Hz, 1H,  $CONH$ ), 7.01-7.07 (m, 2H, Ph), 7.08-7.27 (m, 15H, Ph), 7.27-7.32 (m, 3H, Ph)

$^{13}C$  NMR (75.5 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : -4.8 ( $SiCH_3$ ), -4.3 ( $SiCH_3$ ), 18.0 ( $SiC(CH_3)_3$ ), 22.3 ( $CHCH_3$ ), 22.4 ( $CHCH_3$ ), 24.8 ( $CHCH_3$ ), 25.9 ( $SiC(CH_3)_3$ ), 32.4 ( $PhCH_2C$ ), 42.4 ( $CH_2CHC(CH_3)_2$ ), 50.6 ( $NHCHCOO$ ), 54.3 ( $N(CH_2Ph)_2$ ), 63.8 ( $CHNBn_2$ ), 67.0 ( $COOCH_2Ph$ ), 72.4 ( $CHOTBS$ ), 125.7 ( $CH_{Ph}$ ), 126.6 ( $CH_{Ph}$ ), 127.9 ( $CH_{Ph}$ ), 128.0 ( $CH_{Ph}$ ), 128.2 ( $CH_{Ph}$ ), 128.3 ( $CH_{Ph}$ ), 128.5 ( $CH_{Ph}$ ), 128.6 ( $CH_{Ph}$ ), 129.7 ( $CH_{Ph}$ ), 135.1 ( $C_{Ph}$ ), 139.7 ( $C_{Ph}$ ), 139.8 ( $C_{Ph}$ ), 172.0 ( $COOBn$ ), 172.8 ( $CONH$ )

### Benzyl ((1*S*,2*R*) and (1*R*,2*R*)-1-cyano-2-(dibenzylamino)-3-phenylpropyl)-L-leucinate (**301**<sub>M,m</sub>).



$\alpha$ -Amino nitrile **301**<sub>M,m</sub> was observed in the MAC reaction of *N,N*-dibenzyl-D-phenylalaninal **D-13** (132 mg, 0.40 mol), H-MAC-TBS **148g** (189 mg, 0.96 mmol), benzyl-L-Leucinate **299** (106 mg, 0.48 mmol) and DMAP (98 mg, 0.80 mol) in  $Et_2O$  (4 mL), according to the general procedure B.  $\alpha$ -Amino nitrile **301**<sub>M,m</sub> (dr 55:45, 28 mg, 13%) has been isolated as a yellow oil next to the MAC reaction products **300a,b** (dr 14:86, 67 mg, 30%) during the flash column chromatography (pentane/ $Et_2O$ , 20:1). The 55:45 ratio of **301**<sub>M,m</sub> was determined by  $^1H$  NMR analysis ( $CDCl_3$  at 293 K) by integration of the  $N(CH_2Ph)_2$  signals. Identification of the major (M) and the minor (m) diastereomers was not achieved.

TLC  $R_f = 0.63$  (pentane/ $Et_2O$ , 5:1)

HRMS ( $ES^+$ ): calcd. for  $C_{37}H_{42}N_3O_2$   $[M+H]^+$  560.3272; found 560.3249

Spectroscopic data for the 55/45 mixture of diastereomers **301**<sub>M</sub> and **301**<sub>m</sub>:

$^1H$  NMR (360 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : 0.71 (d,  $J = 6.5$  Hz, 1.35H,  $(CHCH_3)_m$ ), 0.78 (d,  $J = 6.1$  Hz, 1.65H,  $(CHCH_3)_M$ ), 0.88 (d,  $J = 6.5$  Hz, 1.35H,  $(CHCH_3)_m$ ), 0.89 (d,  $J = 6.1$  Hz, 1.65H,  $(CHCH_3)_M$ ), 1.40-1.44 (m, 1H,  $(CH(CH_3)_{2M+m})$ ), 1.44-1.62 (m, 2H,  $(CH_2CH(CH_3)_{2M+m})$ ), 1.96 (br s, 1H,  $NH_{M+m}$ ), 2.96-3.01 (m, 0.55H) and 3.15-3.20 (m, 0.55H) (AB part of ABX syst.,  $(PhCH_2CH)_M$ ), 3.05-3.13 (m, 0.90H,  $(PhCH_2CH)_m$ ), 3.20-3.34 (m, 2H,  $(CHNBn_2)_{M+m} + (NHCHCOO)_{M+m}$ ), 3.52 (d,  $J = 13.3$  Hz, 0.55H) and 4.13 (d,  $J = 13.3$  Hz, 0.55H) (AB syst.,  $(N(CH_2Ph)_2)_M$ ), 3.61 (s, 0.90H,  $N(CH_2Ph)_2_m$ ), 3.58-3.67 (m, 0.45H,  $(CHCN)_m$ ), 3.86 (br d,  $J = 6.1$  Hz, 0.55H,  $(CHCN)_M$ ), 5.15 (d,  $J = 12.1$  Hz, 0.55H) and 5.26 (d,  $J = 12.1$  Hz, 0.55H) (AB syst.,  $OCH_2Ph_M$ ), 5.17 (s, 0.90H,  $OCH_2Ph_m$ ), 7.11-7.42 (m, 20H,  $Ph_{M+m}$ )

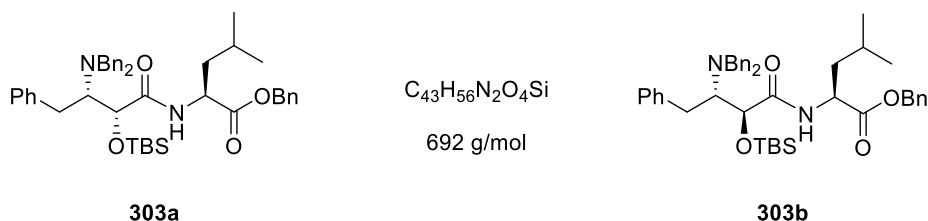
$^{13}C$  NMR (90.6 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : 21.6 ( $CHCH_3$ )<sub>m</sub>, 22.3 ( $CHCH_3$ )<sub>m</sub>, 22.5 ( $CHCH_3$ )<sub>M</sub>, 22.9 ( $CHCH_3$ )<sub>M</sub>, 24.4 ( $CHCH_3$ )<sub>M</sub>, 24.6 ( $CHCH_3$ )<sub>m</sub>, 32.0 ( $PhCH_2CH$ )<sub>M</sub>, 34.3 ( $PhCH_2CH$ )<sub>m</sub>, 42.1 ( $CH_2CH(CH_3)_2$ )<sub>m</sub>, 42.9 ( $CH_2CH(CH_3)_2$ )<sub>M</sub>, 50.0 ( $CHCN$ )<sub>M</sub>, 50.3 ( $(CHCN)_m$ ), 53.6 ( $N(CH_2Ph)_2$ )<sub>m</sub>, 54.8 ( $N(CH_2Ph)_2$ )<sub>M</sub>, 57.0 ( $NHCHCOO$ )<sub>M</sub>, 58.3 ( $NHCHCOO$ )<sub>m</sub>, 61.8 ( $CHNBn_2$ )<sub>m</sub>, 61.9 ( $CHNBn_2$ )<sub>M</sub>, 66.6 ( $OCH_2Ph$ )<sub>M+m</sub>, 119.4 ( $CN$ )<sub>M</sub>, 119.4 ( $CN$ )<sub>m</sub>, 126.5 ( $CH_{Ph}$ )<sub>m</sub>, 126.5 ( $CH_{Ph}$ )<sub>M</sub>, 127.1 ( $CH_{Ph}$ )<sub>m</sub>, 127.2 ( $CH_{Ph}$ )<sub>M</sub>, 128.2 ( $CH_{Ph}$ )<sub>M</sub>, 128.3 ( $CH_{Ph}$ )<sub>m</sub>, 128.3 ( $CH_{Ph}$ )<sub>m</sub>, 128.4 ( $CH_{Ph}$ )<sub>M</sub>, 128.4 ( $CH_{Ph}$ )<sub>m</sub>, 128.5 ( $CH_{Ph}$ )<sub>M</sub>, 128.5 ( $CH_{Ph}$ )<sub>M</sub>, 128.6 ( $CH_{Ph}$ )<sub>m</sub>, 128.8 ( $CH_{Ph}$ )<sub>m</sub>, 128.8 ( $CH_{Ph}$ )<sub>M</sub>, 128.9

(CH<sub>Ph</sub>)<sub>M</sub>, 129.1 (CH<sub>Ph</sub>)<sub>m</sub>, 129.3 (CH<sub>Ph</sub>)<sub>M</sub>, 129.6 (CH<sub>Ph</sub>)<sub>m</sub>, 135.6 (C<sub>Ph</sub>)<sub>M</sub>, 135.6 (C<sub>Ph</sub>)<sub>m</sub>, 138.3 (C<sub>Ph</sub>)<sub>m</sub>, 138.6 (C<sub>Ph</sub>)<sub>M</sub>, 138.7 (C<sub>Ph</sub>)<sub>M</sub>, 138.8 (C<sub>Ph</sub>)<sub>m</sub>, 174.5 (COOBn)<sub>m</sub>, 174.8 (COOBn)<sub>M</sub>

## Towards the synthesis of (2*S*,3*S*,*S*)-epibestatin

### MAC reaction.

**Benzyl ((2*R*,3*S*)- and (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoyl)-L-leucinate (303a and 303b).**



According to the general procedure C, the MAC reaction was performed with *N,N*-dibenzyl-L-phenylalaninal **L-13** (101 mg, 0.31 mmol), H-MAC-TBS **148g** (145 mg, 0.74 mmol), DMAP (76 mg, 0.62 mmol) and L-leucine benzyl ester **299** (80  $\mu$ L, 0.37 mmol), in Et<sub>2</sub>O (3 mL). A 11:89 ratio of the (2*R*,3*S*,*S*)- and (2*S*,3*S*,*S*)-diastereomers **303a/303b** was determined by <sup>1</sup>H NMR analysis (CDCl<sub>3</sub> at 293 K) by integration of the Me groups of the TBS signals. Flash column chromatography (pentane/Et<sub>2</sub>O/DCM, 10:1:1 then pentane/Et<sub>2</sub>O, 10:1) gave inseparable MAC reaction products **303a,b** (dr 12:88, 183 mg, 85%), as a pale-yellow oil.

**TLC** *R<sub>f</sub>* = 0.33 (pentane/Et<sub>2</sub>O/DCM, 10:1:1)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3423, 3063, 3027, 2956, 2928, 2857, 1741, 1673, 1601, 1494, 1454, 1367, 1254, 1184, 1150, 1093

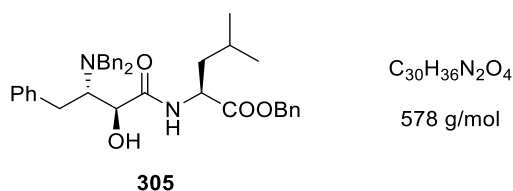
**HRMS** (ES<sup>+</sup>): calcd. for C<sub>43</sub>H<sub>57</sub>N<sub>2</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> 693.4082; found 693.4050

*Spectroscopic data for the major anti (2*S*,3*S*,*S*)-diastereomer (303b):*

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.08 (s, 3H, SiCH<sub>3</sub>), 0.00 (s, 3H, SiCH<sub>3</sub>), 0.76 (d, *J* = 6.0 Hz, 3H, NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 0.78 (d, *J* = 6.4 Hz, 3H, NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 0.92 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.24-1.36 (m, 1H) and 1.41-1.51 (m, 1H) (AB syst., NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 1.41-1.51 (m, 1H, NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 3.00 (dd, *J* = 14.4, 7.6 Hz, 1H) and 3.03 (dd, *J* = 14.4, 8.0 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.36 (ddd, *J* = 8.0, 7.6, 2.4 Hz, 1H, CHNBn<sub>2</sub>), 3.72 (d, *J* = 14.2 Hz, 2H) and 3.81 (d, *J* = 14.2 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.42 (d, *J* = 2.4 Hz, 1H, CHOTBS), 4.42-4.52 (m, 1H, NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 5.15 (s, 2H, OCH<sub>2</sub>Ph), 6.84 (br d, *J* = 8.4 Hz, 1H, CONH), 7.09-7.12 (m, 2H, Ph), 7.15-7.23 (m, 13H, Ph), 7.31-7.37 (m, 5H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.2 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 18.0 (SiC(CH<sub>3</sub>)<sub>3</sub>), 22.1 (NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 22.3 (NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 24.8 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 32.0 (PhCH<sub>2</sub>CH), 41.4 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 50.7 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 64.1 (CHNBn<sub>2</sub>), 66.9 (OCH<sub>2</sub>Ph), 72.1 (CHOTBS), 125.9 (CH<sub>Ph</sub>), 126.7 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.3 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.7 (CH<sub>Ph</sub>), 135.4 (C<sub>Ph</sub>), 139.7 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 172.2 (CO<sub>2</sub>Bn), 172.9 (CONH)



**Benzyl ((2S,3S)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoyl)-L-leucinate (305).**

To a stirred solution of MAC products **303a,b** (dr 12:88, 69 mg, 0.10 mmol) in dry THF (3 mL) at 0 °C under argon, was added dropwise TBAF (1 M in THF, 150  $\mu$ L, 0.15 mmol). After stirring for 4 hours at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous  $NH_4Cl$  solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/EtOAc, 10:1 then 5:1 and 3:1) to furnish the *anti*-alcohol **305** (51 mg, 88%), as a colorless oil.

**TLC**  $R_f$  = 0.27 (pentane/EtOAc, 3:1)

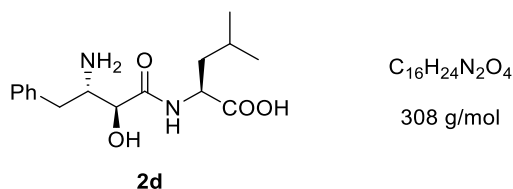
**OR**  $[\alpha]_D^{24} = -19.0$  (c 1.0,  $CHCl_3$ )

**IR** (ATR),  $\nu$  ( $cm^{-1}$ ): 3396 (br), 3062, 3027, 2959, 2871, 2805, 1740, 1673, 1654, 1603, 1515, 1496, 1454, 1367, 1271, 1194, 1153

**HRMS** ( $ES^+$ ): calcd. for  $C_{37}H_{43}N_2O_4$   $[M+H]^+$  579.3217; found 579.3192

**$^1H$  NMR** (360 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : 0.64 (d,  $J$  = 5.8 Hz, 3H,  $NCH(CH_2CHCH_3)$ ), 0.66 (d,  $J$  = 6.1 Hz, 3H,  $NCH(CH_2CHCH_3)$ ), 1.27-1.39 (m, 1H,  $NCH(CH_2CH(CH_3)_2)$ ), 1.27-1.39 (m, 1H) and 1.40-1.51 (m, 1H) (AB syst.,  $NCH(CH_2CH(CH_3)_2)$ ), 3.07-3.17 (m, 1H) and 3.26-3.40 (m, 1H) (AB part of ABX syst.,  $PhCH_2CH$ ), 3.26-3.40 (m, 1H,  $CHNBn_2$ ), 3.59 (d,  $J$  = 13.7 Hz, 2H) and 3.79 (d,  $J$  = 13.7 Hz, 3H) (AB syst.,  $N(CH_2Ph)_2$ , OH), 3.89-3.95 (m, 1H,  $CHOH$ ), 4.52 (ddd,  $J$  = 8.6, 8.3, 5.8 Hz, 1H,  $NCH(CH_2CH(CH_3)_2)$ ), 5.10 (d,  $J$  = 12.2 Hz, 1H) and 5.15 (d,  $J$  = 12.2 Hz, 1H) (AB syst.,  $OCH_2Ph$ ), 7.19-7.37 (m, 21H, Ph, CONH)

**$^{13}C$  NMR** (100.6 MHz,  $CDCl_3$ ),  $\delta$  (ppm) : 21.5 ( $NCH(CH_2CHCH_3)$ ), 22.4 ( $NCH(CH_2CHCH_3)$ ), 24.6 ( $NCH(CH_2CH(CH_3)_2)$ ), 30.3 ( $PhCH_2CH$ ), 41.1 ( $NCH(CH_2CH(CH_3)_2)$ ), 50.5 ( $NCH(CH_2CH(CH_3)_2)$ ), 54.8 ( $N(CH_2Ph)_2$ ), 63.3 ( $CHNBn_2$ ), 66.9 ( $OCH_2Ph$ ), 68.6 ( $CHOH$ ), 126.1 ( $CH_{Ph}$ ), 127.4 ( $CH_{Ph}$ ), 128.1 ( $CH_{Ph}$ ), 128.3 ( $CH_{Ph}$ ), 128.6 ( $CH_{Ph}$ ), 128.7 ( $CH_{Ph}$ ), 129.6 ( $CH_{Ph}$ ), 135.4 ( $C_{Ph}$ ), 138.9 ( $C_{Ph}$ ), 139.5 ( $C_{Ph}$ ), 172.3 ( $CO_2Bn$ ), 173.4 (CONH)

**((2S,3S)-3-Amino-2-hydroxy-4-phenylbutanoyl)-L-leucine, (2S,3S,S)-epibestatin (2d).**

Palladium hydroxide (20 wt.%) on activated carbon (12 mg) was added to a solution of benzyl ((2S,3S)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoyl)-L-leucinate **305** (118 mg, 0.20 mmol) in MeOH (8 mL). The resulting mixture was stirred under  $H_2$  (1 atm pressure) for 2 hours at room temperature and then filtered through a short pad of Celite which was washed through with further MeOH. The combined filtrates were concentrated under reduced pressure and dried under high vacuum to furnish (2S,3S,S)-

epibestatin **2d** (61 mg, 99%), as a very sticky colorless oil, which precipitated in pentane as a white solid.

**Mp** = 208 °C (dec.)

**TLC**  $R_f$  = 0.73 (MeOH)

**OR**  $[\alpha]_D^{24} = -34.5$  (c 1.0, H<sub>2</sub>O) and  $[\alpha]_D^{26} = -28.2$  (c 1.0, MeOH) and  $[\alpha]_D^{23} = -29.7$  (c 1.0, AcOH)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3340, 3206, 3061, 2955, 2928, 2863, 1663, 1587, 1548, 1455, 1398, 1378, 1258, 1110, 1069

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>16</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup> 309.1809; found 309.1803

**HRMS** (ES<sup>-</sup>): calcd. for C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub> [M-H]<sup>-</sup> 307.1663; found 307.1649

**<sup>1</sup>H NMR** (400 MHz, D<sub>2</sub>O),  $\delta$  (ppm) : 0.91 (d,  $J$  = 5.6 Hz, 3H, NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 0.93 (d,  $J$  = 5.6 Hz, 3H, NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 1.53-1.75 (m, 3H, NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 2.68 (dd,  $J$  = 14.0, 10.4 Hz, 1H) and 2.82 (dd,  $J$  = 14.0, 3.6 Hz, 1H) (AB part of ABX syst., PhCH<sub>2</sub>CH), 3.54-3.60 (m, 1H, CHNH<sub>2</sub>), 4.26-4.31 (m, 1H, NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 4.37 (br d,  $J$  = 3.2 Hz, 1H, CHOH), 7.26-7.48 (m, 5H, Ph)

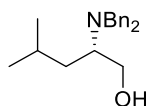
**<sup>13</sup>C NMR** (100.6 MHz, D<sub>2</sub>O),  $\delta$  (ppm) : 20.8 (NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 22.4 (NCH(CH<sub>2</sub>CHCH<sub>3</sub>)), 24.7 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 35.5 (PhCH<sub>2</sub>CH), 40.6 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 53.5 (NCH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)), 54.5 (CHNH<sub>2</sub>), 73.7 (CHOH), 127.0 (CH<sub>Ph</sub>), 128.9 (CH<sub>Ph</sub>), 129.4 (CH<sub>Ph</sub>), 137.7 (C<sub>Ph</sub>), 173.3 (CONH), 179.6 (COOH)

## Chapter 4: MAC reactions on various *N,N*-dibenzyl-L- $\alpha$ -amino aldehydes

### From L-leucinal

#### *N,N*-Dibenzyl-L-leucinal's synthesis.

##### *N,N*-Dibenzyl-L-leucinol (L-309).



L-309

C<sub>20</sub>H<sub>27</sub>NO

297 g/mol

According to the general method, commercially available L-leucinol **L-308** (2.0 g, 17.06 mmol) was *N,N*-dibenzylated with K<sub>2</sub>CO<sub>3</sub> (5.2 g, 37.62 mmol), BnBr (4.5 mL, 37.88 mmol) in CH<sub>3</sub>CN (30 mL). The crude residue was purified by column chromatography (pentane/EtOAc, 10:1 then 5:1 then 3:1) to give *N,N*-dibenzyl-L-Leucinol **L-309** (4.13 g, 82%) as a turbid pale yellow oil.

TLC R<sub>f</sub> = 0.63 (pentane/EtOAc, 5:1)

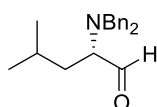
OR [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +79.5 (c 1.0, CHCl<sub>3</sub>), lit.<sup>251</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +86.4 (c 1.0, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.86 (d, *J* = 6.0 Hz, 3H, CH<sub>3</sub>CH), 0.93 (d, *J* = 6.0 Hz, 3H, CH<sub>3</sub>CH), 1.11-1.22 (m, 1H) and 1.46-1.58 (m, 1H) (AB syst., (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 1.46-1.58 (m, 1H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 2.85 (dddd, *J* = 11.2, 9.6, 4.8, 2.0 Hz, 1H, CHNBn<sub>2</sub>), 3.25 (br s, 1H, OH), 3.37 (d, *J* = 13.2 Hz, 2H) and 3.81 (d, *J* = 13.2 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.40-3.52 (m, 2H, CH<sub>2</sub>OH), 7.16-7.42 (m, 10H, Ph)

<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 22.0 (CH<sub>3</sub>CH), 24.1 (CH<sub>3</sub>CH), 25.4 ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 33.9 ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 53.0 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 56.8 (CHNBn<sub>2</sub>), 61.0 (CH<sub>2</sub>OH), 127.2 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 129.0 (CH<sub>Ph</sub>), 139.4 (C<sub>Ph</sub>)

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>251</sup>

##### *N,N*-Dibenzyl-L-leucinal (L-310).



L-310

C<sub>20</sub>H<sub>25</sub>NO

295 g/mol

According to the general procedure, Swern oxidation of *N,N*-dibenzyl-L-leucinol **L-309** (927 mg, 3.12 mmol) was performed with DMSO (660  $\mu$ L, 9.10 mmol), oxalyl chloride (430  $\mu$ L, 4.30 mmol) in DCM (20 mL), followed by the addition of NEt<sub>3</sub> (1.1 mL, 7.84 mmol). Crude *N,N*-dibenzyl-L-leucinal **L-310** (814 mg, 88%) was isolated as a viscous yellow liquid. It was used without any purification in the MAC reaction.

TLC R<sub>f</sub> = 0.62 (pentane/EtOAc, 10:1)

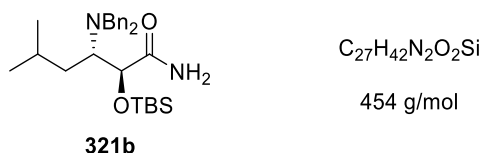
OR [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -63.6 (c 1.0, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ (ppm) : 0.78 (d, *J* = 6.3 Hz, 3H, CH<sub>3</sub>CH), 0.82 (d, *J* = 6.0 Hz, 3H, CH<sub>3</sub>CH), 1.44-1.55 (m, 1H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 1.55-1.80 (m, 2H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 3.22 (t, *J* = 6.9 Hz, 1H, CHNBn<sub>2</sub>), 3.70 (d, *J* = 14.0 Hz, 2H) and 3.79 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 7.20-7.47 (m, 10H, Ph), 9.75 (s, 1H, CHO)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>192</sup>

### MAC reactions.

#### (2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)-5-methylhexanamide (**321b**).



According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-leucinal **L-310** (94 mg, 0.32 mmol), H-MAC-TBS **148g** (150 mg, 0.76 mmol), ammonia (0.5 M in THF, 1.7 mL, 0.85 mmol) and DMAP (70.3 mg, 0.63 mmol) in Et<sub>2</sub>O (3 mL). Flash column chromatography (pentane/Et<sub>2</sub>O/DCM, 5:1:1) gave the MAC reaction product **321b** (dr <2:98, 84 mg, 58%), as a yellow oil.

TLC *R<sub>f</sub>* = 0.24 (pentane/Et<sub>2</sub>O/DCM, 5:1:1)

OR [α]<sub>D</sub><sup>24</sup> = -41.4 (c 1.0, CHCl<sub>3</sub>)

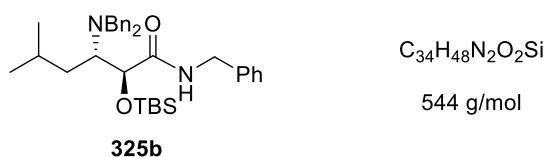
IR (ATR), ν (cm<sup>-1</sup>): 3482, 3282, 3063, 3028, 2953, 2929, 2858, 1687, 1585, 1494, 1454, 1385, 1361, 1254, 1089, 1073

HRMS (ES<sup>+</sup>): calcd. for C<sub>27</sub>H<sub>43</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 455.3088; found 455.3079

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ (ppm) : 0.12 (s, 3H, SiCH<sub>3</sub>), 0.20 (s, 3H, SiCH<sub>3</sub>), 0.49 (d, *J* = 6.4 Hz, 3H, CH<sub>3</sub>CHCH<sub>2</sub>CH), 0.85 (d, *J* = 6.4 Hz, 3H, CH<sub>3</sub>CHCH<sub>2</sub>CH), 0.95 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.15 (ddd, *J* = 14.0, 9.2, 4.4 Hz, 1H) and 1.68 (ddd, *J* = 14.0, 9.2, 4.4 Hz, 1H) (AB syst., (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 1.77-1.91 (m, 1H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 2.98 (td, *J* = 9.2, 3.2 Hz, 1H, CHNBn<sub>2</sub>), 3.61 (d, *J* = 14.0 Hz, 2H) and 3.83 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.49 (d, *J* = 3.2 Hz, 1H, CHOTBS), 6.12 (br s, 1H, CONH), 6.22 (br s, 1H, CONH), 7.15-7.25 (m, 2H, Ph), 7.25-7.33 (m, 4H, Ph), 7.33-7.42 (m, 4H, Ph)

<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -4.7 (SiCH<sub>3</sub>), -4.5 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 21.5 (CH<sub>3</sub>CHCH<sub>2</sub>CH), 23.7 (CH<sub>3</sub>CHCH<sub>2</sub>CH), 24.4 ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 36.0 ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 54.2 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 59.3 (CHNBn<sub>2</sub>), 73.4 (CHOTBS), 126.7 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 129.1 (CH<sub>Ph</sub>), 140.1 (C<sub>Ph</sub>), 176.8 (CONH)

#### (2*S*,3*S*)-*N*-Benzyl-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-5-methylhexanamide (**325b**).



According to the general procedure B, the MAC reaction was performed with *N,N*-dibenzyl-L-leucinal **L-13** (141 mg, 0.48 mmol), H-MAC-TBS **148g** (226 mg, 1.15 mmol), benzylamine (65 μL, 0.58 mmol) and

DMAP (117 mg, 0.96 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 10:1 then 5:1) gave the MAC reaction product **325b** (dr <2:98, 173 mg, 66 %), as a yellow oil.

**TLC**  $R_f$  = 0.47 (pentane/Et<sub>2</sub>O, 5:1)

**OR**  $[\alpha]_D^{24} = -54.4$  (c 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3435, 3063, 3029, 2954, 2931, 2859, 2805, 1677, 1604, 1512, 1496, 1454, 1364, 1255, 1088, 1071

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>34</sub>H<sub>49</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 545.3558; found 545.3540

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.05 (s, 3H, SiCH<sub>3</sub>), 0.13 (s, 3H, SiCH<sub>3</sub>), 0.48 (d,  $J$  = 6.4 Hz, 3H, CH<sub>3</sub>CHCH<sub>2</sub>CH), 0.81 (d,  $J$  = 6.8 Hz, 3H, CH<sub>3</sub>CHCH<sub>2</sub>CH), 0.83 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.12 (ddd,  $J$  = 14.0, 8.8, 4.8 Hz, 1H) and 1.61 (ddd,  $J$  = 14.0, 8.8, 4.8 Hz, 1H) (AB syst., (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 1.72-1.84 (m, 1H, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 3.00-3.04 (m, 1H, CHNBn<sub>2</sub>), 3.60 (d,  $J$  = 14.0 Hz, 2H) and 3.81 (d,  $J$  = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.26 (dd,  $J$  = 14.4, 5.6 Hz, 1H) and 4.42 (dd,  $J$  = 14.4, 6.4 Hz, 1H) (AB part of ABX syst., NHCH<sub>2</sub>Ph), 4.53 (d,  $J$  = 3.2 Hz, 1H, CHOTBS), 6.48 (br dd,  $J$  = 6.4, 5.6 Hz, 1H, CONH), 7.16-7.32 (m, 11H, Ph), 7.33-7.38 (m, 4H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -4.8 (SiCH<sub>3</sub>), -4.4 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 21.6 (CH<sub>3</sub>CHCH<sub>2</sub>CH), 23.6 (CH<sub>3</sub>CHCH<sub>2</sub>CH), 24.4 ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 35.7 ((CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH), 43.2 (NHCH<sub>2</sub>Ph), 54.3 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 59.4 (CHNBn<sub>2</sub>), 73.2 (CHOTBS), 126.7 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 128.1 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.6 (CH<sub>Ph</sub>), 129.0 (CH<sub>Ph</sub>), 137.7 (C<sub>Ph</sub>), 140.1 (C<sub>Ph</sub>), 173.1 (CONH)

## From L-valinal

### *N,N*-Dibenzyl-L-valinal's synthesis.

#### *N,N*-Dibenzyl-L-valinol (**L-312**).



**L-312**

According to the general method, commercially available L-valinol **L-311** (2.0 g, 19.39 mmol) was *N,N*-dibenzylated with K<sub>2</sub>CO<sub>3</sub> (5.90 g, 42.66 mmol), BnBr (5.1 mL, 42.66 mmol) in CH<sub>3</sub>CN (20 mL). The crude residue was purified by column chromatography (pentane/EtOAc, 10:1 then 5:1 then 3:1) to give *N,N*-dibenzyl-L-valinol **L-312** (4.18 g, 76%), as a turbid colorless oil.

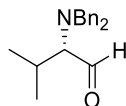
**TLC**  $R_f$  = 0.73 (pentane/EtOAc, 5:1)

**OR**  $[\alpha]_D^{22} = +24.8$  (c 1.0, CHCl<sub>3</sub>), lit.<sup>252</sup>  $[\alpha]_D^{28} = +23.1$  (c 1.0, CHCl<sub>3</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.89 (d,  $J$  = 6.8 Hz, 3H, CH<sub>3</sub>CH), 1.14 (d,  $J$  = 6.8 Hz, 3H, CH<sub>3</sub>CH), 2.06 (dq,  $J$  = 14.0, 6.8 Hz, (CH<sub>3</sub>)<sub>2</sub>CHCH), 2.85 (ddd,  $J$  = 14.0, 10.4, 4.8 Hz, 1H, CHNBn<sub>2</sub>), 3.04 (br s, 1H, OH), 3.44 (dd,  $J$  = 10.4, 10.4 Hz, 1H) and 3.57 (dd,  $J$  = 10.4, 4.8 Hz, 1H) (AB syst., CH<sub>2</sub>OH), 3.68 (d,  $J$  = 13.2 Hz, 2H) and 3.89 (d,  $J$  = 13.2 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 7.21-7.27 (m, 6H, Ph), 7.28-7.34 (m, 4H, Ph)

$^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 20.1 ( $\text{CH}_3\text{CH}$ ), 22.7 ( $\text{CH}_3\text{CH}$ ), 27.6 ( $(\text{CH}_3)_2\text{CHCH}$ ), 54.1 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 59.2 ( $\text{CH}_2\text{OH}$ ), 64.6 ( $\text{CHNBN}_2$ ), 127.1 ( $\text{CH}_{\text{Ph}}$ ), 128.4 ( $\text{CH}_{\text{Ph}}$ ), 129.2 ( $\text{CH}_{\text{Ph}}$ ), 139.6 ( $\text{C}_{\text{Ph}}$ )  
 $^1\text{H}$  and  $^{13}\text{C}$  NMR data were in agreement with those described in literature.<sup>252</sup>

### *N,N*-Dibenzyl-L-valinal (**L-313**).



$\text{C}_{19}\text{H}_{23}\text{NO}$

281 g/mol

**L-313**

According to the general procedure, Swern oxidation of *N,N*-dibenzyl-L-valinol **L-312** (709 mg, 2.50 mmol) was performed with DMSO (465  $\mu\text{L}$ , 6.50 mmol), oxalyl chloride (220  $\mu\text{L}$ , 3.30 mmol) in DCM (6 mL), followed by the addition of  $\text{NEt}_3$  (1.1 mL, 7.84 mmol). Crude *N,N*-dibenzyl-L-valinal **L-313** (557 mg, 79%) was isolated as a pale yellow oil. It was used without any purification in the MAC reaction.

TLC  $R_f$  = 0.59 (pentane/EtOAc, 5:1)

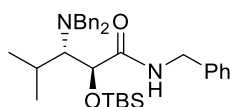
OR  $[\alpha]_{\text{D}}^{27} = -56.0$  ( $c$  1.0,  $\text{CHCl}_3$ ), lit.<sup>252</sup>  $[\alpha]_{\text{D}}^{24} = -63.4$  ( $c$  1.0,  $\text{CHCl}_3$ )

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : 0.87 (d,  $J = 6.6$  Hz, 3H,  $\text{CH}_3\text{CH}$ ), 1.09 (d,  $J = 6.6$  Hz, 3H,  $\text{CH}_3\text{CH}$ ), 1.44-1.55 (m, 1H,  $(\text{CH}_3)_2\text{CHCH}$ ), 3.22 (dd,  $J = 10.2, 3.6$  Hz, 1H,  $\text{CHNBN}_2$ ), 3.71 (d,  $J = 13.8$  Hz, 2H) and 4.03 (d,  $J = 13.8$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 7.20-7.40 (m, 10H, Ph), 9.86 (d,  $J = 3.6$  Hz, 1H, CHO)

$^1\text{H}$  NMR data were in agreement with those described in literature.<sup>252</sup>

### MAC reaction.

#### (2*S*,3*S*)-*N*-Benzyl-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-methylpentanamide (**326b**).



$\text{C}_{33}\text{H}_{46}\text{N}_2\text{O}_2\text{Si}$

530 g/mol

**326b**

According to the general procedure B, the MAC reaction was performed with freshly prepared *N,N*-dibenzyl-L-valinal **L-313** (142 mg, 0.50 mmol), H-MAC-TBS **148g** (236 mg, 1.20 mmol), benzylamine (65  $\mu\text{L}$ , 0.60 mmol) and DMAP (122 mg, 1.00 mmol) in  $\text{Et}_2\text{O}$  (5 mL). Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ /DCM, 10:1:1) gave the MAC reaction product **326b** (dr <2:98, 103 mg, 39 %), as a colorless oil.

According to the general procedure C, the MAC reaction was performed with freshly prepared *N,N*-dibenzyl-L-valinal **L-313** (141 mg, 0.50 mmol), H-MAC-TBS **148g** (236 mg, 1.20 mmol), DMAP (122 mg, 1.00 mmol) and benzylamine (65  $\mu\text{L}$ , 0.60 mmol) in  $\text{Et}_2\text{O}$  (5 mL). Flash column chromatography (pentane/ $\text{Et}_2\text{O}$ , 5:1 then 2:1) gave the MAC reaction product **326b** (dr <2:98, 175 mg, 67 %), as a colorless oil.

TLC  $R_f$  = 0.29 (pentane/ $\text{Et}_2\text{O}$ , 5:1) and 0.59 (pentane/ $\text{Et}_2\text{O}$ , 2:1),

**OR**  $[\alpha]_D^{24} = -48.2$  (*c* 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3441, 3063, 3028, 2953, 2928, 2857, 2802, 1673, 1603, 1510, 1495, 1454, 1362, 1253, 1137, 1094, 1070

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>33</sub>H<sub>47</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 531.3401; found 531.3385

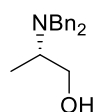
**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.02 (s, 3H, SiCH<sub>3</sub>), 0.16 (s, 3H, SiCH<sub>3</sub>), 0.83 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.87 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>CHCH), 1.00 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>CHCH), 2.22 (octuplet, *J* = 6.8 Hz, 1H, (CH<sub>3</sub>)<sub>2</sub>CHCH), 2.78 (br dd, *J* = 6.8, 2.5 Hz, 1H, CHNBn<sub>2</sub>), 3.63 (d, *J* = 14.0 Hz, 2H) and 3.86 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.24 (dd, *J* = 14.0, 5.0 Hz, 1H) and 4.48 (dd, *J* = 14.0, 5.8 Hz, 1H) (AB part of ABX syst., NHCH<sub>2</sub>Ph), 4.62 (d, *J* = 2.5 Hz, 1H, CHOTBS), 6.53 (br dd, *J* = 5.8, 5.0 Hz, 1H, CONH), 7.16-7.30 (m, 11H, Ph), 7.35-7.43 (m, 4H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -4.5 (SiCH<sub>3</sub>), -4.0 (SiCH<sub>3</sub>), 18.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 21.2 (CH<sub>3</sub>CHCH), 21.6 (CH<sub>3</sub>CHCH), 25.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 27.3 ((CH<sub>3</sub>)<sub>2</sub>CHCH), 43.6 (NHCH<sub>2</sub>Ph), 55.0 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 68.0 (CHNBn<sub>2</sub>), 72.5 (CHOTBS), 126.7 (C<sub>Ph</sub>), 127.7 (C<sub>Ph</sub>), 128.0 (C<sub>Ph</sub>), 128.4 (C<sub>Ph</sub>), 128.7 (C<sub>Ph</sub>), 129.1 (C<sub>Ph</sub>), 137.5 (C<sub>Ph</sub>), 140.0 (C<sub>Ph</sub>), 173.8 (CONH)

## From L-alaninal

### *N,N*-Dibenzyl-L-alaninal's synthesis.

#### *N,N*-Dibenzyl-L-alaninol (**L-315**).



C<sub>17</sub>H<sub>21</sub>NO

255 g/mol

**L-315**

According to the general method, commercially available L-alaninol **L-314** (2.0 g, 26.63 mmol) was *N,N*-dibenzylated with K<sub>2</sub>CO<sub>3</sub> (8.09 g, 58.53 mmol), BnBr (7.0 mL, 58.93 mmol) in CH<sub>3</sub>CN (30 mL). The crude residue was purified by column chromatography (pentane/EtOAc, 10:1 then 5:1 then 3:1) to give *N,N*-dibenzyl-L-alaninol **L-315** (4.95 g, 73%), as a white solid.

**Mp** = 42 °C (lit.<sup>254</sup> 41 °C)

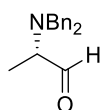
**TLC** R<sub>f</sub> = 0.63 (pentane/EtOAc, 5:1)

**OR**  $[\alpha]_D^{24} = +85.5$  (*c* 1.0, CHCl<sub>3</sub>), lit.<sup>253</sup>  $[\alpha]_D^{26} = +109.0$  (*c* 1.0, CHCl<sub>3</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.98 (d, *J* = 6.4 Hz, 3H, CH<sub>3</sub>CH), 2.94-3.04 (m, 1H, CHNBn<sub>2</sub>), 3.15 (br s, 1H, OH), 3.36 (d, *J* = 13.4 Hz, 2H) and 3.82 (d, *J* = 13.4 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.36 (dd, *J* = 10.4, 5.2 Hz, 1H) and 3.46 (dd, *J* = 10.4, 10.4 Hz, 1H) (AB syst., CH<sub>2</sub>OH), 7.22-7.35 (m, 10H, Ph)

**<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 8.6 (CH<sub>3</sub>CH), 52.9 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 54.1 (CHNBn<sub>2</sub>), 62.7 (CH<sub>2</sub>OH), 127.2 (C<sub>Ph</sub>), 128.5 (C<sub>Ph</sub>), 129.0 (C<sub>Ph</sub>), 139.2 (C<sub>Ph</sub>)

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>253</sup>

***N,N*-Dibenzyl-L-alaninal (L-316).**C<sub>17</sub>H<sub>19</sub>NO

253 g/mol

**L-316**

According to the general procedure, Swern oxidation of *N,N*-dibenzyl-L-alaninol **L-315** (638 mg, 2.50 mmol) was performed with DMSO (460  $\mu$ L, 6.50 mmol), oxalyl chloride (220  $\mu$ L, 3.30 mmol) in DCM (6 mL), followed by the addition of NEt<sub>3</sub> (1.1 mL, 7.84 mmol). Crude *N,N*-dibenzyl-L-alaninal **L-316** (438 mg, 79%) was isolated as a colorless turbid liquid, which turned very quickly into yellow and finally into a dark red oil by standing 1 hour under vacuum). It was used without any purification in the MAC reaction.

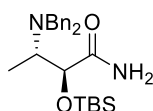
*Note: This aldehyde is very unstable, so both the characterization and the MAC reaction should be done quickly.*

**TLC** R<sub>f</sub> = 0.70 (pentane/EtOAc, 5:1)

**OR** [ $\alpha$ ]<sub>D</sub><sup>27</sup> = -38.7 (c 1.0, CHCl<sub>3</sub>), lit.<sup>293</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -31.9 (c 1.0, CHCl<sub>3</sub>)

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 1.19 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>CH), 3.33 (q, *J* = 6.8 Hz, 1H, CHNBn<sub>2</sub>), 3.56 (d, *J* = 13.7 Hz, 2H) and 3.73 (d, *J* = 13.7 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 7.21-7.28 (m, 2H, Ph), 7.29-7.35 (m, 4H, Ph), 7.37-7.44 (m, 4H, Ph), 9.73 (br s, 1H, CHO)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>293</sup>

**MAC reactions.****(2*S*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-(dibenzylamino)butanamide (323b).**C<sub>24</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>Si

412 g/mol

**323b**

According to the general procedure B, the MAC reaction was performed with freshly prepared *N,N*-dibenzyl-L-alaninal **L-13** (127 mg, 0.50 mmol), H-MAC-TBS **148g** (236 mg, 1.20 mmol), ammonia (0.5 M in THF, 1.2 mL, 0.60 mmol) and DMAP (122 mg, 1.00 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 10:1 then 2:1) gave the MAC reaction product **323b** (dr <2:98, 103 mg, 50 %), as a yellow oil.

According to the general procedure C, the MAC reaction was performed with freshly prepared *N,N*-dibenzyl-L-alaninal **L-13** (127 mg, 0.50 mmol), H-MAC-TBS **148g** (236 mg, 1.20 mmol), DMAP (122 mg, 1.00 mmol) and ammonia (0.5 M in THF, 1.2 mL, 0.60 mmol) in Et<sub>2</sub>O (5 mL). Flash column chromatography (pentane/Et<sub>2</sub>O, 10:1 then 2:1) gave the MAC reaction product **323b** (dr <2:98, 127 mg, 61 %), as a yellow oil.

**TLC** R<sub>f</sub> = 0.19 (pentane/Et<sub>2</sub>O, 2:1)



**OR**  $[\alpha]_D^{24} = +1.7$  (*c* 1.0, CHCl<sub>3</sub>)

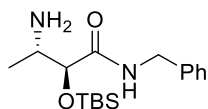
**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3482, 3065, 3026, 2955, 2929, 2857, 1685, 1588, 1587, 1494, 1454, 1385, 1362, 1254, 1080, 1029

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>24</sub>H<sub>37</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 413.2619; found 413.2607

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.08 (s, 3H, SiCH<sub>3</sub>), 0.10 (s, 3H, SiCH<sub>3</sub>), 0.89 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.16 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>CH), 3.00 (quintet, *J* = 6.8 Hz, 1H, CHNBn<sub>2</sub>), 3.50 (d, *J* = 13.8 Hz, 2H) and 3.79 (d, *J* = 13.8 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.18 (d, *J* = 6.8 Hz, 1H, CHOTBS), 5.32 (s, 1H, CONH), 5.89 (s, 1H, CONH), 7.16-7.22 (m, 2H, Ph), 7.24-7.31 (m, 4H, Ph), 7.37-7.42 (m, 4H, Ph)

**<sup>13</sup>C NMR** (90.6 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.0 (SiCH<sub>3</sub>), -5.0 (SiCH<sub>3</sub>), 9.8 (CH<sub>3</sub>CH), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 54.1 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 57.5 (CHNBn<sub>2</sub>), 76.3 (CHOTBS), 126.7 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 139.8 (C<sub>Ph</sub>), 176.2 (CONH)

**(2S,3S)-N-Benzyl-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)butanamide (327b).**



C<sub>31</sub>H<sub>42</sub>N<sub>2</sub>O<sub>2</sub>Si

502 g/mol

**327b**

According to the general procedure B, the MAC reaction was performed with freshly prepared *N,N*-dibenzyl-L-alaninal **L-13** (97 mg, 0.38 mmol), H-MAC-TBS **148g** (179 mg, 0.91 mmol), benzylamine (50  $\mu$ L, 0.46 mmol) and DMAP (93 mg, 0.76 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/DCM/Et<sub>2</sub>O, 10:1:1) gave the MAC reaction product **327b** (dr <2:98, 159 mg, 83 %), as a yellow oil.

According to the general procedure C, the MAC reaction was performed with freshly prepared *N,N*-dibenzyl-L-alaninal **L-13** (97 mg, 0.38 mmol), H-MAC-TBS **148g** (179 mg, 0.91 mmol), DMAP (93 mg, 0.76 mmol) and benzylamine (50  $\mu$ L, 0.46 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/DCM/Et<sub>2</sub>O, 10:1:1) gave the MAC reaction product **327b** (dr <2:98, 175 mg, 92 %), as a yellow oil.

**TLC** *R<sub>f</sub>* = 0.22 (pentane/DCM/Et<sub>2</sub>O, 10:1:1)

**OR**  $[\alpha]_D^{24} = -37.1$  (*c* 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3433, 3064, 3026, 2953, 2930, 2855, 1678, 1603, 1515, 1496, 1454, 1361, 1253, 1153, 1077

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>31</sub>H<sub>43</sub>N<sub>2</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 503.3088; found 503.3065

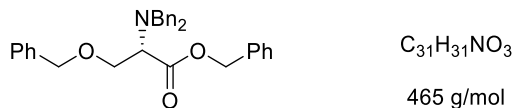
**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -0.07 (s, 3H, SiCH<sub>3</sub>), 0.05 (s, 3H, SiCH<sub>3</sub>), 0.79 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.14 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>CH), 3.01 (quintet, *J* = 6.8 Hz, 1H, CHNBn<sub>2</sub>), 3.50 (d, *J* = 13.7 Hz, 2H) and 3.79 (d, *J* = 13.7 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.08 (dd, *J* = 14.2, 4.7 Hz, 1H) and 4.56 (dd, *J* = 14.2, 6.8 Hz, 1H) (AB part of ABX syst., NHCH<sub>2</sub>Ph), 4.24 (d, *J* = 6.8 Hz, 1H, CHOTBS), 6.32 (br dd, *J* = 6.8, 4.7 Hz, 1H, CONH), 7.16-7.33 (m, 11H, Ph), 7.35-7.41 (m, 4H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : -5.1 (SiCH<sub>3</sub>), -5.0 (SiCH<sub>3</sub>), 9.8 (CH<sub>3</sub>CH), 17.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.6 (SiC(CH<sub>3</sub>)<sub>3</sub>), 43.1 (NHCH<sub>2</sub>Ph), 54.2 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 57.6 (CHNBn<sub>2</sub>), 76.0 (CHOTBS), 126.7 (CH<sub>Ph</sub>), 127.4 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 137.9 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 172.5 (CONH)

## From *N,N,O*-tribenzyl-L-serinal

### *N,N,O*-Tribenzyl-L-serinal's synthesis.

#### Benzyl *N,N,O*-tribenzyl-L-serinate (**L-318**).



**L-318**

To a solution of commercially available *O*-Bn-L-serine **L-317** (3.0 g, 5.12 mmol) in CH<sub>3</sub>CN (20 mL) were added K<sub>2</sub>CO<sub>3</sub> (2.50 g, 17.90 mmol) and BnBr (2.1 mL, 17.65 mmol) and the reaction mixture was stirred overnight at reflux. After cooling down to room temperature, EtOAc (20 mL) and water (20 mL) was added, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give benzyl *N,N,O*-tribenzyl-L-serinate **L-318** (2.40 g, quant.) as a colorless oil. The crude compound is pure enough to be engaged in the next step reaction.

TLC R<sub>f</sub> = 0.57 (pentane/EtOAc, 5:1)

OR [α]<sub>D</sub><sup>27</sup> = -98.4 (c 1.0, CHCl<sub>3</sub>), lit.<sup>254</sup> [α]<sub>D</sub><sup>20</sup> = -48.5 (c 1.0, EtOAc)

IR (ATR), ν (cm<sup>-1</sup>): 3085, 3063, 3029, 2950, 2853, 1729, 1602, 1493, 1454, 1363, 1252, 1103, 1027

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>), δ (ppm) : 3.67 (d, *J* = 14.0 Hz, 2H) and 3.91 (d, *J* = 14.0 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.71-3.76 (m, 1H) and 3.85-3.91 (m, 1H) (AB part of ABX syst., OCH<sub>2</sub>CH), 3.76-3.82 (m, 1H, CHNBn<sub>2</sub>), 4.42 (d, *J* = 12.0 Hz, 1H) and 4.46 (d, *J* = 12.0 Hz, 1H) (AB syst., PhCH<sub>2</sub>O), 5.20 (d, *J* = 12.2 Hz, 1H) and 5.27 (d, *J* = 12.2 Hz, 1H) (AB syst., COOCH<sub>2</sub>Ph), 7.17-7.44 (m, 20H, Ph)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : 55.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.0 (CHNBn<sub>2</sub>), 66.1 (COOCH<sub>2</sub>Ph), 69.6 (OCH<sub>2</sub>CH), 73.2 (PhCH<sub>2</sub>O), 127.0 (CH<sub>Ph</sub>), 127.5 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 128.3 (CH<sub>Ph</sub>), 128.3 (CH<sub>Ph</sub>), 128.5 (CH<sub>Ph</sub>), 128.7 (CH<sub>Ph</sub>), 136.0 (C<sub>Ph</sub>), 138.0 (C<sub>Ph</sub>), 139.6 (C<sub>Ph</sub>), 171.3 (COOBn)

<sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with those described in literature.<sup>254</sup>

#### *N,N,O*-Tribenzyl-L-serinol (**L-319**).



**L-319**

Benzyl *N,N,O*-tribenzyl-L-serinate **L-318** (932 mg, 2.0 mmol) was dissolved in dry Et<sub>2</sub>O (2 mL) under argon and LAH (65 mg, 1.7 mmol) was added very carefully to the solution at 0 °C. The reaction mixture was stirred at room temperature for 12 hours (until the TLC showed no more starting benzyl ester).

The reaction was cooled down to 0 °C, water (0.1 mL) was added dropwise followed by a 15 % aqueous NaOH solution (0.2 mL). After addition of water (0.3 mL), the mixture was stirred for 15 minutes at room temperature (until the solution became clear). Na<sub>2</sub>SO<sub>4</sub> (~ 2 g) was introduced in one portion and the mixture was stirred for an additional 15 minutes. After filtration through cotton, the filtrate was concentrated under reduced pressure and purified by column chromatography (pentane/Et<sub>2</sub>O, 20:1 then 2:1) to give *N,N,O*-tribenzyl-L-serinol **L-319** (561 mg, 65%), as a colorless oil.

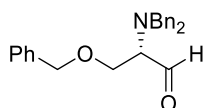
TLC R<sub>f</sub> = 0.63 (pentane/EtOAc, 5:1)

OR [α]<sub>D</sub><sup>23</sup> = +55.5 (c 1.0, EtOAc), lit.<sup>254</sup> [α]<sub>D</sub><sup>20</sup> = +65.4 (c 1.0, EtOAc)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ (ppm) : 2.90 (br s, 1H, OH), 3.08-3.22 (m, 1H, CHNBn<sub>2</sub>), 3.53 (dd, *J* = 9.9, 5.7 Hz, 1H) and 3.75 (d, *J* = 9.9, 5.7 Hz, 1H) (AB part of ABX syst., OCH<sub>2</sub>CH), 3.55 (br d, *J* = 8.4 Hz, 2H, CH<sub>2</sub>OH), 3.60 (d, *J* = 13.2 Hz, 2H) and 3.87 (d, *J* = 13.2 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.51 (d, *J* = 12.0 Hz, 1H) and 4.56 (d, *J* = 12.0 Hz, 1H) (AB syst., PhCH<sub>2</sub>O), 7.20-7.43 (m, 15H, Ph)

<sup>1</sup>H NMR data were in agreement with those described in literature.<sup>254</sup>

#### *N,N,O*-Tribenzyl-L-serinal (**L-320**).



C<sub>24</sub>H<sub>25</sub>NO<sub>2</sub>

359 g/mol

**L-320**

According to the general procedure, Swern oxidation of *N,N,O*-tribenzyl-L-serinol **L-319** (427 mg, 1.18 mmol) was performed with DMSO (220 μL, 3.07 mmol), oxalyl chloride (130 μL, 1.54 mmol) in DCM (5 mL), followed by the addition of NEt<sub>3</sub> (1.1 mL, 7.84 mmol). Crude *N,N*-dibenzyl-L-serinal **L-320** (424 mg, quant.) was isolated as a colorless turbid liquid. It was used without any purification in the MAC reaction.

*Note: This aldehyde is very unstable, so both the characterization and the MAC reaction should be done quickly.*

TLC R<sub>f</sub> = 0.86 (pentane/Et<sub>2</sub>O, 2:1)

OR [α]<sub>D</sub><sup>24</sup> = -7.1 (c 1.0, CHCl<sub>3</sub>)

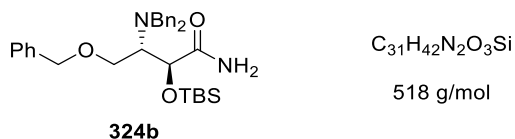
IR (ATR), ν (cm<sup>-1</sup>): 3085, 3063, 3029, 2922, 2855, 1725, 1602, 1494, 1454, 1360, 1249, 1206, 1101, 1028

HRMS (ES<sup>+</sup>): calcd. for C<sub>24</sub>H<sub>26</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 360.1958; found 360.1950

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ (ppm) : 3.54 (t, *J* = 5.7 Hz, 1H, CHNBn<sub>2</sub>), 3.80 (d, *J* = 13.8 Hz, 2H) and 3.87 (d, *J* = 13.8 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.90 (d, *J* = 5.7 Hz, 2H, OCH<sub>2</sub>CH), 4.51 (d, *J* = 12.0 Hz, 1H) and 4.57 (d, *J* = 12.0 Hz, 1H) (AB syst., PhCH<sub>2</sub>O), 7.20-7.42 (m, 15H, Ph), 9.70 (s, 1H, CHO)

<sup>13</sup>C NMR (90.6 MHz, CDCl<sub>3</sub>), δ (ppm) : 55.6 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 66.4 (CHNBn<sub>2</sub>), 66.4 (OCH<sub>2</sub>CH), 73.5 (PhCH<sub>2</sub>O), 127.2 (CH<sub>Ph</sub>), 127.6 (CH<sub>Ph</sub>), 127.7 (CH<sub>Ph</sub>), 128.3 (CH<sub>Ph</sub>), 128.4 (CH<sub>Ph</sub>), 128.8 (CH<sub>Ph</sub>), 138.0 (C<sub>Ph</sub>), 139.2 (C<sub>Ph</sub>), 202.5 (CHO)

## MAC reactions.

**(2S,3S)-4-(Benzyloxy)-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)butanamide (324b).**

According to the general procedure B, the MAC reaction was performed with freshly prepared *N,N,O*-tribenzyl-L-serinal **L-320** (144 mg, 0.40 mmol), H-MAC-TBS **148g** (188 mg, 0.96 mmol), ammonia (0.5 M in THF, 0.96 mL, 0.48 mmol) and DMAP (97 mg, 0.80 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/EtOAc, 5:1) gave the MAC reaction product **324b** (dr <2:98, 150 mg, 72 %), as a yellow oil.

**TLC**  $R_f$  = 0.17 (pentane/EtOAc, 5:1)

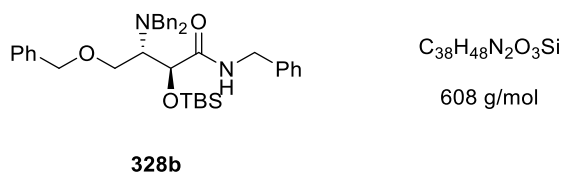
**OR**  $[\alpha]_D^{25}$  = +23.9 (*c* 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  (cm<sup>-1</sup>): 3481, 3063, 3028, 2954, 2929, 2884, 2856, 1690, 1600, 1495, 1453, 1389, 1361, 1253, 1206, 1093

**HRMS** (ES<sup>+</sup>): calcd. for C<sub>31</sub>H<sub>43</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup> 519.3037; found 519.3017

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : 0.05 (s, 3H, SiCH<sub>3</sub>), 0.06 (s, 3H, SiCH<sub>3</sub>), 0.87 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 3.16 (ddd, *J* = 6.5, 6.1, 4.3 Hz, 1H, CHNBn<sub>2</sub>), 3.72 (d, *J* = 13.7 Hz, 2H) and 3.92 (d, *J* = 13.7 Hz, 2H) (AB syst., N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.82 (dd, *J* = 10.1, 6.1 Hz, 1H) and 3.89 (d, *J* = 10.1, 4.3 Hz, 1H) (AB part of ABX syst., OCH<sub>2</sub>CH), 4.41 (d, *J* = 6.5 Hz, 1H, CHOTBS), 4.50 (s, 2H, PhCH<sub>2</sub>O), 5.98 (s, 1H, CONH), 6.18 (s, 1H, CONH), 7.16-7.22 (m, 2H, Ph), 7.24-7.38 (m, 9H, Ph), 7.40-7.46 (m, 4H, Ph)

**<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm) : -5.3 (SiCH<sub>3</sub>), -5.2 (SiCH<sub>3</sub>), 17.9 (SiC(CH<sub>3</sub>)<sub>3</sub>), 25.7 (SiC(CH<sub>3</sub>)<sub>3</sub>), 55.1 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 61.3 (CHNBn<sub>2</sub>), 67.1 (OCH<sub>2</sub>CH), 73.0 (PhCH<sub>2</sub>O), 73.2 (CHOTBS), 126.7 (CH<sub>Ph</sub>), 127.4 (CH<sub>Ph</sub>), 127.4 (CH<sub>Ph</sub>), 128.0 (CH<sub>Ph</sub>), 128.2 (CH<sub>Ph</sub>), 129.0 (CH<sub>Ph</sub>), 138.2 (C<sub>Ph</sub>), 139.9 (C<sub>Ph</sub>), 176.1 (CONH)

**(2S,3S)-N-Benzyl-4-(benzyloxy)-2-(tert-butyldimethylsilyloxy)-3-(dibenzylamino)butanamide (328b).**

According to the general procedure B, the MAC reaction was performed with freshly prepared *N,N,O*-tribenzyl-L-serinal **L-320** (144 mg, 0.40 mmol), H-MAC-TBS **148g** (188 mg, 0.96 mmol), benzylamine (52  $\mu$ L, 0.48 mmol) and DMAP (97 mg, 0.80 mmol) in Et<sub>2</sub>O (4 mL). Flash column chromatography (pentane/Et<sub>2</sub>O/DCM 10:1:1) gave the MAC reaction product **328b** (dr <2:98, 181 mg, 75 %), as a yellow oil.

**TLC**  $R_f$  = 0.08 (pentane/DCM/Et<sub>2</sub>O, 10:1:1)

**OR**  $[\alpha]_D^{25}$  = -18.1 (*c* 1.0, CHCl<sub>3</sub>)

**IR** (ATR),  $\nu$  ( $\text{cm}^{-1}$ ): 3427, 3062, 3028, 2952, 2928, 2856, 2803, 1676, 1602, 1515, 1495, 1454, 1360, 1254, 1092, 1075

**HRMS** ( $\text{ES}^+$ ): calcd. for  $\text{C}_{38}\text{H}_{49}\text{N}_2\text{O}_3\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$  609.3507; found 609.3480

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -0.11 (s, 3H,  $\text{SiCH}_3$ ), -0.03 (s, 3H,  $\text{SiCH}_3$ ), 0.75 (s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 3.20 (ddd,  $J = 6.3, 6.0, 5.7$  Hz, 1H,  $\text{CHNBn}_2$ ), 3.71 (d,  $J = 14.1$  Hz, 2H) and 3.88 (d,  $J = 14.1$  Hz, 2H) (AB syst.,  $\text{N}(\text{CH}_2\text{Ph})_2$ ), 3.79 (dd,  $J = 9.9, 6.0$  Hz, 1H) and 3.85-3.91 (m, 1H) (AB part of ABX syst.,  $\text{OCH}_2\text{CH}$ ), 3.94 (dd,  $J = 14.1, 4.2$  Hz, 1H) and 4.54 (dd,  $J = 14.1, 6.9$  Hz, 1H) (AB part of ABX syst.,  $\text{NHCH}_2\text{Ph}$ ), 4.43 (br d,  $J = 6.3$  Hz, 1H,  $\text{CHOTBS}$ ), 4.46 (s, 2H,  $\text{PhCH}_2\text{O}$ ), 6.39 (dd,  $J = 6.9, 4.2$  Hz, 1H, CONH), 7.11-7.35 (m, 16H, Ph), 7.36-7.42 (m, 4H, Ph)

**$^{13}\text{C}$  NMR** (75.5 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm) : -5.3 ( $\text{SiCH}_3$ ), -5.2 ( $\text{SiCH}_3$ ), 17.8 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.6 ( $\text{SiC}(\text{CH}_3)_3$ ), 43.2 ( $\text{NHCH}_2\text{Ph}$ ), 55.1 ( $\text{N}(\text{CH}_2\text{Ph})_2$ ), 61.4 ( $\text{CHNBn}_2$ ), 67.3 ( $\text{OCH}_2\text{CH}$ ), 73.0 ( $\text{PhCH}_2\text{O}$ ), 73.1 ( $\text{CHOTBS}$ ), 126.6 ( $\text{CH}_{\text{Ph}}$ ), 127.4 ( $\text{CH}_{\text{Ph}}$ ), 127.5 ( $\text{CH}_{\text{Ph}}$ ), 128.0 ( $\text{CH}_{\text{Ph}}$ ), 128.2 ( $\text{CH}_{\text{Ph}}$ ), 128.4 ( $\text{CH}_{\text{Ph}}$ ), 128.9 ( $\text{CH}_{\text{Ph}}$ ), 137.7 ( $\text{C}_{\text{Ph}}$ ), 138.2 ( $\text{C}_{\text{Ph}}$ ), 139.9 ( $\text{C}_{\text{Ph}}$ ), 172.4 (CONH)

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# Bibliography

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## Bibliography

- <sup>1</sup> Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93* (9), 2325–2327.
- <sup>2</sup> Johnson, R. L. *J. Med. Chem.* **1982**, *25*(5), 605–610
- <sup>3</sup> Sano, T.; Kaya, K. *Phytochemistry* **1997**, *44* (8), 1503–1505.
- <sup>4</sup> Calabro, K.; Genta-Jouve, G.; Thomas, O. P. *J. Nat. Prod.* **2019**, *82* (4), 1040–1044.
- <sup>5</sup> Fujii, K.; Sivonen, K.; Kashiwagi, T.; Hirayama, K.; Harada, K. I. Nostophycin, *J. Org. Chem.* **1999**, *64* (16), 5777–5782.
- <sup>6</sup> Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53* (6), 1298–1307.
- <sup>7</sup> Sepe, V.; D’Auria, M. V.; Bifulco, G.; Ummarino, R.; Zampella, A. *Tetrahedron* **2010**, *66* (38), 7520–7526.
- <sup>8</sup> Murai, Y.; Mori, S.; Konno, H.; Hikichi, Y.; Kai, K. *Org. Lett.* **2017**, *19* (16), 4175–4178.
- <sup>9</sup> Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29* (1), 100–101.
- <sup>10</sup> Suda, H.; Aoyagi, T.; Takeuchi, T.; Umezawa, H. *Arch. Biochem. Biophys.* **1976**, *177* (1), 196–200.
- <sup>11</sup> Muskardin, D. T.; Voelkel, N. F.; Fitzpatrick, F. A. *Biochem. Pharmacol.* **1994**, *48* (1), 131–137.
- <sup>12</sup> Sekine, K.; Fujii, H.; Abe, F. *Leukemia* **1999**, *13* (5), 729–734.
- <sup>13</sup> Harbut, M. B.; Velmourougane, G.; Dalal, S.; Reiss, G.; Whisstock, J. C.; Onder, O.; Brisson, D.; McGowan, S.; Klemba, M.; Greenbaum, D. C. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108* (34), 526–534.
- <sup>14</sup> Ishizuka, M.; Aoyagi, T.; Takeuchi, T.; Umezawa, H. Clinical Experiences In The Use Of Bestatin In The Treatment Of Locally Advanced Cancers: Case Report In *Small molecular immunomodifiers of microbial origin: fundamental and clinical studies of bestatin*. Elsevier. **1981**; 17–38
- <sup>15</sup> Wang, X.; Shi, L.; Deng, Y.; Qu, M.; Mao, S.; Xu, L.; Xu, W.; Fang, C. *Eur. J. Pharmacol.* **2015**, *768*, 116–122.
- <sup>16</sup> Hitzerd, S. M.; Verbrugge, S. E.; Ossenkoppele, G.; Jansen, G.; Peters, G. J. *Amino Acids* **2014**, *46* (4), 793–808.
- <sup>17</sup> Tian, W.; Rockson, S. G.; Jiang, X.; Kim, J.; Begaye, A.; Shuffle, E. M.; Tu, A. B.; Cribb, M.; Nepiyushchikh, Z.; Feroze, A. H. *Sci. Transl. Med.* **2017**, *9* (389), 1–14.
- <sup>18</sup> Yuan, W.; Wong, C-H.; Samuelson, N.; Munoz, B. WO Pat, WO94/00420, **1993**.
- <sup>19</sup> Kawaguchi, M.; Okabe, T.; Terai, T.; Hanaoka, K.; Kojima, H.; Minegishi, I.; Nagano, T. *Chem. Eur. J.* **2010**, *16* (45), 13479–13486.
- <sup>20</sup> Yoshida, S.; Nakamura, Y.; Naganawa, H.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1990**, *43* (2), 149–153.
- <sup>21</sup> Jiang, Y.; Li, X.; Hou, J.; Huang, Y.; Wang, X.; Jia, Y.; Wang, Q.; Xu, W.; Zhang, J.; Zhang, Y. *Eur. J. Med. Chem.* **2018**, *143*, 334–347.
- <sup>22</sup> Nagai, M.; Kojima, F.; Naganawa, H.; Hamada, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50* (1), 82–84.
- <sup>23</sup> Prechel, M. M.; Orawski, A. T.; Maggiora, L. L.; Simmons, W. H. *J. Pharmacol. Exp. Ther.* **1995**, *275* (3), 1136–1142.
- <sup>24</sup> Maggiora, L. L.; Orawski, A. T.; Simmons, W. H. *J. Med. Chem.* **1999**, *42* (13), 2394–2402.
- <sup>25</sup> Wolfrum, S.; Richardt, G.; Dominiak, P.; Katus, H. A.; Dendorfer, A. *Br. J. Pharmacol.* **2001**, *134* (2), 370–374.
- <sup>26</sup> Kho, Y.-H.; Ko, H.-R.; Chun, H.-K.; Jung, M.-C. *J. Microbiol. Biotechnol.* **1995**, *5* (1), 36–40.

- <sup>27</sup> Rao, M.; Li, Q.; Feng, L.; Xia, X.; Ruan, L.; Sheng, X.; Ge, M. *Anal. Bioanal. Chem.* **2011**, *401* (2), 699–706.
- <sup>28</sup> Yang, Y.; Shen, D.; He, P.; Du, L.; Wan, D.; Wang, P.; Wang, T.; Feng, M. *Bioorg. Med. Chem. Lett.* **2019**, *29* (14), 1719–1726
- <sup>29</sup> Komai, T.; Yagi, R.; Suzuki-Sunagawa, H.; Sakurai, M.; Higashida, S.; Sugano, M.; Handa, H.; Mohri, H.; Yasuoka, A.; Oka, S.; Yabe, Y.; Nishigaki, T.; Kimura S.; Shimada, K.; *Biol. Pharm. Bull.* **1997**, *20* (2), 175–180.
- <sup>30</sup> Rusconi, S.; Viganò, O. *Therapy* **2006**, *3* (1), 79–88.
- <sup>31</sup> Stellbrink, H. J. *Antivir. Chem. Chemother.* **2008**, *19* (5), 189–200.
- <sup>32</sup> Burke, B. J.; Hawking, E. L.; Hoffman, R. L.; Kania, R. S.; Lillis, J. R.; O'Brien Laramy, M. N.; Pencheva, K. D.; Sullivan, B. P.; Thiel, A. J.; Ticehurst, M. D. WO Pat, WO2021176369A1, **2021**.
- <sup>33</sup> Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1992**, *40* (8), 2251–2253.
- <sup>34</sup> Hawkins, V.; Shen, Q.; Chiueh, C. C. *J. Biomed. Sci.* **1999**, *6* (6), 433–438.
- <sup>35</sup> Suzuki, K.; Hamada, Y.; Nguyen, J.-T.; Kiso, Y. *Bioorg. Med. Chem.* **2013**, *21* (21), 6665–6673.
- <sup>36</sup> Hampel, H.; Vassar, R.; De Strooper, B.; Hardy, J.; Willem, M.; Singh, N.; Zhou, J.; Yan, R.; Vanmechelen, E.; De Vos, A.; Nisticò, R.; Corbo, M.; Imbimbo, B. P. Streffer, J. Voytyuk, I.; Timmers, M.; Tahami M.; Amir A.; Irizarry, M.; Albala, B.; Koyama, A.; Watanabe, N.; Kimura, T.; Yarenis, L.; Lista, S.; Kramer, L.; Vergallo, A. *Biol. Psychiatry* **2021**, *89* (8), 745–756
- <sup>37</sup> Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29* (5), 600–601.
- <sup>38</sup> Nishizawa, R.; Saino, T.; Takita, T.; Suda, H.; Aoyagi, T.; Umezawa, H. *J. Med. Chem.* **1977**, *20* (4), 510–515.
- <sup>39</sup> Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33* (10), 2707–2714.
- <sup>40</sup> Abell, A. D.; Foulds, G. J. *J. Chem. Soc. Perkin Trans. 1* **1997**, (17), 2475–2482.
- <sup>41</sup> Kitano, H.; Kondo, Y.; Saito, D.; Gemmei-Ide, M.; Morita, H.; Kanayama, N. *Colloids Surfaces B Biointerfaces* **2010**, *78* (2), 155–162
- <sup>42</sup> Harbeson, S. L.; Abelleira, S. M.; Akiyama, A.; Barrett, R.; Carroll, R. M.; Straub, J. A.; Tkacz, J. N.; Wu, C.; Musso, G. F. *J. Med. Chem.* **1994**, *37* (18), 2918–2929.
- <sup>43</sup> Jastaniah, A.; Gaisina, I. N.; Knopp, R. C.; Thatcher, G. R. J. *ChemMedChem* **2020**, *15* (23), 2280–2285.
- <sup>44</sup> Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1990**, *55* (7), 2232–2234.
- <sup>45</sup> Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65* (2), 360–365.
- <sup>46</sup> Herranz, R.; Castro-Pichel, J.; García-López, T. *Synthesis* **1989**, (9), 703–706.
- <sup>47</sup> Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; García-López, M. T. *J. Chem. Soc. Chem. Commun.* **1989**, (14), 938–939.
- <sup>48</sup> Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29* (27), 3295–3298.
- <sup>49</sup> Shibata, N.; Itoh, E.; Terashima, S. *Chem. Pharm. Bull.* **1998**, *46* (4), 733–735.
- <sup>50</sup> Andrés, J. M.; Martínez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Asymmetry* **2001**, *12* (2), 347–353.
- <sup>51</sup> Lei, L.; He, X.; Bai, D. *Synth. Commun.* **2005**, *35* (11), 1535–1540.
- <sup>52</sup> Manickam, G.; Nogami, H.; Kanai, M.; Gröger, H.; Shibasaki, M. *Synlett* **2001**, (5), 617–620.
- <sup>53</sup> Nogami, H.; Kanai, M.; Shibasaki, M. *Chem. Pharm. Bull.* **2003**, *51* (6), 702–709.
- <sup>54</sup> Ziegler, T.; Kaisers, H. J.; Schlömer, R.; Koch, C. *Tetrahedron* **1999**, *55* (28), 8397–8408.



- <sup>55</sup> Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2* (18), 2769–2772.
- <sup>56</sup> Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, (11), 985–986.
- <sup>57</sup> Umbreen, S. Synthesis and Biological Evaluation of E -Secretase Inhibitors, Proteasome Inhibitors and Losartan Active Metabolites, PhD thesis, Technischen Universität Darmstadt, Darmstadt, **2007**.
- <sup>58</sup> Umbreen, S.; Brockhaus, M.; Ehrenberg, H.; Schmidt, B. *Euro. J. Org. Chem.* **2006**, (20), 4585–4595.
- <sup>59</sup> Semple, J. E.; Levy, O. E.; Minami, N. K.; Owens, T. D.; Siev, D. V. *Bioorganic Med. Chem. Lett.* **2000**, *10* (20), 2305–2309.
- <sup>60</sup> Pacifico, S.; Ferretti, V.; Albanese, V.; Fantinati, A.; Gallerani, E.; Nicoli, F.; Gavioli, R.; Zamberlan, F.; Preti, D.; Marastoni, M. *ACS Med. Chem. Lett.* **2019**, *10* (7), 1086–1092.
- <sup>61</sup> Zimuwandeyi, M.; Kola, F.; Lemmerer, A.; Brady, D.; Rousseau, A. L.; Bode, M. L. *Tetrahedron* **2018**, *74* (24), 2925–2941.
- <sup>62</sup> Cuny, G.; Gámez-Montaño, R.; Zhu, J. *Tetrahedron* **2004**, *60* (22), 4879–4885.
- <sup>63</sup> Shang, S.; Willems, A. V.; Chauhan, S. S. *J. Pept. Sci.* **2018**, *24* (3), e3067.
- <sup>64</sup> Sasai, H.; Kim, W. S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Tetrahedron Lett.* **1994**, *35* (33), 6123–6126.
- <sup>65</sup> Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114* (11), 4418–4420.
- <sup>66</sup> Hormuth, S.; Reißig, H.-U.; Dorsch, D. *Liebigs Ann. der Chemie.* **1994**, (2), 121–127.
- <sup>67</sup> Lee, B. W.; Lee, J. H.; Jang, K. C.; Kang, J. E.; Kim, J. H.; Park, K. M.; Park, K. H. *Tetrahedron Lett.* **2003**, *44* (31), 5905–5907.
- <sup>68</sup> George, S.; Suryavanshi, G. S.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49* (48), 6791–6793.
- <sup>69</sup> Ikunaka, M.; Matsumoto, J.; Nishimoto, Y. *Tetrahedron Asymmetry* **2002**, *13* (11), 1201–1208
- <sup>70</sup> Velmourougane, G.; Harbut, M. B.; Dalal, S.; McGowan, S.; Oellig, C. A.; Meinhardt, N.; Whisstock, J. C.; Klemba, M.; Greenbaum, D. C. *J. Med. Chem.* **2011**, *54* (6), 1655–1666.
- <sup>71</sup> Harbut, M. B.; Velmourougane, G.; Dalal, S.; Reiss, G.; Whisstock, J. C.; Onder, O.; Brisson, D.; McGowan, S.; Klemba, M.; Greenbaum, D. C. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108* (34), 526–534.
- <sup>72</sup> May, B. C. H.; Abell, A. D. *Synth. Commun.* **1999**, *29* (14), 2515–2525.
- <sup>73</sup> Wasserman, H. H.; Xia, M.; Petersen, A. K.; Jorgensen, M. R.; Curtis, E. A. *Tetrahedron Lett.* **1999**, *40* (34), 6163–6166.
- <sup>74</sup> Wasserman, H. H.; Petersen, A. K.; Xia, M. *Tetrahedron* **2003**, *59* (35), 6771–6784.
- <sup>75</sup> Slee, D. H.; Laslo, K. L.; Elder, J. H.; Ollmann, I. R.; Gustchina, A.; Kervinen, J.; Zdanov, A.; Wlodawer, A.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117* (48), 11867–11878.
- <sup>76</sup> Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54* (16), 3913–3916.
- <sup>77</sup> Suzuki, T.; Honda, Y.; Izawa, K.; Williams, R. M. *J. Org. Chem.* **2005**, *70* (18), 7317–7323.
- <sup>78</sup> Akhtar, R.; Naqvi, S. A. R.; Zahoor, A. F.; Saleem, S. *Mol. Divers.* **2018**, *22* (2), 447–501.
- <sup>79</sup> Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Taga, T.; Miwa, Y. *Tetrahedron Lett.* **1990**, *31* (46), 6663–6666.
- <sup>80</sup> Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Fuji, K. *Tetrahedron Lett.* **1993**, *34* (32), 5127–5130.
- <sup>81</sup> Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y. *Heterocycles* **1996**, *42* (2), 701–721.
- <sup>82</sup> Kang, S. H.; Ryu, D. H. *Bioorganic Med. Chem. Lett.* **1995**, *5* (24), 2959–2962.
- <sup>83</sup> Pégulier, L.; Haddad, M.; Larchevêque, M. *Synlett* **1996**, (6), 585–586.

- <sup>84</sup> Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68* (18), 7041–7045.
- <sup>85</sup> Rodrigues, J. A. R.; Milagre, H. M. S.; Milagre, C. D. F.; Moran, P. J. S. *Tetrahedron Asymmetry* **2005**, *16* (18), 3099–3106.
- <sup>86</sup> Feske, B. D.; Stewart, J. D. *Tetrahedron Asymmetry* **2005**, *16* (18), 3124–3127.
- <sup>87</sup> Kato, K.; Saino, T.; Nishizawa, R.; Takita, T.; Umezawa, H. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1618–1621.
- <sup>88</sup> Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31* (21), 3031–3034.
- <sup>89</sup> Palomo, C.; Arrieta, A.; Cossío, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31* (44), 6429–6432.
- <sup>90</sup> Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc. Chem. Commun.* **1994**, (17), 1957–1958.
- <sup>91</sup> Ha, H. J.; Ahn, Y. G.; Lee, G. S. *Tetrahedron Asymmetry* **1999**, *10* (12), 2327–2336.
- <sup>92</sup> Shimizu, M.; Hayashi, Y.; Hamanaka, R.; Hachiya, I. *Heterocycles* **2007**, *73* (1), 191–195.
- <sup>93</sup> Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25* (44), 5079–5082.
- <sup>94</sup> Norman, B. H.; Morris, M. L. *Tetrahedron Lett.* **1992**, *33* (45), 6803–6806.
- <sup>95</sup> Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64* (8), 2852–2859.
- <sup>96</sup> Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54* (17), 4235–4237.
- <sup>97</sup> Pearson, W. H.; Cheng, M. C. *J. Org. Chem.* **1987**, *52* (14), 3176–3178.
- <sup>98</sup> Koseki, K.; Ebata, T.; Matsushita, H. *Biosci. Biotechnol. Biochem.* **1996**, *60* (3), 534–536.
- <sup>99</sup> Lee, J. H.; Lee, B. W.; Jang, K. C.; Jeong, I. Y.; Yang, M. S.; Lee, S. G.; Park, K. H. *Synthesis* **2003**, *2* (6), 829–836.
- <sup>100</sup> Jefford, C. W.; McNulty, J.; Lu, Z.-H.; Wang, J. B. *Helv. Chim. Acta* **1996**, *79* (4), 1203–1216.
- <sup>101</sup> Seki, M.; Matsumoto, K. *Synthesis* **1999**, (6), 924–926.
- <sup>102</sup> Seki, M.; Matsumoto, K. *Biosci. Biotechnol. Biochem.* **1996**, *60* (5), 916–917.
- <sup>103</sup> Caputo, R.; Cecere, G.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Eur. J. Org. Chem.* **2002**, (17), 3050–3054.
- <sup>104</sup> Jain, V. K. *SynOpen* **2019**, *3* (04), 114–123.
- <sup>105</sup> Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125* (36), 10808–10809.
- <sup>106</sup> Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *Synlett* **1993**, (10), 731–732.
- <sup>107</sup> Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92* (5), 919–934.
- <sup>108</sup> Hidasová, D.; Janák, M.; Jahn, E.; Císařová, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2018**, *2018* (37), 5222–5230.
- <sup>109</sup> Richter, A.; Hedberg, C. *Synthesis* **2010**, (12), 2039–2042.
- <sup>110</sup> Jiang, Y.; Chen, X.; Zheng, Y.; Xue, Z.; Shu, C.; Yuan, W.; Zhang, X. *Angew. Chem.* **2011**, *123* (32), 7442–7445.
- <sup>111</sup> Dai, X.; Weng, G.; Yu, S.; Chen, H.; Zhang, J.; Cheng, S.; Xu, X.; Yuan, W.; Wang, Z.; Zhang, X. *Org. Chem. Front.* **2018**, *5* (19), 2787–2793.
- <sup>112</sup> Nishizawa, R.; Saino, T.; Suzuki, M.; Fujii, T.; Shirai, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1983**, *36* (6), 695–699.
- <sup>113</sup> Kise, N.; Inakoshi, N.; Matsumura, Y. *Tetrahedron Lett.* **1995**, *36* (6), 909–912.
- <sup>114</sup> Kudyba, I.; Raczko, J.; Jurczak, J. *Tetrahedron Lett.* **2003**, *44* (48), 8685–8687.
- <sup>115</sup> Kudyba, I.; Raczko, J.; Jurczak, J. *J. Org. Chem.* **2004**, *69* (8), 2844–2850.

- <sup>116</sup> Gogoi, N.; Boruwa, J.; Barua, N. C. *Tetrahedron Lett.* **2005**, *46* (44), 7581–7582.
- <sup>117</sup> Mallik, S.; Bhajammanavar, V.; Ramakrishna, I.; Baidya, M. *Org. Lett.* **2017**, *19* (14), 3843–3846.
- <sup>118</sup> Jung, D. Y.; Kang, S.; Chang, S.; Kim, Y. H. *Synlett* **2006**, (1), 86–90.
- <sup>119</sup> Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed.* **1965**, *4* (12), 1075–1077.
- <sup>120</sup> Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40* (2), 231–237.
- <sup>121</sup> Smith, A. B.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37* (6), 365–377.
- <sup>122</sup> Stetter, H.; Kuhlmann, H. The Catalyzed Nucleophilic Addition of Aldehydes to Electrophilic Double Bonds. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **1991**; 407–496.
- <sup>123</sup> Adlington, R. M.; Baldwin, J. E.; Bottaro, J. C.; Perry, M. W. D. *J. Chem. Soc. Chem. Commun.* **1983**, *1* (18), 1040–1041.
- <sup>124</sup> Rosini, G. The Henry (Nitroaldol) Reaction. In *Comprehensive Organic Synthesis*; Elsevier, **1991**; 321–340.
- <sup>125</sup> Baldwin, J. E.; Hoefle, G. A.; Lever, O. W. J. *J. Am. Chem. Soc.* **1974**, *96* (22), 7125–7127.
- <sup>126</sup> Walborsky, H. M.; Morrison, W. H.; Niznik, G. E. *J. Am. Chem. Soc.* **1970**, *92* (22), 6675–6676.
- <sup>127</sup> Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41* (9), 3511–3522.
- <sup>128</sup> Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55* (15), 4515–4516.
- <sup>129</sup> Nemoto, H.; Ibaragi, T.; Bando, M.; Kido, M.; Shibuya, M. *Tetrahedron Lett.* **1999**, *40* (7), 1319–1322.
- <sup>130</sup> Nemoto, H. Protected Dicyanomethanol (H-MAC-R). In *Encyclopedia of Reagents for Organic Synthesis*, Wiley, **2007**.
- <sup>131</sup> Esgulian, M. *Oxyhomologation Diastéréosélective de La Sérine : Développement de La Méthodologie MAC*, PhD thesis, Université Paris-Saclay, Orsay, **2017**.
- <sup>132</sup> Nemoto, H.; Ma, R.; Ibaragi, T.; Suzuki, I.; Shibuya, M. *Tetrahedron* **2000**, *56* (11), 1463–1468.
- <sup>133</sup> Nemoto, H.; Ma, R.; Kawamura, T.; Kamiya, M.; Shibuya, M. *J. Org. Chem.* **2006**, *71* (16), 6038–6043.
- <sup>134</sup> Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Chem. Soc. Chem. Commun.* **1994**, 1665–1666.
- <sup>135</sup> Inoue, M.; Ogoshi, T.; Furukawa, T.; Machida, T.; Mitani, I.; Harada, K.; Nakagawa, Y.; Yamaoka, N. *US pat*, US20220162220A1, **2022**.
- <sup>136</sup> Nemoto, H.; Kubota, Y.; Sasaki, N.; Yamamoto, Y. *Synlett* **1993**, (7), 465–466.
- <sup>137</sup> Nemoto, H.; Ma, R.; Kawamura, T.; Kamiya, M.; Shibuya, M. *J. Org. Chem.* **2006**, *71* (16), 6038–6043.
- <sup>138</sup> Yamamoto, Y.; Kubota, Y.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116* (7), 3161–3162.
- <sup>139</sup> Kubota, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56* (26), 7195–7196.
- <sup>140</sup> Nemoto, H.; Ma, R.; Moriguchi, H.; Suzuki, I.; Shibuya, M. *J. Organomet. Chem.* **2000**, *611* (1–2), 445–448.
- <sup>141</sup> Nemoto, H.; Moriguchi, H.; Ma, R.; Kawamura, T.; Kamiya, M.; Shibuya, M. *Tetrahedron Asymmetry* **2007**, *18* (3), 383–389.
- <sup>142</sup> Yamatsugu, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2009**, *65* (31), 6017–6024.
- <sup>143</sup> Yang, K. S.; Rawal, V. H. *J. Am. Chem. Soc.* **2014**, *136* (46), 16148–16151.
- <sup>144</sup> He, C.; Chu, H.; Stratton, T. P.; Kossler, D.; Eberle, K. J.; Flood, D. T.; Baran, P. S. *J. Am. Chem. Soc.* **2020**, *142* (32), 13683–13688.

- <sup>145</sup> Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135* (43), 16050–16053.
- <sup>146</sup> De Bo, G.; Leigh, D. A.; McTernan, C. T.; Wang, S. *Chem. Sci.* **2017**, *8* (10), 7077–7081.
- <sup>147</sup> Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135* (43), 16050–16053.
- <sup>148</sup> Grimm, J. B.; Tkachuk, A. N.; Xie, L.; Choi, H.; Mohar, B.; Falco, N.; Schaefer, K.; Patel, R.; Zheng, Q.; Liu, Z.; Lippincott-Schwartz, J.; Brown, T. A.; Lavis, L. D. *Nat. Methods* **2020**, *17* (8), 815–821.
- <sup>149</sup> Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2017**, *56* (38), 11545–11548.
- <sup>150</sup> Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. *Org. Lett.* **2017**, *19* (7), 1527–1529.
- <sup>151</sup> Butcher, T. W.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2018**, *57* (40), 13125–13129.
- <sup>152</sup> Butcher, T. W.; Yang, J. L.; Amberg, W. M.; Watkins, N. B.; Wilkinson, N. D.; Hartwig, J. F. *Nature* **2020**, *58*, 548–553.
- <sup>153</sup> Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, *48* (6), 1070–1076.
- <sup>154</sup> Nakamura, S.; Matsumoto, N.; Kibe, M.; Abe, K.; Takehara, T.; Suzuki, T. *Adv. Synth. Catal.* **2022**, *364* (4), 781–786.
- <sup>155</sup> Kagawa, N.; Nibbs, A. E.; Rawal, V. H. *Org. Lett.* **2016**, *18* (10), 2363–2366.
- <sup>156</sup> Adamson, N. J.; Park, S.; Zhou, P.; Nguyen, A. L.; Malcolmson, S. J. *Org. Lett.* **2020**, *22* (5), 2032–2037.
- <sup>157</sup> Nemoto, H.; Ibaragi, T.; Bando, M.; Kido, M.; Shibuya, M. *Tetrahedron Lett.* **1999**, *40* (7), 1319–1322.
- <sup>158</sup> Kawamura, T.; Matsuo, N.; Yamauchi, D.; Tanabe, Y.; Nemoto, H. *Tetrahedron* **2013**, *69* (26), 5331–5341.
- <sup>159</sup> Zhao, K.; Zhi, Y.; Wang, A.; Enders, D. *Synthesis* **2018**, *50* (04), 872–880.
- <sup>160</sup> Nemoto, H.; Kawamura, T.; Miyoshi, N. *J. Am. Chem. Soc.* **2005**, *127* (42), 14546–14547.
- <sup>161</sup> Tong, X.; Shi, B.; Liang, K.; Liu, Q.; Xia, C. *Angew. Chem. Int. Ed.* **2019**, *58* (16), 5443–5446.
- <sup>162</sup> Nemoto, H.; Kawamura, T.; Kitasaki, K.; Yatsuzuka, K.; Kamiya, M.; Yoshioka, Y. *Synthesis* **2009**, (10), 1694–1702.
- <sup>163</sup> Nemoto, H.; Ma, R.; Suzuki, I.; Shibuya, M. *Org. Lett.* **2000**, *2* (26), 4245–4247.
- <sup>164</sup> Nemoto, H.; Ma, R.; Moriguchi, H.; Kawamura, T.; Kamiya, M.; Shibuya, M. *J. Org. Chem.* **2007**, *72* (25), 9850–9853.
- <sup>165</sup> Jentsch, N. G.; Hume, J. D.; Crull, E. B.; Beauti, S. M.; Pham, A. H.; Pigza, J. A.; Kessl, J. J.; Donahue, M. G. *Beilstein J. Org. Chem.* **2018**, *14*, 2529–2536.
- <sup>166</sup> Nomura, Y.; Thuaud, F.; Sekine, D.; Ito, A.; Maeda, S.; Koshino, H.; Hashizume, D.; Muranaka, A.; Cruchter, T.; Uchiyama, M.; Ichikawa, S.; Matsuda, A.; Yoshida, M.; Hirai, G.; Sodeoka, M. *Chem. Eur. J.* **2019**, *25* (35), 8387–8392.
- <sup>167</sup> Nemoto, H.; Ma, R.; Kawamura, T.; Yatsuzuka, K.; Kamiya, M.; Shibuya, M. *Synthesis* **2008**, *2008* (23), 3819–3827.
- <sup>168</sup> Mahapatra, S.; Carter, R. G. *J. Am. Chem. Soc.* **2013**, *135* (29), 10792–10803.
- <sup>169</sup> Nemoto, H.; Ma, R.; Li, X.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2001**, *42* (11), 2145–2147.
- <sup>170</sup> Roche, S. P.; Faure, S.; Aitken, D. J. *Angew. Chem. Int. Ed.* **2008**, *47* (36), 6840–6842.
- <sup>171</sup> Nakao, Y.; Matsunaga, S.; Fusetani, N. *Bioorganic Med. Chem.* **1995**, *3* (8), 1115–1122.
- <sup>172</sup> Kher, S. S.; Penzo, M.; Fulle, S.; Finn, P. W.; Blackman, M. J.; Jirgensons, A. *Bioorg. Med. Chem. Lett.* **2014**, *24* (18), 4486–4489.

- <sup>173</sup> Cui, Y.; Zhang, M.; Xu, H.; Zhang, T.; Zhang, S.; Zhao, X.; Jiang, P.; Li, J.; Ye, B.; Sun, Y.; Wang, M.; Deng, Y.; Meng, Q.; Liu, Y.; Fu, Q.; Lin, J.; Wang, J.; Chen, Y. *J. Med. Chem.* **2022**, *65* (4), 2971–2987.
- <sup>174</sup> Esgulian, M.; Belot, V.; Guillot, R.; Deloisy, S.; Aitken, D. J. *Org. Biomol. Chem.* **2017**, *15* (6), 1453–1462.
- <sup>175</sup> Esgulian, M.; Buchotte, M.; Guillot, R.; Deloisy, S.; Aitken, D. J. *Org. Lett.* **2019**, *21* (7), 2378–2382.
- <sup>176</sup> Martin, M. J.; Rodriguez-Acebes, R.; Garcia-Ramos, Y.; Martinez, V.; Murcia, C.; Digon, I.; Marco, I.; Pelay-Gimeno, M.; Fernández, R.; Reyes, F.; Francesch, A. M.; Munt, S.; Tulla-Puche, J.; Albericio, F.; Cuevas, C. *J. Am. Chem. Soc.* **2014**, *136* (18), 6754–6762.
- <sup>177</sup> Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55* (5), 1439–1446.
- <sup>178</sup> Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2003**, *44* (1), 73–75.
- <sup>179</sup> Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135* (43), 16050–16053.
- <sup>180</sup> Hori, I.; Midorikawa, H. *Sci. Papers Inst. Phys. Chem. Res.* **1962**, (*1*), 216–217.
- <sup>181</sup> Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis.* **1982**, (01), 1–26.
- <sup>182</sup> Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22* (36), 3455–3458.
- <sup>183</sup> Vloon, W. J.; van Den Bos, J. C.; Willard, N. P.; Koomen, G. -J.; Pandit, U. K. *Recl. des Trav. Chim. des Pays-Bas* **1991**, *110* (10), 414–419.
- <sup>184</sup> Dimopoulos, P.; George, J.; Tocher, D. A.; Manaviazar, S.; Hale, K. J. *Org. Lett.* **2005**, *7* (24), 5377–5380.
- <sup>185</sup> Patschinski, P.; Zipse, H. *Org. Lett.* **2015**, *17* (13), 3318–3321.
- <sup>186</sup> Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem. Int. Ed.* **2015**, *54* (46), 13729–13733.
- <sup>187</sup> Chénard, E.; Hanessian, S. *Org. Lett.* **2014**, *16* (10), 2668–2671.
- <sup>188</sup> Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23* (12), 3081–3087.
- <sup>189</sup> Marcovici-Mizrahi, D.; Gottlieb, H. E.; Marks, V.; Nudelman, A. *J. Org. Chem.* **1996**, *61* (24), 8402–8406.
- <sup>190</sup> Adams, H.; Bawa, R. A.; Jones, S. *Org. Biomol. Chem.* **2006**, *4* (22), 4206–4213.
- <sup>191</sup> Zamani, F.; Pyne, S. G.; Hyland, C. J. T. *J. Org. Chem.* **2017**, *82* (13), 6819–6830.
- <sup>192</sup> Neouchy, Z.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2018**, *20* (19), 6017–6021.
- <sup>193</sup> Turgut, Y.; Işgin, E. S.; Hoşgören, H. *J. Chem. Res.* **2004**, (9), 605–607.
- <sup>194</sup> Dias, L. C.; De Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005**, *70* (6), 2225–2234.
- <sup>195</sup> Burwell, R. L. *J. Am. Chem. Soc.* **1942**, *64* (5), 1025–1031.
- <sup>196</sup> Sun, X.; Chen, Y.; Wu, N.; Kang, C. S.; Song, H. A.; Jin, S.; Fu, Y.; Bryant, H.; Frank, J. A.; Chong, H. S. *RSC Adv.* **2015**, *5* (115), 94571–94581.
- <sup>197</sup> Richmond, E.; Ling, K. B.; Duguet, N.; Manton, L. B.; Çelebi-Ölçüm, N.; Lam, Y. H.; Alsancak, S.; Slawin, A. M. Z.; Houk, K. N.; Smith, A. D. *Org. Biomol. Chem.* **2015**, *13* (6), 1807–1817.
- <sup>198</sup> Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41* (9), 1359–1362.
- <sup>199</sup> Haghshenas, P.; Gravel, M. *Org. Lett.* **2016**, *18* (18), 4518–4521.
- <sup>200</sup> More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4* (17), 3001–3003.
- <sup>201</sup> O'Brien P. *Enantio- and diastereoselective reactions with phosphine oxides*, PhD thesis, University of Cambridge, Cambridge, **1995**.
- <sup>202</sup> Brünjes, M.; Kujat, C.; Monenschein, H.; Kirschning, A. *Euro. J. Org. Chem.* **2004**, (5), 1149–1160.

- <sup>203</sup> Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99* (5), 1191–1223.
- <sup>204</sup> Hili, R.; Baktharaman, S.; Yudin, A. K. *Euro. J. Org. Chem.* **2008**, (31), 5201–5213.
- <sup>205</sup> Reetz, M. T. *Chem. Rev.* **1999**, *99* (5), 1121–1162.
- <sup>206</sup> Gillard, J. W.; Fortin, R.; Morton, H. E.; Quesnelle, C. A.; Daignault, S.; Guindon, Y.; Yoakim, C. *J. Org. Chem.* **1988**, *53* (11), 2602–2608.
- <sup>207</sup> Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, (9), 1031–1069.
- <sup>208</sup> Yuan, W.; Munoz, B.; Wong, C. H.; Haeggström, J. Z.; Wetterholm, A.; Samuelsson, B. *J. Med. Chem.* **1993**, *36* (2), 211–220.
- <sup>209</sup> Harvey, A. J.; Abell, A. D. *Tetrahedron* **2000**, *56* (50), 9763–9771.
- <sup>210</sup> Abell, A. D.; Harvey, A. J. *Arkivoc* **2005**, (3), 72–76.
- <sup>211</sup> Kucera D. J.; Scott R. W. US Pat, US 20050124673A1, **2005**.
- <sup>212</sup> Krantz A.; Tam T. F.; Castelhana A. L.; Nestor Jr J. J. WO Pat, 9313066A1, **1993**.
- <sup>213</sup> Sato M.; Mukoyama H., Kobayashi, J.; Tsuyuki S.; Tokutake K.; Akaba S. Jpn. Pat, 2001055366A, **2001**.
- <sup>214</sup> Hershberg, E. B.; Oliveto, E.; Rubin, M.; Staeudle, H.; Kuhlen, L. *J. Am. Chem. Soc.* **1951**, *73* (3), 1144–1145.
- <sup>215</sup> Li, Y.; Manickam, G.; Ghoshal, A.; Subramaniam, P. *Synth. Commun.* **2006**, *36* (7), 925–928.
- <sup>216</sup> Xu, C. P.; Xiao, Z. H.; Zhuo, B. Q.; Wang, Y. H.; Huang, P. Q. *Chem. Commun.* **2010**, *46* (41), 7834–7836.
- <sup>217</sup> Seki, M.; Matsumoto, K. *Synthesis* **1999**, (6), 924–926.
- <sup>218</sup> Yuan, W.; Zhong, Z.; Wong, C. H.; Haeggström, J. Z.; Wetterholm, A.; Samuelsson, B. *Bioorganic Med. Chem. Lett.* **1991**, *1* (10), 551–556.
- <sup>219</sup> Adaligil, E.; Song, A.; Hallenbeck, K. K.; Cunningham, C. N.; Fairbrother, W. J. *ACS Chem. Biol.* **2021**, *16* (6), 1011–1018.
- <sup>220</sup> Jagdmann, G. E.; Munson, H. R.; Gero, T. W. *Synth. Commun.* **1990**, *20* (8), 1203–1208.
- <sup>221</sup> Wipf, P.; Takada, T.; Rishel, M. J. *Org. Lett.* **2004**, *6* (22), 4057–4060.
- <sup>222</sup> Trapentsier, P. T.; Kalvin'sh, I. Y.; Liepin'sh, E. E.; Lukevits, E. Ya. *Chem. Heterocycl. Compd.* **1983**, *19* (3), 283–285.
- <sup>223</sup> Kung, C. H.; Kwon, C. H. *Med. Chem. Res.* **2010**, *19* (5), 498–513.
- <sup>224</sup> Kishore Kumar, G. D.; Baskaran, S. *J. Org. Chem.* **2005**, *70* (11), 4520–4523.
- <sup>225</sup> Sultane, P. R.; Bielawski, C. W. *J. Org. Chem.* **2017**, *82* (2), 1046–1052.
- <sup>226</sup> Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41* (9), 1359–1362.
- <sup>227</sup> Gryko, D.; Chałko, J.; Jurczak, J. *Chirality.* **2003**, *15*(6), 514–541.
- <sup>228</sup> Tagad, H. D.; Hamada, Y.; Nguyen, J. T.; Hamada, T.; Abdel-Rahman, H.; Yamani, A.; Nagamine, A.; Ikari, H.; Igawa, N.; Hidaka, K.; Sohma Y.; Kimura, T.; Kiso, Y. *Bioorganic Med. Chem.* **2010**, *18* (9), 3175–3186.
- <sup>229</sup> Nowrouzi, N.; Farahi, S.; Irajzadeh, M. *Tetrahedron Lett.* **2015**, *56* (5), 739–742.
- <sup>230</sup> Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123* (31), 7727–7729.
- <sup>231</sup> El Dine, T. M.; Rouden, J.; Blanchet, J. *Chem. Commun.* **2015**, *51* (89), 16084–16087.
- <sup>232</sup> Rivero, I. A.; Heredia, S.; Ochoa, A. *Synth. Commun.* **2001**, *31* (14), 2169–2175.)

- <sup>233</sup> Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Tetrahedron Asymmetry* **2004**, *15* (4), 593–601.
- <sup>234</sup> Weil, K.; Kuhn, W. *Helv. Chim. Acta* **1946**, *29* (4), 784–796.
- <sup>235</sup> Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29* (5), 1475–1478.
- <sup>236</sup> Trotter, N. S.; Brimble, M. A.; Harris, P. W. R.; Callis, D. J.; Sieg, F. *Bioorganic Med. Chem.* **2005**, *13* (2), 501–517.
- <sup>237</sup> Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42* (5), 1653–1658.
- <sup>238</sup> Lisiecki, K.; Krawczyk, K. K.; Roszkowski, P.; Maurin, J. K.; Budzianowski, A.; Czarnocki, Z. *Tetrahedron* **2017**, *73* (44), 6316–6328.
- <sup>239</sup> Riache, N.; Bailly, C.; Deville, A.; Dubost, L.; Nay, B. *Euro. J. Org. Chem.* **2010**, *28*, 5402–5408.
- <sup>240</sup> Bruckner, S.; Weise, M.; Schobert, R. *J. Org. Chem.* **2018**, *83* (18), 10805–10812.
- <sup>241</sup> Smith, G. G.; Sivakua, T. *J. Org. Chem.* **1983**, *48* (5), 627–634.
- <sup>242</sup> Dilek, I.; Madrid, M.; Singh, R.; Urrea, C. P.; Armitage, B. A. *J. Am. Chem. Soc.* **2005**, *127* (10), 3339–3345.
- <sup>243</sup> Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17* (7), 522–524.
- <sup>244</sup> Hatano, M.; Tabata, Y.; Yoshida, Y.; Toh, K.; Yamashita, K.; Ogura, Y.; Ishihara, K. *Green Chem.* **2018**, *20* (6), 1193–1198.
- <sup>245</sup> Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29* (5), 359–373.
- <sup>246</sup> Zimuwandeyi, M.; Kola, F.; Lemmerer, A.; Brady, D.; Rousseau, A. L.; Bode, M. L. *Tetrahedron* **2018**, *74* (24), 2925–2941.
- <sup>247</sup> Palomo, C.; Arrieta, A.; Cossío, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31* (44), 6429–6432.
- <sup>248</sup> Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35* (23/24), 2813–2817.
- <sup>249</sup> Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120* (2), 431–432.
- <sup>250</sup> Shi, T.; Jing, C.; Qian, Y.; Xu, X.; Alavala, G. K. R.; Lv, X.; Hu, W. *Org. Biomol. Chem.* **2019**, *17* (45), 9792–9798.
- <sup>251</sup> Métro, T. X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2007**, *72* (17), 6556–6561.
- <sup>252</sup> Poh, J.-S. S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. *Angew. Chem. Int. Ed.* **2017**, *56* (7), 1864–1868.
- <sup>253</sup> Chong, H. S.; Chen, Y. *Org. Lett.* **2013**, *15* (23), 5912–5915.
- <sup>254</sup> Dix, D.; Imming, P. *Arch. Pharm.* **1995**, *328* (2), 203–205.
- <sup>255</sup> Miller, E. J.; Mays, S. G.; Baillie, M. T.; Howard, R. B.; Culver, D. G.; Saindane, M.; Pruett, S. T.; Holt, J. J.; Menaldino, D. S.; Evers, T. J.; Reddy, P.; Arrendale, R. F.; Natchus, M. G.; Petros, J. A.; Liotta, D. C. *ACS Med. Chem. Lett.* **2016**, *7* (5), 537–542.
- <sup>256</sup> Rich, D. H.; Moon, B. J.; Boparai, A. S. *J. Org. Chem.* **1981**, *46* (26), 5458.
- <sup>257</sup> Martin, M. J.; Rodriguez-Acebes, R.; Garcia-Ramos, Y.; Martinez, V.; Murcia, C.; Digon, I.; Marco, I.; Pelay-Gimeno, M.; Fernández, R.; Reyes, F.; Francesch, A. M.; Munt, S.; Tulla-Puche, J.; Albericio, F.; Cuevas, C. *J. Am. Chem. Soc.* **2014**, *136* (18), 6754–6762.
- <sup>258</sup> Ghosh, A. K.; Dawson, Z. L.; Mitsuya, H. *Bioorganic Med. Chem.* **2007**, *15* (24), 7576–7580.
- <sup>259</sup> Fung, H. B.; Kirschenbaum, H. L.; Hameed, R. *Clin. Ther.* **2000**, *22* (5), 549–572.
- <sup>260</sup> Noble, S.; Faulds, D. *Drugs*. **1996**, *52* (1), 93–112.

- <sup>261</sup> Vloon, W. J.; van der Bas, J. C.; Willard, N. P.; Koomen, G.-J.; Pandit, U. K. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 414–419.
- <sup>262</sup> Bassindale, A. R.; Stout, T. *J. Organomet. Chem.* **1984**, *271*, 1–3.
- <sup>263</sup> Chénard, E.; Hanessian, S. *Org. Lett.* **2014**, *16* (10), 2668–2671.
- <sup>264</sup> Ivkovic, J.; Lembacher-Fadum, C.; Breinbauer, R. *Org. Biomol. Chem.* **2015**, *13* (42), 10456–10460.
- <sup>265</sup> Turgut, Y.; İşgin, E. S.; Hoşgören, H. *J. Chem. Res.* **2004**, *9*, 605–607.
- <sup>266</sup> Haghshenas, P.; Quail, J. W.; Gravel, M. *J. Org. Chem.* **2016**, *81* (24), 12075–12083.
- <sup>267</sup> Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60* (24), 8074–8080.
- <sup>268</sup> Dias, L. C.; De Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005**, *70* (6), 2225–2234.
- <sup>269</sup> Kawase, Y.; Yamagishi, T.; Kutsuma, T.; Kataoka, T.; Ueda, K.; Iwakuma, T.; Nakata, T.; Yokomatsu, T. *Synthesis* **2010**, (10), 1673–1677.
- <sup>270</sup> Brünjes, M.; Kujat, C.; Monenschein, H.; Kirschning, A. *European J. Org. Chem.* **2004**, *2004* (5), 1149–1160.
- <sup>271</sup> Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Ichihara, O. *Tetrahedron* **1994**, *50* (13), 3975–3986.
- <sup>272</sup> Seki, M.; Matsumoto, K. *Synthesis* **1999**, (6), 924–926.
- <sup>273</sup> Kung, C. H.; Kwon, C. H. *Med. Chem. Res.* **2010**, *19* (5), 498–513.
- <sup>274</sup> Kishore Kumar, G. D.; Baskaran, S. *J. Org. Chem.* **2005**, *70* (11), 4520–4523.
- <sup>275</sup> Sultane, P. R.; Bielawski, C. W. *J. Org. Chem.* **2017**, *82* (2), 1046–1052.
- <sup>276</sup> Doherty, W.; Evans, P. *J. Org. Chem.* **2016**, *81* (4), 1416–1424.
- <sup>277</sup> Tagad, H. D.; Hamada, Y.; Nguyen, J. T.; Hamada, T.; Abdel-Rahman, H.; Yamani, A.; Nagamine, A.; Ikari, H.; Igawa, N.; Hidaka, K.; Sohma, Y.; Kimura, T.; Kiso, Y. *Bioorganic Med. Chem.* **2010**, *18* (9), 3175–3186.
- <sup>278</sup> Mikolaichuk, O. V.; Zarubaev, V. V.; Muryleva, A.; Esaulkova, Y. L.; Spasibenko, D. V.; Batyrenko, A.; Korniyakov, I. V.; Trifonov, R. *Chem. Heterocycl. Compd.* **2021**, *57* (4), 442–447.
- <sup>279</sup> Bagherzadeh, N.; Sardarian, A. R.; Eslahi, H. *Mol. Catal.* **2021**, *504*, 111489.
- <sup>280</sup> Khalili, D.; Evazi, R.; Neshat, A.; Aboonajmi, J. *ChemistrySelect* **2021**, *6* (4), 746–753.
- <sup>281</sup> Nowrouzi, N.; Farahi, S.; Irajzadeh, M. *Tetrahedron Lett.* **2015**, *56* (5), 739–742.
- <sup>282</sup> Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123* (31), 7727–7729.
- <sup>283</sup> Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* **2002**, *32* (2), 189–193.
- <sup>284</sup> Weil, K.; Kuhn, W. *Helv. Chim. Acta* **1946**, *29* (4), 784–796.
- <sup>285</sup> Yamada, T.; Lukac, P. J.; Yu, T.; Weiss, R. G. *Chem. Mater.* **2007**, *19* (19), 4761–4768.
- <sup>286</sup> Fan, S.; Ding, Y.; Chen, X.; Gao, Y.; Fu, L.; Li, S.; Li, G. *J. Org. Chem.* **2019**, *84* (20), 13003–13012.
- <sup>287</sup> Zhang, Y.; Liu, P.; Zhang, H. *Macromolecules* **2010**, *43* (1), 27–29.
- <sup>288</sup> Rydzik, A. M.; Leung, I. K. H.; Kochan, G. T.; Thalhammer, A.; Oppermann, U.; Claridge, T. D. W.; Schofield, C. *J. ChemBioChem* **2012**, *13* (11), 1559–1563.
- <sup>289</sup> Odriozola, A.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2017**, *23* (52), 12758–12762.
- <sup>290</sup> Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17* (7), 522–524.
- <sup>291</sup> Hartwig, S.; Schwarz, J.; Hecht, S. *J. Org. Chem.* **2010**, *75* (3), 772–782.
- <sup>292</sup> Hatano, M.; Tabata, Y.; Yoshida, Y.; Toh, K.; Yamashita, K.; Ogura, Y.; Ishihara, K. *Green Chem.* **2018**, *20* (6), 1193–1198.



<sup>293</sup> Miller, E. J.; Mays, S. G.; Baillie, M. T.; Howard, R. B.; Culver, D. G.; Saindane, M.; Pruett, S. T.; Holt, J. J.; Menaldino, D. S.; Evers, T. J.; Reddy, G. P.; Arrendale, R. F.; Natchus, M. G.; Petros, J. A.; Liotta, D. C. *ACS Med. Chem. Lett.* **2016**, 7 (5), 537–542.

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# Résumé en français

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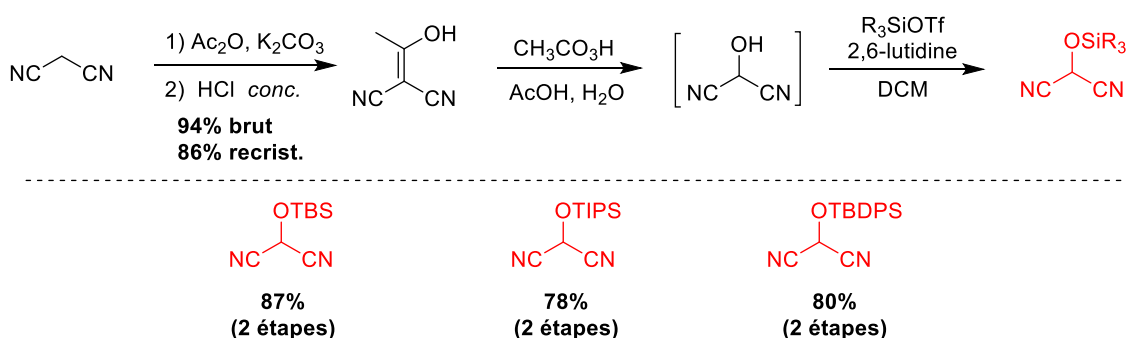
## Résumé en français

Les  $\alpha$ -hydroxy- $\beta$ -amino acides (AHBA) sont largement présents dans des produits naturels tels que l'Amastatine, le Taxol<sup>®</sup> et certains peptides macrocycliques. Parmi eux, les acides 3-amino-2-hydroxy-4-phénylbutyriques (AHPBA) sont de grand intérêt. On trouve ces motifs non seulement dans des produits naturels tels que la (-)-Bestatine et la Phébestine, mais aussi dans des produits synthétiques utilisés comme inhibiteurs du VIH-1. Au cours des six dernières décennies, de nombreuses méthodologies de synthèse ont été développées pour construire ces AHPBAs ; parmi elles, la méthodologie MAC semble être très prometteuse.

La méthodologie MAC consiste à employer des réactifs *umpolung* pour permettre l'insertion formelle d'une fonction carbonyle entre un électrophile et un nucléophile. Lorsque l' $\alpha$ -amino aldéhyde est choisi comme électrophile, la réaction conduit à l'AHBA homologué sous forme de deux diastéréoisomères *syn* et *anti*. Jusqu'à présent, la plupart des réactions MAC *one-pot* décrites dans la littérature ont conduit à une diastéréosélectivité en faveur de l'isomère *syn* (ratio *syn/anti* 80 : 20). Un seul exemple, issu du laboratoire d'accueil, a donné une diastéréosélectivité *anti* (ratio *syn/anti* 10 : 90) à partir de l'aldéhyde de Garner.

Cette thèse est consacrée au contrôle de la diastéréosélectivité de la méthodologie MAC *one-pot* à trois composants pour l'accès à des dérivés orthogonalement protégés d'AHBAs de configuration *anti*.

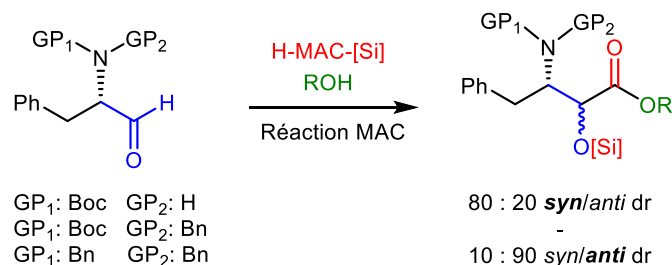
Dans un premier chapitre, nous avons d'abord optimisé chacune des trois étapes de la synthèse des réactifs MAC à partir du malononitrile. Le résultat le plus significatif est l'utilisation de triflates de silyle au lieu des chlorures de silyle habituellement utilisés dans l'étape de protection du 2-hydroxymalononitrile. Ainsi, nous avons pu établir une synthèse plus efficace et surtout reproductible de trois réactifs MAC silylés : H-MAC-TBS, H-MAC-TIPS et H-MAC-TBDPS.



### Synthèse des réactifs MAC silylés

Dans un deuxième chapitre, trois dérivés *N*-protégés du L-phénylalaninal ont ensuite été étudiés dans des réactions MAC en présence d'alcools. L'emploi du *N*-Boc-L-phénylalaninal a conduit aux  $\alpha$ -hydroxy- $\beta$ -amino esters correspondants dans un ratio 80 : 20 en faveur de l'isomère *syn* ; ce qui était conforme avec la littérature. En utilisant le *N*-Boc-*N*-Bn-L-phénylalaninal, le H-MAC-TBS et le méthanol, les esters

méthyliques d'oxyhomologation ont été isolés sous forme d'un mélange de deux diastéréoisomères, pour lesquels les configurations n'ont pas pu être attribuées. Enfin, l'oxyhomologation du *N,N*-dibenzyl-L-phénylalaninal en présence de chacun des trois réactifs MAC et de méthanol a conduit aux produits d'oxyhomologation souhaités avec de bons rendements et une haute sélectivité *anti* (ratio  $\leq 10 : 90$  *syn/anti*) ; la diastéréosélectivité n'ayant pas été influencée par la nature du réactif MAC.



#### Réactions MAC à partir de dérivés du L-phénylalaninal N-protégés

La diastéréosélectivité de la réaction MAC *one-pot* du L-phénylalaninal diversement protégé est uniquement liée à la nature des groupements protecteurs de la fonction amine. Lorsque l'amine est mono-protégée, l'hydrogène porté par l'atome d'azote semble former une liaison Hydrogène avec l'oxygène de la fonction aldéhyde pour conduire au diastéréoisomère *syn* (selon un modèle anti Felkin-Anh). Alors que lorsque la fonction amine est doublement protégée par un benzyle, le diastéréoisomère *anti* devient le produit majoritaire ; cette sélectivité peut être expliquée par un modèle de Felkin-Anh.

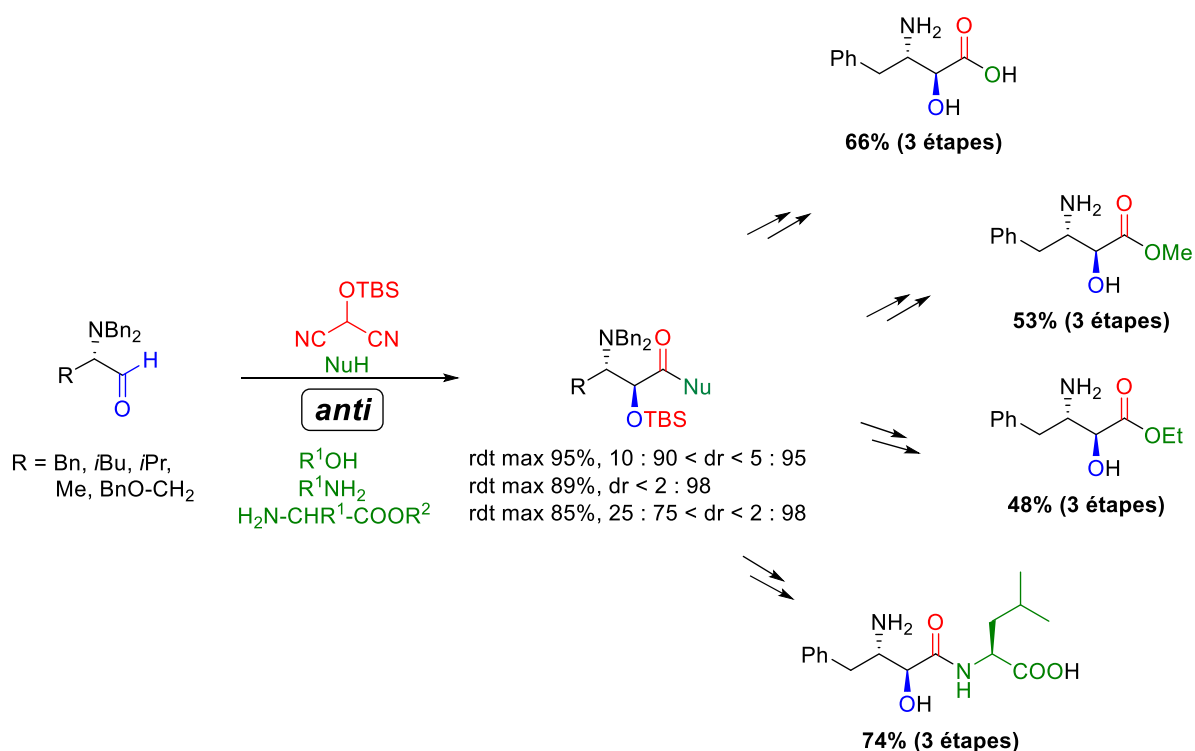
Dans un troisième chapitre, la réaction MAC a ensuite été réalisée en présence du *N,N*-dibenzyl-L-phénylalaninal, du H-MAC-TBS et de divers nucléophiles.

Lorsque des alcools ont été utilisés comme réactifs nucléophiles (11 exemples,) les esters dérivés de l'acide 3-amino-2-hydroxy-4-phénylbutyrique ont été obtenus avec des rendements allant jusqu'à 95%. Les alcools primaires ont donné les rendements les plus élevés, tandis que les alcools secondaires ont fourni les produits de réaction MAC avec de faibles rendements. Dans tous les cas, le ratio diastéréoisomérique (*syn/anti*  $\leq 10 : 90$ ) est resté constant en faveur de l'isomère *anti*. En utilisant une séquence de réactions MAC/désilylation diastéréosélective/hydrogénolyse des groupements benzyles, nous avons réussi à obtenir efficacement les esters méthylique et éthylique dérivés du (2*S*,3*S*)-AHPBA, ainsi que la (-)-allophénylnorstatine.

Le résultat le plus saillant de cette étude est la diastéréosélectivité des réactions d'oxyhomologation du *N,N*-dibenzyl-L-phénylalaninal avec l'ammoniac et des amines. Dans tous les cas, la réaction MAC a fourni uniquement le diastéréoisomère *anti* (10 exemples, rendements allant jusqu'à 89%, ratio *syn/anti*  $< 2 : 98$ ). Dans le cas de l'ammoniac comme nucléophile, le ratio diastéréoisomérique *syn/anti* a été confirmé comme étant 1.8 : 98.2 ( $< 2 : 98$ ) et la configuration *anti* du produit majoritaire a été confirmée par analyse de diffraction des rayons X. L'excès énantiomérique du produit MAC *anti* a également été établi (ee  $> 97\%$ ), confirmant qu'aucune érosion de la pureté énantiomérique inhérente au substrat aldéhydique ne s'est produite au cours de la réaction MAC.

Des  $\alpha$ -amino esters ont également été criblés comme nucléophiles dans la réaction MAC du *N,N*-dibenzyl-L-phénylalaninal avec le H-MAC-TBS. Une bibliothèque de dipeptides contenant les motifs AHPBA *anti* a été efficacement synthétisée (11 exemples, rendements allant jusqu'à 85 %, 25 : 75  $\leq$  ratio *syn/anti* < 2 : 98). Nous avons constaté que le ratio diastéréoisomérique était lié à l'encombrement stérique de la chaîne latérale de l' $\alpha$ -amino ester de départ : un ratio *syn/anti* de <2 : 98 a été observé à partir du glycinate de méthyle, tandis que le ratio diminuait à 25 : 75 lorsque le L-*tert*-leucinate de méthyle était employé. En utilisant un  $\alpha$ -amino ester achiral stériquement encombré (le ACC-OMe) dans la réaction MAC, nous avons pu confirmer que la chute ainsi observée du ratio diastéréomérique *syn/anti* (19 : 81) n'était pas inhérente à la chiralité de l' $\alpha$ -amino ester.

Pour la synthèse de l'épibestatine, le L-H-Leu-OBn a été criblé comme nucléophile. Dans la réaction MAC du *N,N*-dibenzyl-D-phénylalaninal avec le H-MAC-TBS, nous avons réussi à isoler et à identifier un sous-produit principal, à savoir un  $\alpha$ -amino nitrile. Nous avons ensuite optimisé les conditions de la réaction MAC afin de minimiser cet  $\alpha$ -amino nitrile ; cependant, les meilleures conditions réactionnelles n'ont conduit qu'à un rendement de 36 % en produit MAC (ratio *syn/anti* 14 : 86). Lorsque nous avons utilisé le *N,N*-dibenzyl-L-phénylalaninal comme substrat, un rendement de 85% en produit MAC a été obtenu (ratio *syn/anti* 12 : 88) ; indiquant la possibilité d'un phénomène de type match-mismatch dans cette réaction MAC. Après désilylation diastéréosélective suivie d'une hydrogénéolyse, la (2*S*,3*S*, *S*)-épibestatine a pu être isolée avec un rendement global de 74% sur 3 étapes.



#### Récapitulatif des résultats présentés

Enfin, dans un quatrième chapitre, divers  $\alpha$ -amino aldéhydes *N,N*-dibenzylés (issus de la leucine, valine, alanine, sérine) ont également été testés dans des réactions MAC en présence du H-MAC-TBS et d'ammoniac ou de la benzylamine comme nucléophile. Les  $\alpha$ -hydroxy- $\beta$ -amino amides correspondants

ont été obtenus avec des rendements modérés à élevés, et surtout une très haute diastéréosélectivité *anti* a été maintenue (7 exemples, rendements allant jusqu'à 92%, ratio *syn/anti* <2 : 98).

Tous ces résultats ont confirmé que le contrôle élevé de la diastéréosélectivité *anti* de la réaction MAC a été induit par l'utilisation des groupements *N,N*-dibenzyles portés par l' $\alpha$ -amino aldéhyde de départ.