Synthetic studies toward plakortolides : asymmetric synthesis of ent-plakortolide I and seco-plakortolide E

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Synthetic studies toward plakortolides: asymmetric synthesis of *ent*-plakortolide I and *seco*-plakortolide E

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Résumé de la thèse

Dans ce mémoire de thèse sont décrits nos efforts synthétiques qui ont conduits à la première synthèse totale de deux produits naturels isolés d'éponges marines du genre *Plakortis*.Deux approches synthétiques des plakortolides ont été successivement étudiées pour finalement aboutir à la synthèse de la plakortolide I qui comporte un cycle endoperoxide à 6 chainons (1,2-dioxane).

La première approche qui est une extension d'une méthode développée au laboratoire consistait à créer le cycle 1,2-dioxane par une ouverture intramoléculaire d'un époxyde vinylique par un groupement hydroperoxyde en β de l'époxyde. Cette cyclisation de type 6-*endo*-tet devait être favorisée par la présence du groupe vinyle qui stabilise le carbocation en α dans l'état de transition.

Dans un premier temps, nos nous sommes intéressés à la préparation d'un intermédiaire de synthèse, un alkoxyméthylhexa-2,5-dien-1-ol, toutes les méthodes envisagées n'ont pas donné de résultats satisfaisants en termes de rendements et/ou temps de réaction. Par le biais d'une éne reaction, nous avons réussi à synthétiser l'homologue supérieur de ce dièn ol. Celui-ci a été transformé de façon efficace en quelques étapes en un 1,2-dioxane fonctionnalisé vérifiant ainsi notre hypothèse concernant le rôle du groupe vinyle dans la stéréosélectivité de la réaction de cyclisation. L'étape suivante l'oxydation d'un alcool a échoué en raison de la fragmentation de l'endoperoxyde.

Nous avons aussi tenté de créer le cycle 1,2-dioxane par une double ouverture d'un di époxyde 1,5 par de l'eau oxygénée. Nous n'avons pas observé la formation d'endoperoxides mais d'un dérivé tétrahydropyranique obtenu par ouverture de l'époxyde par l'oxygène de l'autre fonction oxirane.

Nous avons ensuite modifié notre stratégie de synthèse en introduisant au début de la synthèse la chaine latérale de la plakortolide I en partant de la *R*-épichlorhydrine commerciale. Nous avons ainsi synthétisé le β-hydroperoxy vinyl époxyde trisubstitué, précurseur du cycle 1,2-dioxane. Lors de cette synthèse, nous avons mis au point une méthode efficace et chimiosélective de méthylenation d'une cétone en présence d'un ester utilisant le réactif de Nysted catalysé par $Ti(O\textit{i}Pr)_2Cl_2$ .La cyclisation, dans différentes conditions acides, s'effectuent exclusivement selon un mode 5-*endo*-tet pour donner le dérivé 1,2-dioxolane montrant ainsi que dans le cas de cyclisation d'époxydes *cis* trisubstitués les effets stéreoélectroniques prennent le pas sur l'effet régioinducteur d'un vinyle.

En milieu basique, en remplaçant le groupe vinyle par un groupe méthoxycarbonyle sur ces mêmes composés, a été obtenu avec un excellent rendement un dérivé 1,2-dioxolanique dont la déhydroxylation fournira un accés facile à un produit naturel : l'acide andavadoique.

La seconde approche du système bicyclique peroxylactone fait appel à une addition de Michael intramoléculaire d'un hydroperoxyde sur la double liaison d'un buténolide. Cette voie fut couronnée de succès car la (-)-*ent*-plakortolide I et la *seco*-plakortolide E ont été synthétisées.

Abstract

In this thesis manuscript are described our synthetic efforts and the first total synthesis of two natural products isolated from the sponges of the genus *Plakortis*. In total, two different synthetic approaches were studied to finally accomplish the synthesis of plakortolide I.

The first approach is an extension of the method developed by our group which consists in the creation of the 1,2-dioxane cycle by intramolecular opening of vinyl epoxide with β-hydroperoxy group. This 6-*endo*-tet cyclization should be favourable due to stabilisation of the carbocationic transition state in α position to double bond.

Firstly, we was interested in the preparation of alkoxymethylhexa-2,5-dien-1-ol, a synthetic intermediate, but all the methods that have been tested felt to give the product with satisfactory yields and/or reaction times. The higher homologue of this dienol synthesised by ene reaction, was transformed to functionalized 1,2-dioxan in a few steps. Oxidation of the alcohol was felt due to fragmentation of endoperoxide.

We have also tried to create the 1,2-dioxane cycle by double opening of bis-1,5-epoxide with hydrogen peroxide. Exclusive formation of tetrahydropyran derivatives obtained by epoxide opening by the oxygen of the second oxiran function was observed in acid conditions.

Further more we have synthesised trisubstituted β-hydroperoxy vinyl epoxide, precursor of 1,2-dioxan ring, from R-epichlorohydrin. During this synthesis a procedure of chemoselective methylenation of ketone in the presence of epoxide by Nysted reagent and $Ti(O\textit{i}Pr)_2Cl_2$ was developed. Exclusive 5-*exo*-tet cyclization to give 1,2-dioxolane derivative showed that in the case of trisubstituted *cis*-epoxides cyclization, stereoelectronic effects become more important than directing effect of the vinyl group.

The analogue of hydroperoxide where vinyl activating group was replaced by ester, in the basic conditions gave 1,2-dioxolan derivative which is closely related to natural andavadoic acid.

Finally, (-)-*ent*-plakortolide I and *seco*-plakortolide E were synthesised by intramolecular Michael addition of hydroperoxide to double bond of the butenolide moiety.

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Finally, I thank my parents, my wife Natalia, relations and Ukrainian friends for their love, understanding and support.

CONTENT

ABBREVIATIONS

$[\alpha]_D^{20}$	optical rotation
18-C-6	18-crown-6
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
acac	acetylacetonate
AIBN	*α,α′*-azoisobutyronitrile
alc.	alcohol
Alk	Alkyl
aq.	aqueous
Ar	Aryl
BAIB	bisacetoxyiodobenzene
BCIH	bis(sym-collidine)iodine(I) hexafluorophosphate
Bn	benzyl
Bu	butyl
c	concentration g/100 mL
cat.	catalytic or catalyst
CI	chemical ionisation
CM	cross metathesis
conv.	conversion
Cp	cyclopentadienyl
CSA	camphorsulphonic acid
DAA	decarboxylative allylic alkylation
DAAA	decarboxylative asymmetric allylic alkylation
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBPO	di-*t*-butyl peroxyoxalate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N′-dicyclohexylcarbodiimide
DCE	dichlorethane
DCM	dichloromethane
DET	diethyl tartrate
DIBAL	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
e^-	electron
E1cB	**E**limination **U**nimolecular **c**onjugate **B**ase
ee	enantiomeric excess
EI	electron ionisation
equiv.	equivalent

ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
G.r.	Grignard reagent
GCMS	gas chromatography - mass spectrometry
h	hour
HDA	hetero Diels-Alder
HetAr	heteroaryl
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
hν	irradiation
i	iso
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lit.	literature
M	molar concentration
m	*meta*
MBH	Morita-Baylis-Hillman
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
modp	1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentadione
mol	mole
MS	molecular sieves
MS	mass spectrometry
Ms	mesyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MW	micro wawe
N	normal concentration
n.d.	not determined
N.r.	Nysted reagent
NaHMDS	hexamethyldisilazane sodium salt
NCS	N-chlorosuccinimide
NHPI	N-hydroxyphthalimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	prostaglandin
PG	protecting group
Ph	phenyl
Piv	pivaloyl
pK_a	$-\log K_a$ (acidity constant)
PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
ppm	part per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
pTSA	*p*-toluenesulfonic acid
Py	pyridine
quant.	quantitative
R	radical
rac.	racemate
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
rt	room temperature
salen	salicylidene
SAR	structure activity relationship
SR-Ca^{2+} ATPase	sarcoplasmic reticulum Ca2+ ATPase (SERCA)
st. mat.	starting material
t	*tert*
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilane
TBHP	tertbutyl hydroperoxide
TBS	tert-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	triflate
TFE	2,2,2-trifluoroethanol
thd	2,2,6,6-tetramethylheptane-3,5-dienoate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMS	trimethylsilyl
TOCO	thiol olefin co-oxidation
TPP	tetraphenylporphyrin
Ts	tosyl

UV	ultra violet
V-70	2,2'-azobis(4-methoxy-2.4-dimethyl valeronitrile)
W	watt
δ	chemical shift
Δ	heating
µg	microgram

FOREWORD

Since ancient times, herbs and animals were used in traditional medecine to treat diseases. With the development of analytical methods and synthetic organic chemistry, the active substances of many plants were identified and modified chemically or natural product mimics were synthesized in order to find the most active structures. The analysis of the origin of drugs developed between 1981 and 2002 showed that natural products or remedies derived from natural products stand for 28 % of all chemical entities introduced to the market.

A large variety of marine natural products within the last 30 years with unique structures and promising activities against inflammatory response, cancer, infections and neurological disorders have been identified. To date approximatively 16000 marine products have been isolated from marine microorganisms. The utility of marine natural products as a potentially sustainable drug source is hampered by several significant limitations. In particular, compounds are often isolated in minute amounts. Therefore, if the structure is complex, it is an arduous, often impossible, task to isolate enough natural material for clinical trials. This is where synthetic chemistry can come to the help of the clinician. Marine natural products are often wonderful challenges to synthetic chemists.

Sponges have been amongst the most studied of marine organisms and furnish a large proportion of marine natural products. Among them, members of the genus *Plakortis and Plakinastrella* are particularly fascinating with respect to the variety of unusual metabolites they generate. In our thesis, we described our efforts to synthesize two members isolated from these sponges: plakortolide I possessing a 1,2-dioxane ring unit and seco-plakortolide E.

Sponge of Plakortis species

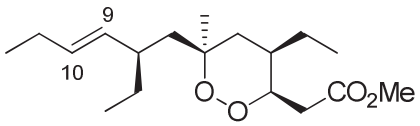
I. Bibliographical data

I.1. Endoperoxides isolated from *Plakortis* and *Plakinastrella* sponges

I.1.1. Introduction

Marine sponges of the family Plakinidae have proven to be a prolific source of oxygenated polyketides, many of them exhibiting antimicrobial, antifungal, antitumor and antimalarial activity.[1] The majority of these natural products contain six-membered peroxide rings. In addition, a few 1,2-dioxolane carboxylates have been reported.

Plakortin **I-1** (Figure I-1) was the first of the six-membered ring endoperoxides to be isolated from the sponges of the genus *Plakortis* (5.7 % dry weight).[2] Its structure was deduced from spectroscopic data and by chemical degradation and its absolute stereochemistry by the Mosher's ester method.[3] It possesses a significant antimalarial activity against chloroquine-resistant strains.[4]

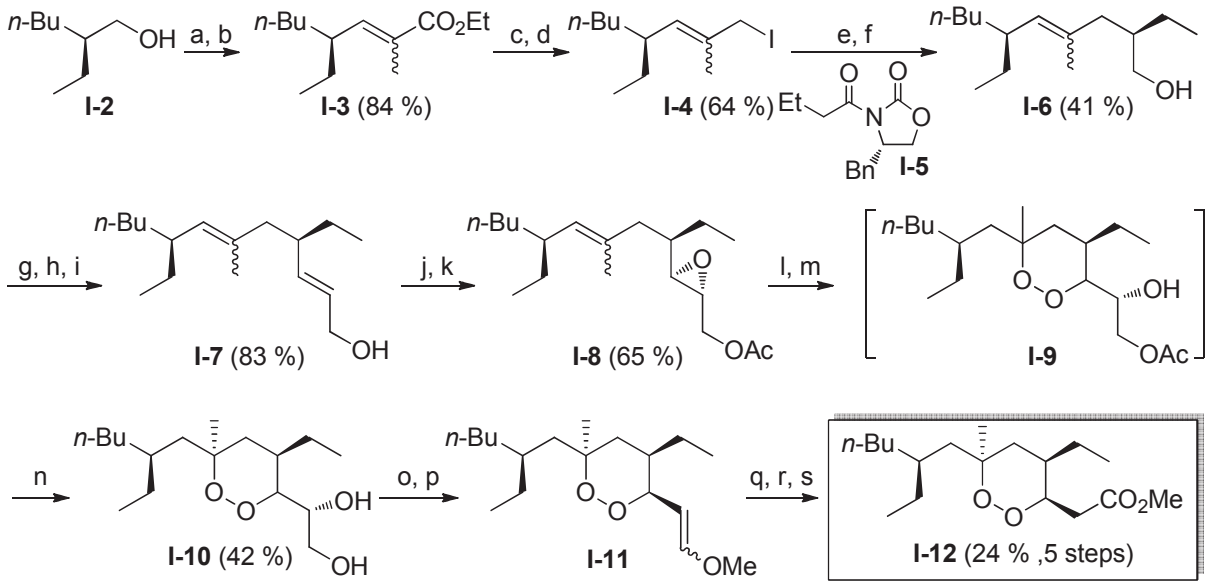


I-1

Figure I-1

SAR studies for a series of antimalarial endoperoxides based on the plakortin scaffold have shown, besides confirming the crucial role of cycloperoxide functionality, that the western side chain, the dioxane ring conformation and the absolute configuration of the stereogenic carbons are critical for antimalarial activity.[5] Only the total synthesis of the 9,10-dihydro derivative of plakortin, compound **I-12** has been recently reported and is described in Scheme I-1.[6]

The synthesis commenced by the oxidation of **I-2**, readily available by Evans's method, followed by Wittig olefination to give the α,β-unsaturated ester **I-3** as a 20:1 *E/Z* isomer mixture. Reduction of the ester function and iodination afforded the iodo **I-4**. Alkylation of the sodium enolate of **I-5** with **I-4** and cleavage of the chiral auxiliary with $LiBH_4$ provide **I-6,** which by standard functional group manipulations, furnished the allylic alcohol **I-7**. Sharplesss epoxidation of **I-7** and acetylation of the epoxyalcohol gave **I-8**. Mukaiyama-Isayama regioselective hydroperoxysilylation of **I-8** and in situ Amberlyst-15 catalyzed 6-exo-tet-cyclization gave the 1,2-dioxane **I-9** as a 1:1 mixture of diastereomers. After separation of the two diastereomers as a diol **I-10** by column chromatography, oxidative cleavage of the 1,2-diol and one-carbon Wittig olefination afforded the enol ether **I-11**. Completion of the synthesis was realized by hydrolysis of the enol ether, oxidation of the resulting aldehyde to acid by the Sharpless method and esterification to afford natural 9,10-dihydroplakortin **I-12**.



Scheme I-1

Scheme I-1. Reagents and conditions: (a) PCC, silica gel, rt; (b) $Ph_3P=C(Me)CO_2Et$, CH_2Cl_2, 16 h; (c) DIBAL-H, CH_2Cl_2, -78 °C, 1.5 h; (d) PPh_3, imidazole, I_2, $MeCN/Et_2O$, 0 °C, 1.5 h; (e) **I-5**, NaHMDS, THF, -78 °C, 1.5 h then **I-4**, -35 °C, 5 h; (f) $LiBH_4$, EtOH, Et_2O, 0 °C, 3 h; (g) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 4 h; (h) NaH, $(EtO)_2POCH_2CO_2Et$, THF, 0 °C, 2 h; (i) DIBAL-H, CH_2Cl_2, -78 °C, 1.5 h; (j) 4Å MS, $Ti(OiPr)_4$, (-)-DIPT, *t*BuOOH, CH_2Cl_2, -25 °C, 48 h; (k) Ac_2O, Pyr., DMAP, CH_2Cl_2, 0 °C, 3 h; (l) $Co(thd)_2$, Et_3SiH, O_2, $(CH_2Cl)_2$, 25 °C, 5 h; (m) Amberlyst-15, CH_2Cl_2, 25 °C, 18 h; (n) K_2CO_3, MeOH, 3 h, 0 °C; (o) $NaIO_4$, $MeOH/H_2O$, 25 °C, 1 h; (p) $(MeOCH_2)PPh_3^+ Cl^-$, NaHMDS, -78 °C→0 °C; (q) 6 N HCl, acetone, 25 °C, 0.5 h; (r) $RuCl_3$, $NaIO_4$, $MeCN/H_2O$, 25 °C, 1 h; (s) CH_2N_2, Et_2O, 25 °C, 0.5 h.

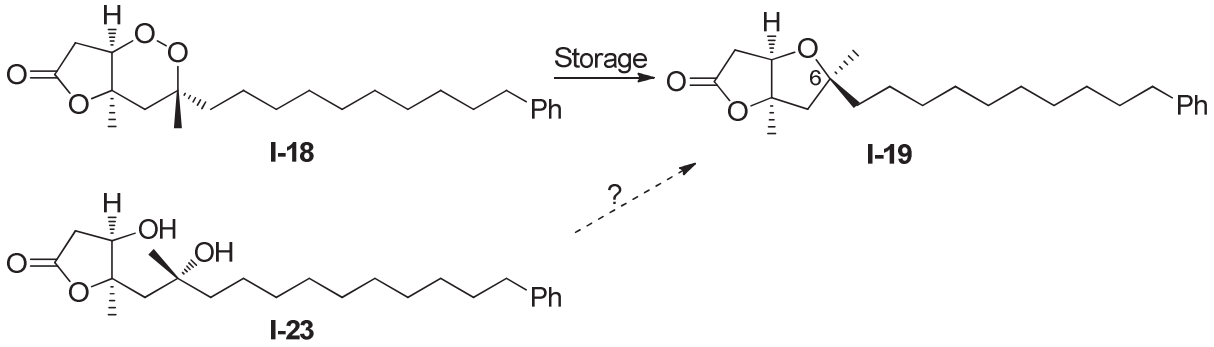
Since the isolation of plakortin, a large number of stable endoperoxides have been isolated and categorized as belonging to the plakortolide, plakortide, 3,6-dihydro-1,2-dioxin, endoperoxy acetal and plakinic acid families.

I.1.2. Plakortolides

I.1.2.1. Structures and biological activities

In 1980, Faulkner and Stierle described the isolation of the first peroxylactone **I-13**, metabolite of the sponge *Plakortis halichondrioides* (Figure I-2).[7] Its structure was first established by interpretation of spectral data and later on its relative and absolute stereochemistry have been determined by optical rotation computations.[8] This plakortolide **I-13** exhibited potent inhibitory effect against the protozoan *Toxoplasma gondii*, a major cause of morbidity and mortality in AIDS patients.[8] Since the paper of Faulkner, twenty-one plakortolides have been isolated from sponges of the family Plakinidae.[9-16] These plakortolides exhibit variation in side chain length (in general C8 or C10 or C12, one example of C9 and C16), in its degree of unsaturation or methylation and terminal group (generally a phenyl; few examples with *p*-hydroxyphenyl group). Plakortolides F **I-14** and J **I-15**, isolated from Puerto Rican sponge *Plakortis halichondrioides*, are the rare examples of plakortolides

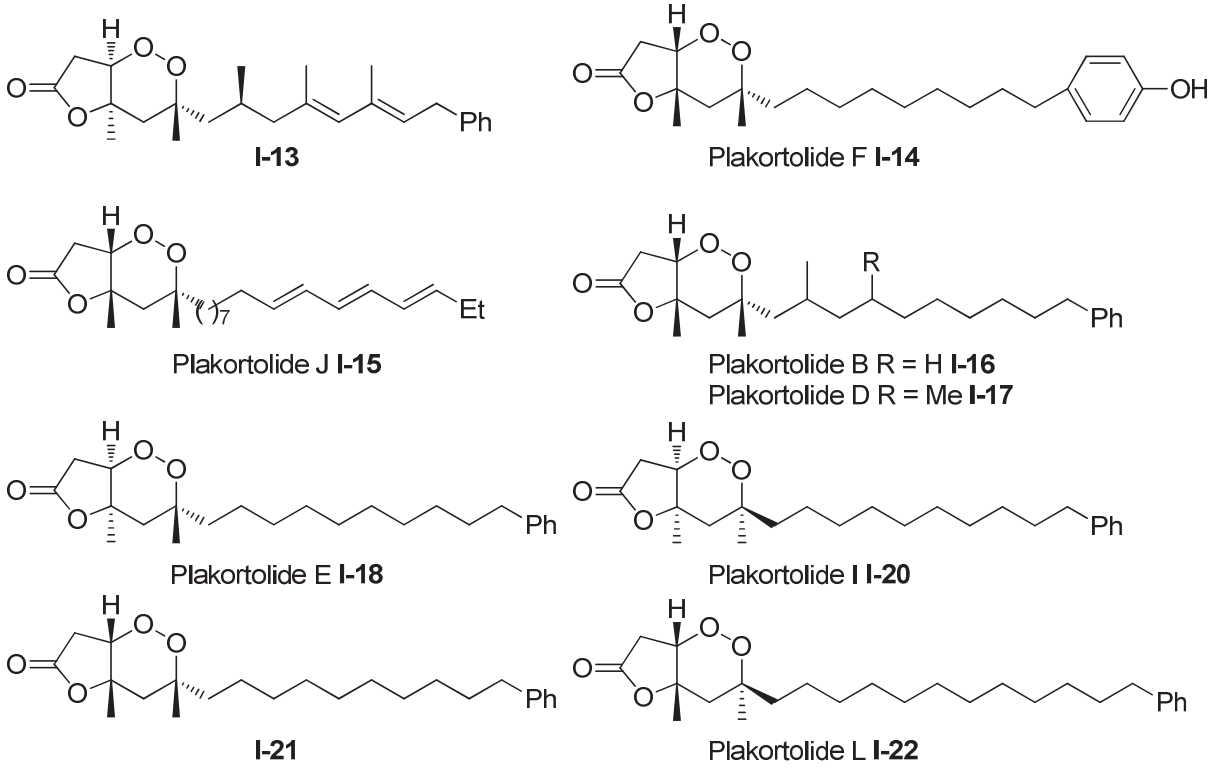
bearing a side chain respectively in C9 and C16.[10,11] They are inactive against *Plasmodium falciparum* and *Candida albicans*. Plakortolides B **I-16** and D **I-17** bearing a branched side chain by one or two methyl groups were found cytotoxic against A549 human lung carcinoma and P388 murine leukemia cell lines.[12] In 1995 Crews and Coll. isolated, from Fijian sponge *plakortis sp*. plakortolide E **I-18**. Its structure and the relative stereochemistry of the bicyclic ring substituents were established from 2D NMR data.[13] The absolute configuration of the three stereogenic centers was assigned using the modified Mosher's method. The authors had noted that during one year storage of **I-18**, it rearranged to plakortolide ether **I-19** (Scheme I-2).



I-18 **I-19** **I-23**

Scheme I-2

Few years later, were isolated plakortolide I **I-20** and compound **I-21**, diastereomers of **I-18**.[14,15] Very recently, nine new plakortolides were described By Garson and Coll., among them plakortolide L **I-22,** with a C12 chain, an homologue of plakortolide E **I-18**.[16]



I-13

Plakortolide F **I-14**

Plakortolide J **I-15**

Plakortolide B R = H **I-16**
Plakortolide D R = Me **I-17**

Plakortolide E **I-18**

Plakortolide I **I-20**

I-21

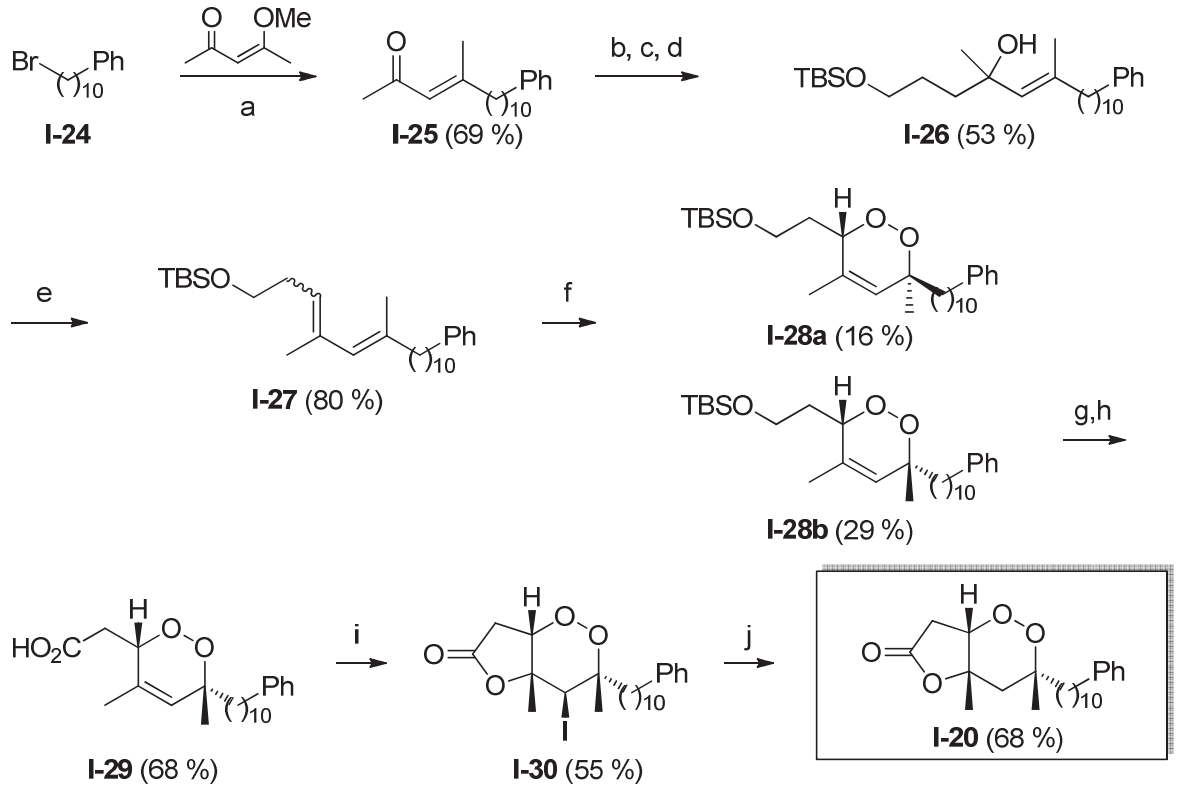
Plakortolide L **I-22**

Figure I-2

These authors compared NMR data of the bicyclic core of the new peroxylactone **I-22** with that of **I-18** and noticed a large difference particularly for C-3, C-4 and C-6 Me group (compound **I-22**: C-3, δ_H=4.43; δ_C=81.0; C-4, δ_C=82.5; C-6 δ_C=79.9; and C-24 δ_H=1.27; δ_C=22.2; for plakortolide E **I-18**: C-3: δ_H=4.19; δ_C=73.7; C-4,δ_C=90.1; C-6 δ_C=72.9 and C-24 δ_H=1.35; δ_C=29.9). The same NMR data discrepancies were observed between that of plakorlolide E **I-18** and those of its diastereomers **I-20, I-21**.[14,15] Finally, Garson and Coll. showed that the structure of "plakortolide E" matched better with that of the diol **I-23** (Scheme I-2). It still remains a question: by what mechanism the diol **I-23** can be transformed to plakortone **I-19** with inversion of the configuration at C-6 (Scheme I-2)?

I.1.2.2. Total synthesis of (±)-plakortolide I 20

To date, there is only one total synthesis of one of the plakortolides: plakortolide I **I-20** (Scheme I-3).[17] The synthesis started by reaction of the Grignard reagent derived from commercially available 1-bromo-10-phenyldecane **I-24** with 4-methoxy-pent-3-en-2-one to give the *E* α,β-unsaturated ketone **I-25** in good yield. Addition of allylmagnesium bromide to ketone **I-25** followed by chemioselective hydroboration of the terminal olefin and selective protection of the resulting alcohol as a *t*-butyldimethylsilyl ether afforded the tertiary allylic alcohol **I-26** in 53 % for the three steps.



Scheme I-3

Scheme I-3. Reagents and conditions: (a) Mg, ether, rt, 2 h; (b) allylmagnesium bromide, ether, 0 °C, 1.5 h; (c) 9-BBN, rt, then 3N $NaOH/H_2O_2$; (d) TBSCl, imidazole, DMF, rt, 4 h; (e) TsOH cat., $CaCl_2$, benzene, rt, 2 h; (f) O_2, 500-W lamp, rose Bengal, 0 °C, CH_2Cl_2-MeOH, 6 h; (g) 10 % HCl, THF-MeOH, rt, 1 h; (h) Jones'reagent, acetone, rt, 48 h; (i) $NaHCO_3$-I_2, $CHCl_3$-H_2O, rt, 48 h; (j) AIBN, Bu_3SnH, benzene, 80 °C, 1 h.

Acid-induced dehydration of alcohol led to the substituted 1,3-diene **I-27**, obtained as a mixture of isomers (*E/E:Z/E* in 1.8:1 ratio), in excellent yield. [4+2] Photocycloaddition between **I-27** and singlet oxygen, in the presence of rose bengal, at 0 °C, afforded the mixture of endoperoxides **I-28a,b** in 45 % yield. Deprotection of TBDMS ether followed by Jones oxidation of the resulting alcohol gave the acid **I-29** in 68 % yield. α-Face directed iodolactonisation of **I-29** gave the 5-β-iodo-plakortolide I **I-30** in moderate yield. Radical reduction of **I-30** afforded racemic plakortolide I **I-20**.

I.1.3. Plakortides

Plakortides, which are structurally closely related to plakortin, are the largest family of 1,2-dioxanes. They have in common an ethyl substituent in C-4 and C-6, a carboxymethyl group in C-3 and differ by their side chain in C-6 and by their relative stereochemistry. These compounds possess cytotoxic, antimalarial, and antileishmanial activity. They are also activator of cardiac SR-Ca^{2+} ATPase. Representative examples of plakortides are depicted in figure I-3.

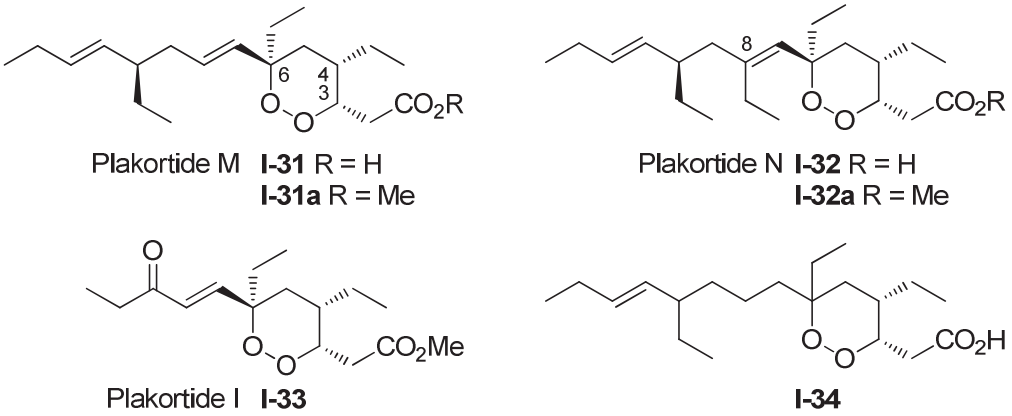
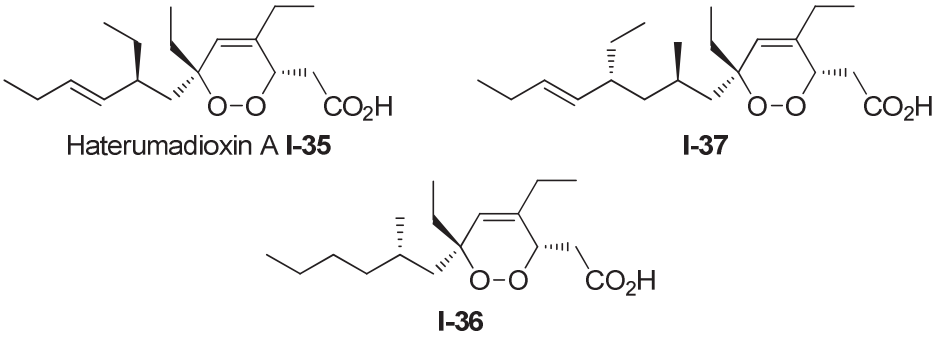


Figure I-3

As observed for plakortin, the structure of the side chain of plakortides has a large influence on their biological activities. For example, Plakortide M methyl ester **I-31a** displayed strong antimalarial activity against *Plasmodium falciparum* whereas plakortide N methyl ester **I-32a** which differs from **I-31a** by an ethyl group in C-8 has only a modest antimalarial activity (IC_{50} 8 for **I-31a** and ≥50 µg/mL for **I-32a**).[18] On the other hand, plakortide N **I-32** is a potent antiparasitic compound against *Leishmania chagasi* and *Trypanosoma cruzi* and exhibited antineuroinfammatory activity.[19] Plakortide I **I-33,** possessing an α,β-unsaturated function, has a significant antimalarial activity against W2 clone *Plasmodium falciparum*.[20] Finally, Compound **I-34**, isolated from *Plakortis halichondrioides*, is cytotoxic against P-388 murine leukemia (IC_{50}=0.5 µg/mL).[21]

I.1.4. Endoperoxides bearing a 3,6-dehydro-1,2-dioxan ring

This family consists of eight members, isolated from sponges collected in different parts of the world (Norway, Japan, Venezuela, Palau), some of which have interesting cytotoxic properties (Figure I-4). Thus, haterumadioxin A **I-35** inhibited the growth of P 388 cell in a small concentration (IC_{50} = 0.0055 µg/mL).[22]



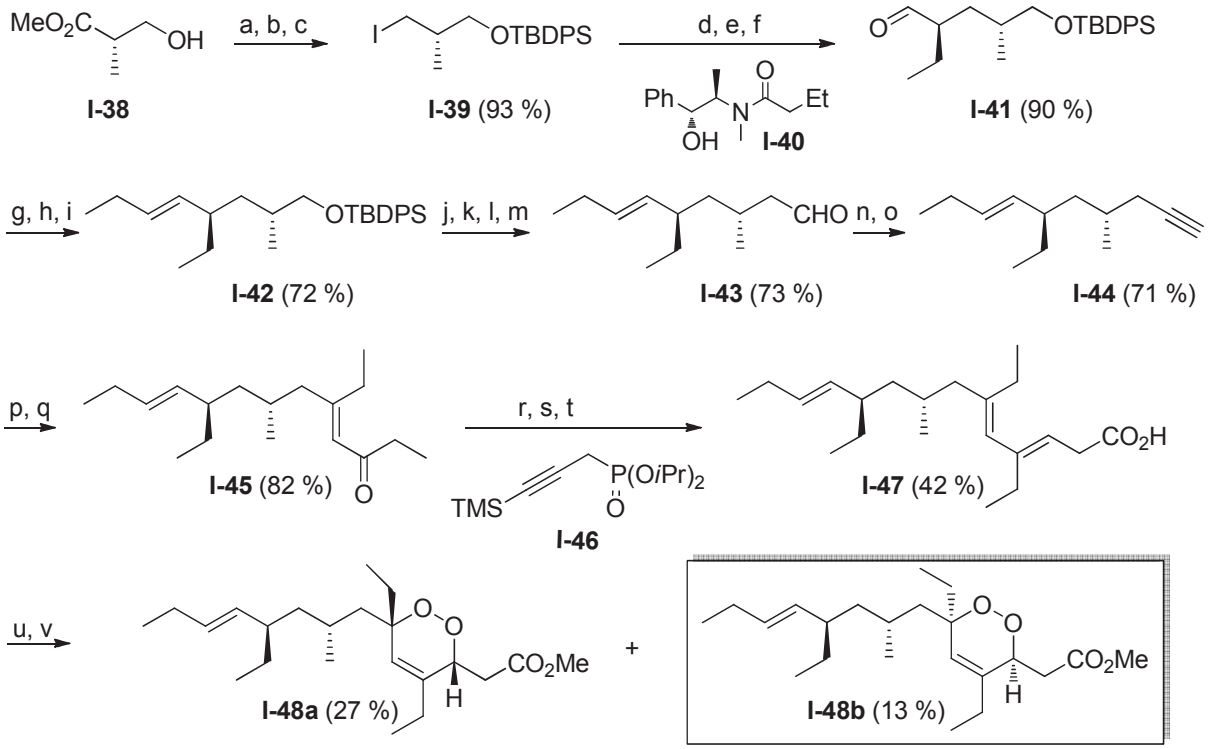
Haterumadioxin A **I-35** **I-37** **I-36**

Figure I-4

Compound **I-36**, found in the Paluan sponge *Plakortis angulospiculatus* showed strong antiproliferative effect on *Leishmania Mexicana*.[23] Compound **I-37**, isolated from the Venezuelian marine sponge *Plakortis angulospiculatus*, is a potent cytotoxic agent against murine leukemia P-388 (IC_{50} = 0,3 µg/mL) and possesses an interesting antifungal activity against *Candida Albicans*.[24] A total synthesis of compound **I-37** methyl ester **(I-48b)** was recently reported and is outlined in Scheme I-4.[25]

Synthesis the methyl ester of **I-37**, compound **I-48b**, commenced by a protection of the primary alcohol of the commercially available compound **I-38** as a *t*-butyldiphenylsilyl ether followed by reduction of the ester function with DIBAL and iodination of the resulting alcohol to give **I-39**. Asymmetric alkylation of the lithium salt of **I-40** derived from (+)-pseudoephedrine with the iodo **I-39**, removal of the chiral auxiliary by reduction to an alcohol function which in turn is oxidized by Swern's method to the aldehyde **I-41** in an excellent overall yield. Compound **I-41** was submitted to Julia-Lythgoe olefination followed by acetylation of the resulting hydroxyl sulfones and reduction of the acetoxy sulfones with magnesium amalgam to afford a 6:1 *E:Z* ratio of **I-42** . Oxidative one-carbon homologation was effected by TBDPS removal, iodination, substitution of the iodide by a nitrile function and finally reduction with DIBAL to afford the aldehyde **I-43** in 73 % yield for the four steps. The aldehyde **I-43** was transformed to alkyne **I-44** by a two-step procedure developed by Corey. Addition of $EtCu[Me_2S]MgBr_2$ at low temperature to alkyne **I-44** generated a gem disubstituted alkenylcuprate which was acylated, in situ, with propionyl chloride to afford the enone **I-45** in high diastereomeric purity. Olefination of the ketone of **I-45** was effected with the lithium salt of the phoshonate **I-46** bearing a protected alkyne function and then the carboxymethyl function was unmasked by treatment of the dienyne under the conditions developed by Zweifel and Backlung which consists on a regioselective hydroboration with dicyclohexyldiborane followed by oxidation of the resultant 1-boryl-1-silylalkene with H_2O_2 to provide the trienic acid **I-47**. The stage was now set up to introduce the endoperoxide function. To attain this goal, **I-47** was irradiated with a sun lamp in the presence of rose

bengal and oxygen to give a 2:1 mixture of peroxy carboxylic acids which after esterification afforded **I-48a,b** in 40 % overall yield. After separation of the two diastereomers by reverse phase HPLC, the absolute configuration of C-3 and C-6 stereogenic centers of **I-48a,b** was established using the Mosher's method.



Scheme I-4

Scheme I-4. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, 5 h; (b) DIBAL, toluene, - 78 °C→ rt, 2 h; (c) PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C→rt, 2 h; (d) **I-40**, LDA, 0 °C →rt, 24 h; (e) LiH_2NBH_3, THF, 0 °C→ rt, 8 h; (f) $(COCl)_2$, DMSO, -78 °C then Et_3N, -78 °C →rt; (g) *n*-$PrSO_2Ph$, BuLi, THF, -78 °C; (h) Ac_2O, TEA, DMAP; (i) Mg, $HgCl_2$, EtOH, rt; (j) TBAF, THF, rt; (k) I_2, PPh_3, imidazole, toluene, rt; (l) NaCN, DMF, rt; (m) DIBAL, Et_2O, -78 °C→0 °C; (n) PPh_3, CBr_4, K_2CO_3, CH_2Cl_2, 0 °C→rt; (o) *n*-BuLi, THF, -78 °C; (p) EtCu[Me_2S]$MgBr_2$ /Et_2O/Me_2S, -25 °C, 12 h; (q) HMPA, THF, EtCOCl, $Pd(PPh_3)_4$, -30 °C→rt; (r) **I-46**, *t*-BuLi, THF, -78 °C→rt; (s) $(C_6H_{11})_2BH$, THF, 0 °C; (t) H_2O_2, NaOH, 0 °C; (u) $^1O_2$, hν, rose bengal, MeOH, CH_2Cl_2, 8 h; (v) CH_2N_2.

I.1.5. Endoperoxy acetals (3-methoxy-1,2-dioxanes)

A large number of members of this family have been isolated from different species of genus *Plakortis*. As seen in Figure I-5, the structure of these compounds is quite diversified. Among them, there are peroxyplakoric acids such as peroxyplakoric acids A_3 **I-49a** and B_3 **I-49b**, which are diastereomers, and showed strong and similar anti-malarial potency against *Plasmodium falciparum*.[26]

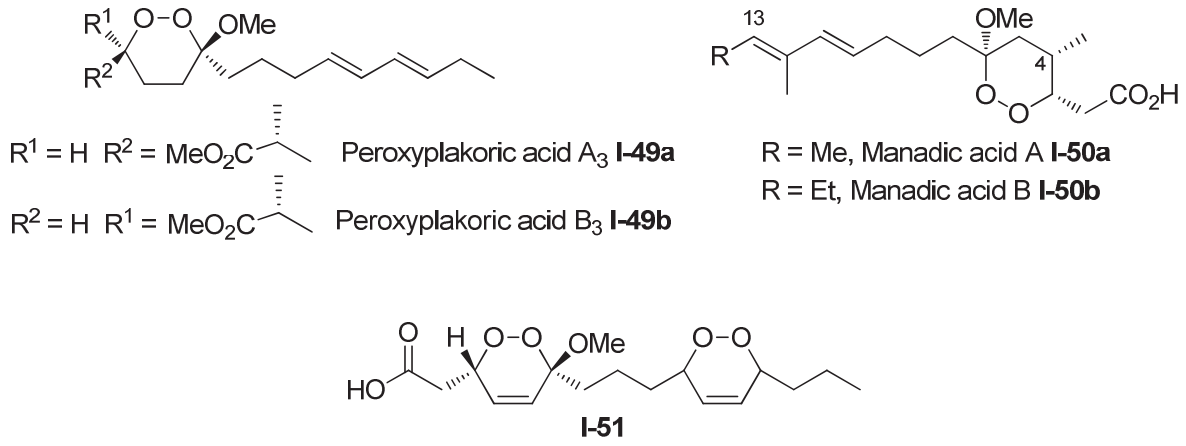


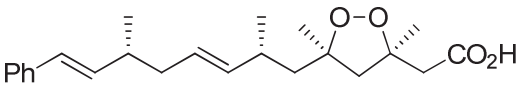
Figure I-5

Manadic acids A **I-50a** and B **I-50b,** which bear a methyl substituent in C-4 and differ by the substituent in C-13, are significantly active against several antitumor cell lines.[27] The structure of compound **I-51** is noteworthy because it is the first example of bis-1,2-dioxene polyketide. This compound is cytotoxic to P388 murine leukemia cells (IC_{50} < 0.1 µg/mL).[28]

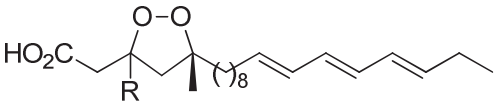
I.1.6. Plakinic acids

I.1.6.1. Bearing a 1,2-dioxolane ring

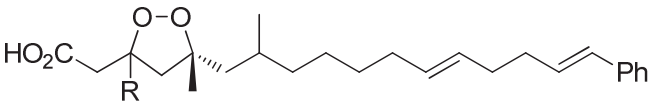
A number of bioactive molecules containing a 1,2-dioxolane subunit have been isolated from sponges *Plakortis* and *Plakisnastrella*. Other common features of these naturally occurring 1,2-dioxolanes are methyl substituents at the C-3 and C-5 positions and a CH_2CO_2H group at the C-3 position (Figure I-6). It is also noteworthy that in most sponges these 1,2-dioxolanes exist as a mixture of diastereomers (mixture of 3,5-*cis* and 3,5-*trans*).[10-29] In 1983 was isolated the first compound of this class: plakinic acid A **I-52** which displayed potent antimicrobial activity.[30] Its structure was assigned by spectroscopic techniques and chemical degradation[30] and the relative and absolute configuration of its stereogenic centers by total synthesis.[31] In 1991 Davidson isolated from Fijian *Plakortis* sponges four new 1,2-dioxolanes among them plakinic acid C **I-53a** and its 3-epimer **I-53b** which exhibit high cytotoxicity against a number of cancer cell lines (for example IC_{50} for L 1210 murine leukemia : 0.017 µg/mL for **I-53a** and 0.026 µg/mL for **I-53b**).[9] In *Plakinastrella* sponges were isolated antifungal plakinic acids **I-54a-b** which contain a conjugated triene functionality.[10] Interestingly, in Puerto Rican sponge *Plakortis halichondrioides,* only epiplakinic acid F **I-54b** was found.[11] From the extract of the sponge which contains plakortolide I **I-20** has been isolated andavadoic acid **I-55** which displayed significant activity against 13 tumor cells with IC_{50} values in the submicromolar range.[13]



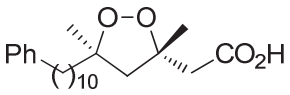
Plakinic acid A **I-52**



R = β-Me Plakinic acid F **I-54a**
R = α-Me Epiplakinic acid F **I-54b**



R = β-Me Plakinic acid C **I-53a**
R = α-Me Epiplakinic acid C **I-53b**

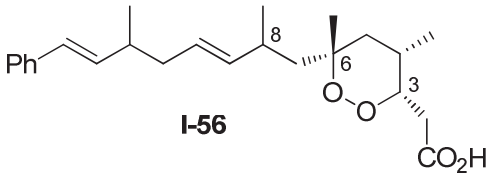


Andavadoic acid **I-55**

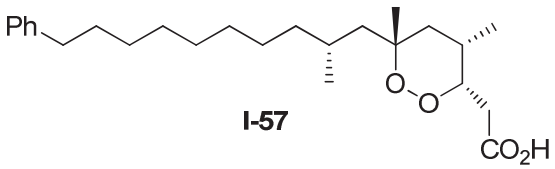
Figure I-6

I.1.6.2. Bearing a 1,2-dioxane ring

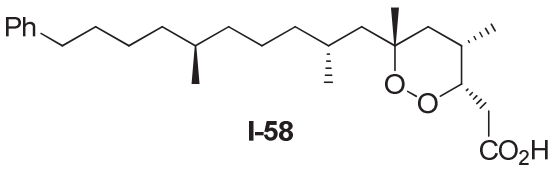
This family consists on only very few members which have in common a methyl substituent in C-3 and C-6 (Figure I-7). Plakinic acid A **I-56,** bearing a C8 side chain**,** was isolated in the same time than that plakinic acid A **I-52** and is a quite active antifungal agent.[30] Very recently were isolated, from the symbiotic sponge association *Plakortis halichondrioides-Xestospongia deweerdtae,* plakinic acis I **I-57** and K **I-58** which showed high potent antifungal activity against seven strains (MICs ≤ 0.50µg/mL).[32]



I-56



I-57



I-58

Figure I-7

I.2. Construction of 1,2-dioxanes

I.2.1. Introduction

The chemistry of endoperoxides has been associated with the isolation and synthesis of naturally occurring endoperoxides as well as with the study of their physiological properties and their biosynthesis. Ascaridole **I-59** was the first naturally occurring product possessing the 1,2-dioxane framework (Figure I-8). It was isolated from chenopodium oil in 1911 and used as an anthelmintic drug.[33] In the 1970s, the recognition of the central role of endoperoxides in various vital biological processes has led to a great acceleration in the

chemistry of endoperoxides. Following the postulation of prostaglandin endoperoxides as biosynthetic products, unstable PGH_2 (**I-60a**) and PGG_2 **(I-60b)** were isolated and identified as key intermediates in prostaglandin's biosynthesis from arachidonic acid.[34] Few years later, the total synthesis of PGH_2 and PGG_2 was reported.[35,36] The interest in prostaglandin endoperoxides has led to the development of new methods for the synthesis of endoperoxides. Yingzhaosu A **I-61**[37] and Artemisinin **I-62**,[38] two powerful antimalarial agents isolated from plants in 1979 and later on endoperoxides isolated from marine sponges, many of which exhibiting antimalarial activity, have been responsible for the resurgence in the development of new synthetic methods for cyclic peroxides, in quest of new antimalarial drugs active against multidrug resistant *Plasmodium falciparum* strains. Chemistry and synthesis of 1,2-dioxanes and other endoperoxides have been abundantly reviewed.[39]

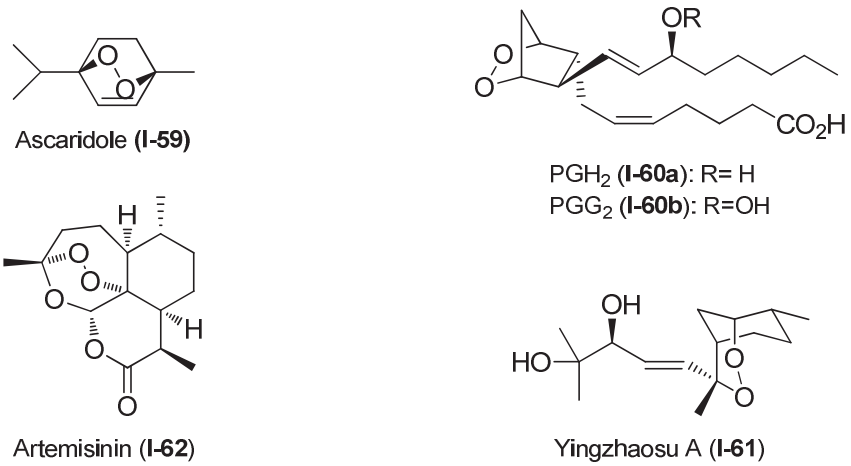


Figure I-8

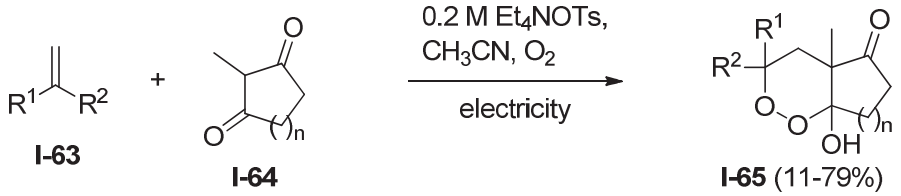
As seen above, if there are a large number of methods for the 1,2-dioxane synthesis, only few are sufficiently versatile to be applicable in the synthesis of natural compounds and analogues. Among the most useful methods to build a six-membered endoperoxide ring, there is the cycloaddition of singlet oxygen with 1,3-dienes, peroxy radical addition on alkenes and cyclization of hydroperoxides through nucleophile substitution and addition to carbon-carbon double bonds.

I.2.2. Formal [2+2+2] cycloaddition

1,2-dioxanes can be obtained, via formal [2+2+2] cycloaddition, from radical reaction between an alkene, a β-dicarbonyl derivative and O_2, initiated by electricity, radical initiators or Mn(III) salts or by photooxygenation of diaryl alkenes catalyzed by TiO_2. Unfortunately, application of these reactions to target-oriented synthesis is limited due to specific functional groups needed for the starting materials.

I.2.2.1. [2+2+2] Cycloaddition with β-ketocarbonyl compounds

Electrochemical oxidation of 1,3-dicarbonyl compounds **I-64**, in the presence of alkenes **I-63** and oxygen, produces 1,2-dioxane-3-ols **I-65**, the product of formal [2+2+2] cycloaddition, with 11-79 % yields (Scheme I-6).[40] It is interesting to note that only catalytic amount of electricity was needed to initiate the process and consequently an electroinitiated radical chain mechanism was proposed. This mechanism proposal prompted authors to investigate the use of radical initiators instead of electricity. AIBN was found to be an effective initiator for this reaction and the products were obtained in 12-90 % yields.



n= 1,2

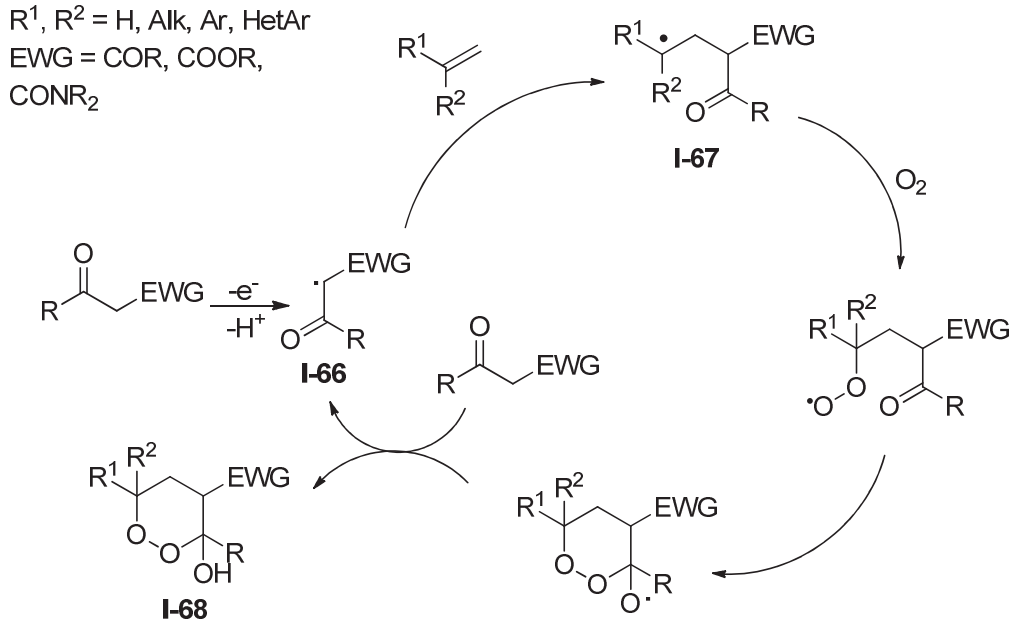
R^1 = Ph, EtO, $TMSCH_2$, Alk;

R^2 = H, Me

Scheme I-6

In 1990 Nishino and coworkers reported that Mn(III)-mediated radical cyclization of alkenes and 1,3-dicarbonyl compounds in the presence of oxygen at room temperature to give 1,2-dioxane-3-ols in good yields (50-90 %).[41] Only alkenes substituted by aryl groups gave the desired products in correct yields. It should be noted that monocabonyl compound was also used in the similar reaction, catalyzed by Mn(II), but in this case the presence of an aryl group on alkene seems to be important.[42]

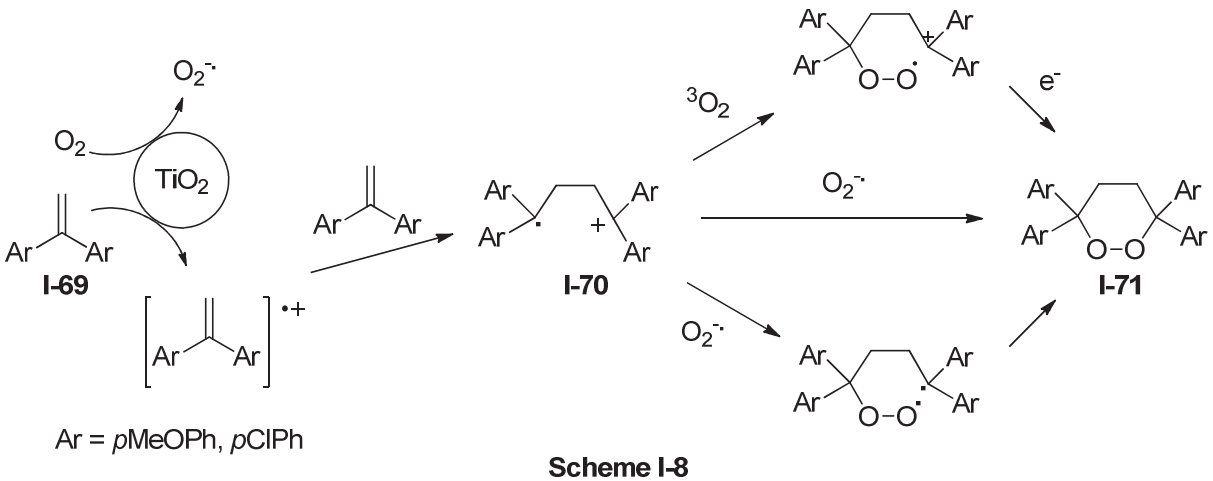
A general mechanism for this [2+2+2] radical cycloaddition, outlined in Scheme I-7, involves a radical formation of 1,3-dicarbonyl compound **I-66**. This ambident radical adds to the olefin to give the radical intermediate **I-67**, trapped by molecular oxygen followed by cyclization. Abstraction of hydrogen from another molecule of 1,3-dicarbonyl compound produces the cyclic peroxide **I-68** and regenerates the radical species.



Scheme I-7

I.2.2.2. Cycloaddition of triplet oxygen with cation radicals

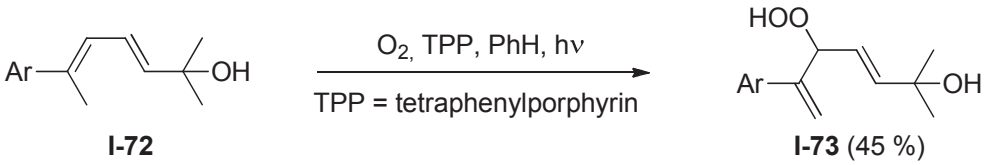
Utilization of semiconductors (TiO_2, CdS, ZnS) as redox type heterogeneous photocatalysts for various photoinduced electron transfer reactions, using photoexcitation from their valence bands to conduction bands, is well precedented. The semiconductor catalyzed photoreactions of alkenes, in the presence of oxygen, produce carbonyl derivatives, epoxides and hydroperoxides. In 2004 Mizuno and coworkers described a [2+2+2] cycloaddition of 1,1-diarylethenes **I-69** with O_2 to give 3,3,6,6-tetraaryl-1,2-dioxanes **I-71** in moderate to good yields.[43] The proposed mechanism involves carbocation-radical **I-70** formation and subsequent reaction with triplet oxygen or superoxide ion (Scheme I-8). The reaction is limited to alkenes with two electron rich aryl groups.[44]



Scheme I-8

I.2.3. [4+2] Cycloaddition of singlet oxygen with 1,3-dienes

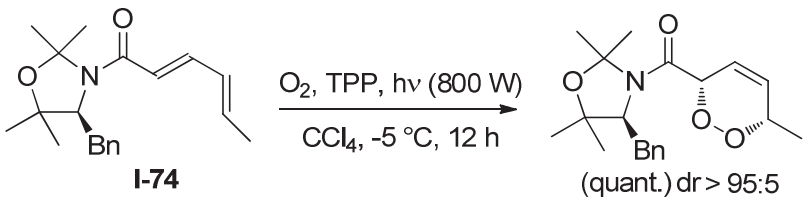
Cycloaddition of singlet oxygen to an acyclic 1,3-diene offers a most direct synthetic route to unsaturated 1,2-dioxanes. Nevertheless, competing chemical reactions such as dioxetane formation and the ene reaction are the weak points of this 1,2-dioxane ring forming.[45] For example, an attempt preparation of a dehydro derivative of yingzhaosu C by photooxygenation of the diene **I-72** afforded the hydroperoxide **I-73** resulting from the ene reaction (Scheme I-9).[46]



I-72 **I-73** (45 %)

Scheme I-9

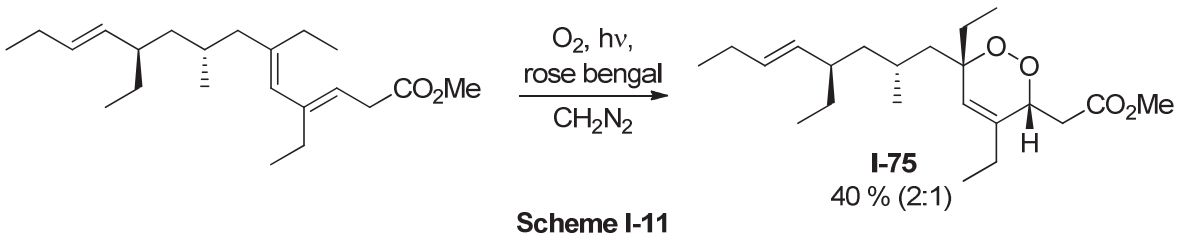
Some aspects of the reaction mechanism of this photocycloaddition are noticeable such as the relative configuration of the product is dependent on the stereochemistry of the diene as a consequence of a pseudo-concerted mechanism reaction with an oxygen addition in a *syn*-fashion. Also, the s-*cis* conformation requirement of the butadiene derivatives has for consequence that the *E,E*-isomer which has a higher population of this conformation reacts much faster than the *E,Z* and *Z,Z* isomers. High π-facial selectivity was observed in the [4+2]-cycloaddition between optically active 2,2-dimethyloxazolidine derivative of sorbic acid **I-74** and singlet oxygen (Scheme I-10).[47]



I-74 (quant.) dr > 95:5

Scheme I-10

This Diels-alder reaction was applied to the synthesis of several cyclic peroxides and analogues isolated from marine sponges *Plakortis species*.[5b,17,25] Thus, Steliou et al synthesized the natural product **I-75**, a potent antitumoral and antifungal compound, having a 3,6-dihydro 1,2-dioxin ring , using [4+2] photocycloaddition as a key step (Scheme I-11).[25]

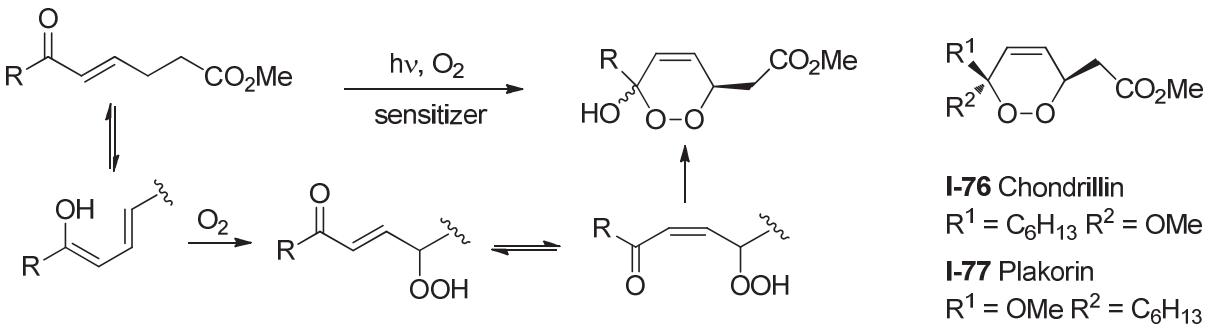


I-75
40 % (2:1)

Scheme I-11

A related photooxygenation procedure, developed by Snider et al, involves a photoenolization of an α,β-unsaturated ketone to a dienol followed by an oxygenation to form

an intermediate (*E*)-4-hydroxyperoxyenone. Photochemically induced *E* to *Z* isomerization followed by spontaneous ring closure give a dioxinol (Scheme I-12).[48]

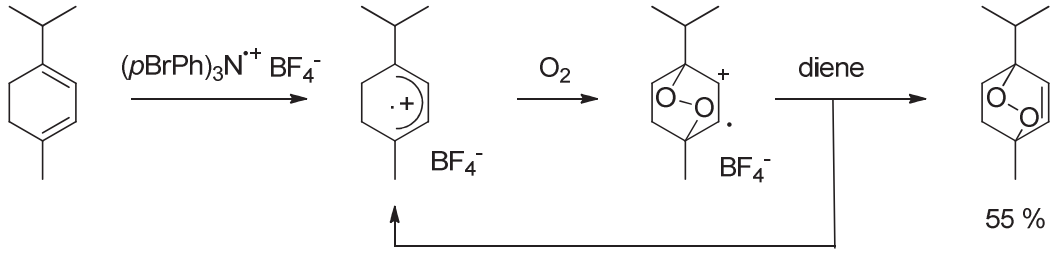


Scheme I-12

This photooxygenation was applied to the synthesis of natural cyclic peroxy ketals such as chondrillin **I-76** and plakorin **I-77**. [6,49]

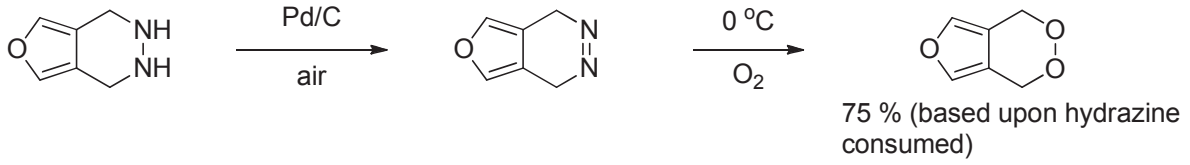
I.2.4. Cycloaddition of triplet oxygen with diradicals and cation radicals

If the reaction of dienes with $^1O_2$ was known since 1867, [4+2] cycloaddition with triplet oxygen was discovered more than a century later. In 1972, Barton and coworkers described the cycloaddition of ergosteryl acetate with triplet oxygen in the presence of trityl tetrafluoroborate or tris-(*p*-bromophenyl)aminium radical-cation.[50] The most plausible mechanism involves a single-electron oxidation of diene, addition of triplet oxygen and consequent abstraction of an electron from another molecule of diene (Scheme I-13).[51]



Scheme I-13

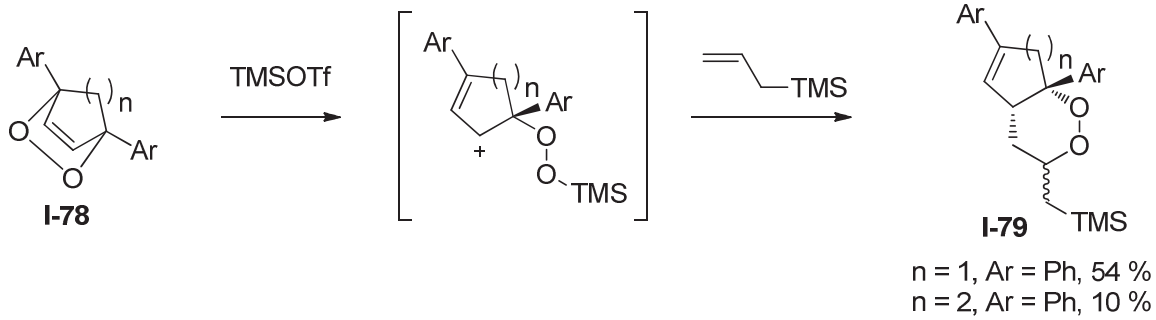
Thermally or photochemically generated triplet diradicals from diazenes react with triplet oxygen to give cyclic peroxides in variable yields (Scheme I-14).[52]



Scheme I-14

I.2.5. Lewis acid-catalyzed rearrangement of unsaturated bicyclic endoperoxides in the presence of vinyl silanes

Reaction of endoperoxides **I-78** with allyltrimethylsilane in the presence of TMSOTf give the *cis*-configured 1,2-dioxanes **I-79** in good to moderate yields (Scheme I-15). This reaction proceeds via attack of the allyl silane on the carbocation derived from heterocyclic cleavage of the endoperoxide bridge.[53] The same reaction using 1,3-diphenyl cyclopentadiene in place of vinyl silanes has been reported. [54]



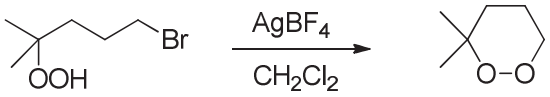
Scheme I-15

I.2.6. Intramolecular nucleophilic substitution

The intramolecular cyclization of hydroperoxides with appropriately substituted side chains provides one of the major route to 1,2-dioxanes.

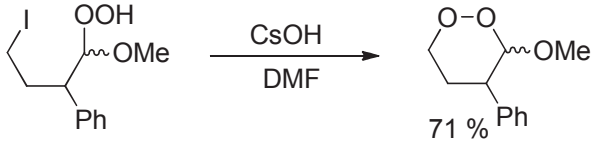
I.2.6.1. On a primary site

Porter and co-workers showed that peroxy bromides can form 6-membered endoperoxides in the presence of silver salts (Scheme I-16)[55].



Scheme I-16

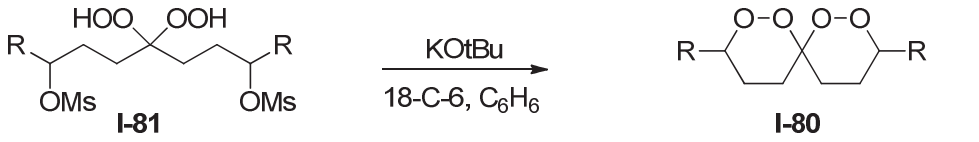
In the presence of cesium hydroxide, 4-iodo-hydroxyperoxyacetal gave the methoxy-1,2-dioxane in an excellent yield (Scheme I-17).[56]



Scheme I-17

I.2.6.2. On a secondary site

Spirocyclic bis 1,2-dioxanes **I-80** were built by a nucleophilic displacement of bis-mesylate **I-81** by gem-dihydroperoxyl groups in good yields (Scheme I-18).[57]

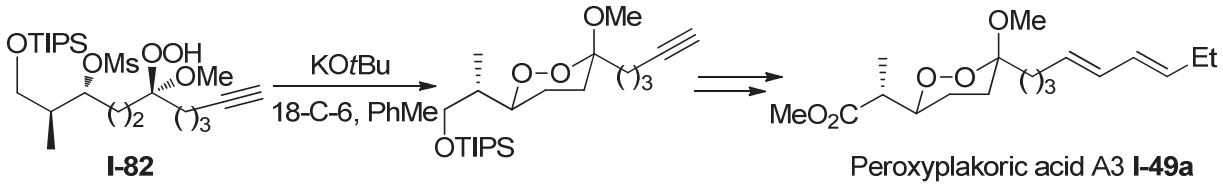


I-81 **I-80**

80 % (mixture of diastereomers)

Scheme I-18

This intramolecular alkylation was recently applied to the synthesis of peroxyplakoric acid **I-49a** (Scheme I-19).[58]



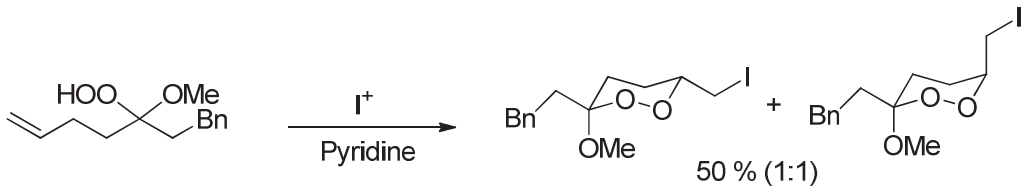
I-82 Peroxyplakoric acid A3 **I-49a**

Scheme I-19

I.2.7. Intramolecular attack of an hydroperoxyl group to halonium ions

This method was at first explored to synthesize 1,2,4-trioxane derivatives,[59] structure found in artemisinin and also to produce natural products analogues such as those of yingzhaosu A.[60,61] This type of 1,2-dioxane ring formation is not general and the yield of the desired product is function of the substrate.

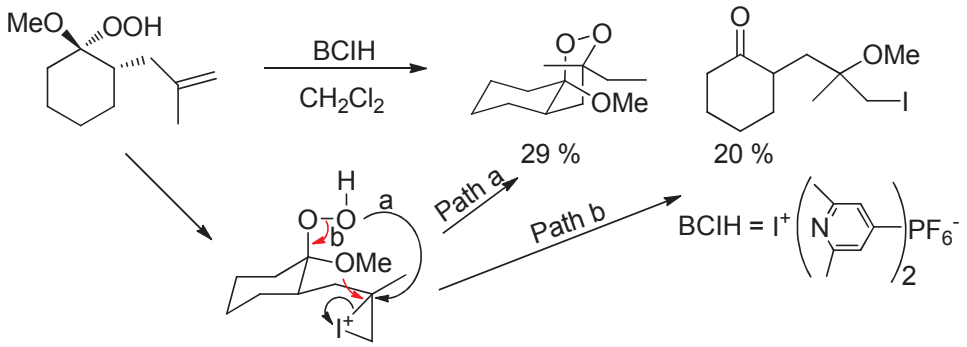
For example, aliphatic 4-alkenyl hydroperoxyacetals undergo electrophilic cyclization, in the presence of I_2 and a base, to afford 1,2-dioxanes in moderate yields (Scheme I-20).[59]



50 % (1:1)

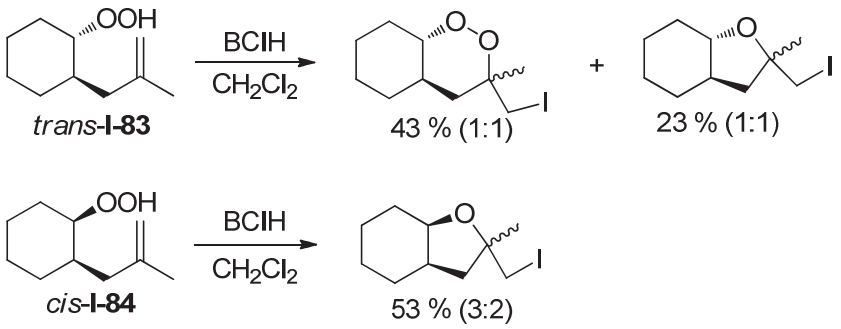
Scheme I-20

In cyclic systems, halonium ion-mediated reaction of unsaturated hydroperoxy acetals gave low yields of 1,2-dioxanes because of the intramolecular migration of a methoxy group (Scheme I-21).[60,61]



Scheme I-21

In cyclic unsaturated hydroperoxides, there is a competition between the terminal oxygen of the hydroperoxy group and the inner oxygen to act as a nucleophile in the iodonium-catalyzed cyclization (Scheme I-22).[62]

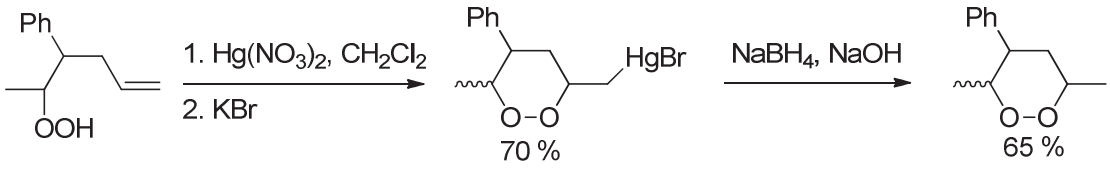


Scheme I-22

Thus, *trans*-**I-83** gave a mixture of endoperoxide and of oxolane whereas *cis*-**I-84** afforded exclusively the 5-membered ring because the terminal oxygen of the hydroperoxy group is directed away from the cyclohexane ring, allowing the nucleophilic attack of the inner oxygen to occur predominantly.

I.2.8. Cycloperoxymercuration of unsaturated hydroperoxides

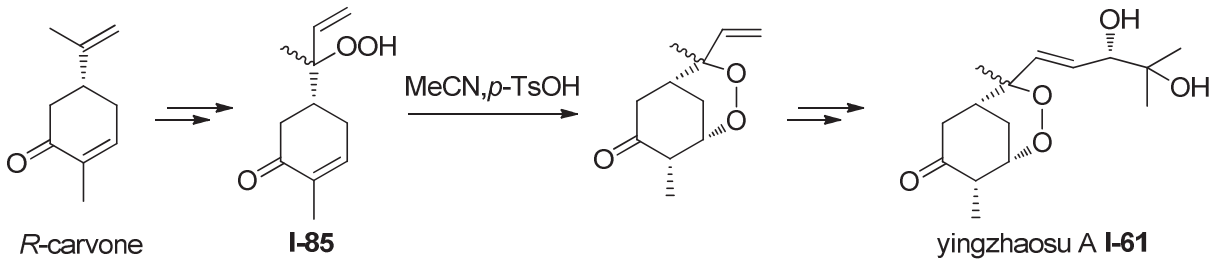
Bloodworth et al studied in details the preparation of 1,2-dioxanes by intramolecular attack of an hydroperoxy group to mercuronium ions.[63,64] They shown that the stereo- and the regioselectivity of the cyclization are a function of the salt used. The drawback of this method is that side reactions can accompany reductive demercuriation, depending upon the experimental conditions and the structure of cycloperoxymercurial compounds.[64] On the example depicted in Scheme I-23, peroxymercuriation-hydridodemercuration occurred in a reasonable yield for the sequence.[63]



Scheme I-23

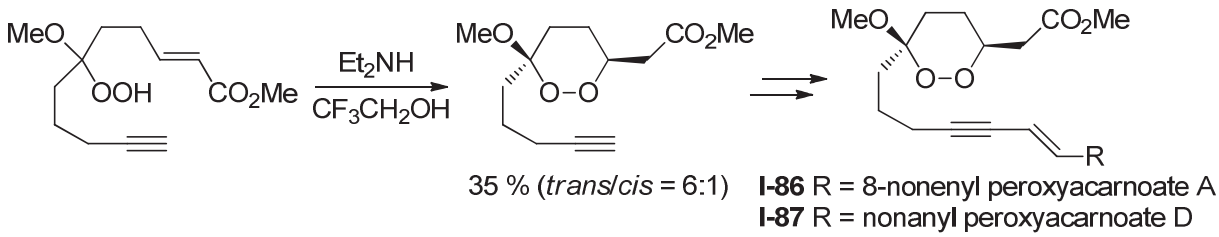
I.2.9. Formation of 1,2-dioxanes by Michael addition of an hydroperoxy group to unsaturated carbonyl derivatives

There are a large number of reports dedicated to the synthesis of 1,2-dioxanes by base or acid-catalyzed intramolecular addition of hydroperoxides to α,β-unsaturated carbonyl derivatives and applied to the synthesis of natural products.[65-72] For example, this type of intramolecular Michael addition is one of the key steps in the total synthesis of yingzhaosu A **I-61** which possesses potent antimalarial activity (Scheme I-24).[65,66]



Scheme I-24

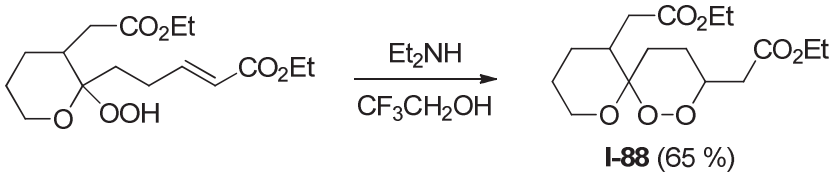
An approach of peroxyacarnoates A **I-86** and D **I-87**[67], which display activity against fungal and/or cancer lines, and simpler congeners[68,69] used to construct the peroxyacetal ring system a conjugate addition to α,β-unsaturated esters (Scheme I-25).



Scheme I-25

A number of unnatural antimalarial spiro-peroxyacetals have been synthesized by constructing the 1,2-dioxane ring by intramolecular Michael addition.[70,71] Thus, compound **I-**

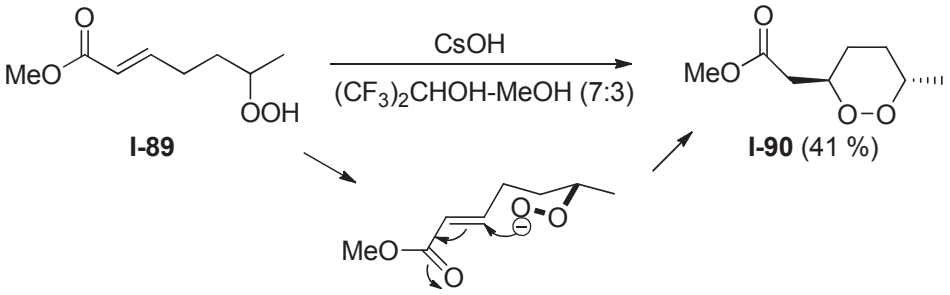
88, a simpler analogue of peroxyplakoric acids, showed in vitro antimalarial activity comparable to that of natural compounds (Scheme I-26).[71]



I-88 (65 %)

Scheme I- 26

In contrast to the above examples where the hydroperoxide nucleophile was attached to a quaternary carbon, Michael addition of the secondary hydroperoxide **I-89**, in the presence of cesium hydroxide, afforded exclusively the *trans* 3,6-disubstituted endoperoxide **I-90** in a moderate yield (Scheme I-27).[72] This stereochemical outcome can be explained in considering that the precursor adopts a chair-like conformation with the methyl and the unsaturated ester in equatorial positions.

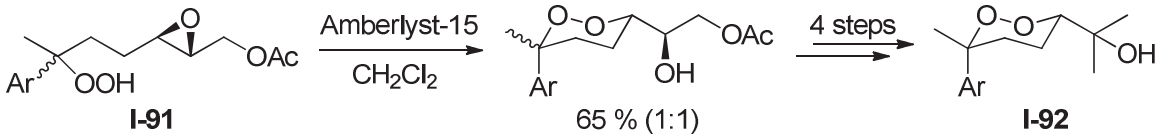


I-89 **I-90** (41 %)

Scheme I-27

I.2.10. Acid-catalyzed intramolecular ring-opening of oxiranes and oxetanes by hydroperoxides

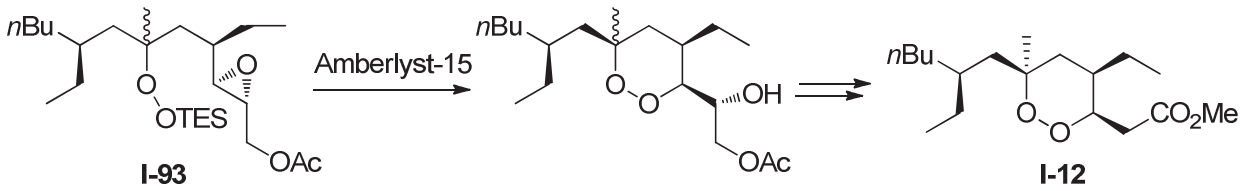
There are only few examples of 1,2-dioxane synthesis through intramolecular addition of hydroperoxides to epoxides and oxetanes.[73-75] In all cases, the cyclization proceeded via a 6-*exo*-mode following Baldwin's rules. Two natural compounds have been synthesized using this cyclization protocol. Thus, the endoperoxide part of yingzhaosu C **I-92** was built by cyclization of γ- hydroperoxy epoxide **I-91** in the presence of Amberlyst-15 (Scheme I-28).[74]



I-91 65 % (1:1) **I-92**

Scheme I-28

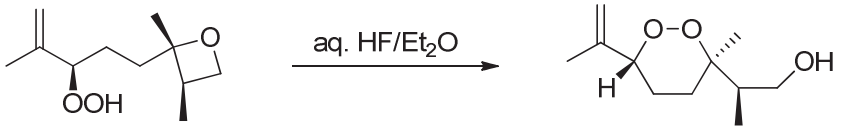
In a recent paper describing the synthesis of antimalarial 9,10-dihydroplakortin **I-12**, the formation of the 1,2-dioxane ring was effected by peroxide attack on the epoxide of compound **I-93** (Scheme I-29).[6]



I-93 **I-12**

Scheme I-29

The 6-*exo* ring opening of oxetanes with an internal hydroperoxide, in the presence of aqueous HF, furnished 1,2-dioxanes in moderate to good yields (Scheme I-30).[75]



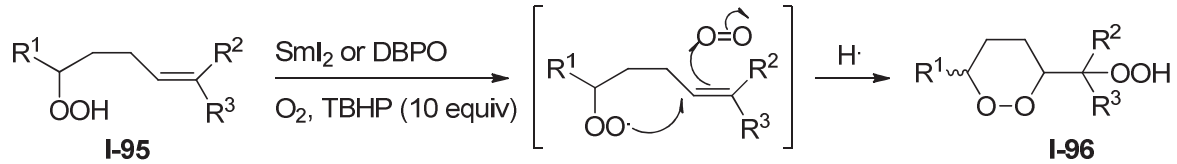
I-94 48 % (7:1)

Scheme I-30

I.2.11. Peroxyl radical addition on alkenes

I.2.11.1. From unsaturated hydroperoxides

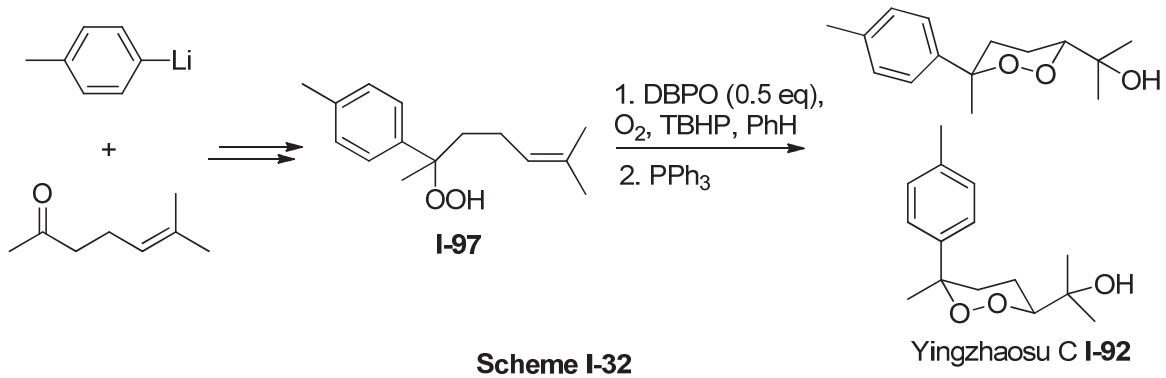
In the presence of O_2 and catalytic SmI_2[76] or catalytic di-*t*-butyl peroxyoxalate (DBPO), O_2 and an excess of TBHP, unsaturated γ-hydroperoxy compounds **I-95** afforded endoperoxy hydroperoxides **I-96**, via a 6-*exo*-trig cyclization, in good yields (Scheme I-31).[77,78,79]



I-95 **I-96**

Scheme I-31

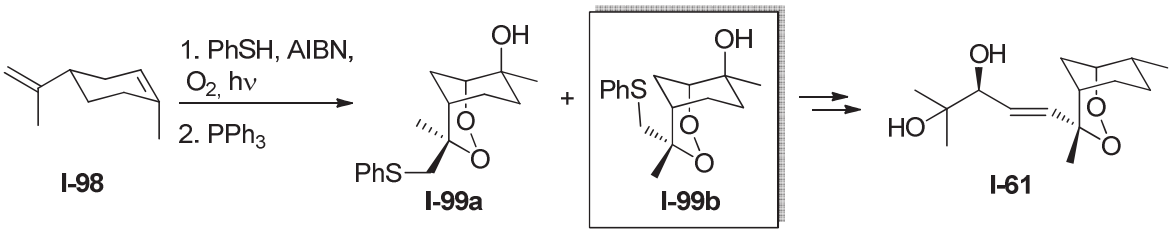
Using this methodology, a concise synthesis of (±)-yingzhaosu C **I-92** has been described (Scheme I-32).[78]



Scheme I-32

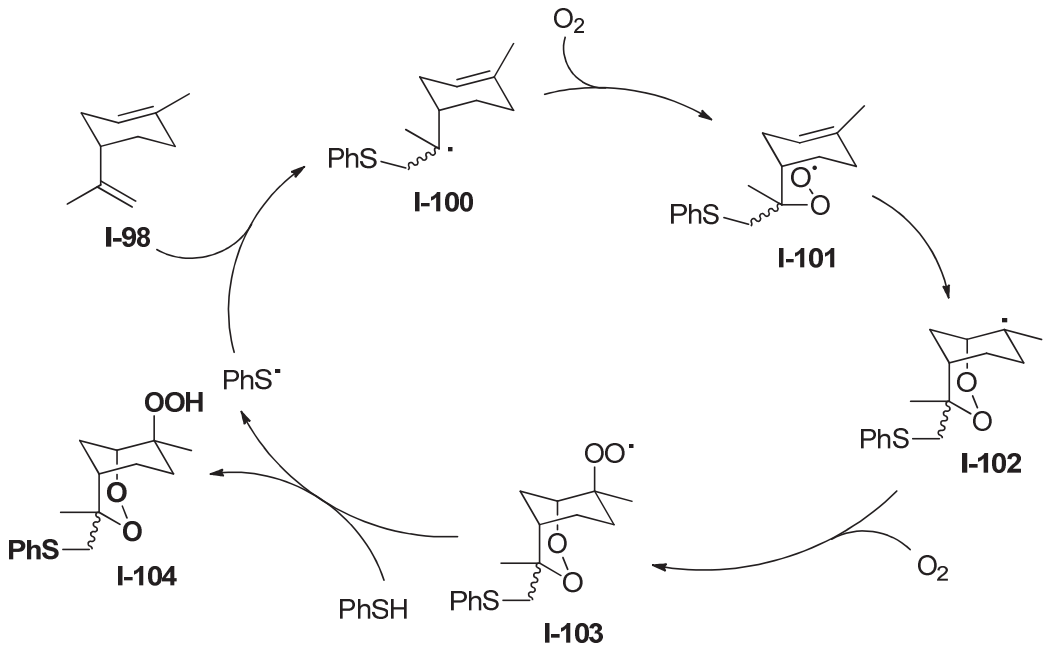
I.2.11.2. From 1,5-dienes via thiol olefin co-oxidation (TOCO reaction)

The co-oxidation reaction between a thiol, an olefin and oxygen, studied and exemplified by Szmant and Coll.,[80] has been expanded to the synthesis of 1,2-dioxolanes from 1,4-dienes by Beckwith and Wagner[81] and latter on by Bachi and coworkers to 1,5-dienes to form 1,2-dioxanes.[82] The endoperoxide part of antimalarial yingzhaosu A **I-61** was elaborated using this protocol.[82c] Thus, limonene **I-98** , in the presence of thiophenol, oxygen and a catalytic amount of AIBN, under UV irradiation, followed by treatment with PPh_3 afforded a 1:1 mixture of endoperoxides **I-99a,b**. Compound **I-99b** was transformed, in few steps, to **I-61** (Scheme I-33).



Scheme I-33

The straightforward approach of the yingzhaosu A skeleton in which four components interact through a sequential free-radical reaction follow the pattern described in Scheme I-34.

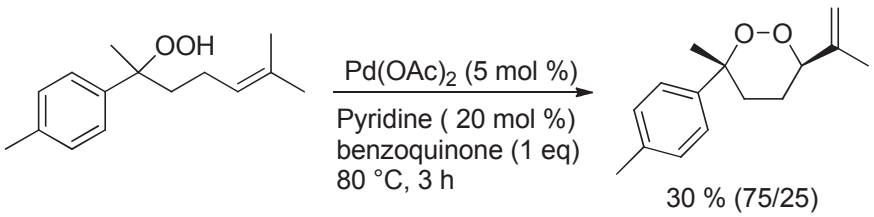


Scheme I-34

Regiochemical addition of PhS· to the terminal end of the isopropenyl double bond of limonene gives the tertiary radical **I-100** which is trapped by oxygen to yield the peroxy radical **I-101** which in turn undergoes a 6-exo intramolecular addition to endocyclic double bond generating a tertiary peroxy radical **I-102**. This radical is trapped by a second equivalent of oxygen giving the radical **I-103** which abstracts a hydrogen atom to PhSH to provide the bicyclic hydroperoxide **I-104**.

I.2.12. Palladium-catalyzed cyclization of unsaturated hydroperoxides

Cyclization of γ,δ-unsaturated tertiary hydroperoxides, in the presence of Pd(II), afforded 1,2-dioxanes in modest yields (Scheme I-35).[83]

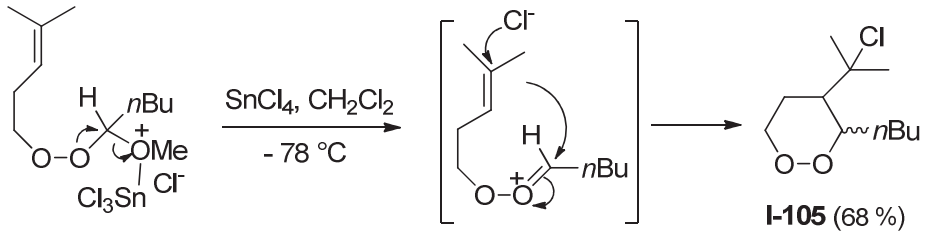


Scheme I-35

This reaction is limited to tertiary hydroperoxides, no reaction occurred with primary ones.

I.2.13. Cyclization of peroxycarbenium ions derived from unsaturated peroxyketals

As seen in Scheme I-36, intramolecular attack of an alkene onto a peroxycarbenium ion, obtained by reaction of peroxyacetal with $SnCl_4$, at low temperature, gave the 1,2-dioxane **I-105** in a good yield.[84]



Scheme I-36

I.3. Methods for the Introduction of a tertiary hydroperoxide group

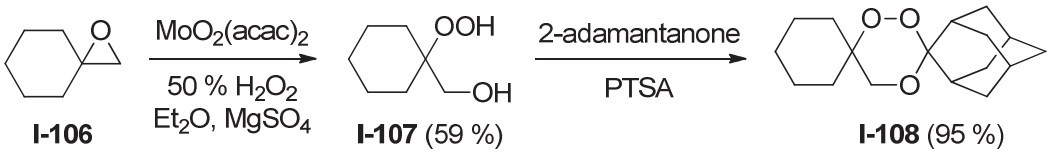
I.3.1. Introduction

Among the methods described above for the synthesis of 1,2-dioxanes, a number of them use an intramolecular cyclization of hydroperoxides. Thus, the obvious next step in our bibliographic search was to have an overview on the main methods of hydroperoxide synthesis. In the context of the synthesis of plakortolides and in relation to our strategy of synthesis, we described in this section the methods to prepare tertiary hydroperoxides.

I.3.2. Ring-opening of epoxides and oxetanes with H_2O_2

I.3.2.1. Ring-opening of oxiranes with H_2O_2

In 1970, Perrotti and Coll. obtained a β-hydroxyperoxide by reaction between isobutylene oxide and anhydrous H_2O_2, a potential explosive, in the presence of $MoO_2(acac)_2$.[85] This procedure was improved by the use of 50 % H_2O_2 in ether in the presence of $MgSO_4$ and applied to the synthesis of analogues of artemisinin such as **I-108** starting from the spiro epoxide **I-106** (Scheme I-37).[86] As seen in the Scheme I-37, the ring-opening occurred at the sterically most crowded quaternary center to give the tertiary hydroperoxide **I-107**.

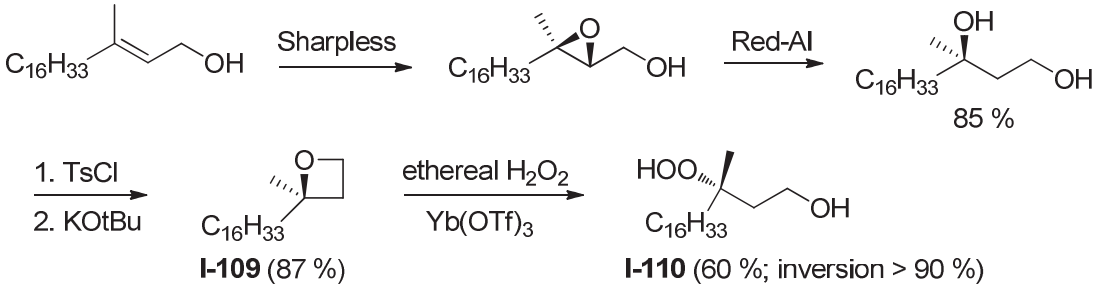


Scheme I-37

With anhydrous H_2O_2, others catalysts have been used such as $HClO_4$,[87] CF_3CO_2H,[88] $SbCl_3/SiO_2$,[89] phosphomolybdic acid ($H_3Mo_{12}O_{40}P$)[90] for the peroxydation of epoxides.

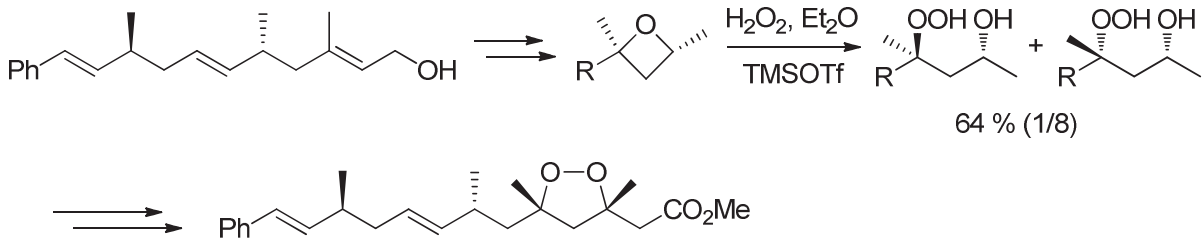
I.3.2.2. Ring opening of substituted oxetanes

In 2002, Dussault and Coll. described an interesting study on the Lewis acid-catalyzed ring opening of 2,2-di- or 2,2,3-trisubstituted enantioenriched oxetanes with anhydrous hydrogen peroxide.[91] These oxetanes are readily obtained from trisubstituted allylic alcohols via asymmetric Sharpless epoxidation as seen in Scheme I-38.



Scheme I-38

Good yields of 3-hydroperoxy-1-alkanols **I-110** from **I-109** and high percent of inversion were obtained using trimethysilyl triflate or $Yb(OTf)_3$ as catalysts. This methodology for the formation of enantiomerically enriched tertiary hydroperoxides has been applied to the asymmetric synthesis of four stereoisomers of plakinic acid A, allowing at the same time its configurational assignment (Scheme I-39).[31]



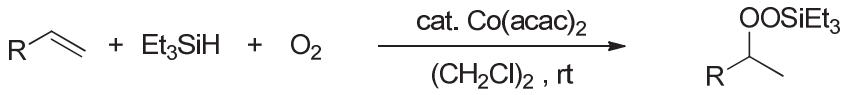
Scheme I-39

I.3.3. Tertiary alcohol peroxidation

There are a large number of reports on the preparation of tertiary hydroperoxides from alcohols. In most cases, the formation of tertiary hydroperoxides involves the treatment of alcohols with aqueous or anhydrous H_2O_2 in the presence of an acid such as concentrated sulfuric acid,[92] Amberlyst-15,[78] *para*-toluenesulfonic acid.[93,94] This method of hydroperoxide formation was applied to the synthesis of natural products bearing an hydroperoxy group [93,95] and to an intermediate in the synthesis yingzhaosu C.[78] Tertiary hydroperoxides can also be prepared from alcohols by, first substitution of the hydroxyl group by a bromide or a iodide, followed by treatment with H_2O_2 in the presence of silver salts.[96,83]

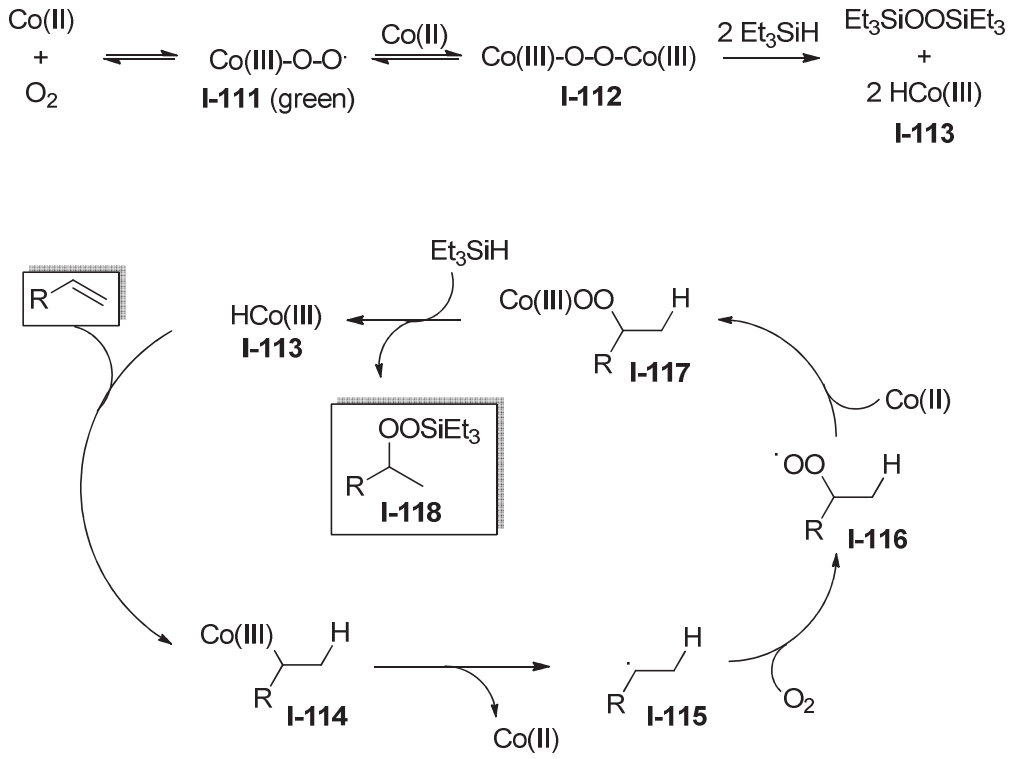
I.3.4. Hydroperoxysilylation of alkenes

In 1989, Mukaiyama and Isayama reported an original and efficient method for hydroperoxide formation which is based on Co(II)-catalyzed hydroperoxysilylation of alkenes with molecular oxygen in the presence of triethylsilane (Scheme I-40).[97,98]



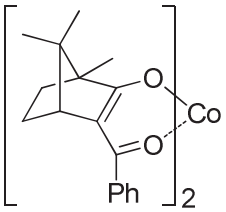
Scheme I-40

The interesting features of this reaction are its mildness, predictable regioselectivity in favor of the "Markovnikov" product and the high yield of formed triethylsilylperoxides. A mechanism for this radical Co(II)-catalyzed autoxidation of alkenes with Et_3SiH was proposed by Nojima and co-workers (Scheme I-41).[99] In the initiation step, Co(II) complex is oxidized by molecular oxygen to give superoxocobalt (III) **I-111** which is in equilibrium with μ-peroxocobalt (III) **I-112**.[99] Transmetallation of **I-112** with Et_3SiH would give the Co(III)-hydride complex **I-113**. Then insertion of alkene into H-Co bond of **I-113** provides Co(III)-alkyl complex **I-114**. Homolysis of the Co-carbon bond then ensues to produce a carbon centered radical **I-115** which in the presence of triplet oxygen gives the peroxy radical **I-116** which is reduced to Co(III)-alkylperoxo complex **I-117**. Finally, complex **I-117** undergoes transmetallation with Et_3SiH resulting in the formation of the triethylsilylperoxide **I-118** and regeneration of Co(III)-hydride complex **I-113**.

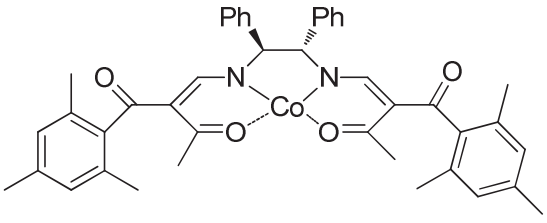


Scheme I-41

As seen in Scheme I-41, creation of the stereogenic center of **I-118** occurred by peroxydation of the radical **I-115**. This radical can capture oxygen from either face of the radical center which explains the complete lack of asymmetric induction using chiral complexes **I-119** and **I-120**.[100]

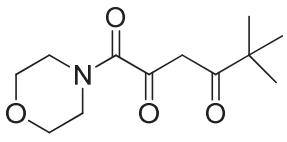


I-119

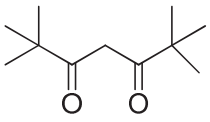


I-120

A number of parameters of this reaction have been studied. First of all, dichloroethane is the solvent of choice for this reaction.[97] Ligands such as 1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentadione (modp) **I-121** and 2,2,6,6-tetramethylheptane-3,5-dione (thd) **I-122** have been found superior to acetylacetonate (acac) in terms of yields and length of the induction period.[97,98,100] Moreover, this induction period can be shortened by addition of a small amount of *t*BuOOH.[98]

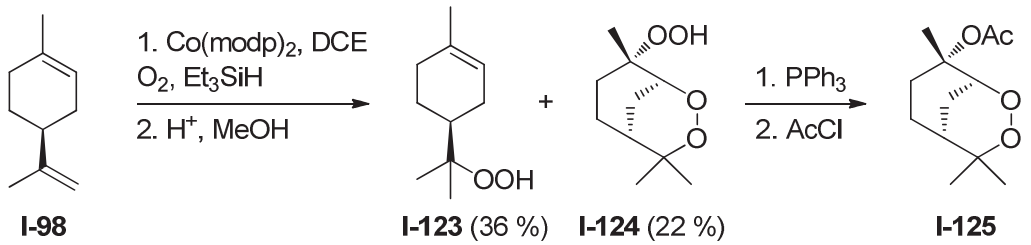


I-121



I-122

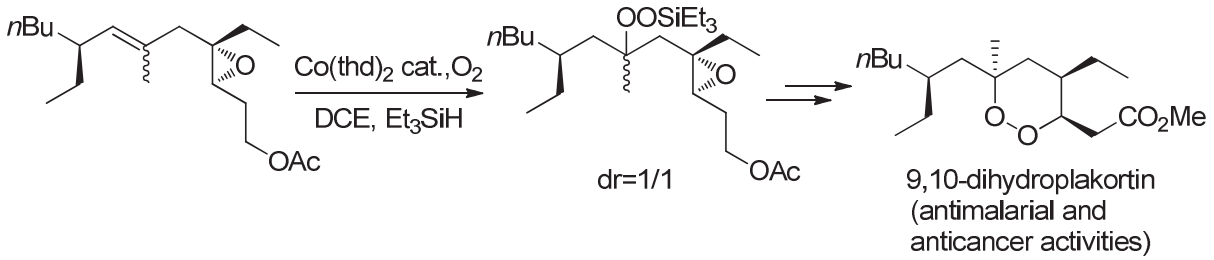
An investigation of the structural effect of silanes on the Co-catalyzed reductive oxygenation of alkenes showed that the efficiency of the reaction decreases with the increase of the steric bulk of the silanes.[101] The authors proposed that the inefficiency of silanes such as Ph_3SiH and $(iPr)_3SiH$ could be explained by the difficult formation of the complex HCo(III) **I-113** because of the steric hindrance of the two reactants: silanes and μ-peroxocobalt(III) **I-112.** During the study concerning the relative reactivities of alkene substrates, it was found that the reactivity is influenced by three major factors: (1) relative stability of the intermediate carbon-centered radical formed by the reaction of the alkene with HCo(III) **I-113**, (2) steric effects around the C=C double bond, and electronic factors associated with the C=C double bond.[102] The same authors extended their studies to 1,5-dienes and showed that the product composition was influenced by the structure of the dienes and besides the expected acyclic unsaturated triethylsilylperoxides, 1,2-dioxolane and 1,2-dioxane derivatives were also obtained.[102] For example, peroxidation of limonene **I-98** followed by acid treatment afforded the unsaturated hydroperoxide **I-123** and 1,2-dioxane **I-124,** a simpler analogue of yingzhaosu A. The latter, after hydroperoxide reduction and acetylation gave **I-125** which showed antimalarial activity against *P. falciparum* superior to artemisinin (Scheme I-42).[103]



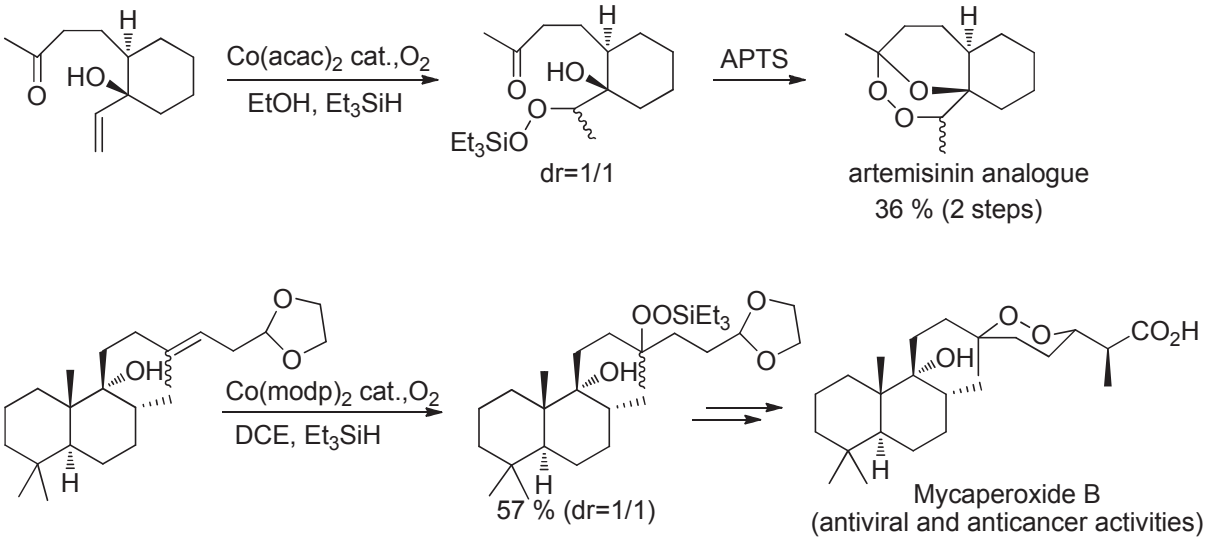
I-98 **I-123** (36 %) **I-124** (22 %) **I-125**

Scheme I-42

A number of natural products and of their simpler analogues have been synthesized using as a key step the Mukaiyama-Isayama hydroperoxysilylation. Below are described some examples of the application of this reaction in synthesis (Scheme I-43 and I-44).[6,73b,104, 105]



Scheme I-43

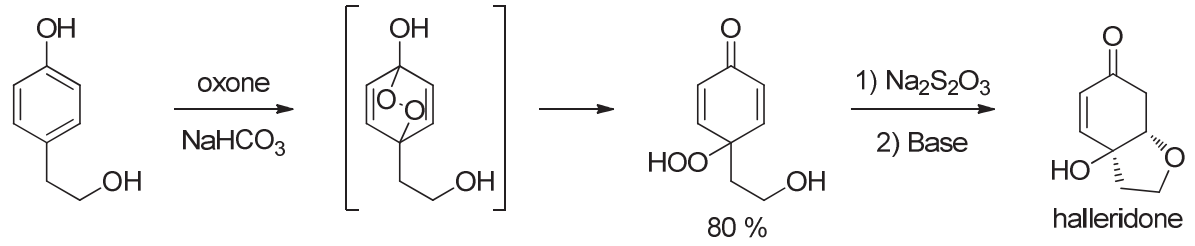


Scheme I-44

As shown on these examples, there is an absence of diastereoselection in the Co(II)-catalyzed hydroperoxydation of alkenes bearing stereogenic centers which constitutes the only drawback of this reaction.

I.3.5. Oxidative dearomatization of *para*-alkyl phenols

Para-substituted phenols could be peroxidized to *para*-peroxyquinols by means of [4+2]-cycloaddition with singlet oxygen, which can be generated photochemically or chemically (Scheme I-45).[106] Actually, applications of this method are limited to the preparation of *para*-peroxyquinol and *para*-quinol moieties frequently founded in natural products.



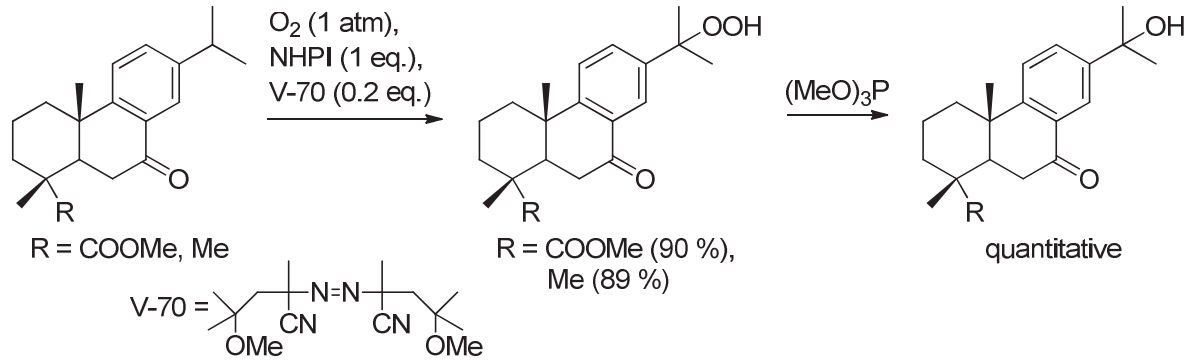
Scheme I-45

I.3.6. Addition of triplet oxygen to radicals

Oxygen in its persistent diradical ground state rapidly reacts with carbon-centered radicals. This property of oxygen is widely used in modern organic chemistry especially in the cases when "carboradical" could be generated in regioselective manner. Among a huge amount of radical decarboxylation, dehalogenation, demercuration, and carbocyclization oxydation processes hydroperoxydes could be the main products sometimes.

I.3.6.1. Aerobic oxidation

The oxidation of isopropyl-aromatic hydrocarbons to hydroperoxides, catalyzed by transition metals (Cu(I)/Cu(II), Co(II)/(III) and Mn(II)/(III)), is well known as a key step for the industrial synthesis of acetone and phenols. N-hydroxyphthalimide (NHPI) has been demonstrated to be a good catalyst for radical oxidations and moreover does not accelerate peroxide decomposition in contrast to transition metals.[107] Recently this method was applied to functionalized substrates.[108] Thus, several abietane and podocarpane terpenes have been synthesized in excellent yields from hydroperoxides (Scheme I-46).

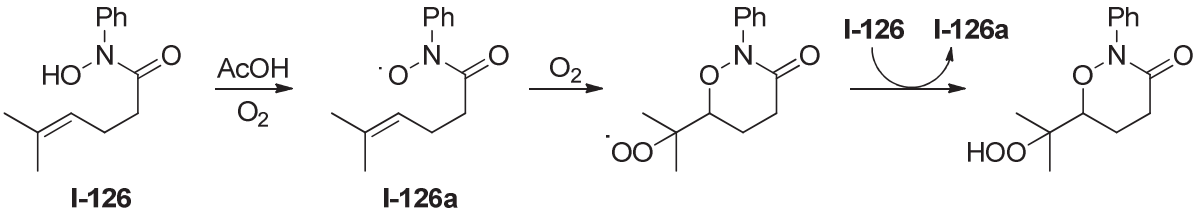


Scheme I-46

There are few methods that permit peroxidation of alkanes into hydroperoxides, but most of them do not distinguish between primary, secondary and tertiary hydrogens.[109]

I.3.6.2. Peroxidation of unsaturated N-aryl hydroxamic acids

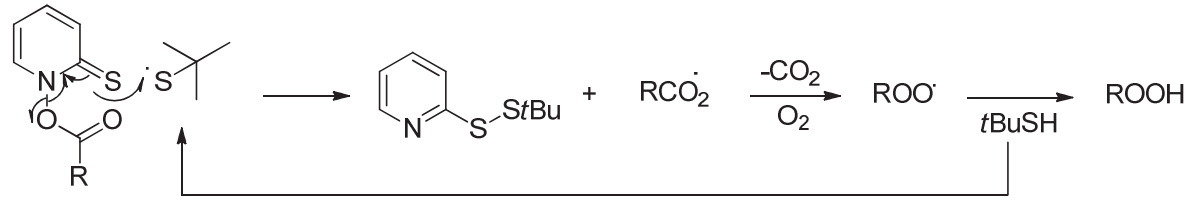
Recently Schmidt and Alexanian described a ring-closing peroxidation of unsaturated hydroxamic acids based on preliminary work of Perkins and coworkers.[110] They found that oxidation of hydroxamic acids to amidoxyl radicals proceeded smoothly at 60 °C without transition metal catalysis. The mechanism is depicted in Scheme I-47 and involves amidoxyl radical addition to a double bond, subsequent reaction with molecular oxygen and hydrogen abstraction from hydroxamic acid **I-126** generating an amidoxyl radical and affording an alkylhydroperoxide.



Scheme I-47

I.3.6.3. Decarboxylative hydroperoxydation

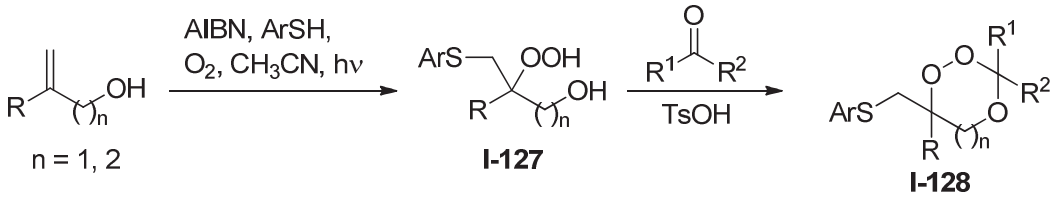
In 1983 Barton and coworkers described an interesting method for the generation of carbon radicals from carboxylic acids via thiohydroxamic esters. One year later, they successfully applied this method to alcohol preparation by reducing of hydroperoxides which are the primary products of this reaction.[111] Proposed mechanism for this reaction is depicted in Scheme I-48. Utilization of thiols and epimerization are the drawbacks of this method.



Scheme I-48

I.3.6.4. Thiol olefin co-oxidation (TOCO reaction) of allylic and homo-allylic alcohols

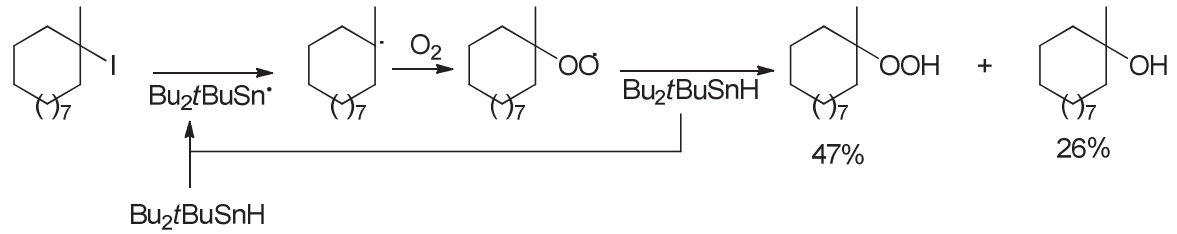
TOCO reaction between thiols, alkenes and molecular oxygen was described for the first time in 1951 by Kharasch and coworkers (for the mechanism of TOCO reaction see Scheme I-34). Since then, this reaction was thoroughly studied and widely applied to the synthesis of new biologically active compounds.[84c] For example, this method was used for the synthesis and antimalarial evaluation of 1,2,4-trioxanes and 1,2,4-trioxepanes **I-128** (Scheme I-49).[112]



Scheme I-49

I.3.6.5. Aerobic reductive oxygenation of alkylhalides

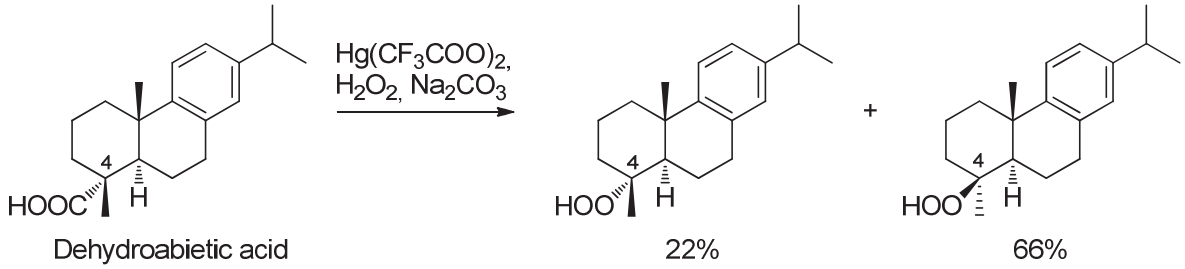
Ultrasound irradiation of an aerated solution of an equimolar mixture of alkyl halides $Bu_2tBuSnH$, at 0 °C, produces alkylhydroperoxides in moderate yields (Scheme I-50).[113] Addition of oxygen to alkyl radical before abstraction of hydrogen from $Bu_2tBuSnH$ is the sole difference in the mechanism from radical reduction of alkylhalides. A moderate yield of hydroperoxides due to overreduction to corresponding alcohols is the drawback of this reaction.



Scheme I-50

I.3.6.6. Oxidative decarboxylation by hydrogen peroxide and a mercury (II) salt

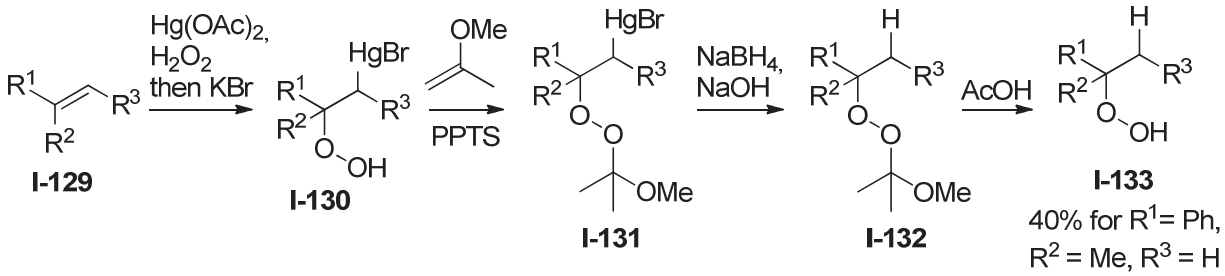
In 1994 Tkachev and coworkers described the preparation of hydroperoxides by treatment of carboxylic acids with mercury(II) salts and hydrogen peroxide.[114] Transformation of dehydroabietic acid to the epimeric mixture of hydroperoxides suggested formation of a free radical as an intermediate species. Although tertiary hydroperoxides were obtained in excellent yields, this method did not find broad applications due to the use of toxic mercury salts.



Scheme I-51

I.3.7. Hydroperoxymercuriation of alkenes

The reaction of hydroperoxymercuration has been known since 1970, but the first study of this reaction was published only in1990 by Bloodworth and coworkers.[115] They showed that 30% aqueous H_2O_2 could be used instead of concentrated or anhydrous hydrogen peroxide. Thus hydroperoxymercurials were obtained in variable yields by treatment of alkenes with $Hg(OAc)_2$ and aqueous hydrogen peroxide. Unfortunately, demercuration cannot be performed in the presence of unprotected hydroperoxides. Two years later, the synthesis of hydroperoxides was described by the same group.[116] Their method consists on hydroperoxymercuration of alkenes **I-129** followed by protection of the hydroperoxy group, demercuration and deprotection (Scheme I-52). Hydroperoxides **I-126** have been obtained in 30-54% yields for the four steps.

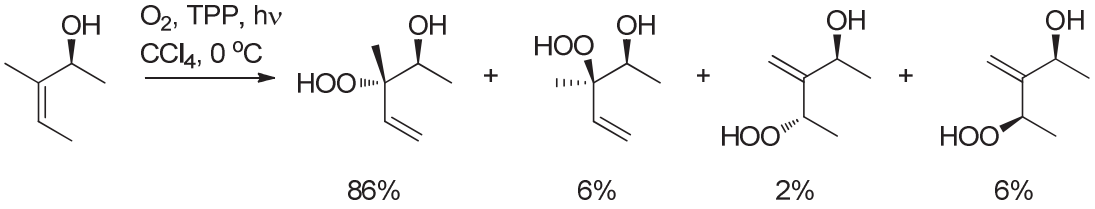


Scheme I-52

This method suffers from the use of toxic mercury derivatives and of the multistep sequence.

I.3.8. Singlet oxygen ene reaction

The reaction of singlet molecular oxygen with alkenes that bear allylic hydrogen atoms, to form allylic hydroperoxides, is a valuable and environmentally useful methodology in organic synthesis. This method tolerates many functional groups because of the mildness of the reaction conditions. The main features of this $^1O_2$ ene reaction concerning its regio-, stereo- and diastereoselectivity have been recently reviewed.[117] The regio- and diastereoselectivity in the photooxgenation of chiral allylic alcohols is particularly high (Scheme I-53).[118]

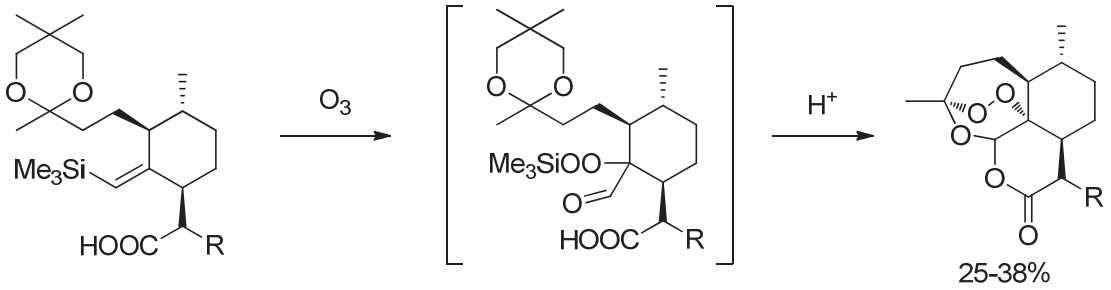


Scheme I-53

As shown by Nardello and coworkers, the diastereoselectivity of singlet oxygen ene reaction with allylic alcohols is sensitive to the reaction conditions such as medium effects and the source of $^1O_2$.[119] Both chemical (arene endoperoxides,[120] $Et_3SiOOOH$,[121] phosphite ozonides[122] or monoactivated derivatives of 1,1-dihydroperoxides[123]) and photochemical sources of singlet oxygen are suitable for this reaction.

I.3.9. Vinylsilane ozonolyzis

Treatment of vinylsilanes with ozone at low temperatures affords an easy access to α-hydroperoxy aldehydes with moderate to low yields.[124] This method was applied to the synthesis of a number of artemisinin analogs (Scheme I-54).[125]

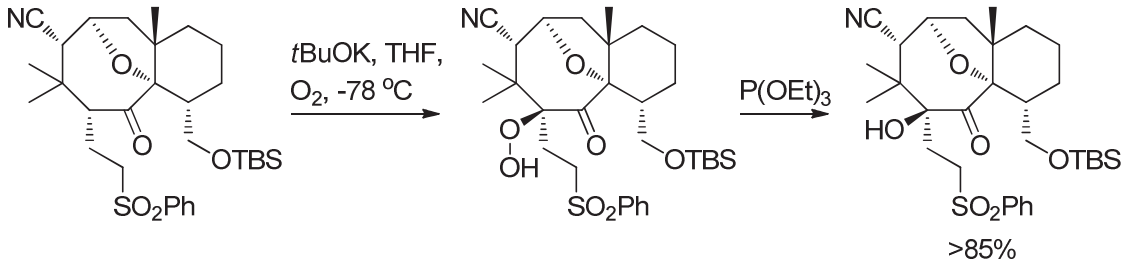


Scheme I-54

I.3.10. Molecular oxygen addition to carbanions

A property of organometallics to react quickly with molecular oxygen has been known since the beginning of the nineteenth century when Bodroux[126] and Bouveault[127] investigated this reaction on Grignard reagents. Although alcohols are the main products, an intermediate hydroperoxides were postulated by Wuyts to explain his observation on the oxidative properties of the reaction mixture on the acidic KI solution.[128] His hypothesis was confirmed by detailed study of Buckler and coworkers in 1955. They showed that good yields of hydroperoxides (57-92 %) could be obtained by slow addition of Grignard reagent (~0.5 M) to oxygen saturated ether at -70 °C.[129] The best results could be obtained with alkylmagnesium chlorides, alkylmagnesium bromides, alkyl lithium and dialkyl zinc furnished hydroperoxides in somewhat lower yields.

This property of carbanions is often utilizable in organic synthesis especially when hydroxyl or hydroperoxy groups must be introduced in place of enolizable protons. The advantages of this method are good yields, relative mildness of the reaction conditions and, therefore, tolerability to the majority of functional groups. For example this method was successfully utilized during the synthesis of taxane diterpenes (Scheme I-55).[130]



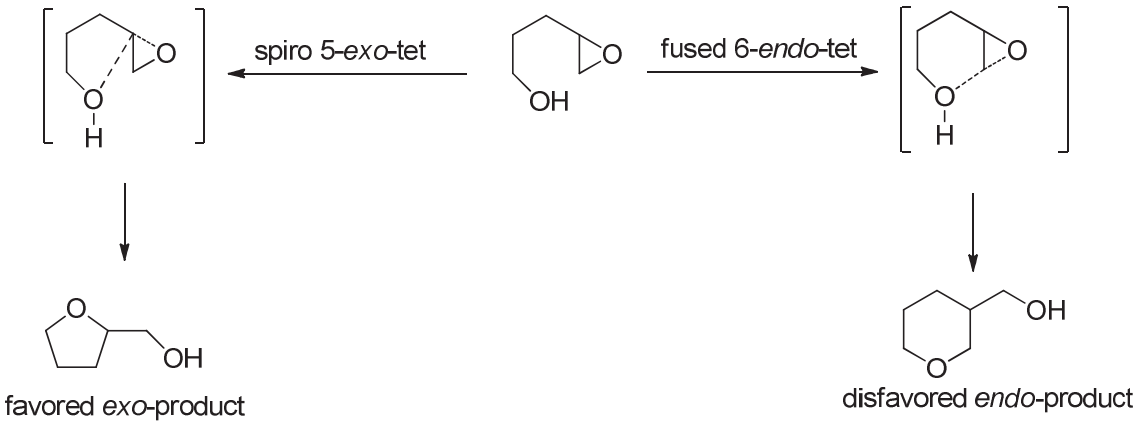
Scheme I-55

II. Results and discussion

II.1. Introduction

Ring-forming reactions are in great interest for organic chemists. Baldwin's rules of ring closure, empirical guidelines for the evaluation of ring forming processes, are generally used to predict the overcome of ring-forming reactions.[131] The size of the formed ring, the position of the bond that is broken relative to the smallest formed ring, and the geometry of the electrophile are the criteria used to classify ring-forming reactions. If the position of the bond broken during the reaction is outside of the newly formed ring, then the reaction is classified as *exo*. If the broken bond is within the smallest formed ring, the reaction is classified as *endo*. In Baldwin's classification, reactions involving sp^3 hybridized electrophiles are described as *tet* due to the tetragonal geometry of the electrophile (sp^2 hybridized electrophiles are *trig*, and *sp* electrophiles are digonal or *dig*). Based on this classification, Baldwin formulated a simple set of guidelines to predict the relative feasibility of different ring-closing reactions. Although empirical, these rules are based on stereoelectronic considerations.[132] The favored ring-closing reactions are those in which the length and nature of the linking chain enable the terminal atoms to achieve the proper geometries for the reaction. The disfavored ring closing processes require distortions of bond angles and bond distances rendering these reaction pathways higher in energy.

Baldwin's rules were not specifically formulated for epoxide-opening reactions. However, intramolecular epoxide openings tend to follow the rules that lie between those for tetrahedral and trigonal systems, generally favoring the *exo* processes, which proceed *via* spiro transition state. Intramolecular epoxide-opening reactions, with few exceptions, favor the smaller over the larger heterocycle (Scheme II-1). Baldwin's rules classify the fused and spiro transition states as *endo* and *exo*, respectively.

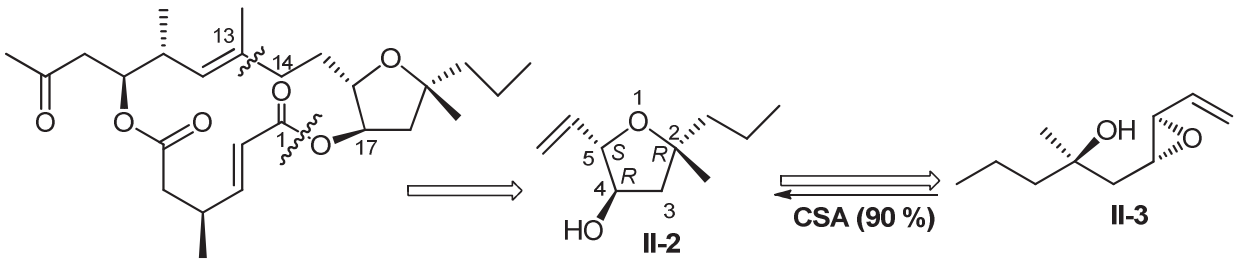


Scheme II-1

Since the *exo* mode of cyclization is typically preferred, methods to facilitate *endo* selective cyclization have constituted a particularly active area of research. Most of the approaches to promote *endo* outcome of intramolecular epoxide openings rely on the effects

of directing groups covalently attached to the epoxides. Pioneering studies of the activation of the 6-*endo* over 5-*exo* epoxide-opening pathway of 4,5-epoxyalcohols were reported by Nicolaou and co-workers in 1985.[133] They were able to override the natural preference for the undesired 5-*exo* cyclization by placing a carbon–carbon double bond adjacent to the epoxide moiety. This reversal of ring selectivity is attributed to the stabilization by the proximal π orbital of the developing electron-deficient carbon atom in the transition state. This strategy for constructing cyclic ethers via hydroxyl vinyl epoxides has been applied in a large number of total syntheses of natural products particularly of marine polycyclic polyethers.[134]

Our group became interested in the synthesis of amphidinolide X **II-1** (Scheme II-2). In our retrosynthetic plan, we envisaged that C13-C14 bond can be formed via a B-alkyl Suzuki-Miyaura cross-coupling reaction. Subsequent disconnection of the ester linkage of the secondary alcohol of the tetrahydrofuran moiety led to the building block **II-2**. It was envisioned that the five-membered ring oxygen can be obtained via an "anti-Baldwin" 5-*endo*-tet cyclization of compound **II-3**. Treatment of vinyl epoxide **II-3** with camphorsulfonic acid gave indeed the 5-*endo* product **II-2** in excellent yield.[135]



Amphidinolide X (II-1)

Scheme II-2

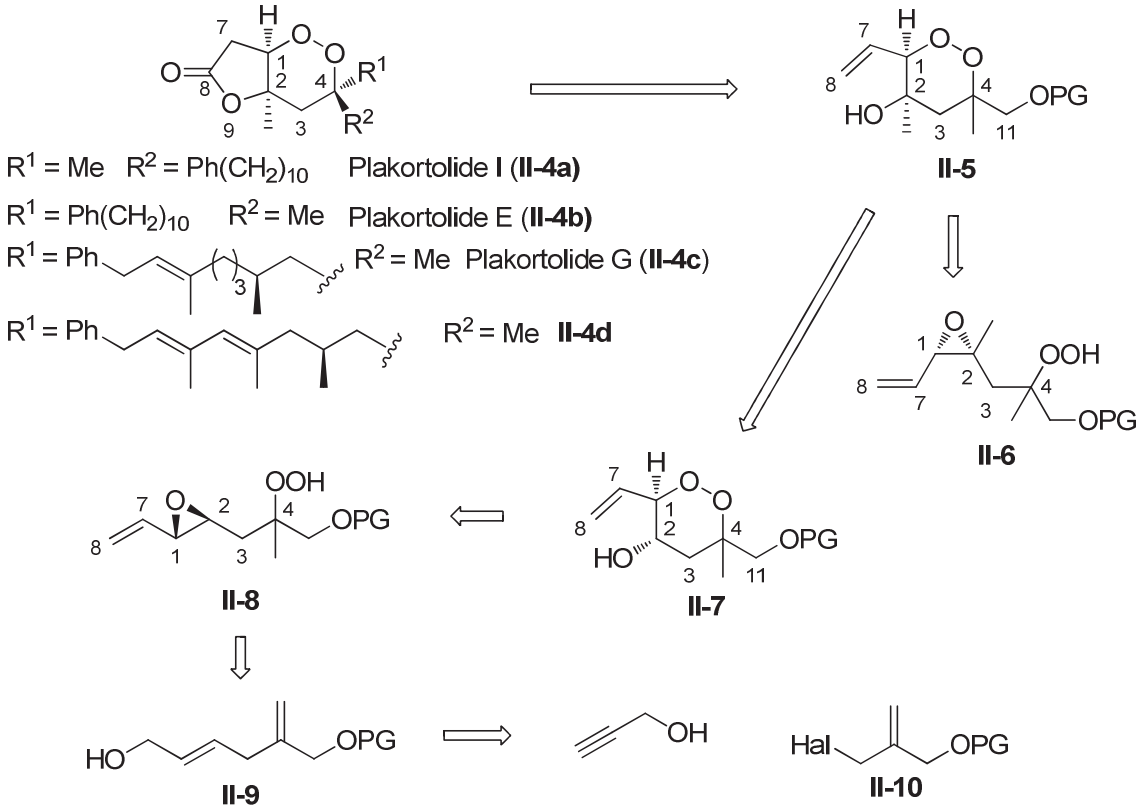
We next wondered if this concept of *endo*-selective epoxide-opening cyclization could be applied to the synthesis of 1,2-dioxanes via β-hydroperoxy vinyl epoxides and we choose as natural targets bearing 1,2-dioxane core: plakortolides. As often in synthesis, the first synthetic strategy did not work and we had to modify or completely change a number of time our synthetic plan to succeed in the synthesis of two plakortolides. In this chapter, are presented our efforts to get to the targets through five different approaches.

II.2. First synthetic approach of plakortolides

II.2.1. Retrosynthesis

Our first retrosynthesis was dictated in part by our strategy of 1,2-dioxane forming and also by the fact we wanted to synthesize a common intermediate for the synthesis of several plakortolides **II-4a-d**. This strategy led to intermediate **II-5** in which the secondary

homoallylic alcohol could be transformed to a lactone via standard methods and the hydroxymethyl in C11 elongated to the different side chains of plakortolides (Scheme II-3). For the creation of the proper stereochemistry at C1 and C2, *cis*-epoxide **II-6** was required in the cyclization reaction. We supposed, that the stereo- and regiochemical outcome of cyclization of hydroperoxy vinylepoxides must be similar that those of the corresponding epoxyalcohols. If the cyclization of hydroxy *trans* di-or trisubstituted unsaturated epoxides are, in most of cases, completely *endo*-selective and well-precedented, it is not the case of corresponding *cis* epoxides.[136] In the few examples described in the literature concerning the intramolecular opening of *cis*-epoxides a mixture of *endo*- and *exo*-cyclized products was observed.[137]. Using as directing group a styryl group in place of a vinyl group and carrying the reaction in basic medium (NaH) improved both stereo- and regioselectivity of the cyclization of hydroxy trisubstituted *cis*-epoxides.[137a]



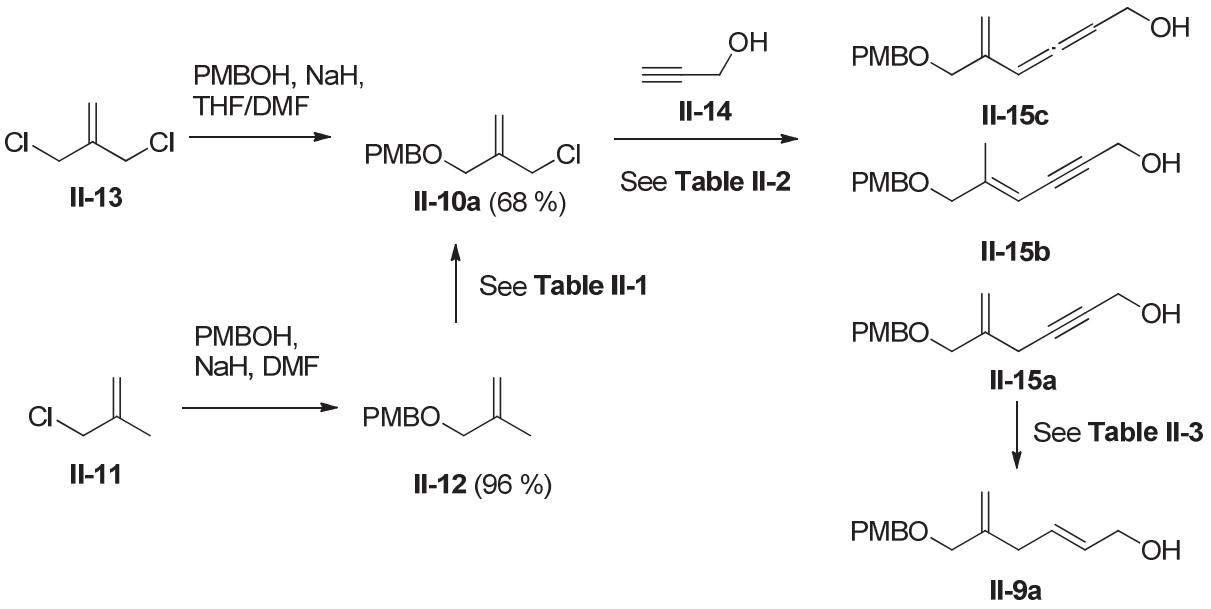
Scheme II-3

In order to overcome potential difficulties related to cyclization of *cis*-vinylepoxides, we decided to study first the cyclization of *trans* disubstituted epoxide **II-8** and to introduce the methyl group in C2 by addition of an organometallic to a carbonyl compound obtained by oxidation of the alcohol function of **II-7**. Compound **II-8** should be available from diene **II-9** via Sharpless asymmetric epoxidation, hydroperoxide incorporation and transformation of hydroxymethyl group into vinyl group by common means. Among the different existing methods to incorporate the hydroperoxide group described in the bibliographic part, hydroperoxysilylation of alkenes, developed by Mukaiyama and Isayama, was chosen due to its mildness, regioselectivity and it avoids the use of anhydrous hydrogen peroxide.[97] Diene

II-9 could arise from Cu(I)-catalyzed coupling between propargyl alcohol and allylic halide **II-10** and triple bond reduction sequence.

II.2.2. Synthesis of monoprotected dienol II-9a (PG = PMB)

At first, the *para*-methoxybenzyl group was chosen as protecting group because of its stability in a large number of acid and base conditions and its mild cleavage conditions compatible with most other protecting groups. The first method to synthesize the precursor of **II-9a**: allylic chloride **II-10a** involved the quantitative substitution of chlorine of 1-chloro-2-methyl-2-propene **II-11** by sodium *p*-methoxybenzyl alcoholate[138] followed by allylic chlorination (Scheme II-4). Among the large number of existing methods for allylic chlorination, the procedure of Massanet and coworkers[139] was considered as the most mild and tolerant in respect to PMB ether. In the presence of an excess of sodium hypochlorite and cerium trichloride heptahydrate in a two-phase system (dichloromethane-water), the desired chloro compound **II-10a** was obtained in low yields accompanied by polychlorination and oxidative deprotection products as seen from ^{1}H NMR of the crude mixture (Table II-1, entries 1-3). Ceschi and coworkers revisited Massanet protocol by changing the ratio between $CeCl_3$ and NaOCl or by replacing $CeCl_3$ by $InCl_3$ which in both cases improved the chlorination yield.[140] These conditions were applied to our substrate. If the ratio between NaClO and $CeCl_3$ had only a slight effect on the yield (entries 4, 7), this latter was increased dramatically when cerium salt was replaced by indium chloride (entries 5, 6). It should be noted that yield and purity of the product depend directly upon the stirring.



Scheme II-4

We also tested another method already reported for the synthesis of this substrate (Entry 8),[141] but the desired allylic chloride **II-10a** was obtained in only 30 % yield.

Table II-1. Study of allylic chlorination of allyl PMB ether **II-12**

Entry	Reagents (equiv.) [b]	Solvents	Time, h	Yield, %
1	2 Cl_2, 2 $CeCl_3 \cdot 7H_2O$	CH_2Cl_2:H_2O = 1:1	0.66	Traces
2	3 Cl_2, 3 $CeCl_3 \cdot 7H_2O$	CH_2Cl_2:H_2O = 1:1	5	Decompos.
3	2 Cl_2, 2 $CeCl_3 \cdot 7H_2O$	CH_2Cl_2:H_2O = 1:1	19	25[a]
4	4 Cl_2, 1.1 $CeCl_3 \cdot 7H_2O$	CH_2Cl_2:H_2O = 1:1	0.5	34
5	4 Cl_2, 1.1 $InCl_3$	CH_2Cl_2:H_2O = 1:1	0.3	48[a]
6	4 Cl_2, 1.1 $InCl_3$	CH_2Cl_2:H_2O = 1:1	0.2	68
7	4 Cl_2, 1.1 $CeCl_3 \cdot 7H_2O$	CH_2Cl_2:H_2O = 1:1	0.3	20
8	0.2 $LiClO_4$, 1.2 Py, 1.2SO_2Cl_2[c]	CH_2Cl_2	0.16	30[a,d]

[a] Determined by ^{1}H NMR of the crude product; [b] in entries 1-7, all reactions were carried out at 0 °C and commercial NaClO (13-15 % available chlorine) was used as a source of chlorine; [c] the reaction was carried out at -78 °C, warmed up to 0 °C and quenched; [d] lit.[141] 40% yield.

The chloro compound **II-10a** was also obtained in good yield, by a one-step procedure, by reaction of the alcoholate of *p*-methoxybenzyl alcohol with the commercially available 3-chloro-2-chloromethyl-1-propene **II-13** (Scheme II-4).[142] Because of the non-reproductibility of the Ceschi protocol and the difficulties encountered during the purification of the chloro derivative, the one-step method, which can be done on a large scale, using commercially available starting materials was the method of choice for the preparation of **II-10a**.

Table II-2.[a] Copper(I)-catalyzed coupling of allylic chloride **II-10a** and propargyl alcohol **II-14**

Entry	**II-14** (equiv.)	Reagents (equiv.)	Base (equiv.)	Time, h	Yield of **II-15a**, %
1	1.1	0.15 TBAB, 0.05 CuI	2 K_2CO_3	24	47
2	1.1	0.15 TBAB, 0.05CuI	2 K_2CO_3	30	45
3	1.5	0.15 TBAB, 0.05 CuI	2 K_2CO_3	48	57 (15)[b]
4	1.5	0.15 TBAB, 0.05 CuI	2 Cs_2CO_3	24	-(21, 20)[c]
5	1.5	NaI, CuI	1.5 K_2CO_3	24	62
6	1.5	NaI, CuI	1.5 K_2CO_3	24	56

[a] All reactions were carried out at room temperature in DMF; [b] yield of **II-15c** by NMR of the crude product; [c] yields of **II-15c** and **II-15b** respectively.

With **II-10a** in hand, we began to study the coupling reaction between this allyl chloride and propargyl alcohol. In Jeffery conditions, [143] i.e.in the presence of catalytic amounts of CuI and tetra-*n*-butylammonium bromide (TBAB) and K_2CO_3 as a base, the coupling product **II-**

15a was obtained in 57 % yield (Table II-2, entry 3). As it can be seen on Table II-2, the increase of propargyl alcohol loading led to a slight improvement of the yield (entry 1 versus entry 3). Replacement of K_2CO_3 by Cs_2CO_3 led exclusively to isomerization to yield products **II-15b** and **II-15c**. The best yield in **II-15a** was obtained by using stoechiometric amounts of NaI and CuI (entry 4).[144]

The stage was now set up for the reduction of the triple bond within **II-15** into the *trans*-alkene **II-9a**. All attempts to perform this transformation with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) as reducing reagent in both THF and Et_2O were unsuccessful, even at low temperatures, and *p*-methoxybenzyl alcohol was the sole characterized product of the reaction (entries 1-3).[145] Poor yields of the desired product were obtained when **II-15a** was treated with $LiAlH_4$ in refluxing THF (entry 4-6).[146] As determined by ^{1}H NMR, $LiAlH_4$ reduction is quite clean at low percentages of conversion of **II-15a** but prolonged reaction times led to decomposition.

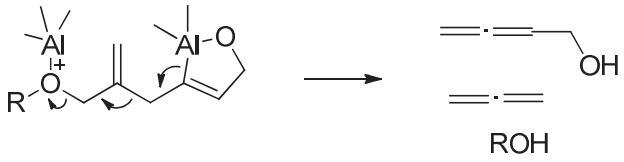
Table II-3. Study of the reduction of propargyl alcohol **II-15a** to *trans* allylic alcohol **II-9a**

Entry	Solvent	Reductive system (equiv.)	T, °C	Time	Yield, % (conv.)
1	THF	1.7 Red-Al	0 → rt	10 h	Decomposition
2	THF	2 Red-Al	0	40 min	Decomposition
3	Et_2O	2 Red-Al	-20 → 0	1 h	Decomposition
4	THF	1.5 $LiAlH_4$	reflux	2 h	No reaction
5	THF	3 $LiAlH_4$	reflux	10 h	30 (70)[a]
6	THF	4 $LiAlH_4$	reflux	24 h	28[a]
7	THF	1.8 Red-Al, 2 NaOMe	-23 → 0	30 h	Dec. (24)[a]
8	THF	3 Red-Al, 6 NaOMe	-25	4 h	Dec (<10)[a]
9	THF	3 DIBAL	rt	20 h	No reaction
10	THF	1.1 *n*-BuLi, 1.7 DIBAL	0	40 h	No reaction
11	DMF:H_2O	4 $CrCl_2$, 0.35 Na_2SO_4, 0.35 NaOAc	50	7 d	33 (50)
12	DMF:H_2O	8 $CrCl_2$, 4 Na_2SO_4, 2 HCl	50	21 d	61 (83)
13	DMF:H_2O	8 $CrCl_2$, 4 Na_2SO_4, 0.2 $Yb(OTf)_3$	50	21 d	33 (33)[a]

[a] Determined by ^{1}H NMR

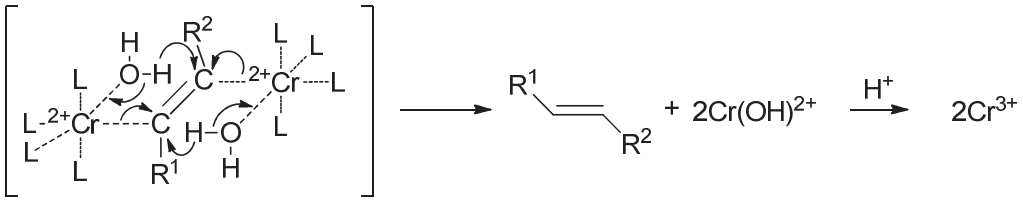
We supposed that electrophilic aluminium species, present in the reaction medium, could coordinate with the oxygen of allyl ether catalyzing thus the fragmentation of alanate by the pathway described in Scheme II-5. Addition of NaOMe to Red-Al solution, in order to convert any electrophilic aluminium hydride species to the corresponding ate complex, has been reported.[147] Application of this protocol to our substrate did not result in the formation of

allylic alcohol, but the decomposition process was much slower (entries 7, 8). No reaction was observed when propargyl alcohol **II-15a** (entry 9) or its alcoholate (entry 10) were treated with DIBAL.[148]



Scheme II-5

Finally we studied the reduction of alkynol **II-15** with low-valent Cr(II) salts (entries 11-13). Castro and Stephens have shown that propargyl alcohols could be stereoselectively reduced to *trans* allylic alcohols at room temperature by chromous salts in deoxygenated aqueous dimethylformamide.[149,150] A mechanism of this reduction suggested by the authors involved the formation of a transition state where the alkyne is complexed by two chromous ions and where a concomitant departure of chromium and back-sided proton transfer from the solvatation spheres of the metal ions explained the *trans* stereochemistry of the formed double bond (Scheme II-6).



Scheme II-6

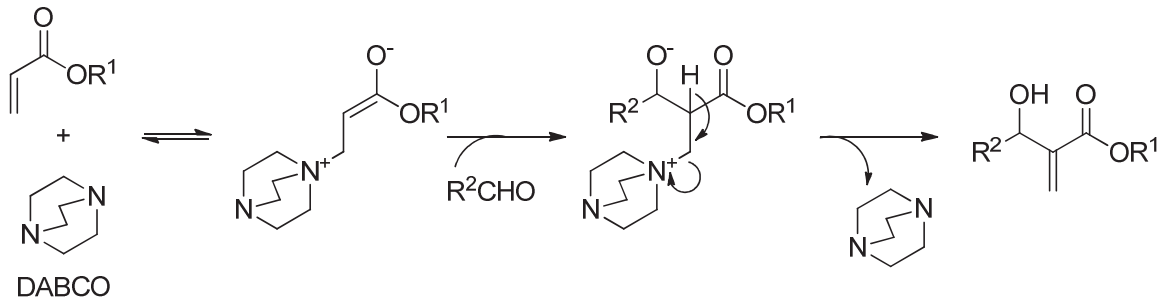
After a number of experimentations, we found that correct yields in the desired allylic alcohol **II-9a** could be achieved by treatment of **II-15a** with 8 equivalents of $CrCl_2$, in the presence of 2 equivalents of HCl, at 50 ^{o}C during 3 weeks (entry 12). Prolonged reaction times and incomplete conversion are the important drawbacks of this method. So, we turned our attention to another approach of the monoprotected 1,4-enyne diol.

II.2.3. Studies toward the synthesis of II-9b (PG = TBS)

First of all, because we thought that fragmentation occurring during the reduction the triple bond of **II-15a** with aluminium hydrides was facilitated by the chelation of PMB ether by aluminium, we decided to replace the PMB group by a more hindered protecting such as a *tert*-butyldimethysilyl group. We also decided to find a more efficient synthesis of the allylic halide **II-10**. We thought that the Baylis-Hillman reaction,[151] an atom-economical and extremely useful C-C bond forming reaction, could help us to succeed in our project.

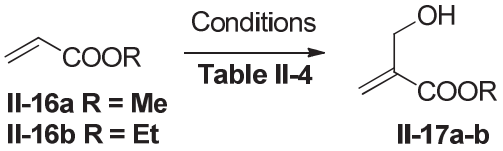
As illustrated in Scheme II-7, the widely accepted mechanism of the Baylis-Hillman reaction consists of three steps: (1) nucleophilic Michael addition of base such DABCO to acrylate, forming a zwitterionic intermediate; (2) an aldol-type reaction of the intermediate

with the aldehyde, forming a second zwitterionic intermediate; and (3) the subsequent release of the base via β-elimination, leading to the formation of the Baylis-Hillman reaction product.



Scheme II-7

Study of the Baylis-Hillman reaction between acrylate and formaldehyde in different experimental conditions is outlined in Table II-4. In the presence of DABCO, a standard catalyst used for this reaction, the best result was obtained by using aqueous formaldehyde in dioxane:water, however α-(hydroxymethyl)acrylate **II-17a** was obtained in only 22 % yield (entry 3). Conversely, a quantitative yield of the α-substituted acrylate **II-17b** was obtained by using a large excess of ethyl acrylate, paraformaldehyde in an aqueous solution of trimethylamine (entry 4).



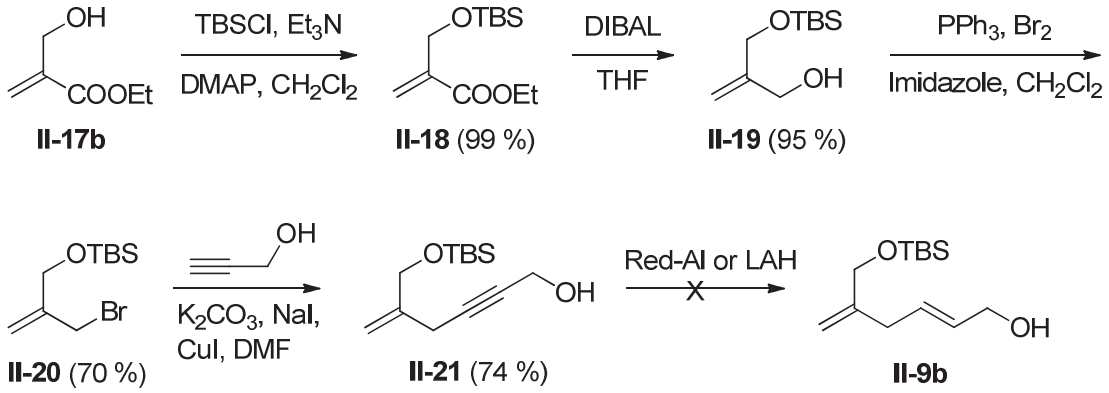
Scheme II-8

Table II-4. Optimization of the Baylis-Hillman reaction between Me and Et acrylates and formaldehyde

Entry	R	Conditions (equiv.)	Temp., °C	Time, h	Yield, %	Ref.
1	Me	1.1 CH_2O aq., 0.1 DABCO, THF	rt	60	17 (crude)	
2	Me	1.1 $(CH_2O)_n$, H_3PO_4 cat., 0.1 DABCO, THF	rt	60	nd	[152]
3	Me	0.3 CH_2O aq., 0.3 DABCO, dioxane:H_2O	rt	20	22	[153]
4	Et	0.25 $(CH_2O)_n$, 0.25 Me_3N, H_2O	50	12	97	[154]
5	Et	0.25 $(CH_2O)_n$, 0.25 Me_3N, H_2O	50	20	77	[154]

Having the Baylis-Hillman product **II-17b** in hand, its alcohol function was protected as a TBS group, and treatment of the resulting silyl ether **II-18** by DIBAL afforded in near quantitative yield the allylic alcohol **II-19** (Scheme II-9). Conversion of the allylic alcohol

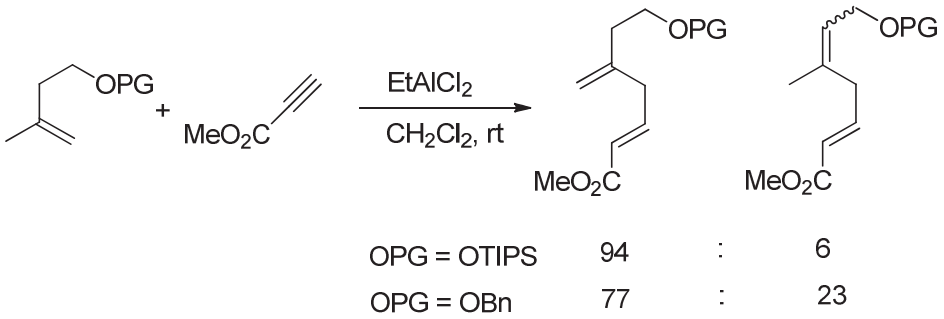
into allyl bromide **II-20** was accomplished in a good yield by employing triphenylphosphine and bromine in the presence of imidazole.[155] Coupling of **II-20** with propargyl alcohol, using the same protocol than that used for the preparation of **II-15a** (Table II-4), namely in presence of stoichiometric amounts of CuI and NaI and an excess of K_2CO_3 furnished **II-21** in a good yield. Unfortunately, all attempts to reduce the triple bond by aluminium hydrides gave only decomposition of the starting material.



Scheme II-9

II.2.4. Attempts II-9 synthesis by ene reaction

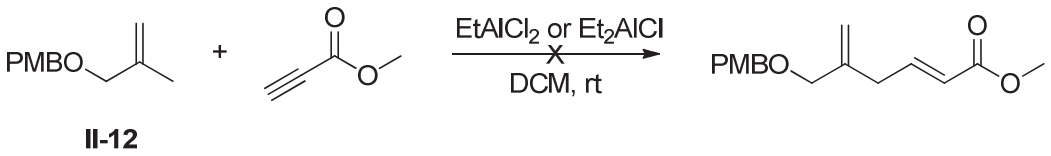
In order to bypass difficulties connected with the formation of *trans* double bond by stereoselective reduction of a triple bond, we turned our attention to methods allowing the direct construction of 1,4-dienes. Our first choice was the catalyzed acetylene-ene reaction. There are only few examples in the literature of ene reaction between propiolate and unsaturated ethers.[156] In the presence of $EtAlCl_2$, this type of ene reaction is regioselective; the degree of regioselectivity depending of the protecting group as seen in Scheme II-10.



Scheme II-10

In the presence of Lewis acids, a mixture of methyl propiolate and the allylic ether **II-12** did not give any detectable ene product by ^1H NMR (Scheme II-11). In fact, we have shown

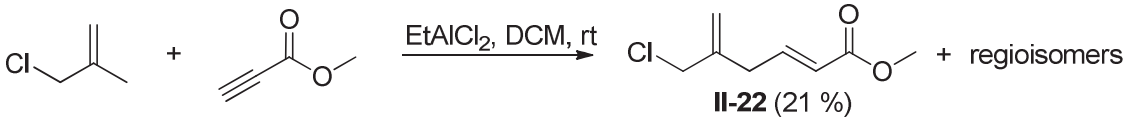
that the ene reaction failed because of the unstability of allylic ether **II-12** in the reaction conditions.



II-12

Scheme II-11

We did not have more success with methallyl chloride **II-11** which gave with methyl propiolate, in the presence of one equivalent of ethylaluminium dichloride, after 5 days at room temperature, an inseparable mixture of **II-22** and of regioisomers obtained in 21 % yield (Scheme II-12).



II-11

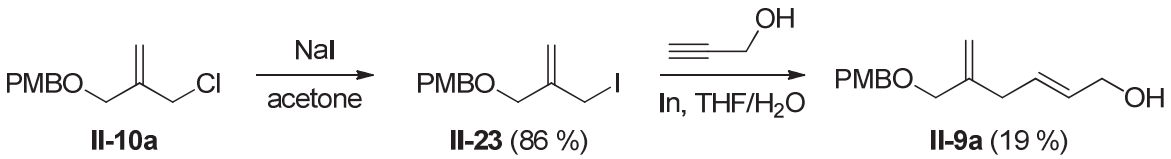
II-22 (21 %)

Scheme II-12

Poor yields incited us to abandon this approach of dienol **II-9**.

II.2.5. Application of carboindation reaction to the synthesis of II-9

We next explore the interesting properties of allylindium reagents to add regioselectively to alkynes to give 1,4 -dienes.[157] Because indium is not very reactive towards allyl chloride, the chlorine atom in **II-10a** was interchanged by iodine by a standard procedure (Finkelstein reaction). Treatment of propargyl alcohol with two-fold excess of allyl iodide **II-23** in THF in presence of indium metal furnished the alcohol **II-9a** in a poor yield. The reaction was repeated three times avoiding the presence of air oxygen, but the yield was unchanged.



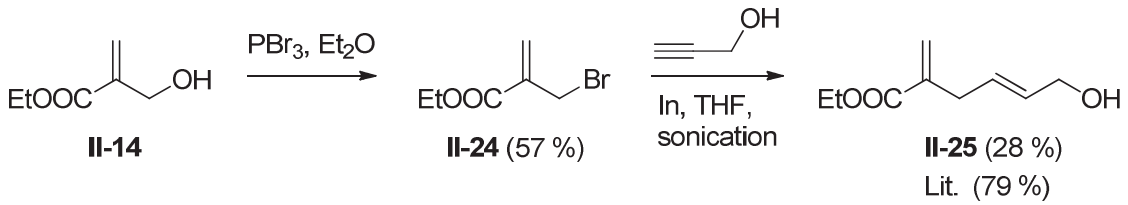
II-10a

II-23 (86 %)

II-9a (19 %)

Scheme II-13

It has been reported that α-bromomethacrylate **II-24** reacted smoothly with propargyl alcohol, in the presence of indium to give regioselectively 6-hydroxy-2-methylen-hex-4-enoate **II-25** in good yield.[157b] In our hands, using exactly the same protocol as described by Klaps and Schmid,[157b] this reaction afforded **II-25** in only 28 % yield (Scheme II-14).



Scheme II-14

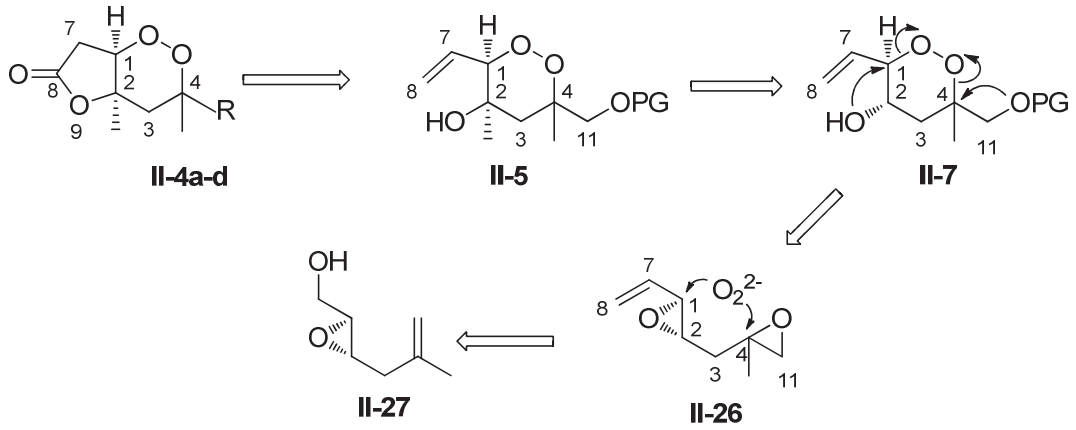
II.2.6. Conclusion

None of the approaches of dienol **II-9** studied gave satisfactory results. In the first approach, we did not find reducing agent to transform the triple bond of the enyne to a *trans* double bond in a good yield and/or a reasonable reaction time. Other approaches were stopped at the coupling stage (ene or carboindation reactions) because of low yields. Thus a new strategy toward plakortolide synthesis was required.

II.3. Second approach of the precursor II-7

II.3.1. Retrosynthesis

We reexamined the first synthetic plan and we imagined that the β,β'-dihydroxy-1,2-dioxane moiety of the precursor **II-7** could be obtained by a double epoxide-opening with a peroxide dianion equivalent (H_2O_2) which led to the diepoxide **II-26**. This latter can arise from *m*CPBA epoxidation of the unsaturated epoxy alcohol **II-27** which synthesis has been already reported (Scheme II-15).[158]



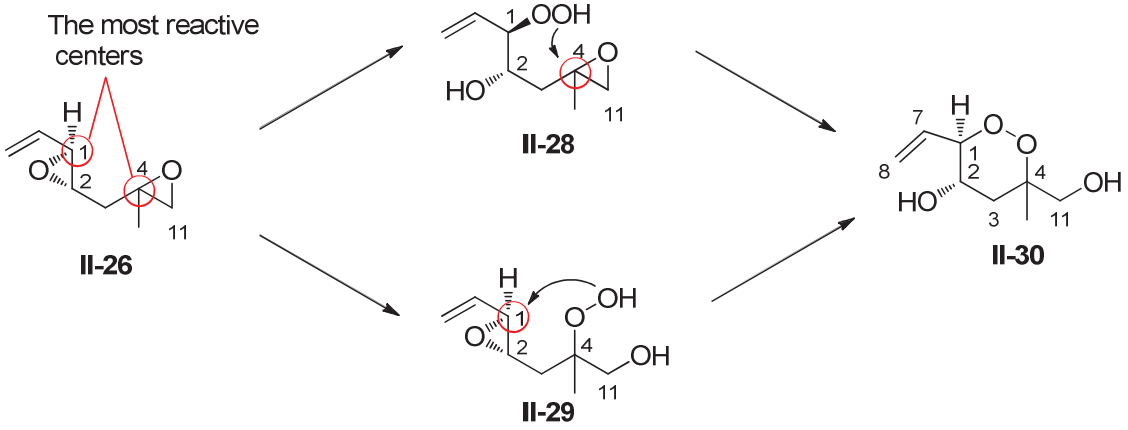
Scheme II-15

The success of this strategy depended upon the correct outcome of the regioselectivity of the epoxide opening of the two epoxides within **II-26** by the right nucleophile. It seemed obvious for us that, in acid conditions, the most reactive centers in **II-26** are the quaternary center in C4 and the secondary center C1 in which the incipient cation is stabilized by the

double bond in α-position. Initial attack of hydrogen peroxide could take place either on these centers to give **II-28** and **II-29** respectively (Scheme II-16); both of these molecules have four possibilities to cyclize: hydroxy or hydroperoxy groups can attack either the two centers of each epoxide. Fortunately, as we will see further, only one of them is favorable in each case.

This approach calls for a question: among the hydroxy and perhydroxy groups what is the best nucleophile? If to a large extent the nucleophile strength is correlated with basicity, there are exceptions thus if hydroxide is 16000 times more basic than hydroperoxide, this latter is about 400 times more nucleophilic than hydroxide. This enhancement of the nucleophilicity that in found when the atom adjacent to nucleophilic site bears a lone pair of electrons is called the α-effect.[159] Prevalent theories on the α-effect phenomenon include ground-state destabilization and solvent effects. In the first theory, the electrostatic repulsion between the electron pair of the reacting atom and the free electron pair of the adjacent electronegative atom raise the ground state energy of the nucleophile, thus lowering the energy of activation, making the nucleophile more reactive.[160] The solvent effects is explained by the inductive withdrawal by the negative charge of the adjacent oxygen in hydroperoxide makes this nucleophile less solvated and hence more reactive.[161] This theory is supported by the fact that the heat of hydratation of OH^- is 23 kcal/mol more exothermic than that of OOH^-.[162]

The ring closure in **II-28**, with the hydroperoxide as nucleophile, must follow the Baldwin's rule to give the 6-*exo*-tet cyclization product **II-30** by attack on the quaternary center C4. Keeping the hypothesis that hydroperoxide is a better nucleophile than alcohol, the cyclization of compound **II-29** will be directed by the vinyl group to afford also **II-30**.

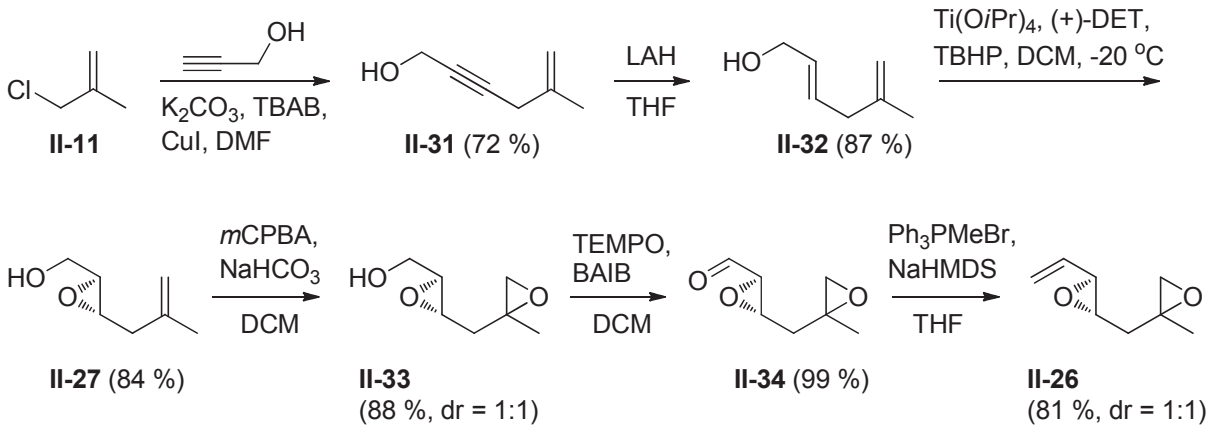


Scheme II-16

Thus, it was expected that treatment of **II-26** with hydrogen peroxide, in acid conditions, would give preferentially **II-30**.

II.3.2. Synthetic studies toward II-30

The synthesis of the intermediate vinyl diepoxide **II-26** started by a copper-catalyzed coupling between methallyl chloride and propargyl alcohol followed by reduction of triple bond with $LiAlH_4$ and Sharpless epoxidation of the resulting allyl alcohol **II-32** to give **II-27** in good overall yield (Scheme II-17). The optical purity of the epoxide was determined to be ~90 % ee by comparison of its $[\alpha]_D$ to that described in the literature.[158] Epoxidation of the second double bond was performed by means of *m*CPBA to give an unseparable mixture of diastereomers **II-33.** The epoxyalcohol **II-33** was then oxidized with TEMPO/BAIB mixture[163] to give aldehyde **II-34** which was transformed to **II-26** by Wittig methylenation. It should be noted that utilization of NaHMDS as a base is crucial for reaction success, otherwise with BuLi only traces of the desired product were obtained possibly due to epoxide opening catalyzed by lithium cation.



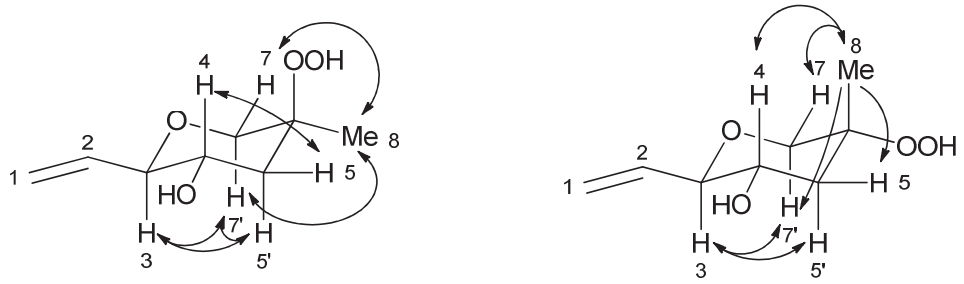
II-11 | **II-31** (72 %) | **II-32** (87 %)

II-27 (84 %) | **II-33** (88 %, dr = 1:1) | **II-34** (99 %) | **II-26** (81 %, dr = 1:1)

Scheme II-17

With the diepoxide **II-26** in hand, we tested the tandem epoxide opening-cyclization reaction with anhydrous hydrogen peroxide and different acid catalysts (Scheme II-18, Table II-5). Unfortunately, the reaction using 2 equivalents of H_2O_2 and a range of potential catalysts such as phosphomolybdic acid (PMA),[90] TMSOTf or lanthanide triflate did not give the endoperoxide **II-30**. In all cases, the hydroperoxides **II-36a** and **II-36b** were the main products isolated (dr ~ 1:1). Absence of compounds bearing a 1,2-dioxane ring in the reaction mixture was proved by comparison of its mass spectrum with and without PPh_3 additive. If **II-30**, not reducible by PPh_3 even at ESI conditions (proved by ESIMS spectrum mesurement of the mixture of 1,2-dioxane **II-152** and PPh_3 where no degradation of **II-152** was observed), was formed during the reaction between **II-26** and hydrogen peroxide, the signal at 197.1 that correspond to [**II-30**+Na^+] ion should appear in the mass spectrum of the reaction mixture containing PPh_3 (Figure II-1). The structure of **II-36a,b** was ascertained by NMR spectroscopy. HMBC correlations between CH_3 and CH_2-7 proved the presence of CH_3-O-CH_2-7 connection in the molecule. The most representative NOESY correlations which ascertain the relative stereochemistries of both diastereomers are presented below:

The most representative NOE correlations



II-36a **II-36b**

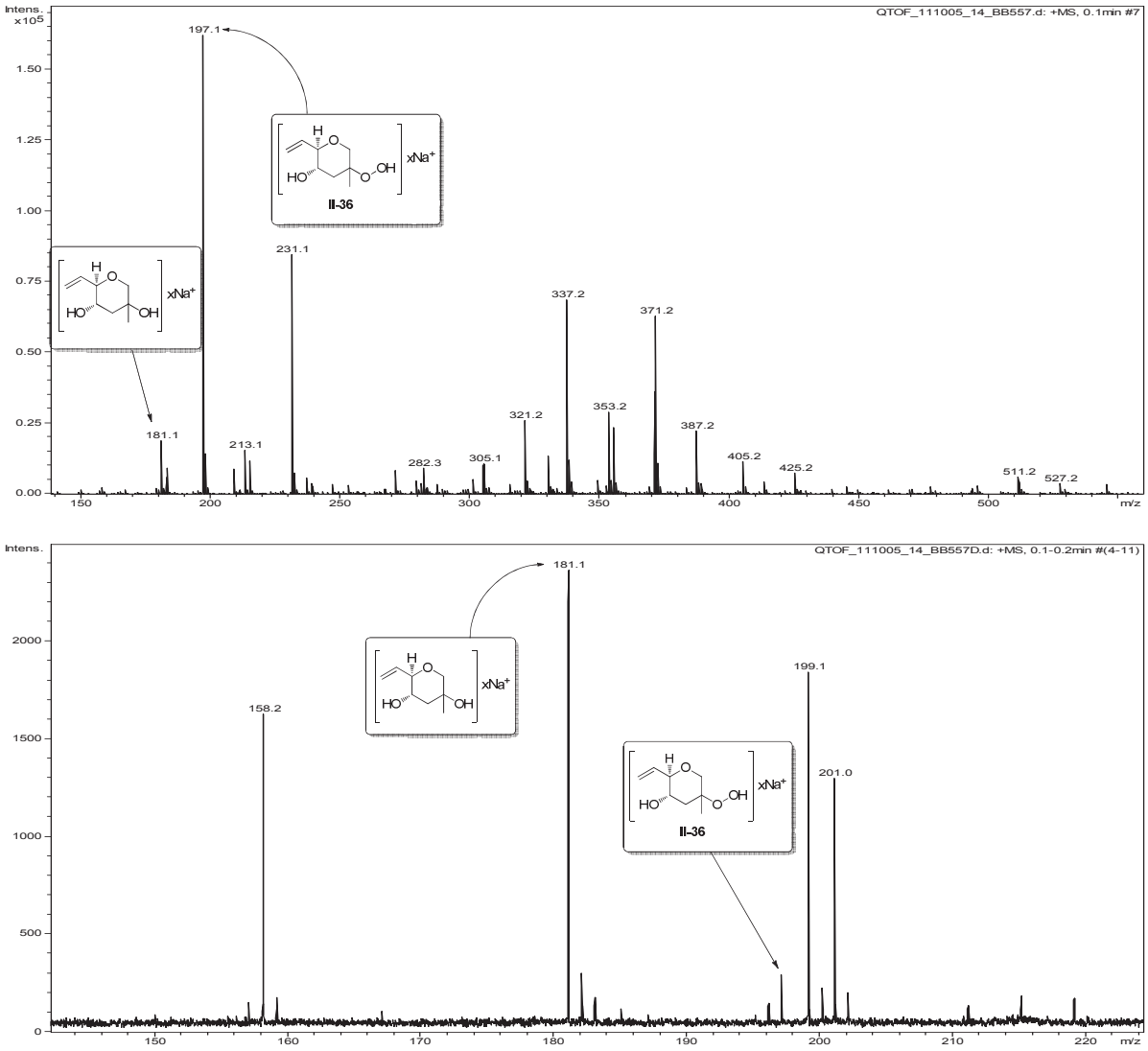
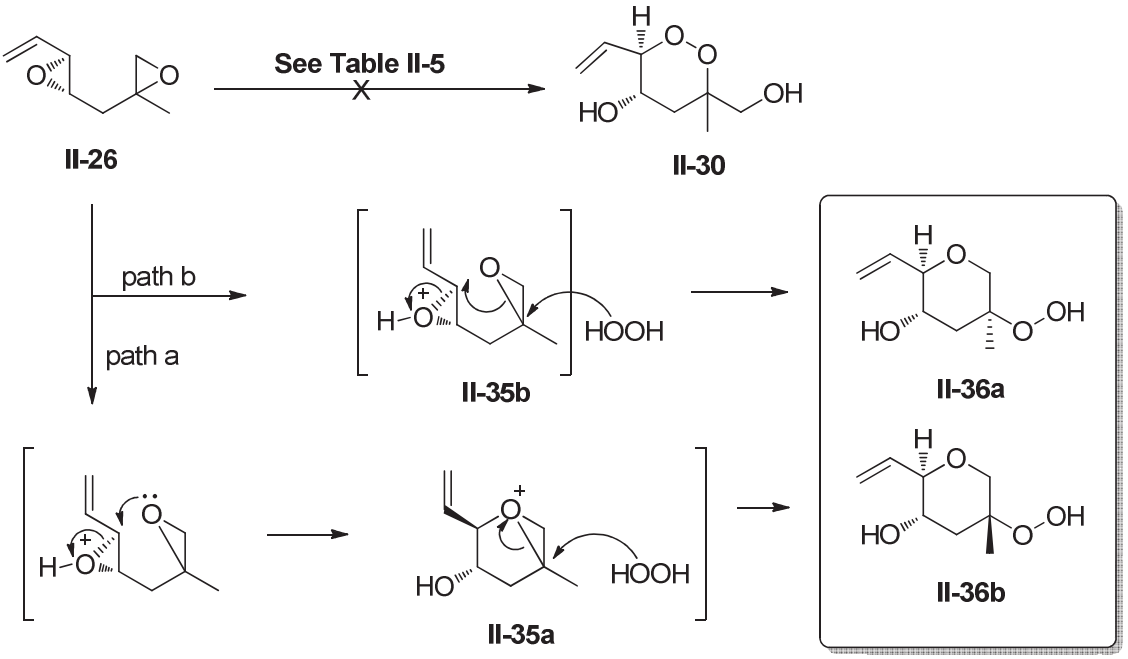


Figure II-1. Mass spectra of the reaction mixture (**II-26** + H_2O_2) without (above) and with ~1.5 equiv. of PPh_3 (below).



Scheme II-18

Table II-5[a]. Addition of hydrogen peroxide to the diepoxide **II-26**

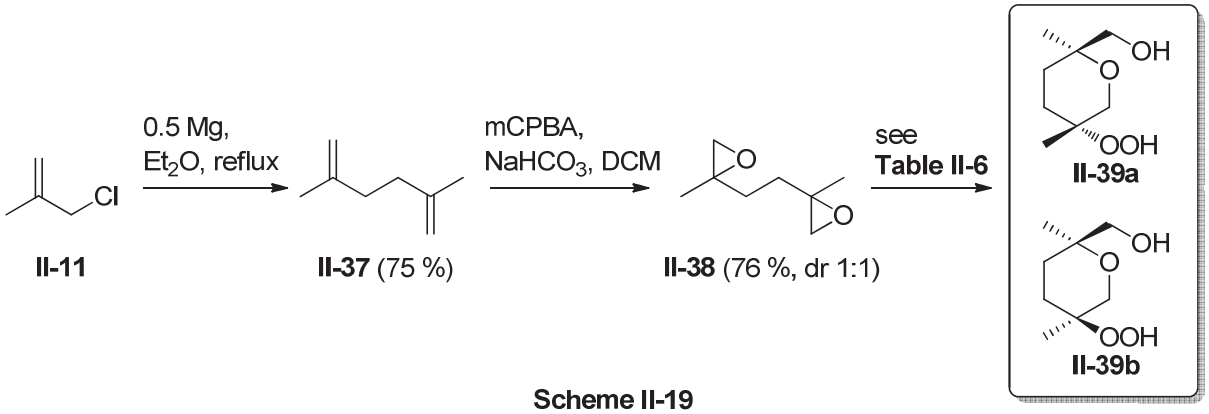
Entry	Conditions (equiv.)	Time, h	Yield, % (dr)
1	0.1 PMA, 2 H_2O_2	1	23 (1:1)
2	0.01 PMA, 2 H_2O_2	0.5	37 (1:1)
3	0.05 TMSOTf, 2 H_2O_2	15	complex mixture
4	0.1 $La(OTf)_3$, 2 H_2O_2	6	23 (1:1)
5	0.01 PMA, 6.8 H_2O_2	2	28 (1:1)
6	0.005 PMA, 5 H_2O_2	1	40[b] (1:1)

[a] All reactions were carried out in Et_2O at room temperature, and after completion of the reaction, they were evaporated and chromatographed; [b] The reaction mixture was filtered through a small pad of silica gel, evaporated and chromatographed.

This result was contradictory with the above-mentioned assumption that the cyclization might occur via epoxide opening by an internal hydroperoxide. Based on the mechanism of oxacyclization of polyepoxides to fused polycylic ether natural product skeletons reported by McDonald and co-workers,[164] we assumed that the tetrahydrofuranique derivative **II-36** was formed by activation of the vinyl epoxide by a Lewis acid followed by intramolecular addition of the other epoxide to give intermediate epoxonium ion **II-35a** and nucleophilic addition of hydrogen peroxide to the more highly substituted carbon (route a) (Scheme II-18). Alternatively, a concerted mechanism via **II-35b** may also be involved (route b).

Because we have limited amounts of vinyl diepoxide **II-26**, we pursued the study of the double opening of diepoxide with hydrogen peroxide on a simple substrate readily prepared on a large scale.

The symmetric bis-epoxide **II-38** was prepared in 2 steps by Wurtz coupling of methallyl chloride, in the presence of magnesium, and bis epoxidation of the resulting diene **II-37** with *m*CPBA (Scheme II-19).



II-11 **II-37** (75 %) **II-38** (76 %, dr 1:1) **II-39a** **II-39b**

Scheme II-19

Table II-6. Study of addition of hydrogen peroxide and derivatives to the diepoxide **II-38.**

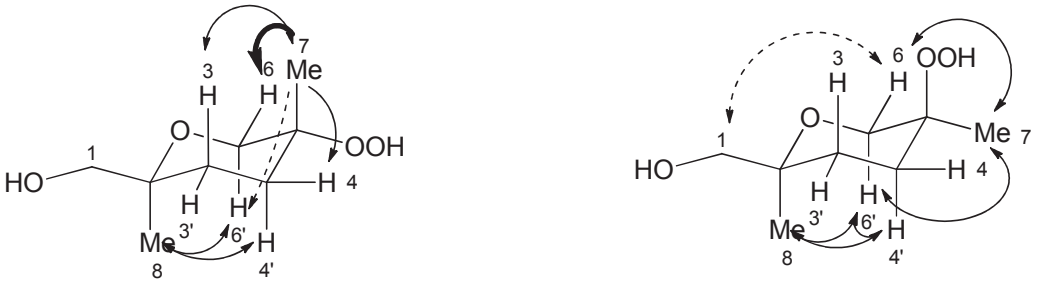
Entry	Conditions (equiv.)	Time (h)	Yield, % (dr)
1	0.1 I_2, 4 H_2O_2, CH_3CN, rt	20	12 (1:1)
2	0.1 $Sc(OTf)_3$, 4 H_2O_2, Et_2O, reflux	1	nd
3	0.01 PMA, 2 H_2O_2, Et_2O, reflux	1	6 (1:1)
4	0.01 PMA, 2 H_2O_2, Et_2O, reflux	1	nd
5	0.1 TMSOTf, 2 H_2O_2, Et_2O, reflux	1	nd
6	0.01 PMA, 2 H_2O_2, Et_2O, rt	5	8 (1:1)
7	0.005 PMA, 4 H_2O_2, Et_2O, rt	1	23 (1:1)
8	Amberlyst-15, 4 H_2O_2, Et_2O, rt	48	35[a] (1:1)
9	0.1 TMSOTf, TMSOOTMS, DCM, -78 ^oC - rt	1 h	-
10	0.008 PMA, 3 H_2O_2, Et_2O, rt	1	45 (1:1)

[a] Determined by ^1H NMR spectroscopy of the reaction mixture.

Tandem acid-catalyzed H_2O_2 oxirane opening-cyclization reaction was next studied in different conditions and the results are presented in Table II-6. Treatment of **II-38** with two to four fold excess of hydrogen peroxide in diethyl ether in the presence of different Lewis/Bronsted acids (entries 1-10) provided diastereomeric mixture of hydroperoxides **II-39a** and **II-39b** as the only characterized products. Disappearance of the signal at 199.1 that correspond to $[C_8H_{16}O_4Na]^+$ ion in the mass spectrum of the reaction mixture treated with PPh_3, bring to light the absence of 1,2-dioxan in the reaction mixture (Figure II-2). The

relative stereochemistries of both diastereomers were determined by NOE correlations and are presented below (bold and dashed arrows correspond to strong and weak NOE effect respectively):

The most representative NOE correlations



II-39a **II-39b**

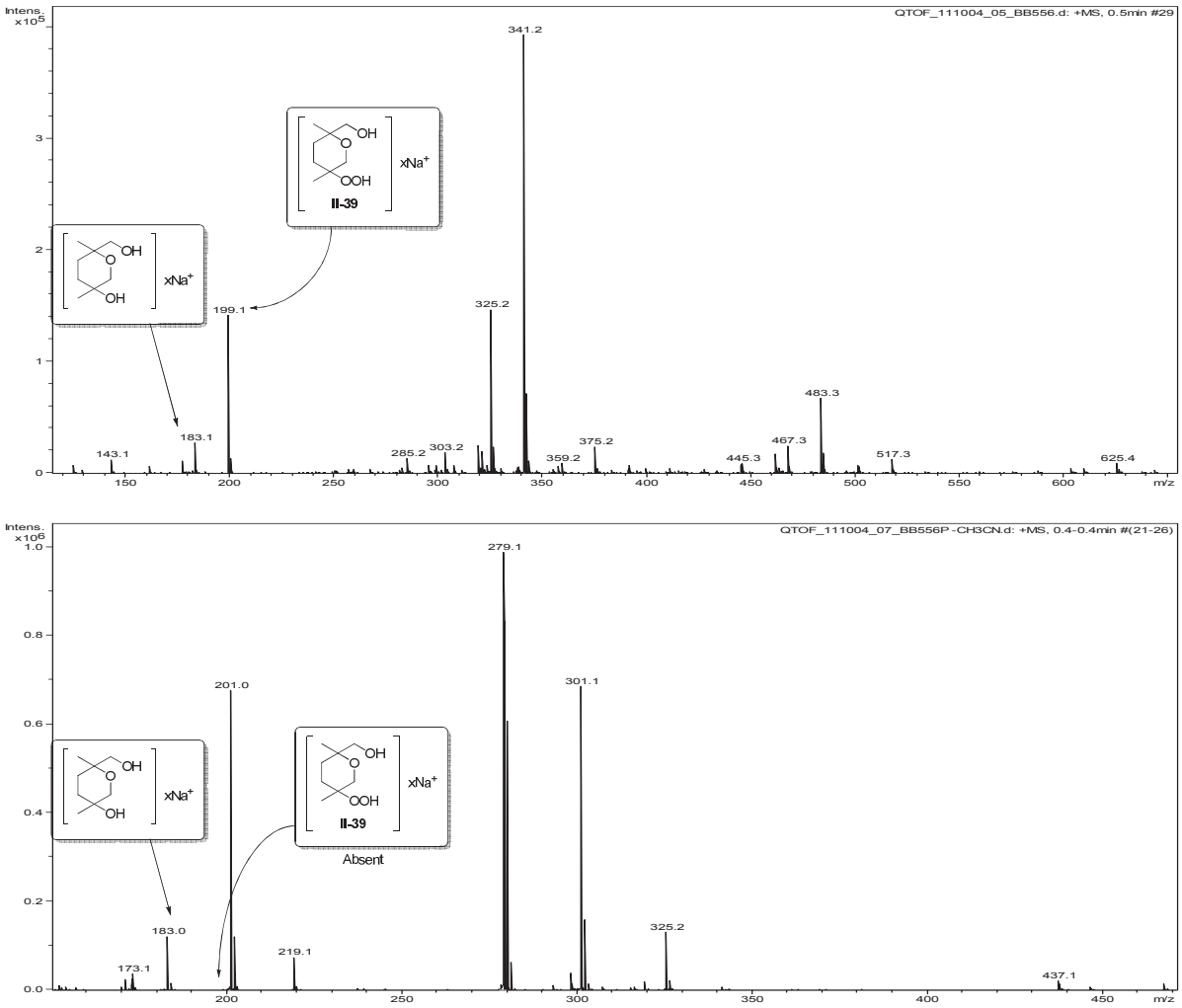
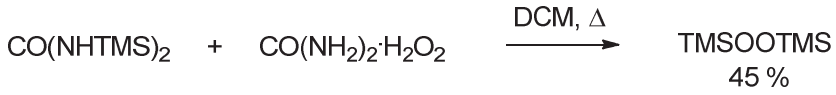


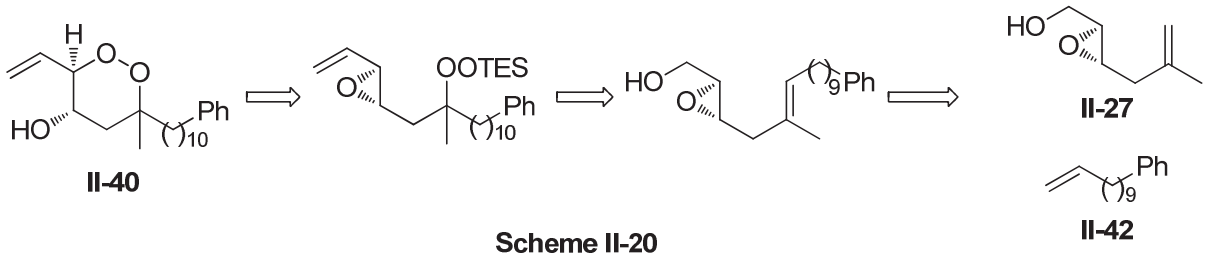
Figure II-2. Mass spectra of the reaction mixture (**II-38** + H_2O_2) without (above) and with ~1.5 equiv. of PPh_3 (below).

Bistrimethylsilyl peroxide was also tested in the reaction with bisepoxide **II-38** catalyzed with catalytic amount of trimethylsilyl triflate (Entry 9), but only undetermined mixture of products were obtained. Bistrimethylsilyl peroxide[165] was synthesized from urea·H_2O_2 adduct and bis-trimethysilyl urea as follows:



II.3.3. Studies on metathesis reaction with II-27

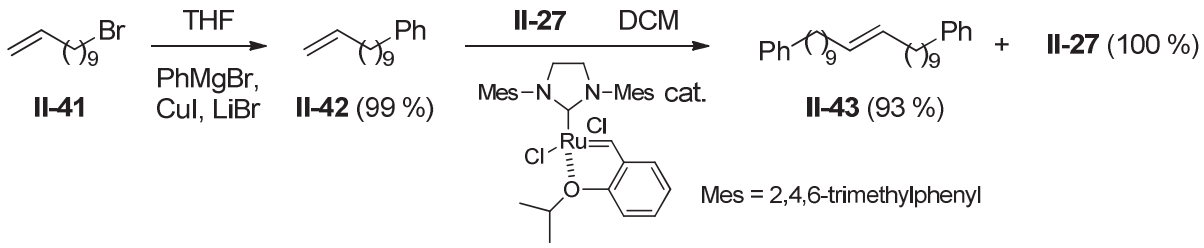
A parenthesis of this failed strategy was that we thought that the key intermediate: compound **II-27** (see Scheme II-17) could be transformed to plakortolides I and E by a different set of reactions. We imagined that the side chain could be introduced at the early stage of the synthesis via a cross coupling methathesis with **II-27** followed by hydroperoxysilylation of the trisubstituted double bond and cyclization which should lead to the advanced intermediate of plakortolides: compound **II-40** (Scheme II-20).



Scheme II-20

First of all, we wondered if the two olefins **II-27** and **II-42** are good partners in terms of selectivity in the cross metathesis (CM). In the context of a predictive model for catalytic CM selectivity, Grubbs and co-workers have proposed a categorization of olefins according to relative rates of homodimerization and as a function of the type of metathesis catalyst used.[166] According to this rule, **II-42** is a type I olefin which means reactive olefin being able to give rapid homodimerisation while **II-27** is a type III olefin, not very reactive in CM. Grubbs and coworkers have studied CM between these two types of olefins and showed that in using an excess of type I olefin, coupling products: trisubstituted olefins could be obtained in good yields.[167]

Treatment of the mixture of **II-27** and three equivalents alkene **II-42,** readily available from **II-41**, with Hoveyda-Grubbs 2nd generation catalyst in dichloromethane led to no cross-coupling product formation.[168] Homocoupling product **II-43** and starting alcohol **II-27** were obtained in nearly quantitative yields.



Scheme II-21

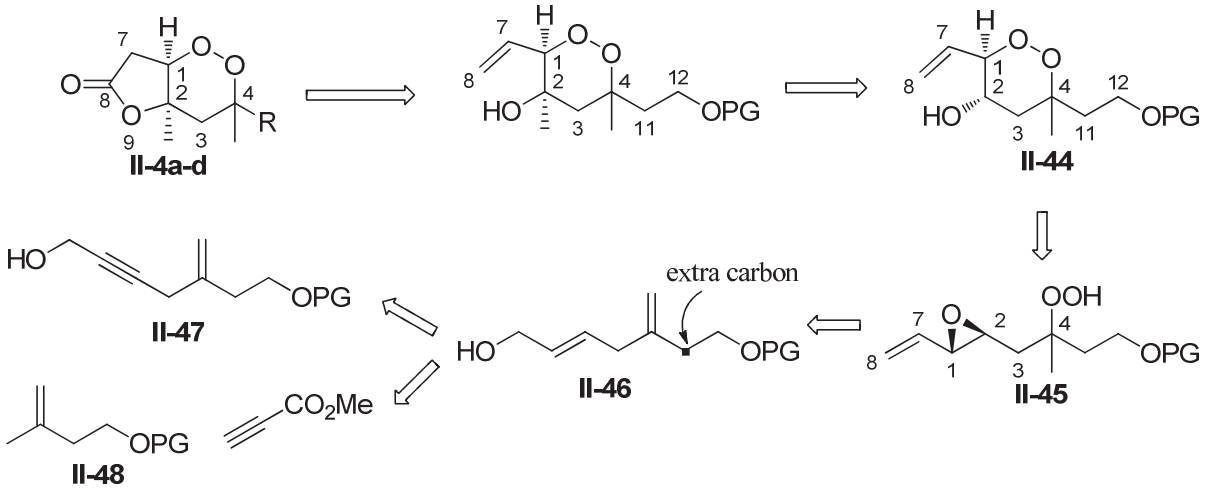
II.3.4. Conclusion

In this second approach, if we took into account a number of factors that might guarantee its success (relative nucleophilicity of potential nucleophiles, regioselectivity of the epoxide-opening based on Baldwin's rules and on the relative reactivity of the epoxide centers), we underestimated the property of epoxide to act as an internal nucleophile, this intramolecular nucleophilic substitution being faster than that involving external hydroperoxide nucleophile.[169]

II.4. Third synthetic approach

II.4.1. Retrosynthesis

In the first approach, we did not succeed in the synthesis of the dienol precursor **II-9** (Scheme II-4) either because of a fragmentation, facilitated by the chelation of the allylic ether, during attempts of triple bond reduction with aluminium hydrides or due to the unstability of the allylic ether **II-12** (Scheme II-11) in the propiolate-ene reaction. In order to overcome these obstacles in both approaches of dienol **II-9**, we thought to add an extra carbon between the *gem*-disubstituted alkene and the protected alcohol. Synthesis of the new target: homoallylic ether **II-46** has already been reported via ene reaction (see Scheme II-10).

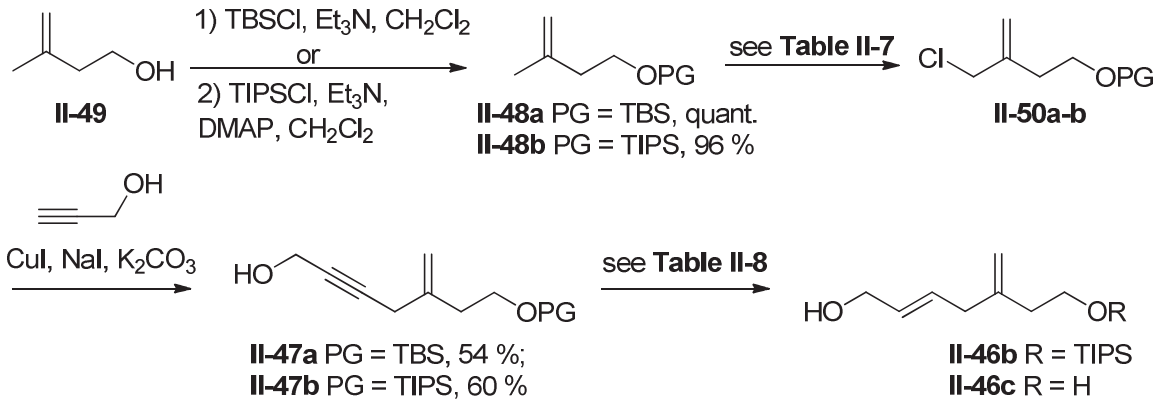


Scheme II-22

Except this one-carbon homologation of dienol **II-9**, the first synthetic plan for the construction of the functionalized 1,2-dioxane (**II-44**) remained unchanged (Scheme II-22).

II.4.2. Synthesis dienol II-46 by reduction of triple bond of enyne II-47

The synthesis of **II-46** commenced by protection of commercially available 3-methyl-3-buten-1-ol **II-49** as TBS and TIPS silyl ethers (Scheme II-23). The next step was the allylic chlorination of **II-48a-b** and the results of this study are presented in Table II-7. Our study of allylic chlorination of PMB ether of methallyl alcohol had shown that sodium hypochlorite in the presence of $CeCl_3$ or $InCl_3$ are efficient reagents for this reaction (Table II-1). As seen in Table II-7 (entries 3,4), compounds **II-48a-b** were efficiently chlorinated with two equivalents of $CeCl_3$ and sodium hypochlorite under vigorous stirring for 30 min. Prolonged reaction times or changing the catalytic system (entries 1,2) increased the yield of polychlorinated products. Then copper-catalyzed coupling of TIPS and TBS ethers **II-50a-b** with propargyl alcohol furnished **II-47a** and **II-47b** in moderate yields.



Scheme II-23

Table II-7[a]. Allylic chlorination of homoallylic silyl ethers **II-48a-b**

Entry	Starting material	Reagents[b] (equiv.)	Time, min	Product	Yield, %
1	**II-48a**	2 Cl_2, 2 $CeCl_3 \cdot 7H_2O$	40	**II-50a**[d]	30[c]
2	**II-48a**	4 Cl_2, 1.1 $InCl_3$	30	-[d]	-
3	**II-48a**	2 Cl_2, 2 $CeCl_3 \cdot 7H_2O$	30	**II-50a**[d]	78
4	**II-48b**	2 Cl_2, 2 $CeCl_3 \cdot 7H_2O$	30	**II-50b**	96

[a] All reactions were carried out in the mixture CH_2Cl_2:H_2O = 1:1 at 0 °C. [b] Commercial NaClO (13-15 % available chlorine) was used as a source of chlorine. [c] Determined by ^{1}H NMR of the crude product. [d] Polychlorinated byproducts were observed on the crude product by ^{1}H NMR.

The stage was set up to transform the triple bond of **II-47a-b** to a *trans* double bond. Reduction of propargyl alcohol **II-47a** with Red-Al, at ambient temperature, was unsuccessful, only decomposition of the starting material took place (Table II-8, entry 1). Treatment of **II-47b** with an excess of $LiAlH_4$ in refluxing THF furnished the desired product **II-46b** in only 21 % yield; the desilylated product **II-46c** was the main product obtained (Entry 2). Conversely, $LiAlH_4$ reduction of **II-47b** at room temperature yielded the *trans* allylic alcohol **II-46b** in a fair yield (Entry 3).

Table II-8. *Trans* reduction of alkynes **II-47a-b** with aluminium hydrides

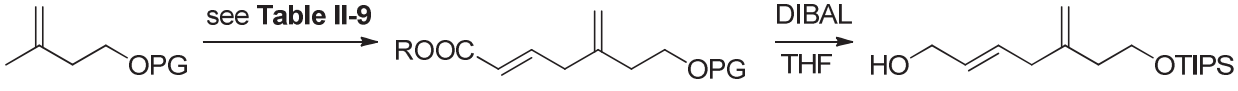
Entry	Starting material	Conditions, (equiv.)	Time, h	Yield, %	
				II-46a-b	**II-46c**
1	**II-47a**	1.5 Red-Al, Et_2O, 0 →rt	12	Decomposition	
2	**II-47b**	4 $LiAlH_4$, THF, reflux	2	21[a]	61
3	**II-47b**	2 $LiAlH_4$, THF, rt	20	66	-

[a] Determined by ^{1}H NMR of the crude product.

II.4.3. Synthesis of II-46b by ene reaction

$EtAlCl_2$-catalyzed ene reaction between TIPS and TBDPS ethers of 3-methyl-3-buten-1-ol and methyl propiolate has been previously reported (Scheme II-10).[156] Nevertheless, first attempts to reproduce these results with both silyl ethers were unsuccessful and poor yields of the desired product were obtained (Table II-9, entries 1-5). In all cases, variable amounts of desilylated adduct **II-51c** were detected indicating very likely the presence of water in the reaction medium which by reaction with $EtAlCl_2$ gave HCl that cleaved silyl ethers. In the presence of 4Å molecular sieves, no ene product or alcohol **II-49** were found by ^{1}H NMR of the crude mixture (entry 6). Finally, it was found that the reaction yield could be significantly improved by using freshly distilled dichloromethane, ethyl propiolate and performing the reaction on few grams scale (Table II-9, entry 9).

Reduction of unsaturated ester **II-51b** with an excess of DIBAL at low temperature afforded the allylic alcohol **II-46b** in good yield.



II-48a PG = TBS
II-48b PG = TIPS

II-51a R = Me; PG = TIPS (55%)
II-51b R = Et; PG = TIPS (77 %)
II-51c R = Me PG = H (13 %)

II-46b (85 %)

Scheme II-24

Table II-9[a]. Optimization of the reaction conditions of the ene reaction between Me and Et propiolate and homoallylic ethers **II-48a-b**

Entry	Starting material	R	HC≡≡CCO$_2$R, equiv.	EtAlCl$_2$, equiv.	Time, days	Yield, %
1	**II-48a**	Me	1	1	5	-[b]
2	**II-48b**	Me	1	1	5	35[c]
3	**II-48b**	Me	1.5	1	5	27[c]
4	**II-48b**	Me	1.05	2	2	33[c]
5	**II-48b**	Me	1.05	1	7	45
6	**II-48a**	Me	1	1	5	-[d]
7	**II-48b**	Me	1	1.05	7	55[c]
8	**II-48b**	Et	1	1.05	7	55[c]
9	**II-48b**	Et	1	1.02	7	77[e]

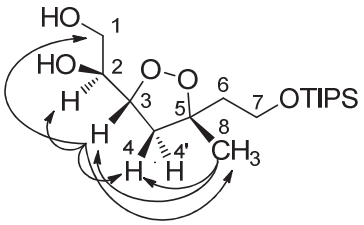
[a] All reactions were carried out in dry CH_2Cl_2 as solvent under N_2 atmosphere; [b] 13 % of desilylated product was obtained; [c] regioisomers and desilylated product were also observed on the ^{1}H NMR spectrum of the crude product; [d] the reaction was carried out in the presence of 4Å MS (0.5g/1g of **II-48b**); [e] freshly distilled CH_2Cl_2 was used.

During the present work last approach to **II-46b** was preferably used due to the following reasons: (1) low reproducibility of the allylic chlorination reaction on the large scale and (2) lower overall yield of the first approach in comparison to the last one.

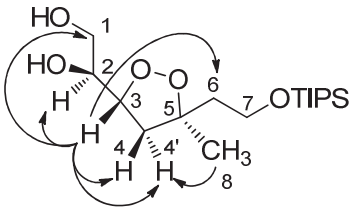
II.4.4. Attempted synthesis of the intermediate II-44

Having reach the target molecule (**II-46b**), we started the construction of the 1,2-dioxane ring (Scheme II-25). Subjection of **II-46b** to Sharpless asymmetric epoxidation conditions led to the formation of epoxyalcohol **II-52** in an excellent yield. The next step: the introduction of the hydroperoxide function by peroxysilylation of Mukayama-Isayama of the gem disubstituted double bond within **II-52** proved to be problematic. Utilization of commercial available Co(acac)$_2$ as catalyst in either ethanol or dichloroethane at room temperature led predominantly to formation of 1,2-dioxolanes **II-54a** and **II-54b** (Table II-10, entries 1,2) which structure was ascertained by the presence of COSY and HMBC correlations between H-4, H-4' and CH bearing peroxy group which is readily distinguishable from others because its signals are shifted in weak field (4.3, 4.3 and 81.4, 81.7 ppm). Absolute stereochemistry of less polar **II-54a** at C5 was proved by the presence of NOE effects at H-4, H-3 and H-4, CH_3-8 when irradiated at CH_3-8 and H-3 respectively. NOE effects at H-4, CH_2-6 and H-4' when irradiated at H-3 and CH_3-8 proved *trans* stereochemistry of **II-54b**.

The most representative NOE effects

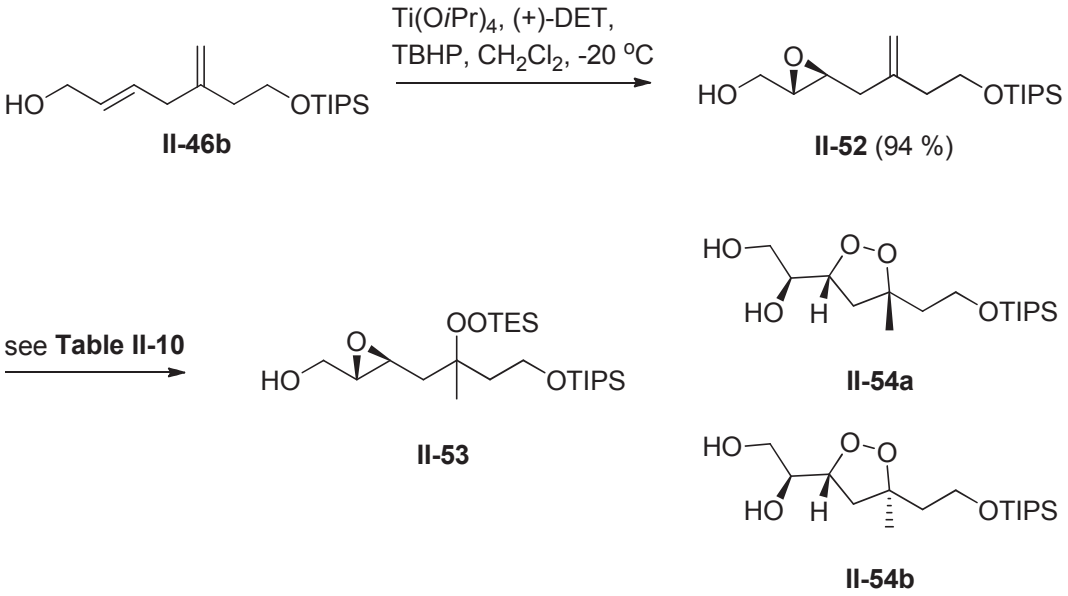


II-54a



II-54b

Considerable amounts of byproducts were also observed by ^{1}H NMR of the crude mixture. It seems that prolonged reaction times are responsible for observable deprotection of peroxy group that led to subsequent intramolecular cyclization and also for reduction of hydroperoxide to alcohol catalyzed by Co species.[170]



II-46b

II-52 (94 %)

II-53

II-54a

II-54b

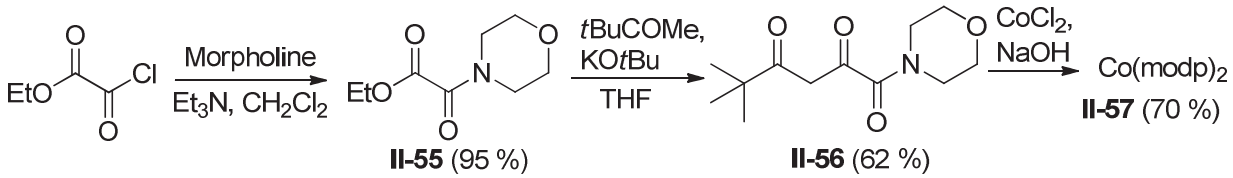
Scheme II-25

Table II-10[a]. Study of the effect of the ligand of Co(II) salts on the hydroperoxysilylation of alkene **II-52**

Entry	Catalyst	Solvent	Time, h	Conversion, %	Yield, %	
					II-53	**II-54**
1	$Co(acac)_2$	EtOH	16	94	6	41
2	$Co(acac)_2$	DCE	16	84	5	15
3	$Co(modp)_2$	DCE	4	100	41	-
4	$Co(thd)_2$	DCE	0.7	100	31	nd

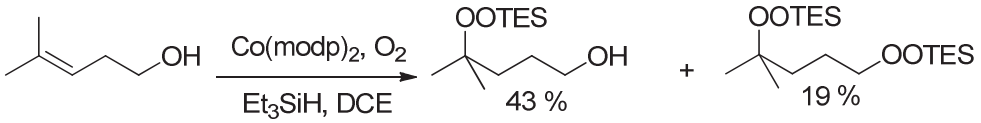
[a] All reactions were carried out under oxygen atmosphere with 10 % mol. of catalyst and twofold excess of triethylsilane.

In order to overcome these difficulties, we decided to use $Co(modp)_2$ **II-57**, one of the most active catalysts for this reaction (Scheme II-26).[97] The ligand of this cobalt salt was prepared in two steps by first addition of morpholine to ethyl oxalyl chloride followed by Claisen reaction between the resulting product **II-55** and 3,3-dimethyl-2-butanone in the presence of *t*BuOK to afford **II-56** in a moderate yield (Scheme II-26).[171] Treatment of a basic solution of ligand **II-56** with cobalt(II) chloride furnished $Co(modp)_2$ as a light brown powder in 70 % yield.[98]



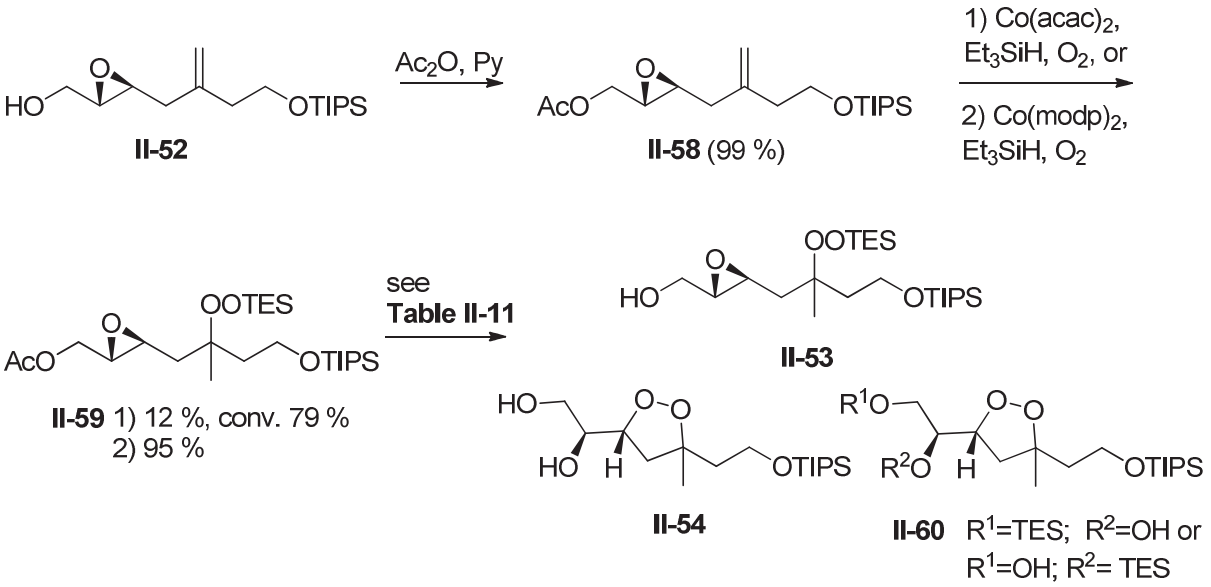
Scheme II-26

As seen in entry 3 (Table II-10), $Co(modp)_2$ as catalyst considerably shortened the reaction time and increased the yield in **II-53** which was however only moderate (41 %). $Co(thd)_2$ has shortened the reaction time even more than $Co(modp)_2$ but without any positive impact on the reaction yield. In order to improve the efficiency of this process the hydroxyl function of **II-52** was protected by an acetate group (Scheme II-27). Indeed, it is known that hydroperoxysilylation of alkenes bearing a hydroxyl group gives along with the desired hydroxyl triethylsilyl peroxy ether, variable amounts of the bissilylated analogue such as in example below.[105]



The formation of the bissilylylated by-product can be explained by ligand exchange between the Co(III)-alkylperoxo complex and the primary alcohol.[172]

As seen in Scheme II-27, $Co(acac)_2$ was proved again to be inefficient in the peroxysilylation reactions of our substrates particularly for **II-58**. In contrast, $Co(modp)_2$ effected the oxidation of **II-58** to give **II-59** in nearly quantitative yield. Compound **II-59** was obtained as a 1:1 mixture of diastereomers.



Scheme II-27

Table II-11. Cleavage of the acetyl group of **II-59**

Entry	Conditions (equiv.)	T, °C	Time	Yield, %		
				II-53	**II-54**	**II-60**
1	K_2CO_3, MeOH/THF = 1:2	0	40 min	-	39	-
2	2.2 DIBAL, DCM	-78	4 h	37	-	55
3	0.02 K_2CO_3, MeOH	0	1.5 h	-	80[a]	-

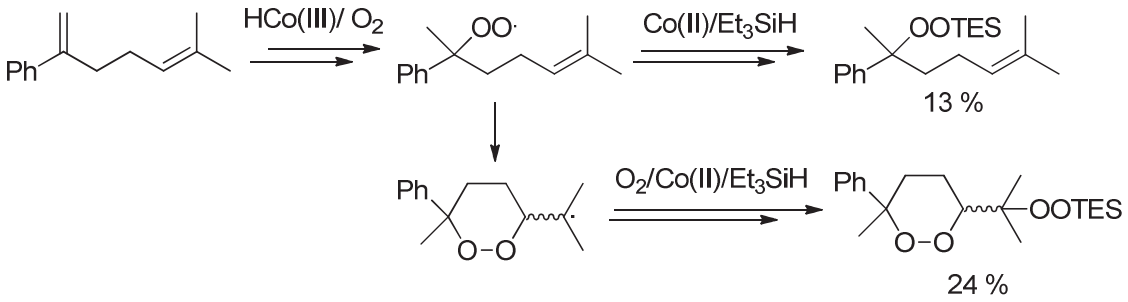
[a] Determined by ^{1}H NMR of the crude product.

The stage was now set up to transform the acetoxymethylene group into a vinyl group which required at first the saponification of the acetate function. Treatment of **II-59** with either a stoechiometric or catalytic amounts of potassium carbonate at 0 °C led to deprotection of both acetyl and triethylsilyl functions followed by 5-*exo*-tet cyclization. Dioxolane **II-54** was the sole characterized product in both cases (Table II-11, entries 1, 3).

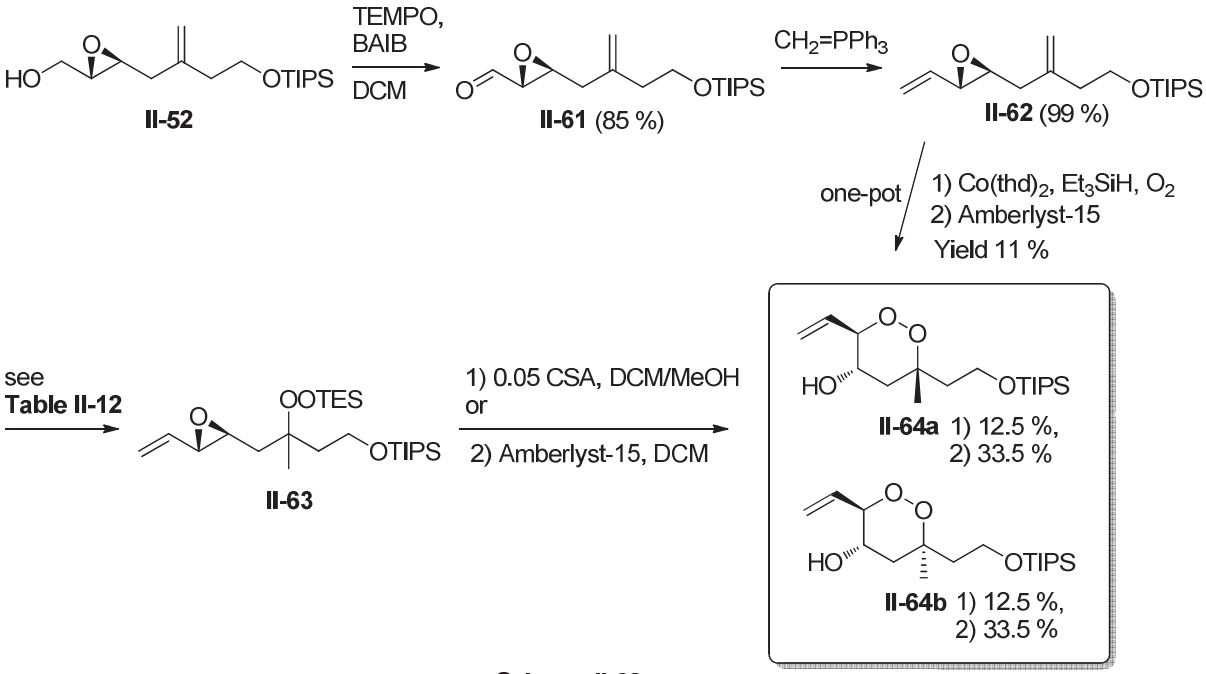
During the synthesis of spiro-bisperoxyketals, Dussault and coworkers have shown that an acetate group could be chemoselectively cleaved with DIBAL in the presence of triethylsilylperoxy groups.[173] Thus, treatment of **II-59** with an excess of DIBAL in dichloromethane, at low temperature, furnished alcohol **II-53** in 37 % yield accompanied by dioxolan **II-60** which bears a TES group (position undetermined).

As this three-step second approach of epoxy TES hydroperoxide **II-53** from the olefinic epoxide **II-52** was still unsatisfying in terms of yield (35 %), we decided again to modify our synthetic plan by introducing the vinyl group before the peroxysilylation. Based on the literature data on relative reactivity of different alkenes,[102] we expected that gem-disubstituted double bond should be more reactive than the vinyl group in the peroxidation reaction. A side reaction that could occur in the case of dienes consists in the intramolecular addition of

intermediate hydroperoxyl radical to the second double bond followed by capture of the resulting carbon radical by oxygen to furnish bisperoxides as exemplified above.[101-103]



Fortunately, in the case of our substrate **II-62**, this process could not take place because of the presence of the *trans* epoxide which forbidden the 1,2-dioxepane ring formation.



Scheme II-28

The synthesis of diene **II-62**, depicted in Scheme II-28, commenced by the oxidation of alcohol **II-52** to aldehyde **II-61** followed by Wittig methylenation to furnish diene **II-62** in 85 % overall yield. We then studied the regioselective Mukayama-Isayama reaction with different solvents and Co(II) salts and the results of this study are shown on Table II-12. $Co(acac)_2$ proved to be a poor catalyst of oxygenation for this substrate (entries 1,2). Somewhat better results were obtained with $Co(modp)_2$ but the reaction was not reproducible due to long induction periods and reaction times which led to partial decomposition (entries 3,4). Addition of catalytic amounts of TBHP had a positive effect on the reaction rate, but the yields remained unsatisfactory (entries 5,6).[98] Replacement of $Co(modp)_2$ by commercially available bis(2,2,6,6-tetramethyl-3,5-heptanedionato)cobalt(II) $Co(thd)_2$ considerably

increased the yield of **II-63** (1:1 mixture of diastereomers) and shortened reaction times (entries 7-9).[100] The activity of $Co(thd)_2$ is so high that there was no need to add TBHP to initiate the reaction.

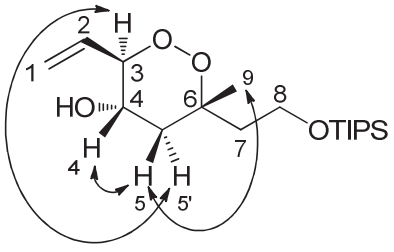
Table II-12. Study of the regioselective peroxidation of diene **II-62**

Entry	Catalyst	Solvent	Time, h	Conversion, %	Yield, %
1	$Co(acac)_2$	DCE	7	71[b]	19[b]
2	$Co(acac)_2$[c]	EtOH	24	93[b]	3[b]
3	$Co(modp)_2$	DCE	8	100	36
4	$Co(modp)_2$	DCE	24	0[b]	-
5	$Co(modp)_2$[c]	DCE	10	100	45
6	$Co(modp)_2$[c]	DCE	6	50[b]	50[b]
7	$Co(thd)_2$	DCE	4	100	71
8	$Co(thd)_2$	DCE	8	100	42
9	$Co(thd)_2$	DCE	2	100	62

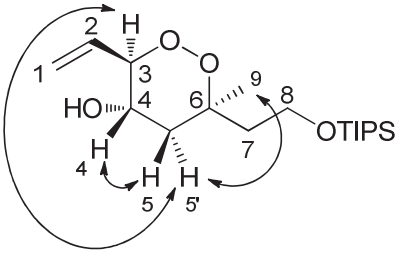
[a] All reactions were carried out at room temperature with two-fold excess of Et_3SiH and 10 % mol. of catalyst; [b] Determined by ^1H NMR of the crude product; [c] 1 drop of 5.5 M TBHP was added as an initiator.

Treatment of peroxide **II-63** with strongly acid resin Amberlyst-15 in CH_2Cl_2 furnished mixture of 1,2-dioxanes **II-64a** and **II-64b** in 67 % yield via deprotection of the silyl-protected hydroperoxide, whereas camphorsulfonic acid-catalyzed cyclization gave only poor yield of the desired products (Scheme II-28). The presence of 1,2-dioxane unit in **II-64a** and **II-64b** was determined by the presence of CH_2-1 – CHOO (4.20, 87.0 and 4.17, 86.8 respectively) and absence of CH_2-1 – CHOH (3.82, 66.3 and 3.83, 66.3 respectively) correlations in HMBC spectrums. COSY correlations also proved that vinyl is directly attached to CH-OO group. Relative stereochemistry of the products was determined by NOESY experiments:

The most representative NOE correlations



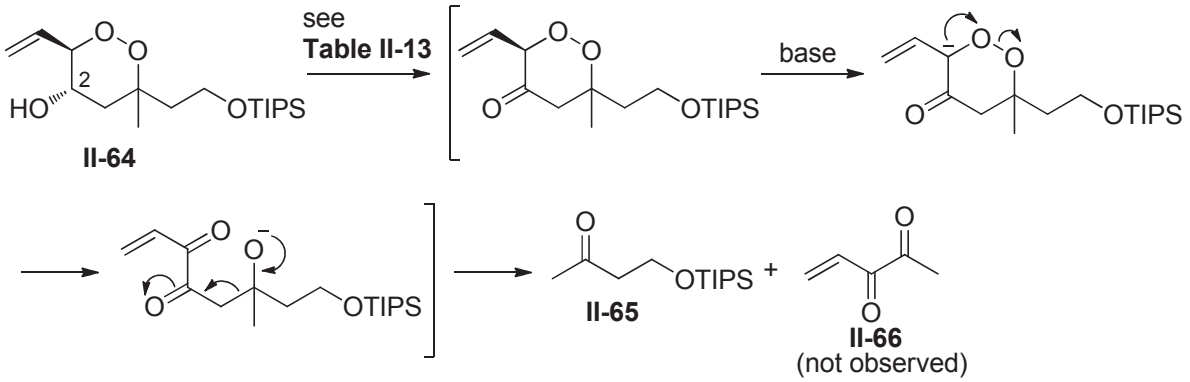
II-64a



II-64b

During the synthesis of dihydroplakortin, Campiani and coworkers performed peroxydation-cyclization in a one-pot sequence in order to improve the overall yield of the process.[6,73b] In our case, this one-pot three step procedure was not as efficient as stepwise protocol (11 % versus 48 %).

In order to introduce a methyl group in C2 of **II-64**, the secondary alcohol has to be oxidized. Whatever the oxidizing reagent used (TEMPO, iodine(V) reagents, Cr(VI) reagents) no carbonyl derivative was obtained (Table II-13). ^{1}H NMR of the reaction mixture revealed as the sole identifiable product: 4-triisopropylsilyloxy-butan-2-one **II-65** (entries 2,3). The formation of this fragmentation product can be explained by first deprotonation in α position of the carbonyl followed by an E1cB fragmentation and finally retroaldol reaction (Scheme II-29). The vinyl 1,2-diketone **II-66** was not identified in the reaction mixture may be because of its volatility. The decomposition of α-peroxy alcohols in the presence of oxidants has been already reported.[174]



Scheme II-29

Table II-13[a]. Attempt oxidation of secondary alcohol **II-64**

Entry	Conditions (equiv.)	Time, h	Conversion, %	**II-65**, %
1	0.1 TEMPO, 1.3 BAIB, DCM, rt	16	0	0
2	3 PDC, DCM, rt	70	45	36
3	3 PCC, DCM, rt	6	50[b]	15
4	2 IBX, DMSO, rt	6	100	0
5	2 DMP, DCM, rt	20	100	traces

[a] All conversion rates and yields were determined by analysis of ^{1}H NMR of the crude mixture; [b] ~50 % of the starting material was recovered.

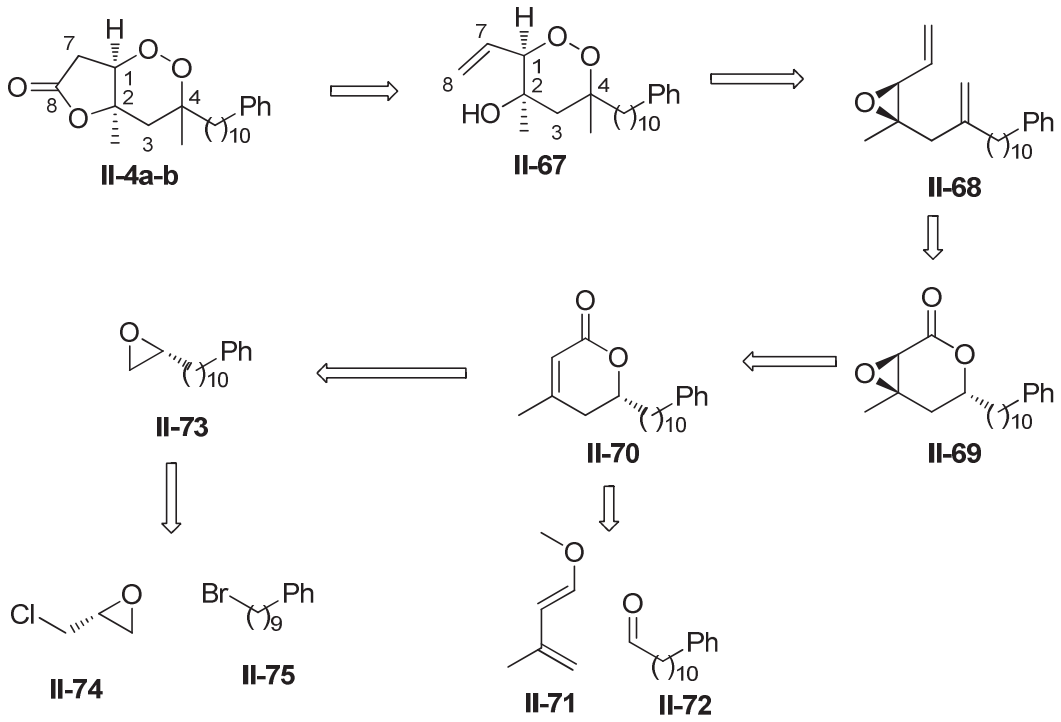
II.4.5. Conclusion

1,2-dioxane **II-64** has been synthesized in 8 steps and 23 % overall yield. Unfortunately, in the presence of oxidants, compound **II-64** decomposed to give fragmentation products. The lesson of this failed strategy is that the methyl group in C-2 of plakortolides has to be introduced at the early stage of the synthesis and before the creation of the 1,2-dioxan cycle.

II.5. Fourth approach of plakortolides

II.5.1. Retrosynthesis

What we learned from our failed strategies is: (1) the methyl group at C2 has to be introduced at the beginning of the synthesis; (2) the two double bonds have to be installed before the peroxidation; (3) interestingly, the peroxidation of epoxy diene is chemoselective in favor of the most substituted olefin. The previous approaches were devised with the goal to generate a common precursor to four plakortolides. This intermediate could be then transformed to these plakortolides by elongation of the hydroxymethyl or ethyl in C4. In the fourth approach, we decided to use a common intermediate for plakortolides E and I which have the same alkyl side chain and are epimer in C4. If we agree that this approach will be less elegant or at least less general, the introduction of the side chain in once will make it more efficient.



Scheme II-30

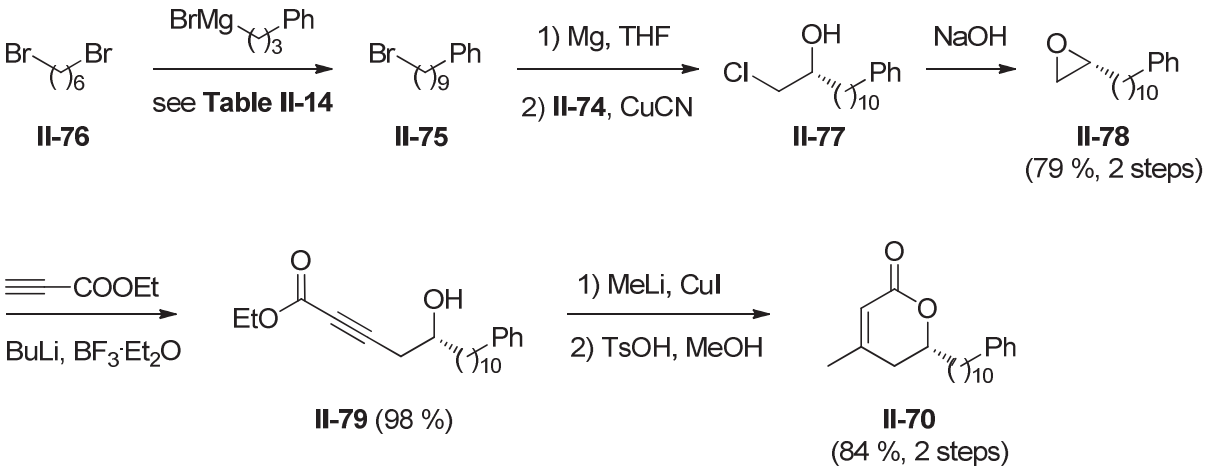
Except for the introduction of the side chain, our retrosynthetic plan was similar for the first steps of the previous ones: introduction of the lactone function via homoallylic alcohol

II-67, 1,2-dioxane formation by intramolecular epoxide opening with hydroperoxide guided by a vinyl group obtained by regioselective peroxidation of diene **II-68**. This product contains a *cis* trisubstituted epoxide unit which can be installed enantioselectively in various ways. In general, *Z*-trisubstituted olefins are not good substrates to asymmetric Sharpless epoxidation and the enantiomeric excess is modest (~70 % ee). Other methods for asymmetric epoxidation of these types of olefins have been described such as Shi[175], Yamamoto[176] and Katsuki[177] epoxidations. The disadvantages of these methods are that catalysts for these epoxidations are either expensive or have to be synthesized.

Well-precedented diastereoselective epoxidation of substituted pentenolides is an interesting technique to create *cis* epoxides and perfectly adapted for our purpose.[178] Thus, we thought that **II-68** could originate from epoxy lactone **II-69** itself obtained from the pentenolide **II-70**. Synthon **II-70** could be prepared by either two methods: enantioselective hetero-Diels-Alder reaction between aldehyde **II-72** and 1-methoxy-3-methyl 1,3-butadiene **II-71**[179] or from epoxide **II-73** by epoxide opening with ethyl propiolate anion followed by Michael addition of methylcopper and cyclization.[180] Epoxide **II-73** could arise from (*R*)-epichlorhydrin and (9-phenylnonyl)magnesium bromide.

II.5.2. Synthesis of pentenolide II-70 from (*R*)-epichlorhydrin

The synthesis commenced by preparation of 9-phenylnonylbromide **II-75** from 1,6-dibromohexane and the Grignard reagent derived from 1-bromo-3-phenylpropane. In the reaction conditions reported[181] a large amount of bis-coupling product was obtained and the yield in **II-75** was low (Table II-14, entry 1). In order to favor formation of **II-75** threefold excess of 1,6-dibromohexane was used in the coupling reaction. Good to excellent yields of **II-75** was obtained and near 2 equivalents of **II-76** were recovered after fractional distillation under reduced pressure.



Scheme II-31

A copper catalyzed-epoxide ring opening of (*R*)-epichlorohydrin **II-74** with (9-phenylnonyl)magnesium bromide followed by treatment of the resulting chlorohydrin **II-77** with NaOH gave the epoxide **II-78** in 79 % yield (Scheme II-31). Compound **II-78** was regioselectively opened with the lithium salt of ethyl propiolate, in the presence of $BF_3{\cdot}Et_2O$, to provide the secondary alcohol **II-79** in nearly quantitative yield. Stereoselective addition of lithium dimethylcuprate[182] to the triple bond and subsequent lactonization of the resulting (*Z*)-enoate with *p*-toluenesulfonic acid in methanol at room temperature furnished the lactone **II-70** in 84 % overall yield.

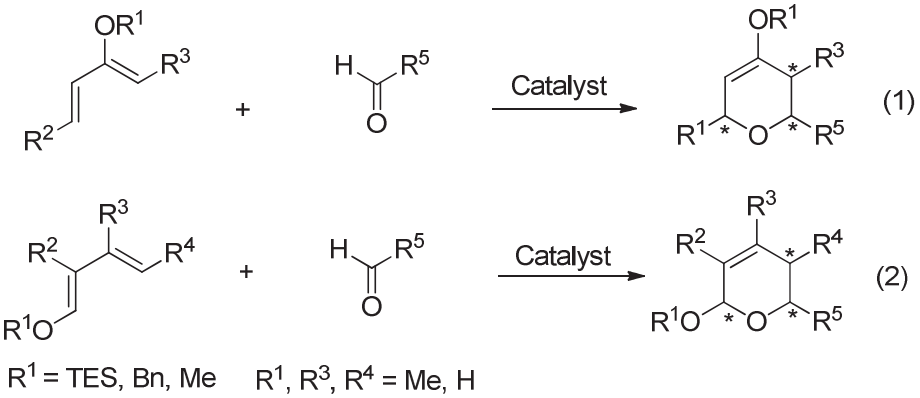
Table II-14[a]. Optimization of the coupling reaction between **II-76** and (3-phenylpropyl)magnesium bromide

Entry	Conditions (equiv.)	Yield, %	
		II-75	**II-76**(recovery)
1	1 **II-76**, 0.01 CuBr, 0.02 LiCl	37	n.d.
2	3 **II-76**, 0.01 CuBr, 0.02 LiCl	**92**	69
3	3 **II-76**, 0.01 CuBr, 0.02 LiCl	74	69
4	3 **II-76**, 0.01 Li_2CuCl_4	61.3[b]	57

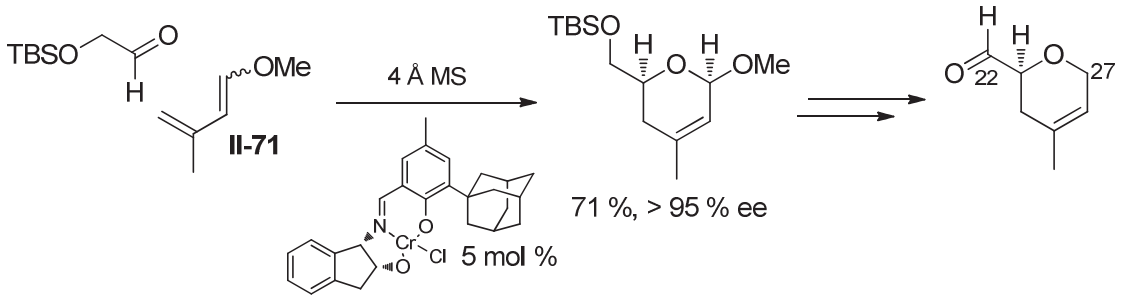
[a] All reactions were carried out in THF for 20 h at rt; [b] distilled twice.

II.5.3. Synthesis of II-70 by enantioselective hetero Diels-Alder reaction

In 1999, Jacobsen and coworkers described a highly enantio- and diastereoselective hetero Diels-Alder reaction (HDA) between oxygenated dienes [eq. (1) and (2)] and unactivated carbonyl compounds catalyzed by chiral tridentate chromium (III) catalysts.[179a]



During the synthesis of laulimalide, Paterson and coworkers exploited the Jacobsen HDA chemistry for the construction of the side chain dihydropyran (C22-C27 subunit), obtained in high ee (> 95 %) using methoxydiene **II-71** (Scheme II-32).[183]

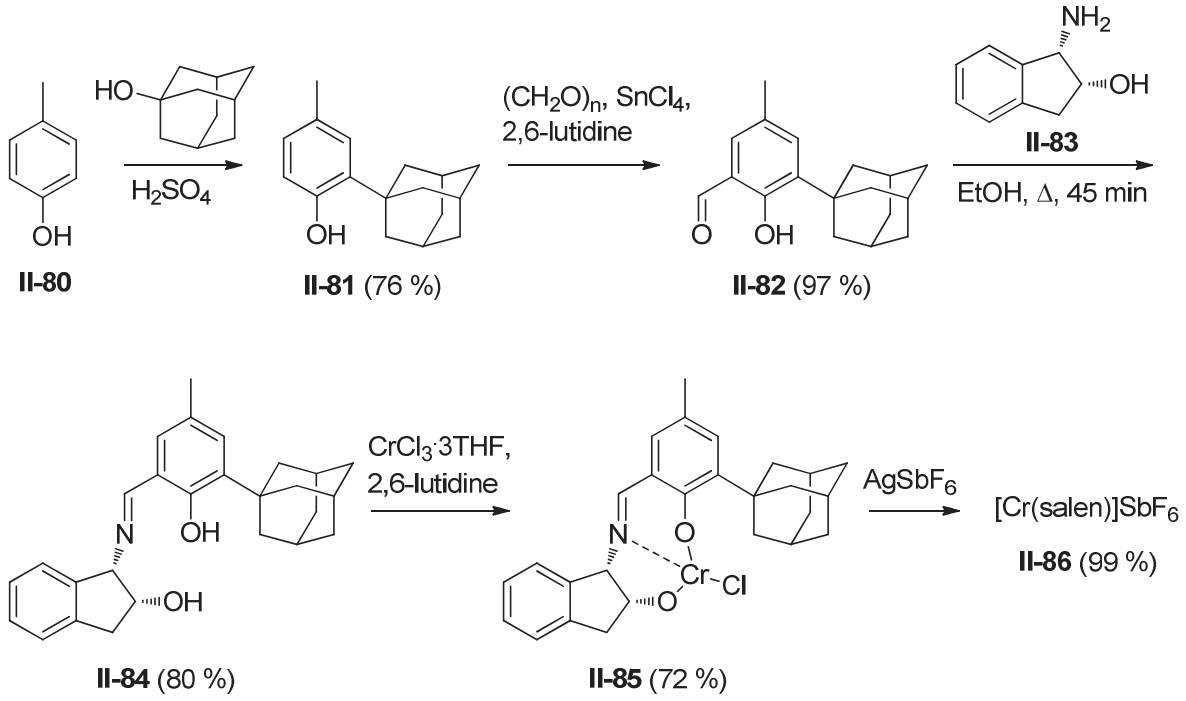


Scheme II-32

Before studying the HDA between diene **II-71** and aldehyde **II-72**, we had to prepare these two reagents as well as the catalyst.

II.5.3.1. Synthesis of Cr(salen) catalyst

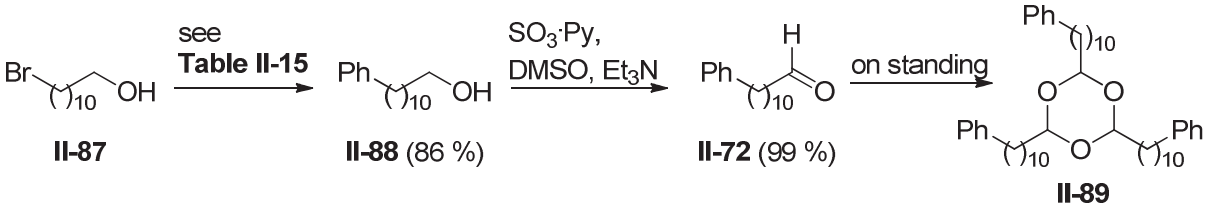
Cr(salen) complex was prepared from readily accessible components by procedure of Jacobsen and Chavez (Scheme II-33).[179c] Friedel-Crafts alkylation of *p*-cresol with adamantanol in the presence of sulfuric acid provided 2-(1-adamantyl)-4-methylphenol in 76 % yield. Formylation of **II-81** with paraformaldehyde in the presence of $SnCl_4$ and 2,6-lutidine, followed by Schiff base formation with *cis*-1-amino-2-indanol and metal ion complexation afforded the Cr(III)Cl complex in good overall yield. Counterion exchange accomplished with $AgSbF_6$ in *tert*-butyl methyl ether yielded the corresponding hexafluoroantimonate complex **II-86** in nearly quantitative yield.



Scheme II-33

II.5.3.2. Synthesis of the dienophile II-72

Synthesis of aldehyde **II-72** has been already described.[184] One of the reported syntheses started from commercially available bromide **II-87** and used protection-coupling-deprotection sequence to transform it into alcohol **II-88** and oxidation with PCC. We decided to improve this synthesis by excluding protection-deprotection steps and by using environmentally more friendly reagents. Thus copper-catalyzed coupling between **II-87** and phenylmagnesium bromide was studied and the results are shown in Table II-15. After some experimentations, it was found that sixfold excess of Grignard reagent were needed in order to achieve complete conversion of **II-87** into **II-88** (Scheme II-34). Oxidation of **II-88** with SO_3·Pyridine complex in the presence of DMSO and triethylamine (Parikh-Doering method)[185] furnished aldehyde **II-72** in quantitative yield.



II-87 **II-88** (86 %) **II-72** (99 %) **II-89**

Scheme II-34

Table II-15[a]. Study of the Cu(I)-catalyzed coupling between **II-87** and PhMgBr

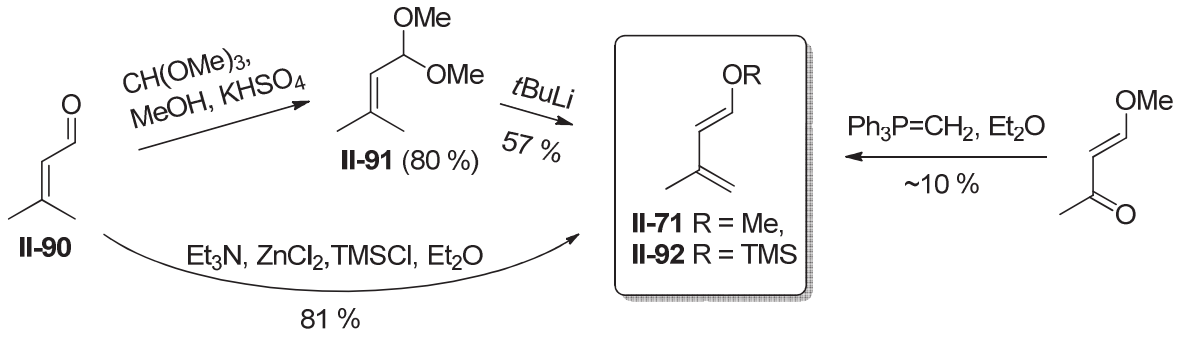
Entry	Conditions (equiv.)	Time	Yield, %	
			II-87	**II-88**
1	2.8 PhMgBr, 0.1 CuBr, 0.2 LiBr	18	36[b]	64[b]
2	3.3 PhMgBr, 0.1 CuBr, 0.2 LiBr	18	27[b]	73[b]
3	4 PhMgBr, 0.2 CuBr, 0.4 LiBr	18	30[b]	70[b]
4	4 PhMgBr, 0.5 CuBr, 1 LiBr, 60 °C	15	12[b]	88[b]
5	6 PhMgBr, 1CuBr, 2 LiBr	18	-	85
6	6 PhMgBr, 0.1 CuBr, 0.2 LiBr	18	-	86

[a] General conditions: 1 equiv. of **II-87**, THF, -20 °C→rt, PhMgBr was prepared from PhBr and used without titration; [b] determined by ^{1}H NMR spectroscopy.

Aldehyde **II-72** has to be used freshly prepared, otherwise it slowly trimerized to **II-89** on storage, even in the fridge.

II.5.3.3. Synthesis of the diene II-71 and its benzyl analog

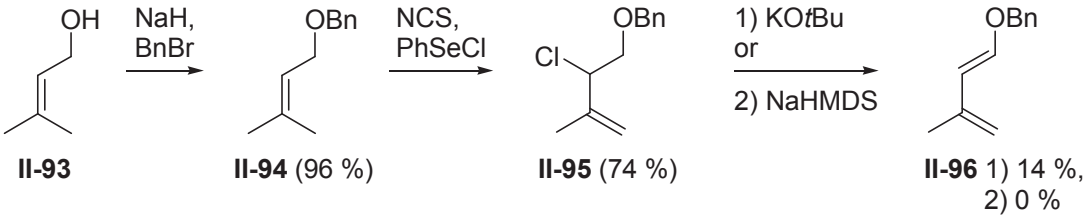
A one-step synthesis of **II-71** from commercially available *trans*-4-methoxy-3-buten-2-one was tested but the yield was considerably lower than those reported for the analogs (Scheme II-35).[186] In addition purification of the product was rather difficult due to presence of a huge amount of phosphor derivatives that incited us to abandon this method.



Scheme II-35

We studied another approach which involved acid-catalyzed transformation of prenal into its dimethyl acetal **II-91** by treatment with trimethyl orthoformate as the first step (Scheme II-35).[187] Treatment of **II-91** with *tert*-butyllithium in diethyl ether furnished (*E*)-ether dienol **II-71** in 57 % yield after purification by distillation.[188]

Readily available from prenal dienol ether **II-92** was also prepared in order to test it in HDA reaction (Scheme II-35).

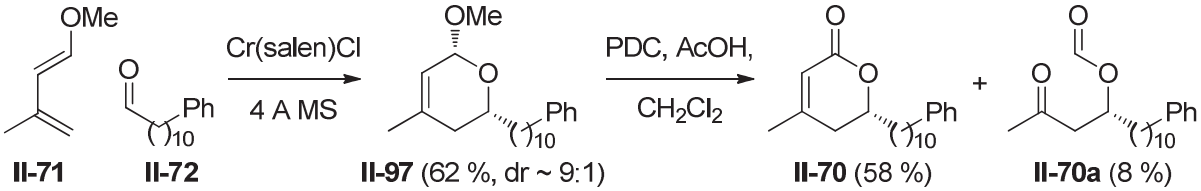


Scheme II-36

In the synthesis of fostriecin, Chavez and Jacobsen reported that among a variety of 1-alkoxybutadiene derivatives tested in hetero-Diels-Alder reaction, benzyloxy derivative led to products with highest yield. Thus, we decided to prepare benzyl ether **II-96** simultaneously with **II-71** and to test both of them in Diels-Alder reaction. Treatment of sodium 3-methylbut-2-en-1-olate with benzyl bromide gave ether **II-94** followed by selenium-catalyzed allylic halogenation led to **II-95** in 71 % for the two steps (Scheme II-36).[189] Base-induced β-elimination with potassium *tert*butoxide was not regioselective producing a mixture of benzyl alcohol and the desired diene **II-96,** obtained in only 14 % yield. Utilization of more sterically hindered NaHMDS led exclusively to decomposition.

II.5.3.4. Diels-Alder reaction

Solvent free enantioselective HDA reaction between aldehyde **II-72** and dienol ether **II-71**, in the presence of 4 Å MS and Jacobsen catalyst, gave, after stirring for 24 h, cyclic acetal **II-97** in moderate yield as 9:1 diastereomeric mixture. TMS ether **II-92** proved to be unstable in the same reaction conditions and no HDA adduct was obtained after 3 days stirring at room temperature. Treatment of **II-97** with pyridinium dichromate and acetic acid in DCM gave, after 3 h stirring, the desired lactone **II-70** in moderate yield together with small amounts of formiate **II-70a**. Although the first approach to **II-70** from (*R*)-epichlorohydrin should give the product with ee > 95 %, comparison of its optical power (-71.4) with this (-86.3) obtained by HDA reaction show that apparently partial racemisation was happened during the reaction sequence. The reaction conditions of both steps presented in Scheme II-37 were not optimized.

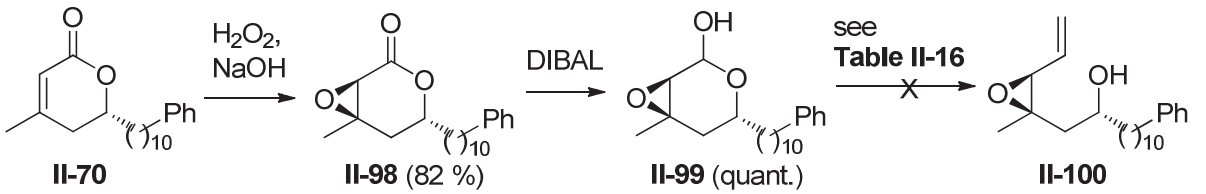


II-71 **II-72** **II-97** (62 %, dr ~ 9:1) **II-70** (58 %) **II-70a** (8 %)

Scheme II-37

II.5.4. Synthesis of the epoxydiene II-68

Having the pentenolide **II-70** in hand, we next explored the feasibility of our synthetic plan to epoxy diene **II-68**. Exposure of **II-70** to alkaline hydrogen peroxide in methanol gave the epoxide **II-98**, as a single diastereomer, in 82 % yield (Scheme II-38). After DIBAL reduction of **II-98** to lactol **II-99**, the stage was now set up to introduce the double bond in the α-position to the oxirane functionality. In order to attain this goal, lactol **II-99** was subjected to a number of methylenation conditions (Table II-16), but all failed to give the desired hydroxy vinyl epoxide **II-100**. It seems that Wittig reaction conditions (entries 1,2) are too basic for epoxy group present in the molecule. Less basic Petasis[190] and Tebbe[191] reagents also furnished complex mixture of products (entries 3,4).

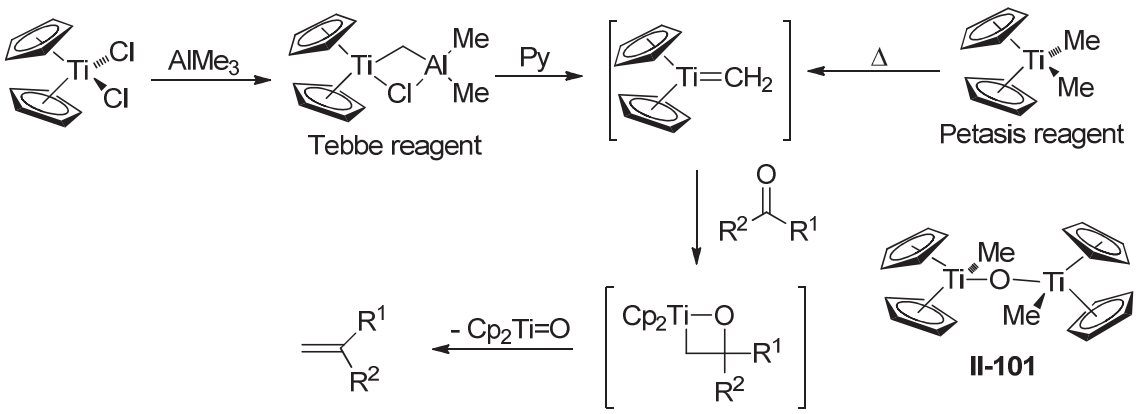


II-70 **II-98** (82 %) **II-99** (quant.) **II-100**

Scheme II-38

These two titanium-based carbenoids, commonly used to convert carbonyl groups into alkenes, are commercially available. Tebbe and Petasis reagents, represented in Scheme II-39,

generates either by Lewis base catalysis or heating a reactive titanocene methylidene (a Schrock carbene). This carbene which is nucleophilic at carbon and electrophilic at titanium reacts with carbonyl compounds to form oxatitanecyclobutanes which decomposes with elimination of $Cp_2Ti=O$ to give alkenes. In the case of the methylenation by Petasis reagent, addition of a catalytic amount of titanocene dichloride (Cp_2TiCl_2) improves yields by aiding purification by formation of an oxo-bridged titanocene dimer **II-101** easily precipitated by heptane.[192]



Scheme II-39

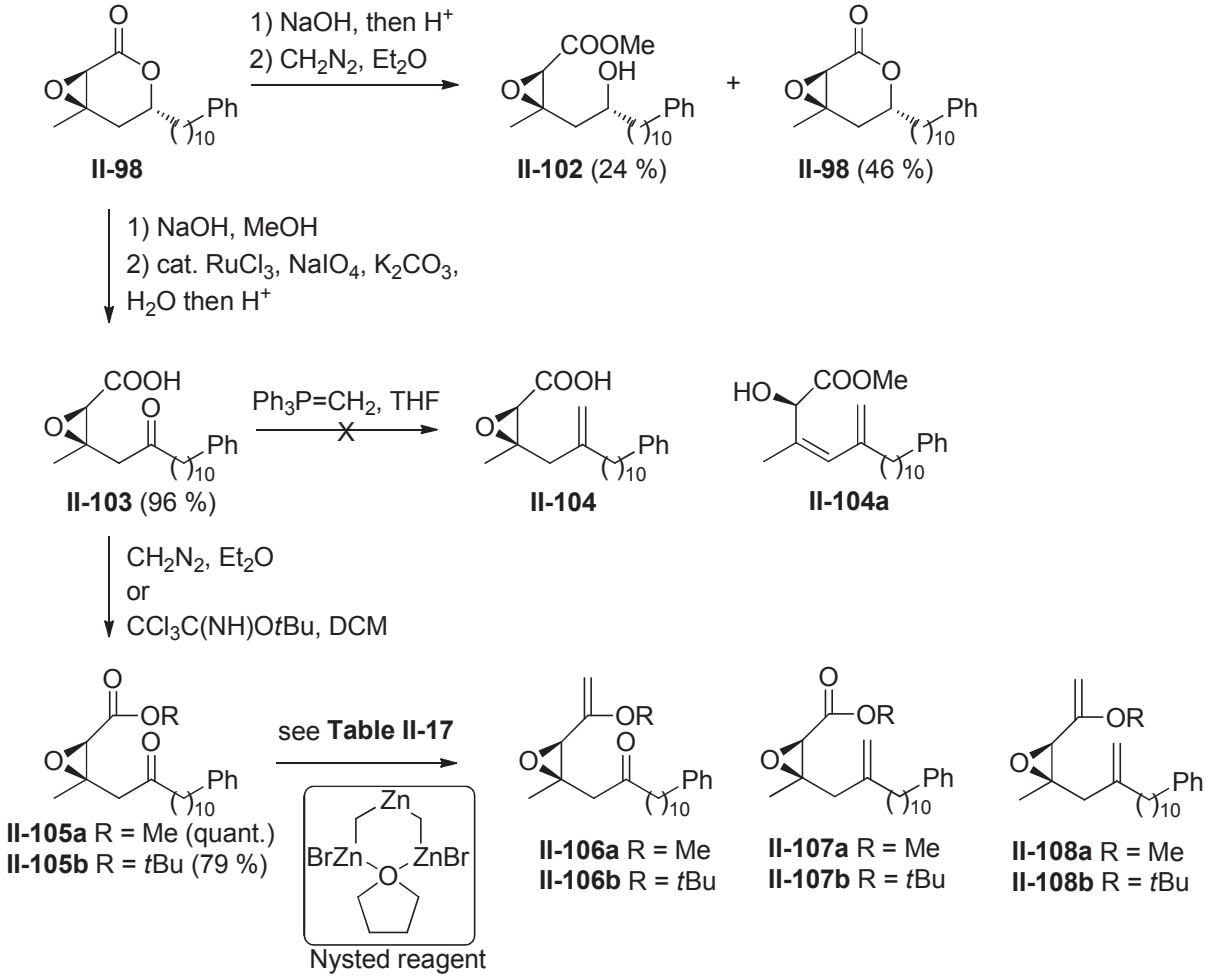
Table II-16. Attempted methylenation of the lactol **II-99**.

Entry	Conditions (equiv)	Time, h	Yield, % (Conv.)
1	3 $CH_2=PPh_3$, THF, reflux	7	- (100)
2	2.8 $CH_2=PPh_3$, THF, rt	5	- (40)
3	1.5 $Cp_2TiClCH_2AlMe_2$, 3 Py, THF, -78→rt	5	- (100)
4	3 Cp_2TiMe_2, toluene, 80 ^oC	20	- (100)

We next explored another strategy to introduce the two double bonds based on the ability of titanium carbenoid reagents to effect, under mild conditions, chemoselective methylenation of ketones in the presence of esters.[193] In the first place, we thought that lactone **II-98** could be transformed to ketoester **II-105** by saponification, esterification and oxidation of the secondary alcohol within **II-102**. This route was abandoned because of spontaneous lactonization of **II-102** during the methylation reaction (Scheme II-40).

In order to overcome the problems associated with self-catalyzed lactonization, a new strategy was developed which consisted on oxidizing the sodium salt of carboxylic acid in aqueous conditions obtained by saponification of **II-98** before esterification. A one-pot saponification of the lactone function of **II-98** followed by RuO_4 oxidation[194] of the resulting hydroxy sodium carboxylate and acidification gave the keto acid **II-103** in nearly quantitative yield. Attempted Wittig methylenation of **II-103** was unsuccessful and only decomposition of the starting material was observed.

After esterification **II-103** with diazomethane, we studied the monomethylenation of **II-105a** which turned out to be somewhat troublesome as seen in Table II-17. In the presence of methylene triphenylphosphorane or using the Lombardo protocol,[195] only polar products were formed (entries 1, 2). In the latter case, Ti(III) present in the reaction medium is known to act as a reducing agent to form epoxide opening by-products.[196] In the presence of the Tebbe reagent, compound **II-105a** gave **II-107a** in low yield (entry 3).



Scheme II-40

Exposure of **II-105a** to Petasis reagent and its catalyzed version[192] afforded about a 1/1 mixture of mono- and dimethylenation products even at **II-105a** low conversion rates (entries 4-6). We thought that sterically more hindered esters could increase the chemoselectivity of this transformation. Treatment of *t*-butyl ester **II-105b,** obtained from **II-103** by reaction with *t*-butyl trichloroacetamidate,[197] with Petasis reagent led to **II-107b** in good yield but as a mixture of diastereomers (entry 7). ^{1}H NMR of **II-107b** revealed that epimerization in either α or β position of the ester function occurred. GCMS also showed that **II-107b** consists of two products with the same mass. We thought that the large excess of very reactive titanium carbene ($Cp_2Ti{=}CH_2$) present in the reaction medium could be responsible for the epimerization, we added ethyl pivalate with the aim of trapping the excess of this carbene.[198,193] Unfortunately, the additive had no effect on the diastereomeric ratio (entry 8).

Next, we moved our attention to commercially available Nysted reagent: a *gem*-bimetallic reagent which is believed to have the structure shown in Scheme II-40.[199] Thus, keto ester **II-105a**, treated with Nysted reagent and $TiCl_4$, afforded **II-107a** in a low yield probably due to acid-catalyzed epoxide opening (entries 9-11).[200] In association with Nysted reagent, less acidic reagents such as zirconocene dichloride or titanocene dichloride gave no reaction. (entries 12-13).

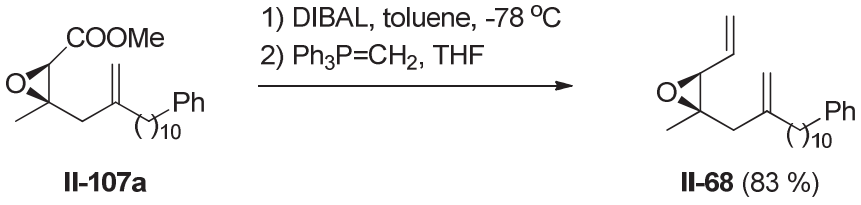
Table II-17.[a] Study on the chemoselective monomethylenation of ketoesters **II-105a-b**

Entry	Conditions (equiv)	Time, h	Yield, %			
			II-105	**II-106**	**II-107**	**II-108**
1	3 $Ph_3P{=}CH_2$, THF, 0 °C – rt[b]	3	-	-	-	-
2	5 Zn, 1.7 CH_2Br_2, 1.2 $TiCl_4$, rt	4	-	-	-	-
3	1.2 $Cp_2TiClCH_2AlMe_2$, 1.6 Py, -78 °C -rt	14	-	-	23	-
4	2 Cp_2TiMe_2, C_6D_6, 80 °C	20	-	nd	25	nd
5	4 Cp_2TiMe_2, Cp_2TiCl_2 cat., PhMe, 80 °C	6	21	3	31	27
6	1.5 Cp_2TiMe_2, PhMe, 80 °C	21	22	3	34	41
7	3 Cp_2TiMe_2, PhMe, 80 °C	6	-	-	73	-
8	4 Cp_2TiMe_2, PivOEt, THF, reflux	20	-	-	71	-
9	3 $TiCl_4$, 3.6 N.r., DCM, 0 °C	2	-	-	19[c]	-
10	1.5 $TiCl_4$, 1.9 N.r., DCM, 0 °C	1.5	-	-[c]	41[c]	-[c]
11	1.5 $TiCl_4$, 1.9 N.r., DCM, 0 °C -rt	2	-	-	-	-[c]
12	1.2 Cp_2ZrCl_2, 1.2 N.r., THF, rt	30	99[c]	-	tr.	-
13	1.2 Cp_2TiCl_2, 1.2 N.r., THF, rt	20	99[c]	-	tr.	-
14	**2 $Ti(OiPr)_2Cl_2$, 2.5 N.r., DCM, 0- 15 °C**	**0.25**	**16**	**-**	**76**	**-**
15	2 $Ti(OiPr)_2Cl_2$, 2.5 N.r., DCM, 0- 15 °C	[d]	-	-	43	-
16	4 $Ti(OiPr)_2Cl_2$, 5 N.r., DCM, 0 °C	0.5	34	-	44	-
17	4 $Ti(OiPr)_2Cl_2$, 5 N.r., DCM, 0 - rt	0.2	14	-	59	-
18	4 $Ti(OiPr)_2Cl_2$, 5 N.r., DCM, 0- 15 °C	0.25	nd	-	60	-
19	2.5 $Ti(OiPr)_2Cl_2$, 3.1 N.r., DCM, 0- 15 °C	0.25	15	-	58	-
20	2.5 $Ti(OiPr)_2Cl_2$, 3.1 N.r., DCM, 0- 15 °C	0.25	nd	-	67	-

[a] All the reactions was performed with **II-105a** except the entries 7,8 where **II-105b** was used as substrate; N.r. = Nysted reagent; [b] small amounts of **II-104a** were obtained; [c] determined by TLC (^{1}H NMR); [d] the reaction was stopped at ~50 % conv. after stirring at 0 °C for 20 min and even increasing the temperature had no influence on it, so another portion of reagents were added and the reaction mixture was stirred for 15 min at 15 °C.

Takai and co-workers reported[201] that replacing $TiCl_4$ by $Ti(OiPr)_4$ in combination with the couple Zn/CH_2I_2 allowed the chemoselective methylenation of aldehydes in the presence of ketones. With these results in mind, we thought that using a weaker Lewis acid than $TiCl_4$ such as $TiCl_3(OiPr)$ or $TiCl_2(OiPr)_2$ could improve the yield of methylenation with Nysted reagent. We set our choice on $Ti(OiPr)_2Cl_2$. Gratifyingly, this Lewis acid, prepared by mixing an equal amounts of $TiCl_4$ and $Ti(OiPr)_4$,[202] in combination with Nysted reagent improved considerably the yield of **II-107a** (entry 14).

Repetition of this experiment showed that it is not reproducible (entries 14-19). It was noted that whereas reaction mixtures before and after treatment were extremely clean as determined by TLC, it was not the case for residues after evaporation of solvents. It was supposed that traces of metallic species present in the solution were responsible for partial decomposition of the product during its concentration. When organic extracts were filtered through a short pad of silica gel or washed few times with brine, the product was obtained in correct yields (entries 20, 14). It also should be noted that if the reaction mixture was not warmed up to near 15 °C after addition of reagents but maintained at 0 °C, it stopped at near of 50 % conversion and no further conversion was observed even at the room temperature (entry 15).



II-107a **II-68** (83 %)

Scheme II-41

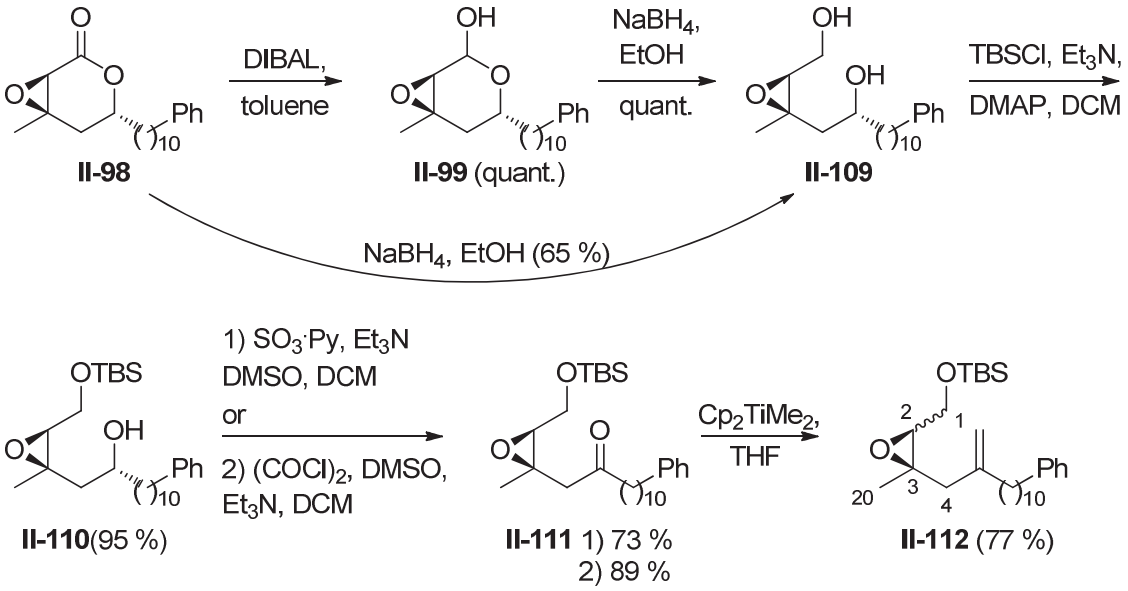
Having attained our challenging target: the olefinic epoxy ester **II-107a**, its transformation to **II-68** was effected in 83 % yield via standard functional manipulations (Scheme II-41).

II.5.5. Second approach to diene II-68

Another procedure to attain target molecule **II-68** was developed at the same time than that described above. The main idea consists in utilization of compounds related to **II-104** where the ester function is replaced by a protected hydroxymethyl group in order to avoid concurrent reaction during the methylenation.

To this purpose, compound **II-98** was reduced with a large excess of sodium borohydride to furnish diol **II-109** in 65 % yield, whereas two-step procedure including reduction of lactone to lactol **II-99** followed by further reduction with sodium borohydride led to diol **II-109** quantitatively (Scheme II-42). Protection of primary alcohol as TBS ether and further oxidation of secondary alcohol produced the ketone **II-111** which was treated with

dimethyltitanocene in THF at reflux to give **II-112** obtained as a mixture of diastereomers. NOESY-spectrum of **II-112** showed that two products with CH2-$CH_3$20 and $CH_2$1- $CH_3$20 correlations respectively are present in the mixture. GCMS spectrum of **II-112** also proved that it consists of two products with the same mass. Because, epimerization at C2 or C3 took place during methylenation reaction, this route was abandoned.



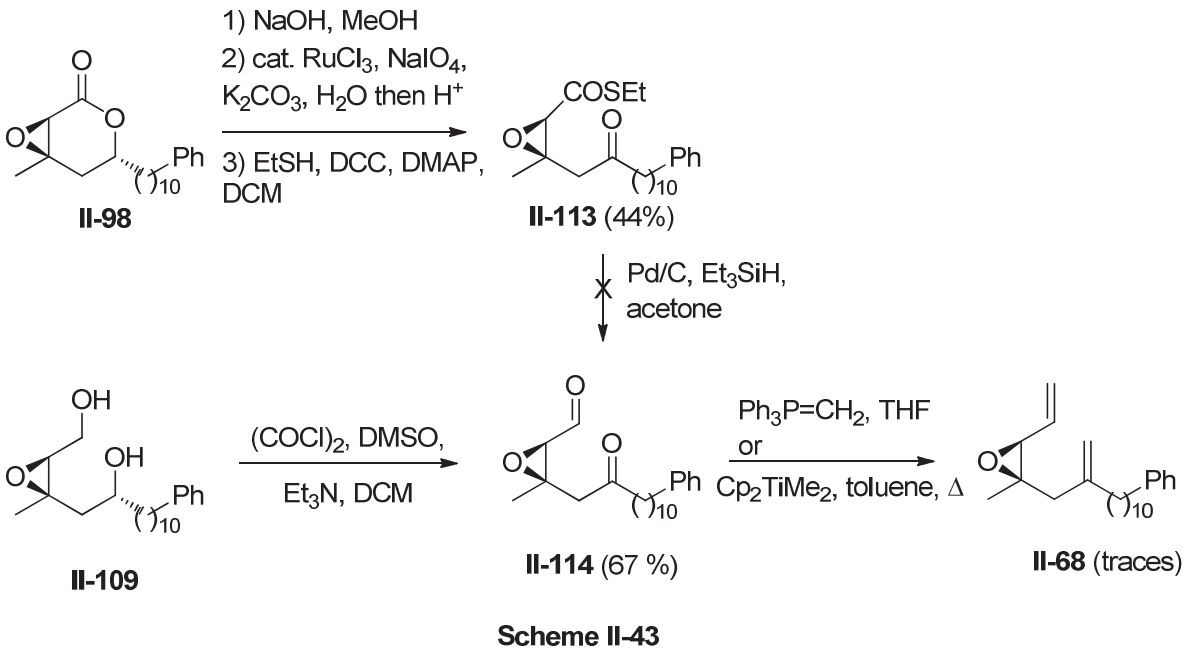
Scheme II-42

II.5.6. Third approach to diene II-68

We also tried to introduce the two double bonds simultaneously from dicarbonyl compound **II-114** (Scheme II-43). To this aim, one-pot saponification of the lactone function of **II-98** followed by RuO_4 oxidation and thioesterification with ethane thiol gave **II-113** in a moderate yield. Subjection of thioester to Fukuyama reduction[203] resulted only in slow decomposition of the starting material.

Another attempt to reach **II-114** synthesis was made by Swern oxidation of the diol **II-109** (see Scheme II-42) that led to ketoaldehyde **II-114** in 67 % overall yield. Unfortunately, in the presence of an excess of methylenetriphenylphosphorane or Petasis reagent, compound **II-114** led exclusively to decomposition.

Even if these last approaches to **II-68** failed, the first successful approach allowed us to synthesize enough material in **II-68** to pursue our goal.

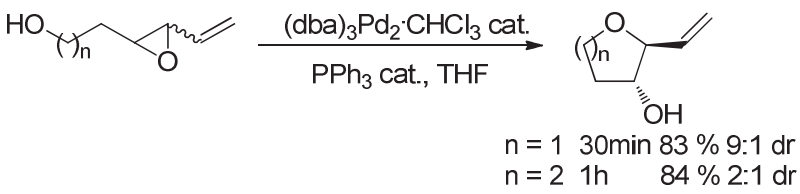


Scheme II-43

II.5.7. Studies on cyclization reaction

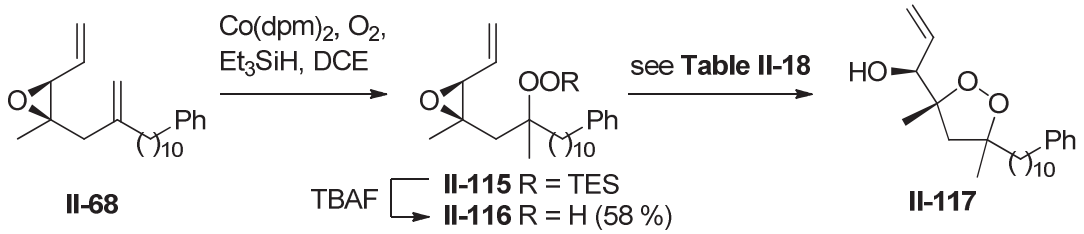
We were at the stage to study the chemoselective peroxidation of epoxydiene **II-68**. The best results, in terms of yield and chemoselectivity, were obtained by reaction of **II-68** with oxygen and triethysilane in dichloroethane, in the presence of bis(2,2,6,6-tetramethylheptane-3,5-dienoate) Co(II) ($Co(thd)_2$) and by stopping the reaction at about 80 % of conversion in order to avoid the bisperoxidation. The unseparable mixture of **II-68** and **II-115**, purified through a short pad of silica gel for removing the catalyst, was treated with strongly acidic resin Amberlyst-15 which effected the TES group cleavage and concomitant cyclization to afford exclusively the 5-*exo* cyclized product **II-117** in variable yields (Scheme II-44, Table II-18, entries 1-3). No 6-*endo* product was detected by ^1H NMR of the crude mixture. The structure of **II-117**, obtained as a 1:1 mixture of diastereomers, was ascertained by 2D-NMR experiments. A stepwise procedure for the formation of endoperoxide involving the deprotection of the hydroperoxy group with NBu_4F affording **II-116** and acid-promoted ring closure in the presence of Amberlyst-15 or 12 N HCl in acetonitrile[204] again gave exclusively **II-117** but in lower yields than in the one-pot reaction (entries 4,6). As precedented in the literature for hydroxyl and protected amino vinyl-*cis*-epoxides, the *cis* configuration seems to disfavour the 6-*endo* ring closure perhaps because these systems cannot assume planar arrangement necessary for maximum stabilization in the transition state may be for steric interactions.[137b, 205]

An interesting procedure for 6-*endo*-tet cyclization of hydroxy vinyl *cis*- or *trans*-epoxides via π-allylpalladium intermediates was reported by the groups of Trost and Hirama.[206] For example, β- and γ- hydroxy vinyl epoxides, in the presence of Pd(0), afforded with good yields and regioselectivity corresponding vinyl tetrahydrofuran and tetrahydropyran compounds (Scheme II-44).[206a]



Scheme II-44

The mildness of this method incited us to test its feasibility to hydroperoxy-containing substrates. Unfortunately treatment of **II-116** with catalytic amount of $Pd_2(dba)_3$ and PPh_3 gave complex mixture of products, possibly due to reduction of hydroperoxide with triphenylphosphine that led to decomposition of starting material and catalytic species (entry 5).



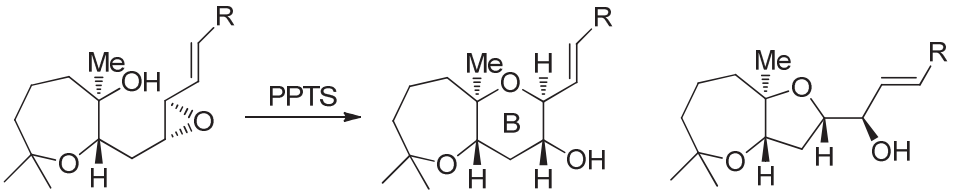
Scheme II-45

Table II-18. Study of the cyclization of hydroperoxy vinyl epoxide **II-116** and of its TES peroxyether **II-115**

Entry	R	Conditions (equiv)	Yield[a] of **II-117**, %
1	TES	0.5 Amberlyst-15, DCM, rt, 5 h	38
2	TES	0.5 Amberlyst-15, DCM, rt, 3 h	34
3	TES	1 Amberlyst-15, DCM, rt, 2 h	51
4	H	0.5 Amberlyst-15, DCM, 0 ^oC, 3 h	18
5	H	0.04 $Pd_2(dba)_3$, 0.16 PPh_3, DCM, rt, 0.5 h	decomposition
6	H	12 M HCl (6 equiv), CH_3CN, rt, 5 h	19

[a] Overall yield from **II-68**.

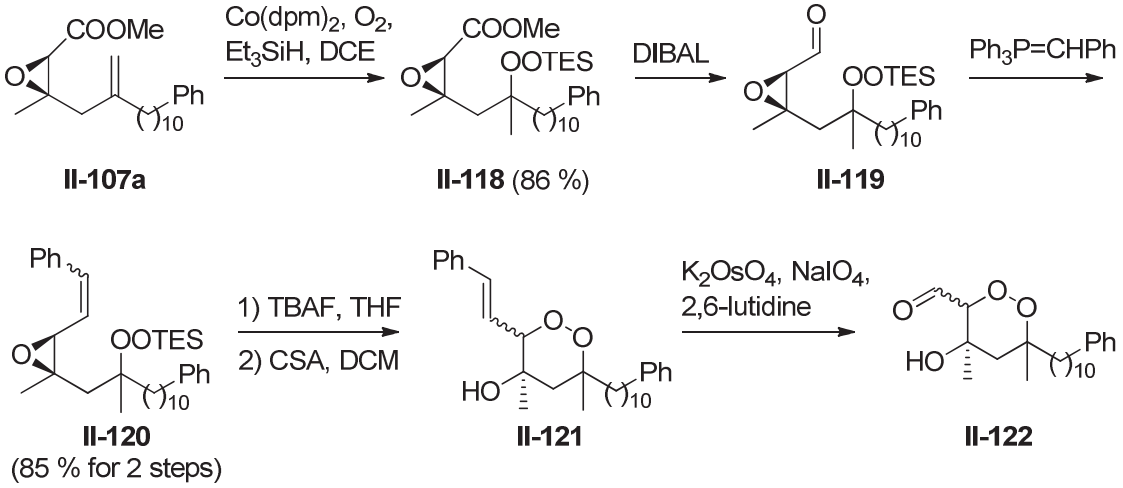
During the synthesis of hemibrevetoxin B, Nakata and coworkers constructed the B-ring system via a 6-*endo* cyclization of hydroxy styrylepoxide. They showed that the styryl group enhances the endo selectivity in comparison with the vinyl group as depicted in Scheme II-46.[207]



R = H	1	:	1	(86 %)
R = Ph	**1**	**:**	**0**	**(86 %)** ***E*/*Z*=1/8**

Scheme II-46

In order to test the applicability of styryl group-directed *endo* selectivity on our substrates, hydroperoxy styryl epoxide **II-120** was prepared from ester **II-107a**. Hydroperoxysilylation of the *gem*-disubstituted olefin **II-107a** under Mukaiyama and Isayama conditions yielded a 1:1 diastereomeric mixture of the triethylsilylperoxy ester **II-118** in 86% yield (Scheme II-47). This peroxide was then reduced to aldehyde **II-119** with DIBAL followed by Wittig reaction to gave **II-120** with good overall yield and moderate purity. **II-120** was treated with TBAF in THF, filtered through a small pad of silicagel and the residue, after evaporation, was treated with CSA in dichloromethane to give a complex mixture of isomers that was directly subjected to osmate catalyzed oxidative cleavage. Unfortunately product mixture after cleavage was too complex and isolation of **II-122** was not possible.

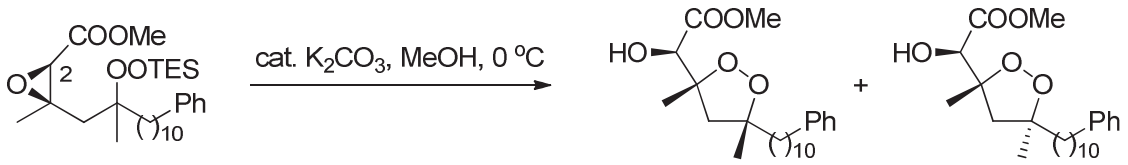


II-107a | **II-118** (86 %) | **II-119**

II-120 (85 % for 2 steps) | **II-121** | **II-122**

Scheme II-47

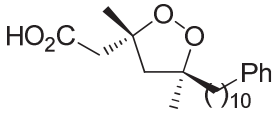
Finally, we tested another strategy based on the expectations that a peroxy anion derived from a δ-hydroperoxy epoxy ester such as **II-118** should undergo a cylization at the less hindered and more electrophilic position of the oxirane, namely at the C-2 position (Scheme II-48).



II-118 **II-123a** (36 %) **II-123b** (39 %)

Scheme II-48

Treatment of **II-118** with a catalytic amount of potassium carbonate gave, after TES cleavage, again exclusively a 1,2-dioxolane derivative: **II-123a**,**b**, obtained in a good yield as a mixture of diastereomers, separable by preparative TLC. The relative configuration of the five-membered peroxide ring of each diastereomer was assigned by NOE experiments. Interestingly, **II-123a,b** are structurally closely related to one member of plakinic acid family: andavadoic acid.



Andavadoic acid

II.5.8. Conclusion

During the work on this last approach, few functionalized epoxy hydroperoxides were prepared and subjected to cyclization in different reaction conditions. In all cases exclusive 5-*exo* cyclization or decomposition of the starting material were observed. In light of these results, it becomes clear that another strategy that would not involve the creation of 1,2-dioxan ring system by anti-Baldwin cyclization should be elaborated.

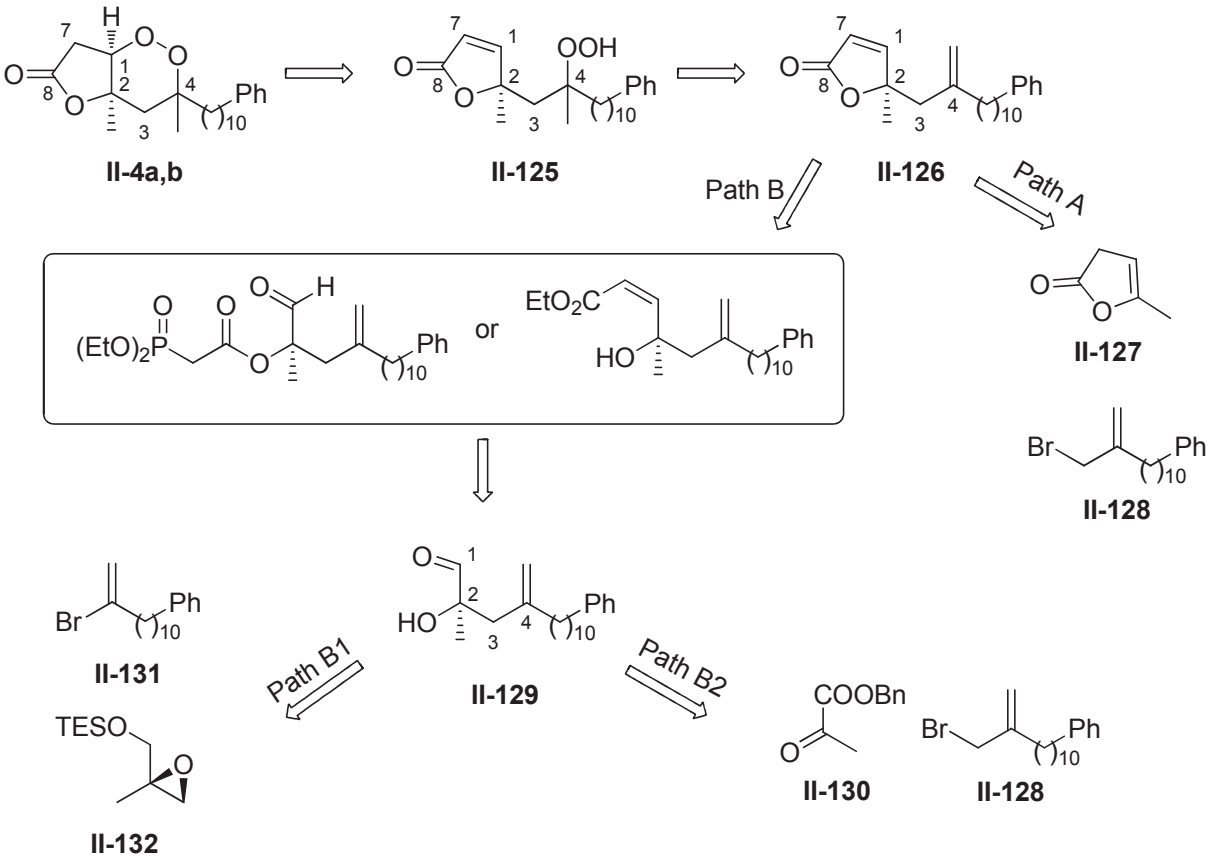
II.6. Fifth approach to plakortolides

II.6.1. Retrosynthesis

We imagined a new strategy to build the peroxylactone core based on an intramolecular addition of a hydroperoxide group to a butenolide. Indeed, formation of **II-124** type bicycle[208] via Michael addition of an hydroxyl group to a butenolide as well as construction of 1,2-dioxanes by intramolecular addition of hydroperoxy groups to α,β-unsaturated carbonyl derivatives are well-precedented (See bibliographic data chapter, paragraph 1.2.8).[65-72]

II-124

These literature reports encouraged us to perform disconnection of C1-O bond as the first step of the retrosynthesis (Scheme II-49). Hydroperoxide **II-125** could arise from butenolide **II-126** via regioselective hydroperoxysilylation. Based on literature studies,[102] we supposed that the nonconjugated double bond of **II-126** should be more reactive than conjugated one under peroxidation conditions.

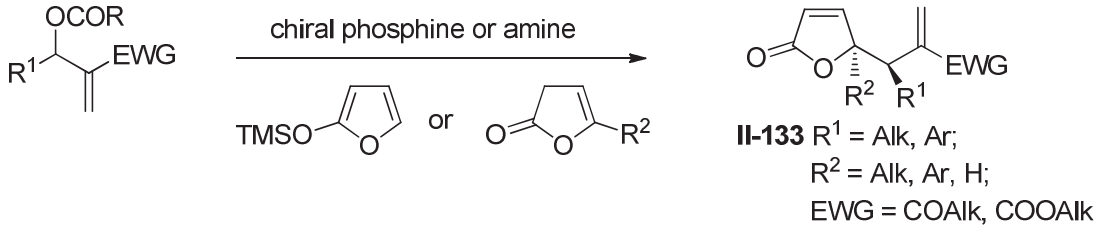


Scheme II-49

Butenolide **II-126** could be retrosynthetically dissected in two ways. The first one, and the most attractive, consists in coupling of commercially available α-angelicalactone **II-127** with readily available allyl bromide **II-128**. The second route to **II-126** is more classic and involved the formation of butenolide from α-hydroxyaldehyde **II-129** by Wittig or Horner-Wadsworth-Emmons reactions. We believed that **II-129** could be prepared by either of the two methods: epoxide opening of **II-132** with vinylmetal derived from **II-131** or by enantioselective allylation of pyruvic acid ester such as **II-130** with allylic bromide **II-128**.

II.6.2. Model studies toward allylbutenolides synthesis via Tsuji-Trost reaction (Path A)

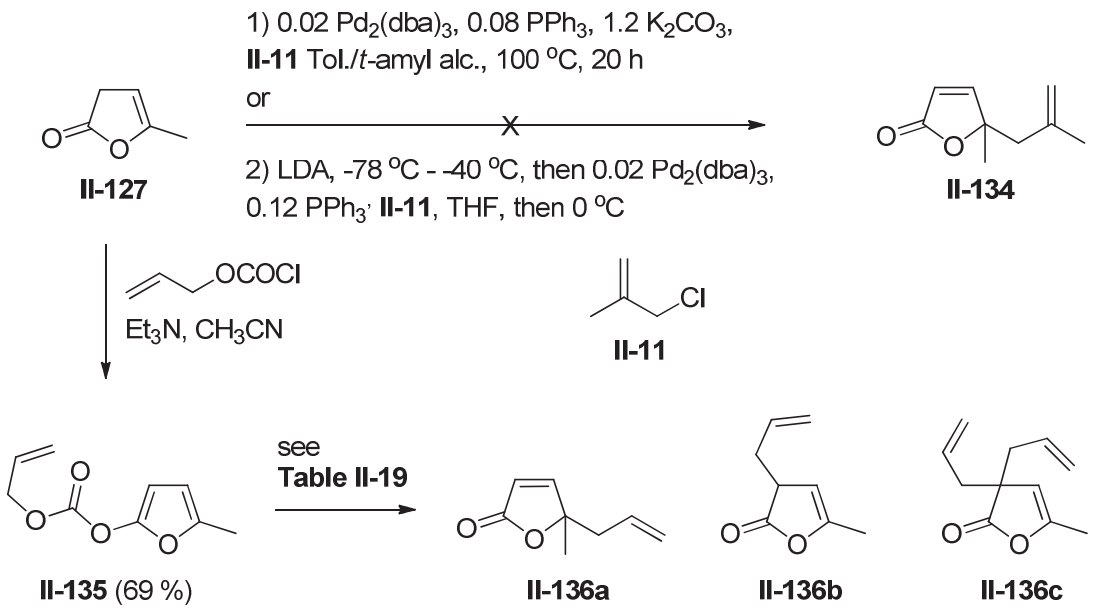
A few methods have been described for direct allylation of α-angelicalactone or alkoxyfurane derivatives. Among them, Ag^{+}-catalyzed allylation of 2-trimethylsiloxyfurans[209] or iodide-catalyzed allylation of 2-methoxyfurans[210] were not considered as potentially useful for us because enantioselective version of them could be with difficulty imagined. Recently a few publications describing asymmetric synthesis of butenolides through amine or phosphine-catalyzed substitution of Morita-Baylis-Hillman (MBH) derivatives have appeared in the literature (Scheme II-50).[211] Yields and enantiomeric excesses of these reactions were remarkably high but, to the best of our knowledge, this type of transformation was not studied with simplest MBH derivatives where R^1 = H.



Scheme II-50

Another especially interesting type of transformations is Pd-catalyzed couplings because they are well studied and asymmetric variant of them could be easily performed in most cases by choosing the appropriate chiral phosphine ligand. Dynamic kinetic asymmetric transformation of 5-acyloxy-2-(5H)-furanone into 5-aryloxy-2-(5H)-furanone described by Trost[212] and γ-arylation of unsaturated 5-alkyl-furanones[213] are the only examples of application of Pd-catalysis synthesis of 5,5-disubstituted butenolides from lactones. Unfortunately, above mentioned Trost approach could not be applied in our case as Tsuji-Trost reaction with hard nucleophiles are known to give poor ee.[214] Thus we decided to inverse the polarity of reagents: the anion of α-angelicalactone will be the nucleophile and allyl halide the electrophile.

First of all, we studied the direct allylation of α-angelicalactone with **II-11**. Heating a solution of **II-127** and **II-11** at 100 °C with catalytic amounts of $Pd_2(dba)_3$ and PPh_3 in toluene/*t*-amyl alcohol mixture resulted in no product formation (Scheme II-51). Only slow decomposition of starting materials was observed. Preformation of carbanion of **II-127** at -78 °C followed by treatment with catalyst and **II-11** at -40 °C led exclusively to decomposition of starting materials.



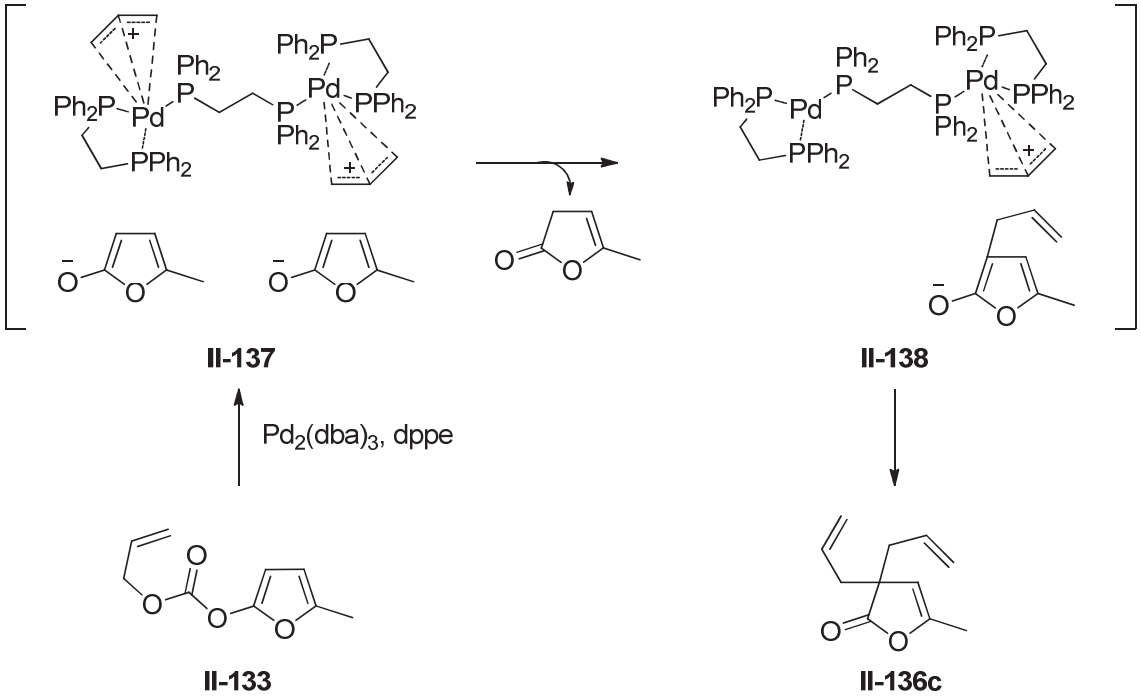
Scheme II-51

Table II-19. Studies on DAA reaction with **II-135**.

Entry	Conditions	Time (h)	Yield, % (% by ^{1}H NMR)		
			II-136a	**II-136b**	**II-136c**
1	0.02 $Pd_2(dba)_3$, 0.12 PPh_3, THF, rt	40	13	65	-
2	0.01 $Pd_2(dba)_3$, 0.03 dppe, THF, 0 °C	18	(4)	(14)	25 (41)
3	0.02 $Pd_2(dba)_3$, 0.12 PPh_3, DCM, rt	0.5	(17)	(83)	-
4	0.02 $Pd_2(dba)_3$, 0.12 PPh_3, PhMe, rt	0.5	(9)	(91)	-

Then we turned our attention to decarboxylative version of Tsuji-Trost reaction which has the advantage that both anionic and cationic species forms are close to each other and therefore subsequent collapsing to products is very fast minimizing possible side reactions. Furthermore, palladium-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) give better levels of enantioselectivity with nonstabilized enolates ($pK_a > 25$) in comparison to standard procedures.[215] Allyl 5-methyl-2-furyl carbonate was chosen as a model substrate for DAA (decarboxylative allylic alkylation) reaction because it could be easily prepared from commercially available starting materials. Treatment of α-angelicalactone with allyl chloroformate in the presence of triethylamine furnished carbonate **II-135**. Unfortunately palladium-catalyzed DAA reaction led to preferential formation of the α-alkylated product **II-136b** over **II-136a** whatever the solvent used (Table II-19, entries 1,3,4). Surprisingly utilization of dppe instead of triphenyl phosphine as a ligand gave majoratively the α,α'-dialkylated compound **II-136c**. This result could be explained by formation of the bis-π-allyl

complex **II-137** which after first coupling reaction followed by proton transfer gave π-allyl complex **II-138**. The second coupling would furnish **II-136c** (Scheme II-52). It should be noted that this is the first example of such a disproportionation in DAA reactions.

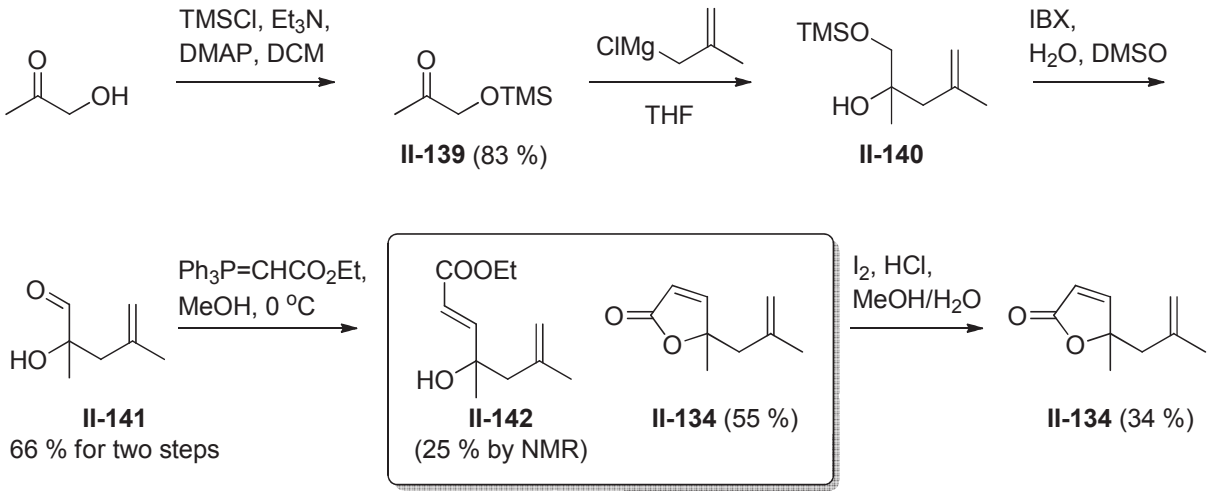


Scheme II-52

II.6.3. Studies on construction of the butenolide ring of II-126 by olefination (Path B)

II.6.3.1. Model study using Wittig reaction

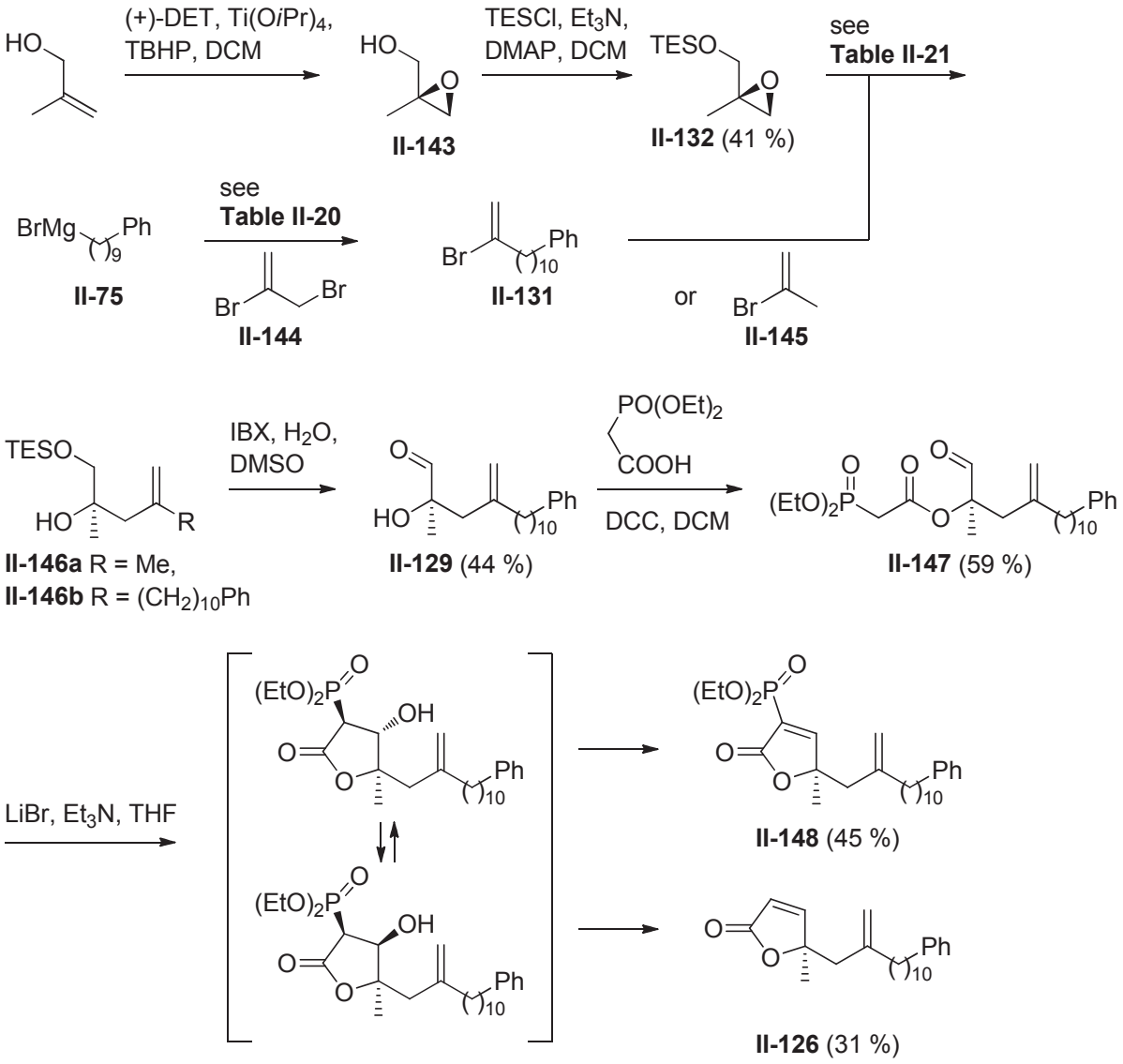
The synthesis of model allylbutenolide **II-134** was pursued using a standard approach. TMS-ether **II-139**, obtained from hydroxyacetone, was treated with methallylmagnesium chloride, prepared from 3-chloro-2-methyl-1-propene, to give tertiary alcohol **II-140** (Scheme II-53). Attempt performing deprotective oxidation of the latter by applying Swern procedure was unsuccessful. Treatment of **II-140** with IBX and water in DMSO[216] gave the α-hydroxyaldehyde **II-141** in 66 % overall yield for the two steps. It should be noted that slow dimerization of **II-141** was observed during storage in the fridge. Wittig reaction of this aldehyde with ethyl (triphenylphosphoranylidene)acetate in methanol at 0 °C afforded a 2:1 mixture of **II-134** and **II-142,** which were separated by column chromatography. If the mixture was directly subjected to iodine-catalyzed *E*→*Z* isomerisation process, **II-134** was obtained in a poor yield due to concomitant decomposition.



Scheme II-53

II.6.3.2. Studies toward the synthesis of II-126 using Horner-Wadsworth-Emmons (path B1)

Asymmetric synthesis of **II-126** commenced by Sharpless asymmetric epoxidation of 2-methallyl alcohol[217] followed by protection of the resulting (*S*)-epoxyalcohol as triethylsilyl ether with triethylsilyl chloride in presence of triethylamine to give **II-132** in 41 % overall yield (Scheme II-54). The stage was set up to introduce the 1-(10-phenyldecyl)vinyl group. To attain this goal, we had first to prepare vinyl bromide **II-131**. Among the different methods to achieve its synthesis, we chose the most direct one: cross coupling between 2,3-dibromopropene and 9-phenylnonylmagnesium bromide.[218] Unfortunately, yields were moderated whatever the reaction conditions (Table II-20, entries 1-5). Grignard reagent concentration was determined by No-D NMR spectroscopy (or no-deuterium Proton NMR) which involves recording ^{1}H NMR spectra of samples dissolved in ordinary, non-deuterium-enriched, laboratory solvents.[219] No-D NMR spectroscopy showed that the concentration was only 50-60 % from the theoretical value. It means that an important quantity of Grignard reagent was lost due to Wurtz reaction. In order to suppress Wurtz reaction, magnesium Rieke was prepared from magnesium dichloride and lithium metal.[220] Treatment of Mg Rieke with **II-75** at 0 °C furnished 9-phenylnonylmagnesium bromide (concentration 64 % from theoretical) which was subjected to reaction with 2,3-dibromopropene to give **II-131** in 67 % yield calculated from ^{1}H NMR spectrum of the crude mixture. Separation of **II-131** from Wurtz by-product was impossible either by flash chromatography or by distillation, therefore this mixture was used in the next step.



Scheme II-54

Table II-20. Cross-coupling between 2,3-dibromopropene and 9-phenylnonylmagnesium bromide **II-75**

Entry	G.r., M[a]	Conditions[b,c]	Time, h	Yield, %[d]
1	0.8	0.05 CuI, **II-144**, THF, 1 h, then G.r.	3	48
2	1	0.05 CuI, **II-144**, THF, 1 h, then G.r.	18	51
3	0.8	0.05 CuI, **II-144**, THF, 1 h, then G.r.	18	48
4	0.5	0.05 CuI, **II-144**, THF, 1 h, then G.r.	3	60
5	0.5	0.05 CuI, **II-144**, Et_2O, then G.r.	2	42
6	0.48	0.05 CuI, **II-144**, THF, 10 min, then G.r.[e]	18	67

[a] Grignard reagent (G.r.) was prepared from 1 eq of **II-75** and 1.2-2 eq of Mg; [b] distilled **II-144** was used in all entries except 1 and 2; [c] all reactions were performed at 0 °C except for entry 5 where the reaction was performed at rt; [d] determined by ^{1}H NMR spectroscopy; [e] Mg Rieke was used for the preparation of G.r.

Firstly we tested epoxide ring opening with isopropenylmagnesium bromide **II-145** catalyzed with substoichiometric amounts of copper iodide in THF. Alcohol **II-146a** was obtained in relatively moderate yield after reaction work-up (Table II-21, entry 1). In the case of **II-131**, prolonged heating of magnesium with this allylic bromide is required to obtain 1-(10-phenyldecyl)vinyl magnesium bromide as seen in entries 2,3 (Table II-21) otherwise no coupling product **II-146b** was obtained. Being unsatisfied by reaction yields, we turned our attention to Lewis acid-catalyzed epoxide opening with lithium organocuprates that was shown by Alexakis and coworkers to be a method of choice in terms of selectivity, yield and loading of metallo-organic compounds.[221] Application of this procedure to our substrate led exclusively to decomposition (entry 4). Finally **II-146b** was obtained in 70 % yield when the epoxide **II-132** was added to the solution of lithium bis[1-(10-phenyldecyl)vinyl] cyano cuprate in diethyl ether at -25 ^{o}C followed by slowly warming up the temperature to 0 ^{o}C during 1 h (entry 5).

Table II-21. Cu(I)-Catalyzed addition of organometallics derived from allylic bromide **II-131** to epoxide **II-132**

Entry	Conditions (equiv. reagent)	Yield, %
1	2 **II-145**, 2.2 Mg, 30 min,[a] 0.5 CuI, **II-132**, -40 → 0 ^{o}C, 2 h	42
2	1.5 **II-131**, 3 Mg, 30 min,[a] 0.1 CuI, **II-132**, -30 → 0 ^{o}C, 2 h	-
3	1.5 **II-131**, 3 Mg, 3 h,[a] 0.1 CuI, **II-132**, -30 → 0 ^{o}C, 18 h	52
4	2 **II-131**, 4.2 *t*BuLi, 0.5 h,[b] CuCN, **II-132**, $BF_3.Et_2O$, -78 → 0 ^{o}C, 1 h	-
5	2 **II-131**, 4.2 *t*BuLi, 0.5 h,[b] CuCN, **II-132**, -25 →0 ^{o}C, 1 h	70

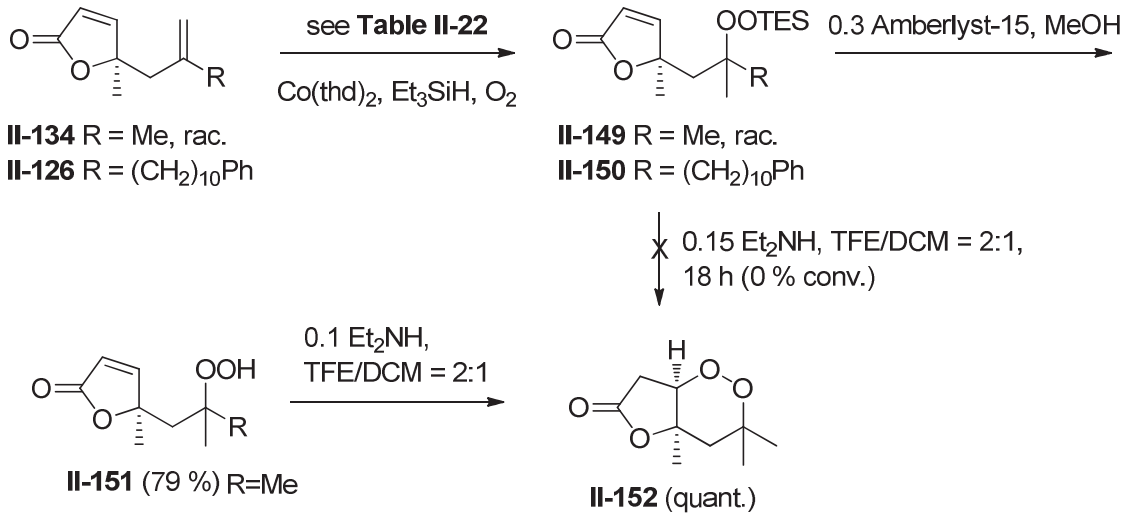
[a] reflux in THF; [b] Et_2O, -78 ^{o}C.

Oxidative deprotection of **II-146b** with IBX in presence of 1 equivalent of water in DMSO followed by esterification with diethylphosphonoacetic acid in the presence of DCC gave phosphonate **II-147** required for the intramolecular Horner–Emmons reaction. Surprisingly, treatment of **II-147** with LiBr and Et_3N provided desired butenolide **II-126** together with **II-148** in 31 and 45 % yield respectively.[222] In order to explain this result we supposed that the *trans*-hydroxyphosphonate intermediate underwent a dehydration facilitated by the presence of the acidic proton α to the carbonyl function (Scheme II-54).

II.6.4. Studies on peroxysilylation of allylbutenolides

Chemoselectivity in the peroxysilylation reaction was tested on both allyl butenolides **II-134** and **II-126** and the results are presented in Table II-22. At low conversion rate of **II-134**, peroxide **II-149** was obtained in nearly quantitative yield, whereas only 20 % of **II-149**

was obtained at high conversion rate (entries 1,2). The chemoselectivity was even worse with **II-126** as a complex mixture of products was obtained when the reaction was stopped at 38 % conversion (entry 3). The intensity of all vinylic hydrogens in ^{1}H NMR spectrum of the crude mixture was equal what means that the rate of hydroperoxysilylation reaction with conjugated and isolated double bonds of **II-126** was nearly the same.



Scheme II-55

Table II-22. Study of the regioselective peroxydation of unsaturated butenolides **II-126** and **II-134**

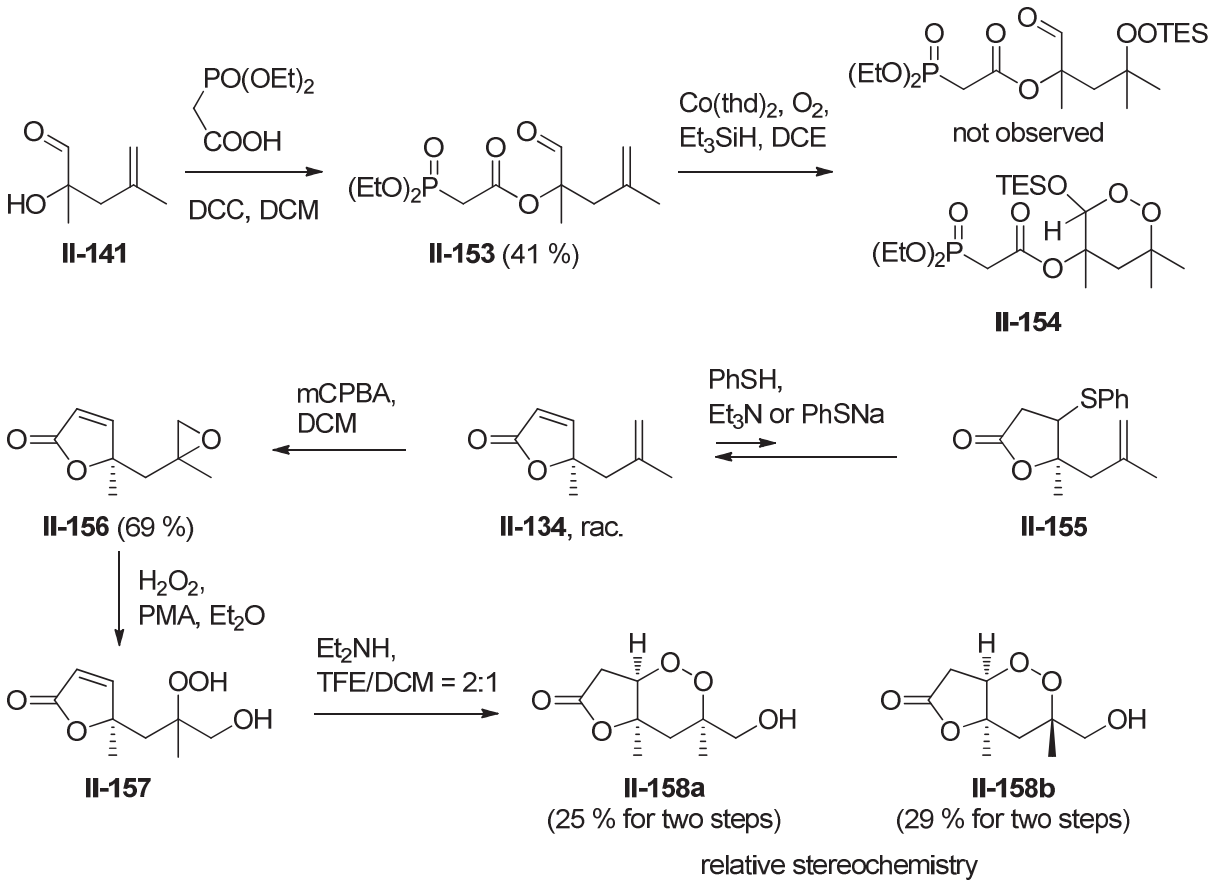
Entry	Conditions [a]	Starting material (%)	Product (%)
1	1.3 Et_3SiH, 0.1 $Co(thd)_2$, O_2, 3 h	**II-134** (80)	**II-149** (20)
2	2 Et_3SiH, 0.1 $Co(thd)_2$, O_2, 6 h	**II-134** (<10)	**II-149** (20)
3	1.5 Et_3SiH, 0.1 $Co(thd)_2$, O_2, 6 h	**II-126** (62)[b]	**II-150** (nd)[b,c]

[a] All reactions were carried out in DCE; [b] determined by ^{1}H NMR spectroscopy; [c] complex mixture of compounds.

Studies on the bicyclic peroxylactone core creation were continued with peroxide **II-149**. Firstly, the possibility of successive desilylation and cyclization of **II-149** under Kobayashi conditions[68] was envisaged. Unfortunately, pure starting material was obtained after evaporation of the reaction mixture (Scheme II-55). Acid-catalyzed deprotection of **II-149** in methanol gave hydroperoxide **II-151** which was further treated with catalytic amounts of diethylamine in TFE/DCM mixture to give simplest analog of plakortolides **II-152** quantitatively.

Having failed to realize regioselective peroxidation of the disubstituted olefin of butenolide **II-126**, several other routes were envisaged in which the peroxidation of the gem

disubstituted olefin was effected before the double bond formation of the butenolide. In the first approach, the peroxysilylation reaction was planned be performed just before the creation of butenolide cycle. Additionally, it was interesting to test the tolerance of Mukaiyama-Isayama reaction toward aldehyde functional group, as this question has never been studied. Treatment of hydroxyaldehyde **II-141** with diethylphosphonoacetic acid and DCC led to the phosphonate **II-153** in 41 % yield which was treated with triethylsilane and oxygen in the presence of $Co(thd)_2$ as catalyst (Scheme II-56). ^1H NMR spectrum of the residue after evaporation of the solvent revealed that other processes took place during the reaction as the intensities of aldehyde and triethylsilyl groups were 13 % and 50 % of the theoretical value respectively. Formation of peroxoacetal **II-154** by peroxy radical trapping by aldehyde was considered as a possible side reaction but because the intensity of the signals at 5.3-5.8 ppm corresponding to the peroxyacetal proton was only 38 % from the theoretical value, other different processes must also be involved.



Scheme II-56

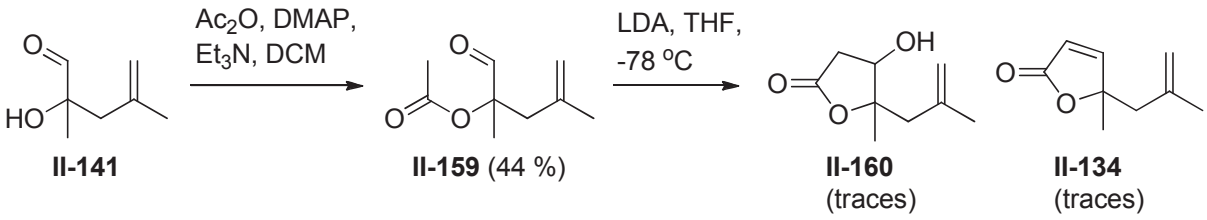
In order to increase the efficiency of plakortolide bicyclic core construction, we decided to protect the conjugated double bond (used a masked form of the double bond) before hydroperoxysilylation step. One suitable method for the protection-deprotection of conjugated double bond involved base-catalyzed addition of ArSH to conjugated alkene and its removal either by treatment with DBU or by oxidation to sulfone followed by heating or treatment with a base.[223] **II-132** was treated with an excess (1.3-3 equiv.) of thiophenol under a large variety of conditions (in the presence of Et_3N or PhSNa as catalyst or without; at room

temperature in DCM or at 70 °C in acetonitrile) but all failed to give pure adduct **II-155**. In all cases, the shift of the equilibrium toward starting material was observed by ^{1}H NMR spectroscopy. These results were quite unexpected as adducts of thiophenol with disubstituted butenolides have been already described by different groups.[223]

Having in our possession allylbutenolide **II-134**, we decided to synthesize few functionalized analogs of **II-152** for biological tests (Scheme II-56). Chemoselective epoxidation of **II-134** with *m*CPBA in dichloromethane gave epoxide **II-156**. PMA-catalyzed epoxide ring opening with H_2O_2 followed by intramolecular Michael addition reaction furnished bicyclic products **II-158a** and **II-158b** with 25 % and 29 % yield respectively.

II.6.5. Second approach to model peroxylactone II-152

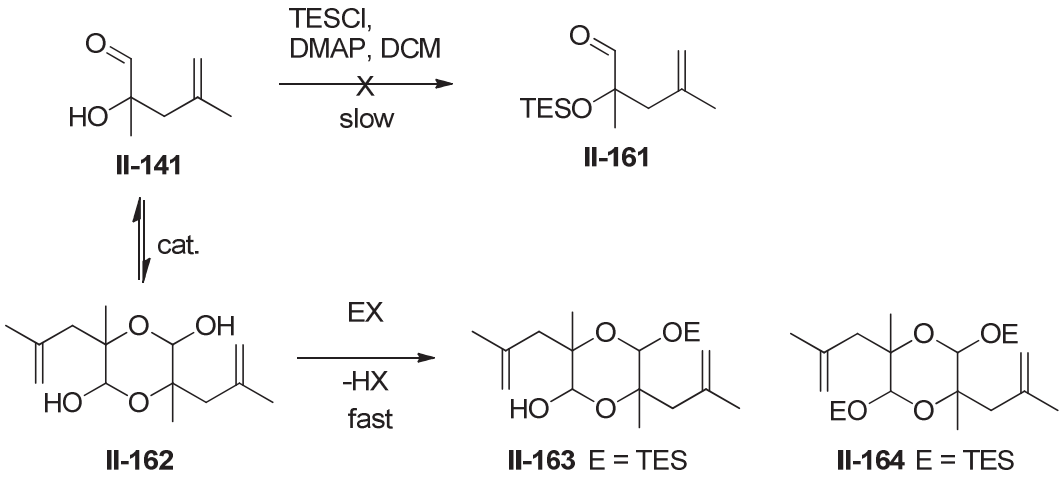
As protection of conjugated double bond in **II-134** turned out to be unsuccessful, we decided to synthesize 4-substituted dihydrofuranone by other means. We turned our attention to the synthesis of 4-hydroxy-5-methyl-5-(2-methylprop-2-enyl)dihydrofuran-2(3*H*)-one **II-160**, a masked form of butenolide **II-134**. The first attempt of **II-160** synthesis was made by acylation of **II-141** followed by treatment of the resulting ester **II-159** with LDA at -78 °C. Only complex mixture of products was obtained after reaction treatment at low temperature.



II-141 | **II-159** (44 %) | **II-160** (traces) | **II-134** (traces)

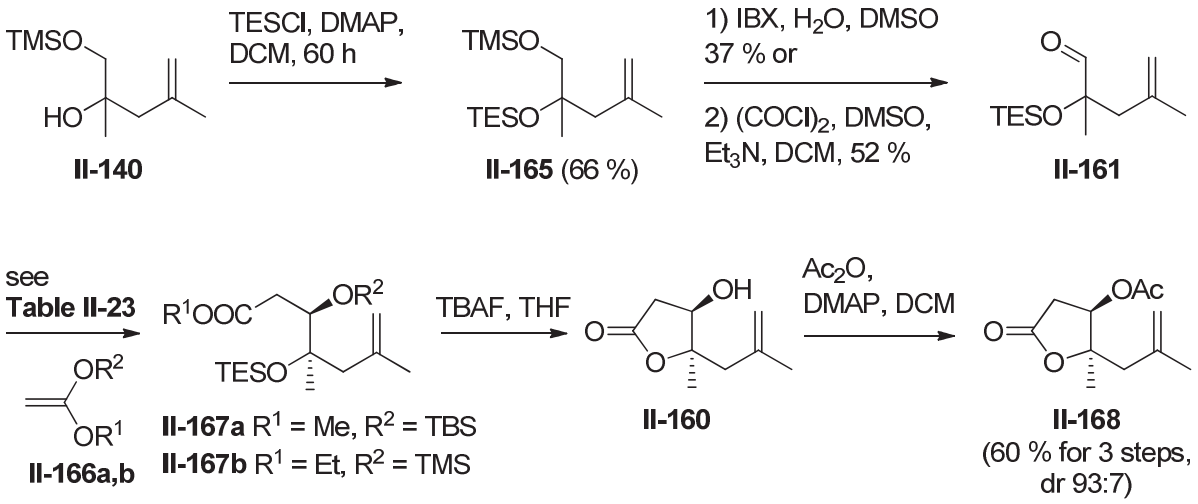
Scheme II-57

Fortunately, we could achieve the synthesis of **II-160** using a Mukaiyama-aldol reaction.[224] For this purpose, the alcohol **II-141** was treated with triethylsilyl chloride in the presence of DMAP, but the silyl product **II-161** was not detected by ^{1}H NMR spectroscopy of the crude reaction mixture. Low yields of esterification or etherification of alcohol **II-141** (see Schemes II-56-58) pushed us to find the origins of these results. We supposed the existence of fast equilibrium between monomeric and dimeric forms of the starting material in the reaction solution. Apparently, the reaction of electrophile with less sterically hindered secondary hemiacetalic hydroxy group of **II-162** is faster than that with tertiary alcohol **II-141**.This rate difference becomes more important with the increase of electrophile size and may explain that no TES-ether **II-161** was formed under the silylation conditions. This is corroborated by examination of the ^{1}H NMR spectrum of the crude mixture of silylated products which showed signals which could correspond to that of the mixture of diastereomers of **II-163** and **II-164**. An example of α-hydroxyaldehyde silylation that led to 2,5-bis((trimethylsilyl)oxy)-1,4-dioxane-type product has recently appeared in the literature.[225]



Scheme II-58

Finally, compound **II-161** was synthesized by a two-step procedure involving transformation of tertiary alcohol **II-140** into TES-ether **II-165** followed by oxidative deprotection into **II-161** by a mixture of IBX in DMSO-water or Swern oxidation in 37 and 52 % yield respectively (Scheme II-59). Then we turned our attention to the study of Mukaiyama aldol reaction with O-silyl ketene acetal in the presence of various Lewis acids. Treatment of α-acetoxy aldehyde **II-159** and commercially available 1-(tert-Butyldimethylsilyloxy)-1-methoxyethene **II-166a** with twofold excess of $LiClO_4$[226] in diethyl ether led to complex mixture of products (Table II-23, entry 1). α-Triethylsiloxy aldehyde **II-161,** in the same conditions, gave **II-167a** in 43 % yield as a 1:2 diastereomeric mixture (Table II-23,entry 2). Recently Hashimoto and coworkers showed that Mukaiyama aldol reaction of silyl ketene acetals with aldehydes could be effected with excellent yields by using pulverized 4Å molecular sieves (4Å MS) as a promoter.[227] Mildness of the reaction conditions and the ease of product purification consisting in a simple filtration, and purification by flash chromatography are the major advantages of this method. Unfortunately, there was no reaction between **II-161** and 1-trimethylsilyloxy-1-ethoxyethene either in the presence of pulverized 4Å MS or using a mixture of MS and $LiClO_4$ (entries 3,4). Finally **II-167b** was synthesized with an excellent yield and selectivity by treatment of the mixture of **II-161** and 1-trimethylsilyloxy-1-ethoxyethene with $TiCl_2(O\textit{i}Pr)_2$ in dichloromethane at -78 ^oC (entries 5,6).[228] The crude product, after treatment of the reaction mixture, was used in the next step without further purification.



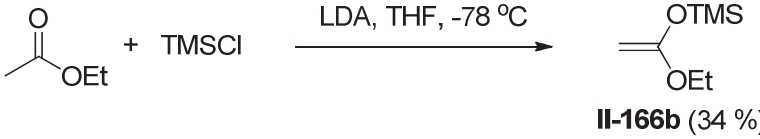
Scheme II-59

Table II-23. Mukaiyama aldol reaction between aldehydes **II-159** and **II-161** and silyl ketene acetals **II-166a,b**.

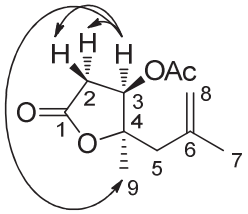
Entry	Conditions	R^1, R^2	Yield, % (dr)
1	1.1 **II-166a**, 2 $LiClO_4$, Et_2O, rt, 4 h	Me, TBS	-[a]
2	1.3 **II-166a**, 2 $LiClO_4$, Et_2O, rt, 4 h	Me, TBS	43 (1:2)
3	2 **II-166b**, 4 Å MS, DCM, rt, 20 h	Et, TMS	No reaction
4	2 **II-166b**, 4 Å MS, 2 $LiClO_4$, DCM/Et_2O, rt, 20 h	Et, TMS	No reaction
5	2 **II-166b**, $TiCl_2(OiPr)_2$, DCM, -78 °C, 4h	Et, TMS	>90 (>95:5)[b]
6	1.5 **II-166b**, 1.1$TiCl_2(OiPr)_2$, DCM, -78 °C, 4h	Et, TMS	>90 (>95:5)[b]

[a] acetate **II-159** was used as a substrate; [b] determined by ^{1}H NMR spectroscopy.

As outlined above, 1-trimethylsilyloxy-1-methoxyethene **II-166b** was prepared by a modified Corey's internal quench method (means that the enolate is formed in the presence of TMSCl)[229] which consists in addition of the solution of AcOEt and TMSCl in THF to LDA at low temperature.

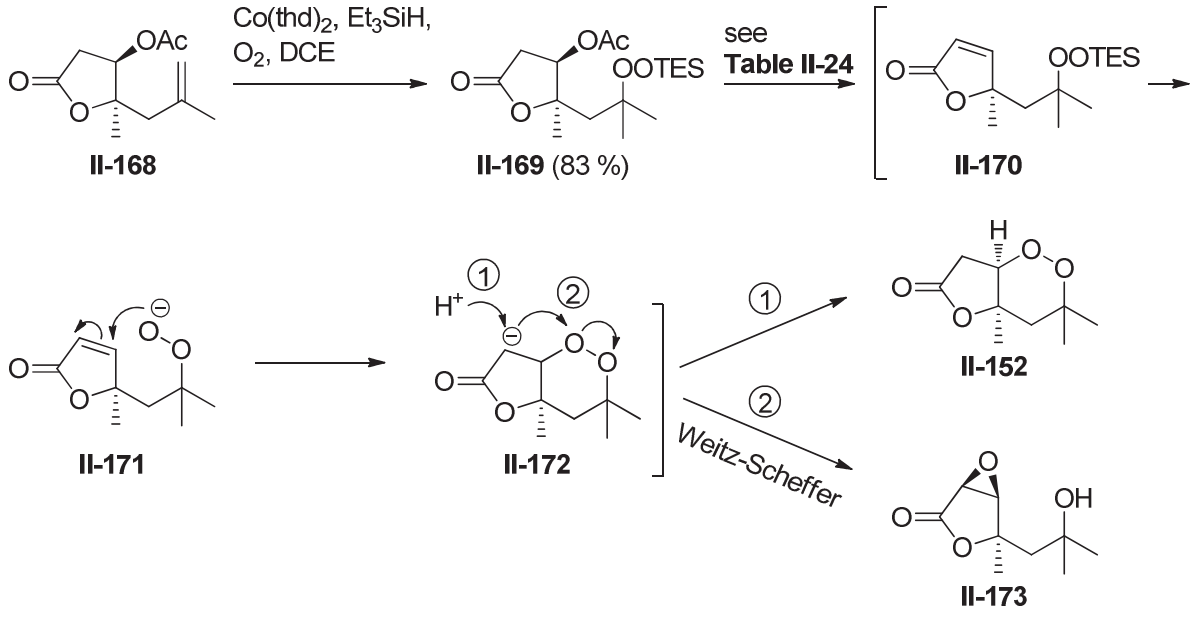


Treatment of either **II-167a** or **II-167b** with TBAF led to hydroxylactone **II-160** which was then acylated with acetic anhydride to give **II-168** with 60 % overall yield for the three steps (Scheme II-59). The presence of NOE effect on CH_3-9 and its absence on CH_2-5 is consistent with *cis* relative stereochemistry of **II-168**.



II-168
NOE effects

Having accomplished the synthesis of the acetoxylactone **II-168,** the next task was the construction of the 1,2 dioxane ring. Compound **II-168** was subjected to the peroxydation conditions, using $Co(thd)_2$ as catalyst, to give a 1:1 diastereomeric mixture of **II-169** in excellent yield (Scheme II-60). Base-catalyzed dehydroacetylation gave surprisingly **II-152** as a major product together with a small amount of epoxide **II-173** (Table II-24, entry 1). We observed by TLC, the formation of an intermediate at 0 ^oC which was further transformed into above mentioned products after warming up the reaction mixture to room temperature. This intermediate, butenolide **II-170,** was obtained by stopping the reaction between **II-169** and DBU after stirring the reaction mixture 4 h at 0 ^oC, and purification on silica gel (entry 3). Apparently *in situ* formed DBU·HOAc performed deprotection of triethylsilyl peroxide to hydroperoxide which underwent spontaneous intramolecular Michael addition that led to formation of carbanion **II-172**. This carbanion can either be protonated to give peroxide **II-152** or undergo Weitz-Scheffer type reaction of peroxy group to give epoxide **II-173**. In order to suppress Weitz-Scheffer epoxidation and therefore increase the yield of **II-152,** water as a proton source was added to the reaction mixture after preformation of butenolide **II-170**. As it can be seen on Table II-24, water had no positive effect on the reaction selectivity (entry 2). Finally addition of trifluoroethanol and TBAF led to nearly exclusive formation of peroxide **II-152** (entry 4).



II-168 **II-169** (83 %) **II-170**

II-171 **II-172** **II-152** **II-173**

Scheme II-60

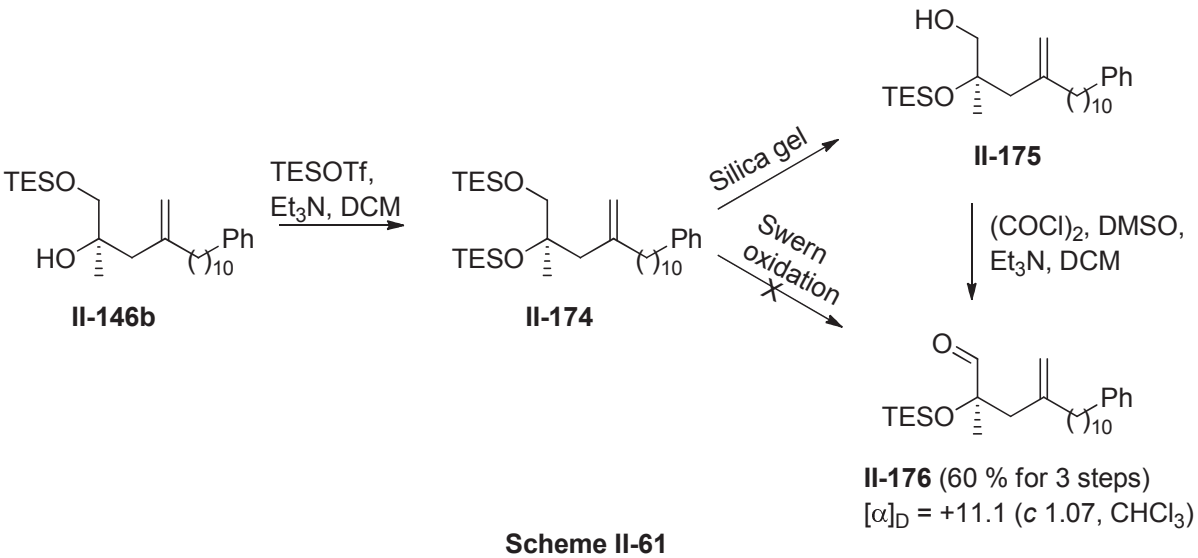
Table II-24. DBU-catalyzed dehydroacetylation-cyclization of the acetoxy lactone **II-169**

Entry	Conditions	Yield, %		
		II-170	**II-152**	**II-173**
1	DBU, THF, 0 °C, 2h, rt, 4 h	-	58	nd
2	1.5 DBU, THF, 0 °C, 4h, 100 H_2O, rt, 6 h	34[a]	27[a]	38[a]
3	1.5 DBU, THF, 0 °C, 4h	48	nd	nd
4	1.2 DBU, THF, 0 °C, 3h, TFE, TBAF, rt, 1 h	-	75	traces [a]
5	1.1 DBU, THF, 0 °C, 3h, rt, 15 h	-	38	21

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

II.6.6. Synthesis of II-176, the advanced intermediate of plakortolides

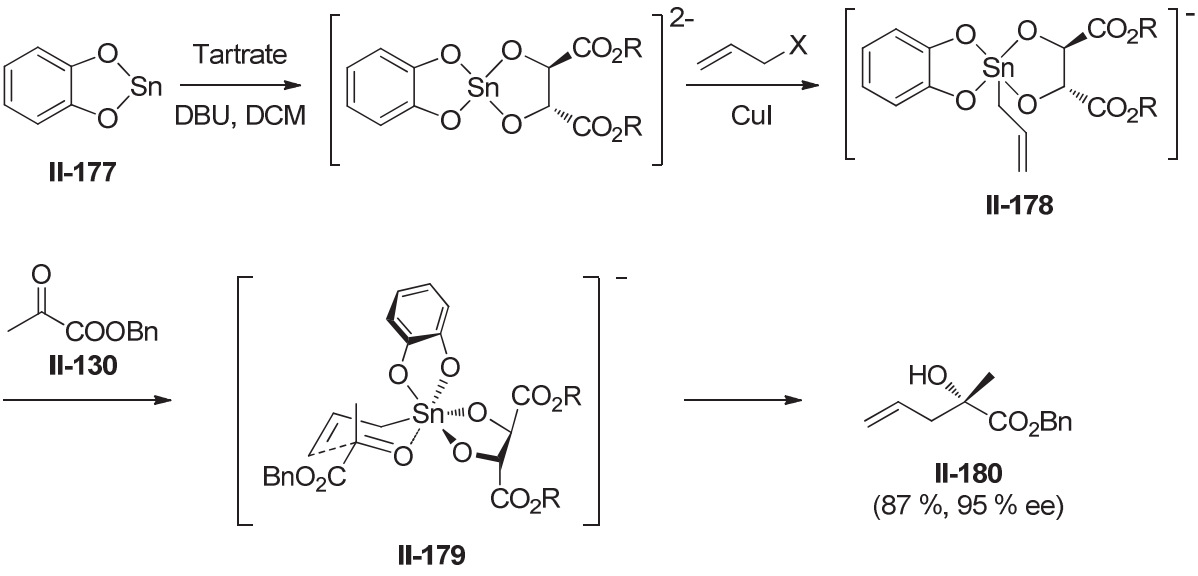
In order to apply the above depicted strategy of the peroxylactone system to the synthesis of plakortolides E and I, analog of **II-161** (Scheme II-59) that contain 10-phenyldecyl chain must be prepared. To this goal, **II-146b** was transformed into bis-TES-ether **II-174** which, without purification, was subjected to Swern conditions in order to oxidatively deprotected the primary silyl ether (Scheme II-61). Surprisingly, pure starting material **II-174** was obtained after work-up of the reaction mixture. Attempt purification of **II-174** by flash column chromatography gave mainly the deprotected primary alcohol **II-175** along with a small amount of tertiary one **II-146b**. It is really surprising that Swern oxidation could not effected the oxidative deprotection of the primary TES ether of **II-174** since it is very well-precedented.[230] We supposed that the steric hindrance of the proximal quaternary center prevented the deprotection of the silyl ether by Cl^-, the supposed silyl deprotecting agent of Swern oxidation.[231] Other acids such as *p*-toluenesulfonic or its pyridinium salt were unsuccessful for the selective deprotection of **II-174**. Thus, flash column chromatography on silica gel was the method of choice for the selective deprotection of bis silyl ether **II-174**. Finally, Swern oxidation of alcohol **II-175** gave aldehyde **II-176** in 60 % overall yield for three steps.



Scheme II-61

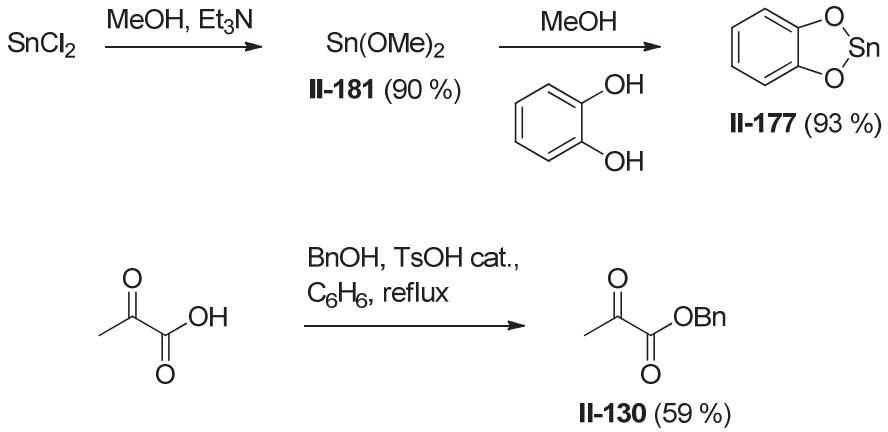
II.6.7. Second approach to II-176 (Path B2)

Addition of allylmetal to the carbonyl function of compounds such as hydroxyacetone or pyruvate is one of the most straightforward approaches to **II-176** synthesis. Unfortunately, the majority of existing methods for the stereoselective allylation of ketones is limited due to low enantioselectivity or is not compatible with a number of functional groups. An exception is the asymmetric allylation of pyruvates described by Mukaiyama and coworkers.[232] This reaction depicted on Scheme II-62 involved the following steps: oxidative addition of the allyl bromide to tin(II) catecholate in the presence of dialkyl tartrates, DBU and catalytic amount of CuI produce intermediate tin(IV) complex **II-178** which reacts with benzyl pyruvate through the transition state **II-179** to give the homoallylic alcohol **II-180** with an excellent yield and selectivity.



Scheme II-62

Tin(II) catecholate was prepared from commercially available tin dichloride via two step procedure according to the literature method.[233] Methanolysis of $SnCl_2$ in the presence of triethylamine led to **II-181** which was further treated with catechol to give **II-177** in good overall yield (Scheme II-63).

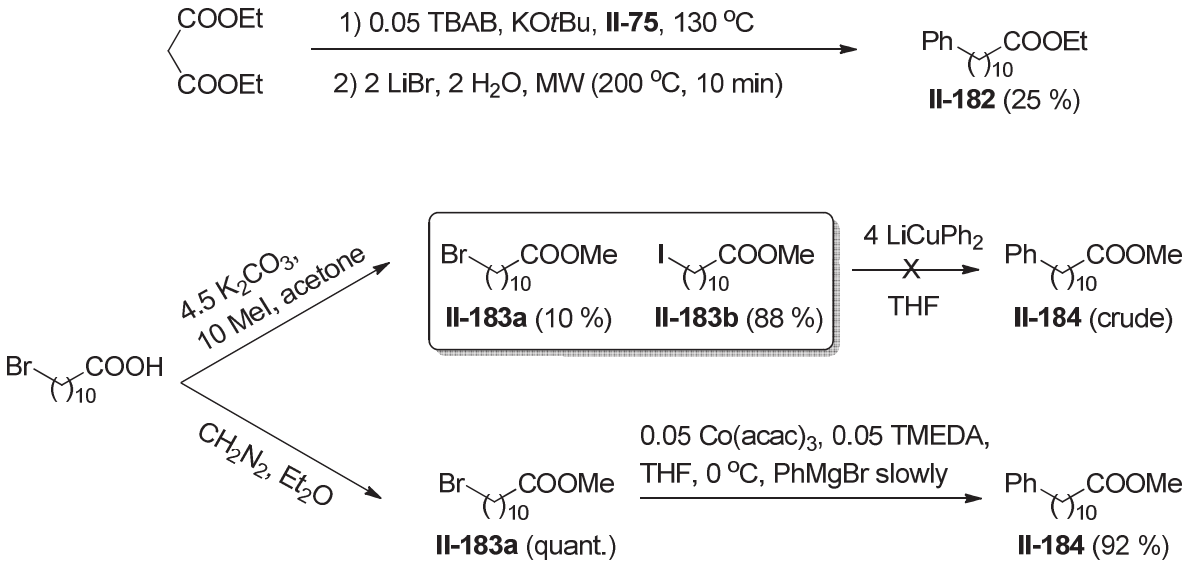


Scheme II-63

Benzyl pyruvate **II-130** was prepared by refluxing a benzene solution of pyruvic acid and benzyl alcohol in the presence of a catalytic amount of TsOH in a Dean-Stark apparatus.

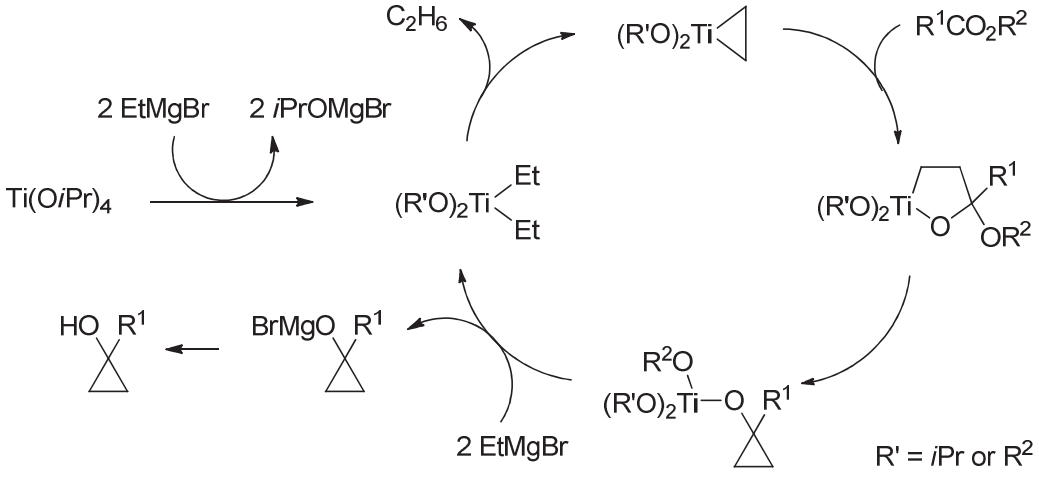
Synthesis of allylbromide **II-128** (See retrosynthesis, Scheme II-49) commenced by the preparation of methyl ester of 11-phenylundecanoic acid. Firstly, we tried a solvent-free alkylation of diethyl malonate with 9-phenylnonyl bromide followed by microwave-activated deethoxycarbonylation (Krapcho reaction) with LiBr and water (Scheme II-64).[234] Having obtained the ester **II-182** in low yield by this method, we modified our strategy by introduction the phenyl group to 10-halogenoundecanoic methyl ester. Treatment of commercially available 11-bromoundecanoic acid with iodomethane and K_2CO_3 afforded a mixture of **II-183a** and **II-183b** in nearly quantitative yield. The synthesis of **II-184** by a coupling reaction between **II-183b** and lithium diphenylcuprate, freshly prepared from CuI and commercially available phenyllithium (Posner'procedure), has been reported.[235] In our hands, it produced a little amount of the desired product as clearly indicated by ^{1}H NMR of the crude mixture.

Recently, Cahiez'group that worked extensively on Mn-, Co- and Fe-catalyzed transformations, described an efficient cobalt-catalyzed cross-coupling reaction between aryl Grignard reagents and alkyl bromides.[236] An advantage of this reaction is that ester, amide, and keto groups are tolerated. Thus, we applied this method to **II-184** synthesis. After esterification of 11-bromoundecanoic acid with diazomethane, the resulting methyl 11-bromoundecanoate **II-183a** was coupled with phenylmagnesium bromide in the presence of $Co(acac)_3$ and TMEDA to give methyl 11-phenylundecanoate **II-184** in an excellent yield.



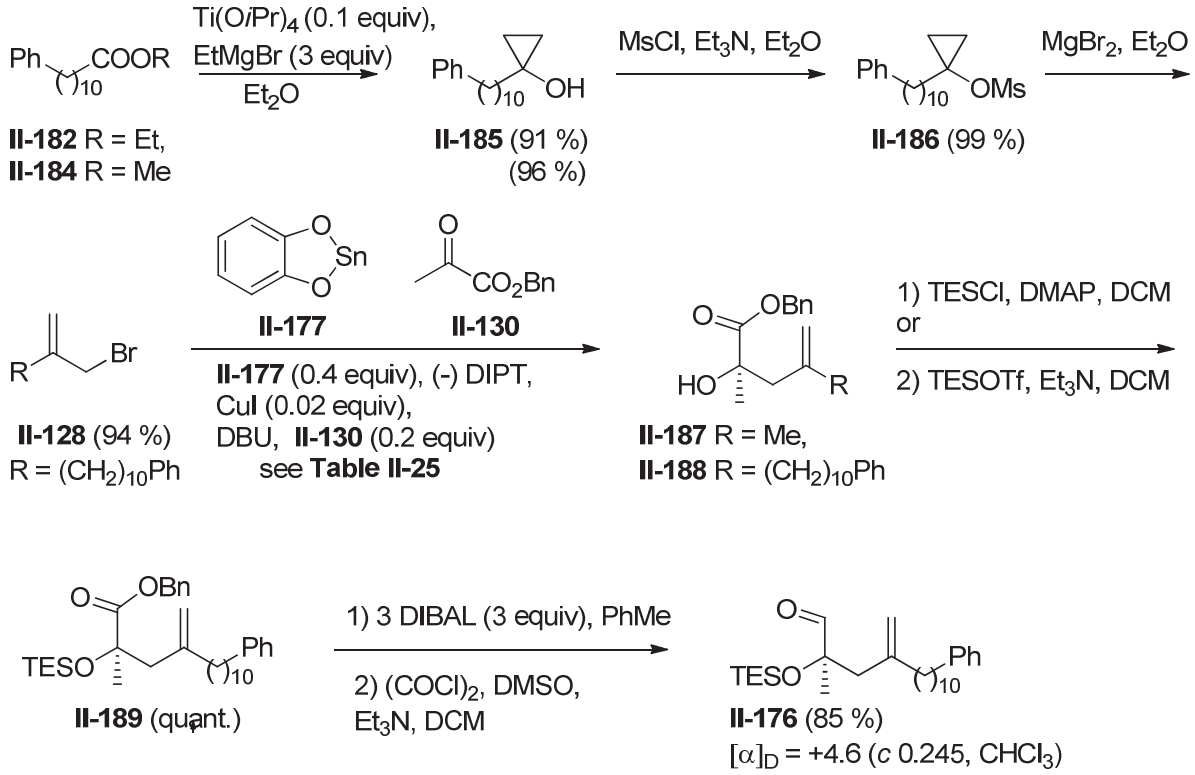
Scheme II-64

In order to obtain our target, compound **II-128,** the ester function of **II-184** had to be transformed into an allyl bromide by a two-carbon homologation. We used a three step procedure involving a carboxy group cylopropanation via Kulinkovich reaction and rearrangement of cyclopropane as the key steps.[237] Accepted mechanism for the reaction of cyclopropanation was firstly proposed by Kulinkovich et al[238] and is depicted in Scheme II-65. It is assumed that thermally unstable diethyltitanium intermediate, formed by exchange reaction between Ti(O*i*Pr)$_4$ and EtMgBr, loses a molecule of ethylene by consecutive β-hydride elimination and reductive elimination to yield titanacyclopropane. Insertion of the ester carbonyl group into titanium-carbon bond gives oxatitanacyclopentane which undergoes ring contraction to produce the titanium cyclopropanolate. The latter reacts with two molecules of the Grignard reagent to reform diethyltitanium intermediate and give the magnesium cyclopropanolate that is eventually hydrolyzed to corresponding cyclopropanol.



Scheme II-65

Subjection of either ethyl **II-182** or methyl **II-184** esters to Kulinkovich reaction conditions led to 1-(10-phenyldecyl)cyclopropanol **II-185** in an excellent yield in both cases (Scheme II-66). Mesylation of this cyclopropanol followed by treatment of the resulting mesylate **II-186** with $MgBr_2$ in diethyl ether at reflux gave bromide **II-128** in nearly quantitative yield.



Scheme II-66

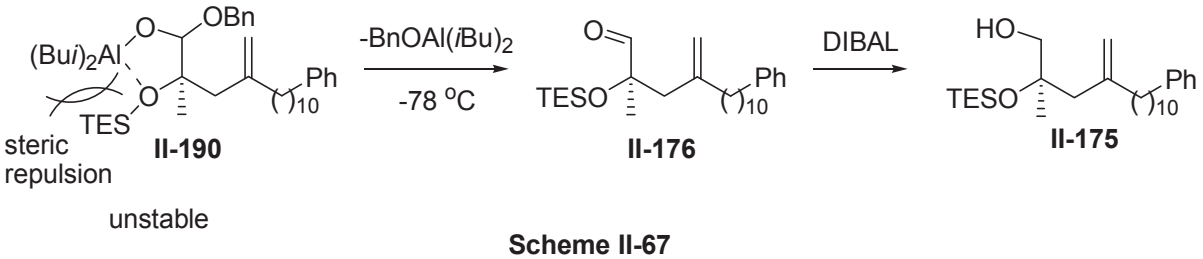
Table II-25[a]. Asymmetric allylation of benzyl pyruvate with **II-128**

Entry	t, °C	Product (yield)	$[\alpha]_D^{20}$, $CHCl_3$
1	-78 → -30	-	-
2	-78	**II-187** (54 %)	-1.7
3	-78	**II-188** (68 %)	+2.05

[a] Twofold excess of allyl bromide in comparison to **II-130** was used in the reaction; 3-bromo-2-methyl-1-propene was used in entries 1,2.

Having attained the synthesis of allyl bromide **II-128,** the next stage was to study the asymmetric Mukaiyama allylation method. Both 3-bromo-2-methyl-1-propene and **II-128** gave comparable yields of α-hydroxyesters **II-187** and **II-188** respectively when they were subjected under standard Mukaiyama conditions with benzyl pyruvate (Table II-25, entries

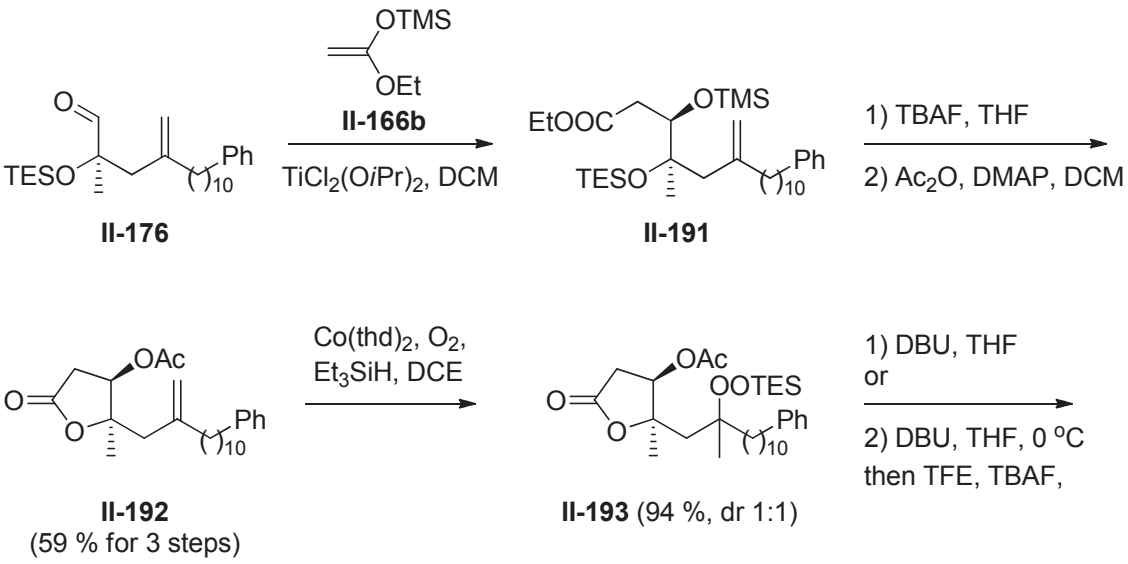
2,3) whereas no product was obtained when the reaction was performed at higher temperatures (entry 1). Protection of the tertiary hydroxyl group of **II-188** as its triethylsilyl ether could be performed quantitatively by either TESCl or TESOTf reagents. Unfortunately it was impossible to stop the reduction of ester **II-188** with DIBAL at the aldehyde stage. Important steric repulsion between two isobutyl and TES groups makes intermediate complex **II-190** unstable even at -78 °C and led to elimination of $BnOAl(iBu)_2$ to give aldehyde **II-176** which undergo further reduction to alcohol **II-175** (Scheme II-67). Swern oxidation of this alcohol affords aldehyde **II-176** in 85 % yield for two steps. Comparison of the optical rotation of **II-176** obtained by Mukaiyama allylation (+4.6) with that obtained from enantiopure epoxide **II-143** (+11.1) showed that enantioselectivity of the Mukaiyama allylation reaction was 41 %.

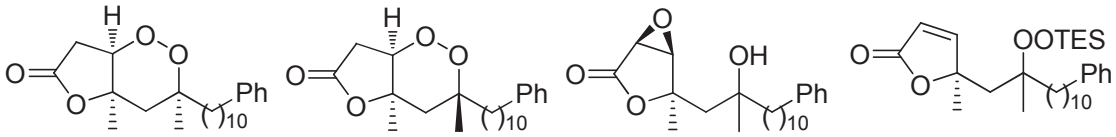


Scheme II-67

II.6.8. Synthesis of plakortolides I and E

With a key aldehyde **II-176** in hand, we continued the synthesis of plakortolides I and E. $TiCl_2(OiPr)_2$-catalyzed Mukaiyama aldol reaction between **II-176** and 1-trimethylsilyloxy-1-ethoxyethene afford **II-191** which was hydrolyzed with TBAF followed by treatment of resulting hydroxy lactone with acetic anhydride to give acetate **II-192** (59 % yield for the three steps) (Scheme II-68). Mukaiyama-Isayama hydroperoxysilylation of **II-192** furnished peroxide **II-193** in an excellent yield. Treatment of this peroxide with DBU for 4 hours at 0 °C followed by heating to room temperature led to the formation of plakortolides I **II-4a** and E **II-4b** accompanied with small amounts of epoxide **II-194** and butenolide **II-195**. Formation of these latter was mainly suppressed using our previously optimized procedure, consisting in elimination of acetic acid with DBU at 0 °C followed by desilylation-cyclization cascade induced by TBAF in the presence of trifluoroethanol. The structure and the relative stereochemistry of plakortolide I and E were confirmed by 2D NMR techniques.





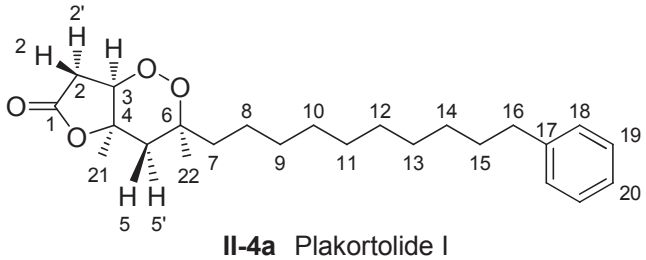
$[\alpha]_D^{20}$= - 9 (*c* 0.7, $CHCl_3$)
litt for (3*R*, 4*R*, 6*S*)
$[\alpha]_D^{20}$=+8 (*c* 0.017, $CHCl_3$)

$[\alpha]_D^{20}$= +14.9
(*c* 0.76, $CHCl_3$)

1	29 %	29 %	15 %	18 % by NMR
2	35 %	37 %	<10 % by NMR	-

Scheme II-68

The physical data of **II-4a** are identical with those of plakortolide I described by Kashman[15] except for the sign of optical rotation. Kashman et al deduced the absolute stereochemistry of their plakortolide I by comparison of its optical rotation with that of its enantiomer reported by Faulkner and coworkers (Comparison of NMR data of **II-4a** and Kashman and Faulkner products is presented in Tables II-26 and II-27).[14] The absolute stereochemistry of (-)-plakortolide I was assigned by Mosher's method on the corresponding *seco*-plakortolide, obtained by reductive cleavage of the peroxide ring. The principle of the Mosher's method is presented on Figure II-3. The main assumption of this technique is that all atoms F_3C-C-(CO)-O-C-H are in the same plane. Due to the diamagnetic effect of the benzene ring, the substituent R^2 is more shielded in the (*R*)-MTPA ester than in the (*S*)-MTPA ester, while R^1 is more shielded in the(*S*)-MTPA ester than in the (*R*)-MTPA ester. The difference between the chemical shift in both esters ($\Delta\delta = \delta s - \delta r$) is the magnitude employed when analyzing the data and in the case represented above, the expected values are: $\Delta\delta$ for $R^1 < 0$ and for $R^2 > 0$.



II-4a Plakortolide I

Table II-26. Comparison of ^{1}H NMR ($CDCl_3$) spectra of synthesized Plakortolide I with those of (+) and (-)-natural compounds.

H	δ_H (mult., *J*)		
	(-)-Synthesized (400 MHz)	(+)-Natural (500 MHz)	(-)-Natural (300 MHz)
2	2.56 (d, 18.5)	2.70 (d, 12.4)	2.59 (dd, 18.6, 1.5)
2’	2.90 (dd, 18.5, 5.9)	2.91 (dd, 12.4, 6.0)	2.91 (dd, 18.6, 6)
3	4.48 (d, 5.9)	4.44 (d, 6.0)	4.49 (d, 6.0)
5	2.27 (d, 15.0)	2.17 (d, 15.0)	2.28 (d, 15.3)
5’	1.65 (d, 15.0)	1.71 (d, 15.0)	1.66 (d, 15.3)
7	1.52 – 1.76 (m)	1.50 (m)	1.75 (m)
8-14	1.26 (m)	1.25 (m)	1.27-130 (m)
15	1.61 (m)	1.58 (m)	1.57 (m)
16	2.60 (t, 7.8)	2.60 (t, 7.0)	2.60 (t, 7.8)
Ph	7.15 – 7.29 (m)	7.20 – 7.25 (m)	7.19 (m), 7.27 (m)
21	1.37 (s)	1.37 (s)	1.38
22	1.20 (s)	1.27 (s)	1.20

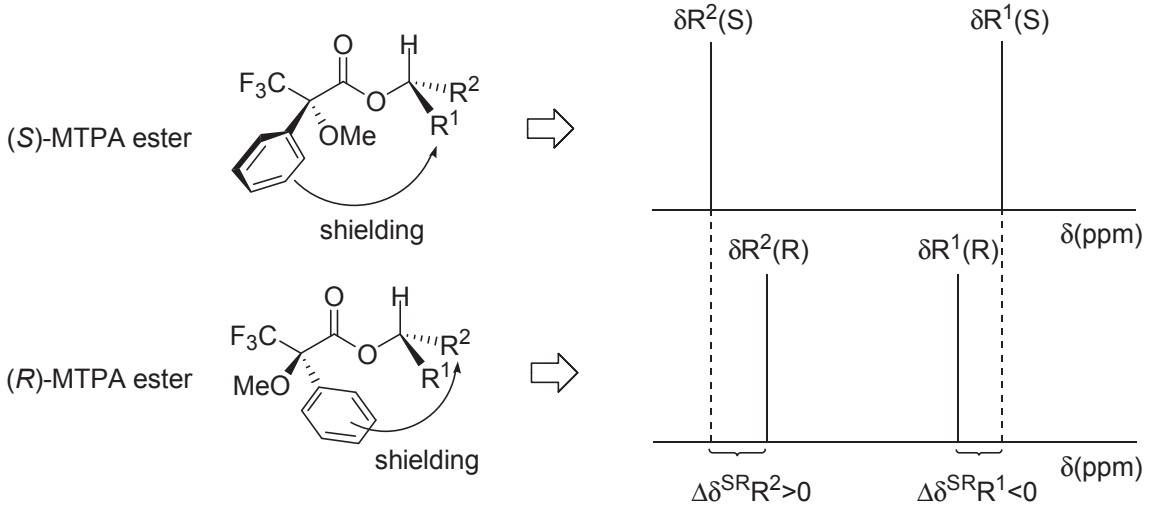
Table II-27. Comparison of ^{13}C NMR ($CDCl_3$) spectra of synthesized Plakortolide I with those of (+) and (-)-natural compounds.

C	δ_C		
	(-)-Synthesized (100 MHz)	(+)-Natural (125 MHz)	(-)-Natural (100 MHz)
1	174.3	174.2	174.1
2	34.2	34.2	34.1
3	81.0	80.1	80.8
4	82.7	82.0	82.5

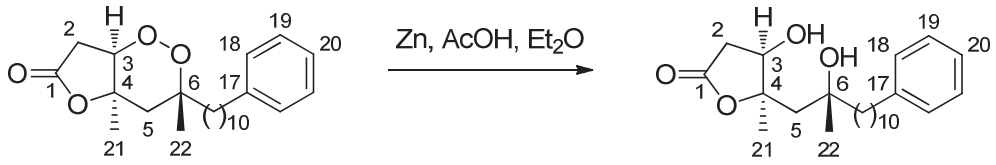
5	40.4	41.0	40.2
6	80.4	80.2	80.2
7	37.0	36.0	36.9
8	23.9	22.4	23.7
9-14	29.5 – 29.7	29.5	29.3 – 29.9
15	31.7	31.4	31.5
16	36.2	39.5	36.0
17	143.1	142.2	143.0
18	128.6 (2C)	128.3 (2C)	128.4
19	128.3 (2C)	128.2 (2C)	128.2
20	125.7	125.5	125.5
21	26.1	25.8	25.9
22	25.0	23.0	24.9

Although this assumption is valid in most cases, other conformations for some derivatives could predominate and be the origin of errors. We suppose that it is the case for Mosher esters of *seco*-plakortolides because any of the common errors[239] that lead to misassignment were present in Faulkner's absolute stereochemistry elucidation. This is corroborated by the conclusion of Garson and coworkers after the configurational assignment of a number of plakortolides, they wrote "On the basis of the current study, a number of literature plakortolide merit stereochemical reinvestigation".[16]

Figure II-3. Conformational models for MTPA esters with their NMR spectra and the meaning of the $\Delta\delta^{SR}$ magnitudes. Arrows indicate the predominant shielding effect caused by the aromatic systems.



Finally plakortolide E was reduced with zinc and acetic acid to *seco*-plakortolide E in 91 % yield (Scheme II-69). Physical data of our product were in perfect agreement with those of plakortolide E described by Crews et al,[13] confirming thus Garson's assumption[16] that the structure of the latter was misassigned and its real structure corresponds to *seco*-plakortolide E (Tables II-28 and II-29).



II-4b
Plakortolide E

II-196 (91 %)
Seco-plakortolide E
$[\alpha]_D^{20}$= + 7.7 (*c* 0.15, $CHCl_3$)
Natural product:
$[\alpha]_D^{20}$= + 10 (*c* 0.09, CH_2Cl_2)

Scheme II-69

Table II-28. Comparison of ^{1}H NMR ($CDCl_3$) spectra of synthesized Plakortolide E and *Seco*-Placortolide E with that of the natural product.

H	δ_H (mult., *J*)		
	Plakortolide E[a]	*Seco*-Placortolide E[b]	Natural
2	2.62 (d, 18.3)	2.55 (dd, 18.2, 1.8)	2.55 (dd, 18.3, 1.8)
2'	2.91 (dd, 18.6, 6.1)	2.92 (dd, 18.2, 6.8)	2.93 (dd, 18.3, 6.7)
3	4.45 (d, 6.1)	4.19 (dd, 6.7, 1.7)	4.19 (dd, 6.7, 1.8)
5	1.70 (d, 14.8)	2.09 (d, 15.1)	2.09 (d, 15.0)
5'	2.17 (d, 14.8)	2.17 (d, 15.0)	2.15 (d, 15.0)
7	1.50 (m)	1.50 – 1.65	1.61, 1.29 (m)
8-14	1.27 (m)	1.28 (m)	1.29 (bs)
15	1.61 (m)	1.50 – 1.65	1.55 (m)
16	2.60 (t, 7.7)	2.60 (t, 7.5)	2.60 (t, 7.4)
Ph	7.15 – 7.29 (m)	7.16 – 7.29 (m)	7.18, 7.26 (m)
21	1.39 (s)	1.44 (s)	1.44 (s)
22	1.29 (s)	1.35 (s)	1.35 (s)

[a] 400 MHz, [b] 500 MHz.

Table II-29. Comparison of ^{13}C NMR ($CDCl_3$) spectra of synthesized Plakortolide E and *Seco*-Placortolide E with that of the natural product.

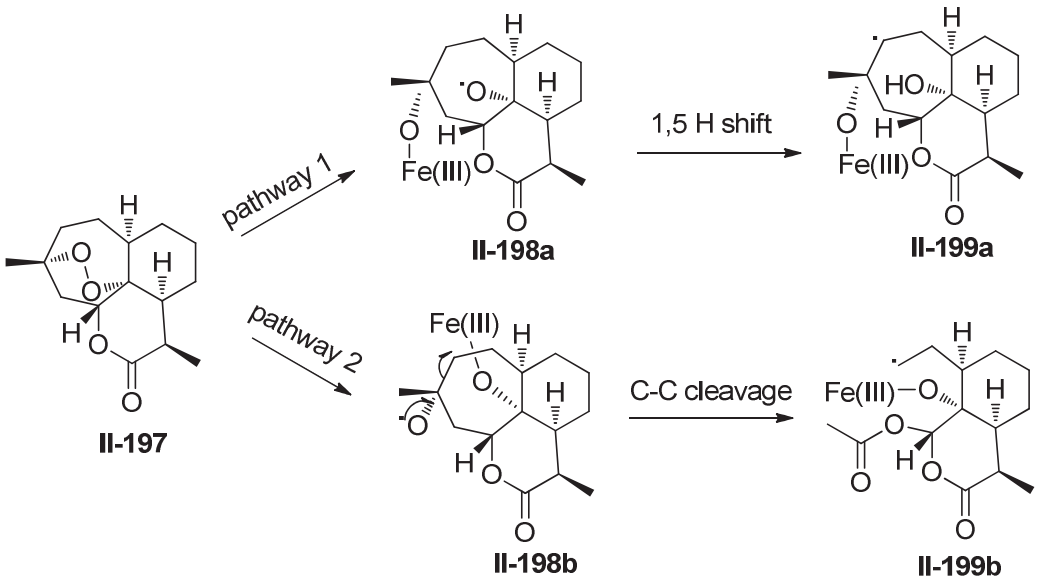
C	δ_C		
	Plakortolide E[a]	*Seco*-Placortolide E[b]	Natural
1	174.4	175.3	175.2
2	34.5	38.2	38.1
3	81.3	74.1	73.8
4	82.9	90.1	90.1
5	40.7	44.0	43.9
6	80.3	73.4	72.9
7	41.2	43.8	43.6
8	23.2	24.5	24.4
9-14	29.5-30.2	29.5-30.1	29.4-30.0
15	31.7	31.7	31.5
16	36.1	36.1	35.9
17	143.1	143.1	142.9
18-19	128.4, 128.5	128.4, 128.5	128.2, 128.3
20	125.7	125.7	125.5
21	26.1	27.0	26.9
22	22.6	30.2	30.0

[a] 101 MHz, [b] 126 MHz.

II.6.9. Mode of action of endoperoxides as antimalarial agents

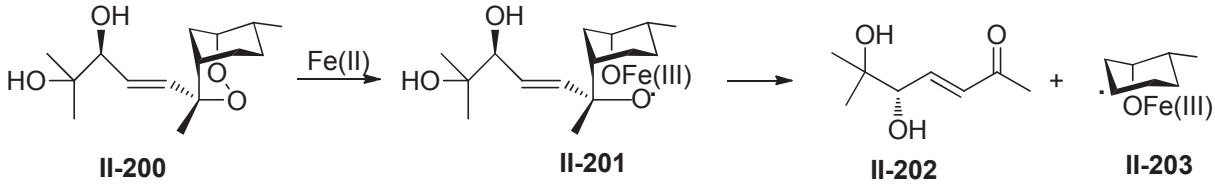
Even if the mechanism of action of artemisinin underlying its biological activity against *Plasmodium* was the object of a large number of studies, it is still a matter of debate.[240] Nevertheless, the ability of artemisinin **II-197** and its analogues to interact with Fe(II)-heme to produce oxidative stress hallmarks in the plasmodium in the infected host cells has been proved. The reaction between endoperoxides and Fe(II) involves a one-electron reduction leading to the cleavage of the O-O bond with formation of an oxygen anion and of an oxygen radical to give **II-198a** or **II-198b** (Scheme II-70).[241] In pathway 1, intramolecular 1,5-H shift leads to **II-199a** bearing a secondary free radical at C4. Fragmentation of the C3-C4 bond in **II-198b** with formation of the primary free radical furnished the acetate **II-199b**. It has been

suggested that these transitory reactive species are responsible for killing the parasites through alkylative and/or oxidative processes.



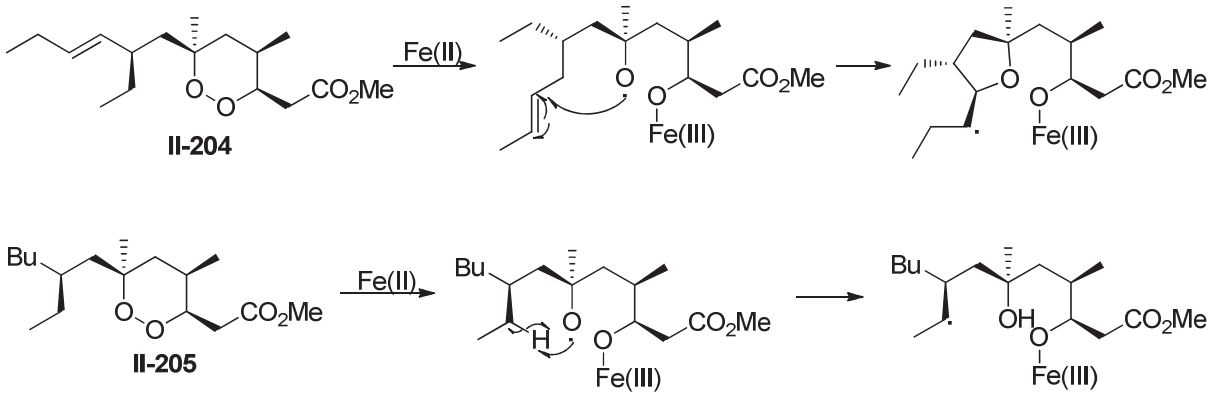
Scheme II-70

Mechanism of action of only few compounds bearing 1,2-dioxane against *Plasmodium* has been studied. Thus, iron(II)-induced degradation of Yingzhaosu A **II-200** would result in the formation of two alkylating agents: unsaturated ketone **II-202** and cyclohexyl radical **II-203** through oxygen radical **II-201** (Scheme II-71).[242]



Scheme II-71

A recent paper reported a study of the mechanism of antimalarial action of plakortin **II-204** and dihydroplakortin **II-205**, simple 1,2-dioxanes isolated from the sponge *Plakortis simplex*.[243] Reaction between Fe(II)heme and **II-204** and **II-205** should involve the peroxide bond cleavage with consequent O radical formation followed by 1,4 or 1,5 intramolecular radical shift to a western side chain (Scheme II-72). These radicals should be the toxic species giving intramolecular reactions with plasmodium molecular targets.



Scheme II-72

Besides the possible mechanism of action of plakortin family, the same group also reported a SAR studies for a series of endoperoxide antimalarials based on plakortin scaffold. This study, besides confirming the crucial role of the cycloperoxide functionality, brought to light other structural features critical for antimalarial activity: (i) the western alkyl chain, (ii) dioxane ring conformation, (iii) the absolute configuration of the stereogenic centers on the dioxane ring.[5a]

II.6.10. Biological activities of synthetic endoperoxides II-152, II-158a,b

Three racemic endoperoxides **II-152**, **II-158a** and **II-158b** were subjected to the preliminary *in vitro* tests against 3D7 and W2 strains of *P. falciparum*. Unfortunately all of them were considerably less active than chloroquine (Table II-30).

Table II-30. Results of *in vitro* tests of **II-152** and **II-158a,b** against 3D7 and W2 strains of *P. falciparum*.

	CI_{50}	
	3D7, nM	W2, nM
II-152	>1600	>1600
II-158a	>1600	>1600
II-158b	>1600	>1600
Chloroquine	23 ± 4	563 ± 54

II.6.11. Conclusion

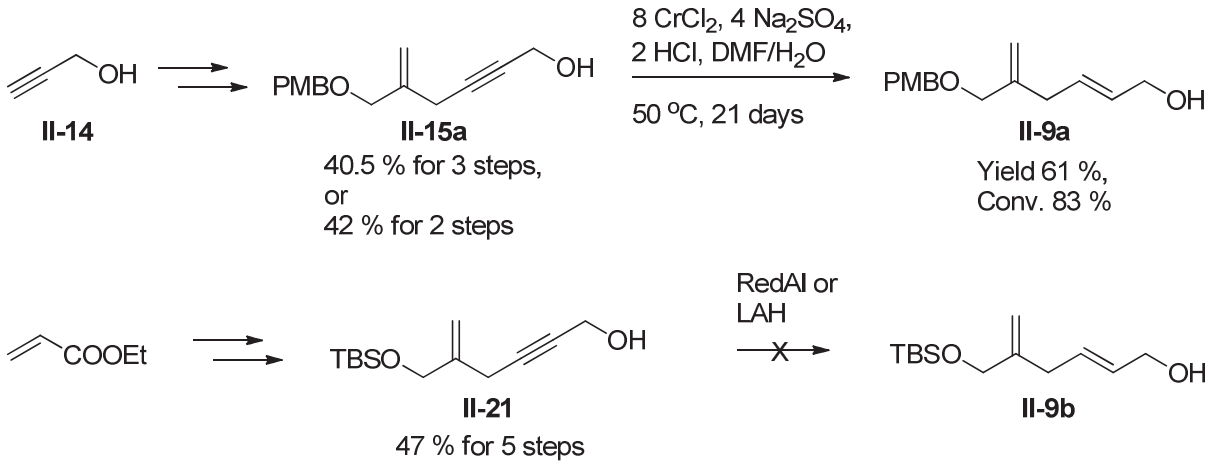
During the work on this retrosynthetic approach two natural products, plakortolide I and *seco*-plakortolide E as well as unnatural plakortolide E, were synthesized in enantiopure form. On the basis of above mentioned products physical data, the absolute stereochemistries of Kashman's plakortolide I, Faulkner's enantiomer of plakortolide I and structure of Crews plakortolide E were revised and proved to be (+)-**II-4a**, **II-4a** and **II-196** respectively.

During the model studies toward peroxylactone core construction three simplest racemic plakortolide analogs **II-152**, **II-158a** and **II-158b** were synthesized and tested *in vitro* against 3D7 and W2 strains of *P. falciparum*. No activity was found in all cases.

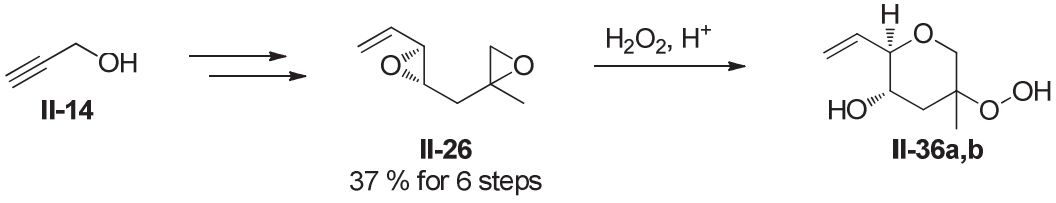
II.7. Conclusions and perspectives

In this thesis manuscript, our synthetic efforts toward plakortolide family natural products were described. In total, two different synthetic approaches: with 6-*endo*-tet cyclization of epoxy hydroperoxide (four retrosyntheses) and intramolecular Michael addition of hydroperoxide (one retrosynthesis) as a key step were studied.

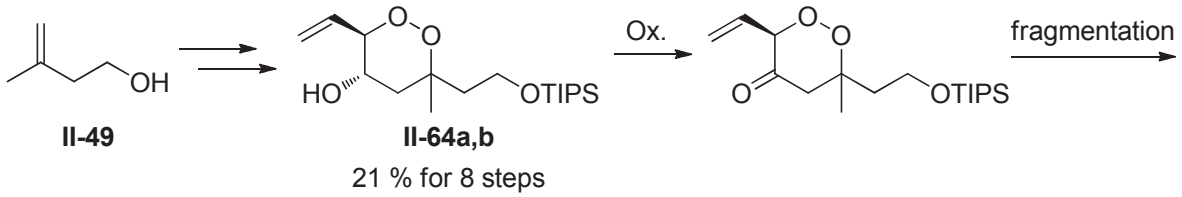
Our original synthetic plan included intermediate synthesis of ether dienol **II-9a** by reduction of propargyl alcohol **II-15a**. All attempts to perform this transformation by aluminium hydrides were unsuccessful. Finally, the reduction of alkynol was achieved in moderate yield by $CrCl_2$ in acidic DMF/H_2O mixture. Incomplete conversion and long reaction time of above mentioned transformation incited us to study the reduction of more sterically hindered and potentially more stable toward electrophilic aluminium species dienol ether **II-21**. Treatment of the latter with Red-Al or LAH led, once again, exclusively to decomposition of the starting material. Other approaches were stopped at the coupling stage (ene or carboindation reactions) because of low yields.



Studies on double epoxide opening of **II-26** with hydrogen peroxide, which was performed in the second retrosynthetic approach, showed that intramolecular nucleophilic attack of the second epoxide is faster than that involving external hydroperoxide nucleophile thus leading to hydroperoxides **II-36a,b** as exclusive products.



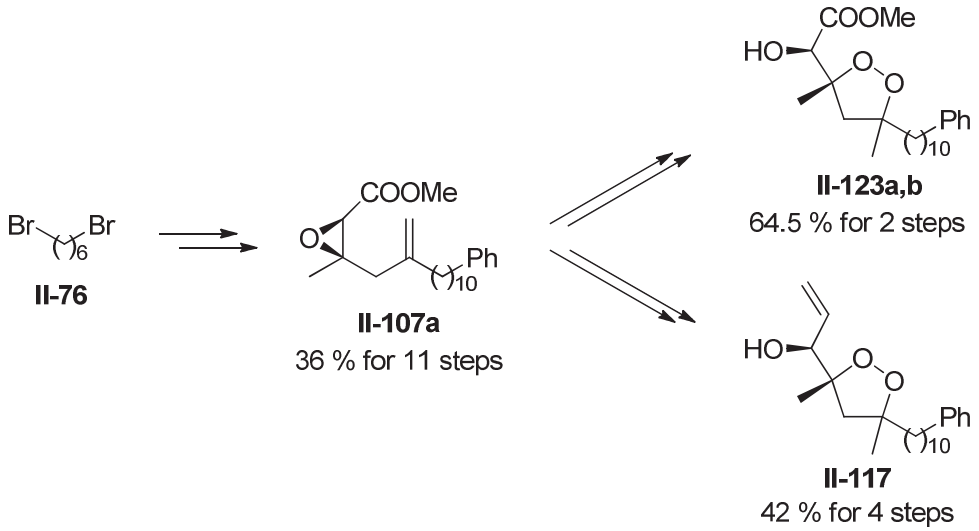
Having changed our original retrosynthetic approach, we succeeded in the synthesis of intermediate 1,2-dioxane **II-64a,b** thus proving the viability of our strategy for the synthesis of peroxidic anti-Baldwin products. All attempts to perform the oxidation of **II-64a,b** into ketone were unsuccessful due to fragmentation of the latter during the reaction.



II-49 **II-64a,b**

21 % for 8 steps

In the fourth approach ester **II-107a** was synthesized in 36 % overall yield for 11 steps. During this synthesis, a new method for chemoselective methylenation of keto group in the presence of ester function by Nysted reagent/Ti(O*i*Pr)$_2$Cl$_2$ mixture was developed. All attempts to perform the cyclization of hydroperoxides derived from **II-107a** in 6-*endo* mode were unsuccessful and in all cases, in sharp contrast to its *trans* analog, exclusively 1,2-dioxolanes were obtained. One of them is structurally related to natural andavadoic acid and in perspective could be transformed into the latter by radical reductive dehydroxylation reaction.



II-76 **II-107a**

36 % for 11 steps

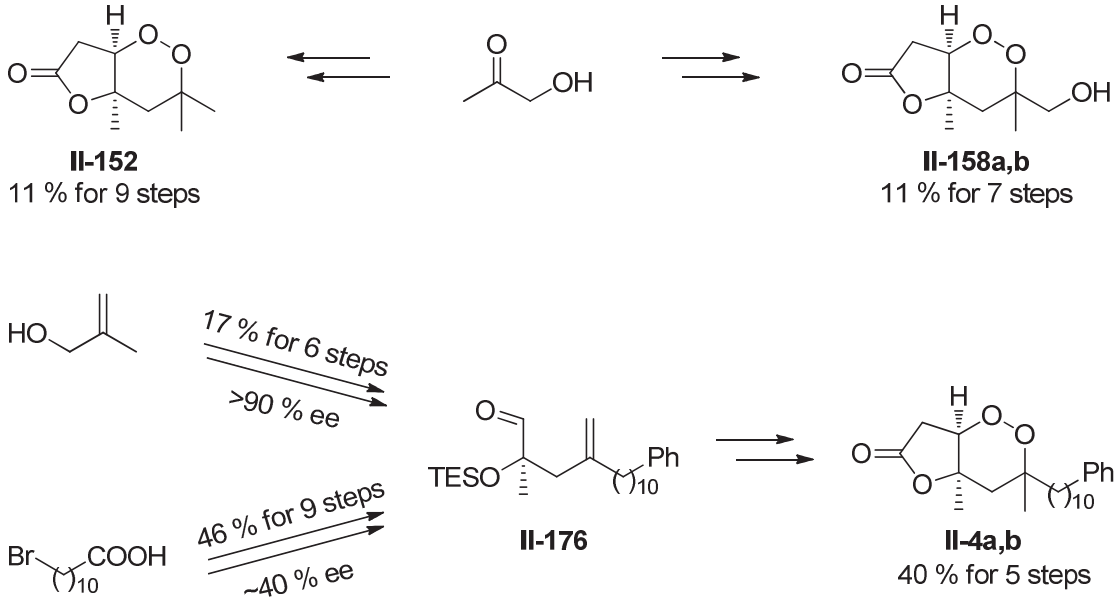
II-123a,b

64.5 % for 2 steps

II-117

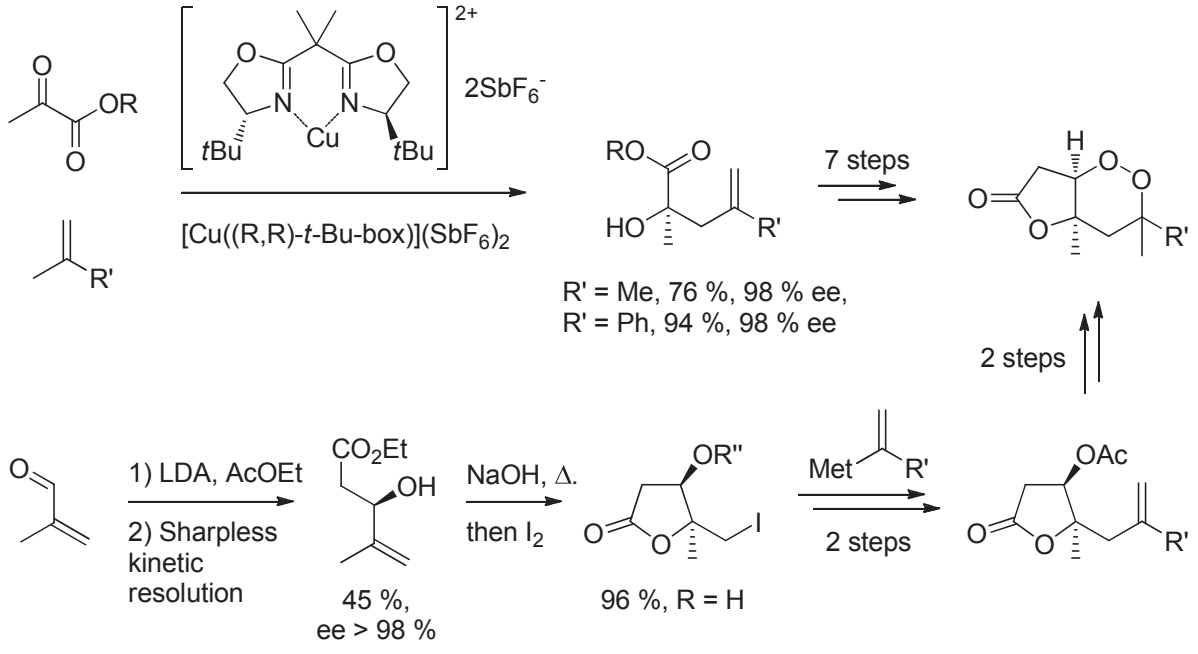
42 % for 4 steps

Finally, plakortolides E and I, *seco*-plakortolide E and a few simplest analogs were synthesized by intramolecular Michael addition of the hydroperoxide to conjugated double bond of butenolide moiety. Present synthetic route to plakortolides E and I include 11 steps 7 purifications and gave the products in 3.44 % yield of each. The structure of plakortolide E and absolute stereochemistry of both enantiomers of plakortolide I were revised.



A few improvements in the synthetic sequence toward plakortolides synthesis were imagined. The purpose of the first one is to replace the multistep synthesis of **II-188** by one/two-step synthesis with enantioselective ene reaction between pyruvate and 1,1-disubstituted ethylene catalyzed by Cu(II)-box complex as a key step. By applying this modification, plakortolides I and E could be prepared in 9 steps.

The second one includes enantioselective three step synthesis of (4*R*,5*S*)-4-hydroxy-5-(iodomethyl)-5-methyldihydrofuran-2(3H)-one followed by acylation and cross-coupling reaction that led to intermediate which could be transformed into plakortolide type products in two steps. If this approach will work, the overall sequence toward plakortolides would be shortened to 7 steps.



III.Experimental

III.1. General indications

Organic peroxides are potentially hazardous compounds and must be handled with great care: avoid direct exposure to strong heat or light, mechanical shock, oxidizable organic materials, or transition-metal ions. A safety shield should be used for all reactions involving large quantities of organic peroxides or H_2O_2.

REAGENTS AND SOLVENTS:

All reactions were performed under an inert atmosphere using dry solvents in anhydrous conditions, unless otherwise stated. Solvents or reagents were purchased from commercial sources and solvents were dried as follows:

- THF: distilled from sodium/benzophenone under atmosphere of the dry nitrogen;
- Et_2O: distilled from sodium/benzophenone under atmosphere of the dry nitrogen or filtered through neutral alumina;[244]
- CH_2Cl_2: distilled from CaH_2 under atmosphere of the dry nitrogen;
- DCE $(CH_2Cl)_2$: distilled from CaH_2 under atmosphere of the dry nitrogen;
- Acetonitrile: distilled from CaH_2 under atmosphere of the dry nitrogen;
- Pyridine: distilled from CaH_2 under atmosphere of the dry nitrogen;
- Et_3N: distilled from Na under atmosphere of the dry nitrogen;
- 2,6-Lutidine: distilled from CaH_2 under atmosphere of the dry nitrogen;
- Acetone: filtered through neutral alumina;
- Toluene: distilled from sodium/benzophenone under atmosphere of the dry nitrogen or filtered through neutral alumina;
- DMSO: distilled from CaH_2 under atmosphere of the dry nitrogen;
- MeOH: distilled from CaH_2 under atmosphere of the dry nitrogen;
- EtOH: distilled from CaH_2 under atmosphere of the dry nitrogen;
- Pentane: filtered through neutral alumina.

CHROMATOGRAPHY:

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates. Spots were visualized using one or more of the following techniques: (a) UV illumination; (b) permanganate or anisaldehyde stain. Preparative thin-layer chromatography (PTLC) was performed on Silicycle plates (F-254, 1000 microns). Flash chromatography was performed on silica gel (230–400 mesh) from Macherey Nagel with such an eluent that R_f of the product was between 0.2 and 0.4.

[α], IR, MS:

[α] were measured on Perkin Elmer 343 apparatus at the sodium D line (598 nm). Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrometer and are reported in wave numbers (cm^{-1}). Mass spectrometry analyses were conducted using a Thermofinigan- MAT 95 XL instrument. Ionization types are described by the abbreviations CI = chemical ionization, ESI = electro-spray ionization, IE = ionization by electrons beam.

NMR:

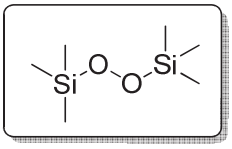
NMR spectra were recorded on Bruker AC 300, AM 300, AM 400 and AV500 instruments. Multiplicity is described by the abbreviations b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts are given in ppm. ^1H NMR spectra were referenced to the residual solvents peaks at δ = 7.26 ($CDCl_3$), 7.15 (C_6H_6), 2.50 (DMSO d_6), 3.31 (CD_3OD), 5.32 (CD_2Cl_2). ^{13}C NMR spectra were referenced to the solvent peak at δ = 77.16 ($CDCl_3$), 53.80 (CD_2Cl_2), 49.00 (CD_3OD).

No-D NMR spectroscopy[219]:

No-D NMR spectroscopy was used for in situ monitoring of reaction mixtures, when it was not possible to do it by TLC and as a quick and reliable method for determining the concentration of organometallic compounds.

No sample preparation is needed for No-D NMR spectroscopy of the reaction mixtures. Samples for determining the concentration of organometallic reagents were prepared as follows: 1,5- cyclooctadiene (COD, ca. 0.1 mL) was added to a weighted 5 mm NMR tube, and the mass of the standard was recorded. A precise volume of the anion solution (0.6 mL) was added; the tube was capped and agitated to homogenize the solution. Values used for all spectra here were at = 20 s, d1 = 20 s, tpwr = 46 and pw = 7.5 μs (resulting in a ca. 22.5° pulse), and nt = 2-4. After data acquisition, the integral value for the appropriate group (for RCH_2Met at δ < 0 ppm) was compared to those of COD.

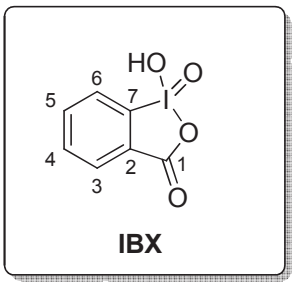
III.2. Experimental



Peroxybis(trimethylsilane).[165] Bis-trimethylsilyl urea (10.2 g, 50 mmol) and finely powdered urea-hydrogen peroxide complex (4.7 g, 50 mmol) were suspended in CH_2Cl_2 (30 mL) and heated at reflux for 12 h with stirring under dry nitrogen. Volatiles were distilled into a receiver cooled to -78 °C by reducing gradually the pressure and reaching the temperature of the oil bath to 80 °C. The solvent from distillate was distilled off at atmospheric pressure and the residue was distilled at 30 mm pressure and 35-40 °C through a vigreux column to give pure product (3.99 g, 45 %) as a colorless liquid.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.19 (s, 18 H).

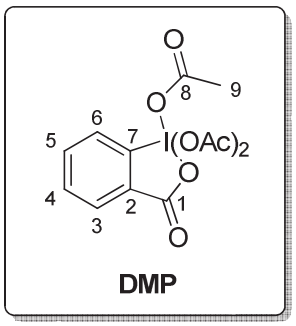
^{13}C NMR (75 MHz, $CDCl_3$): δ = -1.2 (6 C).



IBX

2-Iodoxybenzoic acid (IBX).[245] 2-Iodobenzoic acid (25 g, 100 mmol) was added in once to a solution of oxone (93 g, 151 mol, 1.5 equiv) in deionized water (325 mL, 0.45 M). The reaction mixture was warmed to 70-73 °C over 20 min and mechanically stirred at this temperature for 3 h. The aspect of the mixture varies consistently during the reaction. The initial thick slurry coating the walls of the flask eventually becomes a finely dispersed, easy to stir suspension of a small amount of solid that sedimented easily upon stopping the stirring. The suspension was then cooled to 5 °C and left at this temperature for 1.5 h with slow stirring. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with water (6x50 mL) and acetone (2x50 mL). The white, crystalline solid was dried at room temperature for 16 h and weighed 22.55 g (80 %).

^{1}H NMR (300 MHz, DMSO d_6): δ = 7.84 (t, *J* = 7.2 Hz, 1H), 7.98 – 8.09 (m, 2H), 8.15 (d, *J* = 7.9 Hz, 1H).

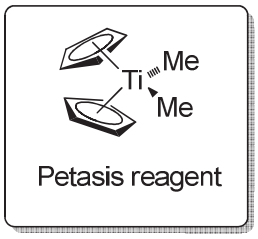


DMP

Dess-Martin periodinane (DMP).[246] A 50 mL round-bottomed flask was charged with solid IBX (3.9 g, 14 mmol), glacial acetic acid (7 ml), and acetic anhydride (14 ml). The flask was flushed with dry nitrogen and maintained under nitrogen atmosphere. The mixture was heated to 85 ^{O}C over 30 min, and kept at this temperature until all the solid was dissolved to afford a colorless to clear yellow solution. Heating and stirring was discontinued and the reaction mixture was allowed to cool slowly to room temperature in the oil bath for 24 h. The resulting crystalline solid was isolated by careful vacuum filtration under argon atmosphere, followed by washing it with anhydrous ether (3x4 mL). Residual solvent was removed under vacuum affording 3.8 g (64 %) of DMP.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 6H, H_9), 2.33 (s, 3H, H_9), 7.90 (td, *J* = 7.4 Hz, 0.8 Hz, 1H, H_{Ar}), 8.07 (m, 1H, H_{Ar}), 8.30 (m, 2H, H_{Ar}).

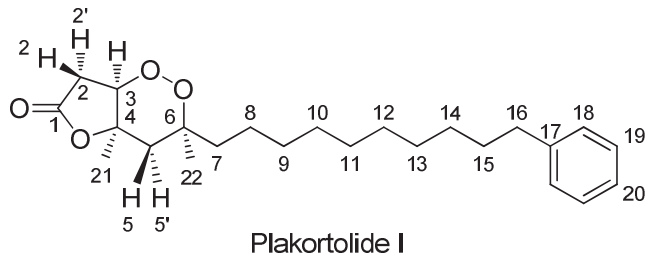
^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4 (C_9), 20.6 (C_9), 126.1, 126.6, 131.9, 133.9, 135.8, 142.4, 166.1, 174.1, 175.9.



Petasis reagent

Petasis reagent (Cp_2TiMe_2). (Modified method of Payack et al.[247]) MeLi (1.4 M in Et_2O, 4.2 mL, 5.88 mmol, 2.2 equiv) was added dropwise to cooled (0 °C) suspension of titanocene dichloride (0.73 g, 2.94 mmol, 1 equiv) in Et_2O (20 mL). When the addition was finished, the reaction mixture was heated to rt and stirred for 2 h. Then it was washed with an aqueous solution of NH_4Cl (6 %), water and brine sequentially. The organic phase was dried with Na_2SO_4 and evaporated at ambient temperature to give pure Cp_2TiMe_2 (0.53 g, 87 %) as a dark-red solid which was dissolved in THF or toluene at sight (pure Cp_2TiMe_2 is unstable). Solutions of Petasis reagent were stored at ≤ 4 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.15 (s, 6H, 2Me), 6.06 (s, 10H, 2Cp).



Plakortolide I

II-4a

Plakortolide I (II-4a). *Method A.* To a cooled (0 °C) solution of (2*R*,3*R*)-2-methyl-2-(2-methyl-12-phenyl-2-((triethylsilyl)peroxy)dodecyl)-5-oxotetrahydrofuran-3-yl acetate (**II-193**, 19 mg, 33.8 μmol, 1 equiv) in dry THF (0.5 mL) was added DBU (5.1 mg, 55.8 μmol, 1 equiv). The reaction mixture was stirred for 4 h at 0 °C, then for 4 h at rt and quenched with water. The resulting solution was extracted with Et_2O (4x2 mL). The combined extracts were dried with Na_2SO_4 and evaporated. Flash chromatography (Et_2O/petroleum ether = 3:2) of the residue gave **II-4a** (3.8 mg, 29 %), **II-4b** (3.8 mg, 29 %), and the epoxide **II-194** (2 mg, 15 %) as colorless oils.

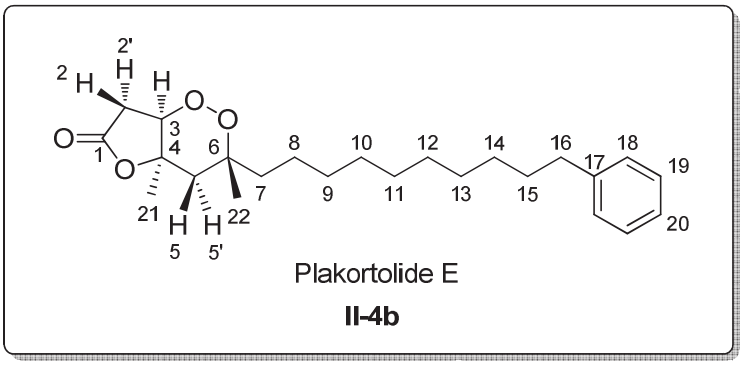
Method B. To a cooled (0 °C) solution of (2*R*,3*R*)-2-methyl-2-(2-methyl-12-phenyl-2-((triethylsilyl)peroxy)dodecyl)-5-oxotetrahydrofuran-3-yl acetate (**II-193**, 64 mg, 114 μmol, 1 equiv) in dry THF (1.3 mL) was added DBU (21 mg, 139 μmol, 1.2 equiv) and the resulting mixture was stirred for 3 h at 0 °C. TFE (1.3 mL) and TBAF (1 M in THF, 139 μL, 139 μmol, 1.2 equiv) were added and the stirring was continued for 3 h at 0 °C. Then it was warmed to rt, stirred for 15 min, quenched with water (2 mL) and extracted with Et_2O (5x3 mL). The combined extracts were dried with Na_2SO_4 and evaporated. The crude mixture was purified by preparative TLC (CH_2Cl_2/pentane = 3:1, 2 elutions) to give **II-4a** (15.2 mg, 34 %) and **II-4b** (16.5 mg, 37 %) as colorless oils.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3H, H_{22}), 1.26 (m, 14H), 1.38 (s, 3H, H_{21}), 1.52 – 1.76 (m, 4H), 1.65 (d, *J* = 15.0 Hz, 1H, $H_{5'}$), 2.27 (d, *J* = 15.0 Hz, 1H, H_5), 2.56 (d, *J* = 18.5 Hz, 1H, H_2), 2.60 (t, *J* = 7.8 Hz, 2H, H_{16}), 2.90 (dd, *J* = 18.5, 5.9 Hz, 1H, $H_{2'}$), 4.48 (d, *J* = 5.9 Hz, 1H, H_3), 7.15 – 7.19 (m, 3H, H_{Ar}), 7.25 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.9, 25.0 (C_{22}), 26.1 (C_{21}), 29.5 – 29.7 (5C), 30.1, 31.7 (C_{15}), 34.2 (C_2), 36.2 (C_{16}), 37.0 (C_7), 40.4 (C_5), 80.4, 81.0 (C_3), 82.7, 125.7 (C_{20}), 128.3 (2C), 128.6 (2C), 143.1 (C_{17}), 174.3 (C_1).

HRMS (ESI): calculated for $C_{24}H_{36}NaO_4$ (MNa^+) 411.2506, found 411.2514.

$[\alpha]_D^{20}$ = -9.0 (*c* 0.7, $CHCl_3$).



Plakortolide E

II-4b

Plakortolide E (II-4b). For experimental procedure see **II-4a**.

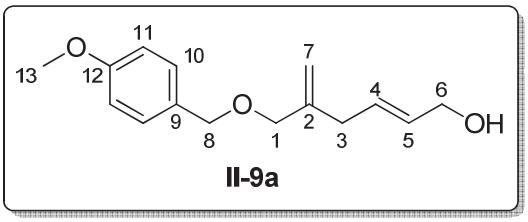
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 14H), 1.29 (s, 3H, H_{22}), 1.39 (s, 3H, H_{21}), 1.44 – 1.62 (m, 4H), 1.70 (d, *J* = 14.8 Hz, 1H, H_5), 2.17 (d, *J* = 14.8 Hz, 1H, H_5), 2.60 (t, *J* = 7.7 Hz, 2H, H_{16}), 2.62 (d, *J* = 18.3 Hz, 1H, H_2), 2.91 (dd, *J* = 18.6, 6.1 Hz, 1H, $H_{2'}$), 4.45 (d, *J* = 6.1 Hz, 1H, H_3), 7.15 – 7.18 (m, 3H, H_{Ar}), 7.25 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.6 (C_{22}), 23.2, 26.1 (C_{21}), 29.5 – 29.7 (5C), 30.2, 31.7, 34.5 (C_2), 36.1 (C_{16}), 40.7 (C_5), 41.2, 80.3, 81.3 (C_3), 82.9, 125.7 (C_{20}), 128.4 (2C), 128.5 (2C), 143.1 (C_{17}), 174.4 (C_1).

HRMS (ESI): calculated for $C_{24}H_{36}NaO_4$ (MNa^+) 411.2506, found 411.2493.

IR (neat): 3025, 2926, 2853, 1785.

$[\alpha]_D^{20}$ = +14.9 (*c* 0.76, $CHCl_3$).



II-9a

(2*E*)-5-(((4-Methoxybenzyl)oxy)methyl)hexa-2,5-dien-1-ol (II-9a). *Method A.* A solution of 5-(((4-methoxybenzyl)oxy)methyl)hex-5-en-2-yn-1-ol (**II-15a**, 0.1 g, 0.4 mmol) in THF (1 ml) was added dropwise to the suspension of LAH (46 mg, 1.2 mmol, 3 equiv) in THF (2 ml) at 0 ^oC. The reaction mixture was refluxed for 8 h, cooled to 0 ^oC, quenched with 1 M HCl (4 ml) and extracted with Et_2O (4x5 ml). The combined organic phases was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to yield **II-9a** (30 mg, 30 %) as a colorless oil.

Method B. $CrCl_2$ (270 mg, 2.1 mmol, 8 equiv) and sodium sulfate (150 mg, 1.1 mmol, 4 equiv) were dissolved in degassed water (1 mL), and solution of the 5-(((4-methoxybenzyl)oxy)methyl)hex-5-en-2-yn-1-ol (**II-15a**, 65 mg, 0.26 mmol) in degassed DMF (1 mL) was added. After, 35 % hydrochloric acid (55 mg, 0.53 mmol, 2 equiv) was added and the reaction mixture was stirred for 21 days. The solution was extracted by Et_2O (3x10 ml) dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to yield **II-9a** (40 mg, 61 %) as a colorless oil, and starting material **II-15a** (11 mg, 17 %).

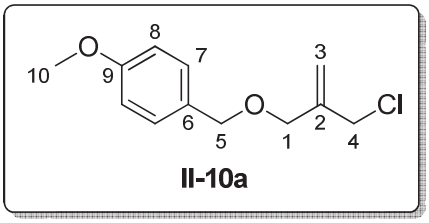
Method C. Indium powder (60 mg, 0.52 mmol, 1.2 equiv) was placed in a reaction vial under argon, followed by the addition of THF (1 mL), 1-(((2-(iodomethyl)prop-2-enyl)oxy)methyl)-4-methoxybenzene (**II-23**, 276 mg, 0.87 mmol, 2 equiv) and propargyl alcohol (24 mg, 0.43 mmol) at rt The reaction mixture was stirred at r.t. for 30 h, quenched with a few drops of diluted hydrochloric acid (1 M). The resulting mixture was stirred for 10 min, and extracted with Et_2O (3x3 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O: petroleum ether = 1:1) to yield **II-9a** (20 mg, 19 %) as a colorless oil (product of dimerisation of allyl iodide **II-23** was also detected).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (br s, 1H, OH), 2.82 (d, J = 4.5 Hz, 2H, H_3), 3.80 (s, 3H, H_{13}), 3.93 (s, 2H, H_1), 4.08 (d, J = 4.5 Hz, 2H, H_6), 4.42 (s, 2H, H_8), 4.95 (s, 1H, H_7), 5.08 (s, 1H, H_7), 5.69 (m, 2H, H_4 + H_5), 6.88 (d, J = 8.7 Hz, 2H, H_{11}), 7.26 (d, J = 8.7 Hz, 2H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2 (C_3), 55.4 (C_{13}), 63.6 (C_6), 71.7 (C_1), 72.6 (C_8), 113.0 (C_7), 113.9 (2C, C_{11}), 129.5 (2C, C_{10}), 129.8 (C_5), 130.5 (C_2), 131.2 (C_4), 144.7 (C_9), 159.3 (C_{12}).

IR (neat): 1514, 1586, 1614, 1651, 2838, 2858, 2909, 2933, 3000, 3396.

HRMS (ESI): calculated for $C_{15}H_{20}NaO_3$ (MNa^+) 271.1305, found 271.1312.



II-10a

1-(((2-(Chloromethyl)allyl)oxy)methyl)-4-methoxybenzene (II-10a). *Method A.*[141] To the solution of 1-methoxy-4-(((2-methylallyl)oxy)methyl)benzene (**II-12**, 0.5 g, 2.6 mmol) in CH_2Cl_2 (25 mL) were added $LiClO_4$ (55 mg, 0.52 mmol) and pyridine (0.25 g, 0.26 mL, 3.1 mmol). The mixture was cooled to -78 ^oC and sulfuryl chloride (0.42 g, 0.25 mL, 3.1 mmol) was added. Stirring and cooling was continued for 10 min and then the temperature was allowed to rise to 0 ^oC. The mixture was poured into cold water containing $NaHCO_3$, extracted with petroleum ether and extracts were dried and concentrated to give crude **II-10a** (30 % by NMR) as a brown oil.

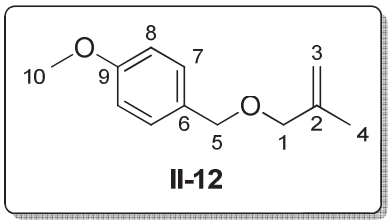
Method B. 1-Methoxy-4-(((2-methylallyl)oxy)methyl)benzene (**II-12**, 0.5 g, 2.6 mmol) in CH_2Cl_2 (13 mL) was added to a vigorously stirred solution of cerium chloride heptahydrate (1.07 g 2.8 mmol) in water (13 mL), cooled externally with an ice bath. To the resulting mixture was added a solution of sodium hypochlorite (4.8 ml, 4 eq) during 12 min and the reaction mixture was stirred at 0 ^oC for 30 min. The reaction was quenched by slow addition of saturated aqueous sodium sulfite. The layers were separated and the aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (petroleum ether/Et_2O = 14:1) to give pure **II-10a** (0.2 g, 34 %) as a colorless oil.

Method C. 1-methoxy-4-(((2-methylallyl)oxy)methyl)benzene (**II-12**, 0.5 g, 2.6 mmol) in CH_2Cl_2 (13 mL) was added to a vigorously stirred solution of indium chloride (0.63 g, 2.8 mmol) in water (13 mL), cooled externally with an ice bath. To the resulting mixture was added solution of sodium hypochlorite (4.8 ml, 4 eq) during 2 min and the reaction mixture was stirred at 0 ^oC for 12 min. The reaction was quenched by the addition of saturated aqueous sodium sulfite. The layers were separated and the aqueous layer was extracted with dichloromethane (3*20 mL). The combined organic layers was dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (petroleum ether/Et_2O = 14:1) to give pure **II-10a** (0.4 g, 68 %) as a colorless oil.

Method D.[142] Sodium hydride (60 % in mineral oil, 2.45 g, 61.3 mmol) was washed with hexane (4x80 ml). After evaporation of residual hexane, THF (45 mL) was added. This suspension was treated dropwise with a solution of 4-methoxybenzyl alcohol (6.5 g, 47.1 mmol) in anhydrous THF (10 mL). Anhydrous DMF (12 mL) was added and the reaction mixture was stirred at r.t. for 30 min, heated at reflux for 1 h, cooled to r.t., and poured into a pressure-equalizing dropping funnel. The reaction flask was rinsed with anhydrous THF (5 mL). This mixture was added dropwise over 60 min to a stirred solution of 3-chloro-2-(chloromethyl)-1-propene (7.66 g, 61.3 mmol) in anhydrous THF (55 mL). The dropping funnel was rinsed with dry THF (5 mL). The reaction mixture was stirred at r.t. overnight and then poured into a separatory funnel containing Et_2O (35 mL), hexanes (35 mL), brine (70 mL), and H_2O (70 mL). The aqueous layer was extracted with Et_2O/hexanes = 1:1. The combined organic extracts were washed with water, dried, concentrated under reduced pressure and purified by flash chromatography (EtOAc/petroleum ether = 1:9) to afford 6.8 g (64 %) of the monoether **II-10a** as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, H_{10}), 4.09 (s, 2H, H_4), 4.13 (s, 2H, H_1), 4.46 (s, 2H, H_5), 5.26 (br s, 1H, H_3), 5.32 (br s, 1H, H_3), 6.89 (d, J = 8.7 Hz, 2H, H_8), 7.28 (d, J = 8.6 Hz, 2H, H_7).

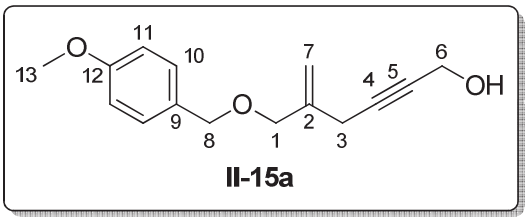
^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.4 (C_3), 55.4 (C_{10}), 70.1 (C_1), 72.2 (C_5), 113.9 (2C, C_8), 116.9 (C_4), 129.5 (2C, C_7), 130.2 (C_6), 142.2 (C_2), 159.4 (C_9).



II-12

1-Methoxy-4-(((2-methylallyl)oxy)methyl)benzene (II-12).[141] To a solution of *p*-methoxybenzyl alcohol (5.42 mL, 43.5 mmol, 1 equiv) in DMF (45 mL) at 0 ^oC was added sodium hydride (60 % in mineral oil) (2.61 g, 65.2 mmol, 1.5 equiv) in two portions. After 2 h, 1-chloro-2-methyl-2-propene (5.1 mL, 52.2 mmol, 1.2 equiv) was added via syringe. The reaction mixture was allowed to slowly warm to r.t. After 20 h the reaction mixture was poured onto Et_2O (120 ml) and water (120 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x40 ml). The combined organic layers were washed with brine (100 ml), dried (Na_2SO_4), filtered and concentrated under vacuum. The crude material was purified by distillation at reduced pressure (0.1 mmHg, 62-67 ^OC) to provide 8.04 g (96 %) of pure **II-12** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (s, 3H, H_4), 3.81 (s, 3H, H_{10}), 3.92 (s, 2H, H_1), 4.44 (s, 2H, H_5), 4.93 (s, 1H, H_3), 5.01 (s, 1H, H_3), 6.89 (d, J = 8.4 Hz, 2H, H_8), 7.29 (d, J = 8.4 Hz, 2H, H_7).



II-15a

5-(((4-Methoxybenzyl)oxy)methyl)hex-5-en-2-yn-1-ol (II-15a). *Method A.* To a stirred solution of propargyl alcohol (200 mg, 3.57 mmol, 1.5 equiv) in dry DMF (2 mL) were added under argon K_2CO_3 (660 mg, 4.76 mmol, 2 equiv), tetrabutylammonium bromide (115 mg, 0.36 mmol, 0.15 equiv) and CuI (23 mg, 0.12 mmol, 0.05 equiv) at room temperature. After 10 min, a solution of 1-(((2-(chloromethyl)allyl)oxy)methyl)-4-methoxybenzene (**II-10a**, 540 mg, 2.4 mmol) in DMF(2 mL) was added. The reaction mixture was stirred at r.t. for 36 h. Then it was poured into the water, extracted with ether (3x15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to yield **II-15a** (335 mg, 57 %) as a colorless oil.

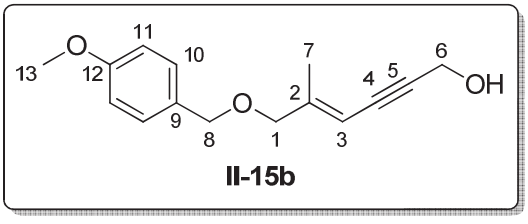
Method B. K_2CO_3 (0.18 g, 1.3 mmol, 1.5 equiv), NaI (0.13 g, 0.88 mmol), CuI (0.17 g, 0.88 mmol) were suspended in dry DMF (10 mL). Subsequently, propargyl alcohol (74 mg, 1.3 mmol, 1.5 equiv) was added at once and kept stirring for 15 min. After, 1-(((2-(chloromethyl)allyl)oxy)methyl)-4-methoxybenzene (**II-10a**, 0.2 g, 0.88 mmol) was added dropwise and the suspension was stirred at r.t. under argon atmosphere for 24 h, then quenched with saturated aqueous solution of ammonium chloride, extracted with diethyl ether (3x10 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to yield **II-15a** (135 mg, 62 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 (br s, 1H, OH), 3.04 (s, 2H, H_3), 3.80 (s, 3H, H_{13}), 3.99 (s, 2H, H_1), 4.25 (t, J = 2.1 Hz, 2H, H_6), 4.41 (s, 2H, H_8), 5.15 (m, 1H, H_7), 5.27 (d, J = 1.5 Hz, 1H, H_7), 6.88 (d, J = 8.7 Hz, 2H, H_{11}), 7.26 (d, J = 8.7 Hz, 2H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4 (C_3), 51.3 (C_6), 55.4 (C_{13}), 71.6, 72.2 (C_1, C_8), 81.1, 82.7 (C_4, C_5), 113.9 (2C, C_{11}), 114.1 (C_7), 129.5 (2C, C_{10}), 130.2 (C_9), 140.9 (C_2), 159.3 (C_{12}).

IR (neat): 1515, 1586, 1614, 1657, 2225, 2286, 2839, 2860, 2915, 2932, 2999, 3406.

HRMS (ESI): calculated for $C_{15}H_{18}NaO_3$ (MNa^+) 269.1148, found 269.1155.



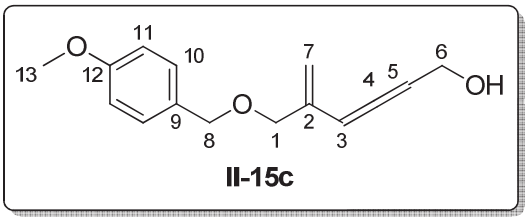
II-15b

6-((4-Methoxybenzyl)oxy)-5-methylhex-4-en-2-yn-1-ol (II-15b). To a stirred solution of propargyl alcohol (230 mg, 4.17 mmol, 1.5 equiv) in dry DMF (2 mL) under argon were added Cs_2CO_3 (1.81 g, 5.56 mmol, 2 equiv), tetrabutylammonium bromide (134 mg, 0.42 mmol, 0.15 equiv) and CuI (26 mg, 0.14 mmol, 0.05 equiv) at room temperature. After 10 min, solution of 1-(((2-(chloromethyl)allyl)oxy)methyl)-4-methoxybenzene (**II-10a**, 630 mg, 2.78 mmol) in DMF (3 mL) was added. The reaction mixture was stirred at rt for 24 h. Then it was poured into water (10 mL), extracted with ether (3x15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to give **II-15b** (145 mg, 21 %) and **II-15c** (135 mg, 20 %) as slightly yellow oils.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (br s, 1H, OH), 1.89 (s, 3H, H_7), 3.81 (s, 3H, H_{13}), 3.95 (s, 2H, H_1), 4.41 (m, 4H, H_6 + H_8), 5.60 (br s, 1H, H_3), 6.88 (d, J = 8.7 Hz, 2H, H_{11}), 7.26 (d, J = 8.7 Hz, 2H, H_{10}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9 (C_7), 51.9 (C_6), 55.4 (C_{13}), 71.9, 73.5 (C_1, C_8), 83.0, 91.3 (C_4, C_5), 105.7 (C_7), 114.0 (2C, C_{11}), 129.5 (2C, C_{10}), 130.2 (C_9), 148.5 (C_2), 159.4 (C_{12}).

MS (CI): m/z 121, 229 (MH^+-H_2O), 247 (MH^+), 349, 367.

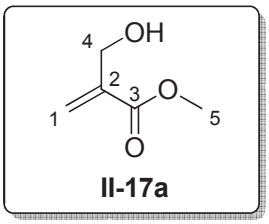


II-15c

5-(((4-Methoxybenzyl)oxy)methyl)hexa-2,3,5-trien-1-ol (II-15c). See experimental procedure for **II-15b**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (br s, 1H, OH), 3.80 (s, 3H, H_{13}), 3.93 (d, J = 12.0 Hz, 1H, H_1), 4.09 (dd, J = 3.0, 5.3 Hz, 2H, H_6), 4.20 (d, J = 12.0 Hz, H, H_1), 4.42 (dd, J = 11.4, 11.4 Hz, 2H, H_8), 5.14 (br s, 1H, H_7), 5.18 (br s, 1H, H_7), 5.61 (dt, J = 5.7, 5.7 Hz, 1H, H_5), 6.04 (dt, J = 3.0, 6.0 Hz, 1H, H_3), 6.88 (d, J = 8.4 Hz, 2H, H_{11}), 7.26 (d, J = 8.4 Hz, 2H, H_{10}).

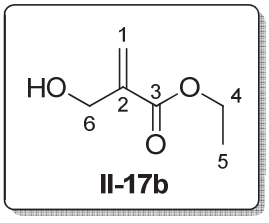
^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (C_{13}), 60.1 (C_6), 70.7, 71.6 (C_1, C_8), 95.3, 96.8 (C_3, C_5), 114.0 (2C, C_{11}), 116.3 (C_7), 129.8 (2C, C_{10}), 132.6 (C_9), 139.1 (C_2), 159.5 (C_{12}), 205.3 (C_4).



II-17a

Methyl 2-(hydroxymethyl)acrylate (II-17a).[153] A solution of formaldehyde (37 % in water, 1.62 g, 20 mmol, 1 equiv) and methyl acrylate (5.4 mL, 60 mmol, 3 equiv) in 1,4-dioxane-water (1:1, v/v, 200 mL) was stirred at room temperature in the presence of DABCO (2.24 g, 20 mmol, 1 equiv), and the reaction progress was monitored by TLC. Upon completion (20 h), NaCl (25 g) was added and the resulting mixture was extracted with diethyl ether (3x100 mL). The organic phase was washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude **II-17a** (0.52 g, 22 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.5 (br s, 1H, OH), 3.78 (s, 3H, H_5), 4.32 (m, 2H, H_4), 5.84 (m, 1H, H_1), 6.25 (d, J = 1.2 Hz, 1H, H_1).

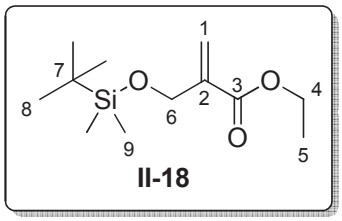


II-17b

Ethyl 2-(hydroxymethyl)acrylate (II-17b).[154] Round-bottomed flask was charged with ethyl acrylate (10g, 0.1 mole, 4 equiv), 98 % by weight of paraformaldehyde (0.77g, 2.5 mmol), an aqueous solution of 30 % by weight of trimethylamine (4.9 g, 2.5 mmol) and a *p*-methoxy phenol (6 mg, 0.05 mmol, 0.02 equiv). The reaction mixture was stirred at 50 ^{O}C for 12 h. Organic phase was separated, and the aqueous phase was extracted with Et_2O (2x10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was fractionally distilled (b.p. 65–82 °C/1 Torr) to afford pure **II-17b** (3.14 g, 97 %) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3H, H_5), 2.83 (s, 1H, OH), 4.22 (q, J =7.2 Hz, 2H, H_4), 4.28 (dd, J = 1.2, 1.2 Hz, 2H, H_6), 5.80 (dt, J = 1.4, 1.4 Hz, 1H, H_1), 6.24 (d, J = 1.2 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.12 (C_5), 60.85 (C_4), 62.52 (C_6), 125.55 (C_1), 139.50 (C_2), 166.33 (C_3).

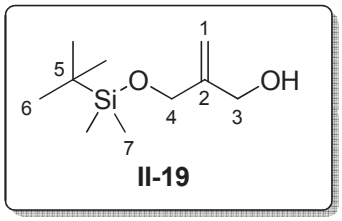


II-18

Ethyl 2-(((*tert*-butyl(dimethyl)silyl)oxy)methyl)acrylate (II-17b).[248] To a stirred solution of ethyl 2-(hydroxymethyl)acrylate (**II-17b**, 500 mg, 3.8 mmol) in DCM (10 mL) were added triethylamine (600 mg, 4.6 mmol, 1.2 equiv) and DMAP (47 mg, 3.8 mmol, 0.1 equiv) followed by dropwise addition of a solution of TBSCl (1.47 ml, 50 % in toluene, 4.2 mmol, 1.1 equiv) at 0 ^{O}C. The reaction mixture was allowed to reach room temperature and was stirred for 15 h. The resulting slurry was filtered and washed with cold 1 N aqueous HCl (4 mL), saturated aqueous sodium bicarbonate (4 mL), and brine (4 mL). Drying ($MgSO_4$) and concentration gave crude **II-17b** (929 mg, 99 %) as a colorless oil. The material was used in the next step without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6H, H_9), 0.92 (s, 9H, H_8), 1.30 (t, J = 7.1 Hz, 3H, H_5), 4.21 (q, J =7.1 Hz, 2H, H_4), 4.37 (dd, J = 2.1, 2.1 Hz, 2H, H_6), 5.90 (dt, J = 2.1, 2.1 Hz, 1H, H_1), 6.25 (dt, J = 2.1, 2.1 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.5 (C_9), 14.2 (C_5), 18.3 (C_7), 25.9 (C_8), 60.5, 61.5 (C_4, C_6), 123.6 (C_1), 139.9 (C_2), 165.9 (C_3).

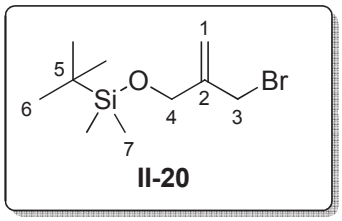


II-19

2-(((*tert*-Butyl(dimethyl)silyl)oxy)methyl)prop-2-en-1-ol (II-17b).[155] To a solution of crude ethyl 2-(((*tert*-butyl(dimethyl)silyl)oxy)methyl)acrylate (**II-18**, 930 mg, 3.8 mmol, 1.0 equiv) in THF (9 mL) cooled to -78 °C was added dropwise DIBAL (1 M, 8.39 mL, 8.4 mmol, 2.2 equiv) over 15 min. The resulting solution was stirred at -78 °C until complete consumption of the starting material by TLC analysis (4:1 hexanes-EtOAc), then excess of DIBAL was quenched with dry EtOAc (0.2 mL). The resulting solution was stirred for 10 min at -78 °C, then warmed to 0 °C and stirred for 30 min. A solution of saturated Rochelle's salt (2 mL) was then added slowly with vigorous stirring. The cooling bath was removed and the reaction mixture was vigorously stirred until two homogeneous layers appeared. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 7 mL), the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **II-17b** as a cloudy colorless oil (732 mg, 95 %). The crude material was used in the next reaction without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6H, H_7), 0.90 (s, 9H, H_6), 2.08 (br s, 1H, OH), 4.16 (s, 2H), 4.23 (s, 2H, H_3, H_4), 5.07 (s, 1H, H_1), 5.09 (s, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.5 (C_7), 18.2 (C_5), 25.8 (C_6), 64.3, 64.9 (C_3, C_4), 110.8 (C_1), 147.5 (C_2).

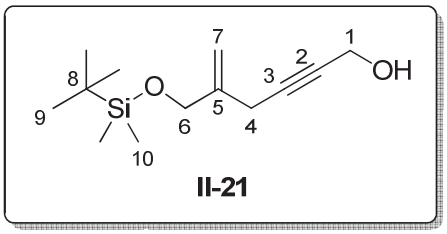


II-20

((2-(Bromomethyl)prop-2-enyl)oxy)(*tert*-butyl)dimethylsilane (II-20).[155] To a solution of triphenylphosphine (1.04 g, 4.0 mmol, 1.1 equiv) in DCM (10 mL) was added dropwise at 0 ^{O}C a solution of bromine (0.64 g, 4.0 mmol, 1.1 equiv) in DCM (1.5 mL). The reaction mixture was stirred until a colorless precipitate indicated the formation of the desired phosphonium salt, which was then added slowly at 0 ^{O}C to a solution of imidazole (0.3 g, 4.35 mmol, 1.2 equiv) and 2-(((*tert*-butyl(dimethyl)silyl)oxy)methyl)prop-2-en-1-ol (**II-19**, 732 mg, 3.6 mmol, 1.0 equiv) in DCM (20 mL). After stirring for 30 min maintaining the temperature at 0 ^{O}C, the reaction mixture was poured into an ice–water mixture and extracted with Et_2O (4x7 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual slurry was re-dissolved in a small amount of DCM and added dropwise into hexane giving rise to a suspension, which was filtered and the remaining residue (Ph_3PO) was washed several times with hexane. The organic phase was evaporated and residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:20) to afford pure **II-20** (673 mg, 70 %), as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 6H, H_7), 0.92 (s, 9H, H_6), 4.01 (s, 2H, H_3), 4.27 (t, J = 1.4 Hz, 2H, H_4), 5.25 (m, 2H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.4 (C_7), 18.3 (C_5), 25.9 (C_6), 32.7 (C_3), 63.5 (C_4), 114.7 (C_1), 144.8 (C_2).



II-21

5-(((*tert*-Butyl(dimethyl)silyl)oxy)methyl)hex-5-en-2-yn-1-ol (II-21). K_2CO_3 (300 mg, 2.2 mmol, 1.5 equiv), NaI (215 mg, 1.4 mmol) and CuI (270 mg, 1.4 mmol) were suspended in dry DMF (10 mL). Subsequently propargyl alcohol (120 mg, 2.1 mmol, 1.5

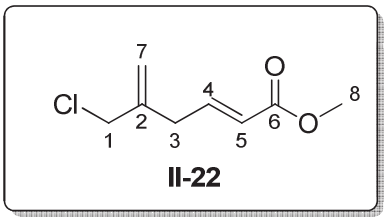
equiv) was added at once and kept stirring for 15 min. Then a solution of ((2-(bromomethyl)prop-2-enyl)oxy)(tert-butyl)dimethylsilane (**II-20**, 380 mg, 1.4 mmol) in DMF (1 ml) was added dropwise and the suspension was stirred at r.t. under argon atmosphere for 20 h, then quenched with saturated aqueous solution of NH_4Cl, extracted with Et_2O (3x10 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to yield **II-21** (254 mg, 74 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6H, H_{10}), 0.89 (s, 9H, H_9), 2.35 (br s, 1H, OH), 2.97 (s, 2H, H_4), 4.11 (s, 2H, H_6), 4.25 (t, J = 2.3 Hz, 2H, H_1), 5.10 (d, J = 1.5 Hz, 1H, H_7), 5.12 (d, J = 1.5 Hz, 1H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.3 (C_{10}), 18.4 (C_8), 22.9 (C_4), 26.0 (C_9), 51.3 (C_1), 65.6 (C_6), 80.9, 82.8 (C_2, C_3), 111.0 (C_7), 143.4 (C_5).

IR (neat): 1660, 2227, 2288, 2858, 2885, 2930, 2955, 3339.

HRMS (CI): calculated for $C_{13}H_{24}O_2Si$ (MH^+) 241.1624, found 241.1624.

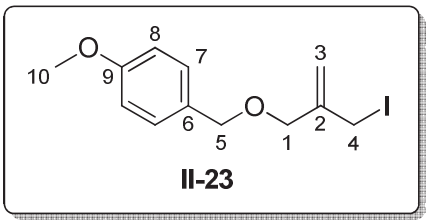


II-22

(*E*)-Methyl 5-(chloromethyl)hexa-2,5-dienoate (II-22). To a vigorously stirred solution of 1-chloro-2-methyl-2-propene (0.22 mL, 2.2 mmol) and methyl propiolate (0.18 mL, 2.2 mmol) in CH_2Cl_2 (8 mL), $EtAlCl_2$ (1 M, 2,3 mL, 2.3 mmol) was added. The reaction mixture was stirred for 5 days, quenched with saturated aqueous solution of NH_4Cl, extracted with Et_2O (4x8 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give crude **II-22** (81 mg, 21 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.04 (d, J = 7.2 Hz, 2H, H_3), 3.71 (s, 3H, H_8), 4.01 (s, 2H, H_1), 5.00 (s, 1H, H_7), 5.21 (s, 1H, H_7), 5.89 (d, J = 15.6 Hz, 1H, H_5), 6.92 (dt, J = 15.6, 7.2 Hz, 2H, H_4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.8 (C_3), 47.8 (C_1), 51.6 (C_8), 117.0 (C_7), 123.3 (C_5), 141.8 (C_2), 145.1 (C_4), 166.7 (C_6).



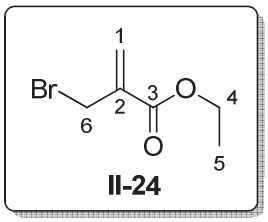
II-23

1-(((2-(Iodomethyl)prop-2-enyl)oxy)methyl)-4-methoxybenzene (II-23). To a solution of 1-(((2-(chloromethyl)allyl)oxy)methyl)-4-methoxybenzene (**II-10a**, 0.47 g, 2.07 mmol) in acetone was added sodium iodide (0.47 g, 3.11 mmol). The mixture was stirred for 24 h. Then water was added, extracted with hexane (4x10 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:12) to yield **II-23** (567 mg, 86 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, H_{10}), 3.99 (s, 2H, H_1), 4.15 (s, 2H, H_4), 4.46 (s, 2H, H_5), 5.20 (m, 1H, H_3), 5.40 (br s, 1H, H_3), 6.89 (d, J = 8.7 Hz, 2H, H_8), 7.28 (d, J = 8.6 Hz, 2H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.3 (C_4), 55.4 (C_{10}), 70.6 (C_1), 72.2 (C_5), 114.0 (2C, C_8), 115.9 (C_3), 129.5 (2C, C_7), 130.2 (C_6), 143.7 (C_2), 159.4 (C_9).

IR (neat): 1614, 2836, 2855, 2908, 2934, 2954, 2999, 3033, 3079.

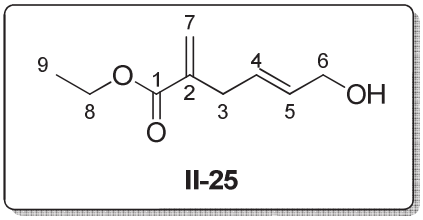


II-24

Ethyl 2-(bromomethyl)acrylate (II-24).[249] In a dry 25-mL round-bottomed flask was placed ethyl 2-(hydroxymethyl)acrylate (**II-17b**, 2.6 g, 20 mmol) and a magnetic stirring bar. The flask was sealed and the ester was dissolved in dry Et_2O (10mL). The solution was cooled to 0 ^oC and PBr_3 (1.34 mL, 3.87 g, 14.3mmol) was added dropwise via syringe. The solution was allowed to warm up to room temperature and stirred for 14h. The flask was again cooled to 0 ^oC and H_2O (3 mL) was slowly added via syringe. After returning to ambient temperature, the reaction mixture was extracted with hexanes (4x10 mL). The organic extracts were washed with 50% saturated aqueous $NaHCO_3$, brine, and dried. Filtration and removal of solvents gave yellow oil. This material was carefully distilled to give 2.19 g (57 %) of colorless, lachrymatory oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 3H, H_5), 4.18 (d, J = 0.9 Hz, 1H, H_6), 4.27 (q, J = 7.2 Hz, 2H, H_4), 5.94 (d, J =0.9 Hz, 1H, H_1), 6.32 (d, J =0.9 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (C_5), 29.5 (C_6), 61.4 (C_4), 129.0 (C_1), 137.7 (C_2), 165.0 (C_3).

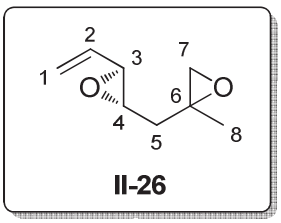


II-25

Ethyl (4*E*)-6-hydroxy-2-methylenehex-4-enoate (II-25).[157b] To a solution of propargyl alcohol (56 mg, 1 mmol) in dry THF (2 ml) were added ethyl 2-(bromomethyl)acrylate (**II-24**, 965 mg, 5 mmol) and indium powder (345 mg, 3 mmol), and the flask was put into an ultrasound cleaning bath. After 6.5 h of sonication, 0.1 mL of 32% aqueous HCl was added at room temperature, followed by extraction with ether after 30 min. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Silica gel column chromatography (Et_2O/petroleum ether = 1:1) yielded **II-25** (47 mg, 28 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.0 Hz, 3H, H_9), 2.68 (br s, 1H, OH), 3.03 (d, J = 4.2 Hz, 2H, H_3), 4.09 (d, J = 4.0 Hz, 2H, H_6), 4.19 (q, J = 7.1 Hz, 2H, H_8), 5.54 (d, J = 1.0 Hz, 1H, H_7), 5.70 (m, 2H, H_4+H_5), 6.16 (s, 1H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (C_9), 34.6 (C_3), 60.9 (C_8), 63.4 (C_6), 125.5 (C_7), 129.0 (C_4), 131.5 (C_5), 139.3 (C_2), 167.0 (C_1).



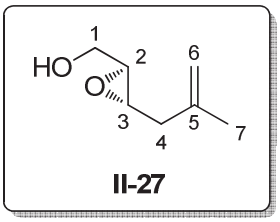
II-26

2-Methyl-2-(((2*S*,3*S*)-3-vinyloxiran-2-yl)methyl)oxirane (II-26). A solution of NaHMDS (2 M, 0.72 mL, 1.44 mmol, 4 equiv) was added to the suspension of Ph_3PMeBr (640 mg, 1.8 mmol, 5 equiv) in 5 mL of freshly distilled THF at 0 ºC under stirring. After 30 min, a solution of (2*R*,3*S*)-3-((2-methyloxiran-2-yl)methyl)oxirane-2-carbaldehyde (**II-34**, 50 mg, 0.36 mmol, 1 equiv) in THF(2mL) was added and the resulting mixture was stirred for 1 h, quenched with water (3 mL) and extracted with Et_2O/petroleum ether = 2:1 (5x5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:2) to yield **II-26** (40 mg, 81 %, dr = 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 1.5H, H_8), 1.42 (s, 1.5H, H_8), 1.71-2.00 (m, 2H, H_5), 2.64 (d, *J* = 4.7 Hz, 1H, H_7), 2.69 (d, *J* = 4.7 Hz, 0.5H, H_7), 2.80 (d, *J* = 4.7 Hz, 0.5H, H_7), 2.89 (ddd, *J* = 2.2, 4.2, 7.1 Hz, 0.5H, H_4), 2.98 (ddd, *J* = 2.1, 4.9, 6.9 Hz, 0.5H, H_4), 3.11 (2dd, *J* = 1.7, 6.7 Hz, 1H, H_3), 5.27-5.31 (m, 1H, H_1), 5.45-5.64 (m, 2H, $H_{1,2}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 22.1 (C_8), 38.8, 39.7 (C_5), 53.3, 53.9 (C_7), 55.4, 55.5 (C_6), 56.6, 57.2, 58.0, 58.4 ($C_{3,4}$), 119.68, 119.69 (C_1), 135.22, 135.25 (C_2).

IR (neat): 1624, 2923, 2984, 3045.



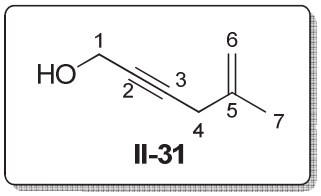
II-27

((2*S*,3*S*)-3-(2-Methylallyl)oxiran-2-yl)methanol (II-27).[158] To the cooled (-20 ºC) mixture of (*E*)-5-methylhexa-2,5-dien-1-ol (**II-32**, 2.55 g, 22.8 mmol, 1 equiv), 4Å MS (700 mg), and CH_2Cl_2 (50 mL) were added Ti(O*i*Pr)$_4$ (1.01 mL, 3.41 mmol, 0.15 equiv) and (+)-DET (0.7 mL, 14.5 mmol, 0.18 equiv) and the resulting mixture was stirred for 30 min. A solution of TBHP in decane (5.5 M, 8.3 mL, 45.5 mmol, 2 equiv) was then added and reaction mixture was placed in a freezer (-25 ºC) for 2 days. The reaction was quenched with water (2 mL) allowed to warm up to rt and then stirred for 30 min. 30 % NaOH aqueous solution saturated with NaCl (3mL) was added and the resulting mixture was stirred for 30-40 min and water(10 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (5x8 mL). The combined organic extracts were washed with water (15 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1→2:1) to yield **II-27** (2.46 g, 84 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (s, 3H, H_7), 2.21 (dd, *J* = 5.4, 15.3 Hz, 1H, H_4), 2.25 (bs, 1H, OH), 2.29 (dd, *J* = 6.3, 15.6 Hz, 1H, H_4), 2.93 (ddd, *J* = 2.4, 2.4, 4.8 Hz, 1H, H_2), 3.06 (ddd, *J* = 2.4, 6.0, 6.0 Hz, 1H, H_3), 3.62 (ddd, *J* = 4.5, 6.6, 12.3 Hz, 1H, H_1), 3.90 (ddd, *J* = 2.4, 5.1, 12.6 Hz, 1H, H_1), 4.79 (s, 1H, H_6), 4.82 (s, 1H, H_6).

IR (neat): 1652, 2936, 2974, 3078, 3423.

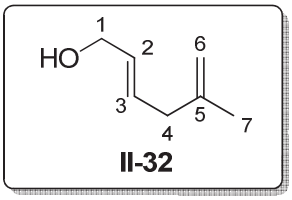
$[\alpha]_D^{20}$ = -31.4 (c 1.56, CH_2Cl_2). [lit. $[\alpha]_D$ = –36.9 (1.1, $CHCl_3$)]



II-31

5-Methylhex-5-en-2-yn-1-ol (II-31).[158] To the suspension of K_2CO_3 (20.7 g, 150 mmol), TBAB (4.83 g, 15 mmol) and CuI (0.95 g, 5 mmol) in dry DMF (80 mL) was added propargyl alcohol (8.7 mL, 150 mmol) and the resulting mixture was stirred for 15 min at rt. Then 1-chloro-2-methyl-2-propene (9.8 mL, 100 mmol) was added and the reaction mixture was stirred for 2 days, poured into water (150 mL) and extracted with ether (4x40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by distillation (87 ºC / 20 torr) to give **II-31** (7.87 g, 72 %) as a colorless oil.

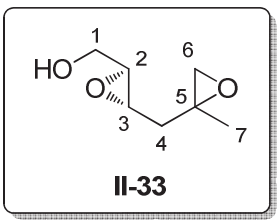
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (s, 3H, H_7), 2.05 (t, J = 5.4 Hz, OH), 2.92 (s, 2H, H_4), 4.27 (m, 2H, H_1), 4.82 (m, 1H, H_6), 4.97 (s, 1H, H_6).



II-32

(*E*)-5-Methylhexa-2,5-dien-1-ol (II-32).[158] To a mixture of $LiAlH_4$ (2.7 g, 71 mmol) in THF (90 mL) at 0 ºC was added dropwise a THF solution (26 mL) of 5-methylhex-5-en-2-yn-1-ol (**II-31**, 7.81 g, 71 mmol) over 20 min. The mixture was brought to r.t., and after 30 min., was warmed to 45 ºC and maintained for 3 h. It was then cooled to 0 ºC, and EtOAc (20 mL) was added carefully over 1 h. Saturated aq. NH_4Cl (80 mL) was then added dropwise over 45 min. The reaction was brought to r.t., and filtered through Celite. The aqueous layer was extracted with Et_2O (3x50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by distillation (80ºC / 25 torr) to give (*E*)-5-methyl-2,5-hexadien-1-ol (6.94 g, 87 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (bs, 1H, OH), 1.71 (s, 3H, H_7), 2.73 (d, *J* = 4.5 Hz, 2H, H_4), 4.10 (d, *J* = 3.3 Hz, 2H, H_1), 4.70 (bs, 1H, H_6), 4.74 (bs, 1H, H_6), 5.69 (m, 2H, $H_{2,3}$).



II-33

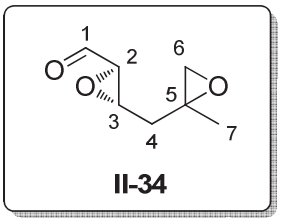
((2*S*,3*S*)-3-((2-Methyloxiran-2-yl)methyl)oxiran-2-yl)methanol (II-33). To a cooled (0 ºC) mixture of ((2*S*,3*S*)-3-(2-methylallyl)oxiran-2-yl)methanol (**II-27**, 0.58 g, 4.55 mmol, 1 equiv), $NaHCO_3$ (2.29 g, 27.3 mmol, 6 equiv) and CH_2Cl_2 (45 mL) was added *m*CPBA (2.35 g, 6.82 mmol, 1.5 equiv). The mixture was stirred for 5 h, evaporated and the residue washed with Et_2O and filtered. The filtrate was evaporated and the residue was purified by flash column chromatography (AcOEt/petroleum ether = 4:1) to yield **II-33** (0.58 g, 88 %, dr = 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 1.5H, H_7), 1.34 (s, 1.5H, H_7), 1.64-1.91 (m, 2H, H_4), 2.58 (d, *J* = 5.4 Hz, 1H, H_6), 2.63 (d, *J* = 4.8 Hz, 0.5H, H_6), 2.72 (d, *J* = 4.5 Hz, 0.5H, H_6), 2.86 (m, 1H, H_2), 2.92 (ddd, *J* = 1.8, 3.9, 6.9 Hz, 0.5H, H_3), 2.92 (ddd, *J* = 2.3, 4.8, 7.0 Hz, 0.5H, H_3), 3.22 (bs, 1H, OH), 3.55 (m, 1H, H_1), 3.80 (d, *J* = 12.6 Hz, 0.5H, H_1), 3.81 (d, *J* = 12.6 Hz, 0.5H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 21.9 (C_7), 38.3, 39.2 (C_4), 52.3, 52.8 (C_3), 53.1, 53.9 (C_6), 55.4, 55.6 (C_5), 57.9, 58.1 (C_2), 61.54, 61.55 (C_1).

HRMS (ESI): calculated for $C_7H_{12}NaO_3$ (MNa^+) 167.0679, found 167.0675.

IR (neat): 2874, 2928, 2985, 3048, 3434.



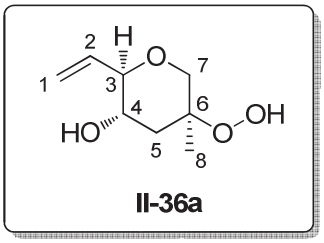
II-34

(2*R*,3*S*)-3-((2-Methyloxiran-2-yl)methyl)oxirane-2-carbaldehyde (II-34). To a solution of ((2*S*,3*S*)-3-((2-methyloxiran-2-yl)methyl)oxiran-2-yl)methanol (**II-33**, 0.46 g, 3.2 mmol, 1 equiv) in CH_2Cl_2 (32 mL) were added successively at 0 ºC TEMPO (50 mg, 0.32 mmol, 0.1 equiv) and BAIB (1.34 g, 4.16 mmol, 1.3 equiv). The reaction mixture was stirred for 20 h at rt, evaporated and the residue was purified by flash column chromatography (AcOEt: petroleum ether = 3:1) to give **II-34** (0.45 g, 99 %, dr = 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 1.5H, H_7), 1.41 (s, 1.5H, H_7), 1.76-2.10 (m, 2H, H_4), 2.65 (m, 1.5H, H_6), 2.79 (d, *J* = 4.5 Hz, 0.5H, H_6), 3.13 (2dd, *J* = 2.1, 6.2 Hz, 1H, H_2), 3.26 (ddd, *J* = 2.0, 3.8, 7.4 Hz, 0.5H, H_3), 3.37 (ddd, *J* = 1.9, 4.3, 7.1 Hz, 0.5H, H_3), 8.99 (2d, *J* = 6.0 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 21.9 (C_7), 37.9, 38.9 (C_4), 53.0, 53.8 (C_6), 53.1, 53.7, 58.2, 58.5 ($C_{2,3}$), 55.0, 55.2 (C_5), 197.8 (C_1).

IR (neat): 1732, 2838, 2930, 2985, 3048, 3444.



II-36a

(2*R*,3*S*)-5-Hydroperoxy-5-methyl-2-vinyltetrahydro-2H-pyran-3-ol (II-36). Ethereal hydrogen peroxide was prepared using a literature procedure.[250] Et_2O (10 mL) was placed in a separatory funnel and "washed" with four portions (6 mL each) of NaCl-saturated H_2O_2 (prepared by stirring the commercially available 30% aqueous hydrogen peroxide with an excess of powdered NaCl at ambient temperature until the initially cloudy liquid phase became a clear solution; the supernatant was used; performed behind a safety shield!). The ethereal layer was then dried over $MgSO_4$. The supernatant (ca. 1.1-1.5 M in H_2O_2 as titrated with 0.1 M $KMnO_4$) was used directly in the PMA catalyzed perhydrolysis.

PMA (11.5 mg, 6.2 μmol, 0.005 equiv) was added to the mixture of 2-methyl-2-(((2*S*,3*S*)-3-vinyloxiran-2-yl)methyl)oxirane (**II-26**, 173 mg, 1.23 mmol, 1 equiv) and ethereal H_2O_2 (1.26 M, 4.9 mL, 6.1 mmol, 5 equiv). The reaction mixture was stirred at rt for 1 h, filtered through a short pad of silicagel and evaporated. The residue after evaporation was purified by flash column chromatography on silica gel (Et_2O/petroleum ether = 2:1) to give pure **II-36a** (13.3 mg), crude **II-36b**, and the mixture of **II-36a** and **II-36b** (52.8 mg). The crude **II-36b** was purified by flash column chromatography (CH_2Cl_2/MeOH = 20:1) to give pure **II-36b** (19.9 mg). Overall yield of **II-36a** and **II-36b** is 40 % (dr ~ 1:1).

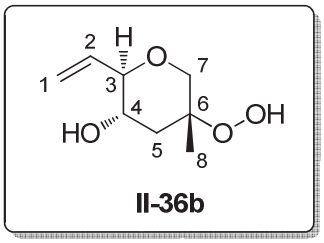
^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.19 (s, 3H, H_8), 1.45 (dd, *J* = 13.8, 11.2 Hz, 1H, H_5), 1.89 (d, *J* = 3.5 Hz, 1H, OH), 2.26 (ddd, *J* = 13.8, 4.9, 2.7 Hz, 1H, H_5), 3.24 (d, *J* = 12.7 Hz, 1H, H_7), 3.43 (dd, *J* = 9.5, 7.0 Hz, 1H, H_3), 3.55 (m, 1H, H_4), 4.05 (dd, *J* = 12.7, 2.7 Hz, 1H, H_7), 5.29 – 5.32 (m, 1H, H_1), 5.38 (d, *J* = 17.3 Hz, 1H, H_1), 5.88 (ddd, *J* = 17.4, 10.6, 6.9 Hz, 1H, H_2), 8.22 (s, 1H, OOH).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 20.7 (C_8), 40.5 (C_5), 66.4 (C_4), 70.5 (C_7), 81.6 (C_6), 83.8 (C_3), 119.1 (C_1), 136.1 (C_2).

IR (neat): 1647, 2853, 2932, 2977, 3318.

MS (CI): 127, 141 (MH^+-H_2O_2), 145, 157 (MH^+-H_2O), 175 (MH^+).

HRMS (CI): calculated for $C_8H_{14}NaO_4$ (MNa^+) 197.0784, found 197.0.782.



II-36b

(2*R*,3*S*,5*R*)-5-Hydroperoxy-5-methyl-2-vinyltetrahydro-2H-pyran-3-ol (II-36b). For experimental procedure see **II-36a**.

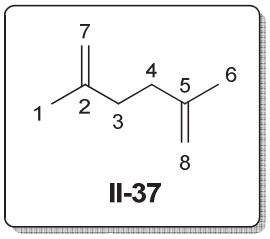
^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.28 (s, 3H, H_8), 1.85 (dd, *J* = 13.2, 7.9 Hz, 1H, H_5), 1.96 (ddd, *J* = 13.2, 4.3, 1.1 Hz, 1H, H_5), 2.54 (bs, 1H, OH), 3.55 (bs, 1H, H_4), 3.61 (d, *J* = 11.7 Hz, 1H, H_7), 3.66 (dd, *J* = 11.5, 1.0 Hz, 1H, H_7), 3.80 (dd, *J* = 6.1, 6.1 Hz, 1H, H_3), 5.31 – 5.38 (m, 2H, H_1), 5.88 (ddd, *J* = 17.0, 10.8, 5.9 Hz, 1H, H_2), 8.15 (bs, 1H, OOH).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 21.2 (C_8), 38.2 (C_5), 68.3 (C_4), 69.5 (C_7), 80.7 (C_6), 82.2 (C_3), 118.9 (C_1), 135.5 (C_2).

IR (neat): 1647, 2853, 2932, 2977, 3318.

MS (CI): 127, 141 (MH^+-H_2O_2), 145, 157 (MH^+-H_2O), 175 (MH^+).

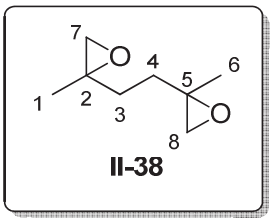
HRMS (CI): calculated for $C_8H_{14}NaO_4$ (MNa^+) 197.0784, found 197.0.788.



II-37

2,5-Dimethylhexa-1,5-diene (II-37).[251] 1-Chloro-2-methyl-2-propene (11.75 g, 130 mmol, 2 equiv) was slowly added to a suspension of magnesium turnings (1.56 g, 65 mmol, 1 equiv) in dry Et_2O (50 mL). After stirring for 16 h, the reaction mixture was quenched with water (20 mL) and extracted with Et_2O (4x10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated to give pure product (5.37 g, 75 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 6H, $H_{1,6}$), 2.15 (s, 4H, $H_{3,4}$), 4.69 (s, 2H, $H_{7,8}$), 4.72 (s, 2H, $H_{7,8}$).

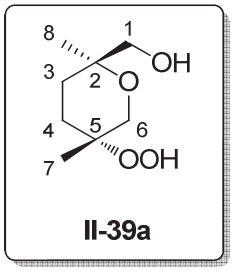


II-38

1,2-bis(2-Methyloxiran-2-yl)ethane (II-38).[252] To a cooled (0 ºC) mixture of 2,5-dimethylhexa-1,5-diene (**II-37**, 5.37 g, 48.8 mmol, 1 equiv), $NaHCO_3$ (32.8 g, 390.5 mmol, 8 equiv) and CH_2Cl_2 (500 mL) was added *m*CPBA (50 %, 50.6 g, 146.5 mmol, 3 equiv). The mixture was stirred for 16 h, quenched with water (200 mL), and extracted with Et_2O (4x50 mL). The combined organic extracts were washed with KOH (0.5 M, 200 mL) dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to afford **II-38** (5.25 g, 76 %, dr = 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (2s, 6H, $H_{1,6}$), 1.60 (s, 4H, $H_{3,4}$), 2.56 (m, 4H, $H_{7,8}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 21.2 ($C_{1,6}$), 32.0, 32.2 ($C_{3,4}$), 53.8, 54.0 ($C_{7,8}$), 56.6, 56.7 ($C_{2,5}$).



II-39a

Rac-((2*S*,5*S*)-5-Hydroperoxy-2,5-dimethyltetrahydro-2H-pyran-2-yl)methanol (II-39a). A mixture of 1,2-bis(2-methyloxiran-2-yl)ethane (**II-38**, 134 mg, 0.94 mmol, 1 equiv), ethereal H_2O_2 (1.15 M, 2.3 mL, 2.65 mmol, 2.8 equiv) and PMA (13.5 mg, 7.4 µmol, 0.008 equiv) was stirred at ambient temperature for 1 h and chromatographed (Et_2O → Et_2O:ether petrole = 10:1) to give pure **II-39a** (26 mg), mixture of **II-39a** and **II-39b** (40.3 mg) and pure **II-39b** (8.7 mg) as a colorless oils. Overall yield is 45 % as ~ a 1:1 diastereomeric mixture.

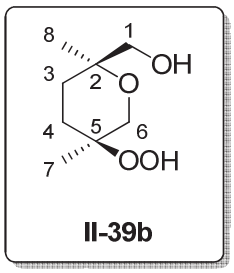
^{1}H NMR (500 MHz, CD_3OD): δ = 1.17 (s, 3H, H_8), 1.20 (s, 3H, H_7), 1.59 (m, 3H, $H_{3,4}$), 1.87 (m, 1H, H_4), 3.39 (d, *J* = 11.4 Hz, 1H, H_1), 3.47 (d, *J* = 12.1 Hz, 1H, H_6), 3.57 (d, *J* = 11.4 Hz, 1H, H_1), 3.70 (d, *J* = 12.1 Hz, 1H, H_6).

^{13}C NMR (75 MHz, CD_3OD): δ = 21.0 (C_7), 22.1 (C_8), 28.9 (C_3), 29.1 (C_4), 66.5 (C_1), 67.1 (C_6), 74.7 (C_2), 79.1 (C_5).

IR (neat): 2873, 2935, 2974, 3311.

MS (CI): 129, 143 (MH^+-H_2O_2), 159 (MH^+-H_2O), 161, 177 (MH^+).

HRMS (CI): calculated for $C_8H_{16}NaO_4$ (MNa^+) 199.0941, found 199.0941.



II-39b

Rac-((2*S*,5*R*)-5-Hydroperoxy-2,5-dimethyltetrahydro-2H-pyran-2-yl)methanol (II-39b). For experimental procedure see **II-39a**.

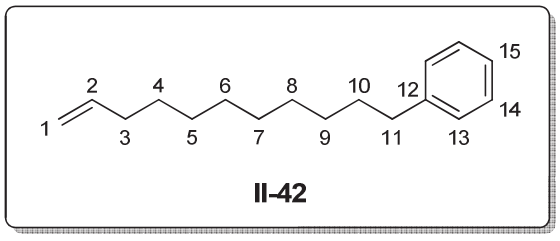
^{1}H NMR (500 MHz, CD_3OD): δ = 1.14 (s, 3H, H_7), 1.17 (s, 3H, H_8), 1.17 – 1.23 (m, 1H, H_3), 1.67 – 1.73 (m, 1H, H_4), 1.82 – 1.90 (m, 2H, $H_{3,4}$), 3.37 (d, *J* = 11.1 Hz, 1H, H_1), 3.40 (d, *J* = 11.1 Hz, 1H, H_1), 3.47 (d, *J* = 12.6 Hz, 1H, H_6), 3.76 (dd, *J* = 12.7, 2.2 Hz, 1H, H_6).

^{13}C NMR (75 MHz, CD_3OD): δ = 18.0 (C_8), 21.3 (C_7), 27.6 (C_3), 28.9 (C_4), 66.1 (C_6), 70.5 (C_1), 74.6 (C_2), 78.7 (C_5).

IR (neat): 2871, 2934, 2972, 3327.

MS (CI): 129, 143 (MH^+-H_2O_2), 159 (MH^+-H_2O), 161, 177 (MH^+).

HRMS (CI): calculated for $C_8H_{16}NaO_4$ (MNa^+) 199.0941, found 199.0940.



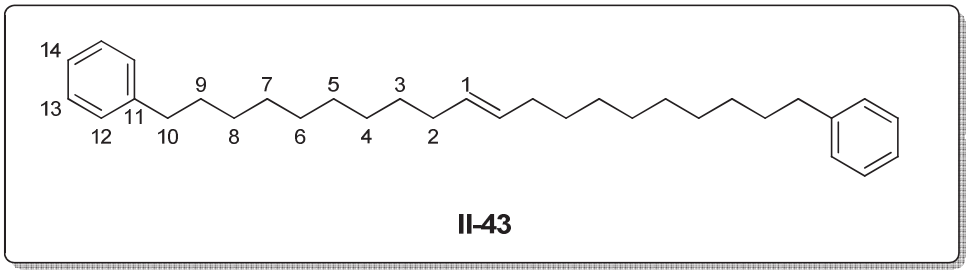
II-42

Undec-10-en-1-ylbenzene (II-42).[253] Magnesium turnings (0.82 g, 34.3 mmol, 8 equiv), one crystal of iodine and freshly distilled THF (10 mL) were placed into a dry flask equipped with reflux condenser under nitrogen atmosphere. This mixture was refluxed until it became colorless. Then PhBr (0.84 mL, 8 mmol, 1.87 equiv) was added dropwise during 20 min and the reaction mixture was stirred for 1 h at rt. 11-Bromoundec-1-ene (1 g, 4.29 mmol, 1 equiv), CuBr (31 mg, 0.11 mmol, 0.025 equiv), LiBr (0.37 g, 4.29 mmol, 1 equiv) and dry THF (16 mL) were placed into a flask flushed with dry nitrogen. The resulting mixture was heated to 50 °C for 30 min. Grignard reagent was transferred dropwise by syringe to the flask. The progress of the reaction was followed by monitoring the disappearance of protons α to Br in the ^{1}H NMR spectrum. After the reaction was complete, the mixture was transferred to a

separatory funnel. Diethyl ether (20 mL) was added, and the organic solution was washed twice with saturated aqueous NH_4Cl and once with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (petroleum ether) to give pure **II-42** (0.975 g, 99 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27-1.39 (m, 12H, $H_{4\text{-}9}$), 1.63 (m, 2H, H_{10}), 2.06 (m, 2H, H_3), 2.62 (t, *J* = 7.8 Hz, 2H, H_{11}), 4.93-5.05 (m, 2H, H_1), 5.84 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H, H_2), 7.19-7.21 (m, 3H, H_{Ar}), 7.27-7.32 (m, 2H, H_{Ar}).

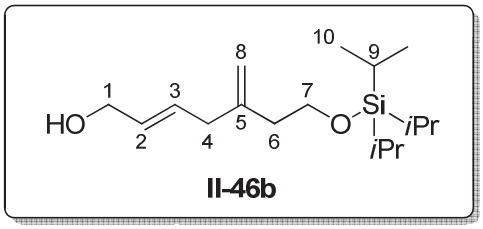
^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.08, 29.28, 29.48, 29.63, 29.64, 29.68, 31.68, 33.97, 36.15 ($C_{3\text{-}11}$), 114.24 (C_1), 125.68 (C_{15}), 128.35 (2C), 128.53 (2C), 139.38 (C_2), 143.08 (C_{12}).



II-43

(*E*)-1,20-Diphenylicos-10-ene (II-43). A vacuum dried 10 mL round bottom flask containing a stirring bar was charged with Hoveyda-Grubbs catalyst (16 mg, 0.025 mmol, 0.05 equiv). Dry, degassed CH_2Cl_2 (2 mL) was then added via syringe. ((2*S*,3*S*)-3-(2-methylallyl)oxiran-2-yl)methanol (**II-27**, 64 mg, 0.5 mmol, 1 equiv) and undec-10-en-1-ylbenzene (**II-42**, 345 mg, 1.5 mmol, 3 equiv) were dissolved in 0.5 mL of CH_2Cl_2, and this solution was added to the flask containing Grubbs catalyst. The flask was then outfitted with reflux condenser and the solution was heated to reflux for 55 h. After cooling to ambient temperature, ethyl vinyl ether (0.5 mL) was added via syringe, the solution was stirred for an addition 10 minutes and evaporated. Purification of the residue by flash column chromatography (Et_2O/petroleum ether = 1:1) gave pure starting material **II-27** (64 mg, 100 %) and **II-43** (300 mg, 93 %) as a colorless oil.

^{1}H NMR for II-43 (300 MHz, $CDCl_3$): δ = 1.28-1.36 (m, 24H, $H_{3\text{-}8}$), 1.63 (m, 4H, H_9), 1.99 (m, 4H, H_2), 2.61 (t, *J* = 7.8 Hz, 4H, H_{10}), 5.35 (m, 2H, H_1), 7.16-7.20 (m, 6H, H_{Ar}), 7.26-7.31 (m, 4H, H_{Ar}).



II-46b

(*E*)-5-Methylene-7-((triisopropylsilyl)oxy)hept-2-en-1-ol (II-46b).[156] *Method A (by ester reduction).* DIBAL (1 M, 12.5 mL, 12.5 mmol, 2.2 equiv) was added over 10 min to a stirred solution of (*E*)-methyl 5-methylene-7-((triisopropylsilyl)oxy)hept-2-enoate (**II-51a**, 1.86 g, 5.7 mmol, 1 equiv) in THF (14 mL) at -78 °C. After 2 h the reaction mixture was warmed to 0 °C, stirred for 30 min, carefully quenched with Rochelle salt and extracted with Et_2O (4x10 mL). Combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:2) to give pure **II-46b** (1.38 g, 81 %) as a colorless oil.

Method B (by ester reduction). DIBAL (1 M, 10.8 mL, 10.8 mmol, 2.3 equiv) was added over 10 min to a stirred solution of (*E*)-ethyl 5-methylene-7-((triisopropylsilyl)oxy)hept-2-enoate (**II-51b**, 1.59 g, 4.68 mmol, 1 equiv) in THF (12 mL) at -78 °C. After 2 h the reaction mixture was warmed to 0 °C, stirred for 30 min, carefully quenched with a Rochelle salt solution and extracted with Et_2O (4x10 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:2) to give pure **II-46b** (1.19 g, 85 %) as a colorless oil.

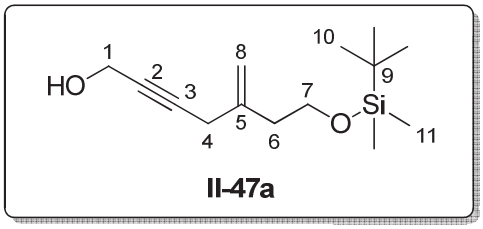
Method C (by alkyne reduction). A solution of 5-methylene-7-((triisopropylsilyl)oxy)hept-2-yn-1-ol (**II-47b**, 71 mg, 0.24 mmol, 1 equiv) in dry THF (1 mL) was added dropwise to a stirred suspension of LAH (18 mg, 0.48 mmol, 2 equiv) in THF (4 mL). After stirring for 20 h, the reaction mixture was quenched by wet Et_2O followed by water and extracted with Et_2O (4x6 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:2) to give the pure allylic alcohol **II-46b** (47 mg, 66 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (m, 21H, $H_{9,10}$), 1.57 (bs, 1H, OH), 2.28 (t, *J* = 6.9 Hz, 2H, H_6), 2.79 (d, *J* = 4.8 Hz, 2H, H_4), 3.78 (t, *J* = 6.9 Hz, 2H, H_7), 4.12 (m, 2H, H_1), 4.80 (s, 2H, H_8), 5.70 (m, 2H, $H_{2,3}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2 (C_9), 18.2 (C_{10}), 39.5, 39.7 ($C_{4,6}$), 62.7 (C_7), 63.8 (C_1), 111.9 (C_8), 130.6, 130.9 ($C_{2,3}$), 145.6 (C_5).

IR (neat): 1646, 2867, 2893, 2943, 3078, 3331.

HRMS (CI): calculated for $C_{17}H_{34}O_2Si$ (MH^+) 299.2406, found 299.2406.



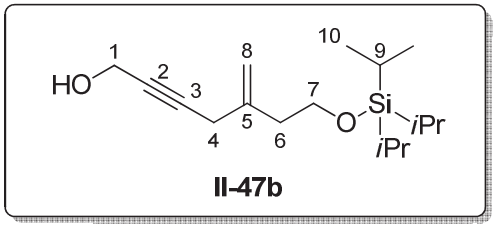
II-47a

7-((*tert*-Butyldimethylsilyl)oxy)-5-methylenehept-2-yn-1-ol (II-47a). K_2CO_3 (0.4 g, 2.9 mmol, 1.5 equiv), NaI (0.29 g, 1.94 mmol, 1 equiv), CuI (0.37 g, 1.94 mmol, 1 equiv) were suspended in dry DMF (15 ml). Subsequently propargyl alcohol (0.17 mL, 2.9 mmol, 1.5 equiv) was added all at once and kept stirring for 15 min. A solution of *tert*-butyl((3-(chloromethyl)but-3-en-1-yl)oxy)dimethylsilane (**II-50a**, 0.45 g, 1.94 mmol, 1 equiv) in 1 mL of DMF was then added and the resulting suspension was stirred at rt under argon atmosphere for 24 h, quenched with saturated aqueous solution of ammonium chloride, extracted with diethyl ether (5x8 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:5) to yield the enyne **II-47a** (266 mg, 54 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6H, H_{11}), 0.88 (s, 9H, H_{10}), 1.74 (bs, 1H, OH), 2.31 (t, *J* = 6.6 Hz, 2H, H_6), 2.99 (bs, 2H, H_4), 3.72 (t, *J* = 6.6 Hz, 2H, H_7), 4.28 (bs, 2H, H_1), 4.87 (s, 1H, H_8), 5.10 (s, 1H, H_8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.2 (C_{11}), 18.4 (C_9), 26.0 (C_{10}), 26.7, 39.0 ($C_{4,6}$), 51.5 (C_1), 62.3 (C_7), 80.9, 83.4 ($C_{2,3}$), 112.7 (C_8), 141.7 (C_5).

IR (neat): 1653, 2179, 2237, 2858, 2886, 2930, 2955, 3348.



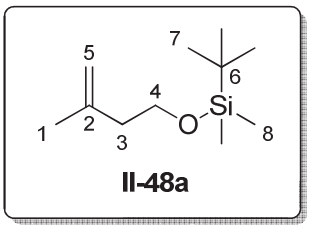
II-47b

5-Methylene-7-((triisopropylsilyl)oxy)hept-2-yn-1-ol (II-47b). K_2CO_3 (0.73 g, 5.3 mmol, 1.5 equiv), NaI (0.53 g, 3.54 mmol, 1 equiv), CuI (0.67 g, 3.54 mmol, 1 equiv) were suspended in dry DMF (25 ml). Subsequently propargyl alcohol (0.31 mL, 5.3 mmol, 1.5 equiv) was added in once and kept stirring for 15 min. Then a solution of ((3-(chloromethyl)but-3-en-1-yl)oxy)triisopropylsilane (**II-50b**, 0.90 g, 3.25 mmol, 0.92 equiv) in DMF (2 mL) was added and the resulting suspension was stirred at rt under argon atmosphere for 36 h, then quenched with saturated aqueous solution of ammonium chloride, extracted with diethyl ether (5x8 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:3) to yield **II-47b** (0.51 g, 53 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (m, 21H, $H_{9,10}$), 1.61 (t, *J* = 6.1 Hz, 1H, OH), 2.34 (t, *J* = 6.6 Hz, 2H, H_6), 3.02 (bs, 2H, H_4), 3.80 (t, *J* = 6.6 Hz, 2H, H_7), 4.28 (dt, *J* = 5.8, 2.1 Hz, 2H, H_1), 4.89 (m, 1H, H_8), 5.10 (m, 1H, H_8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C_9), 18.2 (C_{10}), 26.7, 39.2 ($C_{4,6}$), 51.5 (C_1), 62.7 (C_7), 80.9, 83.6 ($C_{2,3}$), 112.7 (C_8), 141.9 (C_5).

IR (neat): 1652, 2226, 2286, 2867, 2893, 2944, 3357.

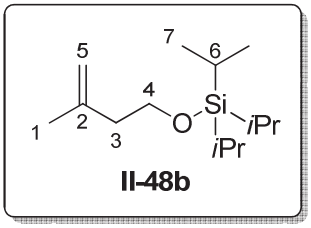


II-48a

***tert*-Butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane (II-48a).**[254] To a stirred solution of 3-methylbut-3-en-1-ol (**II-49**, 1.17 mL, 11.6 mmol, 1 equiv) and Et_3N (4.1 mL, 23.3 mmol, 2 equiv) in CH_2Cl_2 (30 mL) was added dropwise at 0 ^oC, a solution of TBSCl in toluene (50 %, 4.9 mL, 14.0 mmol, 1.2 equiv). The reaction mixture was allowed to reach room temperature, stirred for 14 h and quenched with NH_4Cl saturated aqueous solution(10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (4x10 mL). The combined organic extracts were washed with water (10 mL), dried with Na_2SO_4 and evaporated. The residue was purified by flash chromatography (Et_2O/petroleum ether = 1:10) to give pure TBS ether **II-48a (**2.51 g, quant) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6H, H_8), 0.90 (s, 9H, H_7), 1.75 (s, 3H, H_1), 2.25 (t, *J* = 6.9 Hz, 2H, H_3), 3.72 (t, *J* = 6.9 Hz, 2H, H_4), 4.70 (s, 1H, H_5), 4.76 (s, 1H, H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.1 (C_8), 18.5 (C_6), 23.0 (C_1), 26.1 (C_7), 41.3 (C_3), 62.3 (C_4), 111.6 (C_5), 143.2 (C_2).

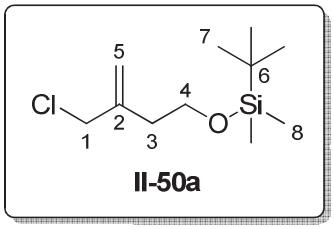


II-48b

Triisopropyl((3-methylbut-3-en-1-yl)oxy)silane (II-48b).[156] To a stirred solution of 3-methylbut-3-en-1-ol (**II-49**, 500 mg, 5.8 mmol, 1 equiv) in CH_2Cl_2 (5 mL) were added Et_3N (1.24 mL, 7.0 mmol, 1.2 equiv) and DMAP (71 mg, 0.58 mmol, 0.1 equiv) followed by the dropwise addition of TIPSCl (1.41 mL, 6.4 mmol, 1.1 equiv) at 0 ^oC. The reaction mixture was allowed to reach room temperature and was stirred overnight. Then it was quenched with saturated aqueous solution of NH_4Cl (5 mL) and water (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (4x8 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ and brine, dried with Na_2SO_4 and evaporated. The residue was purified by flash chromatography (Et_2O/petroleum ether = 1:10) to give pure product (1.36 g, 96 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (m, 21H, $H_{6,7}$), 1.75 (s, 3H, H_1), 2.28 (t, *J* = 6.9 Hz, 2H, H_3), 3.79 (t, *J* = 6.9 Hz, 2H, H_4), 4.70 (m, 1H, H_5), 4.75 (bs, 1H, H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2 (C_6), 18.2 (C_7), 23.1 (C_1), 41.4 (C_3), 62.6 (C_4), 111.5 (C_5), 143.4 (C_2).

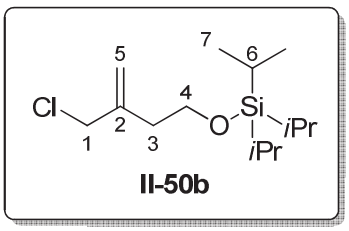


II-50a

***tert*-Butyl((3-(chloromethyl)but-3-en-1-yl)oxy)dimethylsilane (II-50a).**[139] To a cooled (0 °C) solution of *tert*-butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane (**II-48a**, 0.5 g, 2.5 mmol, 1 equiv) in CH_2Cl_2 (13 mL) were added water (13 mL) and cerium chloride heptahydrate (1.86 g, 5 mmol, 2 equiv). To the resulting mixture was added a solution of sodium hypochlorite (2.3 mL, 5 mmol, 2 equiv) during 5 min and the reaction mixture was vigorously stirred at 0 °C for 30 min. The reaction was quenched by the slow addition of saturated aqueous sodium sulfite. The layers were separated and the aqueous layer was extracted with dichloromethane (3x10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (Et_2O/petroleum ether = 1:10) to give pure product (0.454 g, 78 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6H, H_8), 0.89 (s, 9H, H_7), 2.39 (td, *J* = 6.6, 1.0 Hz, 2H, H_3), 3.76 (t, *J* = 6.6 Hz, 2H, H_4), 4.08 (d, *J* = 0.9 Hz, 2H, H_1), 5.00 (m, 1H, H_5), 5.18 (bs, 1H, H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.2 (C_8), 18.4 (C_6), 26.0 (C_7), 36.5 (C_3), 48.8 (C_1), 62.2 (C_4), 116.0 (C_5), 143.1 (C_2).

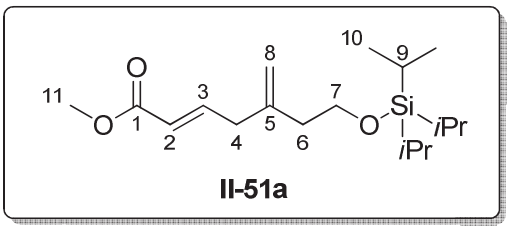


II-50b

((3-(Chloromethyl)but-3-en-1-yl)oxy)triisopropylsilane (II-50b). To a cooled (0 °C) solution of triisopropyl((3-methylbut-3-en-1-yl)oxy)silane (**II-48b**, 1 g, 4.1 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were added water (20 mL) and cerium chloride heptahydrate (3.08 g, 8.2 mmol, 2 equiv). To the resulting mixture was added a solution of sodium hypochlorite (3.8 mL, 8.2 mmol, 2 equiv) during 10 min and the reaction mixture was vigorously stirred at 0 °C for 30 min. The reaction mixture was quenched by a slow addition of saturated aqueous sodium sulfite. The layers were separated and the aqueous layer was extracted with

dichloromethane (4x10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The crude product was filtered through a small pad of silica gel (Et_2O/petroleum ether = 1:10) to give a mixture of products **II-50b**/ **II-48b** = 82:18 (1.1 g, 96 %) which was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (m, 21H, $H_{6,7}$), 2.42 (td, *J* = 6.6, 1.0 Hz, 2H, H_3), 3.84 (t, *J* = 6.6 Hz, 2H, H_4), 4.10 (d, *J* = 0.9 Hz, 2H, H_1), 5.02 (m, 1H, H_5), 5.18 (bs, 1H, H_5).



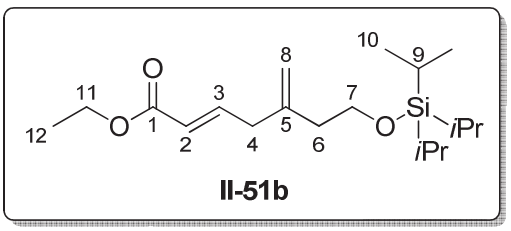
II-51a

(E)-Methyl 5-methylene-7-((triisopropylsilyl)oxy)hept-2-enoate (II-51a).[156] To a vigorously stirred solution of triisopropyl((3-methylbut-3-en-1-yl)oxy)silane (**II-48b**, 2.17 g, 8.98 mmol, 1 equiv) and methyl propiolate (0.75 mL, 8.98 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added, at 0 °C, $EtAlCl_2$ (1 M, 9.43 mL, 9.43 mmol, 1.05 equiv). The reaction mixture was stirred at rt for 7 days and then poured into ice-water. The aqueous layer was extracted with AcOEt (3x10 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4, and evaporated. Flash chromatography (Et_2O/petroleum ether = 1:10) of the residue gave pure dienoate **II-51a** (1.61 g, 55 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (m, 21H, $H_{9,10}$), 2.26 (t, *J* = 6.9 Hz, 2H, H_6), 2.93 (d, *J* = 7.2 Hz, 2H, H_4), 3.71 (s, 3H, H_{11}), 3.77 (t, *J* = 6.9 Hz, 2H, H_7), 4.81 (m, 1H, H_8), 4.86 (s, 1H, H_8), 5.84 (dt, *J* = 15.6, 1.5 Hz, 1H, H_2), 6.96 (dt, *J* = 15.6, 7.1 Hz, 1H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C_9), 18.1 (C_{10}), 39.5, 39.6 ($C_{4,6}$), 51.5 (C_{11}), 62.6 (C_7), 113.4 (C_8), 122.4 (C_2), 143.7 (C_5), 146.8 (C_3), 166.9 (C_1).

MS (CI): 245, 283, 327 (MH^+), 341, 391.



II-51b

(*E*)-Ethyl 5-methylene-7-((triisopropylsilyl)oxy)hept-2-enoate (II-51b). To a vigorously stirred solution of triisopropyl((3-methylbut-3-en-1-yl)oxy)silane (**II-48b**, 3.5 g, 14.5 mmol, 1 equiv) and ethyl propiolate (1.47 mL, 14.5 mmol, 1 equiv) in CH_2Cl_2 (50 mL), was added at 0 °C $EtAlCl_2$ (1 M, 14.8 mL, 14.8 mmol, 1.02 equiv). The reaction mixture was

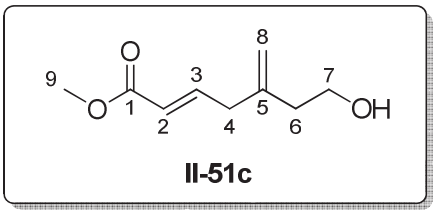
stirred at rt for 7 days and then poured into ice-water. The aqueous layer was extracted with AcOEt (4x10 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4, and evaporated. Flash chromatography (Et_2O/petroleum ether = 1:10) of the residue gave pure **II-51b** (3.8 g, 77 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (m, 21H, $H_{9,10}$), 1.28 (t, *J* = 7.2 Hz, 2H, H_{12}), 2.28 (t, *J* = 6.6 Hz, 2H, H_6), 2.94 (d, *J* = 7.2 Hz, 2H, H_4), 3.78 (t, *J* = 6.6 Hz, 2H, H_7), 4.18 (q, *J* = 7.2 Hz, 2H, H_{11}), 4.82 (m, 1H, H_8), 4.87 (s, 1H, H_8), 5.84 (dt, *J* = 15.3, 1.5 Hz, 1H, H_2), 6.96 (dt, *J* = 15.6, 7.2 Hz, 1H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C_9), 14.4 (C_{12}), 18.2 (C_{10}), 39.5, 39.6 ($C_{4,6}$), 60.3 (C_{11}), 62.6 (C_7), 113.4 (C_8), 122.9 (C_2), 143.8 (C_5), 146.5 (C_3), 166.6 (C_1).

IR (neat): 1652, 1724, 2867, 2944, 3079.

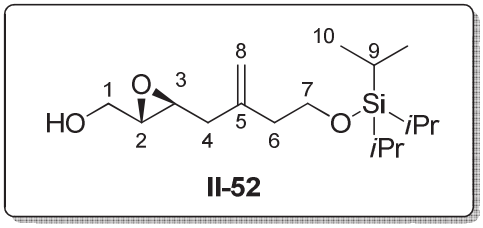
HRMS (ESI): calculated for $C_{19}H_{36}NaO_3Si$ (MNa^+) 363.2326, found 363.2325.



II-51c

(*E*)-Methyl 7-hydroxy-5-methylenehept-2-enoate (II-51c).[255] To a cooled (0 °C) mixture of $EtAlCl_2$ (1 M, 1 mL, 1 mmol, 1 equiv) and CH_2Cl_2 (4 mL), methyl propiolate (0.083 mL, 1 mmol, 1 equiv) and *tert*-butyldimethyl((3-methylbut-3-en-1-yl)oxy)silane (**II-48a**, 0.2 g, 1 mmol, 1 equiv) were added successively. The reaction mixture was stirred at rt for 5 days, a saturated aqueous solution of Rochelle salt (2 mL) was added and the resulting mixture was stirred for 20 min. The organic layer was separated and the aqueous layer was extracted with AcOEt (3x3 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4, and evaporated. Flash chromatography (Et_2O/petroleum ether = 1:1) of the residue after evaporation of solvents gave **II-51c** (22 mg, 13 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (t, *J* = 6.0 Hz, 2H, H_6), 2.93 (d, *J* = 7.2 Hz, 2H, H_4), 3.73 (s, 3H, H_9), 3.73 (t, *J* = 6.3 Hz, 2H, H_7), 4.92 (s, 1H, H_8), 4.94 (s, 1H, H_8), 5.87 (dt, *J* = 15.6, 1.5 Hz, 1H, H_2), 6.96 (dt, *J* = 15.6, 7.2 Hz, 1H, H_3).



II-52

((2*S*,3*S*)-3-(2-Methylene-4-((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methanol (II-52).[156] To the cooled (-25 ºC) mixture of (*E*)-5-methylene-7-((triisopropylsilyl)oxy)hept-2-en-1-ol (**II-46b**, 1.2 g, 4.02 mmol, 1 equiv), 4Å MS (240 mg), and CH_2Cl_2 (11 mL), $Ti(OiPr)_4$ (0.24 mL, 0.803 mmol, 0.2 equiv) and a solution of (+)-DET (0.17 mL, 0.964 mmol, 0.24 equiv) in CH_2Cl_2 (1 mL) were added and the resulting mixture was stirred for 30 min. A solution of TBHP in decane (5.5 M, 1.46 mL, 8.03 mmol, 2 equiv) was then added and the reaction mixture was placed in a freezer (-25 ºC) for 2 days. The reaction was quenched with water (2 mL), allowed to warm up to rt and then stirred for 30 min. 30 % NaOH Aqueous solution saturated with NaCl (0.5 mL) was added and the resulting mixture was stirred for 30-40 min then 10 mL of water was introduced. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5x8 mL). Combined organic extracts were washed once with water (15 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to yield the epoxy alcohol **II-52** (1.19 g, 94 %) as a colorless oil.

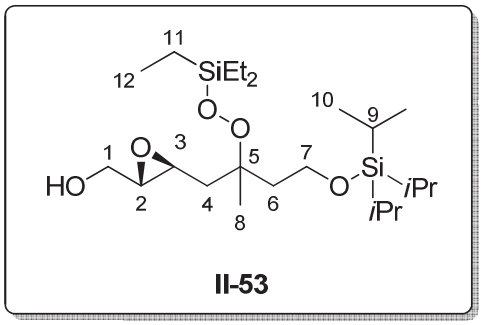
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (m, 21H, $H_{9,10}$), 1.70 (dd, *J* = 7.1, 5.6 Hz, 1H, OH), 2.25-2.41 (m, 4H, $H_{4,6}$), 2.95 (ddd, *J* = 4.7, 2.5, 2.5 Hz, 1H, H_2), 3.09 (td, *J* = 5.8, 5.8, 2.3 Hz, 1H, H_3), 3.65 (ddd, *J* = 12.0, 7.5, 4.5 Hz, 1H, H_1), 3.80 (t, *J* = 6.8 Hz, 2H, H_7), 3.93 (ddd, *J* = 12.6, 5.3, 2.6 Hz, 1H, H_1), 4.89 (s, 1H, H_8), 4.91 (m, 1H, H_8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C_9), 18.2 (C_{10}), 38.8, 40.1 ($C_{4,6}$), 54.8, 58.4 ($C_{2,3}$), 61.7, 62.6 ($C_{1,7}$), 113.1 (C_8), 143.1 (C_5).

IR (neat): 1647, 2867, 2893, 2943, 3426.

MS (CI): 337 (MNa^+), 383, 399.

$[\alpha]_D^{20}$ = -8.6 (*c* 0.69, $CHCl_3$).



II-53

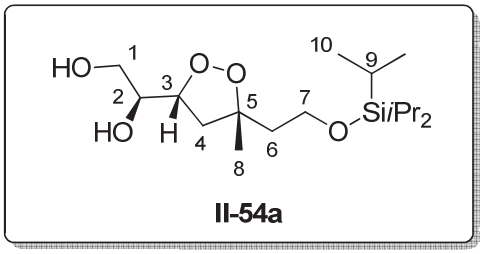
((2*S*,3*S*)-3-(2-Methyl-2-((triethylsilyl)peroxy)-4((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methanol (II-53). ((2*S*,3*S*)-3-(2-methylene-4-((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methanol (**II-52**, 120 mg, 0.38 mmol, 1 equiv), $Co(modp)_2$ (21 mg, 0.038 mmol, 0.1 equiv) and dichloroethane (4 mL) were placed into the flask. The flask was charged with O_2 and Et_3SiH (0.12 mL, 0.76 mmol, 2 equiv) was added. After stirring for 4 h, the reaction mixture was evaporated. Flash chromatography (Et_2O/petroleum ether = 1:1) of the residue gave **II-53** (73 mg, 41 %, dr ~ 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (q, 6H, *J* = 7.8 Hz, H_{11}), 0.97 (t, 9H, *J* = 7.8 Hz, H_{12}), 1.05 (m, 21H, $H_{9,10}$), 1.27 (s, 1.5H, H_8), 1.29 (s, 1.5H, H_8), 1.74-2.02 (m, 5H, OH + $H_{4,6}$), 2.91 (m, 1H), 3.10 (m, 1H), 3.59 (m, 1H, H_1), 3.80 (t, *J* = 6.4 Hz, 2H, H_7), 3.91 (m, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.0 (C_{11}), 6.9 (C_{12}), 12.1 (C_9), 18.2 (C_{10}), 22.3 (C_8), 23.1 (C_8), 39.9, 40.04, 40.06, 41.0 ($C_{4,6}$), 52.8, 52.9, 58.3, 58.6, 59.4, 61.88, 61.94 ($C_{1,2,3,7}$), 82.95 (C_5), 83.00 (C_5).

HRMS (ESI): calculated for $C_{23}H_{50}NaO_5Si_2$ (MNa^+) 485.3089, found485.3098.

IR (neat): 2868, 2944, 2957, 3434.



II-54a

(*S*)-1-((3*R*,5*R*)-5-Methyl-5-(2-((triisopropylsilyl)oxy)ethyl)-1,2-dioxolan-3-yl)ethane-1,2-diol (II-54). ((2*S*,3*S*)-3-(2-methylene-4-((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methanol (**II-52**, 200 mg, 0.64 mmol, 1 equiv), $Co(acac)_2$ (16 mg, 0.064 mmol, 0.1 equiv) and ethanol (4 mL) were placed into the flask. The flask was charged with O_2 and Et_3SiH (0.2 mL, 1.27 mmol, 2 equiv) was added. After stirring for 16 h the reaction mixture was evaporated. Flash chromatography (Et_2O/petroleum ether = 1:1) of the residue afforded **II-53** (18 mg, 6 %), **II-54a** (45 mg, 20.5 %) and **II-54a** (45 mg, 20.5 %) as colorless oils.

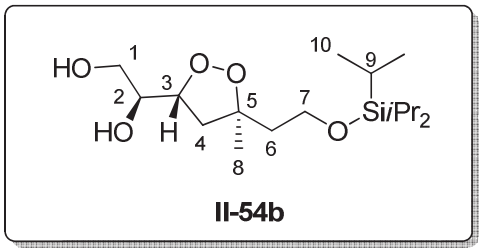
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (m, 21H, $H_{9,10}$), 1.35 (s, 3H, H_8), 1.89 (t, *J* = 6.6 Hz, 2H, H_6), 2.39 (bs, 1H, OH), 2.42 (dd, *J* = 12.3, 8.1 Hz, 1H, H_4), 2.58 (dd, *J* = 12.3, 6.0 Hz, 1H, H_4), 2.83 (bs, 1H, OH), 3.62 (dd, *J* = 11.4, 6.0 Hz, 1H, H_1), 3.71 (dd, *J* = 11.4, 3.0 Hz, 1H, H_1), 3.82 (m, 3H, $H_{2,7}$), 4.33 (dt, *J* = 8.0, 5.8 Hz, 1H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 (C_9), 18.1 (C_{10}), 24.3 (C_8), 40.7 (C_6), 47.0 (C_4), 59.9 (C_7), 63.5 (C_1), 72.4 (C_2), 81.4 (C_3), 85.3 (C_5).

IR (neat): 2867, 2892, 2943, 3390.

HRMS (ESI) (mixture of diastereomers): calculated for $C_{17}H_{36}O_5Si$ (MNa^+) 371.2230, found 371.2233.

$[\alpha]_D^{20}$ = -28.2 (*c* 1.59, $CHCl_3$).



II-54b

(*S*)-1-((3*R*,5*S*)-5-Methyl-5-(2-((triisopropylsilyl)oxy)ethyl)-1,2-dioxolan-3-yl)ethane-1,2-diol (II-54b). For experimental procedure see **II-54a**.

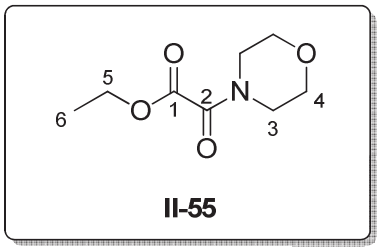
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (m, 21H, $H_{9,10}$), 1.37 (s, 3H, H_8), 1.87 (dt, *J* = 13.9, 6.9 Hz, 1H, H_6), 1.91 (dt, *J* = 12.5, 6.2 Hz, 1H, H_6), 2.36 (dd, *J* = 12.2, 5.8 Hz, 1H, H_4), 2.37 (bs, 1H, OH), 2.70 (dd, *J* = 12.2, 8.2 Hz, 1H, H_4), 2.83 (bs, 1H, OH), 3.62 (dd, *J* = 11.4, 6.1 Hz, 1H, H_1), 3.72 (dd, *J* = 11.4, 3.4 Hz, 1H, H_1), 3.82 (t, *J* = 6.5 Hz, 2H, H_7), 3.82 (m, 1H, H_2), 4.28 (dt, *J* = 8.1, 5.6 Hz, 1H, H_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.0 (C_9), 18.2 (C_{10}), 23.2 (C_8), 41.5 (C_6), 46.9 (C_4), 59.8 (C_7), 63.5 (C_1), 72.4 (C_2), 81.7 (C_3), 85.2 (C_5).

IR (neat): 2867, 2892, 2943, 3386.

HRMS (ESI) (mixture of diastereomers): calculated for $C_{17}H_{36}O_5Si$ (MNa^+) 371.2230, found 371.2233.

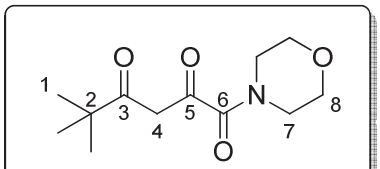
$[\alpha]_D^{20}$ = -45.9 (*c* 1.28, $CHCl_3$).



II-55

Ethyl 2-morpholino-2-oxoacetate (II-55).[171] To a solution of morpholine (4.37 mL, 50 mmol, 1 equiv) and Et_3N (6.96 mL, 50 mmol, 1 equiv) in CH_2Cl_2 (90 mL) was added dropwise at 0 ^oC ethyl oxalylchloride (5.6 mL, 50 mmol, 1 equiv). The mixture was stirred for 30 min, warmed up to rt and stirred for another 16 h, washed with 1M HCl (20 mL), saturated aqueous solution of $NaHCO_3$ (20 mL) and dried (Na_2SO_4). Concentration in vacuo gave **II-55** (8.92 g, 95 %) as a pale yellow oil.

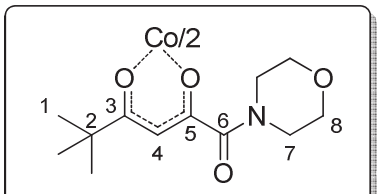
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, 3H, *J* = 6.9 Hz, H_6), 3.45 (m, 2H), 3.63 (m, 2H), 3.70 (m, 4H), 4.32 (q, 2H, *J* = 6.9 Hz, H_5).



II-56

5,5-Dimethyl-1-morpholinohexane-1,2,4-trione (II-56).[171] A solution of *t*-BuOK (2.35 g, 21 mmol, 2.1 equiv) in THF (9 mL) was added via syringe to a solution of pinacolone (1.25 mL, 10 mmol, 1 equiv) and ethyl 2-morpholino-2-oxoacetate (**II-55**, 1.87 g, 10 mmol, 1 equiv) in THF (2 mL) over 40 min at rt. After 3 h, AcOH (2 mL) was added over 5 min and the resulting heterogeneous mixture was filtered and the solid was washed with CH_2Cl_2. The filtrate was washed with $NaHCO_3$, dried with Na_2SO_4 and evaporated. Flash chromatography (Et_2O/petroleum ether = 2:1) of the residue yielded pure **II-56** (1.49 g, 62 %, ratio enol/ketone = 3:1) as a colorless oil.

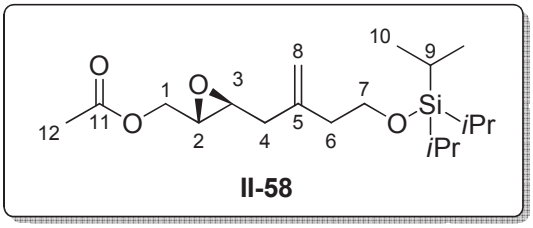
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 2.2H, H_1), 1.20 (s, 6.8H, H_1), 3.62-3.77 (m, 8H, $H_{7,8}$), 4.04 (s, 0.5H, H_4), 6.02 (s, 0.75H, H_4), 15.18 (bs, 0.75H, OH).



II-57 (Co(modp)$_2$)

bis(1-Morpholino-5,5-dimethyl-1,2,4-hexanetrionato)cobalt(II) (II-57).[98] To an aqueous solution (30 mL) of NaOH (0.25 g, 6.17 mmol, 2 equiv) and 5,5-dimethyl-1-morpholinohexane-1,2,4-trione (**II-56**, 1.49 g, 6.17 mmol, 2 equiv) was slowly added an aqueous solution (6 mL) of $CoCl_2$ (0.40 g, 3.09 mmol, 1 equiv). After the mixture had been stirred for 2 h, the precipitate was separated by filtration, washed with water and dried in vacuo to give Co(modp)$_2$ (1.17 g, 70 %) as a light brown powder.

IR (neat): 1520, 1603, 2968.



II-58

((2*S*,3*S*)-3-(2-Methylene-4-((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methyl acetate (II-58). To a solution of ((2*S*,3*S*)-3-(2-methylene-4-((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methanol (**II-52**, 104 mg, 0.33 mmol, 1 equiv) in pyridine (0.45 mL) was added acetic anhydride (0.094 mL, 0.99 mmol, 3 equiv). After being stirred at rt for 4 h the solution was cooled in an ice bath and 10 % HCl (0.8 mL) was added to quench the reaction. Aqueous solution was extracted with Et_2O (5x1 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. Flash chromatography (Et_2O/petroleum ether = 1:2) of the residue afforded the acetate **II-58** (117 mg, 99 %) as a colorless oil.

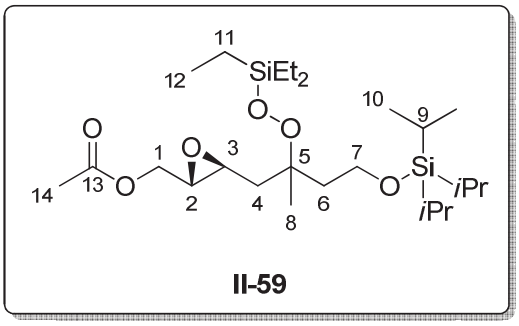
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (m, 21H, $H_{9,10}$), 2.08 (s, 3H, H_{12}), 2.31 (m, 4H, $H_{4,6}$), 2.98 (m, 2H, $H_{2,3}$), 3.79 (t, *J* = 6.9 Hz, 2H, H_7), 3.96 (dd, *J* = 12.3, 6.0 Hz, 1H, H_1), 4.36 (dd, *J* = 12.3, 3.0 Hz, 1H, H_1), 4.89 (s, 1H, H_8), 4.90 (s, 1H, H_8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C_9), 18.1 (C_{10}), 20.9 (C_{12}), 38.7, 40.1, 55.3, 55.4, 62.5 (C_7), 64.7 (C_1), 113.2 (C_8), 143.0 (C_5), 170.9 (C_{11}).

IR (neat): 1647, 1748, 2867, 2893, 2944, 3079.

HRMS (ESI): calculated for $C_{19}H_{36}O_4SiNa$ (MNa^+) 379.2281, found 379.2281.

$[\alpha]_D^{20}$ = -21.5 (*c* 1.25, CH_2Cl_2).



II-59

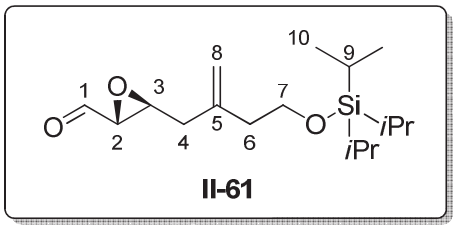
((2*S*,3*S*)-3-(2-Methyl-2-((triethylsilyl)peroxy)-4((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methyl acetate (II-59). ((2*S*,3*S*)-3-(2-methylene-4-((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methyl acetate (**II-58**, 117 mg, 0.33 mmol, 1 equiv), $Co(modp)_2$ (**II-57**, 18 mg, 0.033 mmol, 0.1 equiv) and dichloroethane (2.5 mL) were placed into the flask. The flask was charged with O_2 and Et_3SiH (0.105 mL, 0.66 mmol, 2 equiv) was added. After stirring for 5 h, the reaction mixture was evaporated. Flash chromatography (Et_2O/petroleum ether= 1:2) of the residue led to **II-59** (157 mg, 95 %, dr ~ 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (m, 6H, H_{11}), 0.97 (t, *J* = 7.8 Hz, 9H, H_{12}), 1.06 (m, 21H, $H_{9,10}$), 1.27 (s, 1.5H, H_8), 1.29 (s, 1.5H, H_8), 1.71-2.06 (m, 4H, $H_{4,6}$), 2.08 (s, 3H, H_{14}), 2.97 (m, 1H), 3.03 (m, 1H), 3.79 (t, *J* = 6.6 Hz, 1H, H_7), 3.81 (t, *J* = 6.6 Hz, 1H, H_7), 3.92 (dd, *J* = 12.3, 6.3 Hz, 1H, H_1), 4.38 (dm, *J* = 12.3 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.9 (C_{11}), 6.8 (C_{12}), 12.0 (C_9), 18.1 (C_{10}), 20.8 (C_{14}), 22.2 (C_8), 23.0 (C_8), 39.85, 39.95, 40.00, 40.88 ($C_{4,6}$), 53.2, 53.3, 55.0, 55.3 ($C_{2,3}$), 59.37 (C_1), 59.38 (C_1), 64.7 (C_1), 82.88 (C_5), 82.92 (C_5), 170.7 (C_{13}).

IR (neat): 1750, 2868, 2875, 2944, 2956.

HRMS (ESI): calculated for $C_{25}H_{52}O_6Si_2Na$ (MNa^+) 527.3200, found 527.3197.



II-61

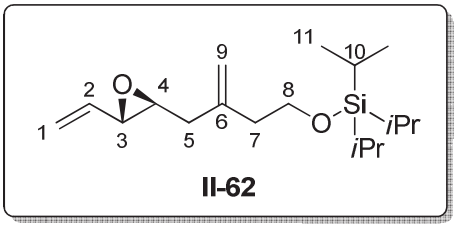
(2*R*,3*S*)-3-(2-Methylene-4-((triisopropylsilyl)oxy)butyl)oxirane-2-carbaldehyde (II-61). To a solution of ((2*S*,3*S*)-3-(2-methylene-4-((triisopropylsilyl)oxy)butyl)oxiran-2-yl)methanol (**II-52**, 57 mg, 0.18 mmol, 1 equiv) in CH_2Cl_2 (1.8 mL), TEMPO (3 mg, 0.018 mmol, 0.1 equiv) and BAIB (76 mg, 0.24 mmol, 1.3 equiv) were added successively at 0 ºC. The reaction mixture was stirred for 6 h at rt, quenched with saturated aqueous solution of Na_2SO_3 (1 mL) and extracted with Et_2O (5x1 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:8) to yield the epoxy aldehyde **II-61** (48 mg, 85 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (m, 21H, $H_{9,10}$), 2.32 (t, *J* = 6.6 Hz, 2H, H_6), 2.42 (m, 2H, H_4), 3.17 (dd, *J* = 6.0, 1.8 Hz, 1H, H_2), 3.37 (ddd, *J* = 6.0, 5.1, 1.8 Hz, 1H, H_3), 3.81 (t, *J* = 6.6 Hz, 2H, H_7), 4.94 (s, 2H, H_8), 9.03 (d, *J* = 6.3 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0 (C_9), 18.1 (C_{10}), 38.2, 39.9 ($C_{4,6}$), 55.6, 59.0 ($C_{2,3}$), 62.5 (C_7), 114.0 (C_8), 142.3 (C_5), 198.2 (C_1).

IR (neat): 1648, 1732, 2867, 2893, 2944.

HRMS (ESI): calculated for $C_{17}H_{32}O_3Si$ (MH^+) 313.2199, found 313.2199.



II-62

Triisopropyl ((3-(((2*S*,3*S*)-3-vinyloxiran-2-yl)methyl)but-3-en-1-yl)oxy)silane (II-62). A solution of NaHMDS (2 M, 5.9 mL, 11.8 mmol, 4 equiv) was added to the suspension

of Ph_3PMeBr (4.42 g, 12.4 mmol, 4.2 equiv) in 50 mL of freshly distilled THF at 0 ºC under stirring. After 30 min, a solution of (2*R*,3*S*)-3-(2-methylene-4-((triisopropylsilyl)oxy)butyl)oxirane-2-carbaldehyde (**II-61**, 0.92 g, 2.95 mmol, 1 equiv) in THF (2 mL) was added and the resulting mixture was stirred for 1 h, quenched with water (40 mL) and extracted with Et_2O/petroleum ether = 2:1 (5x20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:9) to yield the epoxy diene **II-62** (0.911 g, 99.6 %) as a colorless oil.

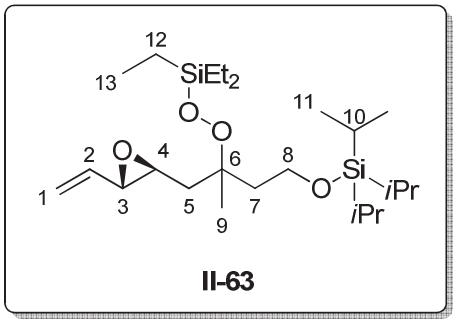
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (m, 21H, $H_{10,11}$), 2.24-2.41 (m, 4H, $H_{5,7}$), 2.95 (ddd, *J* = 5.7, 5.7, 2.2 Hz, 1H, H_4), 3.12 (dd, *J* = 7.2, 2.1 Hz, 1H, H_3), 3.80 (t, *J* = 6.9 Hz, 2H, H_8), 4.88 (s, 1H, H_9), 4.91 (m, 1H, H_9), 5.26 (m, 1H, H_1), 5.46 (dd, *J* = 17.2, 1.8 Hz, 1H, H_1), 5.60 (ddd, *J* = 17.2, 9.9, 7.2 Hz, 1H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (C_{10}), 18.1 (C_{11}), 39.2, 40.1 ($C_{5,7}$), 58.8, 59.2 ($C_{3,4}$), 62.6 (C_8), 113.1 (C_9), 119.3 (C_1), 135.7 (C_2), 143.1 (C_6).

IR (neat): 1645, 2867, 2893, 2943, 2958, 3085.

HRMS (ESI): calculated for $C_{18}H_{34}O_2SiNa$ (MNa^+) 333.2226, found 333.2226.

$[\alpha]_D^{20}$ = +1.0 (*c* 0.92, $CHCl_3$).



II-63

3,3-Diethyl-10,10-diisopropyl-6,11-dimethyl-6-(((2*S*,3*S*)-3-vinyloxiran-2-yl)methyl)-4,5,9-trioxa-3,10-disiladodecane (II-63). *Method A.* To a solution of triisopropyl((3-(((2*S*,3*S*)-3-vinyloxiran-2-yl)methyl)but-3-en-1-yl)oxy)silane (**II-62**, 90 mg, 0.29 mmol, 1 equiv) in DCE (5 mL) was added Co(modp)$_2$ (**II-57**, 16 mg, 0.029 mmol, 0.1 equiv). The flask was charged with O_2 and Et_3SiH (0.093 mL, 0.58 mmol, 2 equiv) was added (If the color of the reaction mixture does not change from rose-brown to green after 30 min, 1 drop of 5.5 M TBHP could be added in order to initiate the reaction). The reaction was stirred under a small pressure of O_2 until consumption of the starting material (visualized by TLC) and evaporated. Flash chromatography (Et_2O/petroleum ether = 1:10) of the residue gave **II-63** (60 mg, 45 %, dr ~ 1:1) as a colorless oil.

Method B. To a solution of triisopropyl((3-(((2*S*,3*S*)-3-vinyloxiran-2-yl)methyl)but-3-en-1-yl)oxy)silane (**II-62**, 70 mg, 0.226 mmol, 1 equiv) in DCE (1.5 ml) was added Co(thd)$_2$

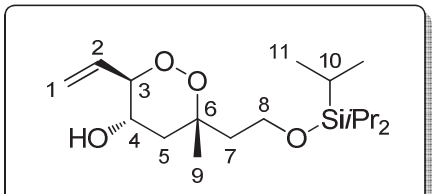
(10 mg, 0.023 mmol, 0.1 equiv) and the flask was charged with O_2. Et_3SiH (0.072 mL, 0.45 mmol, 2 equiv) was added and the reaction mixture was stirred under O_2 atmosphere until the reaction was finished (by TLC,~1.5h). Evaporation and flash chromatography (Et_2O/petroleum ether = 1:10) of the residue gave **II-63** (64 mg, 62 %, dr ~ 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (m, 6H, H_{12}), 0.97 (m, 9H, H_{13}), 1.06 (m, 21H, $H_{10,11}$), 1.27 (s, 1.5H, H_9), 1.29 (s, 1.5H, H_9), 1.76-2.01 (m, 4H, $H_{5,7}$), 2.98 (m, 1H), 3.08 (m, 1H), 3.80 (t, *J* = 6.9 Hz, 1.5H, H_9), 3.82 (t, *J* = 6.9 Hz, 1H, H_9), 5.25 (dd, *J* = 9.9, 1.9 Hz, 1H, H_1), 5.44 (dd, *J* = 17.2, 1.8 Hz, 1H, H_1), 5.57 (ddd, *J* = 17.1, 9.9, 7.2 Hz, 1H, H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.0 (C_{12}), 4.1 (C_{12}), 6.9 (C_{13}), 7.0 (C_{13}), 12.1 (C_{10}), 18.2 (C_{11}), 26.3, 40.2, 40.4 ($C_{5,7}$), 57.2, 58.6, 58.9, 59.5, 82.96 (C_6), 83.04 (C_6), 119.16 (C_1), 119.18 (C_1), 135.93 (C_2), 135.95 (C_2).

HRMS (ESI): calculated for $C_{24}H_{50}NaO_4Si_2$ (MNa^+) 481.3140, found 481.3126.

IR (neat): 1644, 2868, 2944, 2957.



II-64a

(3*R*,4*S*,6*R*)-6-Methyl-6-(2-((triisopropylsilyl)oxy)ethyl)-3-vinyl-1,2-dioxan-4-ol (II-64a). Amberlyst-15 (20 mg, 94 μmol, 0.45 equiv) was added to a solution of 3,3-diethyl-10,10-diisopropyl-6,11-dimethyl-6-(((2*S*,3*S*)-3-vinyloxiran-2-yl)methyl)-4,5,9-trioxa-3,10-disiladodecane (**II-63**, 95 mg, 0.207 mmol, 1 equiv) in dichloromethane (4 mL). The mixture was stirred for 5 h, filtered and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:2) to yield 1,2-dioxanes **II-64a** (24 mg, 33.5 %) and **II-64b** (24 mg, 33.5 %) as colorless oils.

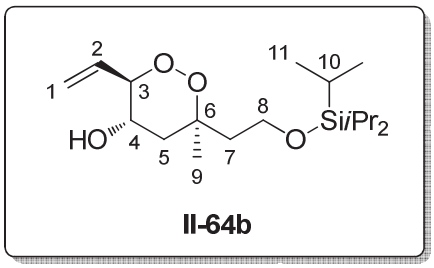
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 – 1.13 (m, 21H, $H_{10,11}$), 1.41 (s, 3H, H_9), 1.71 (dd, *J* = 12.8, 10.2 Hz, 1H, H_5), 1.74 – 1.94 (m, 3H, OH + H_7), 2.08 (dd, *J* = 12.9, 5.1 Hz, 1H, H_5), 3.77 – 3.85 (m, 3H, $H_{4,8}$), 4.20 (t, *J* = 7.9 Hz, 1H, H_3), 5.41 (d, *J* = 10.7 Hz, 1H, H_1), 5.48 (dt, *J* = 17.4, 1.1 Hz, 1H, H_1), 5.78 (ddd, *J* = 17.6, 10.6, 7.2 Hz, 1H, H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1 (C_{10}), 18.2 (C_{11}), 22.7 (C_9), 41.0 (C_5), 43.2 (C_7), 58.8 (C_8), 66.3 (C_4), 81.7 (C_6), 87.0 (C_3), 121.7 (C_1), 132.3 (C_2).

HRMS (ESI): calculated for $C_{18}H_{36}NaO_4Si$ (MNa^+) 367.2275, found 367.2290.

IR (neat): 2867, 2892, 2944, 3446.

$[\alpha]_D^{20}$ = -71.8 (*c* 0.73, $CHCl_3$).



II-64b

(3*R*,4*S*,6*S*)-6-Methyl-6-(2-((triisopropylsilyl)oxy)ethyl)-3-vinyl-1,2-dioxan-4-ol (II-64b). For experimental procedure see **II-64a**.

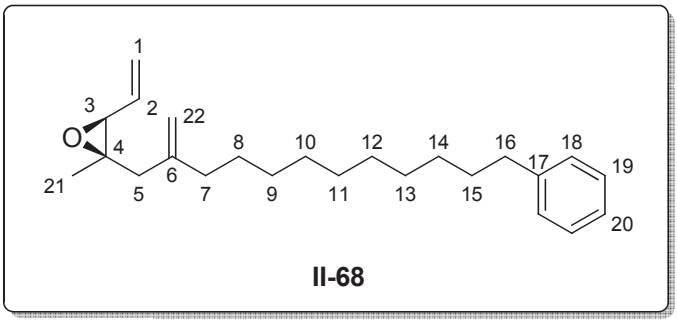
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05 – 1.14 (m, 21H, $H_{10,11}$), 1.23 (s, 3H, H_9), 1.54 (dd, *J* = 12.8, 10.9 Hz, 1H, H_5), 1.64 (bs, 1H, OH), 2.01 (dt, *J* = 14.1, 7.1 Hz, 1H, H_7), 2.09 (dt, *J* = 12.6, 6.3 Hz, 1H, H_7), 2.26 (dd, *J* = 12.8, 5.2 Hz, 1H, H_5), 3.80 – 3.85 (m, 3H, $H_{4,8}$), 4.17 (t, *J* = 16.5 Hz, 1H, H_3), 5.42 (dd, *J* = 10.6, 0.7 Hz, 1H, H_1), 5.49 (d, *J* = 17.3 Hz, 1H, H_1), 5.72 (ddd, *J* = 17.7, 10.6, 7.4 Hz, 1H, H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1 (C_{10}), 18.2 (C_{11}), 25.3 (C_9), 38.8 (C_7), 42.2 (C_5), 59.5 (C_8), 66.3 (C_4), 82.0 (C_6), 86.8 (C_3), 122.1 (C_1), 132.1 (C_2).

HRMS (ESI): calculated for $C_{18}H_{36}NaO_4Si$ (MNa^+) 367.2275, found 367.2287.

IR (neat): 1643, 2867, 2892, 2943, 3436.

$[\alpha]_D^{20}$ = -111.2 (*c* 0.7, $CHCl_3$).



II-68

(2*R*,3*S*)-2-Methyl-2-(2-methylene-12-phenyldodecyl)-3-vinyloxirane (II-68). To a cooled (-90 °C) solution of (2*R*,3*R*)-methyl 3-methyl-3-(2-methylene-12-phenyldodecyl)oxirane-2-carboxylate (**II-107a**, 26 mg, 0.07 mmol, 1 equiv) in toluene (1 mL) was added slowly a solution of DIBAL (1 M in hexanes, 0.35 mL, 0.35 mmol, 5 equiv). After stirring for 30-40 min at -78 °C, the reaction mixture was treated with MeOH (0.2 mL) and saturated aqueous Rochelle salt solution (1 mL). The mixture was warmed up to room temperature, stirred for 20 min and extracted with Et_2O (5x2 mL). The combined extracts

were washed with brine, dried over Na_2SO_4 and evaporated to yield crude aldehyde. *n*-BuLi (2.4 M, 0.12 mL, 0.28 mmol, 4 equiv) was added dropwise to the suspension of Ph_3PMeBr (125 mg, 34.9 mmol, 5 equiv) in THF (1.3 mL) cooled to -78 °C. After the temperature had raised to 0 °C the mixture was stirred for 30 min and the solution of aldehyde in THF (2 mL) was added dropwise. After 30 min, H_2O (3 mL) was added and the mixture was extracted with Et_2O/petroleum ether = 1:2 (5x4 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography on silica gel (Et_2O/petroleum ether = 3:97) gave **II-68** (19.6 mg, 83 %) as a colorless oil.

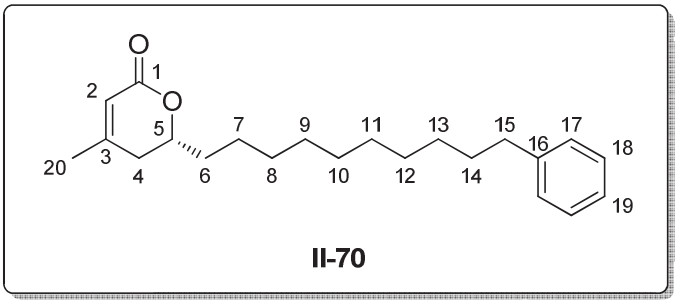
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26-1.43 (br m, 14 H, H_{8-14}), 1.31 (s, 3H, H_{21}), 1.60 (m, 2H, H_{15}), 1.99 (m, 2H, H_7), 2.18 (d, *J* = 15 Hz, 1H, H_5), 2.31 (d, *J* = 15 Hz, 1H, H_5), 2.59 (t, *J* = 7.5 Hz, 2H, H_{16}), 3.23 (d, *J* = 7.2 Hz, 1H, H_3), 4.78 (s, 1H, H_{22}), 4.83 (s, 1H, H_{22}), 5.33 (d, *J* = 10.5 Hz, 1H, H_1), 5.45 (d, *J* = 17.1 Hz, 1H, H_1), 5.78 (ddd, *J* = 7.2 Hz, 10.5 Hz, 17.1 Hz, 1H, H_2), 7.16-7.32 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (C_{21}), 27.8, 29.5-29.7 (6C), 31.7, 36.1, 36.5, 39.5, 62.2 (C_4), 64.2 (C_3), 112.1 (C_{22}), 120.1 (C_1), 125.7 (C_{20}), 128.3 (2C), 128.5 (2C), 133.6 (C_2), 143.1 (C_{17}), 146.1 (C_6).

HRMS (ESI): calculated for $C_{24}H_{36}NaO$ (MNa^+) 363.2658, found 363.2656.

IR (neat): 1643, 2854, 2927, 3026, 3070.

$[\alpha]_D^{20}$ = -3.2 (*c* 0.7, CH_2Cl_2).



II-70

(*R*)-4-Methyl-6-(10-phenyldecyl)-5,6-dihydro-2H-pyran-2-one (II-70). <u>*Method A.*</u> Methyl lithium (1.6 M in Et_2O, 31 mL, 49.6 mmol, 6 equiv) was added to a stirred suspension of CuI (5.03 g, 26.5 mmol, 3.2 equiv) in THF (40 mL) at -78 °C. Once the addition was complete, the mixture was allowed to warm up to 0 °C to help the formation of the cuprate. Once a clear solution had been obtained, the reaction mixture was cooled to -78 °C and (*R*)-ethyl 5-hydroxy-15-phenylpentadec-2-ynoate (**II-79**, 2.96 g, 8.27 mmol, 1 equiv) in THF (30 mL) was added dropwise over 10 min. The resulting solution was allowed to stir for 30 min and was then quenched with sat. aq NH_4Cl and NH_4OH (3:1) at -78 °C. The layers were separated, and the aqueous phase extracted four times with Et_2O (20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. To a stirred solution of residue in MeOH (40 mL) was added a catalytic amount of PTSA (0.157 g, 0.827

mmol, 0.1 equiv) under N_2 atmosphere. After stirring for 3 h at rt the reaction mixture was quenched with solid $NaHCO_3$ and filtered off. The solvent was removed at reduced pressure and the residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:1) to give the butenolide **II-70** (2.28 g, 84 %) as a colorless solid. $[\alpha]_D^{20}$ = -71.4 (*c* 0.78, CH_2Cl_2).

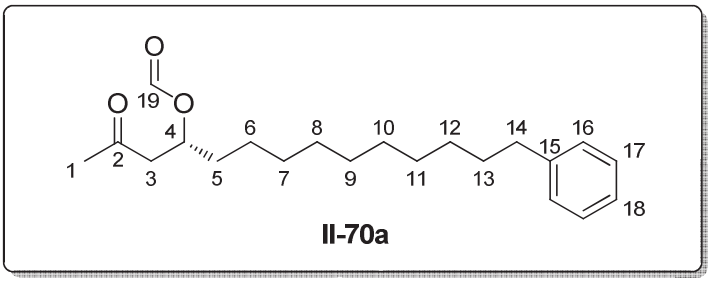
Method B. Pyridinium dichromate (72 mg, 0.19 mmol, 2 equiv) was added to a solution of (2*R*,6*R*)-6-Methoxy-4-methyl-2-(10-phenyldecyl)-3,6-dihydro-2H-pyran (**II-97**, 33 mg, 95.7 µmol, 1 equiv) and AcOH (0.2 mL) in CH_2Cl_2 (1.2 mL). The reaction mixture was stirred at rt for 3 h, then 1.5 mL of Et_2O/petroleum ether (1:1) was added and the resulting mixture was filtered through a pad of Na_2SO_4 (upper layer) and silicagel (lower layer). Combined organics were evaporated and the residue was chromatographed on preparative TLC (MeOH/petroleum ether = 1:20) to give **II-70** (18.2 mg, 58 %) and **II-70a** (2.5 mg, 8 %) as a colorless oisl. $[\alpha]_D^{20}$ = -86.3 (*c* 0.785, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28-1.84 (m, 18H, $H_{6\text{-}14}$), 1.97 (s, 3H, H_{20}), 2.17 (dd, *J* = 17.8, 4.1 Hz, 1H, H_4), 2.31 (dd, *J* = 17.8, 11.6 Hz, 1H, H_4), 2.60 (t, *J* = 7.8 Hz, 2H, H_{15}), 4.36 (m, 1H, H_5), 5.80 (m, 1H, H_2), 7.16-7.19 (m, 3H, H_{Ar}), 7.25-7.30 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1 (C_{20}), 25.0, 29.4, 29.5, 29.56, 29.58, 29.61, 29.63, 31.6, 34.8, 34.9, 36.1, 77.4 (C_5), 116.6 (C_2), 125.6 (C_{19}), 128.3, 128.5 ($C_{17\text{-}18}$), 143.0 (C_{16}), 157.2 (C_3), 165.5 (C_1).

HRMS (CI): calculated for $C_{22}H_{33}O_2$ (MH^+) 329.2481, found 329.2487.

IR (neat): 1720, 2853, 2925, 3026.



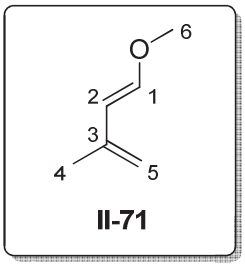
II-70a

(R)-2-oxo-14-phenyltetradecan-4-yl formate (II-70a). For experimental procedure see **II-70** *method B*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (m, 12H), 1.60 (m, 6H), 2.17 (s, 3H, H_1), 2.60 (t, *J* = 7.7 Hz, 2H, H_{14}), 2.63 (m, *J* = 16.8, 5.1 Hz, 1H, H_3), 2.80 (dd, *J* = 16.7, 7.4 Hz, 1H, H_3), 5.34 (m, 1H, H_4), 7.14-7.19 (m, 3H, H_{Ar}), 7.25-7.30 (m, 2H, H_{Ar}), 8.04 (s, 1H, H_{19}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 29.4-29.7 (6C), 30.6, 31.7, 34.2, 36.1, 47.8, 70.5, 125.7, 128.4 (2C), 128.5 (2C), 143.1, 160.8, 205.5.

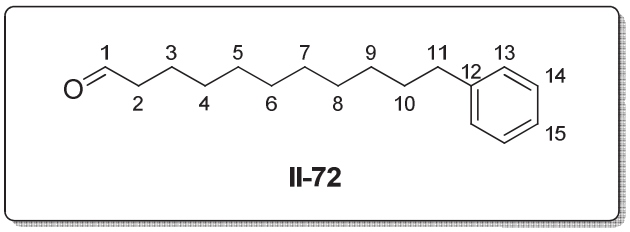
HRMS (CI): calculated for $C_{21}H_{32}O_3Na$ (MNa^+) 355.2244, found 355.2253.



II-71

1-Methoxy-3-methylbuta-1,3-diene (II-71).[188] A solution of *t*-BuLi in pentane (1.7 M, 5.16 mL, 8.77 mmol, 1.2 equiv) was added dropwise to a cooled (-78 ^{o}C) solution of 1,1-dimethoxy-3-methylbut-2-ene (**II-91**, 0.95 g, 7.31 mmol, 1 equiv) in pentane (5 mL). After completion of the addition, the reaction mixture was warmed up slowly to 0 ^{o}C (3 h) and carefully quenched with water. The organic phase was separated and the aqueous phase was extracted with pentane (2x3 mL). The combined organic extracts were dried (Na_2SO_4) and fractionally distilled to give **II-71** (0.41 g, 57 %, bp = 50 ^{o}C at ~20 torr) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (s, 3H, H_4), 3.60 (s, 3H, H_6), 4.69 (s, 1H, H_5), 5.67 (d, *J* = 1.5 Hz, 1H, H_5), 5.64 (d, *J* = 12.6 Hz, 1H, H_2), 6.58 (d, *J* = 12.6 Hz, 1H, H_1).

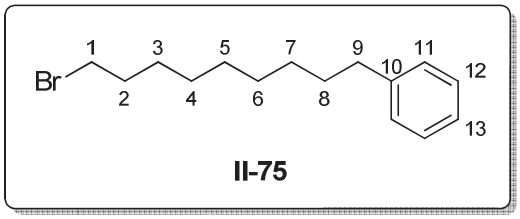


II-72

11-Phenylundecanal (II-72).[184b] To a cooled (0 ^{o}C) solution of 11-phenylundecan-1-ol (**II-88**, 1 g, 4.03 mmol, 1 equiv) and Et_3N (3.36 mL, 24.2 mmol, 6 equiv) in the mixture of dry CH_2Cl_2 (20 mL) and dry DMSO (6 mL) was added SO_3·Py (1.92 g, 12.1 mmol). After stirring for 3h, water (25 mL) was added and the mixture was extracted with Et_2O (4x8 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:10) to give **II-72** (0.98 g, 99 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (m, 12H, H_{4-9}), 1.63 (m, 4H, $H_{3,10}$), 2.42 (dt, *J* = 7.2, 1.8 Hz, 2H, H_2), 2.61 (t, *J* = 7.5 Hz, 2H, H_{11}), 7.17-7.30 (m, 5H, H_{Ar}), 9.77 (t, *J* = 1.8 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 29.3, 29.5-29.6 (5C), 31.7, 36.1, 44.1 (C_{2-11}), 125.7 (C_{15}), 128.3 (2C), 128.5 (2C), 143.1 (C_{12}), 203.1 (C_1).

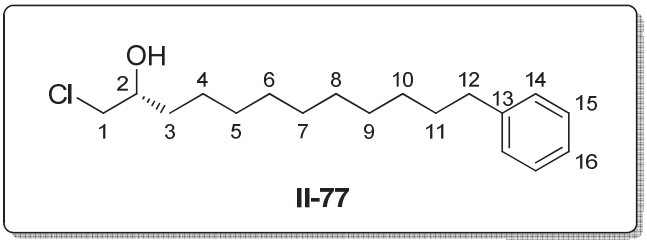


II-75

(9-Bromononyl)benzene (II-75).[181] To a cooled (-10°C) well-stirred solution of 1,6-dibromohexane (17.68 g, 72.5 mmol, 3 equiv.), CuBr (35 mg, 0.24 mmol, 0.01 equiv.) and LiCl (20 mg, 0.48 mmol, 0.02 equiv.) in THF (15 ml). was slowly added 3-phenylpropyl)magnesium bromide in THF (15 ml), prepared from (3-bromopropyl)benzene (3.67 mL, 24.2 mmol, 1 equiv) and Mg (0.65 g, 26.6 mmol, 1.1 equiv). During the addition, the temperature was kept below 0 ^{o}C. Stirring was continued overnight at rt, and saturated solution of NH_4Cl (15 ml) was added. This mixture was extracted by Et_2O (4x10 mL). The combined organic extracts were washed with brine, hydrochloric acid (2 M), a solution of Na_2CO_3 (10 %), water and dried (Na_2SO_4). Evaporation of solvents and fractional distillation of the residue gave 1,6-dibromohexane (12.17 g, 69 %, bp = 95 ^{o}C at 1 torr) and **II-75** (6.26 g, 92 %, bp = 95 ^{o}C at 0.03 torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32-1.47 (m, 10H, H_{3-7}), 1.63 (m, 2H), 1.86 (m, 2H), 2.62 (t, *J* = 7.5 Hz, 2H, H_9), 3.41 (t, *J* = 6.9 Hz, 2H, H_1), 7.16-7.20 (m, 3H, H_{Ar}), 7.27-7.32 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 28.9, 29.4, 29.48, 29.51, 31.6, 33.0, 34.2, 36.1 (C_{1-9}), 125.7 (C_{13}), 128.4, 128.5 (C_{11-12}), 143.0 (C_{10}).

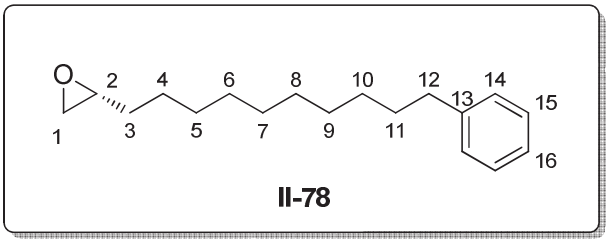


II-77

(2*R*)-1-Chloro-12-phenyldodecan-2-ol (II-77). To a mixture of (*R*)-epichlorohydrin (99% ee, 0.2 g, 0.17 mL, 2.16 mmol, 0.7 equiv), CuCN (28 mg, 0.31 mmol, 0.1 equiv), and THF (3 mL) was added dropwise at -78 °C 9-phenylnonylmagnesium bromide in THF(6 mL), prepared from (9-bromononyl)benzene (**II-75**, 0.88 g, 3.1 mmol, 1 equiv) and Mg turnings (83 mg, 3.4 mmol, 1.1 equiv). The solution was warmed up to 0 °C over 2 h and poured into a mixture of saturated NH_4Cl (10 mL) and Et_2O (10 mL) with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic extracts were dried and concentrated to furnish the crude **II-77** (0.86 g), which was used in the next step without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (m, 14H, $H_{4\text{-}10}$), 1.50-1.63 (m, 4H, $H_{3,11}$), 2.14 (bs, 1H, OH), 2.60 (t, *J* = 7.5 Hz, 2H, H_{12}), 3.45-3.83 (m, 3H, $H_{1,2}$), 7.17-7.19 (m, 3H, H_{Ar}), 7.25-7.30 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7, 29.5, 29.6, 29.7, 29.8, 31.7, 34.3, 36.1, 50.7(C_1), 71.6 (C_2), 125.7 (C_{16}), 128.3, 128.5 ($C_{14\text{-}15}$), 143.0 (C_{13}).



II-78

(2*R*)-2-(10-Phenyldecyl)oxirane (II-78). To a solution of the (2*R*)-1-chloro-12-phenyldodecan-2-ol (0.86 g) in THF (5 mL) was added crushed NaOH (0.618 g, 15.4 mmol). The mixture was stirred vigorously at room temperature for 3 h and poured into water. The product was extracted with Et_2O (4x10 mL). The combined ethereal solutions were washed with saturated NH_4Cl, dried (Na_2SO_4), and concentrated. Purification by flash chromatography of the oily residue (Et_2O/petroleum ether = 5:95) afforded the epoxide **II-78** (0.443 g, 79% for 2 steps).

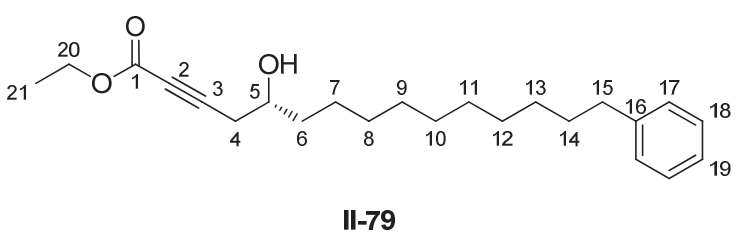
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29-1.63 (m, 18H, $H_{3\text{-}11}$), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H, H_1), 2.61 (t, *J* = 7.5 Hz, 2H, H_{12}), 2.76 (dd, *J* = 4.9, 4.1 Hz, 1H, H_1), 2.92 (m, 1H, H_2), 7.18-7.20 (m, 3H, H_{Ar}), 7.26-7.31 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 29.5-29.7 (6C), 31.7, 32.6, 36.1, 47.3(C_1), 52.5 (C_2), 125.7 (C_{16}), 128.3, 128.5 ($C_{14\text{-}15}$), 143.0 (C_{13}).

HRMS (CI): calculated for $C_{18}H_{29}O$ (MH^+) 261.2218, found 261.2216.

IR (neat): 1604, 2854, 2926, 3027, 3061, 3085.

$[\alpha]_D^{20}$ = +4.2 (*c* 1.22, CH_2Cl_2).



II-79

(*R*)-Ethyl 5-hydroxy-15-phenylpentadec-2-ynoate (II-79). A solution of *n*-butyl lithium (2.5 M in hexanes, 9.92 mL, 24.8 mmol) cooled to -78 °C was added dropwise to a solution of ethyl propiolate (2.51 mL, 24.8 mmol) in THF (44 mL) at -90 °C. After 20 min, $BF_3{\cdot}Et_2O$ (3.15 mL, 24.8 mmol) was added. After a further 10 min, a solution of (2*R*)-2-(10-phenyldecyl)oxirane (**II-78**, 2.15 g, 8.27 mmol) in THF (10 mL) was added dropwise and the resulting solution allowed to warm to rt, stirred for 15 min and cooled to 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl and allowed to warm to rt. The layers were separated and the aqueous phase extracted five times with Et_2O (30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ and brine then dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/petroleum ether = 1:2) to provide **II-79** (2.9 g, 98 %) as a clear oil.

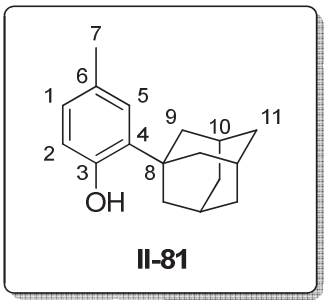
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (m, 14H, $H_{7\text{-}13}$), 1.31 (t, *J* = 7.2 Hz, 3H, H_{21}), 1.52-1.64 (m, 4H, $H_{6,14}$), 2.02 (s, 1H, OH), 2.47 (dd, *J* = 17.1, 6.5 Hz, 1H, H_4), 2.56 (dd, *J* = 17.1, 6.5 Hz, 1H, H_4), 2.60 (t, *J* = 7.5 Hz, 2H, H_{15}), 3.84 (m, 1H, H_5), 4.22 (q, *J* = 7.2 Hz, 2H, H_{20}), 7.17-7.19 (m, 3H, H_{Ar}), 7.25-7.30 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (C_{21}), 25.7, 27.7, 29.5-29.7 (6C), 31.7, 36.1, 36.6, 62.1(C_{20}), 69.7 (C_5), 75.1 (C_2), 86.0 (C_3), 125.7 (C_{19}), 128.3, 128.5 ($C_{17\text{-}18}$), 143.0 (C_{16}), 153.7 (C_1).

HRMS (ESI): calculated for $C_{23}H_{34}O_3Na$ (MNa^+) 381.2400, found 381.2400.

IR (neat): 1604, 1712, 2236, 2854, 2927, 2982, 3026, 3062, 3423.

$[\alpha]_D^{20}$ = -3.7 (*c* 0.965, CH_2Cl_2).

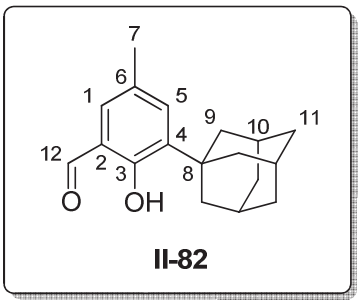


II-81

2-(Adamantan-1-yl)-4-methylphenol (II-81).[179] To a solution of *p*-cresol (0.84 g, 7.78 mmol, 1 equiv) and 1-adamantanol (1.24 g, 8.17 mmol, 1.05 equiv) in CH_2Cl_2 (7 mL) was added dropwise over 10 min concentrated H_2SO_4 (18 M, 0.44 mL). The biphasic mixture was allowed to stir for 20 min and H_2O (7 mL) was added. The mixture was neutralized slowly to pH = 9 by addition of a NaOH (2M). The mixture was extracted with CH_2Cl_2 (3x10mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude mixture was triturated with MeOH (8 mL), heated to reflux, allowed to cool to ambient temperature and filtered. The solid was washed with an additional portion of MeOH (10 mL) and the mother liquor concentrated to give a product as a white solid (1.44 g, 76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (s, 6H, H_{11}), 2.08 (bs, 3H, H_{10}), 2.12 (bs, 6H, H_9), 2.27 (s, 3H, H_7), 2.61 (bs, 1H, OH), 6.56 (d, J = 7.8 Hz, 1H, H_2), 6.85 (d, J = 7.8 Hz, 1H, H_1), 7.01 (bs, 1H, H_5).

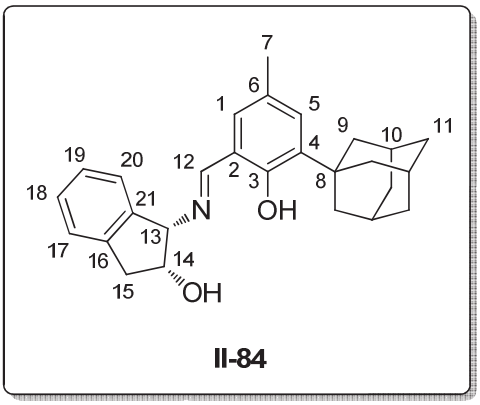
^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 29.2, 36.7, 37.2, 40.7, 116.7, 127.1, 127.7, 129.6, 136.3, 152.5.



II-82

3-(Adamantan-1-yl)-2-hydroxy-5-methylbenzaldehyde (II-82).[179] An oven-dried flask was charged with 2-adamantyl-1-p-cresol (2.53 g, 10.4 mmol, 1 equiv), freshly distilled toluene (22 mL) and 2,6-lutidine (0.895 g, 0.97 mL, 8.35 mmol, 0.8 equiv). $SnCl_4$ (0.544 g, 0.244 mL, 2.09 mmol, 0.2 equiv) was added by syringe over 5 min. The reaction turned pale yellow in color with a pale yellow precipitate. The mixture was allowed to stir at room temperature for 20 min, then solid paraformaldehyde (1.25 g, 41.8 mmol) was added in one portion and the reaction was stirred for an additional 10 min. The reaction flask was placed in a 90-95 ^oC bath and maintained at this temperature for 12 hours. The reaction was allowed to cool to room temperature and filtered through celite-silica gel (1:1, 12 g). The celite-SiO_2 was washed with ethyl acetate (40 ml). The organic filtrate was then washed with water (70 mL), 1N HCl (70 mL) and brine (70mL). The organic layer was dried (Na_2SO_4), filtered and concentrated on a rotary-evaporator, followed by removal of trace solvent on a high vacuum pump (0.5 mmHg) (2.75 g crude, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 6H, H_{11}), 2.09 (bs, 3H, H_{10}), 2.13 (s, 6H, H_9), 2.33 (s, 3H, H_7), 7.16 (m, 1H), 7.27 (d, J = 2.1 Hz, 1H), 9.83 (s, 1H, H_{12}), 11.65 (s, 1H, OH).

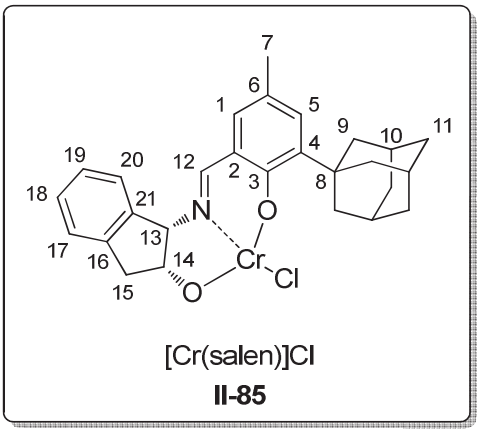


II-84

(1*S*,2*R*)-1-((*E*)-(3-(Adamantan-1-yl)-2-hydroxy-5-methylbenzylidene)amino)-2,3-dihydro-1H-inden-2-ol (II-84).[179] 3-(adamantan-1-yl)-2-hydroxy-5-methylbenzaldehyde (**II-82**, 0.915 g, 3.38 mmol, 1 equiv) was dissolved in 14 mL of ethanol under heating and then (1*S*,2*R*)-1-amino-2,3-dihydro-1H-inden-2-ol (0.53 g, 3.55 mmol, 1.05 equiv) was added in one portion. The reaction mixture was heated at 80 °C for 45 min, cooled to room temperature and allowed to stand for 5 h. The yellow solid product (1.09 g, 80 %) was isolated by filtration, washed with cold ethanol (4 mL) and dried in the air.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (s, 6H, H_{11}), 2.06 (bs, 3H, H_{10}), 2.14 (s, 6H, H_9), 2.31 (s, 3H, H_7), 3.13 (dd, *J* = 15.9, 4.9 Hz, 1H, H_{15}), 3.25 (dd, *J* = 15.9, 5.8 Hz, 1H, H_{15}), 4.69 (ddd, *J* = 5.4, 5.4, 5.1 Hz, 1H, H_{14}), 4.79 (d, *J* = 5.3 Hz, 1H, H_{13}), 6.99 (s, 1H, H_{Ar}), 7.13 (d, *J* = 1.9 Hz, 1H, H_{Ar}), 7.16-7.34 (m, 4H, H_{Ar}), 8.56 (s, 1H, H_{12}), 13.00 (bs, 1H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 29.2, 37.1, 37.2, 39.8, 40.4, 75.3, 75.8, 118.4, 125.1, 125.6, 127.2, 127.3, 128.7, 130.1, 131.5, 137.9, 140.9, 141.0, 158.4, 168.2.

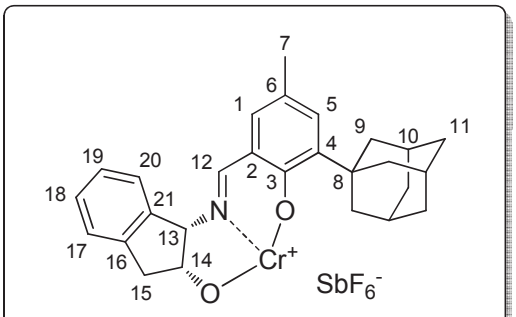


[Cr(salen)]Cl

II-85

[Cr(salen)]Cl (II-85).[179] A 25-mL round-bottomed flask was charged with chromium(III) chloride-tetrahydrofuran complex (0.264 g, 0.71 mmol, 1 equiv) and (1*S*,2*R*)-1-((*E*)-(3-(adamantan-1-yl)-2-hydroxy-5-methylbenzylidene)amino)-2,3-dihydro-1H-inden-2-ol (**II-84**, 0.285 g, 0.71 mmol, 1 equiv). The reaction mixture was placed under a nitrogen atmosphere, and CH_2Cl_2 (6 mL) was added followed by dropwise addition of 2,6-lutidine (0.165 mL, 1.42 mmol, 2 equiv). The solution was stirred for 3 h, diluted with CH_2Cl_2 (30 mL), and washed with water (3x18 mL), then brine (18 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting solid was triturated with acetone (1 mL), filtered, washed with an additional portion of acetone (2 mL), and air-dried to give the chromium complex as a brown solid (0.247 g, 72 %).

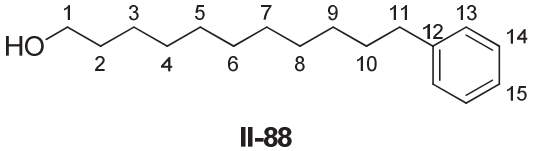
MS (ESI): 919 ($2M^+$-2Cl+H_2O, $C_{54}H_{60}Cr_2N_2O_5$), 933, 947.



[Cr(salen)]SbF_6

II-86

[Cr(salen)]SbF_6 (II-86).[179] A flame-dried, 50-mL, foil wrapped round-bottomed flask equipped with a stirring bar was charged with complex **1a** (93 mg, 0.19 mmol, 1 equiv) and silver hexafluoroantimonate (131 mg, 0.38 mmol, 2 equiv). The flask was placed under a nitrogen atmosphere, *tert*-butyl methyl ether (30 mL) was added, and the mixture was stirred for 3 h. The reaction mixture was then filtered through celite and the solid was washed with *tert*-butyl methyl ether (20 mL). The combined organic layers were concentrated in vacuo to afford the desired complex **II-86** as a brown solid (258 mg, quant).

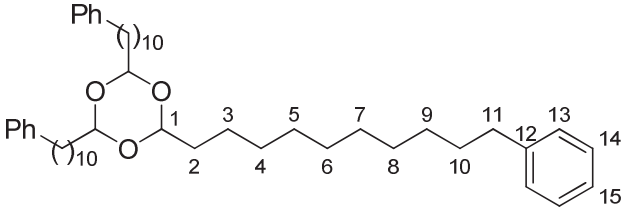


II-88

11-Phenylundecan-1-ol (II-88).[256] A dried flask, equipped with reflux condenser, a N_2 inlet, and a magnetic stirring bar, was charged with Mg turnings (1.08 g, 45 mmol, 9 equiv) and THF (45 mL). A portion of PhBr (3.7 mL, 35 mmol, 7 equiv) was added to the flask via syringe and it was gently warmed. Following Grignard reaction initiation, the rest of bromobenzene was added over 30 min. After heating for 1 h at 50 ^oC, the reaction was cooled to rt. Grignard reagent was transferred into 100 mL flask and cooled to -20 ^oC. Li_2CuCl_4 (0.1 M in THF, 5 mL, 0.5 mmol, 0.1 equiv) was added and stayed stirred for 20 min. A solution of 11-bromoundecan-1-ol (1.26 g, 5 mmol, 1 equiv) in THF (10 mL) was added at -78 ^oC and stayed stirred for 2 days at rt. The reaction mixture was treated with saturated aqueous solution of NH_4Cl (15 mL), water (20 mL) and Et_2O (40 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x20 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$, dried and evaporated. Flash column chromatography (Et_2O/petroleum ether = 1:1) of the residue afforded pure alcohol **II-88** (1.18 g, 95 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28-1.42 (m, 14H, $H_{3\text{-}9}$), 1.59 (m, 4H, $H_{2,10}$), 2.60 (t, *J* = 7.5 Hz, 2H, H_{11}), 3.64 (t, *J* = 6.6 Hz, 2H, H_1), 7.17-7.19 (m, 3H, H_{Ar}), 7.25-7.30 (m, 2H, H_{Ar}).

MS (EI): 91, 104, 117, 131, 248 (M^+).



II-89

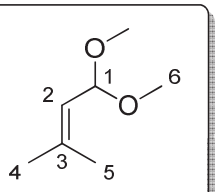
2,4,6-*tris*(10-Phenyldecyl)-1,3,5-trioxane (II-89). 11-phenylundecanal (**II-72**) trimerized slowly during on storage to give compound **II-89**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (m, 42H, $H_{3\text{-}9}$), 1.63 (m, 12H, $H_{2,10}$), 2.59 (t, *J* = 7.5 Hz, 6H, H_{11}), 4.82 (t, *J* = 5.1 Hz, 3H, H_1), 7.16-7.18 (m, 9H, H_{Ar}), 7.24-7.29 (m, 6H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 29.5-29.7, 31.7, 34.6, 36.1, 101.8, 125.7, 128.3, 128.5, 143.0.

HRMS (ESI): calculated for $C_{51}H_{78}O_3Na$ (MNa^+) 761.5843, found 761.5872.

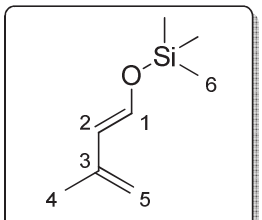
IR (neat): 1605, 1709, 2850, 2922, 3028, 3063, 3086.



II-91

1,1-Dimethoxy-3-methylbut-2-ene (II-91). Prepared by a modified procedure of Hieber and Ebel.[187] 3-methylbut-2-enal (2 mL, 20.8 mmol, 1 equiv) was added dropwise to a stirred and cooled (0 °C) mixture of trimethoxymethane (2.5 mL, 22,8 mmol, 1.1 equiv), $KHSO_4$ (0.14 g, 1.04 mmol, 0.05 equiv) and MeOH (0.84 mL, 20.8 mmol, 1 equiv). After completion of the addition, the reaction mixture was heated to rt and stirred overnight. K_2CO_3 (200 mg) was added and the resulting mixture was stirred for 1 h, filtered and distilled to give **II-91** (2.17 g, 80 %) as a colorless oil.

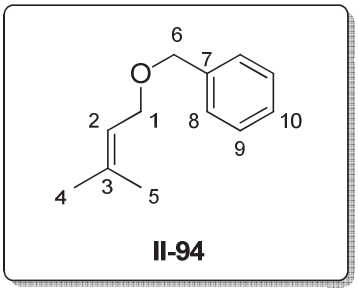
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 1.2 Hz, 1H), 1.76 (d, *J* = 1.1 Hz, 1H), 3.31 (s, 2H), 5.00 (d, *J* = 6.7 Hz, 1H), 5.25 (ddt, *J* = 6.6, 2.7, 1.3 Hz, 1H).



II-92

(*E*)-Trimethyl((3-methylbuta-1,3-dien-1-yl)oxy)silane (II-92). To a solution of 3-methyl-2-butenal (0.84 g, 0.01 mol) in ether (2 mL), triethylamine (2.45 g, 0.019 mol), and dry $ZnCl_2$ (0.014 g) was added dropwise neat chlorotrimethylsilane (1.195 g, 0.011 mol). This solution was warmed at reflux for 25 h. Then 5 mL of *n*-pentane was added at 20 ^oC. The precipited of triethylamine hydrochloride was filtered, and the solution was evaporated. The crude product was distilled (bp_{16} = 55 ^oC) to give pure product (1.271 g, 81%) as a 95:5 mixture of *E* and *Z* isomers.

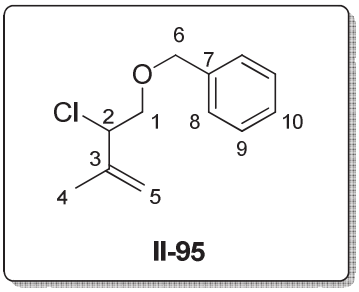
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.21 (9 H, s, H_6), 1.80 (3 H, s, H_5), 4.68 (1 H, s, H_4), 4.75 (1 H, s, H_4), 5.82 (1 H, d, *J* = 12 Hz, H_2), 6.50(1H, d, *J* = 12 Hz, H_1).



II-94

(((3-Methylbut-2-en-1-yl)oxy)methyl)benzene (II-94).[257] To a 0 ºC solution of NaH (60 % in mineral oil, 1.2 g, 30.0 mmol, 1.4 equiv) in 70 mL of THF was added BnBr (2.54 mL, 21.4 mmol, 1 equiv), followed by dropwise addition of 3-methyl-2-butene-1-ol (2.28 mL, 22.5 mmol, 1.05 equiv). The reaction mixture was warmed to ambient temperature and maintained at this temperature for 12 h. The solution was diluted with H_2O (30 mL). The layers were separated, and the aqueous layer was extracted with hexanes (3 x 25 mL). The combined organic layers were washed with 30 mL of saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (Et_2O/petroleum ether = 1:5) to afford **II-94** (3.61 g, 96%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68 (s, 3H), 1.78 (s, 3H), 4.02 (d, *J* = 6.9 Hz, 2H, H_1), 4.52 (s, 2H, H_6), 5.43 (m, 1H, H_2), 7.26-7.37 (m, 5H, H_{Ar}).

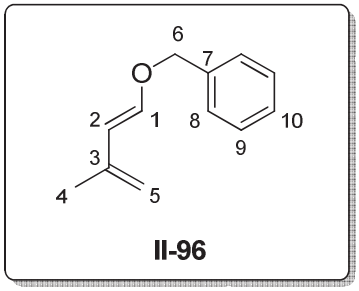


II-95

(((2-Chloro-3-methylbut-3-en-1-yl)oxy)methyl)benzene (II-95).[189] Phenylselenium chloride (0.34 g, 1.77 mmol, 0.1 equiv) was dissolved in CH_3CN (85 mL) (stored over 4 Å MS), producing an orange solution. To this solution was added (((3-methylbut-2-en-1-yl)oxy)methyl)benzene (**II-94**, 3.12 g, 17.7 mmol, 1 equiv). The addition of the olefin resulted in an immediate color change from orange to pale yellow. N-chlorosuccinimide (2.6 g, 19.5 mmol, 1.1 equiv) was then added to the mixture. The reaction mixture was stirred for 12 h, concentrated and Et_2O (100 mL) was added. The ether was decanted from the solid and washed with H_2O (2x30 mL). The resulting ether solution was dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography (Et_2O/petroleum ether = 1:10) to give **II-95** (2.75 g, 74 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3H, H_4), 3.69 (dd, *J* = 8.3, 4.9 Hz, 1H, H_1), 4.54-4.65 (m, 3H, $H_{2,6}$), 5.02 (m, 1H, H_5), 5.13 (s, 1H, H_5), 7.29-7.41 (m, 5H, H_{Ar}).

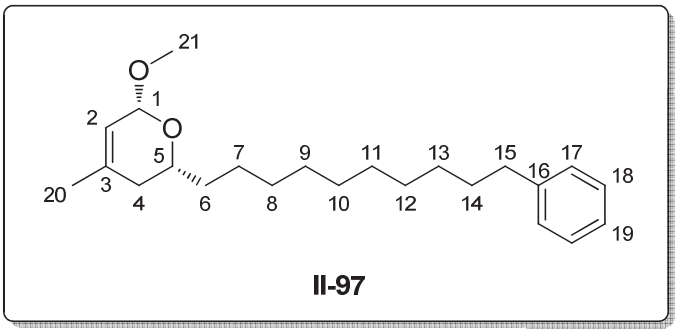
^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (C_4), 63.3 (C_2), 72.1, 73.3 ($C_{1,6}$), 116.1 (C_5), 127.8, 127.9, 128.6 ($C_{8\text{-}10}$), 137.8 (C_7), 142.1 (C_3).



II-96

(*E*)-(((3-methylbuta-1,3-dien-1-yl)oxy)methyl)benzene (II-96).[258] *t*BuOK (294 mg, 2.6 mmol, 1.8 equiv) was dissolved in THF (3 mL) and the solution of (((2-Chloro-3-methylbut-3-en-1-yl)oxy)methyl)benzene (**II-95**, 307 mg, 1.46 mmol, 1 equiv) in 0.5 mL of THF was added dropwise. The reaction mixture was stirred at rt for 3-5 h, quenched with water (0.1 mL), diluted with petroleum ether and filtered. The crude residue, after solvent evaporation, was purified by flash column chromatography (Et_2O/petroleum ether = 1:10) to give **II-96** (35 mg, 14 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (dd, *J* = 1.2, 0.6 Hz, 3H, H_4), 4.63 (m, 1H, H_5), 4.71 (m, 3H, $H_{5,6}$), 5.71 (d, *J* = 12.8 Hz, 1H, H_2), 6.53 (d, *J* = 12.8 Hz, 1H, H_1), 7.17 – 7.30 (m, 5H, H_{Ar}).



II-97

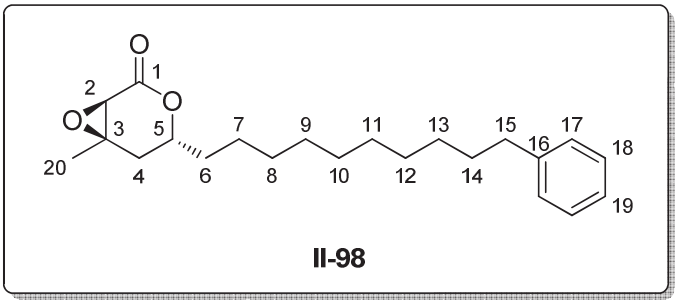
(2*R*,6*R*)-6-Methoxy-4-methyl-2-(10-phenyldecyl)-3,6-dihydro-2H-pyran (II-97). 1-Methoxy-3-methylbuta-1,3-diene (**II-71**, 80 % in pentane, 238 mg, 1.95 mmol, 1.5 equiv) was added to a stirring mixture of 11-phenylundecanal (**II-72**, 314 mg, 1.28 mmol, 1 equiv), [Cr(salen)]Cl (**II-85**, 18 mg, 38 µmol, 0.03 equiv), and 4Å molecular sieves (240 mg) under N_2 at ambient temperature. The mixture was stirred for 24 h and chromatographed on silica gel (Et_2O/petroleum ether/Et_3N = 8:91:1) to furnish **II-72** (35 mg, 11 %) and **II-97** (241 mg, 55 %) as a slight-yellow oil.

^{1}H NMR (300 MHz, C_6D_6): δ = 1.26 (m, 12H), 1.47 (s, 3H, H_{20}), 1.38 – 1.82 (m, 8H), 2.51 (t, *J* = 7.6 Hz, 2H, H_{15}), 3.42 (s, 3H, H_{21}), 3.50 (tdd, *J* = 9.6, 6.5, 4.0 Hz, 1H, H_5), 5.05 (m, 1H, H_1), 5.45 (m, 1H, H_2), 7.05 – 7.11 (m, 3H, H_{Ar}), 7.16 – 7.21 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, C_6D_6): δ = 22.7 (C_{20}), 26.1, 29.7, 30.0 – 30.2 (5C), 32.0, 35.9, 36.1, 36.4, 54.5 (C_{21}), 72.1 (C_5), 99.1 (C_1), 122.6, 126.0, 128.6 (2C), 128.8 (2C), 136.7, 143.0.

HRMS (ESI): calculated for $C_{23}H_{36}NaO_2$ (MNa^+) 367.2608, found 367.2611.

IR (neat): 1604, 1681, 2852, 2923, 3025, 3061.



II-98

(1*R*,4*R*,6*R*)-6-Methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one (II-98). To a solution of (*R*)-4-methyl-6-(10-phenyldecyl)-5,6-dihydro-2H-pyran-2-one (**II-70**, 2.28 g, 6.95 mmol, 1 equiv) in MeOH (100 mL) was added H_2O_2 (35 %, 2.13 mL, 24.3 mmol, 3.5 equiv) and 6 N NaOH (0.7 mL, 4.17 mmol, 0.6 equiv) at 0 °C. After 10 min, a precipitate was formed. The reaction mixture was stirred for 30 min at 0 °C, then warmed to room temperature and stirred until the solution became clear (~3h). Et_2O (100 mL) and H_2O (100 mL) were added and the solution was acidified with HCl (35 %) to pH ~ 3. Water phase was extracted with Et_2O (5x20 mL). The combined organic extracts were dried over Na_2SO_4 and

evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:1) to furnish **II-98** (1.96 g, 82 %,) as an amorphous powder.

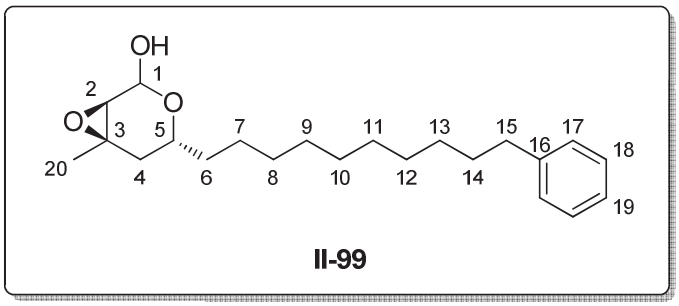
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (m, 14 H, $H_{7\text{-}13}$), 1.50 (s, 3H, H_{20}), 1.60 (m, 4H, $H_{6,14}$), 1.91 (dd, *J*=11.7 Hz, 15 Hz, 1H, H_4), 2.18 (dd, *J*=3 Hz, 15 Hz, 1H, H_4), 2.60 (t, *J*=7.5 Hz, 2H, H_{15}), 3.39 (s, 1H, H_2), 4.48 (m, 1H, H_5), 7.17-7.30 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (C_{20}), 25.0, 29.4-29.6 (6C), 31.7, 34.7, 34.8, 36.1 ($C_{4,\ 6\text{-}15}$), 55.6 (C_2), 59.4 (C_3), 75.0 (C_5), 125.7 (C_{19}), 128.3 (2C), 128.5 (2C), 143.0 (C_{16}), 168.5 (C_1).

HRMS (ESI): calculated for $C_{22}H_{33}O_3$ (MH^+) 345.2424, found 345.2422.

IR (neat): 1735, 2851, 2919, 2947.

$[\alpha]_D^{20}$ = +33.0 (*c* 0.9, CH_2Cl_2).



II-99

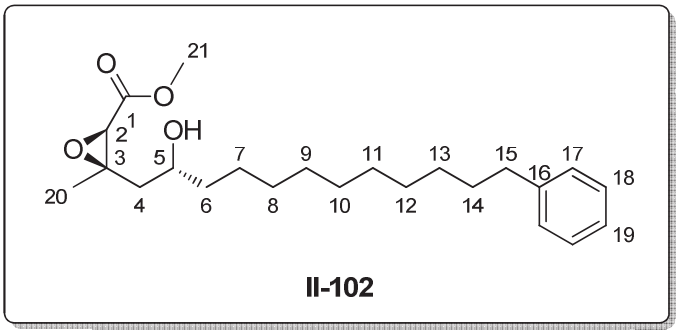
(1*R*,4*R*,6*R*)-6-Methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-ol (II-99). To a cooled (-78 °C) solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one (**II-98**, 96 mg, 0.279 mmol, 1 equiv) in toluene (10 mL) was added dropwise a solution of DIBAL in hexane (1M, 0.33 mL, 0.334 mmol, 1.2 equiv) dropwise. After stirring for 15-20 min the reaction mixture was treated with a few drops of MeOH followed by addition of $Na_2SO_4{\cdot}10H_2O$ and celite. The mixture was allowed to warm up to ambient temperature, stirred for 15 min, and filtered through a pad of celite. Evaporation of the solvent gave **II-99** (97 mg, quantitatif) as a white powder, which was used for the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (m, 16 H, $H_{6\text{-}13}$), 1.42 (s, 3H, H_{20}), 1.60 (m, 3H, $H_{4,14}$), 1.90 (dd, *J* = 2.4 Hz, 14.4 Hz, 1H, H_4), 2.60 (t, *J* = 7.8 Hz, 2H, H_{15}), 3.25 (d, *J* = 3.0 Hz, 1H, H_2), 3.64 (m, 1H, H_5), 5.29 (d, *J* = 3.0 Hz, 1H, H_1), 7.17-7.30 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (C_{20}), 25.4, 29.5-29.7 (6C), 31.7, 35.2, 35.5, 36.1 ($C_{4,\ 6\text{-}15}$), 59.9, 60.4 ($C_{2,3}$), 64.5 (C_5), 88.2 (C_1), 125.6 (C_{19}), 128.3 (2C), 128.5 (2C), 143.1 (C_{16}).

HRMS (ESI): calculated for $C_{22}H_{34}NaO_3$ (MNa^+) 369.2400, found 369.2416.

IR (neat): 1604, 2854, 2926, 3027, 3445.

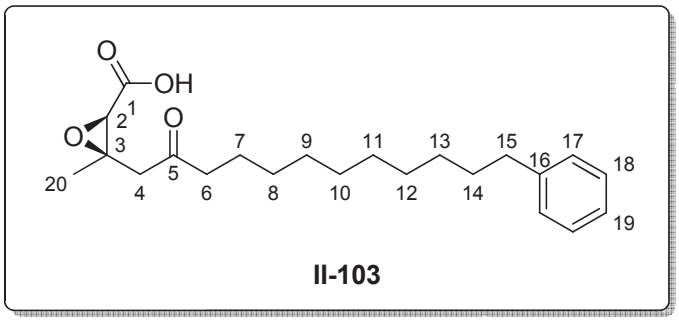


II-102

(2*R*,3*R*)-Methyl 3-((*R*)-2-hydroxy-12-phenyldodecyl)-3-methyloxirane-2-carboxylate (II-102). A solution of NaOH (6M, 0.047 mL, 0.282 mmol, 1.8 equiv) was added at 0 °C to a solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one (**II-98**, 54 mg, 0.157 mmol, 1 equiv) in MeOH (5 mL). The reaction mixture was stirred for 15 min at 0 °C and then for 2 h at rt. Then it was acidified with 10 % aqueous solution of $KHSO_4$ in water to pH 3, filtered, and dried (Na_2SO_4). The resulting solution was concentrated to 50 % of the starting volume and then treated with a solution of CH_2N_2 in Et_2O until persistent slightly yellow color. The solvent was evaporated and the residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:1) to furnish the lactone **II-98** (25 mg, 46 %) and **II-102** (14 mg, 24 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26-1.60 (m, 18 H, $H_{6\text{-}14}$), 1.50 (s, 3H, H_{20}), 1.91 (dd, *J* = 14.9, 11.7 Hz, 1H, H_4), 2.18 (dd, *J* = 14.9, 2.9 Hz, 1H, H_4), 2.59 (t, *J* = 7.8 Hz, 2H, H_{15}), 3.39 (s, 1H, H_2), 3.49 (s, 3H, H_{21}), 3.89 (bs, 1H, OH), 4.47 (s, 1H, H_5), 7.16-7.30 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 25.0, 29.4, 29.5, 29.6-29.7 (5C), 31.65, 34.69, 34.79, 36.12, 55.57, 59.45, 75.01, 125.67, 128.34 (2C), 128.53 (2C), 143.07, 168.51.

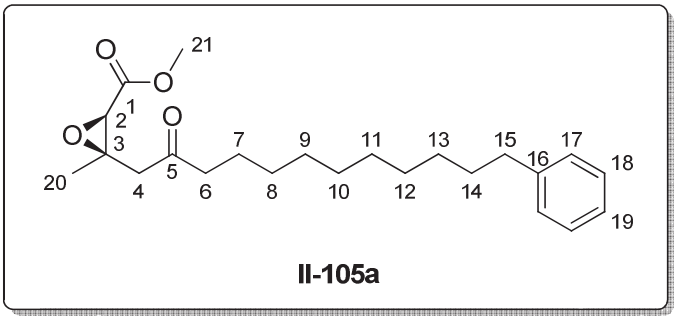


II-103

(2*R*,3*R*)-3-Methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carboxylic acid (II-103). To a solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one (**II-98**, 84 mg, 0.244 mmol, 1 equiv) in MeOH (4 mL) was added NaOH (6 M, 0.073 mL, 0.439 mmol, 1.8 equiv) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in H_2O (5 mL) and $RuCl_3$ (3.1 mg, 12.2 μmol, 0.05 equiv) and K_2CO_3 (67 mg, 0.488 mmol, 2 equiv) were added sequentially followed by addition of an aqueous $NaIO_4$ solution (10 %, 1.04 mL, 0.488 mmol, 2 equiv) by portions (0.2

mL). When the reaction was finished (~3-4 h) the reaction mixture was acidified with HCl (2 M) to pH 3-4, and extracted with EtOAc (6x3 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated to give the crude **II-103** (84 mg, 96 %) as a white powder.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (bm, 12H, $H_{8\text{-}13}$), 1.45 (s, 3H, H_{20}), 1.61 (bm, 4H, $H_{7,14}$), 2.37 (m, 2H, H_6), 2.59 (t, *J*=7.8 Hz, 2H, H_{15}), 2.91 (d, *J* = 17.6 Hz, 1H, H_4), 2.99 (d, *J* = 17.2 Hz, 1H, H_4), 3.44 (s, 1H, H_2), 7.16-7.29 (m, 5H, H_{Ar}), 10.52 (bs, 1H, OH).



II-105a

(*2R*,3*R*)-Methyl 3-methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carboxylate (II-105a). To a solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one (**II-98**, 110 mg, 0.32 mmol, 1 equiv) in MeOH (6 mL) was added NaOH (6 M, 0.1 mL, 0.64 mmol, 2 equiv) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in H_2O (7 mL) and $RuCl_3$ (4 mg, 16 μmol, 0.05 equiv) and K_2CO_3 (88 mg, 0.64 mmol, 2 equiv) were added sequentially followed by addition of an aqueous $NaIO_4$ solution (10 %, 2.01 mL, 0.96 mmol, 3 equiv) by portions (0.3 mL). When the reaction was finished (~3-4 h) the reaction mixture was acidified with HCl (2 M) to pH 3-4, and extracted with EtOAc (6x3 mL). The combined organic extracts were treated with a solution of CH_2N_2 in Et_2O until persistent slightly yellow color, and then dried (Na_2SO_4). Solvents were evaporated and the residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:9) to give **II-105a** (114 mg, 96 %) as a colorless oil.

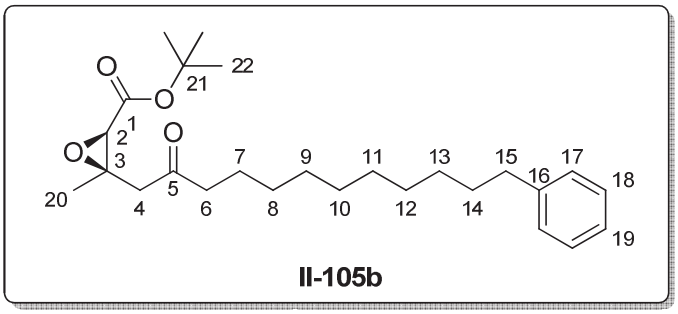
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (bm, 12H, $H_{8\text{-}13}$), 1.43 (s, 3H, H_{20}), 1.56 (bm, 4H, $H_{7,14}$), 2.37 (t, *J* = 7.5 Hz, 2H, H_6), 2.59 (t, *J* = 7.5 Hz, 2H, H_{15}), 2.94 (s, 2H, H_4), 3.42 (s, 1H, H_2), 3.74 (s, 3H, H_{21}), 7.16-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9, 23.7, 29.2-29.6 (6C), 31.6, 36.1, 43.4, 46.0, 52.5, 58.2, 59.8, 125.6, 128.3 (2C), 128.5 (2C), 143.0, 169.1, 207.6.

HRMS (ESI): calculated for $C_{23}H_{34}NaO_4$ (MNa^+) 397.2349, found 397.2344.

IR (neat): 1604, 1715, 1751, 2854, 2927, 3026, 3062.

$[\alpha]_D^{20}$ = -39.5 (*c* 1.2, $CHCl_3$).



II-105b

(2*R*,3*R*)-*tert*-Butyl 3-methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carboxylate (II-105b). To a solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one **II-98** (84 mg, 0.244 mmol, 1 equiv) in MeOH (4 mL) was added NaOH (6 M, 0.0.8 mL, 0.488 mmol, 2 equiv) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in H_2O (5 mL) and $RuCl_3$ (3.1 mg, 12.2 μmol, 0.05 equiv) and K_2CO_3 (34 mg, 0.244 mmol, 1 equiv) were added sequentially followed by addition of an aqueous $NaIO_4$ solution (10 %, 1.04 mL, 0.488 mmol, 2 equiv) by portions (0.3 mL). When the reaction was finished (~3-4 h) the reaction mixture was acidified with HCl (2 M) to pH 3-4, and extracted with EtOAc (6x3 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in 2 mL of dry CH_2Cl_2 (2 mL) and trichloroacetimidate (0.174 mL, 0.975 mmol, 4 equiv) was added. The reaction mixture was stirred for 20 h, evaporated and chromatographed (Et_2O/petroleum ether = 1:5) to give **II-105b** (77 mg, 76 %) as a colorless oil.

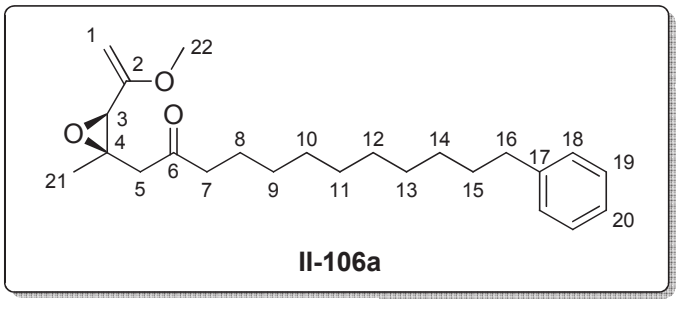
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (bm, 12H, $H_{8\text{-}13}$), 1.41 (s, 3H, H_{20}), 1.45 (s, 9H, H_{22}), 1.43-1.55 (bm, 4H, $H_{7,14}$), 2.36 (t, *J* = 7.5 Hz, 2H, H_6), 2.59 (t, *J* = 7.5 Hz, 2H, H_{15}), 2.91 (d, *J* = 17.4 Hz, 1H, H_4), 2.98 (d, *J* = 17.5 Hz, 1H, H_4), 3.30 (s, 1H, H_2), 7.16-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0 (C_{20}), 23.7, 28.0 (C_{22}), 29.2, 29.4-29.6 (5C), 31.6, 36.1, 43.3, 46.0, 58.9 (C_2), 59.5 (C_3), 82.5 (C_{21}), 125.6, 128.3 (2C), 128.5 (2C), 143.0 (C_{16}), 167.7 (C_1), 207.6 (C_5).

MS (ESI): 245.2, 343.2, 399.3, 439.3 (MNa^+), 471.3, 855.6 (M_2Na^+).

IR (neat): 1604, 1716, 1740, 2855, 2928, 2979, 3026.

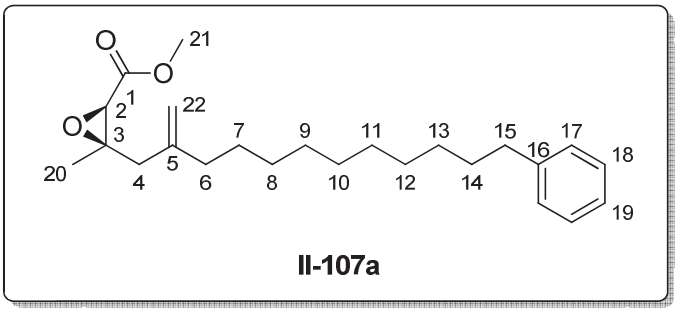
$[\alpha]_D^{20}$ = -26.0 (c 1.3, $CHCl_3$).



II-106a

1-((2*R*,3*S*)-3-(1-Methoxyvinyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-one (II-106a). For experimental procedure see **II-108a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (bm, 12H, $H_{9\text{-}14}$), 1.42 (s, 3H, H_{21}), 1.56 (bm, 4H, $H_{8,15}$), 2.38 (m, 2H, H_7), 2.60 (t, *J* = 7.5 Hz, 2H, H_{16}), 2.71 (s, 2H, H_5), 3.27 (s, 1H, H_3), 3.57 (s, 3H, H_{22}), 7.17-7.30 (m, 5H, H_{Ar}).



II-107a

(2*R*,3*R*)-Methyl 3-methyl-3-(2-methylene-12-phenyldodecyl)oxirane-2-carboxylate (II-107a). To a stirred solution of (2*R*,3*R*)-methyl 3-methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carboxylate **II-105a** (0.219 g, 0.585 mmol) in dry THF (8 mL) was added at 0^{o}C Nysted reagent (20 % in THF, 3.51 mL, 1.83 mmol) followed by dropwise addition of $TiCl_2(O\textit{i}Pr)_2$, prepared from $TiCl_4$ (1 M in dichloromethane, 0.73 mL, 0.73 mmol) and $Ti(O\textit{i}Pr)_4$ (0.217 mL, 0.73 mmol). The reaction mixture was then allowed to reach 15 ^{o}C and stirred for 15 min. The reaction mixture was cooled to 0 ^{o}C, treated carefully with water (1 ml) and extracted with ether (5x8 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution and brine. The ethereal solution was filtered through a small pad of silica gel to remove metal species, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:5) to provide **II-107a** (0.153 g, 70 %) as a colorless oil.

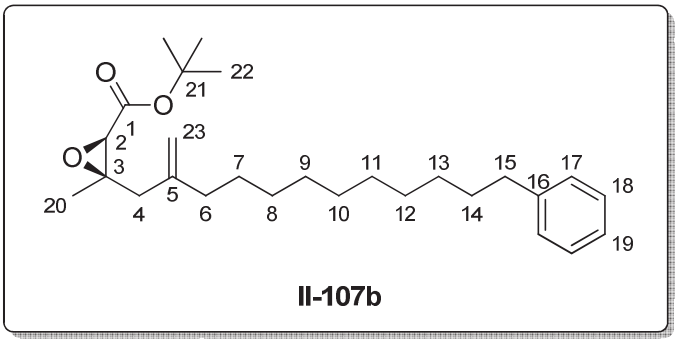
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (bm, 14H, $H_{7\text{-}13}$), 1.38 (s, 3H, H_{20}), 1.60 (m, 2H, H_{14}), 1.95 (m, 2H, H_6), 2.35 (d, *J* = 15 Hz, 1H, H_4), 2.41 (d, *J* = 15 Hz, 1H, H_4), 2.59 (t, *J* = 7.6 Hz, 2H, H_{15}), 3.37 (s, 1H, H_2), 3.76 (s, 3H, H_{21}), 4.79 (s, 1H, H_{22}), 4.85 (s, 1H, H_{22}), 7.16-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (C_{20}), 27.6, 29.4-29.7 (6C), 31.6, 36.1, 36.3, 39.0, 52.3 (C_{21}), 59.0 (C_2), 62.2 (C_3), 112.2 (C_{22}), 125.6 (C_{19}), 128.3 (2C), 128.5 (2C), 143.0 (C_{16}), 145.3 (C_5), 169.0 (C_1).

HRMS (ESI): calculated for $C_{24}H_{36}NaO_3$ (MNa^+) 395.2557, found 395.2557.

IR (neat): 1646, 1736, 1757, 2854, 2927, 3026.

$[\alpha]_D^{20}$ = -29.2 (*c* 1, CH_2Cl_2).



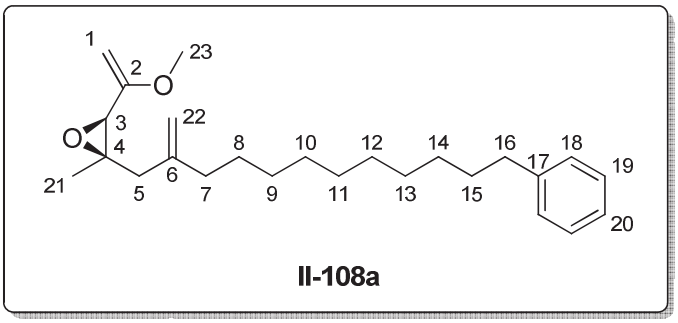
II-107b

(2*R*,3*R*)-*tert*-Butyl 3-methyl-3-(2-methylene-12-phenyldodecyl)oxirane-2-carboxylate (II-107b). (2*R*,3*R*)-tert-butyl 3-methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carboxylate **II-105b** (77 mg, 0.185 mmol, 1 equiv) and a solution of dimethyltitanocene in toluene (0.22 M, 2.52 mL, 0.555 mmol, 3 equiv) were placed in a dry, nitrogen flushed flask wrapped in an aluminium foil. The reaction mixture was heated at 80 ^{o}C for 6 h, cooled to rt and filtered through a small pad of silica gel (Et_2O/petroleum ether = 1:2). The filtrate was evaporated and the residue was purified by flash chromatography (Et_2O/petroleum ether = 1:5) to give **II-107b** (56 mg, 73 %, dr = 2:3) as a slightly yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26-1.50 (bm, 14H, $H_{7\text{-}13}$), 1.31 and 1.36 (2s, 3H, H_{20}), 1.47 and 1.49 (2s, 9H, H_{22}), 1.60 (m, 2H, H_{14}), 2.02 (m, 2H, H_6), 2.22 (d, *J* = 14.6 Hz, 0.44H, H_4), 2.37 (d, *J* = 14.6 Hz, 0.44H, H_4), 2.39 (s, 1.1H, H_4), 2.59 (t, *J* = 7.8 Hz, 2 H, H_{15}), 3.25 (s, 0.34H, H_2), 3.26 (s, 0.56H, H_2), 4.80-4.87 (m, 2H, H_{23}), 7.16-7.29 (m, 5 H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0, 21.9, 27.6, 27.7, 28.18, 28.24, 29.4-29.7, 31.7, 36.1, 36.2, 36.7, 38.8, 44.8, 59.0, 59.6, 61.3, 61.8, 82.3, 111.7, 112.1, 125.7, 128.3, 128.5, 143.1, 145.3, 145.7, 162.4, 167.6.

MS (ESI): 432.1, 437.2 (MNa^+) 696.2, 851.0 (M_2Na^+).



II-108a

(2*R*,3*S*)-3-(1-Methoxyvinyl)-2-methyl-2-(2-methylene-12-phenyldodecyl)oxirane (II-108a). (2*R*,3*R*)-Methyl 3-methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carboxylate (**II-105a**, 139 mg, 0.371 mmol, 1 equiv) and a solution of dimethyltitanocene in toluene (0.22 M, 2.53 mL, 0.557 mmol, 1.5 equiv) were placed in a dry, nitrogen flushed flask wrapped in a aluminium foil. The reaction mixture was heated at 80 ^{o}C for 21 h, cooled to rt and filtered through a small pad of silica gel (Et_2O/petroleum ether = 1:2). The filtrate was evaporated and

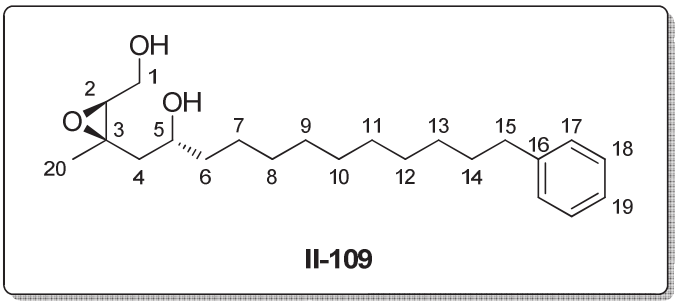
the residue was purified by flash chromatography (Et_2O/petroleum ether = 1:5) to give **II-105a** (31 mg, 22 %), **II-106a** (4 mg, 3 %), **II-107a** (47 mg, 34 %) and **II-108a** (57 mg, 41 %) as slightly yellow oils.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (bm, 14H, $H_{8\text{-}14}$), 1.31 (s, 3H, H_{21}), 1.60 (m, 2H, H_{15}), 1.96 (m, 2H, H_7), 2.28 (s, 2H, H_5), 2.59 (t, *J* = 7.8 Hz, 2H, H_{16}), 3.20 (s, 1H, H_3), 3.57 (s, 3H, H_{23}), 4.13 (d, *J* = 2.3 Hz, 1H, H_1), 4.15 (d, *J* = 2.7 Hz, 1H, H_1), 4.80 (s, 1H, H_{22}), 4.81 (s, 1H, H_{22}), 7.16-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (C_{21}), 27.8, 29.5, 29.7-29.8 (5C), 31.7, 36.1, 36.2, 38.2, 55.2 (C_{23}), 62.0 (C_3), 62.4 (C_4), 82.7 (C_1), 112.2 (C_{22}), 125.7 (C_{20}), 128.3 (2C), 128.5 (2C), 143.1 (C_{17}), 146.3 (C_6), 158.8 (C_2).

HRMS (ESI): calculated for $C_{25}H_{38}NaO_2$ (MNa^+) 393.2764, found 393.2778.

IR (neat): 1645, 1666, 2855, 2927, 3027, 3064, 3084.



II-109

(*R*)-1-((2*R*,3*S*)-3-(Hydroxymethyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-ol (II-109). *Method A.* $NaBH_4$ (9.2 mg, 0.242 mmol, 2 equiv) was added to a solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-ol **II-99** (42 mg, 0.121 mmol, 1 equiv) in EtOH (4 mL). The reaction mixture was stirred at room temperature for 3 h, cooled to 0 °C and treated with saturated aqueous solution of NH_4Cl. The resulting solution was extracted with Et_2O (5x2 mL). The combined organic extracts were washed with saturated aqueous solution of Rochelle salt and water, dried (Na_2SO_4), and evaporated to give **II-109** (43 mg, quantitative) which was used without further purification.

Method B. $NaBH_4$ (19.2 mg, 0.51 mmol, 3 equiv) was added to a solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one **II-98** (58 mg, 0.168 mmol, 1 equiv) in EtOH (6 mL). The reaction mixture was stirred at room temperature for 3 h, and treated with aqueous acetic acid (1 %). The resulting solution was extracted with CH_2Cl_2 (5x3 mL). The combined organic extracts were dried (Na_2SO_4), and evaporated to give **II-109** (38 mg, 65 %) which was used without further purification.

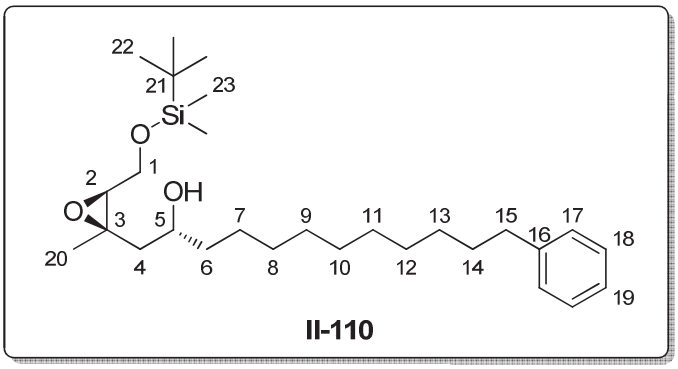
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27-1.63 (m, 19 H, $H_{4,6\text{-}14}$), 1.40 (s, 3H, H_{20}), 1.76 (dd, *J* = 2.4 Hz, 14.7 Hz, 1H, H_4), 2.59 (t, *J* = 7.5 Hz, 2H, H_{15}), 2.96 (dd, *J* = 4.5, 6.3 Hz, 1H, H_2), 3.70 (dd, *J* = 12.1, 6.6 Hz, 1H, H_1), 3.81 (dd, *J* = 12.2, 4.5 Hz, 1H, H_1), 3.99 (m, 1H, H_5), 7.16-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (C_{20}), 25.7, 29.4-29.7 (6C), 31.6, 36.1, 37.8, 38.6, 61.0, 61.2, 63.6 (C_1), 69.4 (C_5), 125.6 (C_{19}), 128.3 (2C), 128.5 (2C), 143.0 (C_{16}).

HRMS (ESI): calculated for $C_{22}H_{36}NaO_3$ (MNa^+) 371.2557, found 371.2569.

IR (neat): 1605, 2855, 2925, 3027, 3063, 3086, 3419.

$[\alpha]_D^{20}$ = -12.8 (*c* 1.28, $CHCl_3$).



II-110

(*R*)-1-((2*R*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-ol (II-110). TBSCl (110 mg, 0.73 mmol, 2.2 equiv) was added to a mixture of (*R*)-1-((2*R*,3*S*)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-ol **II-109** (116 mg, 0.332 mmol, 1 equiv), Et_3N (0.1 mL, 0.73 mmol, 2.2 equiv), DMAP (4.1 mg, 33.2 μmol, 0.1 equiv) and CH_2Cl_2 (1.3 mL) at 0 °C. After 10 min the temperature was raised to rt. The reaction mixture was stirred until no starting material was observed by TLC (~8 h), quenched with water (2 mL) and extracted with Et_2O (5x3 mL). The combined organic extracts were dried (Na_2SO_4), evaporated and chromatographed on silica gel (Et_2O/petroleum ether = 1:3) to give **II-110** (146.5 mg, 95 %) as a colorless oil.

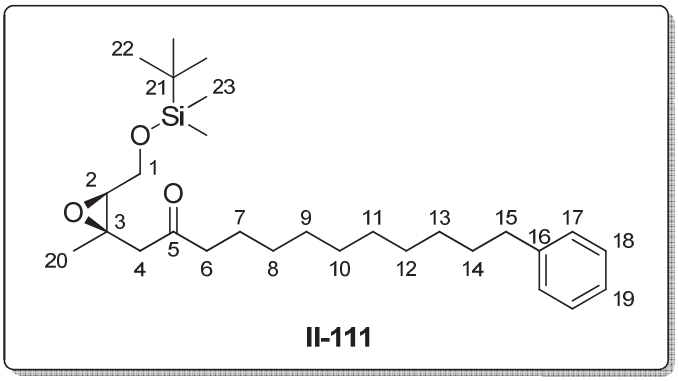
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 3H, H_{23}), 0.10 (s, 3H, H_{23}), 0.92 (s, 9H, H_{22}), 1.27-1.66 (m, 19 H, $H_{4,6\text{-}14}$), 1.40 (s, 3H, H_{20}), 1.73 (dd, *J* = 14.4, 2.4 Hz, 1H), 2.60 (t, *J* = 7.5 Hz, 2H, H_{15}), 2.91 (bs, 1H, OH), 2.91 (t, *J* = 5.4 Hz, 1H, H_2), 3.76 (d, *J* = 5.4 Hz, 1H, H_1), 4.01 (m, 1H, H_5), 7.13-7.18 (m, 3H, H_{Ar}), 7.24-7.29 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.3 (C_{23}), -5.1 (C_{23}), 18.3 (C_{21}), 23.1 (C_{20}), 25.6, 25.9 (C_{22}), 29.4-29.7 (6C), 31.6, 36.1, 37.8, 38.5, 60.8 (C_3), 61.9 (C_1), 63.6 (C_2), 69.3 (C_5), 125.6 (C_{19}), 128.2 (2C), 128.4 (2C), 142.9 (C_{16}).

HRMS (ESI): calculated for $C_{28}H_{50}NaO_3Si$ (MNa^+) 485.3421, found 485.3429.

IR (neat): 1605, 2856, 2928, 3027, 3063, 3086, 3466.

$[\alpha]_D^{20}$ = -6.6 (*c* 1.46, $CHCl_3$).



II-111

1-((2*R*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-one (II-111). *Method A.* To a cooled (0 ^{o}C) solution of (*R*)-1-((2*R*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-ol **II-110** (46 mg, 99.4 μmol, 1 equiv), Et_3N (0.14 mL, 0.994 mmol, 10 equiv) and DMSO (0.2 mL) in CH_2Cl_2 (1.5 mL) was added SO_3·Py (95 mg, 596 mmol, 6 equiv). The reaction mixture was stirred for 30 h, quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O (5x2 mL). The combined organic extracts were dried (Na_2SO_4), evaporated and chromatographed on silica gel (Et_2O/petroleum ether = 1:5) to yield **II-111** (38 mg, 83 %) as a colorless oil.

Method B. To a solution of oxalyl chloride (34 μL, 0.4 mmol, 4 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise at -78 ^{o}C DMSO (57 μL, 0.8 mmol, 8 equiv). After 20 min, (*R*)-1-((2*R*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-ol **II-110** (50 mg, 0.108 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred at -78→-60 ^{o}C for 20 min before Et_3N (111 μL, 0.8 mmol, 8 equiv) was added slowly. After 10 min the reaction mixture was heated to rt, stirred for 20 min, treated carefully with saturated aqueous solution of NH_4Cl and extracted with Et_2O (5x3 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:5) to give **II-111** (44.5 mg, 89 %) as a colorless oil.

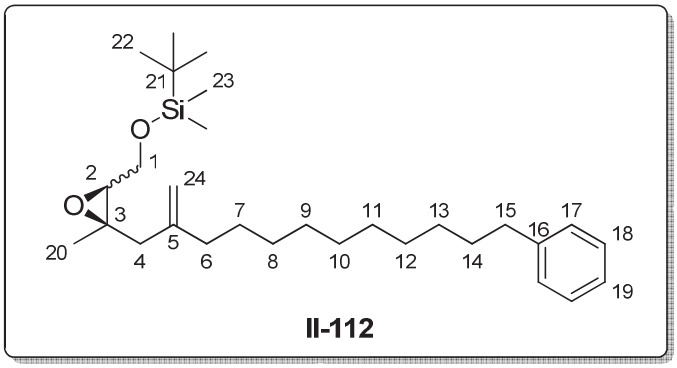
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.078 (s, 3H, H_{23}), 0.082 (s, 3H, H_{23}), 0.90 (s, 9H, H_{22}), 1.27 (m, 12 H, $H_{8\text{-}13}$), 1.35 (s, 3H, H_{20}), 1.58 (m, 4H, $H_{7,14}$), 2.42 (d, *J* = 6.9 Hz, 1H), 2.44 (d, *J* = 6.5 Hz, 1H), 2.56 (d, *J* = 16.4 Hz, 1H, H_4), 2.59 (t, *J* = 7.7 Hz, 2H, H_{15}), 2.80 (d, *J* = 16.6 Hz, 1H, H_4), 2.96 (dd, *J* = 6.0, 4.0 Hz, 1H, H_2), 3.60 (dd, *J* = 11.9, 6.0 Hz, 1H, H_1), 3.86 (dd, *J* = 11.9, 4.0 Hz, 1H, H_1), 7.14-7.19 (m, 3H, H_{Ar}), 7.25-7.30 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.2 (C_{23}), -5.1 (C_{23}), 18.5 (C_{21}), 23.4 (C_{20}), 23.8, 26.0 (C_{22}), 29.3, 29.5-29.6 (5C), 31.7, 36.1, 43.5, 47.2, 57.9 (C_3), 62.2 (C_1), 63.9 (C_2), 125.7 (C_{19}), 128.3 (2C), 128.5 (2C), 143.0 (C_{16}), 208.0 (C_5).

HRMS (ESI): calculated for $C_{28}H_{48}NaO_3Si$ (MNa^+) 483.3265, found 483.3268.

IR (neat): 1604, 1717, 2855, 2928, 3027, 3063, 3085.

$[\alpha]_D^{20}$ = -7.9 (*c* 0.419, $CHCl_3$).



II-112

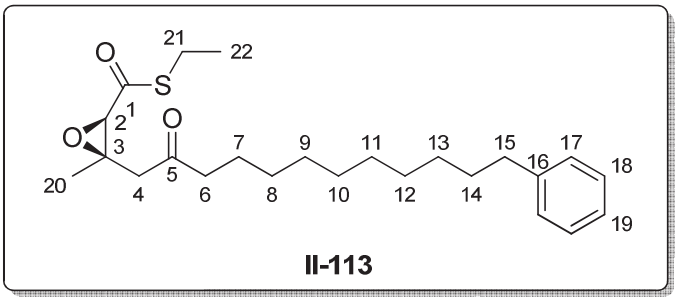
***tert*-Butyldimethyl(((2*S*,3*R*)-3-methyl-3-(2-methylene-12-phenyldodecyl)oxiran-2-yl)methoxy)silane (II-112).** 1-((2*R*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-one **II-111** (38 mg, 82 μmol, 1 equiv) and a solution of dimethyltitanocene in THF (~0.5 M, 0.5 mL, 0.247 mmol, 3 equiv) were placed in a dry, nitrogen flushed flask wrapped in a aluminium foil. The reaction mixture was refluxed for 25 h, cooled to rt and petroleum ether (2 mL) was added (to precipitate the titanium species). The resulting mixture was filtered through a small pad of silica gel and washed with Et_2O/petroleum ether = 1:2. The filtrate was evaporated and the residue was purified by flash chromatography (Et_2O/petroleum ether= 1:20) to give **II-112** (29 mg, 77 %, dr = 2:3) as a slightly yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (2s, 6H, H_{23}), 0.90 (s, 9H, H_{22}), 1.26-1.62 (m, 16 H, $H_{7\text{-}14}$), 1.29 (s, 3H, H_{20}), 2.02 (m, 2H, H_6), 2.08 (d, *J* = 14.4 Hz, 0.3H, H_4), 2.16 (d, *J* = 15.3 Hz, 0.7H, H_4), 2.28 (d, *J* = 15.3 Hz, 0.7H, H_4), 2.37 (d, *J* = 14.4 Hz, 0.3H, H_4), 2.59 (t, *J* = 7.7 Hz, 2H, H_{15}), 2.93 (m, 1H, H_2), 3.69 (dd, *J* = 11.6, 5.8 Hz, 0.7H, H_1), 3.69 (dd, *J* = 11.3, 5.7 Hz, 0.3H, H_1), 3.78 (dd, *J* = 11.4, 5.4 Hz, 0.3H, H_1), 3.81 (dd, *J* = 11.6, 4.9 Hz, 0.7H, H_1), 4.81-4.85 (m, 2H, H_{24}), 7.15-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.19, -5.04, 16.53, 18.47, 22.36, 26.01, 26.04, 27.74, 27.78, 29.49, 29.66, 29.70, 29.72, 29.76, 31.68, 36.14, 36.65, 39.91, 45.64, 59.85, 60.18, 62.21, 62.30, 62.97, 64.10, 111.93, 112.16, 125.68, 128.35, 128.53, 143.08, 145.84, 145.97.

GCMS (ESI): first fraction – 75, 91, 105, 119, 143, 309, 401 (MH^+-$(CH_3)_3CH$); second fraction – 75, 91, 105, 143, 309, 401 (MH^+-$(CH_3)_3CH$).

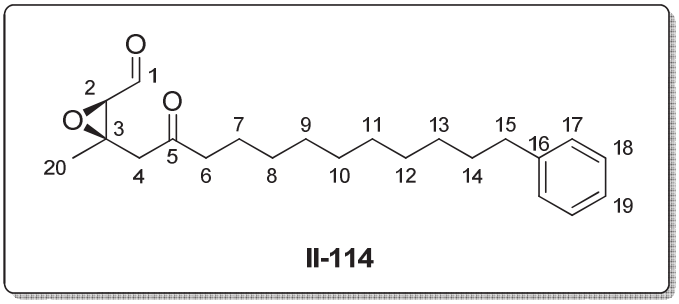
IR (neat): 1605, 1646, 2855, 2928, 3027, 3065, 3085.



II-113

(2*R*,3*R*)-S-Ethyl 3-methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carbothioate (II-113). To a solution of (1*R*,4*R*,6*R*)-6-methyl-4-(10-phenyldecyl)-3,7-dioxabicyclo[4.1.0]heptan-2-one **II-98** (100 mg, 0.29 mmol, 1 equiv) in MeOH (4 mL) was added NaOH (6 M, 0.097 mL, 0.58 mmol, 2 equiv) at room temperature. The reaction mixture was stirred for 2 h and evaporated. The residue was dissolved in H_2O (6 mL) and $RuCl_3$ (4 mg, 14.5 μmol, 0.05 equiv) and K_2CO_3 (40 mg, 0.29 mmol, 1 equiv) were added sequentially followed by addition of an aqueous $NaIO_4$ solution (10 %, 1.24 mL, 0.58 mmol, 2 equiv) by portions (0.3 mL). When the reaction was finished (~3-4 h) the reaction mixture was acidified with HCl (2 M) to pH 3-4, and extracted with EtOAc (6x3 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. To a solution of the residue in 3 mL of dry CH_2Cl_2 were added EtSH (34 μL, 0.465 mmol, 1.6 equiv), one crystal of DMAP and DCC (78 mg, 0.377 mmol, 1.3 equiv). The reaction mixture was stirred for 20 h, filtered through a small pad of silica gel, and the solid was washed with Et_2O/petroleum ether = 1:1. Combined organic extracts were evaporated and the residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:9) to afford the thioester **II-113** (52 mg, 44 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22-1.65 (bm, 19H, $H_{7\text{-}14,\ 22}$), 1.46 (s, 3H, H_{20}), 2.37 (t, *J* = 7.5 Hz, 2H, H_6), 2.59 (t, *J* = 7.5 Hz, 2H, H_{15}), 2.90 (s, 2H, H_4), 2.92 (q, *J* = 7.5 Hz, 2H, H_{21}), 3.54 (s, 1H, H_2), 7.16-7.29 (m, 5H, H_{Ar}).

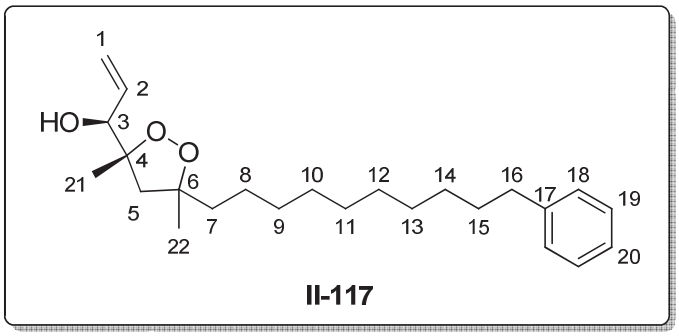


II-114

(2*R*,3*R*)-3-Methyl-3-(2-oxo-12-phenyldodecyl)oxirane-2-carbaldehyde (II-114). To a solution of oxalyl chloride (68 μL, 0.8 mmol, 8 equiv) in CH_2Cl_2 (1 mL) was added dropwise at -78 °C DMSO (114 μL, 1.61 mmol, 16 equiv). After 30 min, (*R*)-1-((2*R*,3*S*)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-12-phenyldodecan-2-ol **II-109** (35 mg, 0.1 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred at -78→-60 °C for 1 h before Et_3N (223 μL, 1.61 mmol, 16 equiv) was added slowly. After 30 min the reaction mixture was heated to rt, stirred for 20 min, treated carefully with saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (5x2 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:1) to give **II-114** (23 mg, 67 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (bm, 12H, $H_{8\text{-}13}$), 1.45 (s, 3H, H_{20}), 1.60 (bm, 4H, $H_{7,14}$), 2.38 (t, *J* = 7.5 Hz, 2H, H_6), 2.60 (t, *J* = 7.5 Hz, 2H, H_{15}), 2.68 (d, *J* = 17.4 Hz, 1H, H_4), 3.03 (d, *J* = 17.4 Hz, 1H, H_4), 3.51 (d, *J* = 2.4 Hz, 1H, H_2), 7.17-7.30 (m, 5H, H_{Ar}) 9.57 (d, *J* = 2.7 Hz, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 23.7, 29.2, 29.4-29.7 (5C), 31.6, 36.1, 43.6, 46.1, 61.2, 63.5, 125.7 (C_{19}), 128.3 (2C), 128.5 (2C), 143.0 (C_{16}), 196.9 (C_1), 207.1 (C_5).



II-117

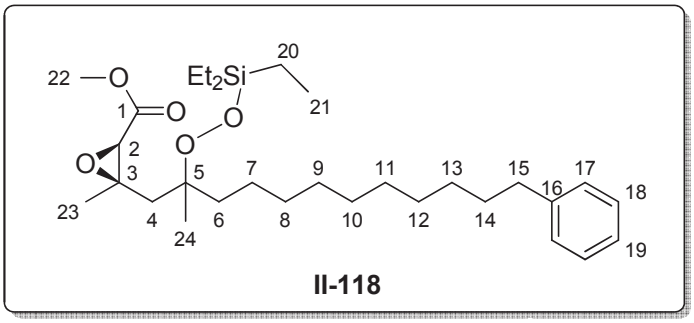
(1*S*)-1-((3*R*)-3,5-Dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)prop-2-en-1-ol (II-117). To a solution of (2*R*,3*S*)-2-methyl-2-(2-methylene-12-phenyldodecyl)-3-vinyloxirane **II-68** (13 mg, 38 μmol) in dichloroethane (0.5 mL) was added Co(II) bis(2,2,6,6-tetramethylheptane-3,5-dienoate) [$Co(thd)_2$] (1.6 mg, 3.8 μmol). The flask was charged with O_2 and Et_3SiH (7.3 μl, 45.8 μmol) was added. The reaction mixture was stirred under O_2 atmosphere for 4 h, filtered through a pad of silica gel and evaporated. The residue was dissolved in dichloromethane (1 mL) and Amberlyst-15 (4.7 meq/g, 8.1 mg) was added. After stirring for 2 h at room temperature, the reaction mixture was filtered and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:3) to provide **II-117** (mixture of 1/1 diastereomers) (7.3 mg, 51 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26-1.43 (bm, 20H), 1.57 (br m, 4H), 2.00 (d, *J* = 12.2 Hz, 0.5H, H_5), 2.12 (d, *J* = 12.3 Hz, 0.5H, H_5), 2.32 (d, *J* = 12.3 Hz, 0.5H, H_5), 2.38 (d, *J* = 12.2 Hz, 0.5H, H_5), 2.53 (d, *J* = 2.7 Hz, 0.5H, OH), 2.54 (d, *J* = 2.7 Hz, 0.5H, OH), 2.60 (t, *J* = 6 Hz, 2H, H_{16}), 4.19 (m, 1H, H_3), 5.27 (d, *J* = 10.5, 1H, H_1), 5.39 (dd, *J* = 17.2, 1.5 Hz, 0.5H, H_1), 5.40 (dd, *J* = 17.2, 1.5 Hz, 0.5H, H_1), 5.81 (m, 1H, H_2), 7.17-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.2, 22.4, 24.6, 25.2, 25.2, 29.5-29.7 (6C), 31.7, 36.1, 38.3, 39.9, 52.8 (C_5), 53.2 (C_5), 76.3 (C_3), 76.4 (C_3), 87.0, 87.3, 87.9, 88.2, 118.3 (C_1), 125.7 (C_{20}), 128.4 (2C), 128.5 (2C), 135.2 (C_2), 135.3 (C_2), 143.1 (C_{17}).

HRMS (ESI): calculated for $C_{24}H_{38}NaO_3$ (MNa^+) 397.2713, found 397.2707.

IR (neat): 1722, 2854, 2927, 3026, 3521.



II-118

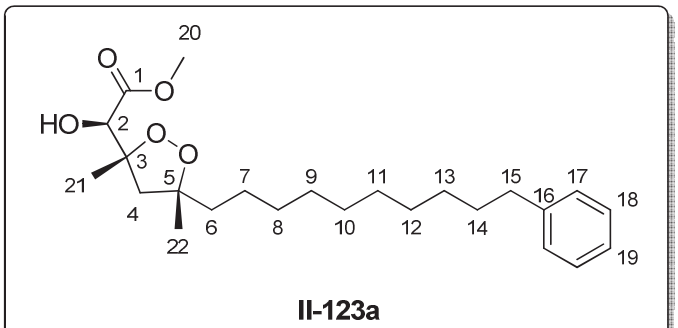
(2*R*,3*R*)-Methyl 3-methyl-3-(2-methyl-12-phenyl-2-((triethylsilyl)peroxy)dodecyl) oxirane-2-carboxylate (II-118). To a solution of (2*R*,3*R*)-methyl 3-methyl-3-(2-methylene-12-phenyldodecyl)oxirane-2-carboxylate **II-107a** (118 mg, 0.32 mmol) in dichloroethane (3 mL) was added $Co(thd)_2$ (13.5 mg, 32 μmol) and the flask was charged with O_2. Et_3SiH (101 μl, 0.63 mmol) was added and the reaction mixture was stirred for 2 h under O_2 atmosphere. Evaporation of the reaction mixture and chromatography of the residue on silica gel (Et_2O/petroleum ether = 1:10) afforded **II-118** (mixture of 1/1 diastereomers) (142 mg, 86 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.67 (q, *J* = 7.8 Hz, 6H, H_{20}), 0.98 (t, *J* = 7.8 Hz, 9H, H_{21}), 1.07 (s, 1.5H), 1.26 (m, 15.5H), 1.51 (s, 1.5H), 1.52 (s, 1.5H), 1.61 (m, 4H), 1.98 (s, 1H, H_4), 2.00 (s, 1H, H_4), 2.59 (t, *J* = 7.5 Hz, 2H, H_{15}), 3.24 (s, 0.5H, H_2), 3.27 (s, 0.5H, H_2), 3.76 (s, 3H, H_{22}), 7.16-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.9 (C_{20}), 6.9 (C_{21}), 21.7, 22.2, 23.4, 23.5, 23.8, 29.5-29.7 (6C), 30.28, 30.30, 31.7, 36.1, 37.2, 37.7, 38.1, 38.5, 52.26 (C_{22}), 52.27 (C_{22}), 59.6 (C_2), 59.7 (C_2), 61.9 (C_3), 62.1 (C_3), 84.1 (C_5), 84.3 (C_5), 125.63 (C_{19}), 125.65 (C_{19}), 128.3 (2C), 128.5 (2C), 143.02 (C_{16}), 143.05 (C_{16}), 169.2 (C_1), 169.3 (C_1).

HRMS (ESI): calculated for $C_{30}H_{52}NaO_5Si$ (MNa^+) 543.3476, found 543.3492.

IR: 1737, 1756, 2854, 2926, 3026.



II-123a

(*R*)-Methyl 2-((3*R*,5*R*)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)-2-hydroxyacetate (II-123a). To an ice-cooled solution of (2*R*,3*R*)-methyl 3-methyl-3-(2-methyl-12-phenyl-2-((triethylsilyl)peroxy)dodecyl)oxirane-2-carboxylate **II-118** (140 mg,

0.269 mmol) in MeOH (5 mL) was added K_2CO_3 (11 mg, 80.7 µmol). The reaction mixture was stirred at 0 °C for 5 h, water (10 mL) was added and the resulting mixture was extracted with Et_2O (5x5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude mixture was purified by preparative TLC (Et_2O/petroleum ether = 1:2, 2 elutions) to give **II-123a** (40 mg, 36 %) and **II-123b** (42 mg, 39 %) as colorless oils.

Physical data for II-123a

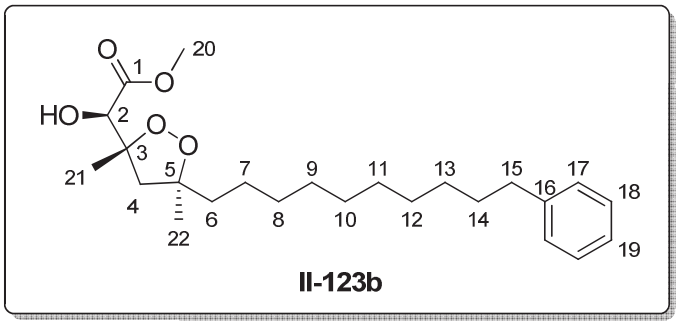
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (m, 14H, $H_{7\text{-}13}$), 1.34 (s, 3H, H_{22}), 1.37 (s, 3H, H_{21}), 1.55 (bm, 4H, $H_{6,14}$), 2.03 (d, J = 12.3 Hz, 1H, H_4), 2.59 (t, J = 7.5 Hz, 2H, H_{15}), 2.78 (d, J = 12.3 Hz, 1H, H_4), 3.01 (d, J = 5.7, 1H, OH), 3.79 (s, 3H, H_{20}), 4.23 (d, J = 5.7, 1H, H_2), 7.16-7.29 (m, 5H, H_{Ar}).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.2 (C_{21}), 24.8, 25.2, 29.4-29.6 (5C), 30.2, 31.6, 36.1, 37.9, 52.4, 52.7, 74.7 (C_2), 86.9, 87.3, 125.7 (C_{19}), 128.3 (2C), 128.5 (2C), 143.0 (C_{16}), 172.5 (C_1).

HRMS (ESI): calculated for $C_{24}H_{38}NaO_5$ (MNa^+) 429.2611, found 429.2623.

IR (neat): 1733, 1738, 2854, 2927, 3498.

$[\alpha]_D^{20}$ = +51.3 (*c* 1.65, $CHCl_3$).



II-123b

(*R*)-Methyl 2-((3*R*,5*S*)-3,5-dimethyl-5-(10-phenyldecyl)-1,2-dioxolan-3-yl)-2-hydroxyacetate (II-123b). For experimental procedure see **II-123a**.

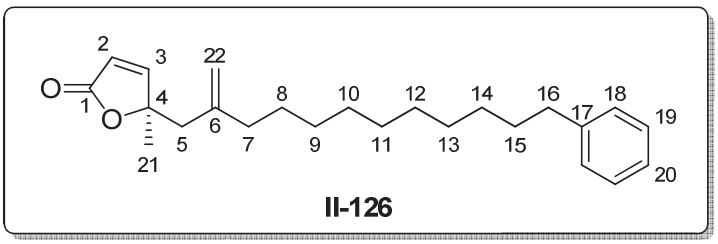
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H, H_{22}), 1.27 (bs, 14H, $H_{7\text{-}13}$), 1.34(s, 3H, H_{21}), 1.50-1.76 (bm, 4H, $H_{6,14}$), 2.13 (d, *J*=12.6 Hz, 1H, H_4), 2.59 (t, *J*=7.7 Hz, 2H, H_{15}), 2.72 (d, *J*=12.6 Hz, 1H, H_4), 3.00 (bs, 1H, OH), 3.80 (s, 3H, H_{20}), 4.24 (s, 1H, H_2), 7.16 – 7.29 (m, 5H, H_{Ar}).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.3 (C_{21}), 21.8 (C_{22}), 24.5, 29.4-29.7 (5C), 30.1, 31.6, 36.1 (C_{15}), 39.8, 52.6, 52.8, 74.8 (C_2), 87.0, 87.2, 125.7 (C_{19}), 128.3 (2C), 128.5 (2C), 143.0 (C_{16}), 172.6 (C_1).

HRMS (ESI): calculated for $C_{24}H_{38}NaO_5$ (MNa^+) 429.2611, found 429.2609.

IR (neat): 1736, 2854, 2926, 3498.

$[\alpha]_D^{20}$ = +46.8 (*c* 2.31, $CHCl_3$).



II-126

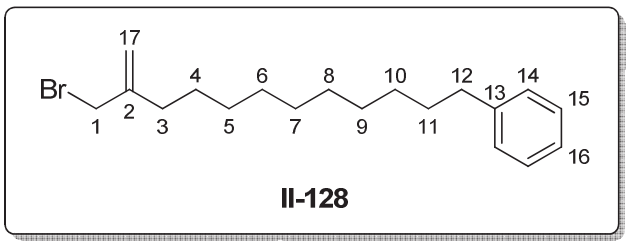
(*R*)-5-Methyl-5-(2-methylene-12-phenyldodecyl)furan-2(5H)-one (II-126). To a solution of (*R*)-2-methyl-4-methylene-1-oxo-14-phenyltetradecan-2-yl 2-(diethoxyphosphoryl)acetate (**II-147**, 44.3 mg, 87.2 μmol, 1 equiv) in THF (2.5 mL) were added LiBr (9.5 mg, 109 μmol, 1.25 equiv) and Et_3N (15 μL, 109 μmol, 1.25 equiv). The reaction mixture was stirred overnight at rt, quenched with water (3 mL), and extracted with Et_2O (4x3 mL). The combined extracts were washed with water (3 mL), brine (3 mL), dried with Na_2SO_4 and evaporated. Purification of the residue by flash column chromatography (Et_2O) gave **II-126** (9.5 mg, 31 %) and the 2-diethylphosphono butenolide **II-148** (19 mg, 45 %) as colorless oils.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 – 1.42 (m, 14H, $H_{8\text{-}14}$), 1.46 (s, 3H, H_{21}), 1.61 (m, 2H, H_{15}), 1.99 (t, *J* = 7.5 Hz, 2H, H_7), 2.40 (d, *J* = 13.8 Hz, 1H, H_5), 2.52 (d, *J* = 13.9 Hz, 1H, H_5), 2.60 (t, *J* = 7.5 Hz, 2H, H_{16}), 4.80 (s, 1H, H_{22}), 4.93 (m, 1H, H_{22}), 6.00 (d, *J* = 5.6 Hz, 1H, H_2), 7.14 – 7.19 (m, 3H, H_{Ar}), 7.25 – 7.30 (m, 2H, H_{Ar}), 7.35 (d, *J* = 5.6 Hz, 1H, H_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1 (C_{21}), 27.9, 29.4 - 29.7 (6C), 31.7, 36.1, 37.1, 44.9, 88.7 (C_4), 115.4 (C_{22}), 120.7 (C_2), 125.7 (C_{20}), 128.4 (2C), 128.6 (2C), 143.1, 143.7, 160.4 (C_3), 172.6 (C_1).

HRMS (ESI): calculated for $C_{24}H_{35}O_2$ (MH^+) 355.2632, found 355.2626.

IR (neat): 1603, 1759, 2854, 2926, 3026, 3063, 3084.



II-128

(11-(Bromomethyl)dodec-11-en-1-yl)benzene (II-128). A solution of $MgBr_2$ prepared from magnesium turnings (0.48 g, 20 mmol, 3 equiv) and 1,2-dibromoethane (1.72 mL, 20 mmol, 3 equiv) in dry Et_2O (12.5 mL) was added to a stirred and refluxed solution of 1-(10-phenyldecyl)cyclopropyl methanesulfonate **II-186** (2.28 g, 6.46 mmol, 1 equiv) in dry diethyl ether (12.5 mL). The reaction mixture was stirred at reflux for 4 h, cooled to rt and then

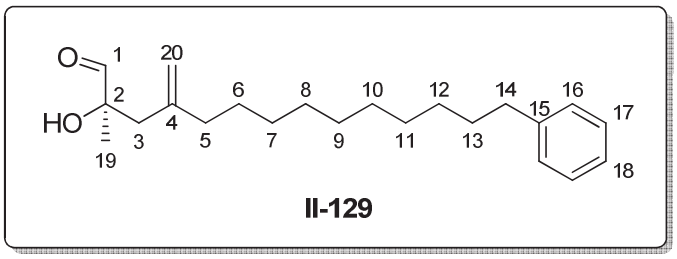
quenched with water (15 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x10 mL). The combined ethereal solutions were dried with Na_2SO_4 and evaporated. Flash column chromatography of the residue (Et_2O/petroleum ether = 1:20) gave pure **II-128** (2.045 g, 94 %) as an yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (m, 12H, $H_{5\text{-}10}$), 1.45 (m, 2H), 1.61 (m, 2H), 2.20 (t, *J* = 7.6 Hz, 2H, H_3), 2.60 (t, *J* = 7.8 Hz, 2H, H_{12}), 3.95 (s, 2H, H_1), 4.94 (m, 1H, H_{17}), 5.14 (s, 1H, H_{17}), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 1H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5, 29.4-29.7 (6C), 31.7, 33.5, 36.1, 37.0, 114.9 (C_{17}), 125.7 (C_{16}), 128.3 (2C), 128.5 (2C), 143.09, 145.89.

MS (CI): 131, 257 (MH^+-HBr), 335, 337 (MH^+), 339 (MH^+).

IR (neat): 1604, 1639, 2854, 2926, 3026, 3062, 3084.

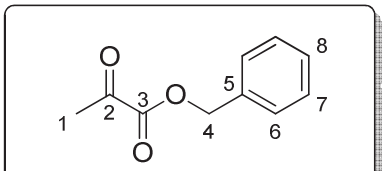


II-129

(*R*)-2-Hydroxy-2-methyl-4-methylene-14-phenyltetradecanal (II-129). Water (6 μL, 0.336 mmol, 1 equiv) and IBX (188 mg, 0.67 mmol, 2 equiv) were sequentially added to a solution of (*R*)-2-methyl-4-methylene-14-phenyl-1-((triethylsilyl)oxy)tetradecan-2-ol **II-146b** (150 mg, 0.336 mmol, 1 equiv) in DMSO (2 mL). The reaction mixture was stirred for 20 h at rt and poured into water (4 mL). Et_2O (5 mL) was added and the mixture was filtered. The organic phase was separated and the aqueous phase was extracted with Et_2O (4x6 mL). The combined organic extracts were washed with water (2x5 mL), dried (Na_2SO_4) and evaporated. Purification of the residue by short column chromatography on silica gel (Et_2O/petroleum ether = 1:1) gave **II-129** (48.5 mg, 44 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 – 1.44 (m, 14H, $H_{6\text{-}12}$), 1.31 (s, 3H, H_{19}), 1.61 (m, 2H, H_{13}), 1.82 (bs, 1H, OH), 2.00 (m, 2H, H_5), 2.36 (d, *J* = 14.0 Hz, 1H, H_3), 2.49 (d, *J* = 14.1 Hz, 1H, H_3), 2.60 (t, *J* = 7.8 Hz, 2H, H_{14}), 4.80 (s, 1H, H_{20}), 4.92 (m, 1H, H_{20}), 7.14-7.19 (m, 3H, H_{Ar}), 7.25 – 7.30 (m, 2H, H_{Ar}), 9.57 (s, 1H, H_1).

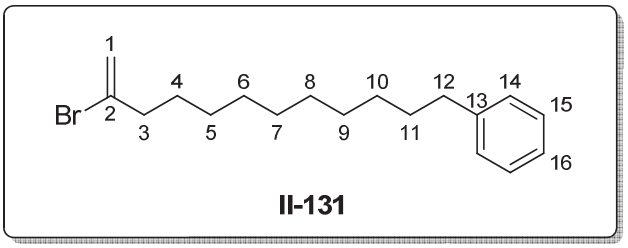
^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1 (C_{19}), 27.8, 29.4-29.7 (6C), 31.7, 36.1, 37.3, 43.8, 77.9 (C_2), 114.5 (C_{20}), 125.6 (C_{18}), 128.3 (2C), 128.5 (2C), 143.0 (C_4), 144.6 (C_{15}), 204.0 (C_1).



II-130

Benzyl 2-oxopropanoate (II-130).[259] A solution of benzyl alcohol (10.3 mL, 0.1 mol, 1 equiv), puryvic acid (7 mL, 0.1 mol, 1 equiv) and a few crystals of $TsOH \cdot H_2O$ in benzene (40 mL) was refluxed with Dean-Stark head for 25 h. Fractional distillation of the reaction mixture gave pure product (10.42 g, 59 %, bp = 73-75 ^oC at ~ 0.3 torr) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3H, H_1), 5.28 (s, 2H, H_4), 7.39 (m, 5H, H_{Ar}).

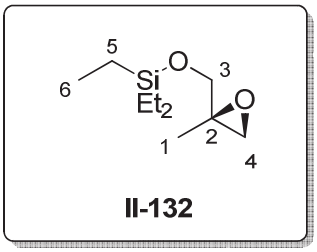


II-131

(11-Bromododec-11-en-1-yl)benzene (II-131). Magnesium Rieke was prepared by modified Rieke procedure[220]: To a suspension of freshly cut lithium (0.745 g, 106 mmol, 2 equiv) in dry THF (40 mL) were added sequentially naphthalene (1.36 g, 10.6 mmol, 0.2 equiv) and $MgCl_2$ (5.055 g, 53.2 mmol, 1 equiv). The mixture was stirred vigorously at rt for 20 h. The stirring was stopped, and after near complete precipitation of Mg (~2 h) 28 mL of THF was carefully removed by syringe and 20 mL of freshly distilled THF was added. Concentration in Mg = 1.56 M.

Method A. Magnesium turnings (0.48 g, 20 mmol, 2 equiv) were suspended in 20 mL of dry THF. A small crystal of iodine was added and the resulting mixture was refluxed until disappearance of the yellow color. (9-bromononyl)benzene (**II-75**, 2.83 g, 10 mmol, 1 equiv) was added dropwise via syringe with such a rate that the reaction mixture was gently refluxed without external heating. When the addition was finished the mixture was stirred for another 1 h. A cooled (0 ^oC) suspension of CuI (95 mg, 0.5 mmol, 0.05 equiv) in dry THF (8 mL) was treated with 2,3-dibromopropene (0.98 mL, 10 mmol, 1 equiv) and stirred for 10 min. Then (9-phenylnonyl)magnesium bromide was added dropwise. The reaction mixture was stirred at 0 ^oC for 3 h, quenched with saturated aqueous solution of NH_4Cl, and extracted with Et_2O (4x8 mL). The combined organics were dried with Na_2SO_4 and evaporated. The residue was dissolved in petrol, filtered through a small pad of silicagel and the filtrate was evaporated. The crude product (2.358 g, 60 % by NMR) was used in the next step without further purification.

Method B. To a cooled (0 °C) suspension of Mg Rieke in THF (1.56 M, 0.77 mL, 1.2 mmol, 1.25 mmol) was added (9-bromononyl)benzene (**II-75**, 272 mg, 0.96 mmol, 1 equiv) dropwise. When the addition was finished,the reaction mixture was warmed to rt and stirred for 1 h (No-D NMR spectroscopy[219] showed that Grignard reagent concentration was 0.31 M whereas theoretical concentration was 0.48 M). A cooled (0 °C) suspension of CuI (9 mg, 48 μmol, 0.05 equiv) in dry THF (0.8 mL) was treated with 2,3-dibromopropene (0.122 mL, 1 mmol, 1.04 equiv) and stirred for 10 min. Then (9-phenylnonyl)magnesium bromide was added dropwise. The reaction mixture was stored in the refrigerator (0-4 °C) overnight, quenched with saturated aqueous solution of NH_4Cl, and extracted with Et_2O (4x3 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in petroleum ether, filtered through a small pad of silica gel and the filtrate was evaporated under reduced pressure. The crude product (320 mg, 67 % by NMR) was used in the next step without further purification.



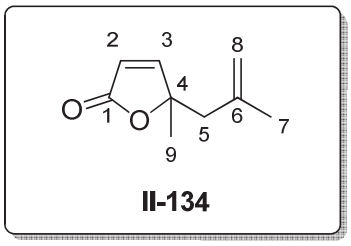
II-132

(*R*)-Triethyl((2-methyloxiran-2-yl)methoxy)silane (II-132).[260] To a cooled (0 °C) solution of the crude (*S*)-2-methylglycidol **II-143** (1.49 g, ~16.9 mmol, 1 equiv), Et_3N (3.06 mL, 22 mmol, 1.3 equiv) and DMAP (103 mg, 0.85 mmol, 0.05 equiv) in CH_2Cl_2 (20 mL) was added dropwise chlorotriethylsilane (3.41 mL, 20.3 mmol, 1.2 equiv). The reaction was allowed to reach rt, stirred for 3h and quenched with water (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (4x10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:20) to give **II-132** (1.65 g, 41 % for 2 steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 (q, *J* = 7.9 Hz, 6H, H_5), 0.95 (t, *J* = 7.9 Hz, 9H, H_6), 1.34 (s, 3H, H_1), 2.60 (d, *J* = 5.0 Hz, 1H, H_4), 2.75 (d, *J* = 5.0 Hz, 1H, H_4), 3.59 (d, *J* = 11.3 Hz, 1H, H_3), 3.65 (d, *J* = 11.3 Hz, 1H, H_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 4.5 (3C, C_5), 6.8 (3C, C_6), 18.2 (C_1), 51.9 (C_4), 57.3 (C_2), 66.4 (C_3).

$[\alpha]_D^{20}$ = +7.0 (*c* 1.02, CH_2Cl_2).



II-134

5-Methyl-5-(2-methylallyl)furan-2(5H)-one (II-134). *Method A.* To a cooled (0 ^{o}C) solution of 2-hydroxy-2,4-dimethylpent-4-enal (**II-141**, 80 mg, 0.63 mmol, 1 equiv) in MeOH (2.5 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (260 mg, 0.75 mmol, 1.2 equiv). The reaction mixture was allowed to stir for 5 h at 0 ^{o}C then warmed up to rt, stirred for another 2 h and evaporated to dryness. The residue was dissolved in Et_2O/petroleum ether = 1:1, filtered through a small pad of silica gel and evaporated. Purification of the crude product by flash column chromatography (CH_2Cl_2) gave **II-134** (49 mg, 52 %) as a colorless oil.

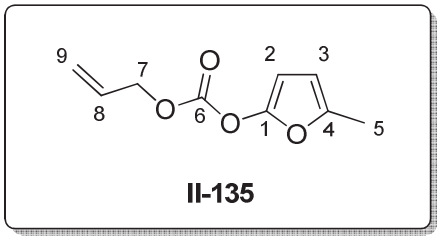
Method B. To a cooled (0 ^{o}C) solution of 2-hydroxy-2,4-dimethylpent-4-enal (**II-141**, 30 mg, 0.23 mmol, 1 equiv) in MeOH (1 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (82 mg, 0.23 mmol, 1 equiv). The reaction mixture was allowed to stir for 3 h at 0 ^{o}C then warmed up to rt, stirred for another 2 h and evaporated. The residue was dissolved in Et_2O/petroleum ether = 1:1, filtered through a small pad of silica gel and evaporated. The residue was dissolved in 2 mL of MeOH and HCl (12 M in water, 0.1 mL) followed by a catalytic amount of I_2 were added. The reaction mixture was refluxed for 2 h, evaporated and treated with saturated aqueous solution of $Na_2S_2O_3$. This mixture was extracted with Et_2O (4x2 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:1) to give the pure 5,5-dimethybutenolide **II-134** (12 mg, 34 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3H, H_9), 1.68 (s, 3H, H_7), 2.32 (d, J = 13.8 Hz, 1H, H_5), 2.47 (d, J = 13.8 Hz, 1H, H_5), 4.69 (m, 1H, H_8), 4.86 (m, 1H, H_8), 5.93 (d, J = 5.6 Hz, 1H, H_2), 7.36 (d, J = 5.6 Hz, 1H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8, 24.0, 46.3 (C_5), 88.5 (C_4), 116.6, 120.3, 139.4 (C_6), 160.5 (C_3), 172.4 (C_1).

HRMS (CI): calculated for $C_9H_{13}O_2$ (MH^+) 153.0910, found 153.0908.

IR (neat): 1604, 1646, 1759, 2934, 2981, 3080.



II-135

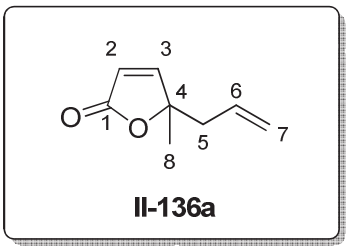
Allyl (5-methylfuran-2-yl) carbonate (II-135). To a cooled (-25 °C) solution of α-angelicalactone (490 mg, 5 mmol, 1 equiv) in dry acetonitrile (1 mL) was added triethylamine (0.84 mL, 6 mmol, 1.2 equiv) under inert atmosphere followed by a dropwise addition of a solution of allyl chloroformate (0.53 mL, 5 mmol, 1 equiv) in acetonitrile (4 mL). The reaction mixture was stirred overnight, treated with water (5 mL) and extracted with Et_2O (5x5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:10) to give the allyl carbonate **II-135** (632 mg, 69 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3H, H_5), 4.74 (dt, *J* = 5.9, 1.3 Hz, 2H, H_7), 5.34 (dq, *J* = 10.4, 1.1 Hz, 1H, H_9), 5.42 (dq, *J* = 17.2, 1.4 Hz, 1H, H_9), 5.72 (d, *J* = 3.2 Hz, 1H, H_2), 5.92-6.04 (m, 2H, $H_{3,8}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (C_5), 69.9 (C_7), 92.9 (C_2), 106.7 (C_3), 120.1 (C_9), 130.7 (C_8), 145.7, 149.2, 151.9.

HRMS (ESI): calculated for $C_9H_{10}NaO_4$ (MNa^+) 205.0471, found 205.0475.

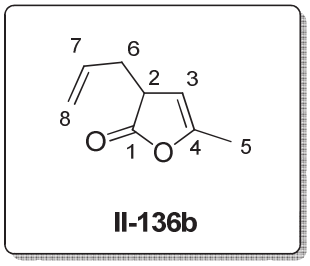
IR (neat): 1580, 1630, 1782, 2888, 2926, 2955, 2988, 3090, 3135.



II-136a

5-Allyl-5-methylfuran-2(5H)-one (II-136a).[261] $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mg, 10 μmol, 0.02 equiv) and PPh_3 (16 mg, 60 μmol, 0.12 equiv) were added into a dry flask. The gas in the flask was evacuated and dry N_2 was introduced (this procedure was repeated 3 times). Dry THF (4 mL) was added and after 15 min, the solution of allyl (5-methylfuran-2-yl) carbonate (**II-135**, 91 mg, 500 μmol, 1 equiv) in THF (1 mL). The reaction mixture was stirred during two days, evaporated and the residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:10→1:1) to give the desired **II-136a** (9 mg, 13 %) and its 3- regioisomer **II-136b** (44.7 mg, 65 %) as colorless oils.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3H, H_8), 2.50 (d, *J* = 7.3 Hz, 2H, H_5), 5.09 – 5.20 (m, 2H, H_7), 5.68 (ddt, *J* = 17.6, 10.4, 7.3 Hz, 1H, H_6), 6.03 (d, *J* = 5.6 Hz, 1H, H_2), 7.35 (d, *J* = 5.6 Hz, 1H, H_3).

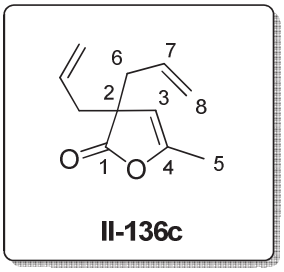


II-136b

3-Allyl-5-methylfuran-2(3H)-one (II-136b).[262] See the experimental procedure for **II-136a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97 (dd, *J* = 2.5, 1.5 Hz, 3H, H_5), 2.24 – 2.37 (m, 1H, H_6), 2.57 (ddddd, *J* = 14.1, 6.4, 5.1, 1.3, 1.3 Hz, 1H, H_6), 3.23 – 3.33 (m, 1H, H_2), 5.05 – 5.14 (m, 3H, $H_{3,8}$), 5.66 – 5.81 (m, 1H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C_5), 35.0 (C_6), 45.1 (C_2), 103.6 (C_3), 118.0 (C_8), 133.8 (C_7), 152.5 (C_4), 178.9 (C_1).



II-136c

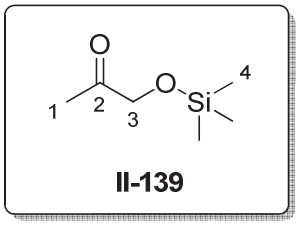
3,3-Diallyl-5-methylfuran-2(3H)-one (II-136c). $Pd_2(dba)_3{\cdot}CHCl_3$ (52 mg, 50 μmol, 0.1 equiv) and dppe (60 mg, 150 μmol, 0.3 equiv) were added into a dry flask. The gas in the flask was evacuated and dry N_2 was introduced (this procedure was repeated 3 times). Dry THF (4 mL) was added and after 15 min, the mixture was cooled (0 ^{o}C) and a solution of allyl (5-methylfuran-2-yl) carbonate (**II-135**, 91 mg, 500 μmol, 1 equiv) in THF (1 mL) was added. The reaction mixture was stored at 0 ^{o}C overnight, evaporated and the residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:10) to give **II-136c** (22.6 mg, 25 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (d, *J* = 1.5 Hz, 3H, H_5), 2.29 – 2.44 (m, 4H, H_6), 5.01 – 5.13 (m, 5H, $H_{3,8}$), 5.56 – 5.71 (m, 2H, H_7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (C_5), 40.8 (C_6), 53.6 (C_2), 106.8 (C_3), 119.3 (C_8), 132.3 (C_7), 151.3 (C_4), 180.6 (C_1).

HRMS (ESI): calculated for $C_{11}H_{14}O_2Na$ (MNa^+) 201.0886 found 201.0892.

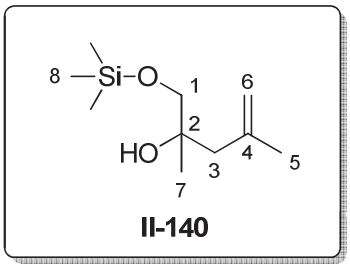
IR (neat): 1642, 1684, 1796, 2856, 2926, 2981, 3080.



II-139

1-((Trimethylsilyl)oxy)propan-2-one (II-139).[263] Chlorotrimethylsilane (7 mL, 55 mmol, 1.1 equiv) was added dropwise to a cooled to 0 °C solution of hydroxyacetone (3.6 mL, 50 mmol, 1 equiv), Et_3N (8.35 mL, 60 mmol, 1.2 equiv) and DMAP (61 mg, 0.5 mmol, 0.01 equiv) in CH_2Cl_2 (30 mL). The reaction mixture was warmed up to rt, stirred for 18 h and quenched with saturated aqueous solution of NH_4Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (5x10 mL). The combined organic extracts were washed with water (15 mL), brine (20 mL), dried (Na_2SO_4) and evaporated to dryness. The crude product (6.07 g, 83 %) was used in the next step without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.15 (s, 9H, H_4), 2.14 (s, 3H, H_1), 4.15 (s, 2H, H_3).



II-140

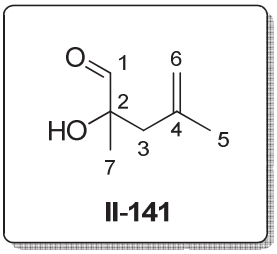
2,4-Dimethyl-1-((trimethylsilyl)oxy)pent-4-en-2-ol (II-140). Magnesium turnings (1.2 g, 49.9 mmol, 3 equiv) were suspended in dry THF (20 mL). A small crystal of iodine was added and the resulting mixture was refluxed until disappearance of the yellow color. 1-chloro-2-methyl-2-propene (1.63 mL, 16.6 mmol, 1 equiv) was added dropwise via syringe at such a rate that the reaction mixture was gently refluxed without external heating. When the addition was finished the mixture was stirred for another 1 h. This solution was added dropwise to a solution of 1-((trimethylsilyl)oxy)propan-2-one (**II-139**, 1.7 g, 11.6 mmol, 0.7 equiv) in THF (7 mL) at 0 °C. The reaction mixture was stirred for 30 min at rt, cooled to 0 °C and quenched with saturated aqueous solution of NH_4Cl (5 mL) and water (30 mL). The resulting mixture was extracted with Et_2O (5x10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product (2.2 g) was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 9H, H_8), 1.12 (s, 3H, H_7), 1.82 (s, 3H, H_5), 2.14 (d, J = 13.2 Hz, 1H, H_3), 2.23 (d, J = 13.2 Hz, 1H, H_3), 2.35 (bs, 1H, OH), 3.32 (d, J = 9.6 Hz, 1H, H_1), 3.40 (d, J = 9.6 Hz, 1H, H_1), 4.70 (m, 1H, H_6) , 4.86 (m, 1H, H_6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -0.4 (C_8), 23.8, 24.7, 46.4, 69.9 (C_1), 72.3 (C_2), 114.5 (C_6), 142.8 (C_4).

HRMS (ESI): calculated for $C_{10}H_{22}SiO_2Na$ (MNa^+) 225.1281 found 225.1276.

IR (neat): 1643, 2866, 2908, 2958, 3074, 3460.



II-141

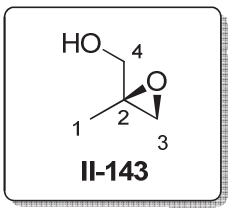
2-Hydroxy-2,4-dimethylpent-4-enal (II-141). Water (0.21 mL, 11.6 mmol, 0.7 equiv) and IBX (4.5 g, 16.1 mmol, 0.97 equiv) were sequentially added to a solution of 2,4-dimethyl-1-((trimethylsilyl)oxy)pent-4-en-2-ol **II-140** (2.2 g) in DMSO (30 mL). The reaction mixture was stirred for 8 h at rt and poured into water (60 mL). Et_2O (50 mL) was added and the mixture was filtered. The organic phase was separated and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic extracts were washed with water (2x5 mL), dried (Na_2SO_4) and evaporated. Purification of the residue through a short column of silica gel (Et_2O: petroleum ether = 1:1) afforded the ketol **II-141** (0.987 g, 66 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3H, H_7), 1.74 (s, 3H, H_5), 2.37 (d, *J* = 13.8 Hz, 1H, H_3), 2.47 (d, *J* = 13.8 Hz, 1H, H_3), 3.50 (bs, 1H, OH), 4.75 (m, 1H, H_6), 4.91 (m, 1H, H_6), 9.57 (s, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 24.3, 45.5 (C_3), 77.9 (C_2), 115.9 (C_6), 140.5 (C_4), 203.9 (C_1).

HRMS (CI): calculated for $C_7H_{13}O_2$ (MH^+) 129.0910, found 129.0911.

IR (neat): 1646, 1734, 2817, 2933, 2976, 3077, 3457.



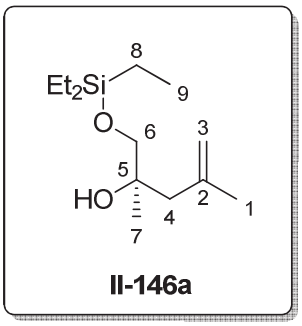
II-143

(*S*)-(2-Methyloxiran-2-yl)methanol (II-143).[217] To a cooled (-20°C) slurry of MS (4 Å, 1.6 g) in CH_2Cl_2 (55 mL) was added (+)-DET (0.48 mL, 2.85 mmol, 0.13 equiv) followed by Ti(O*i*Pr)$_4$ (0.65 mL, 2.2 mmol, 0.1 equiv). The mixture was stirred for 10 min and then TBHP (5.5 M in decane, 8.78 mL, 48 mmol, 2.2 equiv) was added followed by 2-methallyl alcohol (1.84 mL, 21.9 mmol, 1 equiv) over 30 min. The reaction was stirred at -20 °C for 1 h and stored in a fridge (-27 °C) for 2 days, warmed up to 0 °C and quenched with water (10

mL). After warming up to rt, the stirring was continued for 45 min and 2.2 mL of 30 % NaOH aqueous solution saturated with NaCl (2.2 mL) was added and the resulting mixture was stirred for 30-40 min. After introduction of 10 mL of water in the reaction mixture, the organic layer was separated and the aqueous layer was extracted with Et_2O (5x10 mL). The combined organic extracts were washed with water (15 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (Et_2O/petroleum ether = 3:1) of the residue yielded the crude epoxide **II-143** (1.49 g) as a colorless oil. Pure sample of **II-143** was obtained by hydrolysis of the corresponding silyl ether **II-132** with TBAF.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3H, H_1), 2.08 (bs, 1H, OH), 2.64 (d, *J* = 4.8 Hz, 1H, H_3), 2.90 (d, *J* = 4.8 Hz, 1H, H_3), 3.54 – 3.62 (m, 1H, H_4), 3.71 (d, *J* = 12.3 Hz, 1H, H_4).

$[\alpha]_D^{20}$ = -9.75 (*c* 0.4, $CHCl_3$), lit. for (*R*)-isomer +10.7 ($CHCl_3$).



II-146a

(*R*)-2,4-Dimethyl-1-((triethylsilyl)oxy)pent-4-en-2-ol (II-146a). Magnesium turnings (26 mg, 1.1 mmol, 2.2 equiv) were suspended in dry THF(1 mL). A small crystal of iodine was added and the resulting mixture was refluxed until disappearance of the yellow color. 2-bromoprop-1-ene (89 μL, 1.0 mmol, 2 equiv) was then added dropwise via syringe and the reaction mixture was refluxed for 30 min and cooled to rt. Freshly prepared prop-1-en-2-ylmagnesium bromide (~1M) was transferred via syringe to a slurry of CuI (47.5 mg, 0.25 mmol, 0.5 equiv) in THF (1 mL) at -45 ^oC. After stirring for 1 h, a solution of (*R*)-triethyl((2-methyloxiran-2-yl)methoxy)silane **II-132** (101 mg, 0.5 mmol. 1 equiv) in THF (0.5mL) was added slowly. The reaction mixture was stirred at -45 ^oC for 1h, then allowed to warm up to 0 ^oC and stirred for another 1h. It was quenched with a mixture (1:1) of saturated aqueous solution of NH_4Cl and 10 % aqueous solution of NH_4OH, and extracted with Et_2O (4x4 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et_2O/petroleum ether = 1:3) to give **II-146a** (50.9 mg, 42 %) as a colorless oil.

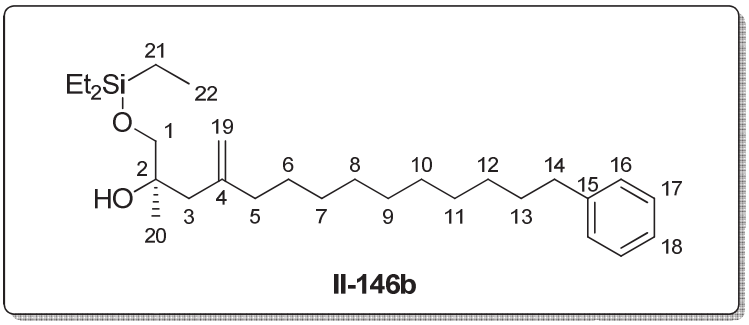
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61 (q, *J* = 7.9 Hz, 6H, H_8), 0.96 (t, *J* = 7.9 Hz, 9H, H_9), 1.13 (s, 3H, H_7), 1.82 (m, 3H, H_1), 2.14 (dd, *J* = 13.4, 0.6 Hz, 1H, H_4), 2.25 (d, *J* = 13.4 Hz, 1H, H_4), 2.37 (bs, 1H, OH), 3.36 (d, *J* = 9.4 Hz, 1H, H_6), 3.44 (d, *J* = 9.3 Hz, 1H, H_6), 4.71 (m, 1H, H_3), 4.86 (m, 1H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.5 (3C, C_8), 6.9 (3C, C_9), 23.8, 24.7, 46.4 (C_4), 70.1 (C_6), 72.5 (C_5), 114.5 (C_3), 142.9 (C_2).

HRMS (ESI): calculated for $C_{13}H_{28}O_2SiNa$ (MNa^+) 267.1751, found 267.1748.

IR (neat): 1643, 2877, 2915, 2954, 3076, 3462.

$[\alpha]_D^{20}$ = +2.05 (*c* 0.44, CH_2Cl_2).



II-146b

(*R*)-2-Methyl-4-methylene-14-phenyl-1-((triethylsilyl)oxy)tetradecan-2-ol (II-146b). *Method A.* Magnesium turnings (48 mg, 2 mmol, 3 equiv) were suspended in dry THF (2 mL). A small crystal of iodine was added and the resulting mixture was refluxed until disappearance of the yellow color. (11-bromododec-11-en-1-yl)benzene (**II-131**, 60 % pur., 538 mg, 1.0 mmol, 1.5 equiv) was then added dropwise via syringe and the reaction mixture was refluxed for 3 h and cooled to rt. Freshly prepared Grignard reagent was transferred via syringe to a slurry of CuI (47.5 mg, 0.25 mmol, 0.5 equiv) in THF (1 mL) at -45 ^oC. After stirring at -30 ^oC for 30 min, a solution of (*R*)-triethyl((2-methyloxiran-2-yl)methoxy)silane (**II-132**, 135 mg, 0.67 mmol, 1 equiv) in THF (0.5 mL) was slowly added. The temperature was reached slowly 0 ^oC and the reaction mixture was stirred at this temperature for 2 h, stored in the refrigerator overnight and quenched with saturated aqueous solution of NH_4Cl. The resulting mixture was extracted with Et_2O (4x6 mL). The c ombined organic phases were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography on silica gel (Et_2O/petroleum ether = 1:15) to give pure **II-146b** (154 mg, 52 %) as a colorless oil.

Method B. To a solution of *t*-BuLi (1.7 M in pentane, 1.24 mL, 2.1 mmol, 4.2 equiv) in Et_2O (1 mL) at -78 ^oC under N_2 atmosphere was added a solution of (11-bromododec-11-en-1-yl)benzene (**II-131**, 60 % pur., 538 mg, 1.0 mmol, 2 equiv) in Et_2O (0.3 mL), and the resulting mixture was stirred for 30 min. CuCN (45 mg, 0.5 mmol, 1 equiv) was then added and the stirring was continued for 10 min at -25 ^oC. A solution of (*R*)-triethyl((2-methyloxiran-2-yl)methoxy)silane (**II-132**, 90 mg, 0.45 mmol, 0.89 equiv) in Et_2O (0.2 mL) was added and the mixture was allowed to warm up to 0 ^oC during 1 h. Then it was treated with a mixture of saturated aqueous solution of NH_4Cl (1 mL), saturated aqueous solution of NH_4OH (0.05 mL) and water (1 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (5x2 mL). The combined organic layers were dried (Na_2SO_4) and

evaporated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/petroleum ether = 1:15) to give pure **II-146b** (138.5 mg, 70 %) as a colorless oil.

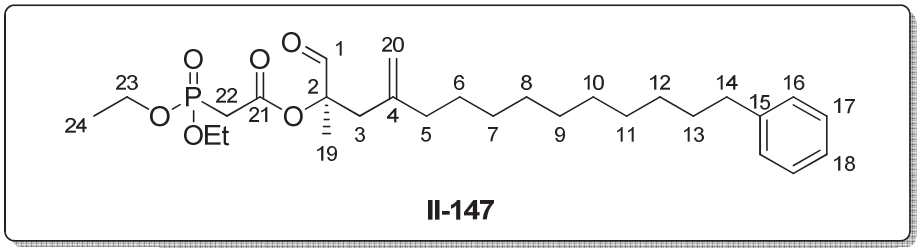
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.62 (q, *J* = 7.8 Hz, 6H, H_{21}), 0.97 (t, *J* = 7.9 Hz, 9H, H_{22}), 1.13 (s, 3H, H_{20}), 1.23 – 1.49 (m, 14H, $H_{6\text{-}12}$), 1.61 (m, 2H, H_{13}), 2.11 (t, *J* = 7.5 Hz, 2H, H_5), 2.13 (d, *J* = 13.8 Hz, 1H, H_3), 2.27 (d, *J* = 13.4 Hz, 1H, H_3), 2.41 (s, 1H, OH), 2.59 (t, *J* = 7.8 Hz, 2H, H_{14}), 3.35 (d, *J* = 9.4 Hz, 1H, H_1), 3.44 (d, *J* = 9.4 Hz, 1H, H_1), 4.77 (s, 1H, H_{19}), 4.87 (m, 1H, H_{19}), 7.15-7.18 (m, 3H, H_{Ar}), 7.23 – 7.30 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.5 (C_{21}), 6.9 (C_{22}), 23.9 (C_{20}), 28.2, 29.5-29.8 (6C), 31.7, 36.1, 37.6, 44.4, 70.0 (C_1), 72.5 (C_2), 113.2 (C_{19}), 125.7 (C_{18}), 128.3 (2C), 128.5 (2C), 143.1 (C_4), 147.0 (C_{15}).

HRMS (ESI): calculated for $C_{28}H_{50}O_2SiNa$ (MNa^+) 469.3472, found 469.3468.

IR (neat): 1640, 2855, 2876, 2927, 3027, 3065, 3480, 3570.

$[\alpha]_D^{20}$ = +8.7 (*c* 1.18, $CHCl_3$).

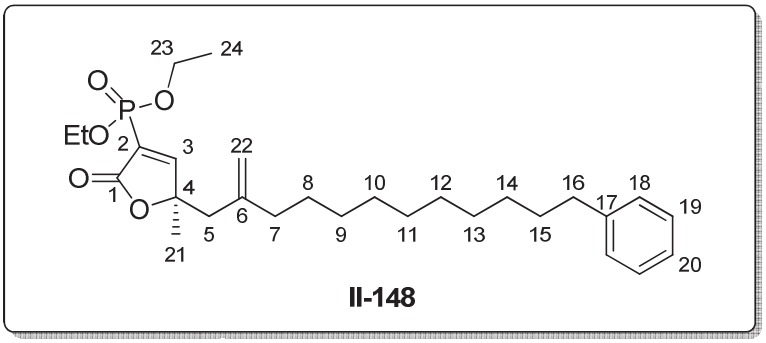


II-147

(*R*)-2-Methyl-4-methylene-1-oxo-14-phenyltetradecan-2-yl 2-(diethoxyphosphoryl) acetate (II-147). To a solution of (*R*)-2-hydroxy-2-methyl-4-methylene-14-phenyltetradecanal **II-129** (48.5 mg, 0.147 mmol, 1 equiv) and diethylphosphonoacetic acid (47 µL, 0.294 mmol, 2 equiv) in CH_2Cl_2 (1 mL) was added a solution of dicyclocarbodiimide (60 mg, 0.294 mmol, 2 equiv) in CH_2Cl_2 (0.5 mL). The reaction mixture was allowed to stir at rt for 2 h and then was directly subjected to flash column chromatography on silica gel (Et_2O) to give pure **II-147** (44.3 mg, 59 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 - 1.43 (m, 14H, $H_{6\text{-}12}$), 1.34 (t, *J* = 7.1 Hz, 6H, H_{24}), 1.45 (s, 3H, H_{19}), 1.60 (m, 2H, H_{13}), 2.03 (t, *J* = 7.5 Hz, 2H, H_5), 2.40 (d, *J* = 14.4 Hz, 1H, H_3), 2.54 (d, *J* = 14.4 Hz, 1H, H_3), 2.59 (t, *J* = 7.5 Hz, 2H, H_{14}), 2.99 (dd, *J* = 21.7, 2.0 Hz, 2H, H_{22}), 4.17 (dq, *J* = 14.2, 7.1 Hz, 4H, H_{23}), 4.83 (s, 1H, H_{20}), 4.94 (m, 1H, H_{20}), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.28 (m, 2H, H_{Ar}), 9.49 (s, 1H, H_1).

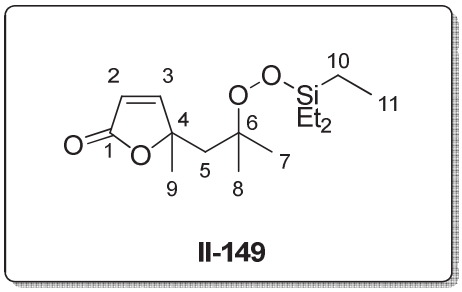
^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (d, *J* = 6.1 Hz, C_{24}), 19.0, 27.8, 29.4 – 29.7 (6C), 31.6, 34.5 (d, *J* = 133.4 Hz, C_{22}), 36.1, 37.3, 41.2, 62.9 (d, *J* = 6.4 Hz, C_{23}), 86.1 (C_2), 115.8 (C_{20}), 125.6 (C_{18}), 128.3 (2C), 128.5 (2C), 143.0 (2C), 165.6 (d, *J* = 6.4 Hz, C_{21}), 198.7 (C_1).



II-148

(*R*)-Diethyl (5-methyl-5-(2-methylene-12-phenyldodecyl)-2-oxo-2,5-dihydrofuran-3-yl)phosphonate (II-148). For experimental procedure see in **II-126**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 – 1.86 (m, 22H), 1.97 (m, 2H), 2.42 (d, *J* = 14.0 Hz, 1H), 2.57 (d, *J* = 13.4 Hz, 1H), 2.59 (t, *J* = 7.7 Hz, 2H), 4.20 (m, 4H), 4.81 (s, 1H), 4.94 (s, 1H), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 2H, H_{Ar}),7.98 (d, *J* = 9.6 Hz, 1H).



II-149

rac-5-Methyl-5-(2-methyl-2-((triethylsilyl)peroxy)propyl)furan-2(5H)-one (II-149). *Method A.* To a solution of 5-methyl-5-(2-methylallyl)furan-2(5H)-one **II-134** (100 mg, 0.66 mmol, 1 equiv) in dichloroethane (5 mL) was added $Co(thd)_2$ (28 mg, 66 μmol, 0.1 equiv) and the flask was charged with O_2. Et_3SiH (136 μl, 0.86 mmol, 1.3 equiv) was added and the reaction mixture was stirred for 3 h under O_2 atmosphere. Evaporation of the reaction mixture and chromatography of the residue on silica gel (Et_2O/Petroleum ether = 1:2) afforded the starting material **II-134** (80 mg, 80 %) and **II-149** (40.2 mg, 20 %) as a colorless oil.

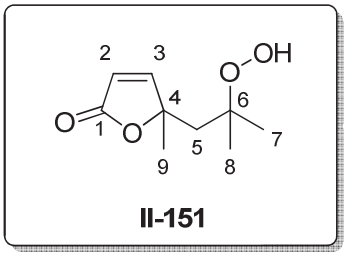
Method B. To a cooled to 0 ^oC solution of rac-(2*R*,3*R*)-2-methyl-2-(2-methyl-2-((triethylsilyl)peroxy)propyl)-5-oxotetrahydrofuran-3-yl acetate (**II-169**, 15 mg, 41.7 μmol, 1 equiv) in dry THF (0.5 mL) was added DBU (9.3 μL, 62.5 μmol, 1.5 equiv) and the reaction mixture was stirred at 0 ^oC for 4 h. When the reaction was finished, water (1 mL) was added and the resulting mixture was extracted with Et_2O (5x2 mL). The combined ethereal solutions were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (Et_2O/petroleum ether = 1:2) gave pure **II-134** (6 mg, 48 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (q, *J* = 7.7 Hz, 6H, H_{10}), 0.98 (t, *J* = 7.9 Hz, 9H, H_{11}), 1.11 (s, 3H), 1.25 (s, 3H), 1.48 (s, 3H), 2.13 (d, *J* = 15.4 Hz, 1H, H_5), 2.24 (d, *J* = 15.4 Hz, 1H, H_5), 5.91 (d, *J* = 5.6 Hz, 1H, H_2), 7.56 (d, *J* = 5.6 Hz, 1H, H_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.0 (C_{10}), 6.9 (C_{11}), 24.8, 26.6, 26.7, 44.8 (C_5), 81.8, 88.3, 118.6 (C_2), 162.7 (C_3), 173.1 (C_1).

HRMS (ESI): calculated for $C_{15}H_{28}O_4SiNa$ (MNa^+) 323.1649, found 323.1652.

IR (neat): 1603, 1763, 2878, 2938, 2957.

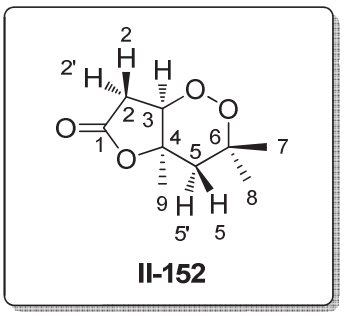


II-151

5-(2-Hydroperoxy-2-methylpropyl)-5-methylfuran-2(5H)-one (II-151). To a solution of 5-methyl-5-(2-methyl-2-((triethylsilyl)peroxy)propyl)furan-2(5H)-one (**II-149**, 40 mg, 0.13 mmol, 1 equiv) were added a small crystal of PTSA and water (3 μL, 17 μL, 1.25 equiv). After completion of the reaction, the reaction mixture was directly chromatographed on silica gel (Et_2O/petroleum ether = 3:1) to give the hydroperoxide **II-151** (19.5 mg, 79 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 1.25 (s, 3H), 1.50 (s, 3H), 2.12 (d, J = 15.3 Hz, 1H, H_5), 2.25 (d, J = 15.6 Hz, 1H, H_5), 5.98 (d, J = 5.6 Hz, 1H, H_2), 7.58 (d, J = 5.6 Hz, 1H, H_3), 8.00 (s, 1H, OOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 26.1, 26.8, 44.5 (C_5), 81.8, 88.3, 119.2 (C_2), 162.1 (C_3), 172.9 (C_1).



II-152

3,3,4a-Trimethyltetrahydrofuro[3,2-c][1,2]dioxin-6(3H)-one (II-152). *Method A.* Et_2NH (1.1 μL, 10.2 μmol, 0.1 equiv) was added to a solution of 5-(2-hydroperoxy-2-methylpropyl)-5-methylfuran-2(5H)-one **II-151** (19 mg, 102 μmol, 1 equiv) in TFE/CH_2Cl_2 = 2:1 (1.8 mL). The reaction mixture was stirred at rt for 12 h and evaporated to give pure **II-152** (19 mg, quantitative) as a colorless oil.

Method B. To a cooled to 0 °C solution of rac-(2*R*,3*R*)-2-methyl-2-(2-methyl-2-((triethylsilyl)peroxy)propyl)-5-oxotetrahydrofuran-3-yl acetate (**II-169**, 20 mg, 55.6 μmol, 1 equiv) in dry THF (0.5 mL), DBU (8.4 mg, 55.6 μmol, 1 equiv) was added, and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was warmed to rt, stirred for 4 h and concentrated to 0.3 mL. Petroleum ether (1 mL) was added and the resulting mixture was chromatographed (Et_2O/Petroleum ether = 2:1) to give **152** (6 mg, 58 %) as a colorless oil.

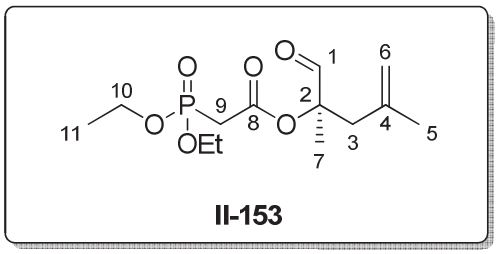
Method C. To a cooled to 0 °C solution of rac-(2*R*,3*R*)-2-methyl-2-(2-methyl-2-((triethylsilyl)peroxy)propyl)-5-oxotetrahydrofuran-3-yl acetate (**II-169**, 18 mg, 50 μmol, 1 equiv) in dry THF (0.5 mL), DBU (9.1 mg, 60 μmol, 1.2 equiv) was added, and the resulting mixture was stirred at 0 °C for 3 h. TFE (0.5 mL) and TBAF (1 M in THF, 50 μL, 50 μmol, 1 equiv) were added and the reaction mixture was stirred for 1 h. Then it was treated with water (2 mL) and extracted with Et_2O (5x2 mL). The combined extracts were dried and evaporated. Purification of the residue by flash column chromatography on silica gel (Et_2O/Petroleum ether = 2:1) gave **152** (7 mg, 75 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H, H_8), 1.33 (s, 3H, H_7), 1.37 (s, 3H, H_9), 1.74 (d, *J* = 14.9 Hz, 1H, $H_{5'}$), 2.20 (d, *J* = 14.9 Hz, 1H, H_5), 2.57 (d, *J* = 18.5 Hz, 1H, H_2), 2.91 (dd, *J* = 18.5, 6.0 Hz, 1H, $H_{2'}$), 4.47 (d, *J* = 5.9 Hz, 1H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (C_7), 25.9 (C_9), 28.2 (C_8), 34.3 (C_2), 41.5 (C_5), 78.1, 81.1 (C_3), 82.8, 174.3 (C_1).

HRMS (ESI): calculated for $C_9H_{15}O_4$ (MH^+) 187.0965, found 187.0964.

IR (neat): 1764, 2947, 2982, 3009.



II-153

2,4-Dimethyl-1-oxopent-4-en-2-yl 2-(diethoxyphosphoryl)acetate (II-153). DCC (618 mg, 3 mmol, 1.5 equiv) was added in one portion to a stirred and cooled solution (0 °C) of 2-hydroxy-2,4-dimethylpent-4-enal **II-141**(256 mg, 2 mmol, 1 equiv) in CH_2Cl_2 (12 mL). Diethylphosphonoacetic acid (588 mg, 3 mmol, 1.5 equiv) was then added dropwise. The reaction mixture was stirred at 0 °C for 30 min, warmed up to rt and stirred for another 30 min. Then it was filtered and concentrated. Flash chromatography (AcOEt) of the residue gave **II-153** (248 mg, 41 %) as a colorless oil.

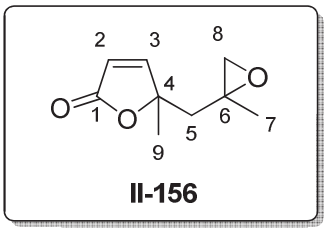
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 6H, H_{11}), 1.46 (s, 3H, H_7), 1.80 (s, 3H, H_5), 2.42 (dd, *J* = 14.3, 0.5 Hz, 1H, H_3), 2.55 (d, *J* = 14.2 Hz, 1H, H_3), 3.01 (dd, *J* = 21.7,

1.7 Hz, 2H, H_9), 4.18 (dq, *J* = 8.3, 7.1 Hz, 4H, H_{10}), 4.78 (m, 1H, H_6), 4.94 (m, 1H, H_6), 9.50 (s, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (d, *J* = 6.3 Hz, C_{11}), 19.0 , 24.3, 34.62 (d, *J* = 133.6 Hz, C_9), 43.1 (C_3), 63.0 (d, *J* = 6.3 Hz, C_{10}), 86.0 (C_2), 117.1 (C_6), 139.1 (C_4), 165.6 (d, *J* = 6.2 Hz, C_8), 198.6 (C_1).

HRMS (CI): calculated for $C_{28}H_{50}O_2SiNa$ (MNa^+) 307.1311, found 307.1306.

IR (neat): 1647, 1733, 2728, 2871, 2913, 2936, 2985, 3078.



II-156

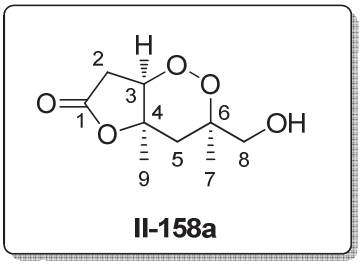
5-Methyl-5-((2-methyloxiran-2-yl)methyl)furan-2(5H)-one (II-156). To a solution of 5-methyl-5-(2-methylallyl)furan-2(5H)-one (**II-134**, 17 mg, 0.112 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added *m*CPBA 75 % (39 mg, 0.168 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 5 h, then Et_2O (2 mL) was added and the organic phase was washed with aqueous solution of NaOH (2 M, 2x1 mL). The combined aqueous layers were extracted with Et_2O (3x3 mL). The combined organic phases were washed with brine (3 mL), dried (Na_2SO_4) and evaporated. Flash chromatography (Et_2O/petroleum ether = 2:1→ Et_2O) of the residue gave the epoxide **II-156** (19 mg, quantitative) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 1.8H), 1.39 (s, 1.4H), 1.47 (s, 1.8H), 1.54 (s, 1.4H), 1.90 (d, *J* = 14.8 Hz, 0.4H, H_5), 1.94 (d, *J* = 14.8 Hz, 0.6H, H_5), 2.06 (d, *J* = 13.1 Hz, 0.6H, H_5), 2.10 (d, *J* = 14.8 Hz, 0.4H, H_5), 2.52 (d, *J* = 4.8 Hz, 0.4H, H_8), 2.55 (d, *J* = 4.8 Hz, 0.4H, H_8), 2.57 (d, *J* = 5.3 Hz, 0.6H, H_8), 2.64 (d, *J* = 4.8 Hz, 0.6H, H_8), 6.01 (d, *J* = 5.6 Hz, 0.4H, H_2), 6.04 (d, *J* = 5.6 Hz, 0.6H, H_2), 7.41 (d, *J* = 5.6 Hz, 0.4H, H_3), 7.48 (d, *J* = 5.6 Hz, 0.6H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 22.5, 24.5, 25.4, 45.5 (C_5), 45.7 (C_5), 54.07, 54.14, 54.3, 54.8, 88.0 (C_4), 88.1 (C_4), 120.4 (C_2), 120.5 (C_2), 160.8 (C_3), 160.9 (C_3), 172.2 (C_1), 172.4 (C_1).

HRMS (ESI): calculated for $C_9H_{12}O_3Na$ (MNa^+) 191.0679, found 191.0683.

IR (neat): 1604, 1748, 1756, 1760, 1766, 2936, 2984, 3049, 3086.



II-158a

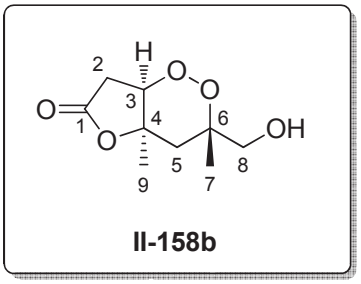
rac-(3*R*,4a*R*,7a*R*)-3-(Hydroxymethyl)-3,4a-dimethyltetrahydrofuro[3,2-c][1,2]dioxin-6(3H)-one (II-158a). A mixture of 5-methyl-5-((2-methyloxiran-2-yl)methyl)furan-2(5H)-one **II-156** (52 mg, 0.31 mmol, 1 equiv), ethereal solution of H_2O_2 (1.16 M, 1.33 mL, 1.55 mmol, 5 equiv) and PMA (6 mg, 3.29 μmol, 0.011 equiv) was stirred at room temperature for 3 h. Then it was filtered through a small pad of silica gel and eluted with Et_2O. Evaporation of the ethereal solution gave the crude hydroperoxide **II-157**, which was dissolved in TFE/CH_2Cl_2 = 2:1 (2.4 mL) and treated with Et_2NH (1.4 μL, 14 μmol). The reaction mixture was stirred at rt overnight and evaporated. Flash chromatography (Et_2O) of the residue gave first **II-158a** (16 mg, 25 %) followed by **II-158b** (18 mg, 29 %) as colorless oils.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H, H_7), 1.39 (s, 3H, H_9), 1.74 (d, *J* = 15.4 Hz, 1H, H_5), 1.82 (bs, 1H, OH), 2.24 (d, *J* = 15.5 Hz, 1H, H_5), 2.45 (d, *J* = 18.6 Hz, 1H, H_2), 2.93 (dd, *J* = 18.5, 5.4 Hz, 1H, H_2), 3.38 (dd, *J* = 11.6, 7.1 Hz, 1H, H_8), 3.98 (d, *J* = 11.5 Hz, 1H, H_8), 4.56 (d, *J* = 5.3 Hz, 1H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (C_7), 25.7 (C_9), 33.9 (C_2), 38.0 (C_5), 64.6 (C_8), 80.3 (C_6), 80.7 (C_3), 81.5 (C_4), 173.7 (C_1).

HRMS (ESI): calculated for $C_9H_{14}O_5Na$ (MNa^+) 225.0733, find 225.0736.

IR (neat): 1774, 2938, 2978, 3455.



II-158b

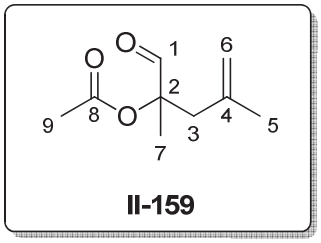
rac-(3*S*,4a*R*,7a*R*)-3-(Hydroxymethyl)-3,4a-dimethyltetrahydrofuro[3,2-c][1,2]dioxin-6(3H)-one (II-158b). For experimental procedure see **II-158a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3H, H_7), 1.44 (s, 3H, H_9), 1.90 (d, *J* = 14.7 Hz, 1H, H_5), 1.97 (bs, 1H, OH), 2.12 (d, *J* = 14.7 Hz, 1H, H_5), 2.76 (d, *J* = 18.7 Hz, 1H, H_2), 2.95 (dd, *J* = 18.7, 6.9 Hz, 1H, H_2), 3.48 (m, 1H, H_8), 3.65 (dd, *J* = 11.8, 3.6 Hz, 1H, H_8), 4.43 (d, *J* = 6.9 Hz, 1H, H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (C_7), 26.1 (C_9), 34.7 (C_2), 36.0 (C_5), 68.2 (C_8), 80.8 (C_6), 81.9 (C_3), 83.5 (C_4), 174.3 (C_1).

HRMS (ESI): calculated for $C_9H_{14}O_5Na$ (MNa^+) 225.0733, found 225.0734.

IR (neat): 1647, 1767, 2877, 2935, 3443.



II-159

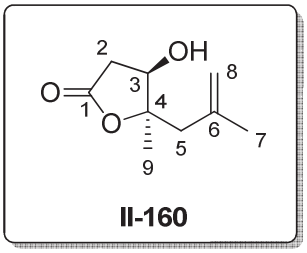
2,4-Dimethyl-1-oxopent-4-en-2-yl acetate (II-159). To a cooled solution (0 °C) of 2-hydroxy-2,4-dimethylpent-4-enal **II-141** (44.5 mg, 0.35 mmol, 1 equiv) in CH_2Cl_2 (3 mL) were successively added DMAP (55 mg, 0.45 mmol, 1.3 equiv) and Ac_2O (43 µL, 0.45 mmol, 1.3 equiv). After stirring at rt for 3 h the reaction mixture was quenched with water (3 mL) and extracted with Et_2O (5x3 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated. Purification of the residue by flash column chromatography (Et_2O/petroleum ether = 1:5 → 1:3) gave **II-159** (52 mg, 31 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3H, H_7), 1.76 (m, 3H, H_5), 2.09 (s, 3H, H_9), 2.39 (dd, J = 14.2, 0.7 Hz, 1H, H_3), 2.55 (d, J = 14.2 Hz, 1H, H_3), 4.74 (m, 1H, H_6), 4.92 (m, 1H, H_6), 9.46 (s, 1H, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 21.1, 24.2, 42.5 (C_3), 84.5 (C_2), 116.8 (C_6), 139.4 (C_4), 170.6 (C_8), 198.9 (C_1).

HRMS (CI): calculated for $C_9H_{15}O_3$ (MH^+) 171.1016, found 171.1018.

IR (neat): 1647, 1733, 1738, 2715, 2823, 2849, 2945, 2982, 3079.

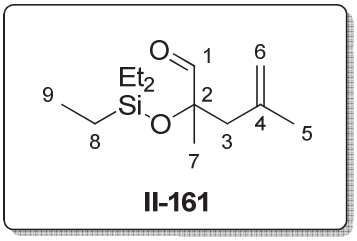


II-160

rac-(4*R*,5*R*)-4-Hydroxy-5-methyl-5-(2-methylallyl)dihydrofuran-2(3H)-one (II-160). To a solution of methyl 3-((tert-butyldimethylsilyl)oxy)-4,6-dimethyl-4-((triethylsilyl)oxy)hept-6-enoate **II-167a** (diastereomer mixture, ratio 1/2) (22 mg, 51.2 µmol,

1 equiv) in dry THF (1 mL) was added TBAF (1 M in THF, 0.15 mL, 0.154 mmol) and the reaction mixture was stirred for 3 h at rt. Water (2 mL) was added and the mixture was extracted with Et_2O (4x3 mL). The combined extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography gave **II-160** (4 mg, 46 %, dr = 1:2) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 2H, H_9), 1.40 (s, 1H, H_9), 1.82 (s, 1H, H_7), 1.85 (s, 2H, H_7), 2.00 (bs, 0.35H, OH), 2.13 (bs, 0.65H, OH), 2.37 – 2.62 (m, 3H, $H_{2,5}$), 2.85 – 2.99 (m, 1H, H_2), 4.27 (m, 0.65H, H_3), 4.37 (m, 0.35H, H_3), 4.82 (m, 1H, H_8), 4.97 (m, 1H, H_8).



II-161

2,4-Dimethyl-2-((triethylsilyl)oxy)pent-4-enal (II-161). *Method A.* Water (7 μL, 0.4 mmol, 0.6 equiv) and IBX (371 mg, 1.33 mmol, 2 equiv) were sequentially added to a solution of the crude 7,7-diethyl-2,2,5-trimethyl-5-(2-methylallyl)-3,6-dioxa-2,7-disilanonane **II-165** (210 mg, ~0.66 mmol) in DMSO (3 mL). The reaction mixture was stirred for 20 h at rt, poured into water (6 mL) followed by addition of Et_2O (5 mL). After stirring for 10 min, the mixture was filtered. The organic phase was separated and the aqueous phase was extracted with Et_2O (5x4 mL). The combined organic layers were washed with water (5 mL), dried (Na_2SO_4) and evaporated. Purification of the residue by a short column chromatography (petroleum ether→Et_2O/petroleum ether = 1:10) gave **II-161** (60 mg, 37 %) as a colorless oil.

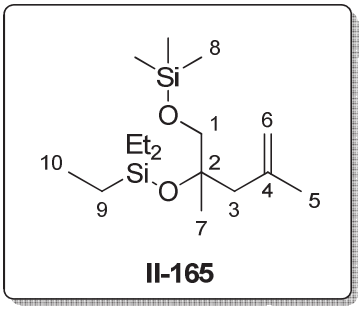
Method B. To a cooled solution (-78 °C) of oxalyl chloride (0.86 mL, 10.2 mmol, 3.6 equiv) in CH_2Cl_2 (3.5 mL) was dropwise added DMSO (1.44 mL, 20.3 mmol, 7.2 equiv). After 15 min stirring, the crude 7,7-diethyl-2,2,5-trimethyl-5-(2-methylallyl)-3,6-dioxa-2,7-disilanonane **II-165** (1.07 g, ~2.8 mmol, ~1 equiv) in CH_2Cl_2 (3.5 mL) was added dropwise. The mixture was stirred at -70 ^{o}C for 20 min followed by 40 min at -40 ^{o}C, and then Et_3N (2.8 mL, 20.3 mmol, 7.2 equiv) was added slowly. After 30 min the reaction mixture was warmed up to rt, stirred for 20 min, treated carefully with ice-cold water and extracted with Et_2O (4x5 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:10) to give **II-161** (351 mg, 52 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61 (q, J = 7.8 Hz, 6H, H_8), 0.95 (t, J = 7.9 Hz, 9H, H_9), 1.29 (s, 3H, H_7), 1.75 (s, 3H, H_5), 2.25 (d, J = 13.7 Hz, 1H, H_3), 2.37 (d, J = 13.7 Hz, 1H, H_3), 4.70 (m, 1H, H_6), 4.85 (m, 1H, H_6), 9.60 (s, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.7 (C), 7.1, 23.2, 24.5, 47.4 (C_3), 80.4 (C_2), 115.4 (C_6), 140.9 (C_4), 205.0 (C_1).

HRMS (ESI): calculated for $C_{13}H_{26}SiO_2Na$ (MNa^+) 265.1594 found 265.1592.

IR (neat): 1648, 1737, 2700, 2799, 2878, 2913, 2956, 3077.

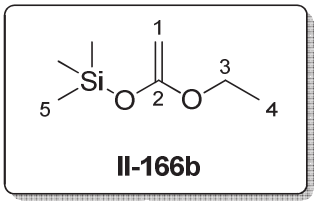


II-165

7,7-Diethyl-2,2,5-trimethyl-5-(2-methylallyl)-3,6-dioxa-2,7-disilanonane (II-165). To a cooled solution (0 °C) of 2,4-dimethyl-1-((trimethylsilyl)oxy)pent-4-en-2-ol **II-140** (203 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (2 mL), DMAP (159 mg, 1.3 mmol, 1.3 equiv) and TESCl (0.22 mL, 1.3 mmol, 1.3 equiv) were added sequentially. The temperature was raised to rt and the mixture was stirred for 2 days, quenched with water and extracted with Et_2O (4x4 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated. The crude **II-165** was used in the next step without further purification. Otherwise it was purified by flash column chromatography (petroleum ether) to give **II-165** (210 mg, 66 %) as a colorless oil. In the case of high silica gel acidity, a small amount of Et_3N should be used as an additive to the eluent in order to prevent the hydrolysis of TMSO group.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 9H, H_8), 0.58 (q, *J* = 7.9 Hz, 6H, H_9), 0.94 (t, *J* = 7.9 Hz, 9H, H_{10}), 1.17 (s, 3H, H_7), 1.81 (s, 3H, H_5), 2.18 (s, 2H, H_3), 3.31 (d, *J* = 9.5 Hz, 1H, H_1), 3.37 (d, *J* = 9.5 Hz, 1H, H_1), 4.69 (s, 1H, H_6), 4.82 (m, 1H, H_6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -0.4 (C_8), 7.0, 7.3, 24.9, 25.2, 47.6 (C_3), 69.8 (C_1), 76.3 (C_2), 113.9 (C_6), 143.5 (C_4).

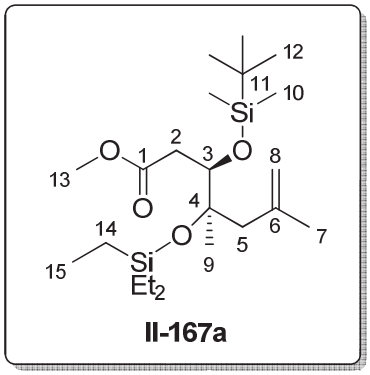


II-166b

((1-Ethoxyvinyl)oxy)trimethylsilane (II-166b). It was synthesized using a Shibasaki modification of Corey's internal quench method.[229] To a solution of *i*Pr_2NH (9.8 mL, 70 mmol, 1.05 equiv) in THF (66 mL), BuLi (2.44 M solution in hexane, 27.3 mL, 66.7 mmol, 1 equiv) was added dropwise in an ice bath, and the mixture was stirred for 15 min. After

cooling to -78 °C, a mixture of AcOEt 5.9 mL, 60.7 mmol, 0.91 equiv) and TMSCl (8.9 mL, 70 mmol, 1.05 mmol) in THF (34 mL) was added. After the addition was completed, the cooling bath was removed, and the mixture was stirred for 3 h at rt. Then, THF was evaporated and hexane was added. The resulting precipitate was filtrated off through a celite pad, and the residue was washed with hexane. The combined filtrates were evaporated at reduced pressure, and the resulting residue was purified by distillation (bp. 60-70 °C/50 mmHg), giving **II-166b** (3.3 g, 34 %) as a colorless liquid.

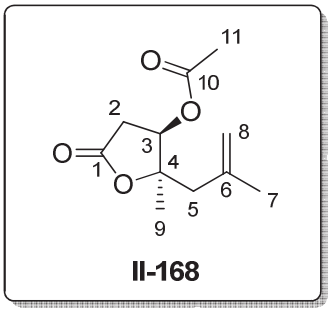
^{1}H NMR (300 MHz, C_6D_6): δ = 0.25 (s, 9H, H_5), 0.95 (t, *J* = 7.2 Hz, 3H, H_4), 3.17 (d, *J* = 2.5 Hz, 1H, H_1), 3.42 (q, *J* = 7.2 Hz, 2H, H_3), 3.59 (d, *J* = 2.5 Hz, 1H, H_1).



II-167a

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-4,6-dimethyl-4-((triethylsilyl)oxy)hept-6-enoate (II-167a). An ethereal solution of $LiClO_4$ was prepared as follows: A magnetic stirring bar and $LiClO_4$ (2.13 g, 20 mmol) were placed into a 25 mL flask, which was then connected to high vacuum pump and heated at 150 ^oC for 3 h. Then the flask was flushed with dry N_2 and allowed to cool to rt. Et_2O (5 mL) was added and the mixture was stirred for 24 h at rt under an atmosphere of dry nitrogen. The resulting white solution (~4M) was used in the synthesis. The ethereal solution of $LiClO_4$ (4M, 1 mL) was added to a mixture of 2,4-dimethyl-2-((triethylsilyl)oxy)pent-4-enal **II-161** (29 mg, 0.12 mmol, 1 equiv) and 1-(*tert*-Butyldimethylsilyloxy)-1-methoxyethene **II-166a** (29 mg, 0.156 mmol, 1.3 equiv). The resulting mixture was stirred at rt for 4 h, and water was added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x2 mL). The combined ethereal solutions were washed with brine, dried (Na_2SO_4) and evaporated. Purification of the residue by flash column chromatography (Et_2O/petroleum ether = 1:5) gave **II-167a** as a colorless oil (22.4 mg, 44 %, dr = 1:2) contaminated by small amounts of impurities.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6H, H_{10}), 0.60 (m, 6H, H_{14}), 0.91 (s, 9H, H_{12}), 0.96 (m, 9H, H_{15}), 1.23 (s, 1H, H_9), 1.26 (s, 2H, H_9), 1.82 (s, 3H, H_7), 2.10 (m, 1H, H_5), 2.38-2.69 (bm, 3H, $H_{2,5}$), 3.71 (s, 3H, H_{13}), 3.93 (m, 1H, H_3), 4.78 (bs, 1H, H_8), 4.89 (bs, 1H, H_8).



II-168

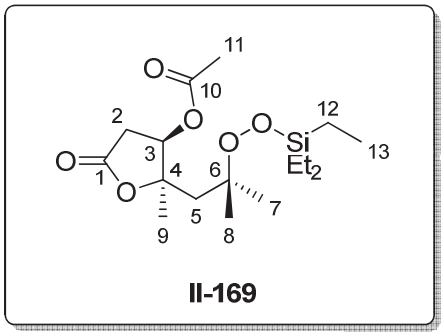
Rac-(2*R*,3*R*)-2-Methyl-2-(2-methylallyl)-5-oxotetrahydrofuran-3-yl acetate (II-168). To a cooled solution (-78 ^{o}C) of 2,4-dimethyl-2-((triethylsilyl)oxy)pent-4-enal (**II-161**, 264 mg, 1.09 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added dropwise, a mixture of $TiCl_4$ (1 M in CH_2Cl_2, 0.55 mL, 0.55 mmol, 0.5 equiv) and Ti(O*i*Pr)$_4$ (0.16 mL, 0.55 mmol, 0.5 equiv) followed by the addition of ((1-ethoxyvinyl)oxy)trimethylsilane (**II-166b**, 262 mg, 1.64 mmol, 1.5 equiv). The reaction mixture was stirred at -78 ^{o}C for 6 h, treated with saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with Et_2O (4x5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The crude β-silyloxy ester **II-167b** was dissolved in THF (5 mL) and TBAF (1 M in THF, 2.18 mL, 2.18 mmol, 2 equiv) was added. The reaction mixture was stirred at rt for 2 h, quenched with saturated aqueous solution of NH_4Cl (5 mL), and extracted with Et_2O (5x4 mL). The combined ethereal solutions were washed with brine, dried (Na_2SO_4) and evaporated. To a cooled solution (0 ^{o}C) of the residue in CH_2Cl_2 (5 mL) were added sequentially DMAP (173 mg, 1.42 mmol, 1.3 equiv) and acetic anhydride (134 μL, 1.42 mmol, 1.3 equiv). The reaction mixture was stirred for 3 h at rt and then concentrated. Purification of the residue by flash column chromatography (Et_2O/petroleum ether = 1:1→1.5:1) gave **II-168** (137 mg, 59 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3H, H_9), 1.80 (s, 3H, H_7), 2.11 (s, 3H, H_{11}), 2.30 (d, *J* = 14.2 Hz, 1H, H_5), 2.51 (dd, *J* = 18.5, 1.7 Hz, 1H, H_2), 2.54 (d, *J* = 14.2 Hz, 1H, H_5), 3.04 (dd, *J* = 18.5, 6.3 Hz, 1H, H_2), 4.77 (m, 1H, H_8), 4.94 (m, 1H, H_8), 5.21 (dd, *J* = 6.3, 1.7 Hz, 1H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 23.3, 23.8, 36.1, 42.5, 75.3, 87.5, 116.4, 140.5, 170.0, 173.8.

HRMS (CI): calculated for $C_{11}H_{17}O_4$ (MH^+) 213.1121 found 213.1118.

IR (neat): 1647, 1742, 1782, 2950, 2981, 3077.



II-169

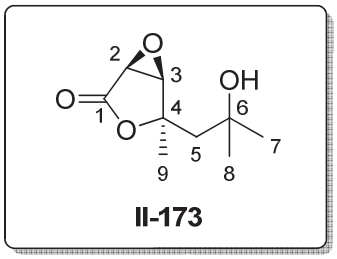
Rac-(2*R*,3*R*)-2-Methyl-2-(2-methyl-2-((triethylsilyl)peroxy)propyl)-5-oxotetrahydrofuran-3-yl acetate (II-169). To a solution of rac-(2*R*,3*R*)-2-methyl-2-(2-methylallyl)-5-oxotetrahydrofuran-3-yl acetate (**II-168**, 135 mg, 0.64 mmol, 1 equiv) in dichloroethane (5 mL) was added $Co(thd)_2$ (27 mg, 64 μmol, 0.1 equiv) and the flask was charged with O_2. Et_3SiH (0.203 mL, 1.27 mmol, 2 equiv) was added and the reaction mixture was stirred for 3 h under O_2 atmosphere. Evaporation of the reaction mixture and chromatography of the residue on silica gel (Et_2O/petroleum ether = 2:3→1:1) afforded **II-169** (190 mg, 83 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.65 (q, *J* = 7.6 Hz, 6H, H_{12}), 0.96 (t, *J* = 7.9 Hz, 9H, H_{13}), 1.23 (s, 3H), 1.31 (s, 3H), 1.53 (s, 3H, H_9), 1.94 (d, *J* = 15.5 Hz, 1H, H_5), 2.10 (s, 3H, H_{11}), 2.18 (d, *J* = 15.5 Hz, 1H, H_5), 2.43 (dd, *J* = 18.5, 1.3 Hz, 1H, H_2), 3.03 (dd, *J* = 18.5, 6.0 Hz, 1H, H_2), 5.11 (dd, *J* = 6.0, 1.3 Hz, 1H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.9 (C_{12}), 6.9 (C_{13}), 21.0, 23.3, 24.9, 27.4, 36.0, 40.0, 76.1, 82.0, 87.8, 169.9, 174.0.

HRMS (CI): calculated for $C_{17}H_{33}O_6Si$ (MH^+) 361.2041, found 361.2043.

IR (neat): 1747, 1785, 2878, 2940, 2957.



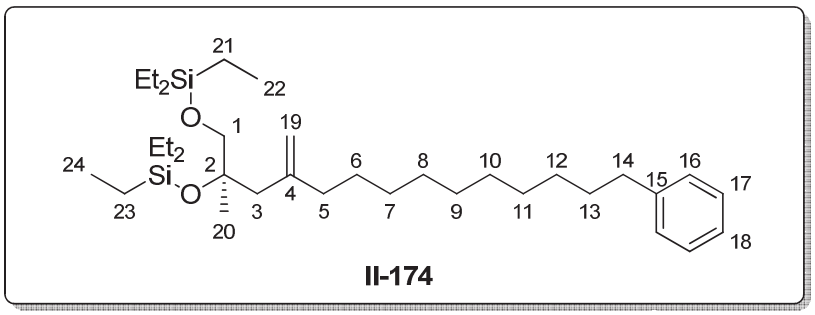
II-173

Rac-(1*S*,4*R*,5*R*)-4-(2-hydroxy-2-methylpropyl)-4-methyl-3,6-dioxabicyclo[3.1.0] hexan-2-one (II-173). To a cooled solution (0 °C) of rac-(2*R*,3*R*)-2-methyl-2-(2-methyl-2-((triethylsilyl)peroxy)propyl)-5-oxotetrahydrofuran-3-yl acetate (**II-169**, 31.7 mg, 88.1 μmol, 1 equiv) in dry THF (0.9 mL) was added DBU (14 μL, 96.9 μmol, 1.1 equiv) and the reaction mixture was stirred for 3 h at 0 °C followed by 15 h at rt. Petroleum ether (1 mL) was added and the resulting mixture was directly chromatographed (Et_2O/petroleum ether = 2:1→ Et_2O) to give **II-152** (6.2 mg, 38 %) and **II-173** (3.4 mg, 21 %) as colorless oils.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3H), 1.36 (s, 3H), 1.43 (s, 1H, OH), 1.59 (s, 3H, H_9), 1.99 (d, *J* = 14.8 Hz, 1H, H_5), 2.07 (d, *J* = 14.8 Hz, 1H, H_5), 3.80 (d, *J* = 2.5 Hz, 1H, H_2), 4.01 (d, *J* = 2.5 Hz, 1H, H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.36, 31.30, 32.03, 46.87, 51.44, 61.20, 70.36, 85.00, 169.85.

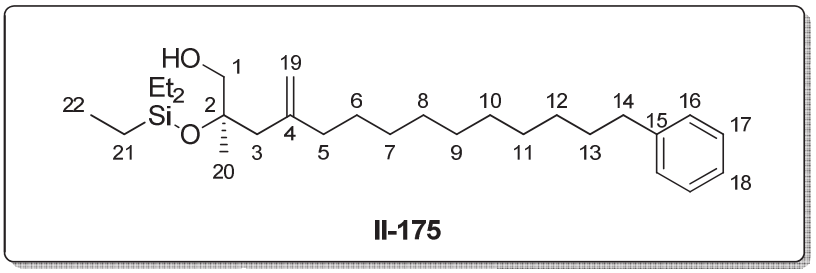
HRMS (ESI): calculated for $C_9H_{14}O_4Na$ (MNa^+) 209.0784, found 209.0786.



II-174

(*R*)-3,3,8,8-Tetraethyl-5-methyl-5-(2-methylene-12-phenyldodecyl)-4,7-dioxa-3,8-disiladecane (II-174). To a cooled solution (0 °C) of (*R*)-2-methyl-4-methylene-14-phenyl-1-((triethylsilyl)oxy)tetradecan-2-ol **II-146b** (125 mg, 0.28 mmol, 1 equiv) in CH_2Cl_2 (2 mL) were successively added Et_3N (47 µL, 0.336 mmol, 1.2 equiv) and TESOTf (76 µL, 0.336 mmol, 1.2 equiv) and then the temperature was warmed up to rt. The reaction mixture was stirred for 1 h, quenched with water and extracted with Et_2O (4x3 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated. The crude product was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.54 – 0.63 (m, 12H, $H_{21,23}$), 0.91 – 0.99 (m, 18H, $H_{22,24}$), 1.17 (s, 3H, H_{20}), 1.27 – 1.64 (m, 16H, $H_{6\text{-}13}$), 2.11 (t, *J* = 7.2 Hz, 2H, H_5), 2.18 (m, 2H, H_3), 2.60 (t, *J* = 7.8 Hz, 2H, H_{14}), 3.32 (d, *J* = 9.3 Hz, 1H, H_1), 3.42 (d, *J* = 9.3 Hz, 1H, H_1), 4.74 (s, 1H, H_{19}), 4.81 (m, 1H, H_{19}), 7.14 – 7.19 (m, 3H, H_{Ar}), 7.25 – 7.30 (m, 2H, H_{Ar}).

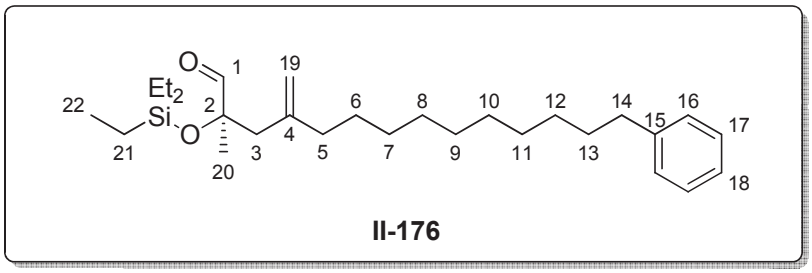


II-175

(*R*)-2-Methyl-4-methylene-14-phenyl-2-((triethylsilyl)oxy)tetradecan-1-ol (II-175). The crude (*R*)-3,3,8,8-tetraethyl-5-methyl-5-(2-methylene-12-phenyldodecyl)-4,7-dioxa-3,8-disiladecane (**II-174**) was deposed on silica gel and eluted first with Et_2O/petroleum ether =

1:100 during 5 min and after with Et_2O/petroleum ether = 1:10. Evaporation of solvents gave the crude **II-175** (100.7 mg) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61 (q, *J* = 7.5 Hz, 6H, H_{21}), 0.96 (t, *J* = 7.9 Hz, 9H, H_{22}), 1.21 (s, 3H, H_{20}), 1.27 – 1.43 (m, 14H, $H_{6\text{-}12}$), 1.61 (m, 2H, H_{13}), 2.00 (bs, 1H, OH), 2.07 (t, *J* = 7.5 Hz, 2H, H_5), 2.23 (d, *J* = 13.1 Hz, 1H, H_3), 2.31 (d, *J* = 13.2 Hz, 1H, H_3), 2.59 (t, *J* = 7.5 Hz, 2H, H_{14}), 3.36 (m, 2H, H_1), 4.78 (s, 1H, H_{19}), 4.85 (s, 1H, H_{19}), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 2H, H_{Ar}).



II-176

(*R*)-2-Methyl-4-methylene-14-phenyl-2-((triethylsilyl)oxy)tetradecanal (II-176). *Method A.* To a cooled solution (78 °C) of oxalyl chloride (54 μL, 0.638 mmol, 3 equiv) in CH_2Cl_2 (0.6 mL) was added dropwise DMSO (90 μL, 1.28 mmol, 6 equiv). After stirring for 15 min, the crude (*R*)-2-methyl-4-methylene-14-phenyl-2-((triethylsilyl)oxy)tetradecan-1-ol **II-175** (95 mg, ~0.21 mmol, ~1 equiv) in CH_2Cl_2 (1 mL) was added dropwise. After stirring the mixture at -70 → -50 °C for 30 min, Et_3N (0.177 mL, 1.28 mmol, 6 equiv) was added slowly. After 10 min, the reaction mixture was warmed up to rt, quenched carefully with ice-cold water and extracted with Et_2O (5x3 mL). The combined organic extracts were washed with brine, dried with (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:50) to give **II-176** (74 mg, 60 % for 3 steps) as a colorless oil.

Method B. To a cooled solution (-78 °C) of (*R*)-benzyl 2-methyl-4-methylene-14-phenyl-2-((triethylsilyl)oxy)tetradecanoate **II-189** (61.5 mg, 0.112 mmol, 1 equiv) in toluene (1 mL) was added dropwise, DIBAL (1 M, 0.335 mL, 0.335 mmol, 3 equiv). The reaction mixture was stirred at -20 °C for 2 h, quenched with Rochelle salt and extracted with Et_2O (4x4 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The crude primary alcohol **II-175** was used for the next step without further purification. To a cooled solution (-78 °C) of oxalyl chloride (28 μL, 0.335 mmol, 3 equiv) in CH_2Cl_2 (0.3 mL) was added dropwise DMSO (47 μL, 0.67 mmol, 6 equiv). After 15 min of stirring, the crude (*R*)-2-methyl-4-methylene-14-phenyl-2-((triethylsilyl)oxy)tetradecan-1-ol **II-175** (~0.11 mmol, ~1 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise. The mixture was stirred at -70→-50 °C for 30 min, and then Et_3N (93 μL, 0.67 mmol, 6 equiv) was added slowly. After 10 min, the reaction mixture was warmed up to rt, quenched carefully with ice-cold water and extracted with Et_2O (5x2 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (Et_2O/petroleum ether = 1:50) to give **II-176** (41.7 mg, 84 %) as a colorless oil.

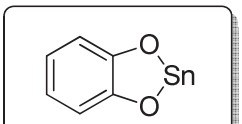
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61 (q, *J* = 7.8 Hz, 6H, H_{21}), 0.95 (t, *J* = 7.9 Hz, 9H, H_{22}), 1.26 – 1.43 (m, 14H, $H_{6\text{-}12}$), 1.28 (s, 3H, H_{20}), 1.61 (m, 2H, H_{13}), 2.04 (t, *J* = 7.5 Hz, 2H, H_5), 2.23 (d, *J* = 13.8 Hz, 1H, H_3), 2.36 (d, *J* = 13.8 Hz, 1H, H_3), 2.60 (t, *J* = 7.8 Hz, 2H, H_{14}), 4.74 (s, 1H, H_{19}), 4.85 (m, 1H, H_{19}), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 2H, H_{Ar}) 9.59 (s, 1H, H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.7 (C_{21}), 7.1 (C_{22}), 23.1 (C_{20}), 27.9, 29.5 – 29.8 (6C), 31.7, 36.1, 37.4, 45.5, 80.5 (C_2), 114.1 (C_{19}), 125.7 (C_{18}), 128.3 (2C), 128.5 (2C), 143.0, 144.9, 204.8 (C_1).

HRMS (CI): calculated for $C_{28}H_{49}O_2Si$ (MH^+) 445.3496, found 445.3497.

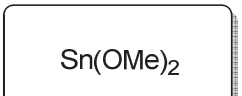
IR (neat): 1642, 1737, 2698, 2800, 2855, 2876, 2927, 2952, 3027, 3064.

$[\alpha]_D^{20}$ = +11.1 (*c* 1.07, $CHCl_3$).



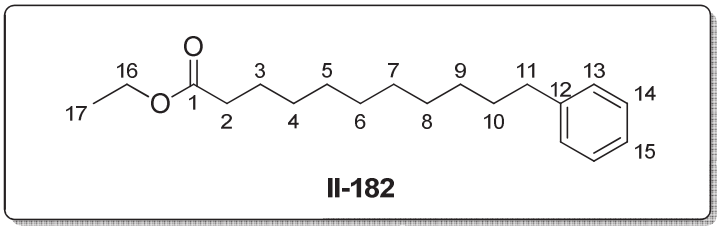
II-177

Tin(II) catecholate (II-177).[233] Tin(II) dimethoxide (**II-181**, 3.34 g, 30.3 mmol, 1 equiv) was added to a solution of catechol (5.49 g, 30.3 mmol, 1 equiv) in methanol (50 mL) and the mixture stirred for 18 h. The white product was filtered and washed with methanol (20 mL) followed by Et_2O (2x20 mL). Drying of the solid gave **II-177** (6.37 g, 93 %), which was used without further purification.



II-181

Tin(II) dimethoxide (II-181).[233] Triethylamine (9.4 mL, 67.5 mmol, 2.01 equiv) was added dropwise to a solution of anhydrous tin(II) chloride (6.38 g, 33.6 mmol, 1 equiv) in methanol (140 mL). An exothermic reaction occurred and tin(II) dimethoxide precipitated as a white solid, which was filtered, washed with several portions of methanol followed by anhydrous diethyl ether. The white solid (5.50 g, 90 %) was stored under N_2 atmosphere and used in the next step without further purification.

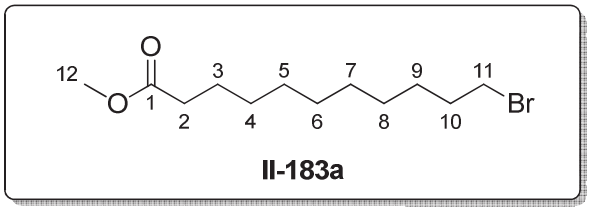


II-182

Ethyl 11-phenylundecanoate (II-182).[264] To a well-stirred mixture of diethyl malonate (0.303 mL, 2 mmol, 1 equiv) and TBAB (32 mg, 0.1 mmol, 0.05 equiv) was added *t*BuOK followed by (9-bromononyl)benzene **II-75** (566 mg, 2 mmol, 1 equiv). The mixture was heated for 10 min inside an oil bath at 130 ^{o}C. After cooling, LiBr (348 mg, 4 mmol, 2 equiv) and water (72 µL, 4 mmol, 2 equiv) were added and the mixture was irradiated with microwaves for 10 min at 200 ^{o}C. Flash column chromatography of the reaction mixture (eluent: Et_2O/petroleum ether=1:10) gave pure **II-182** (143 mg, 25 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.9 Hz, 3H, H_{17}), 1.30 (m, 12H, $H_{4\text{-}9}$), 1.63 (m, 4H, $H_{3,10}$), 2.29 (t, *J* = 7.5 Hz, 2H, H_2), 2.61 t, *J* = 7.8 Hz, 2H, H_{11}), 4.13 (q, *J* = 7.1 Hz, 1H, H_{16}), 7.15 – 7.19 (m, 3H, H_{Ar}), 7.25 – 7.30 (m, 2H, H_{Ar}).

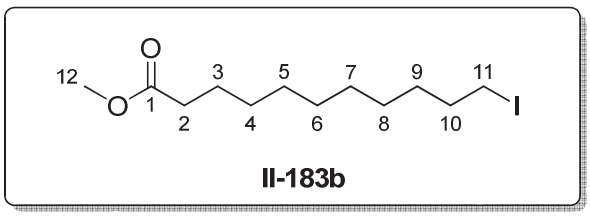
^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (C_{16}), 25.1, 29.2, 29.3, 29.4, 29.5, 29.55, 29.57, 31.6, 34.4, 36.1, 60.2 (C_{16}), 125.6 (C_{12}), 128.3 (2C), 128.4 (2C), 142.9 (C_{15}), 173.8 (C_1).



II-183a

Methyl 11-bromoundecanoate (II-183a).[265] To a solution of 11-bromoundecanoic acid (2.067 g, 7.8 mmol) in Et_2O (10 mL), ethereal solution of diazomethane was added until persistent slightly yellow color. Evaporation of the solvent gave pure **II-183b** (2.176 g, quant) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 10H), 1.39 (m, 2H), 1.59 (m, 2H), 1.20 (m, 2H), 2.27 (t, *J* = 7.5 Hz, 2H, H_2), 3.37 (t, *J* = 6.9 Hz, 2H, H_{11}), 3.63 (s, 3H, H_{12}).

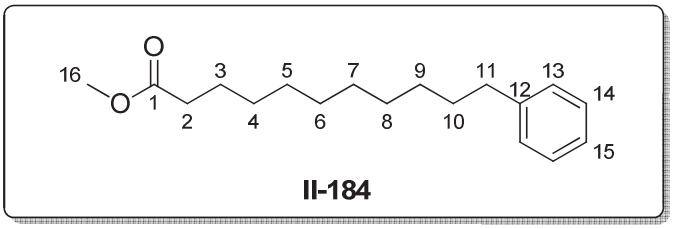


II-183b

Methyl 11-iodoundecanoate (II-183b).[235] To a solution of 11-bromoundecanoic acid (5.3 g, 20 mmol, 1 equiv) and anhydrous K_2CO_3 (12.4 g, 90 mmol, 4.5 equiv) in 130 mL of acetone, was added dropwise over 10 min iodomethane (12.5 mL, 200 mmol, 10 equiv). The mixture was stirred at room temperature for 40 h; the precipitate formed was filtered, and the solvent was evaporated. Flash chromatography (Et_2O/petroleum ether = 1:20) of the residue gave inseparable mixture of the bromo **II-183a** and the iodo **II-183b** (ratio 1:9, 6.319 g, 98 %) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 10H), 1.37 (m, 2H), 1.60 (m, 2H), 1.80 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H, H_2), 3.17 (t, *J* = 7.0 Hz, 2H, H_{11}), 3.65 (s, 3H, H_{12}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.4, 25.1, 28.6, 29.2, 29.3, 29.4, 29.5, 30.6, 33.7, 34.2, 51.6, 174.4.

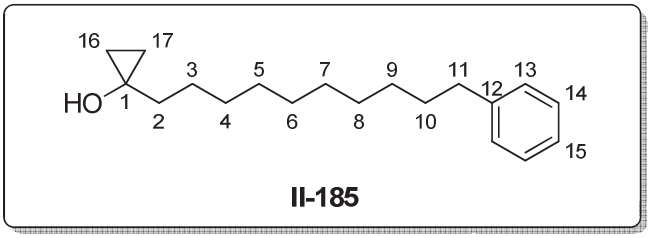


II-184

Methyl 11-phenylundecanoate (II-184).[235] A dry and nitrogen flushed flask was charged with THF (8 mL), methyl 11-bromoundecanoate (**II-183a**, 2.19 g, 7.85 mmol, 1 equiv), $Co(acac)_3$ (140 mg, 0.393 mmol, 0.05 equiv) and TMEDA (59 μL, 0.393 mmol, 0.05 equiv). This mixture was cooled to 0 ^oC and a solution of PhMgBr (~1 M in THF) was added slowly (~50 min) until the color changed from green to brown. At this point, the reaction mixture was quenched with HCl (1 M, 10 mL) and extracted with Et_2O (4x10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (Et_2O/petroleum ether = 1:20) of the residue gave pure **II-184** (2.00 g, 92 %) as a colorless oil. Its physical data were in accordance with those described in the literature.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (bs, 12H), 1.61 (m, 4H), 2.29 (t, *J* = 7.5 Hz, 2H, H_2), 2.59 (t, *J* = 7.5 Hz, 2H, H_{11}), 3.66 (s, 3H, H_{16}), 7.14 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 29.3, 29.4, 29.5, 29.56, 29.61, 29.63, 31.7, 34.3, 36.1, 51.6 (C_{16}), 125.7 (C_{15}), 128.3 (2C), 128.5 (2C), 143.1 (C_{12}), 174.5 (C_1).



II-185

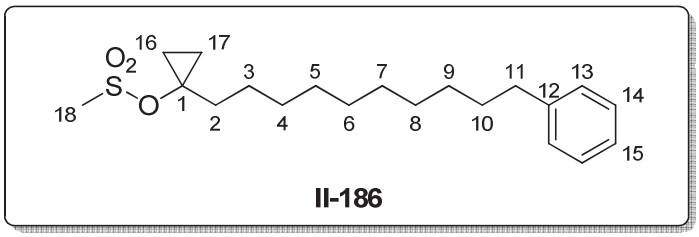
1-(10-Phenyldecyl)cyclopropanol (II-185). A solution of ethylmagnesium bromide (7.25 mL, 21.7 mmol, 3 equiv) was slowly added with stirring to a solution of methyl 11-phenylundecanoate **II-184** (2.0 g, 7.25 mmol, 1 equiv) and titanium tetraisopropoxide (0.215 mL, 0.725 mmol, 0.1 equiv) in dry Et_2O (7 mL). The reaction mixture was then added with stirring and cooling to sulfuric acid (20 % aqueous solution, 11 mL) at such a speed that the temperature did not exceed 10 ^oC. Extractive workup with Et_2O (5x10 mL), $NaHCO_3$ (aqueous saturated solution, 10 mL) and brine (10 mL), drying (Na_2SO_4) and concentration gave the crude cyclopropanol **II-185** (1.903 g, 96 %) which could be used without purification for the next step. An analytical sample of **II-185** was obtained by flash chromatography (Et_2O/petroleum ether = 1:2) as a white amorphous powder.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.42 (m, 2H, $H_{16,17}$), 0.71 (m, 2H, $H_{16,17}$), 1.28 (s, 12H), 1.43 – 1.62 (m, 6H), 1.91 (s, 1H, OH), 2.59 (t, *J* = 7.8 Hz, 2H, H_{11}), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (2C, $C_{16\text{-}17}$), 26.1, 29.5, 29.6 – 29.8 (5C), 31.7, 36.1, 38.4, 56.0 (C_1), 125.7 (C_{15}), 128.3 (2C), 128.5 (2C), 143.0 (C_{12}).

HRMS (ESI): calculated for $C_{19}H_{30}NaO$ (MNa^+) 297.2189, found 297.2187.

IR (neat): 1604, 2847, 2917, 3002, 3083, 3249, 3333.



II-186

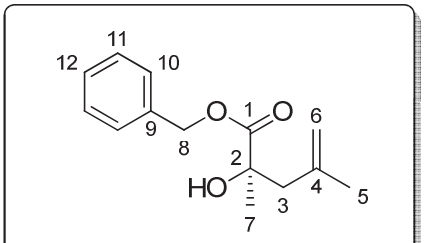
1-(10-Phenyldecyl)cyclopropyl methanesulfonate (II-186). A cooled and stirred solution (0 ^oC) of methanesulfonyl chloride (0.68 mL, 8.73 mmol, 1.3 equiv) in diethyl ether (4 mL) was added dropwise to the solution of 1-(10-phenyldecyl)cyclopropanol **II-185** (1.84 g, 6.72 mmol, 1 equiv) and Et_3N (1.4 mL, 10.1 mmol, 1.5 equiv) in dry Et_2O (20 mL). The reaction mixture was kept at room temperature overnight and then treated with water (10 mL). The water phase was extracted with Et_2O (3x10 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4) and concentrated to give the crude mesylate **II-186** (2.345 g, 99%), which was used without purification in the next step. An analytic sample of **II-186** was obtained by flash chromatography (Et_2O/petroleum ether = 1:5) as a white amorphous powder.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 (m, 2H, $H_{16,17}$), 1.25 (m, 2H, $H_{16,17}$), 1.30 (m, 12H), 1.49 – 1.67 (m, 4H), 1.85 (t, *J* = 7.8 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H, H_{11}), 2.98 (s, 3H, H_{18}), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8 (2C, $C_{16\text{-}17}$), 25.7, 29.4 – 29.6 (6C), 31.6, 36.0, 36.1, 39.9, 67.1 (C_1), 125.6 (C_{15}), 128.3 (2C), 128.5 (2C), 143.0 (C_{12}).

HRMS (ESI): calculated for $C_{20}H_{32}NaO_3S$ (MNa^+) 375.1964, found 375.1966.

IR (neat): 1604, 2854, 2927, 3026, 3062, 3085.



II-187

(*R*)-Benzyl 2-hydroxy-2,4-dimethylpent-4-enoate (II-187). To a suspension of tin(II) catecholate **II-177** (91 mg, 0.4 mmol, 0.4 equiv), (-)-DIPT (234 mg, 1 mmol, 1 equiv) and CuI (3.8 mg, 0.02 mmol, 0.02 equiv) in CH_2Cl_2 (0.6 mL) was added DBU (0.15 mL, 1 mmol, 1 equiv) in CH_2Cl_2 (0.6 mL) at rt under N_2 atmosphere. The reaction mixture turned to a clear solution immediately and stirring was continued for 30 min. Benzypyruvate (**II-130**, 35.6 mg, 0.2 mmol, 0.2 equiv) in CH_2Cl_2 (0.6 mL) and 3-bromo-2-methyl-1-propene (0.04 mL, 0.4 mmol, 0.4 equiv) in CH_2Cl_2 (0.6 mL) were successively introduced at -78 ^oC. After stirring for 16 h at -78 ^oC, HCl (1 M, 15 mL) and petroleum ether (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with petroleum ether/ CH_2Cl_2 = 2:1 mixture. The combined organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (CH_2Cl_2/petroleum ether = 2:1) gave the α–hydroxy benzyl ester **II-187** (25.4 mg, 54 %) as a colorless oil.

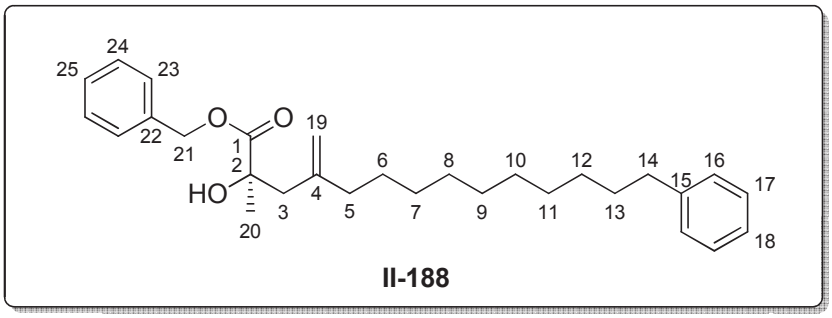
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3H, H_7), 1.64 (s, 3H, H_5), 2.31 (d, *J* = 13.7 Hz, 1H, H_3), 2.47 (d, *J* = 13.7 Hz, 1H, H_3), 3.09 (s, 1H, OH), 4.63 (s, 1H, H_6), 4.85 (m, 1H, H_6), 5.06 (d, *J* = 12.2 Hz, 1H, H_8), 5.14 (d, *J* = 12.2 Hz, 1H, H_8), 7.29 (s, 5H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0, 26.5, 48.0 (C_3), 67.6 (C_8), 74.8 (C_2), 115.2 (C_6), 127.1 (C_{12}), 128.5 (2C), 128.8 (2C), 135.3, 141.2, 176.7 (C_1).

HRMS (ESI): calculated for $C_{14}H_{18}O_3Na$ (MNa^+) 257.1148, found 257.1151.

IR (neat): 1645, 1733, 2951, 2975, 3035, 3070, 3523.

$[\alpha]_D^{20}$ = -1.7 (*c* 1.27, $CHCl_3$).



II-188

(*R*)-Benzyl 2-hydroxy-2-methyl-4-methylene-14-phenyltetradecanoate (II-188). To a suspension of tin(II) catecholate (**II-177**, 91 mg, 0.4 mmol, 0.4 equiv), (-)-DIPT (234 mg, 1 mmol, 1 equiv) and CuI (3.8 mg, 0.02 mmol, 0.02 equiv) in CH_2Cl_2 (0.6 mL) was added DBU (0.15 mL, 1 mmol, 1 equiv) in CH_2Cl_2 (0.6 mL) at rt under N_2 atmosphere. The reaction mixture turned to a clear solution immediately and stirring was continued for 30 min. Benzypyruvate (**II-130**, 35.6 mg, 0.2 mmol, 0.2 equiv) in CH_2Cl_2 (0.6 mL) and (11-(bromomethyl)dodec-11-en-1-yl)benzene (**II-128**, 135 mg, 0.4 mmol, 0.4 equiv) in CH_2Cl_2 (0.6 mL) were successively introduced at -78 ^oC. After stirring for 16 h at -78 ^oC, HCl (1 M, 15 mL) and petroleum ether (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with petroleum ether/ CH_2Cl_2 = 2:1 mixture. The combined organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (Et_2O/petroleum ether = 1:5) gave pure **II-188** (59 mg, 68 %) as a colorless oil.

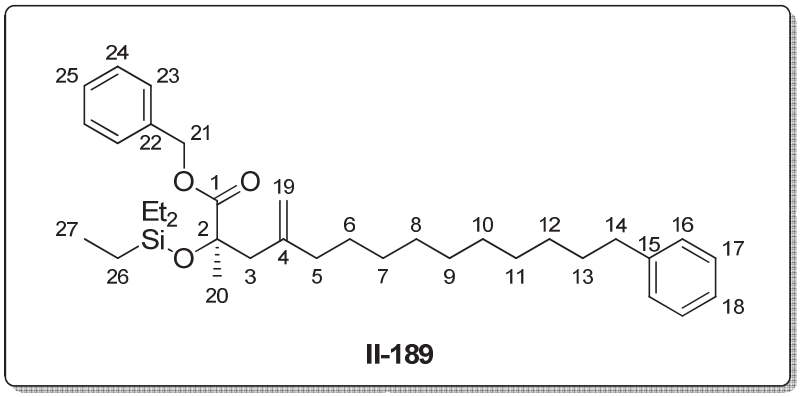
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 – 1.40 (m, 14H), 1.47 (s, 3H, H_{20}), 1.63 (m, 2H), 2.00 (m, 2H, H_5), 2.39 (d, *J* = 13.8 Hz, 1H, H_3), 2.57 (d, *J* = 14.4 Hz, 1H, H_3), 2.62 (t, *J* = 7.8 Hz, 2H, H_{14}), 3.14 (s, 1H, OH), 4.77 (s, 1H, H_{19}), 4.87 (m, 1H, H_{19}), 5.15 (d, *J* = 12.2 Hz, 1H, H_{21}), 5.23 (d, *J* = 12.2 Hz, 1H, H_{21}), 7.16 – 7.21 (m, 3H, H_{Ar}), 7.27 – 7.32 (m, 2H, H_{Ar}), 7.38 (m, 5H, $H_{23\text{-}25}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6 (C_{20}), 27.9, 29.4, 29.5, 29.6, 29.66, 29.70, 29.72, 31.7, 36.1, 37.1, 46.2 (C_3), 67.6 (C_{21}), 74.8 (C_2), 113.8 (C_{19}), 125.7 (C_{18}), 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.6 (C_{25}), 128.7 (2C), 135.3, 143.0, 145.4, 176.7 (C_1).

HRMS (ESI): calculated for $C_{29}H_{40}O_3Na$ (MNa^+) 459.2870, found 459.2865.

IR (neat): 1603, 1638, 2875, 2932, 2962, 3383.

$[\alpha]_D^{20}$ = +2.05 (*c* 0.44, CH_2Cl_2).



II-189

(*R*)-Benzyl 2-methyl-4-methylene-14-phenyl-2-((triethylsilyl)oxy)tetradecanoate (II-189). *Method A.* To a solution of (*R*)-benzyl 2-hydroxy-2-methyl-4-methylene-14-phenyltetradecanoate **II-188** (55 mg, 0.126 mmol, 1 equiv) in CH_2Cl_2 (1 mL) were added sequentially at rt, DMAP (40 mg, 0.324 mmol, 2.4 equiv) and TESCl (54 µL, 0.324 mmol, 2.4 equiv). The reaction mixture was stirred for 2 days, quenched with water (2 mL) and extracted with Et_2O (5x3 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (Et_2O/petroleum ether = 1:50) gave pure **II-189** (70 mg, quantitative) as a colorless oil.

Method B. To a cooled to 0 °C solution of (*R*)-benzyl 2-hydroxy-2-methyl-4-methylene-14-phenyltetradecanoate **II-188** (20 mg, 45.6 µmol, 1 equiv) in CH_2Cl_2 (0.5 mL), Et_3N (8 µL, 54.9 µmol, 1.2 equiv) and TESOTf (12 µL, 54.9 µmol, 1.2 equiv) were added sequentially and the temperature was allowed to warm up to rt. The reaction mixture was stirred for 2 h, quenched with water (1 mL) and extracted with Et_2O (5x2 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (Et_2O/petroleum ether = 1:50) gave the TES ether **II-189** (23.7 mg, 94 %) as a colorless oil.

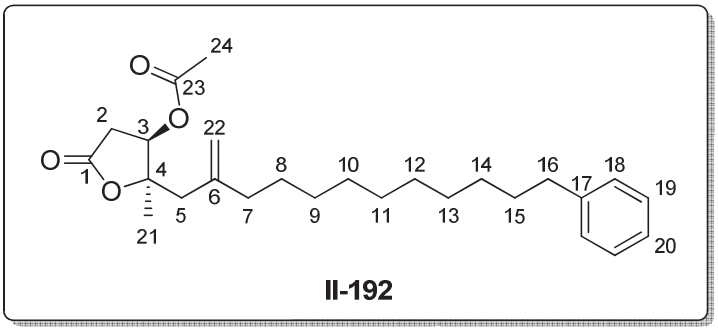
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.57 (m, 6H, H_{26}), 0.91 (t, *J* = 7.9 Hz, 9H, H_{27}), 1.25 - 1.38 (m, 14H), 1.45 (s, 3H, H_{20}), 1.61 (m, 2H), 2.05 (t, *J* = 7.5 Hz, 2H, H_5), 2.35 (d, *J* = 13.5 Hz, 1H, H_3), 2.48 (d, *J* = 13.5 Hz, 1H, H_3), 2.59 (t, *J* = 7.5 Hz, 1H, H_{14}), 4.69 (s, 1H, H_{19}), 4.77 (m, 1H, H_{19}), 5.05 (d, *J* = 12.3 Hz, 1H, H_{21}), 5.15 (d, *J* = 12.3 Hz, 1H, H_{21}), 7.13 – 7.18 (m, 3H, H_{Ar}), 7.24 – 7.29 (m, 2H, H_{Ar}), 7.34 (m, 5H, $H_{23\text{-}25}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.5 (C_{26}), 7.2 (C_{27}), 26.9 (C_{20}), 28.0, 29.5 – 29.8 (6C), 31.7, 36.1, 37.1, 48.1 (C_3), 66.8 (C_{21}), 78.2 (C_2), 113.1 (C_{19}), 125.7 (C_{18}), 128.3 (3C), 128.49 (2C), 128.52 (2C), 128.6 (2C), 135.9, 143.1, 146.2, 175.2 (C_1).

HRMS (ESI): calculated for $C_{35}H_{55}O_3Si$ (MH^+) 551.3915, found 551.3898.

IR (neat): 1625, 1736, 2855, 2876, 2927, 2954, 3030, 3066, 3085.

$[\alpha]_D^{20}$ = -0.84 (*c* 0.597, CH_2Cl_2).



II-192

(2*R*,3*R*)-2-Methyl-2-(2-methylene-12-phenyldodecyl)-5-oxotetrahydrofuran-3-yl acetate (II-192). To a cooled (-78 °C) solution of (*R*)-2-methyl-4-methylene-14-phenyl-2-((triethylsilyl)oxy)tetradecanal **II-176** (70 mg, 0.157 mmol, 1 equiv) in CH_2Cl_2 (0.9 mL), a mixture of $TiCl_4$ (1 M in CH_2Cl_2, 79 µL, 78.7 µmol, 0.5 equiv) and $Ti(OiPr)_4$ (23.4 µL, 78.7 µmol, 0.5 equiv) was added dropwise followed by the addition of ((1-ethoxyvinyl)oxy)trimethylsilane **II-166b** (50 mg, 0.315 mmol, 2 equiv). The reaction mixture was stirred at -78 °C for 3 h, quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL), warmed to rt and extracted with Et_2O (4x3 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude **II-191** was dissolved in THF (1 mL) and TBAF (1 M in THF, 0.31 mL, 0.315 mmol, 2 equiv) was added. The reaction mixture was stirred at rt for 3 h, quenched with water (2 mL), and extracted with Et_2O (5x2 mL). The combined ethereal solutions were dried (Na_2SO_4) and evaporated. To a cooled solution (0 °C) of the residue in CH_2Cl_2 (1 mL) were added sequentially DMAP (23 mg, 0.189 mmol, 1.2 equiv) and acetic anhydride (18 µL, 0.189 mmol, 1.2 equiv). The reaction mixture was stirred for 1-2 h at rt and chromatographed on silica gel (Et_2O/petroleum ether = 1:1, or CH_2Cl_2) to give **II-192** (38.6 mg, 59 %) as a colorless oil.

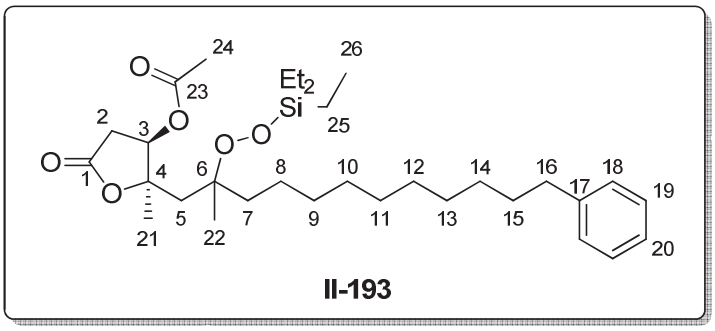
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 – 1.46 (m, 14H), 1.34 (s, 3H, H_{21}), 1.61 (m, 2H), 2.08 (t, *J* = 7.5 Hz, 2H, H_7), 2.12 (s, 3H, H_{24}), 2.27 (d, *J* = 14.5 Hz, 1H, H_5), 2.52 (dd, *J* = 18.5, 1.7 Hz, 1H, H_2), 2.58 (d, *J* = 14.5 Hz, 1H, H_5), 2.60 (t, *J* = 7.8 Hz, 2H, H_{16}), 3.04 (dd, *J* = 18.5, 6.3 Hz, 1H, H_2), 4.81 (s, 1H, H_{22}), 4.95 (m, 1H, H_{22}), 5.21 (dd, *J* = 6.3, 1.7 Hz, 1H, H_3), 7.14 – 7.19 (m, 3H, H_{Ar}), 7.25 – 7.30 (m, 2H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (C_{24}), 23.5 (C_{21}), 27.9, 29.4, 29.5, 29.64, 29.68, 29.70, 29.75, 31.7, 36.1, 36.2, 36.8 (C_7), 40.8 (C_5), 75.4 (C_3), 87.7 (C_4), 114.9 (C_{22}), 125.7 (C_{20}), 128.3 (2C), 128.5 (2C), 143.1, 144.5, 170.0, 173.7.

HRMS (ESI): calculated for $C_{26}H_{38}O_4Na$ (MNa^+) 437.2662, found 437.2646.

IR (neat): 1643, 1746, 1785, 2854, 2927, 3026, 3063, 3084.

$[\alpha]_D^{20}$ = +20.9 (*c* 0.705, $CHCl_3$).



II-193

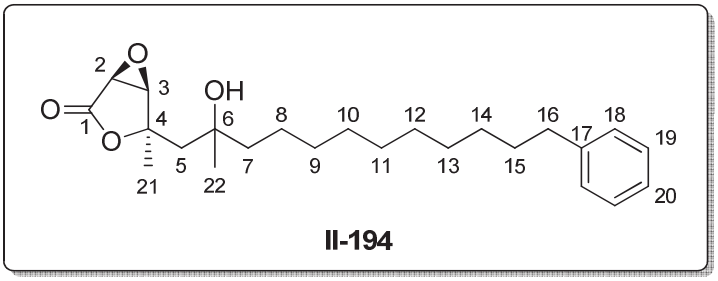
(2*R*,3*R*)-2-Methyl-2-(2-methyl-12-phenyl-2-((triethylsilyl)peroxy)dodecyl)-5-oxotetrahydrofuran-3-yl acetate (II-193). To a solution of (2*R*,3*R*)-2-methyl-2-(2-methylene-12-phenyldodecyl)-5-oxotetrahydrofuran-3-yl acetate **II-192** (20 mg, 48.2 μmol, 1 equiv) in dichloroethane (0.5 mL) was added $Co(thd)_2$ (2.1 mg, 4.8 μmol, 0.1 equiv) and the flask was charged with O_2. Et_3SiH (15.4 μL, 96.5 μmol, 2 equiv) was added and the reaction mixture was stirred for 2 h under O_2 atmosphere. Evaporation of the reaction mixture and chromatography of the residue on silica gel (Et_2O/petroleum ether = 1:2) afforded **II-193** (25.6 mg, 94 %, dr = 1:1) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (q, *J* = 8.0 Hz, 6H, H_{25}), 0.97 (t, *J* = 7.9 Hz, 9H, H_{26}), 1.18 (s, 1.5H, H_{22}), 1.27 (m, 14H), 1.29 (s, 1.5H, H_{22}), 1.55 (s, 3H, H_{21}), 1.59 (m, 4H), 1.94 (d, *J* = 15.6 Hz, 0.5H, H_5), 1.98 (d, *J* = 15.8 Hz, 0.5H, H_5), 2.10 (s, 1.5H, H_{24}), 2.11 (s, 1.5H, H_{24}), 2.15 (d, *J* = 13.9 Hz, 0.5H, H_5), 2.19 (d, *J* = 15.5 Hz, 0.5H, H_5), 2.44 (d, *J* = 18.5 Hz, 1H, H_2), 2.60 (t, *J* = 7.8 Hz, 2H, H_{16}), 3.029 (dd, *J* = 18.5, 6.1 Hz, 0.5H, H_2), 3.034 (dd, *J* = 18.5, 6.0 Hz, 0.5H, H_2), 5.11 (d, *J* = 4.7 Hz, 0.5H, H_3), 5.12 (d, *J* = 4.6 Hz, 0.5H, H_3), 7.15 – 7.19 (m, 3H, H_{Ar}), 7.25 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.0 (C_{25}), 6.9 (C_{26}), 21.0 (0.5C), 21.1 (0.5C), 22.1 (0.5C), 23.4 (0.5C), 23.57 (0.5C), 23.60 (0.5C), 23.8 (0.5C), 24.3 (0.5C), 29.5 – 29.8 (5C), 30.3, 31.7, 35.9 (0.5C), 36.1 (1.5C), 37.6 (0.5C), 38.1 (0.5C), 38.7 (0.5C), 40.1 (0.5C), 76.1 (C_3), 76.3 (C_3), 84.3 (C_6), 84.4 (C_6), 87.8 (C_4), 88.0 (C_4), 125.65 (C_{20}), 125.68 (C_{20}), 128.3 (2C), 128.5 (2C), 143.05 (C_{17}), 143.10 (C_{17}), 169.9, 173.9 (0.5C), 174.1 (0.5C).

HRMS (ESI): calculated for $C_{32}H_{54}O_6SiNa$ (MNa^+) 585.3582, found 585.3597.

IR (neat): 1747, 1786, 2854, 2877, 2928, 3026, 3062, 3085.



II-194

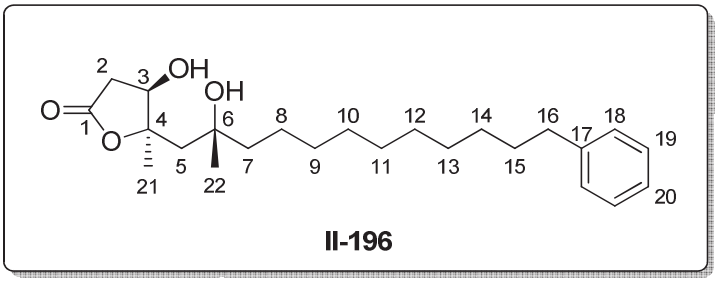
(1*S*,4*R*,5*R*)-4-(2-hydroxy-2-methyl-12-phenyldodecyl)-4-methyl-3,6-dioxabicyclo[3.1.0]hexan-2-one (II-194). For experimental procedure see **II-4a**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (bs, 14H, $H_{8\text{-}14}$), 1.29 (s, 1.5H, H_{22}), 1.31 (s, 1.5H, H_{22}), 1.56 (bm, 5H, OH + $H_{7,15}$), 1.59 (s, 1.5H, H_{21}), 1.60 (s, 1.5H, H_{21}), 1.91 (d, *J* = 14.7 Hz, 0.5H, H_5), 2.00 (s, 1H, H_5), 2.06 (d, *J* = 14.7 Hz, 0.5H, H_5), 2.60 (t, *J* = 7.7 Hz, 2H, H_{16}), 3.78 (s, 0.5H, H_2), 3.80 (s, 0.5H, H_2), 4.01 (s, 1H, H_3), 7.15 – 7.18 (m, 3H, H_{Ar}), 7.26 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.1, 24.2, 24.4 (C_{21}), 24.6 (C_{21}), 28.2 (C_{22}), 28.7 (C_{22}), 29.5 - 29.7 (5C), 30.18, 30.20, 31.7, 36.1 (C_{16}), 44.5 (C_7), 45.05 (C_5), 45.10 (C_5), 45.4 (C_7), 51.4 (C_2), 51.6 (C_2), 61.2 (C_3), 61.5 (C_3), 72.2 (C_6), 72.4 (C_6), 85.1 (C_4), 85.2 (C_4), 125.7 (C_{20}), 128.4 (2C), 128.5 (2C), 143.1 (C_{17}), 169.7 (C_1), 170.0 (C_1).

HRMS (ESI): calculated for $C_{24}H_{36}NaO_4$ (MNa^+) 411.2506, found 411.2504.

IR (neat): 1662, 1778, 2854, 2925, 2961, 3647.



II-196

(4*R*,5*R*)-4-Hydroxy-5-((*R*)-2-hydroxy-2-methyl-12-phenyldodecyl)-5-methyldihydrofuran-2(3H)-one (II-196). Plakortolide E **II-4b** (4.4 mg, 11.3 μmol, 1 equiv) was dissolved in dry Et_2O (1.5 mL) and then treated with AcOH (0.05 mL, 0.87 mmol, 77 equiv) and Zn (30 mg, 0.46 mmol, 41 mmol). The reaction mixture was stirred for 20 h at rt, filtered and evaporated to give **II-196** (4 mg, 91 %) as a colorless oil. Its physical data were in agreement with those described in the literature.[13]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (m, 14H), 1.35 (s, 3H, H_{22}), 1.44 (s, 3H, H_{21}), 1.50 – 1.65 (m, 4H), 1.97 (bs, 1H, OH), 2.09 (d, *J* = 15.1 Hz, 1H, H_5), 2.17 (d, *J* = 15.0 Hz, 1H, H_5), 2.55 (dd, *J* = 18.2, 1.8 Hz, 1H, H_2), 2.60 (t, *J* = 7.5 Hz, 2H, H_{16}), 2.92 (dd, *J* = 18.2, 6.8 Hz, 1H, H_2), 4.19 (dd, *J* = 6.7, 1.7 Hz, 1H, H_3), 4.70 (bs, 1H, OH), 7.16 – 7.18 (m, 3H, H_{Ar}), 7.26 – 7.29 (m, 2H, H_{Ar}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.5, 27.0 (C_{21}), 29.5 – 29.7 (5C), 30.1, 30.2 (C_{22}), 31.7, 36.1 (C_{16}), 38.2 (C_2), 43.8, 44.0 (C_5), 73.4 (C_6), 74.1 (C_3), 90.1 (C_4), 125.7 (C_{20}), 128.4 (2C), 128.5 (2C), 143.1 (C_{17}), 175.3 (C_1).

IR (neat): 1604, 1757, 2853, 2926, 3026, 3062, 3085, 3388.

$[\alpha]_D^{20}$ = +6.9 (*c* 0.15, $CHCl_3$), lit. +10.0 (*c* 0.09, CH_2Cl_2).

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