Towards the total synthesis of vibsatins A and B

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Towards the Total Synthesis of Vibsatins A and B

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Glossary

Abbreviation list

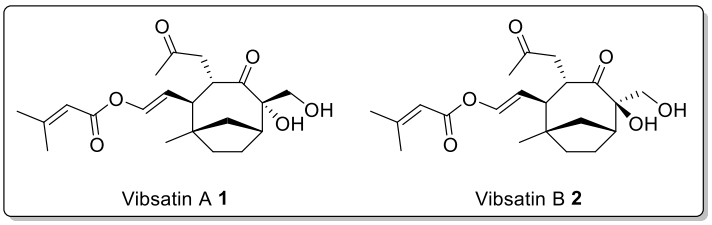
[M]	Metal
[O]	Oxidation
2,2-DMP	2,2-dimethoxypropane
2,4-DMPM	2,4-dimethoxyphenylmethylene
Ac	Acetyl
ACN	Acetonitrile
AIBN	Azabisisobutyronitrile
Ar	Aryl
BARF	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BDNF	Brain-derived neurotrophic factor
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
Bn	Benzyl
Boc	tert-butyloxycarbonyl
BTMSE	*Bis*(trimethylsilyl)ethyne
Bz	Benzoyl
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d.e.	Diastereomeric excess
d.r.	Diastereomeric *ratio*
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloromethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPT	Diisopropyltartrate
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DNBS	2,4-dinitrobenzenesulfonyl
e.e.	Enantiomeric excess
e.r.	Enantiomeric *ratio*
E^+	Electrophile
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq.	Equivalent
Et	Ethyl
EWD	Electron withdrowing
h	Hours
H-G II	Hoveyda-Grubbs 2nd generation
HMDS	Bis(trimethylsilyl)amine

IBX	2-Iodoxybenzoic acid
imid	Imidazole
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazolium
*i*Pr	*iso*-propyl
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L	Ligand
LAH	Lithium alluminium hydride
LDA	Lithium diisopropylamide
liq.	Liquid
m	meta
M	Molar
Martin's Sulfurane	Bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur
Me	Methyl
Mes	Mesityl
min	Minutes
mol	mole
MOM	Methoxymethyl
Ms	Methylsulfonyl (Mesyl)
MS4Å	Molecular sieves 4 Ångstrom
MW	Microwaves
$NaBH_3CN$	Sodium cyanoborohydride
*n*Bu	*normal*-butyl
NDD	Neurodegenerative diseases
NGF	Nerve Growth Factor
NHC	*N*-Heterocyclic carbene
NMO	*N*-Methylmorpholine *N*-oxide
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser effect spectrometry
Ns	Nitrobenzene-1-sulfonyl
NT	Neurotrophin
NTF	Neurotrophin family
Nu^-	Nucleophile
o	orto
p	para
PCC	Pyridinium Chlorochromate
PG	Protective group
Ph	Phenyl
Piv	2,2-Dimethyl-propanoyl (Pivaloyl)
PPTS	Pyridinium p-toluenesulfonate
Pr	*normal*-propyl
ps	polymer supported
PTSA	*p*-Toluenesulfonic acid
pyr	Pyridine

quant.	Quantitative
r.t.	Room temperature
Red-Al	Sodium bis(2-methoxyethoxy)aluminumhydride
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
Tf	Trifluoromethanesulfonyl (Triflate)
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
tol	toluyl
tol.	toluene
Ts	*para*-toluylsulfonyl
TS	Transition state
Xyl	xylyl

Preface

The ever-increasing prevalence of neurodegenerative disorders is an unsolved worldwide problematic for the healthcare system. Nervous system growth factors, *i.e.*, neurotrophins, constitute a promising solution to these disorders; however, the development of these polypeptides is currently limited due to their unfavorable pharmacokinetic profile. In this context, vibsatins A **1** and B **2**, two diterpenoids isolated as very minor metabolites in 2014 from a Chinese plant, have attracted our attention as these compounds were found to greatly enhance neurite outgrowth. Moreover, vibsatins reveal a structurally dense architecture featuring an unprecedented bicyclo[4.2.1]nonane framework. Since no total synthesis has been reported to date, it was important to develop a straightforward chemical route to evaluate and optimize the biological properties of the parent structure. In this context, the total synthesis of vibsatin A and vibsatin B constitutes the aim of this thesis work.



The key-step allowing the access to the dense bridged bicyclo[4.2.1]nonane skeleton of the vibsatins relies on a recently reported 7-*exo*-dig Au(I)-catalyzed cyclization. Notably, an intensive study on the key-step has been realized in order to optimize and scale-up this reaction.

The synthetic work directed towards the vibsatins, was devised exploiting the chiral information induced by the first stereocenter, which was asymmetrically installed at an early stage of the synthesis.

This document is composed of eight chapters:

- Chapter 1: the vibsane family is introduced and the various syntheses realized on parent natural substances are debated.
- Chapter 2: the general characteristics of vibsatin A and vibsatin B are presented along with their proposed biosynthesis and a general overview of the neurotrophic biological activity. An examination of the Conia-ene reaction is the conclusive argument.

- Chapter 3: a review of the carbocyclizations of alkynes catalysed by gold(I) is the main topic of this chapter, an overview of the double activation based methods is also discussed.
- Chapter 4: the first part of our synthetic strategy towards vibsatins A and B is disclosed including the studies upon the 7-*exo*-dig Au(I)-catalyzed cyclization key-step leading to the bridged bicyclic skeleton of the vibsatins.
- Chapter 5: the subjects of this chapter deal with the three different functionalization pathways undertaken toward the accomplishment of the total synthesis of the vibsatins.
- Chapter 6: the deoxygenation problem, encountered in the course of this work, is discussed through all the attempted tests.
- Chapter 7: a summary of the most relevant methodological works and synthetic approaches is discussed, intended to conclude the document.
- Chapter 8: a list of references
- Chapter 9: the experimental part gathering all the technical information and relevant analyses.

I wish you a very good read

1.Vibsane-type diterpenoids

In this chapter, diterpenoid molecules deriving from *Viburnum* genus, *i.e.* vibsanes, will be treated from a general point of view. After a brief introduction upon the general structure of vibsanes and on the major different classes of compounds, the synthetic studies explaining the biogenetic pathway will be explained. In the second part, after a short clarification on the biological activity of this group of molecules, the up-to-date reported total synthesis of various vibsanes will be discussed.

1.1 Introduction

Vibsane-type diterpenoids are considered to be characteristic of the *Viburnum* since they have not been found in other higher plants. The genus *Viburnum* consists of about 150 species of shrubs or small trees that were previously included in the family Adoxaceae.[1] They are distributed in the temperate northern hemisphere, with a few species extending into tropical regions in South America and Southeast Asia, and about 15 species found in Japan.[2]

Kawazu, in 1980, was the first to report the isolation of vibsane-type diterpenoids, from *Viburnum odoratissimum var. awabuki*. Vibsane's skeleton consists of a fumulane framework with five additional carbons that generate an additional lateral chain at C-11 (Figure 1).[3]

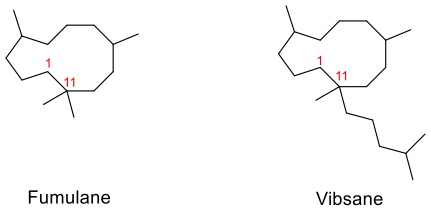


Figure 1

Vibsanins, a class of molecules of the vibsanes family, can be categorized into three subtypes depending on their carbon backbone, consisting of respectively: eleven-membered ring compounds, seven-membered ring compounds and the rearranged type, also known as the neovibsanins (Figure 2). Other sub-classes of seven-membered ring vibsanins include: aldovibsanins, featured by a [5.3.0]-bicyclic fused skeleton between carbons 5 and 10, furanovibsanins, in which the ring fusion is located between carbons 4 and 5, and cyclovibsanins which are composed of a tricyclo[6.3.2.$0^{0.0}$]tridecane skeleton (Figure 2).[4]

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[1] Winkworth R.C.; Donoghue M.J., *Am. J. Bot.* **2005**, 653-666.
[2] Hotta M.; Ogata K.; Nitta A.; Hosikawa K.; Yanagi M.; Yamazaki K., *Useful Plants of the World* **1989**, 1089.
[3] Kubo, M.; Esumi, T.; Imagawa, H.; Fukuyama, Y. *Studies in Natural Products Chemistry* **2014,** *43*, 41-78.
[4] Mak, W.Y.J.; Williams C.M., *Nat. Prod. Rep.* **2012**, *29*, 440-448.

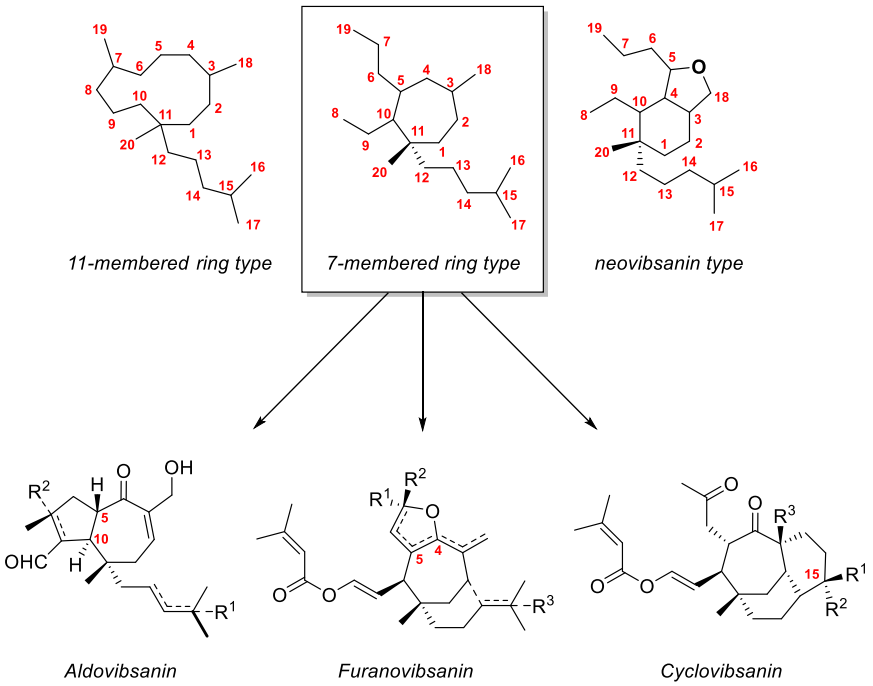


Figure 2

Synthetically, vibsanins have started to attract the attention of organic chemists at the beginning of the 21st century, when the biological activity of these compounds was discovered.

1.2 Structural studies and biogenetic pathway

The first vibsane-type diterpenoids that were reported by Kawazu were vibsanins A, B, and F respectively **3**, **4** and **5** (Figure 3), which possess an 11-membered ring derived from fumulene, and vibsanins C **6**, D **7** and E **8** (Figure 4) characterized by a 7-membered ring. Notably, the structure of vibsanin E is the only one bearing a [6.3.2.$0^{0.0}$]-tricyclic framework.[5]

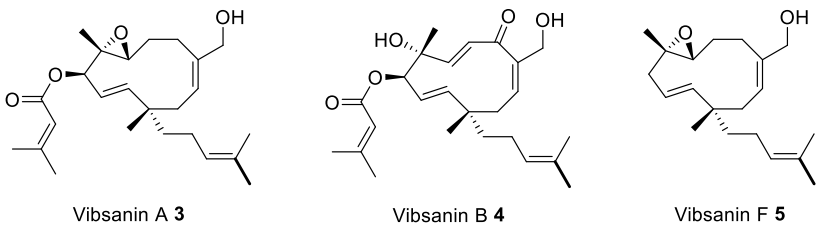


Figure 3

[5] Kawazu, K. *Agric. Biol. Chem.* **1980**, *44*, 1367–1372.

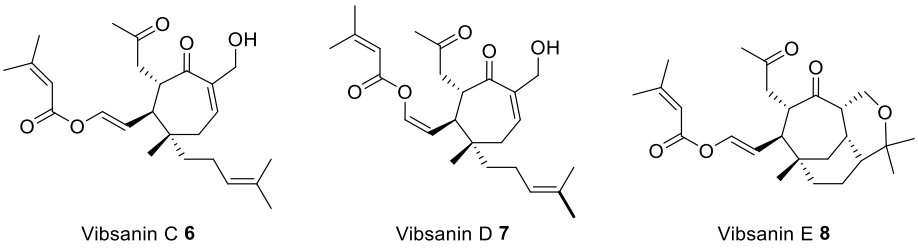
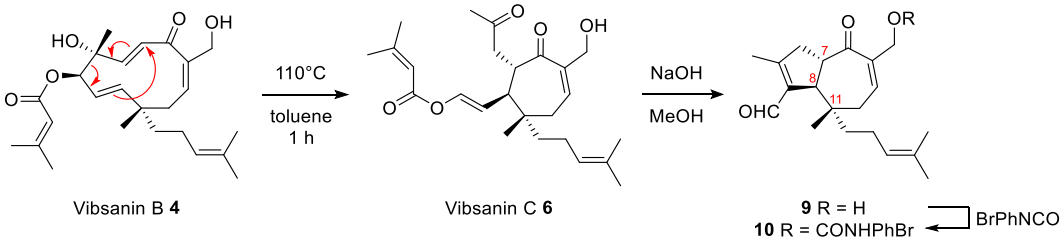


Figure 4

In the course of the structural studies on vibsanin B **4**, Fukuyama and co-workers discovered that heating **4** at 110°C for one hour provided a mixture of four products in which the seven-membered vibsanin C **6** was the prevailing compound (86%) along with 5-*epi*-vibsanin C and two other non-natural epimers. These results led to propose that a plausible biogenetic pathway for the synthesis of seven membered ring vibsanes would involve an oxy-Cope rearrangement (Scheme 1). Thus, the absolute configuration of the 11-membered ring vibsanin B turns out to be completely correlated with that of the 7-membered ring vibsanin C. At this point, saponification of the enol ester function of **6** followed by an intramolecular aldol condensation reaction afforded the resulting aldehyde **9**. Conversion of the alcohol at the C-18 position into the bromophenyl carbamate allowed to perform X-ray crystallographic analysis on **10**, which unambiguously established the absolute 5*S*, 10*S*, and 11*S* configurations of vibsanin C **6**. This result implies that vibsanin B **4** chiral centers are respectively 7*R*, 8*R*, and 11*S*.[6]



Scheme 1

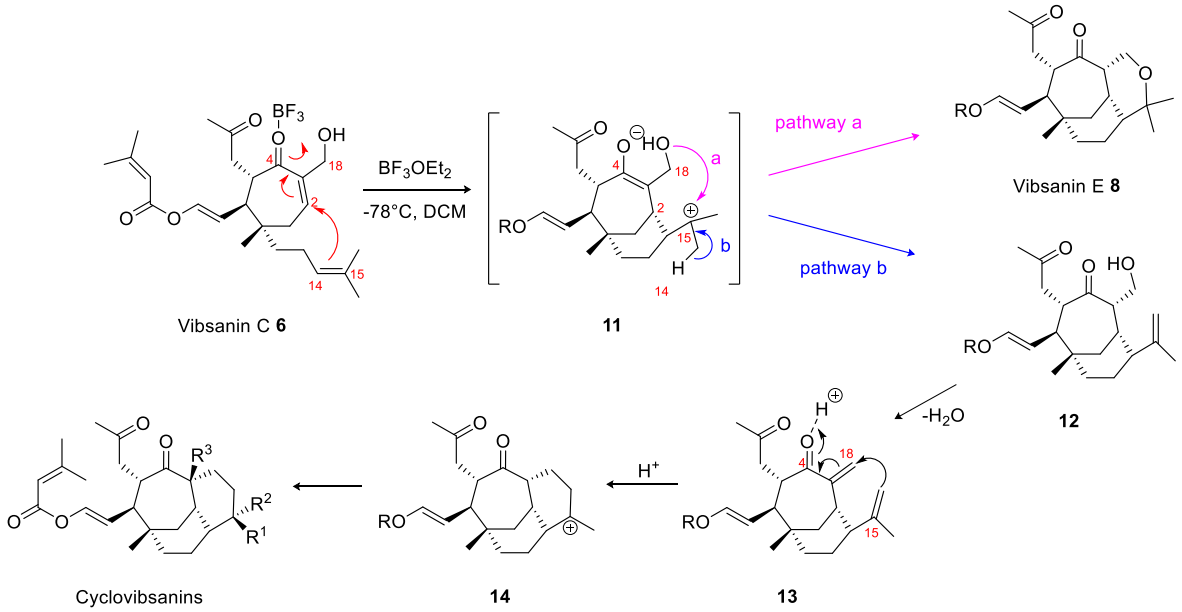
The same group reported the conversion of vibsanin C **6** into vibsanin E **8** through a cationic process, precisely by treating **6** with $BF_3{\cdot}OEt_2$ (Scheme 2).[7]

Coordination of boron complex by the ketone at C4 allows the Michael addition reaction (at C2) of the C14-C15 double bond leading to intermediate **11**. At this point, the alcohol

[6] Fukuyama Y.; Minami H.; Takaoka S.; Kodama M.; Kawazu K.; Nemoto H. *Tetrahedron Lett.* **1997**, *38*, 1435-1438.
[7] Fukuyama, Y.; Minami, H.; Kagawa, M.; Kodama, M.; Kawazu, K. *J. Nat. Prod.* **1999**, *62*, 337-339.

function at C18 traps the carbocation previously formed at C15, providing vibsanin E **8** (pathway a).

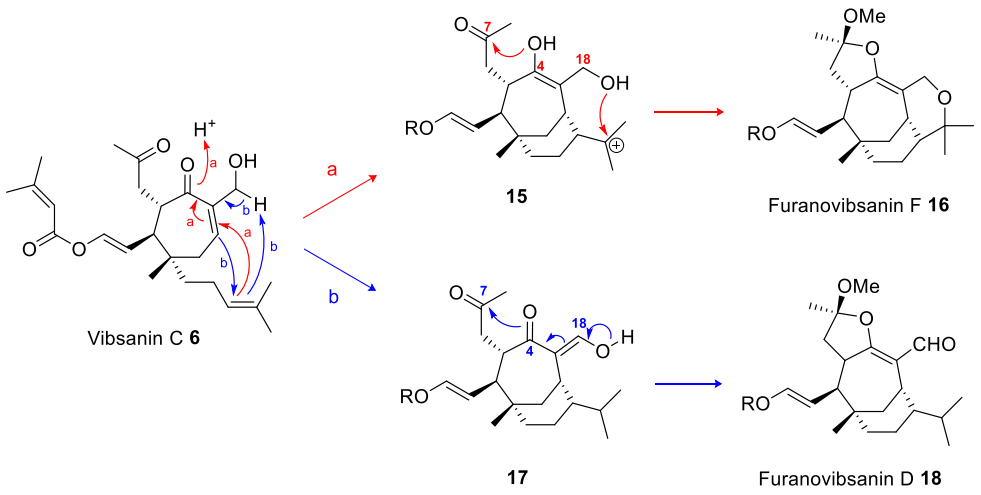
This reaction could even explain the biogenetic pathway that leads to the synthesis of cyclovibsanins. Hence, once the carbocation at C15 is formed, elimination of a proton from one of the two methyl groups in **11** gives rise to **12**. Concomitantly, dehydration produces the exomethylene ketone **13** and then the C-4 carbonyl group is protonated triggering the cyclization that results in the formation of the tricyclic framework present in cyclovibsanins **14** (pathway b).



Scheme 2

A biogenetic pathway for the biosynthesis of furanovibsanins was proposed starting from the same assumption.[8] Biogenetic conversion of vibsanin C **6** to furanovibsanins can be intended by a cationic process (a, Scheme 3) followed by an acetal formation between C4 and C7. Subsequent intramolecular addition of the alcohol at C-18 position onto the isoprenyl cation **15** affords furanovibsanin F **16**. At the same time, another plausible pathway leading to a slightly different product (b, Scheme 3) foresees an Alder-ene transformation providing bicyclic intermediate **17** which will then form an acetal generating the desired furanovibsanin D **18**.[9]

[8] Fukuyama, Y.; Minami, H.; Matsuo, A.; Kitamura, K.; Akizuki, M.; Kubo, M.; Kodama, M. *Chem. Pharm. Bull.* **2002**, *50*, 363-371.
[9] Kubo M.; Fujii T.; Hioki H.; Tanaka M.; Kawazu Y.; Fukuyama Y. *Tetrahedron Lett.* **2001**, *42*, 1081-1083.



Scheme 3

Neovibsanins, which correspond to rearranged type diterpenoids, are, from a biological point of view, the most interesting. Their discovery is relatively more recent since the first neovibsanins extracted were neovibsanin A **19** and neovibsanin B **20** in 1996.[10] It is only in the next decades that the others neovibsanins were discovered. Recently, it was found that neovibsanin A **19** and neovibsanin B **20** are artefacts deriving from treatment of vibsanin **21** in MeOH. Neovibsatins are categorized into three subclasses: ketal neovibsanins, caged neovibsanins and bicyclic neovibsanins (Figure 5).

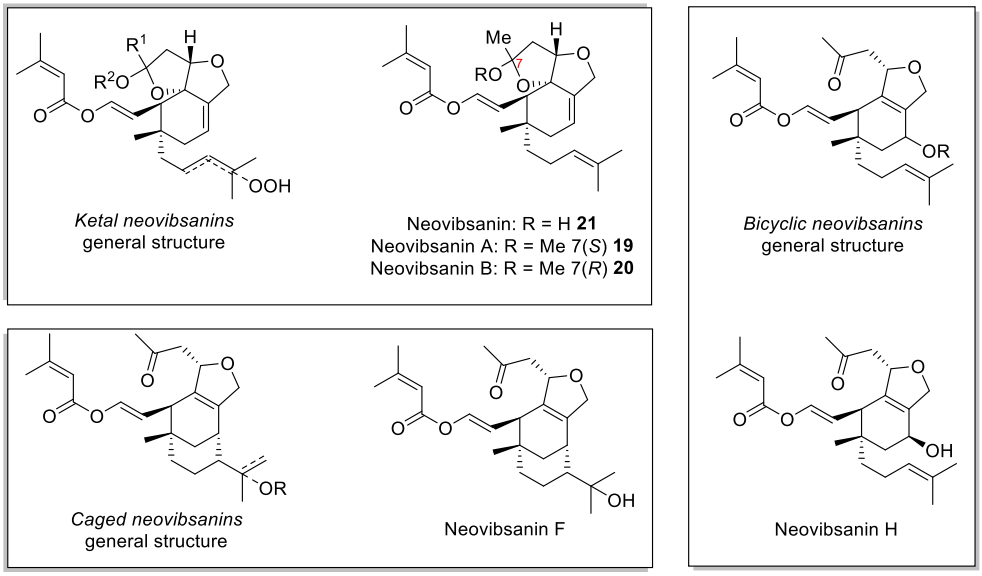
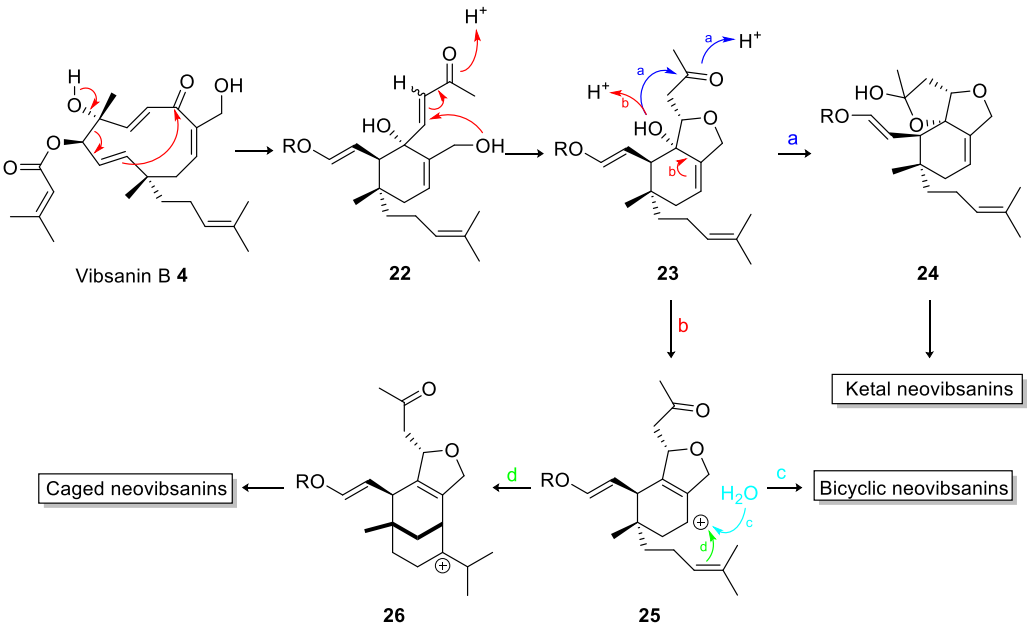


Figure 5

Their biosynthesis was postulated starting from the same starting point: vibsanin B **4**. The first step is assumed to be an acid-catalysed rearrangement of the eleven-membered ring to

[10] Fukuyama Y.; Minami H.; Takeuchi K.; Kodama M.; Kawazu K. *Tetrahedron Lett*. **1996**, *37*, 6767-6770.

give cyclohexene **22** which undergoes acid-catalysed intramolecular conjugate addition of the allylic alcohol to provide intermediate **23**. At this stage, two outcomes are possible: pathway a leads to acid-catalysed hemiketal formation **24**, providing the tricyclic ketal neovibsanins (Scheme 4). Following pathway b, acid-catalysed dehydration to give **25** followed by nucleophilic addition (path c, Scheme 4) delivers bicyclic neovibsanins. However, if cation **25** is intramolecularly trapped by the alkene of the prenyl side-chain (path d, Scheme 4), the caged neovibsanins are formed **26**.



Scheme 4

1.3 Biological activity

In 1980, Kawazu reported the first isolation of a piscicidal compound, vibsanin A **3**, and a plant growth inhibitor, vibsanin B **4**.[11] Later, many vibsane-type diterpenoids were reported, among which, vibsanin C **6**, 5-*epi*-vibsanin C, vibsanol A[12], and vibsanins K and P[13] exhibited significant and/or moderate cytotoxicity against tumor cells.

More interesting is the activity of neovibsanins. Indeed, it has been established that neovibsanin **21**, neovibsanin A **19** and neovibsanin B **20** possess neurotrophic activity, *i.e.* these molecules are capable to enhance the action of nerve growth factor (NGF), a protein implicated in life cycle of neurons, in appropriate cell population.[14] More specifically, it has

[11] Kawazu K., *Agric. Biol. Chem.* **1980**, *44*, 1367-1372.
[12] Shen Y.-H.; Prakash C.V.S.; Wang L.-T.; Chien C.-T.; Hung M.-C., *J. Nat. Prod.* **2002**, *65*, 1052-1055.
[13] (a) Shen Y.-C.; Lin C.-L.; Chien S.-C.; Khalil A.T.; Ko C.-L.; Wang C.-H., *J. Nat. Prod.* **2004**, *67*, 74-77. (b) Tang W.; Kubo M.; Harada K.; Hioki H.; Fukuyama Y., *Bioorg. Med. Chem. Lett.* **2009**, *19*, 882-886.
[14] Brinton R.S.; Yamazaki R.S., *Pharm. Res.* **1998**, *15*, 386-398.

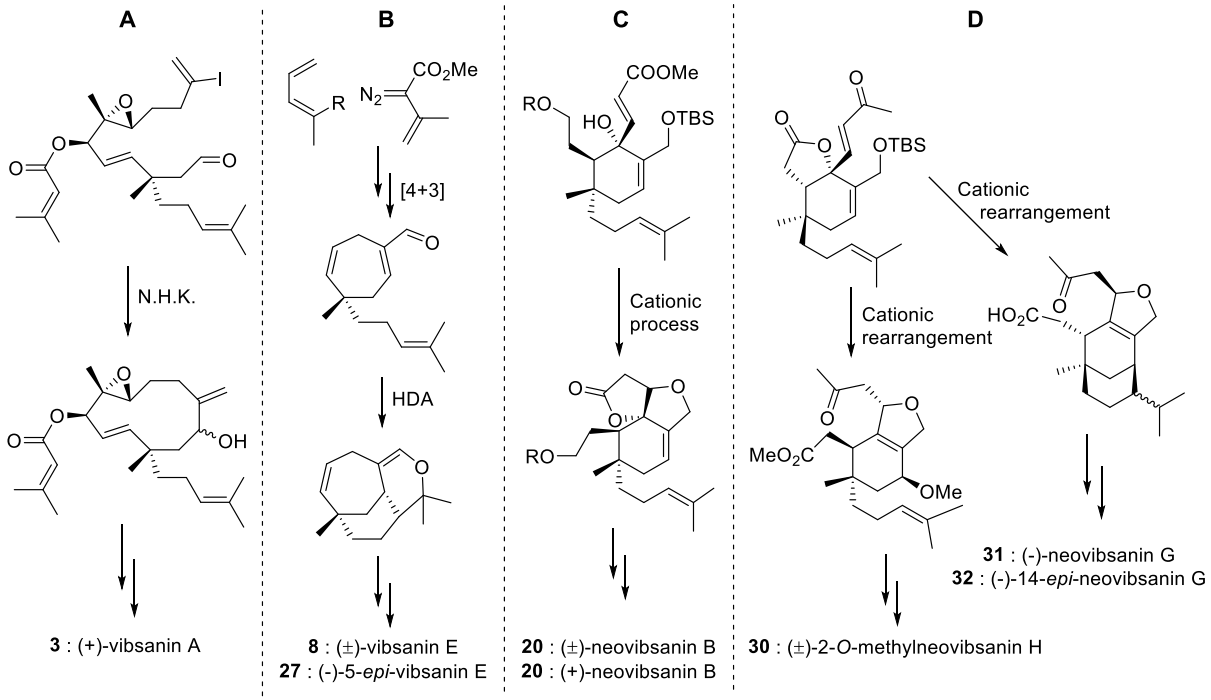
been shown that they promote neurite outgrowth of NGF-mediated PC-12 cells at concentrations ranging from 10 to 40 µM. Among the three compounds, neovibsanin A seems less potent than neovibsanin and neovibsanin B. However, all of them had no effect on morphology of PC12 cells in the absence of NGF. Additionally, other vibsane-type diterpenoids such as 7-membered and 11-membered ring subtypes have not been found to show neurotrophic activity in PC12 cells so far.

However, the neurotrophic activity will be developed and discussed more deeply in chapter 2.2.

1.4 Reported total synthesis

Up to date have been reported seven total synthesis of vibsane-type diterpenoids. One of them aimed to the synthesis of the 11-membered ring (+)-vibsanin A **3** along with two total synthesis of 7-membered ring compounds, specifically (±)-vibsanin E **8** and (-)-5-*epi*-vibsanin E **27**. On the other hand, four total synthesis of rearranged-type vibsanins have been accomplished, respectively: (±)-2-*O*-methylneovibsanin H **30**, (-)-neovibsanin G **31**, (-)-14-*epi*-neovibsanin G **32** and (±)-neovibsanin B **20**. Besides these seven total synthesis, one formal enantioselective synthesis of (+)-neovibsanin B **20** has been described.

The total synthesis of the 11-membered ring of (+)-vibsanin A **3** is based on a ring closure exploiting a Nozaki-Hiyama-Kishi (N.H.K.) reaction (Scheme 5, A). The total synthesis of both (±)-vibsanin E **8** and (-)-5-*epi*-vibsanin E **27** relied on a formal [4+3] cycloaddition in order to construct the 7-membered ring followed by a hetero Diels-Alder reaction to complete the skeleton (Scheme 5, B). One total synthesis of racemic (±)-neovibsanin B **20** was pubblished. This report exploited a cationic process for providing access to the framework of (±)-neovibsanin B **20** (Scheme 5, C). Starting from this assumption, an enantioselective formal synthesis of the same molecule was also reported. (-)-Neovibsanin G **31**, (-)-14-*epi*-neovibsanin G **32** and (±)-2-*O*-methylneovibsanin H **30** have a common point, their skeletons have been set up starting from the same intermediate (Scheme 5, D). The latter undergoes two diverse rearrangements leading to various backbones depending on the reaction conditions.



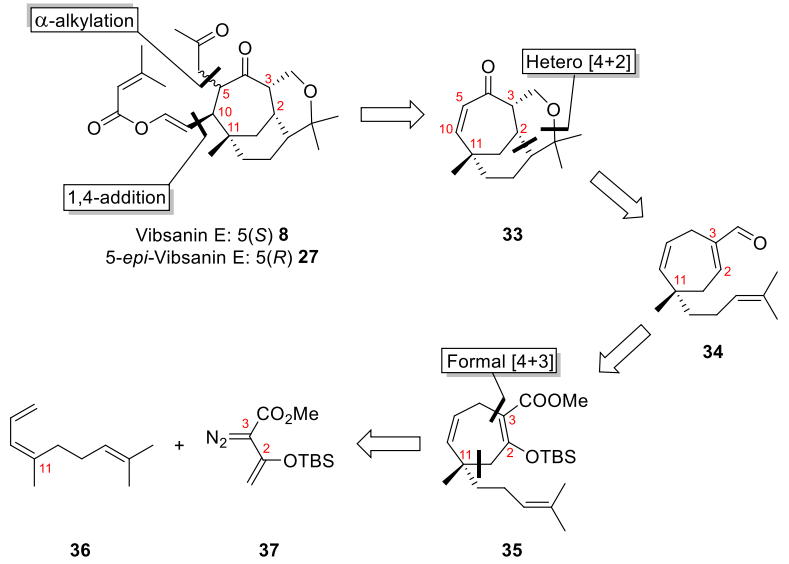
Scheme 5

1.4.1 Total synthesis of (±)-vibsanin E and (-)-5-*epi*-vibsanin E

Vibsanin E **8,**[15] attracted attention of various groups around the world because of its synthetically challenging structure featured by five stereocenters installed on the tricyclic backbone. At the beginning, the Williams group reported the synthesis of the vibsanin E core,[4] while the Srikrishna group investigated a ring closing metathesis approach towards the bicyclic core of the molecule.[5] The total synthesis of this natural product along with its epimer, 5-*epi*-vibsanin E **27**,[16] was completed through a collaborative effort between the Davies and Williams groups. Indeed, they exploited the sequential cycloaddition reaction developed by the Davies group and the Williams extensive experience on vibsatin E structure.[17] Retrosynthetically, Davies and Williams envisaged that the two side-chains of **8** and **27** could be installed through a 1,4-addition followed by an α-alkylation on the corresponding enone **33** (Scheme 6), they expected to obtain a *trans*-configuration between these two stereocenters exploiting chirality transfer throughout the tricyclic structure. The two fused six-membered rings could be formed through a hetero Diels–Alder cyclisation of **34**. Noteworthy, the stereochemical outcome of this reaction at the C2 carbon was logically

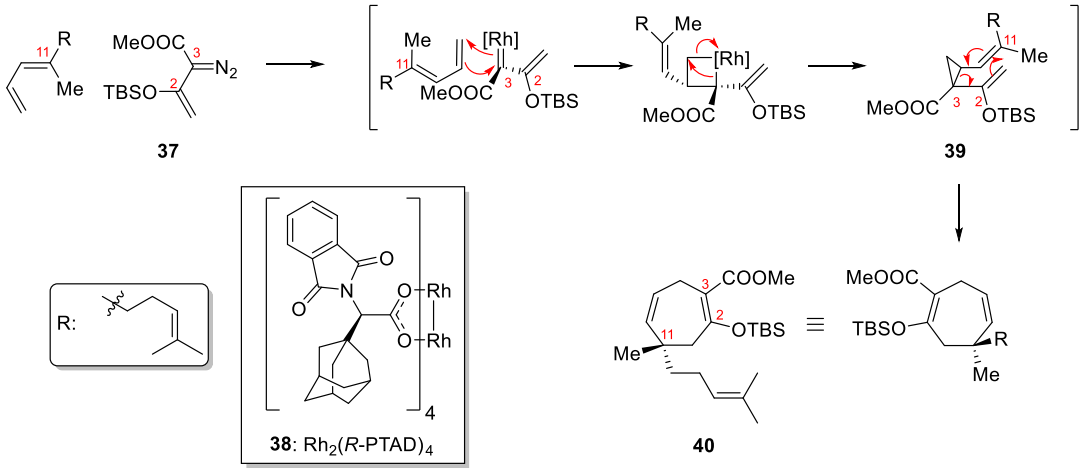
[15] Schwartz B.D.; Denton J.R.; Davies H.M.L.; Williams C.M., *Aust. J. Chem*. **2009**, *62*, 980-982.
[16] Schwartz B.D.; Denton J.R.; Lian Y.; Davies H.M.L.; Williams C.M., *J. Am. Chem. Soc.* **2009**, *131*, 8329-8332.
[17] (a) Davies, H.M.L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Greenwich, CT, 1998; Vol. 5, 119-164. (b) Davies, H.M.L.; Stafford, D.G.; Doan, B.D.; Houser, J.H. *J. Am. Chem. Soc.* **1998**, *120*, 3326-3331. (c) Reddy, R.P.; Davies, H.M.L. *J. Am. Chem. Soc.* **2007**, *129*, 10312-10313.

assumed to follow the configuration at C11, which was previously controlled through a formal asymmetric [4 + 3] cycloaddition.



Scheme 6

The synthesis began with an enantioselective formal [4 + 3] cycloaddition between diene **36** and vinyldiazoacetate **37**, catalysed by the chiral rhodium catalyst Rh_2(R-PTAD)$_4$ **38**. Mechanistically, [Rh]-catalyst inserts into the diazocompound **37** and produces a cyclopropane **39** through a metallacyclobutane. The cyclopropane then rearranges (Cope rearrangement) providing cycloheptadiene **40** in 65% yield and 90% ee (Scheme 7), notably, using this chiral catalyst, the first quaternary stereocenter at C11 was controlled.

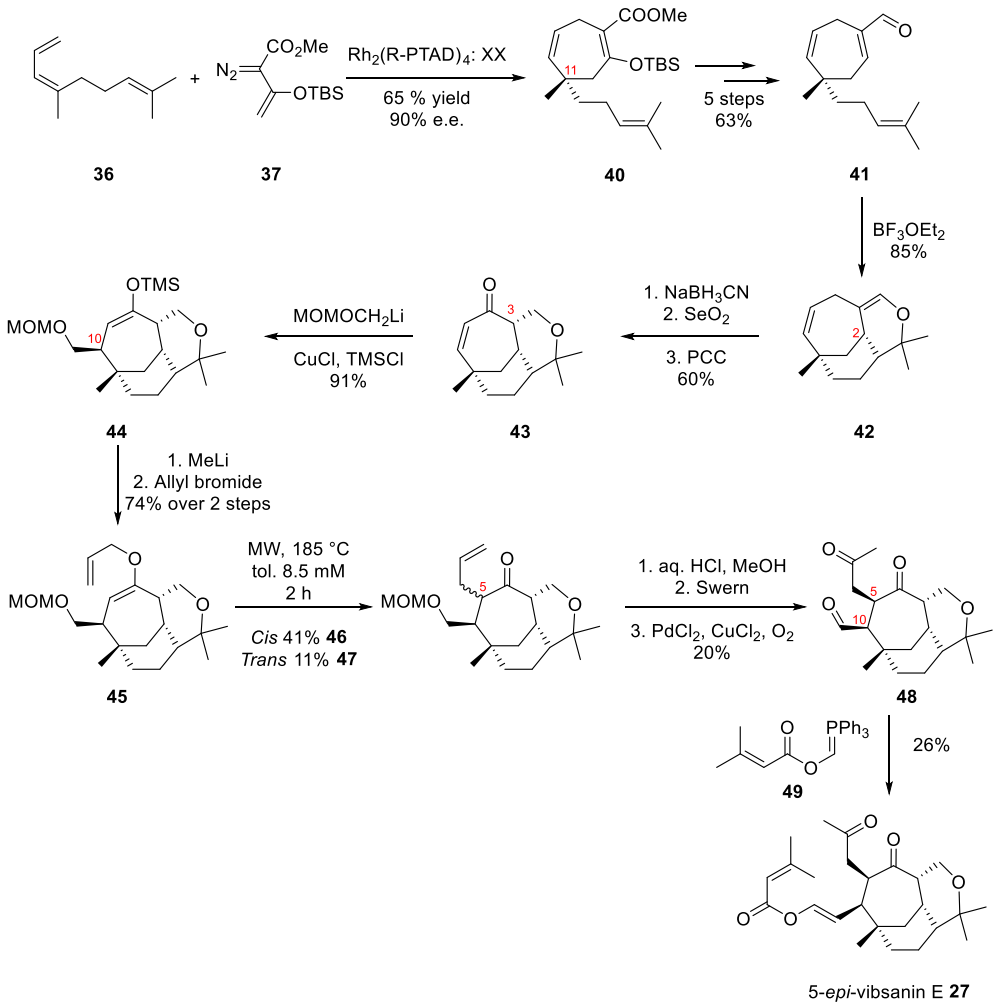


Scheme 7

Once the seven-membered ring was obtained, **40** was converted into aldehyde **41** over 5 steps to give the hetero Diels–Alder precursor (Scheme 8). Subsequent treatment of this aldehyde with BF_3•OEt_2 afforded cycloaddition adduct **42** in 85% yield with the right

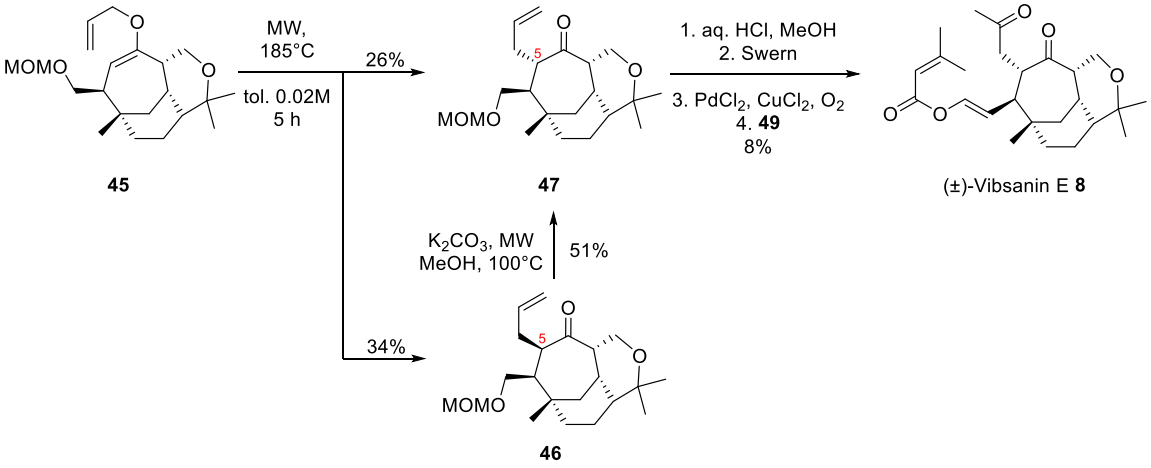
stereoconfiguration at C2. Reduction of enol ether **42** delivered the third stereocenter at the C3 position, sequential allylic oxidations, then, furnished tricycle **43**. With the tricyclic core in hands, stereoselective installation of the C5 and C10 side-chains was achieved. To this aim, Williams group successfully employed the cuprate derived from $MOMOCH_2Li$ to perform a diastereoselective conjugate addition on the enone **43** (91% yield). TMSCl addition was found to be essential in driving this reaction and quenching out the kinetic enolate. Subsequent transmetallation of silyl enol ether **44** with MeLi, followed by trapping of the enolate with allyl bromide provided **45** in 74% yield. Heating **45** under microwave for 2 hours at 185°C in toluene (8.5 mM) resulted in a Claisen rearrangement affording a mixture of 41% *cis* and 11% *trans*-products (respectively **46** and **47**). Although diastereoselectivity was not fully controlled, both epimers were useful; vibsanin E **3** and 5-*epi*-vibsanin E **27** could be accessed through each of these epimers. Towards 5-*epi*-vibsanin E **27**, *cis*-epimer **46** was deprotected to restore the primary alcohol, which was oxidised into the corresponding aldehyde. The allylic lateral chain at the C5 position was oxidized under Wacker conditions allowing the final elaboration of the C10 side-chain starting from **48** through an Anders–Gaβner[18] variant of the Wittig reaction. Indeed, treatment of aldehyde **48** with ylide **49** finally provided 5-*epi*-vibsanin E **27** (Scheme 8).

[18] Schwartz B.D.; Williams C.M.; Anders E.; Bernhardt P.V., *Tetrahedron* **2008**, *64*, 6482–6487.



Scheme 8

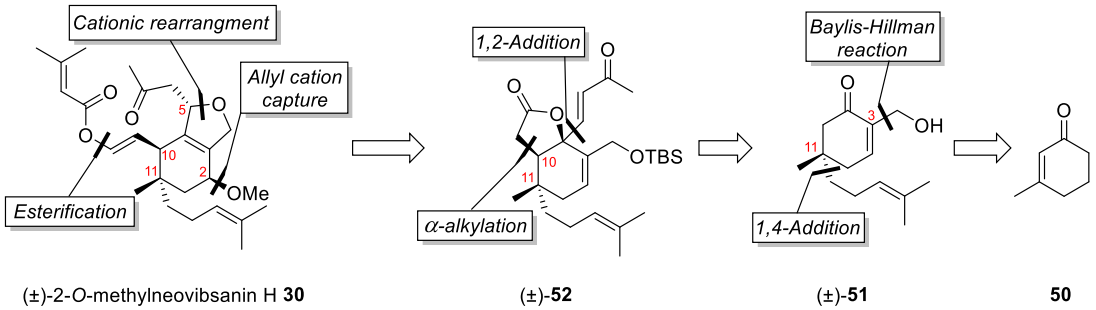
To complete the synthesis of vibsanin E **8**, the yield of **47** had to be improved. Fortunately, the *cis*/*trans ratio* relative to the Claisen rearrangement could be modified: by changing the concentration (0.02M) and the reaction time (5 hours) 34% of the *cis*-isomer **46** and 26% of the desired *trans*-isomer **47** were obtained. It was also found that **46** could be epimerised into **47** in 51% yield using K_2CO_3 in MeOH under microwave irradiation (Scheme 9). This improvement allowed **47** to be obtained in 44% yield from enol **45**. After subjecting **47** to the same conditions asfor the synthesis of the 5-*epi*-vibsanin E **27**, the total synthesis of vibsanin E **8** was achieved.



Scheme 9

1.4.2 Total synthesis of (±)-2-*O*-methylneovibsanin H

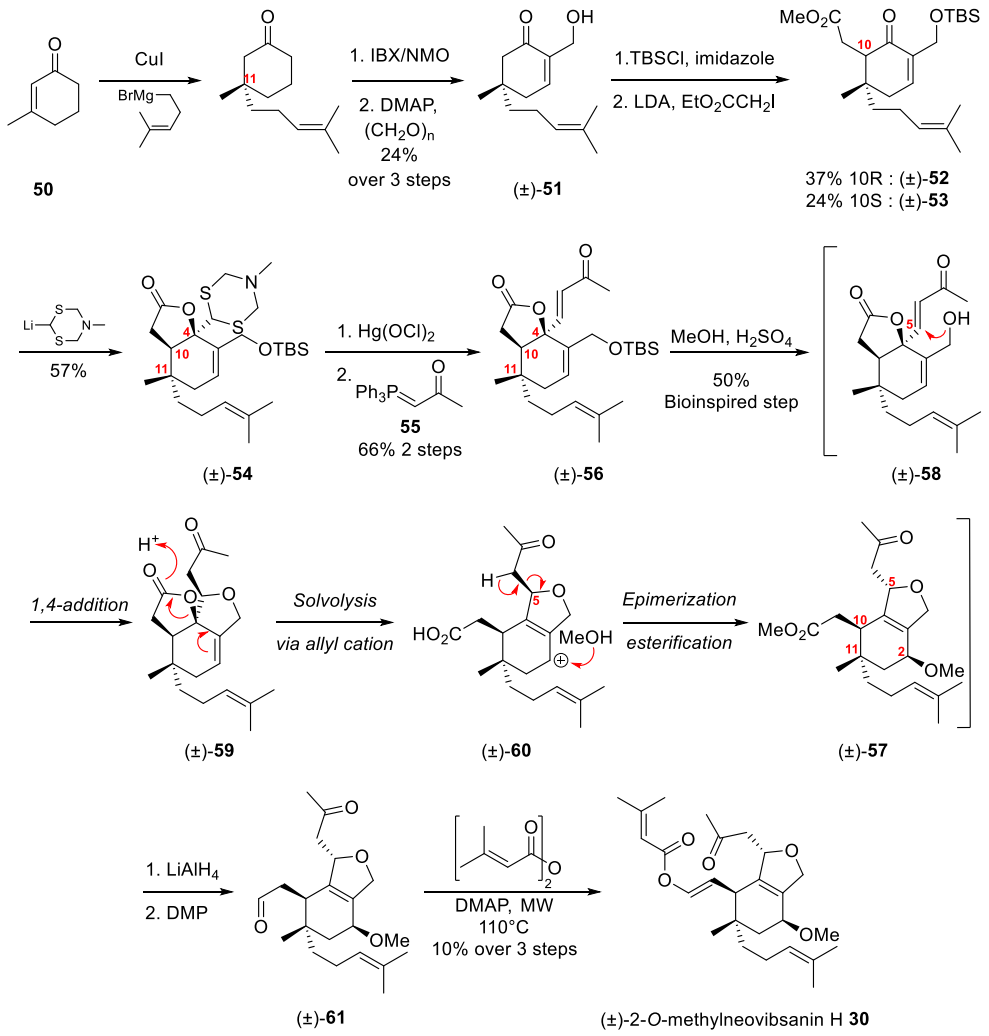
Although vibsanin E **8** and 5-*epi*-vibsanin E **27** have been the target of various groups for several years, the first vibsane natural product to be chemically synthesized was 2-*O*-methylneovibsanin H **30**.[19] This work was reported by the William's group in 2008. The retrosynthetic analysis of **30** (Scheme 10) was inspired from the biogenetic pathway proposed by Fukuyama (Scheme 4). The quaternary center at C11 would be installed by executing a 1,4-addition starting from cyclohexenone **50**. A subsequent Baylis-Hillman reaction would set up the C3 side chain and would provide ketone (±)-**51**. Exploiting the vicinal newly formed quaternary center, C10 side-chain would be inserted by an α-alkylation and, on the same principle, 1,2-addition onto the carbonylic function would provide key-intermediate **52**. From this point, Williams and his group envisaged that the bicyclic core of the molecule could be accessible by exploiting a cationic rearrangement, hypothesized in the Fukuyama biogenesis, in which the intermediate allylic cation is captured by the solvent. An esterification of the aldehyde at the C10 side chain would then provide (±)-2-O-methylneovibsanin H **30**.



Scheme 10

[19] Chen A.P.J.; Williams C.M., *Org. Lett.* **2008**, *10*, 3441–3443.

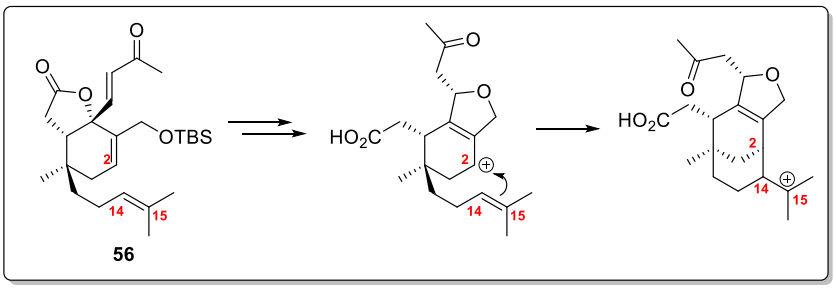
Treatment of cyclohexenone **50** with isoprenyl magnesium bromide in the presence of CuI and subsequent oxidation and Baylis-Hillman reaction afforded keto alcohol (±)-**51** as a racemic mixture in 24% yield over three steps (Scheme 11). The primary alcohol was protected and it was found that treatment of the latter with LDA and ethyl iodoacetate delivered a mixture of diastereoisomers in which (±)-**52** (10*R*) and (±)-**53** (10*S*) were respectively obtained in 37% and 24% yield. Several two-carbon nucleophiles were explored in an attempt to install the enone functionality on (±)-**52**, but without success. A two steps approach was thus employed. Treatment of ketone **52** with lithium dithiazide yielded 57% of the corresponding lactone (±)-**54**, stereo- and chemoselectively. Subsequent deprotection and reaction of the resulting aldehyde with ylide **55** provided enol (±)-**56** in 66% yield (2 steps). Inspired from the biogenetic pathway of neovibsanines, it was discovered that the treatment of the latter enone (±)-**56** with sulphuric acid in methanol at room temperature initiated a five steps cascade leading to (±)-**57** diastereoselectively. Notably, this reaction consists in: deprotection of the primary alcohol (**58**), intramolecular 1,4-addition of the alcohol onto C5 (**59**), solvolysis *via* allyl cation that induces ring opening of the lactone (**60**), epimerisation at the C5 position and final esterification. Once the four stereocenters were relatively controlled, conversion of the ester into the corresponding aldehyde allowed the installation of the side-chain starting from (±)-**61** and using DMAP and 3,3-dimethylacrylic anhydride in order to complete the synthesis of (±)-2-*O*-methylneovibsanin H (±)-**30**. This synthesis was an important milestone in synthetic vibsane chemistry, as it represented the first total synthesis of a vibsane natural product, and lent support to Fukuyama's proposed biosynthesis.



Scheme 11

1.4.3 Total synthesis of (-)-neovibsanin G and (-)-14-*epi*-neovibsanin G

Neovibsanin G **31** and 14-*epi*-neovibsanin G **32** are synthetically intriguing targets due to their structurally dense bicyclo[3.3.1]nonane caged ring system. After having realised the total synthesis of (±)-2-*O*-methylneovibsanin H (±)-**30** exploiting the 5-steps-cascade reaction, the William's group imagined a different route for intermediate **56**. Indeed, in the absence of a nucleophilic solvent like methanol, the secondary carbocation on the C2 position would be trapped by the olefin located at C14-C15 leading to a tricyclic structure featuring a tertiary carbocation at C15 (Scheme 12). Thus, key intermediate **56** had to be obtained in an enantioenriched form in order to pursue an enantioselective synthesis of the targets.



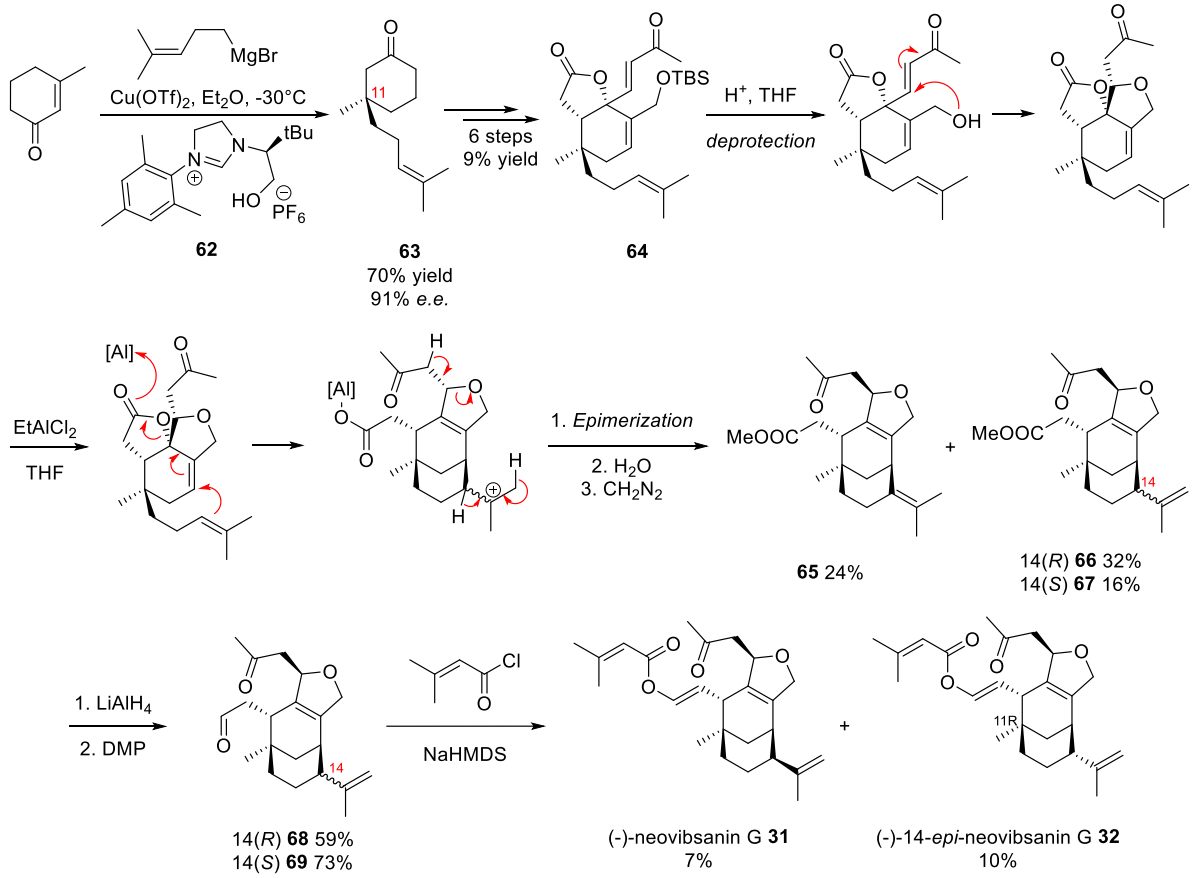
Scheme 12

In order to control all four stereocenters, the key-point was the asymmetric synthesis of the quaternary center at C11 position, the control of the other stereocenters being expected from chirality transfer. A chiral NHC-Cu catalytic system for conjugate additions recently developed by Mauduit and Alexakis seemed to be suitable for this purpose.[20] Indeed, addition of isoprenyl magnesium bromide to 3-methyl-2-cyclohexenone in the presence of chiral NHC **62** as ligand for copper triflate (*i.e.* $Cu(OTf)_2$) enantioselectively delivered ketone **63** (91% *ee*) in 70% yield (Scheme 13). Enantioenriched key intermediate **64** was then synthesized following the formerly route used for (±)-2-*O*-methylneovibsanin H and, at this point, the crucial cyclization to yield the caged core could now be probed. This cyclization was divided into three principal steps: firstly, the TBS deprotection led to the contruction of the furan scaffold, then bicyclo[3.3.1]nonane ring was formed and finally, methylation of the resulting carboxylic acid delivers the desired product (Scheme 13). After extensive investigations, the best conditions explored were the sequential utilization of HCl, $EtAlCl_2$ and CH_2N_2 that afforded alkenes **65, 66** and **67** in respectively 24%, 32% and 16% yield. At this stage, only two further steps were required: after the conversion of **66** and **67** into the corresponding aldehydes **68** and **69**, the enolates derived from NaHMDS were captured by the corresponding acyl chloride to give (-)-neovibsanin G **31** and (-)-14-*epi*-neovibsanin G **32**, respectively.[21] This total synthesis established for the first time that the absolute configuration of these two caged neovibsanins was the same as that of vibsanin B **4** and neovibsanins A **19** and B **20.** These results are amongst the strongest evidence for Fukuyama's proposal that the biosynthetic progenitor of the neovibsanins is vibsanin B **4**. Moreover, the absolute configuration of neovibsanin G **31** and 14-*epi*-neovibsanin G **32** turned out to be 11*S* and not 11*R*.

---

[20] (a) Martin D.; Kehrli S.; d'Augustin M.; Clavier H.; Mauduit M.; Alexakis A. *J. Am. Chem. Soc*. **2006**, *128*, 8416-8417. (b) Kehrli S.; Martin D.; Rix D.; Mauduit M.; Alexakis, A. *Chem. Eur. J*. **2010**, *16*, 9890-9904. (c) Wencel J.; Mauduit M.; Henon H.; Kehrli S.; Alexakis A. *Aldrichimica Acta* **2009**, *42*, 43-50. (d) Clavier, C.; Coutable L.; Toupet L.; Guillemin J.-C.; Mauduit M. *J. Organomet. Chem*. **2005**, *690*, 5237-5254.

[21] (a) Mak J.Y.W.; Williams C.M. *Eur. J. Org. Chem.* **2012**, 2001-2012. (b) Mak J.Y.W.; Williams C.M. *Chem. Commun.* **2012**, *48*, 287-289.



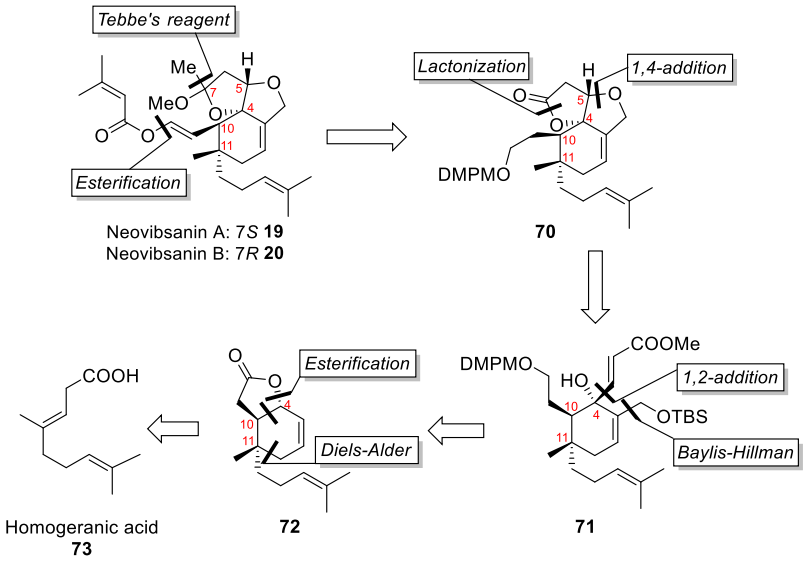
Scheme 13

1.4.4 Total synthesis of (±)-neovibsanin B

As previously mentioned, among the numerous vibsane-type diterpenoid targets, neovibsanins A and B are the most valuable from a biological point of view, therefore, these ketal-bearing neovibsanins have been the subject of a number of synthetic studies from various groups. The Mehta group has investigated the synthesis of the tricyclic core,[22] while the Williams group has completed the synthesis of 4,5-*bis*-*epi*-neovibsanins A and B.[23] The first total synthesis of neovibsanin B **20** was achieved by Imagawa and Nishizawa,[24] in collaboration with Fukuyama, using a biosynthetical-inspired route. Retrosynthetically, the Nishizawa's group started by disconnecting the methyl group in C7 position to give lactone **70** (Scheme 14). They then proposed that the latter lactone would be derived from a biogenetic inspired cascade from cyclohexene **71**. The four carbons required for the two five-membered rings were introduced by 1,2-addition and a Baylis–Hillman reaction on the

[22] Mehta G.; Bhat B.A. *Tetrahedron Lett*. **2009**, *50*, 2474-2477.
[23] (a) Chen A.P.J.; Muller C.C.; Cooper H.M.; Williams C.M. *Tetrahedron* **2010**, *66*, 6842-6850. (b) Chen A.P. J.; Muller C.C.; Cooper H.M.; Williams C.M. *Org. Lett.* **2009**, *11*, 3758-3761.
[24] Imagawa H.; Saijo H.; Kurisaki T.; Yamamoto H.; Kubo M.; Fukuyama Y.; Nishizawa M. *Org. Lett.* **2009**, *11*, 1253-1255.

intermediate **72**, which could be formed using an intramolecular Diels–Alder from homogeranic acid **73**.



Scheme 14

Homogeranic acid **73** was esterified to give tetraene **74** in 79% yield over two steps. Heating the tetraene in 1,3-dimethylimidazolidin-2-one (DMI) as solvent at 200°C afforded lactone (±)-**75** in 56% yield (Scheme 15). Subsequent reduction of the lactone, selective protection of the primary alcohol with 2,4-dimethoxybenzyl chloride (2,4-DMPMCl) and oxidation of the secondary alcohol delivered (±)-**76** in 62% over four steps. A Baylis–Hillman reaction allowed to introduce the hydroxymethyl group, which was subsequently protected to give (±)-**77** in 83% yield, over two steps. To complete the core of neovibsanin B, lithio ethyl propiolate was stereoselectively added in 87% yield to afford (±)-**78**, the stereospecificity and efficacy of this process relying on the coordinating effect of the polyoxygenated 2,4-dimethoxybenzyl protecting group on the lithiated nucleophile (Figure 6).

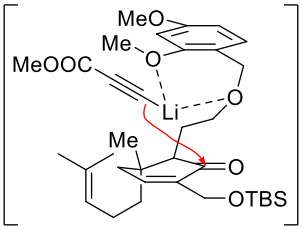
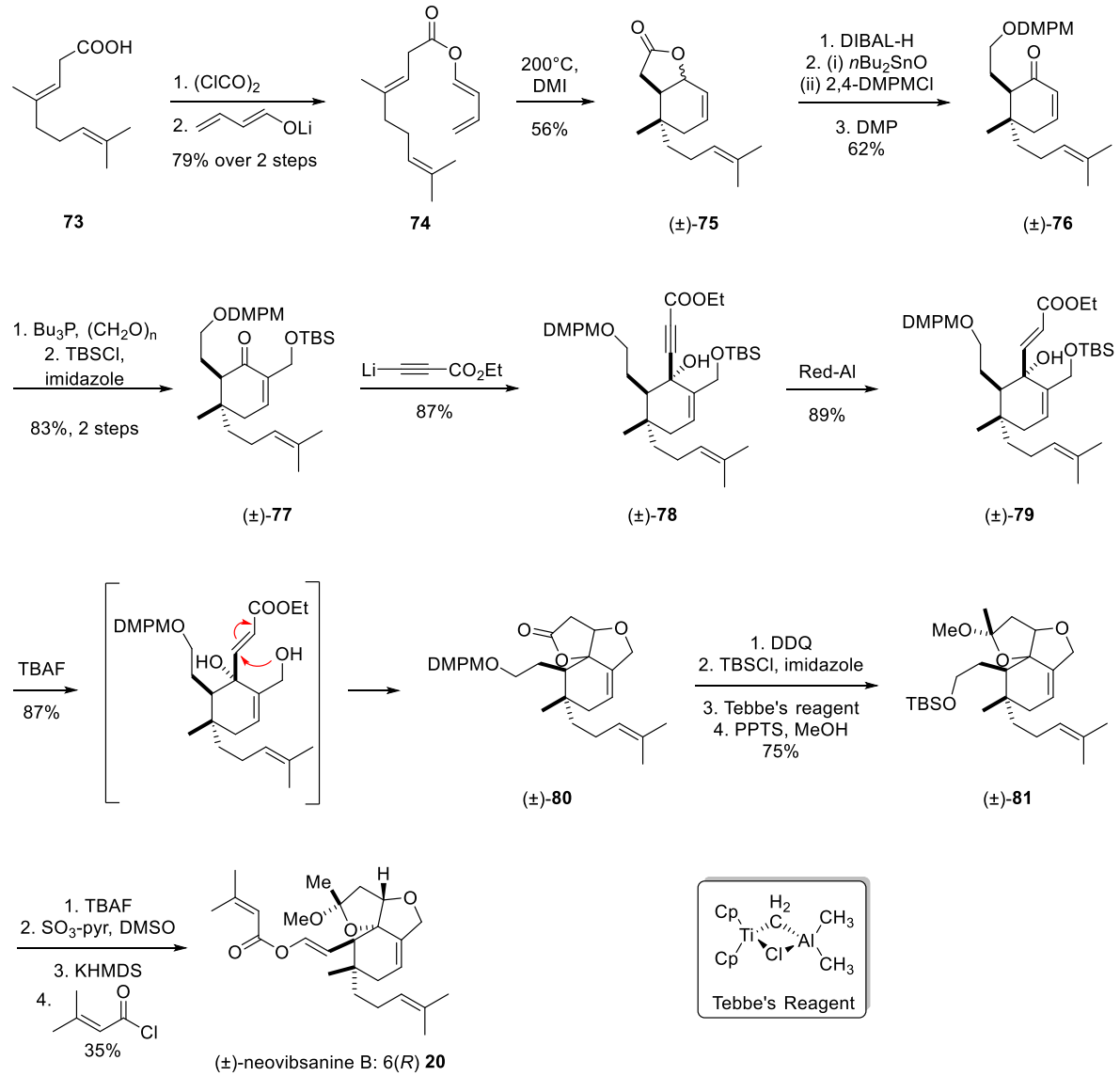


Figure 6

Unsaturated ester (±)-**78** was partially reduced with Red-Al to give the *E*-alkene (±)-**79** in 89% yield. TBS deprotection induced concomitant furan formation and subsequent lactonisation to give (±)-**80** in 87% yield. At this stage, the primary alcohol was transformed

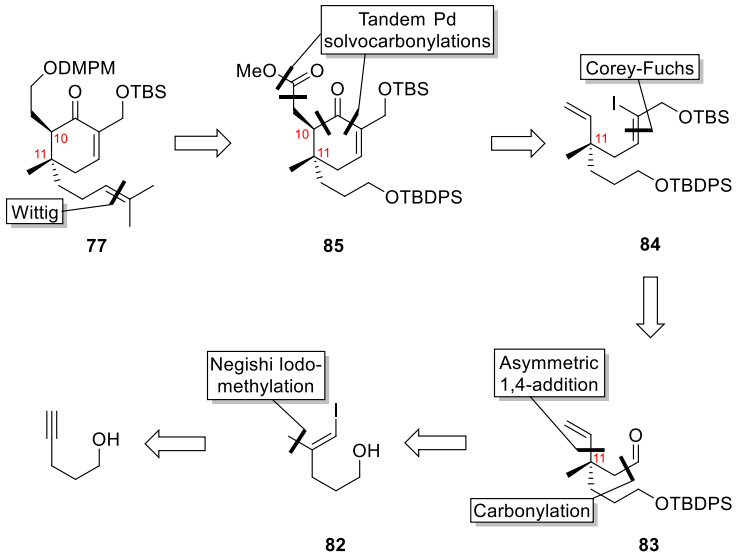
into its –TBS derivative. Elaboration of the characteristic ketal ring system (±)-**81** was completed by action of Tebbe's reagent and subsequent acid catalysed addition of methanol on the resulting vinyl ether in 75% yield over four steps. Finally, synthesis of neovibsanin B (±)-**20** was completed by deprotection of the alcohol, oxidation into aldehyde and trapping of the corresponding potassium enolate by acid chloride. Synthetic (±)-neovibsanin B (±)-**20** was found to have a similar degree of activity on neurite outgrowth as natural (+)-neovibsanin B.



Scheme 15

1.4.5 Formal enantioselective total synthesis of (+)-neovibsanin B

As neovibsanin B **20** was a biologically active target, an enantioselective synthesis of this compound was of primary interest. In this context, the Fukuyama's group reported the formal enantioselective total synthesis of this natural product in 2010.[25] The target of Fukuyama's formal synthesis was enone **77** (Scheme 16). They envisioned a Negishi iodomethylation reaction on 4-pentyn-1-ol in order to get access to **82**. Carbonylation and asymmetric 1,4-addition on the resulting vinyl iodide would control the configuration of C11 and deliver enantioenriched aldehyde **83**. The intermediate **84** would then be provided by a Corey-Fuchs reaction. The cyclohexene core of **85** along with the C10 side-chain arm would then be originated from a one-pot palladium catalyzed double carbonylation cascade and the synthesis would be achieved after a simple Wittig reaction in order to obtain enone **77**.

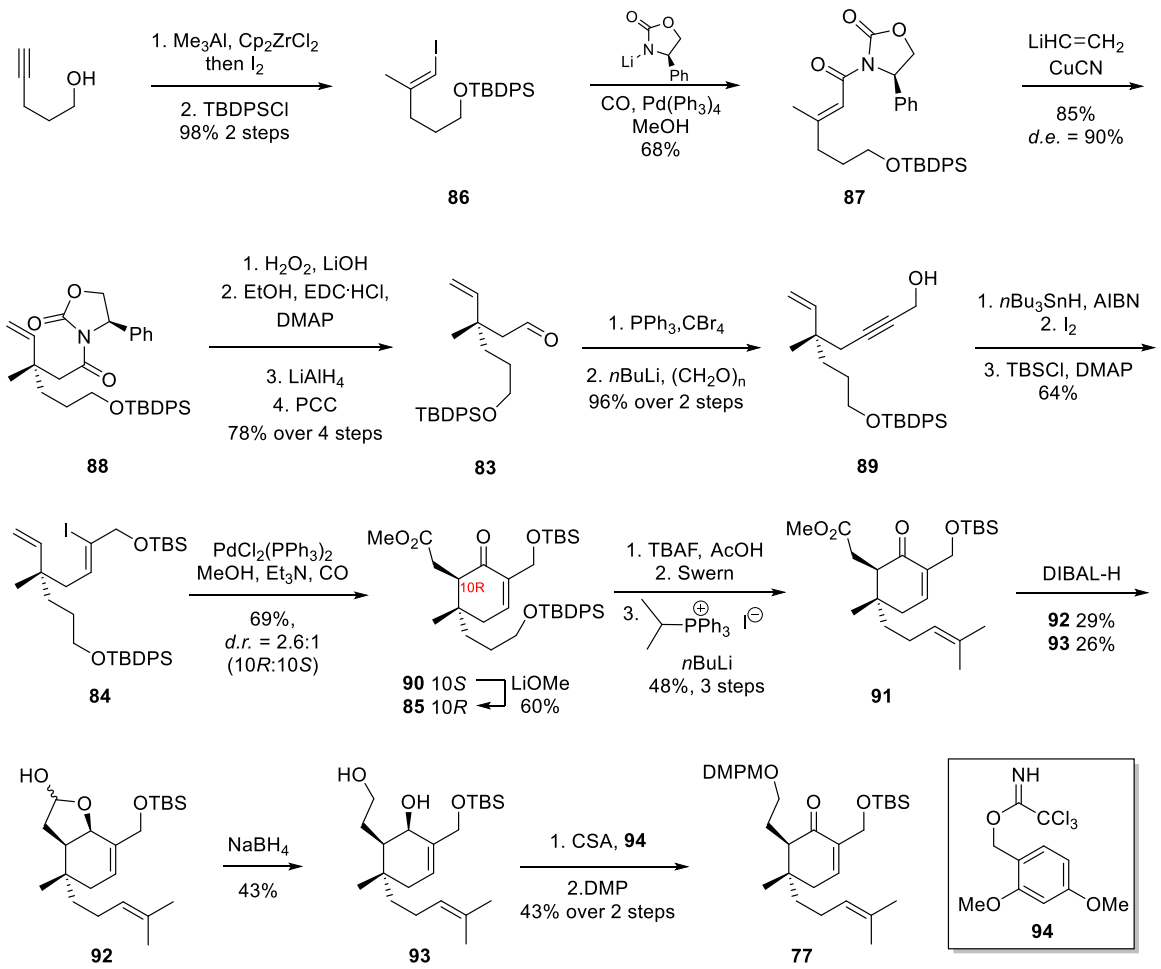


Scheme 16

Vinyl iodide **86** was selectively synthesised in two steps and 98% yield by a Negishi iodomethylation[26] of 4-pentyn-1-ol followed by a protection step (Scheme 15). Vinyl iodide was subjected to a palladium catalysed carbonylation–imidation with (*R*)-4-phenyl-2-oxazolidinone to provide **87** in 68% yield. Having introduced an asymmetric inductive group, the vinyl cuprate selectively attacked the Si-face of the olefin providing **88** in 85% yield diastereoselectively (90% *d.e.*). In this manner, the crucial quaternary center was controlled as 11*S*. At this stage, the imide was converted into the corresponding aldehyde **83** by oxazolidinone removal, esterification and a reduction/oxidation sequence. Then, the

[25] Esumi T.; Mori Y.; Zhao M.; Toyota M.; Fukuyama Y. *Org. Lett.* **2010**, *12*, 888-891.
[26] (a) Ichige T.; Okano Y.; Kanoh N.; Nakata M. *J. Org. Chem.* **2008**, *74*, 230-243. (b) Negishi E.; Van Horn D. E.; King A.O.; Okukado N. *Synthesis* **1979**, 501-502.

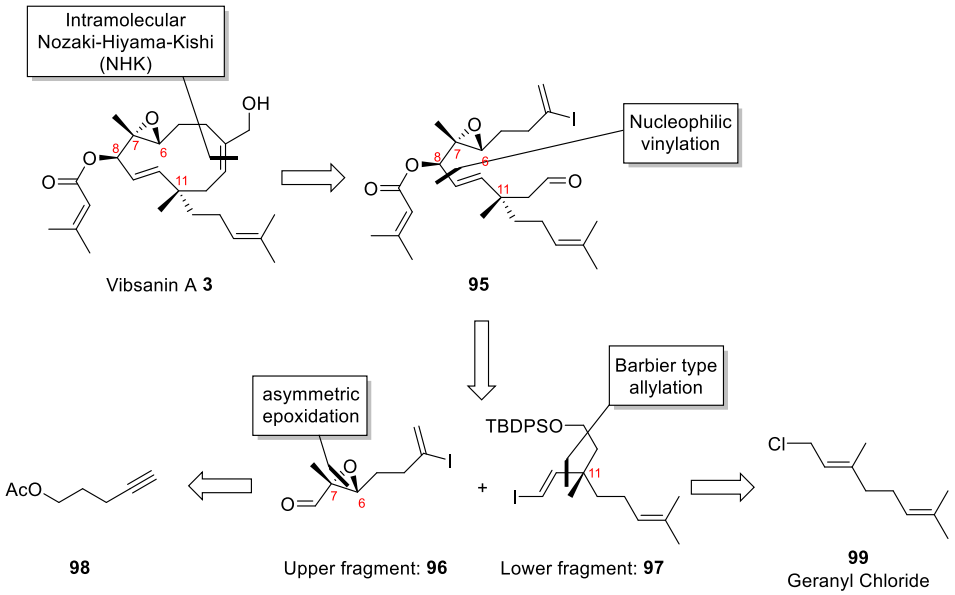
propargylic alcohol was synthesized through a Corey–Fuchs reaction followed by addition of the relative acetylide onto paraformaldehyde to give **89** in 96% yield over 2 steps. Subsequent *anti*-hydrostannylation with Bu_3SnH and iododestannylation, followed by protection furnished vinyl iodide **84** in 64% yield. Next, the crucial tandem palladium-catalyzed carbonylative cyclisation delivered methyl esters **85** and **90** in 69% yield. This cascade is made of two steps: a carbonylative intramolecular Heck reaction followed by a solvocarbonylation of the resulting alkyl palladium adduct. Although the diastereoselectivity was modest (2.6:1 in favour of diastereomer 10(*R*)-**85**), separation of the two diastereomers followed by epimerization of **90** with LiOMe delivered back the expected epimer **85** in 60% yield. In order to complete the formal synthesis, two more objectives were required: the construction of the prenyl side-chain and the conversion of the methyl ester into the protected alcohol. Alcohol was subsequently deprotected, oxidized and treated with the corresponding ylide to provide **91** in 48% over 3 steps. Then, reduction with DIBAL-H afforded a mixture of lactol **92** and diol **93**, fortunately the former could be reduced to diol **93** in 43% yield using $NaBH_4$. Subsequent chemoselective protection of **93** with **94** followed by oxidation provided **77** in 43% over 2 steps, thus completing the formal enantioselective synthesis of (+)-neovibsanin B (+)-**20**.


1. Me3Al, Cp2ZrCl2
then I2
2. TBDPSCl
98% 2 steps
OH
OTBDPS
86
CO, Pd(Ph3)4
MeOH
68%
Li
N
O
Ph
87
LiHC=CH2
CuCN
85%
d.e. = 90%
1. H2O2, LiOH
2. EtOH, EDC·HCl,
DMAP
3. LiAlH4
4. PCC
78% over 4 steps
TBDPSO
88
83
1. PPh3,CBr4
2. nBuLi, (CH2O)n
96% over 2 steps
89
1. nBu3SnH, AIBN
2. I2
3. TBSCl, DMAP
64%
OTBS
84
PdCl2(PPh3)2
MeOH, Et3N, CO
69%,
d.r. = 2.6:1
(10R:10S)
MeO2C
10R
90 10S
85 10R
LiOMe
60%
1. TBAF, AcOH
2. Swern
3.
PPh3
I
nBuLi
48%, 3 steps
91
DIBAL-H
92 29%
93 26%
HO
92
NaBH4
43%
93
1. CSA, 94
2.DMP
43% over 2 steps
DMPMO
77
NH
CCl3
MeO
OMe
94

Scheme 17

1.4.6 Total synthesis of (+)-Vibsanin A

Up to date, the last total synthesis aiming vibsane type diterpenoids, was reported by Tadano and his group in 2016 having as objective (+)-vibsanin A **3**.[27] Their retrosynthetic analysis of (+)-vibsanin A **3** is depicted in Scheme 18. The design of the synthetic plan relied on the combination of an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction and an allylic rearrangement to assemble the 11-membered ring. Substrate **95** for the key NHK reaction would be obtained through a vinylic addition between fragments **96** and **97**, in which the vicinal enantioenriched epoxide would control the stereochemical outcome of the reaction. They envisioned that upper fragment **96** would be obtained from commercially available 4-pentynyl acetate **98** through an asymmetric epoxidation that will control the configuration of stereocenters C6 and C7. A Barbier-type allylation procedure on geranyl chloride **99** would deliver the lower fragment **97**. In the latter case, they assumed that employing a chiral aldehyde like L-glyceraldehyde would allow to control the configuration of the quaternary center C11.

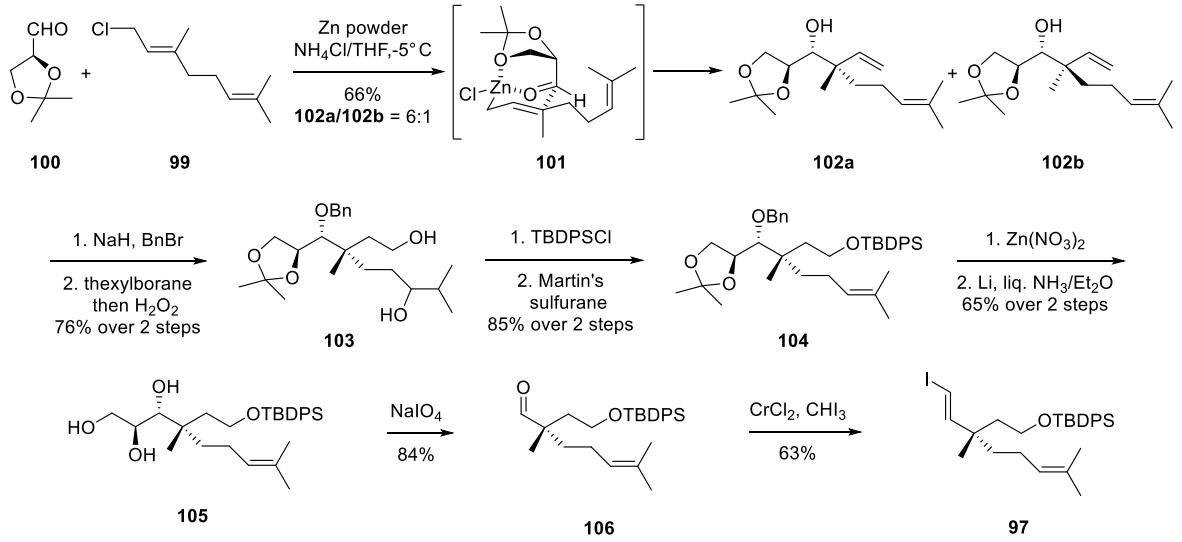


Scheme 18

The synthesis of the lower fragment **97** began with the construction of the quaternary stereocenter (Scheme 19). This stereocenter was installed by a zinc-mediated Barbier-type allylation in an aqueous medium involving L-glyceraldehyde acetonide **100** and geranyl chloride **99** to generate a 6:1 mixture of diastereomers in favour of the desired isomer **102a**. In this reaction, L-glyceraldehyde **100** was employed as the chiral source, indeed, the

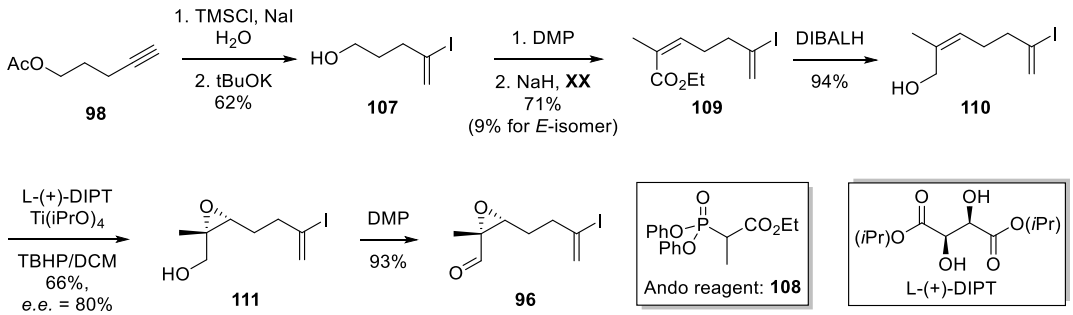
[27] Takao K.I.; Tsunoda K.; Kurisu T.; Sakama A.; Nishimura Y.; Yoshida K.; Tadano K.I. *Org. Lett.* **2015**, *17*, 756–759.

proposed β-chelated/6-membered ring model **101** could easily explain the selective allylation of the *Re*-face of the aldehyde. At this point, benzylation of **102ab** followed by hydroboration with thexylborane and subsequent oxidative work-up provided diol **103** in 76% yield. The minor diastereoisomer, derived from **102b**, was removed at this stage. The primary alcohol was selectively protected and treatment of the secondary alcohol with Martin sulfurane ($Ph_2S[OC(CF_3)_2Ph]_2$) regenerated the trisubstituted olefin **104** as a single isomer in 85% yield. Selective hydrolysis of the isopropylidene acetal and subsequent cleavage of the benzyl group under Birch conditions afforded triol **105** in 65% yield. Oxidative cleavage of **105** provided aldehyde **106**, which was next subjected to Takai olefination to provide enantiomerically pure fragment **97** in 63% yield.



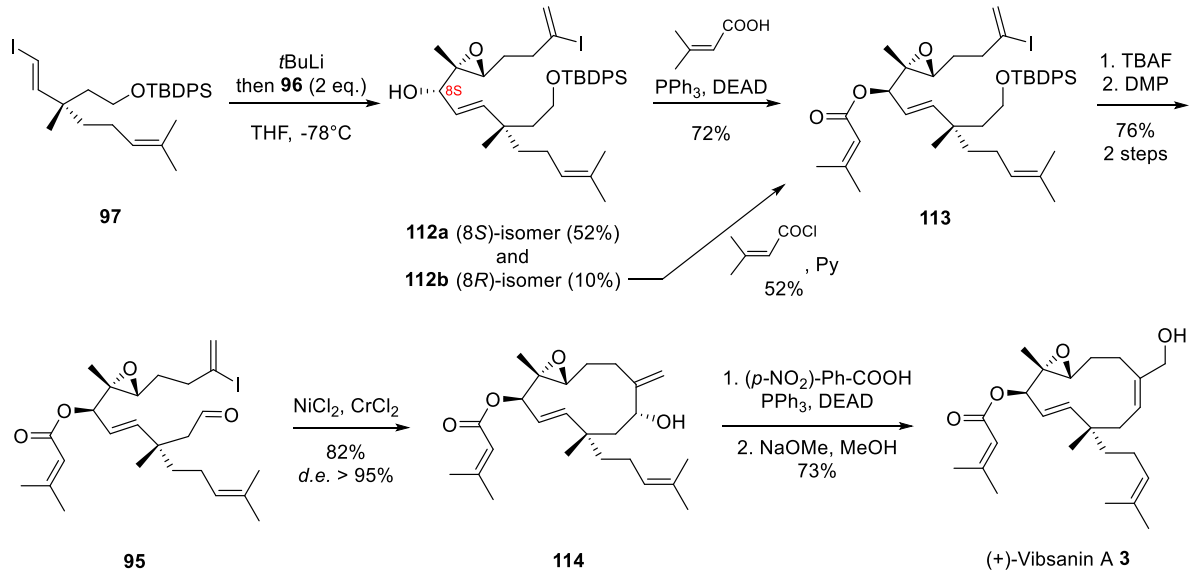
Scheme 19

Upper fragment **96** was prepared starting from 4-pentynyl acetate **98** (Scheme 20). Hydroiodination of the triple bond and deprotection of the alcohol delivered vinyl iodide **107** in 65% yield. Dess-Martin oxidation of alcohol and treatment of the corresponding aldehyde with Ando reagent **108** afforded the *Z*-unsaturated ester **109** in 71% yield along with 9% of the *E*-isomer. Reduction of **109** by DIBAL-H provided allylic alcohol **110**, and asymmetric epoxidation of **110** was next examined. Although moderate enantioselectivity (70% *ee*) was observed for the Sharpless asymmetric epoxidation under catalytic conditions, stoichiometric conditions significantly improved the enantioselectivity to deliver epoxide **111** in 80% *ee*. Finally, oxidation of **111** to aldehyde afforded desired enantioenriched upper fragment **96**.



Scheme 20

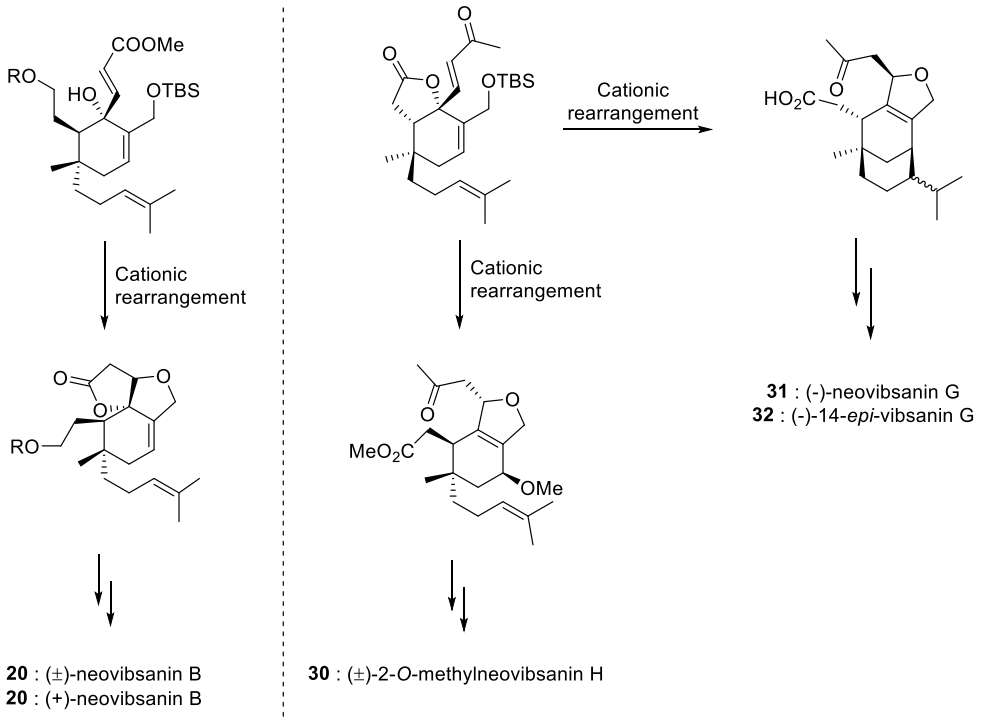
The upper and lower fragments were coupled by treatment of alkenyl iodide **97** with *t*BuLi and addition of two equivalents of aldehyde **96** (Scheme 21). The coupling adducts **112a** and **112b**, relative to isomers 8*S* and 8*R* respectively, were recovered in 52% yield, for **112a**, and 10% for **112b**. Since the newly formed stereogenic center in major isomer **112a** possessed the opposite configuration to the synthetic target, esterification of **112a** under Mitsunobu conditions was explored. Although 3,3-dimethylacrylic acid was a weak acid, the Mitsunobu reaction of **112a** proceeded smoothly providing desired ester **113** with configurational inversion in 72% yield. On the other hand, the minor isomer **112b** was converted into **113** in 52% yield by using a mixture of 3,3-dimethylacryloyl chloride and pyridine. Deprotection of **113** followed by oxidation of the resulting primary alcohol furnished compound **95** in 76% yield. From this aldehyde, it was possible to explore Nozaki-Hiyama-Kishi type reaction: indeed, treatment of dilute solution of **95** (0.005 M) with $CrCl_2$ and catalytic $NiCl_2$ led to the formation of the 11-membered ring and provided the cyclized product **114** as a single isomer in 82% yield. At this stage, the diastereomer derived from the minor enantiomer of the upper fragment **96** was separated by flash chromatography, allowing the isolation of diastereomerically pure **114**. As expected, the allylic rearrangement of **114** into **3** was achieved by Mitsunobu reaction using *p*-nitrobenzoic acid and chemoselective methanolysis of the resulting diester**.** (+)-Vibsanin A **3** was finally obtained in 73% yield.



Scheme 21

1.5 Conclusions

The principal characteristics of vibsane-type diterpenoids have been presented in this chapter. Starting from an introduction of vibsanins and passing through the different classes and subclasses of these natural products, the molecular structures have been elucidated along with the most reliable proposed biogenetic pathways. Even if vibsanin B **4** has been indicated as the natural progenitor of 7-membered ring vibsanins and neovibsanines, the biological origin of 11-membered ring vibsanins is unknown up to now. However, in the course of great work done by Williams and his group aiming the biogenetical inspired total synthesis of (-)-neovibsanin G **31**, (-)-14-*epi*-neovibsanin G **32**, (±)-2-*O*-methylneovibsanin H **30** and (±)-neovibsanin B **20**, the key-steps represented by the three different cationic rearrangements are by far the clearest evidence in support of Fukuyama's proposed biosynthesis (Scheme 22).


COOMe
RO
HO
OTBS
Cationic rearrangement
RO
O
O
O
OTBS
Cationic rearrangement
Cationic rearrangement
HO2C
O
O
MeO2C
O
OMe
31 : (-)-neovibsanin G
32 : (-)-14-epi-vibsanin G
20 : (±)-neovibsanin B
20 : (+)-neovibsanin B
30 : (±)-2-O-methylneovibsanin H

Scheme 22

2. Vibsatins A and B: presentation and synthetic analysis

In this chapter, vibsatin A **1** and vibsatin B **2** will be introduced. Their origins, a proposed biogenetic pathway and their biological properties will be discussed. Our retrosynthetical analysis for the realization of their total synthesis will be presented followed by a focus on the key step reaction, identified as a Conia-ene reaction.

2.1 Vibsatins A and B

In the last chapter, vibsane-type diterpenoids were disclosed together with a presentation of their different subtypes. Very recently, in 2014, a new subtype of these diterpenoids was reported by He and Zhao: vibsatin A **1** and vibsatin B **2** (Figure 7). These two molecules were isolated in low yields, respectively $2.9 \cdot 10^{-5}$% for **1** and $7.3 \cdot 10^{-5}$% for **2**, from *Viburnum tinus cv. variegatus* by extraction with acetone, partition in ethyl acetate and subsequent purifications by flash chromatography.[28] Notably, *Viburnum tinus cv. variegatus* is a cultivated species of *Viburnum tinus*.[29] First phytochemical investigations on this plant resulted only in the isolation of various compounds like iridoids, coumarins, saponins and flavonoids associated with neuroprotective, hepatoprotective, sedative and spasmolytic activities.[30] No new chemical constituents were reported from this plant until the discovery of vibsatin A and vibsatin B.

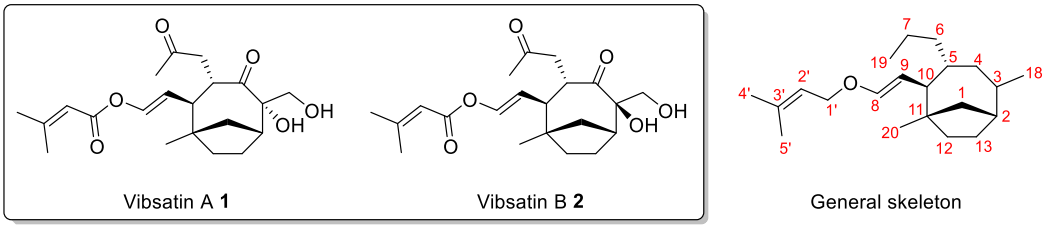


Figure 7

The structure of vibsatins was determined by classic NMR studies and HR-EI-MS. Vibsatins A and B feature a unique bicyclo[4.2.1]nonane core, which had never been observed in natural products, including five stereocenters on C2, C3, C5, C10 and C11. Moreover, compared to all others vibsanins presented the Chapter 1, vibsatins possess four carbons less

[28] Gao, X.; Shao, L.D.; Dong, L.B.; Cheng, X.; Wu, X.D.; Liu, F.; Jiang, W.W.; Peng, L.Y.; He, J.; Zhao, Q.S. *Org. Lett.* **2014**, *16*, 980-983.
[29] Li, Z.-W.; Tang, T.-P. *Landscape Architecture Trees of China*; Liaoning Scientific and Technical Publishers: Shanghai, 2008; pp 130.
[30] (a) Yilmaz, B.S.; Altun, M.L.; Orhan, I.E.; Ergene, B.; Citoglu, G.S. *Food Chem.* **2013**, *141*, 582-528. (b) Mohamed, M.A.; Marzouk, M.S.A.; Moharram, F.A.; El-Sayed, M.M.; Baiuomy, A.R. *Phytochemistry* **2005**, *66*, 2780-2786.

and a new bond between C13 and C2 (Figure 8). The structures and the absolute configurations have been confirmed using X-ray diffraction and vibsatin B **2** proved to be the C3 epimer of vibsatin A **1**. Notably, the configurations confirmed to be: 2*R*, 3*S*, 5*S*, 10*S*, 11*S* for vibsatin A **1** and 2*R*, 3*R*, 5*S*, 10*S*, 11*S* for vibsatin B **2**.

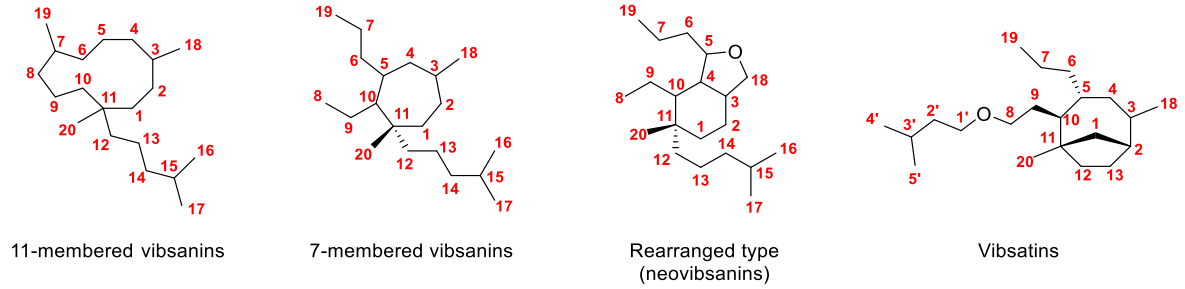
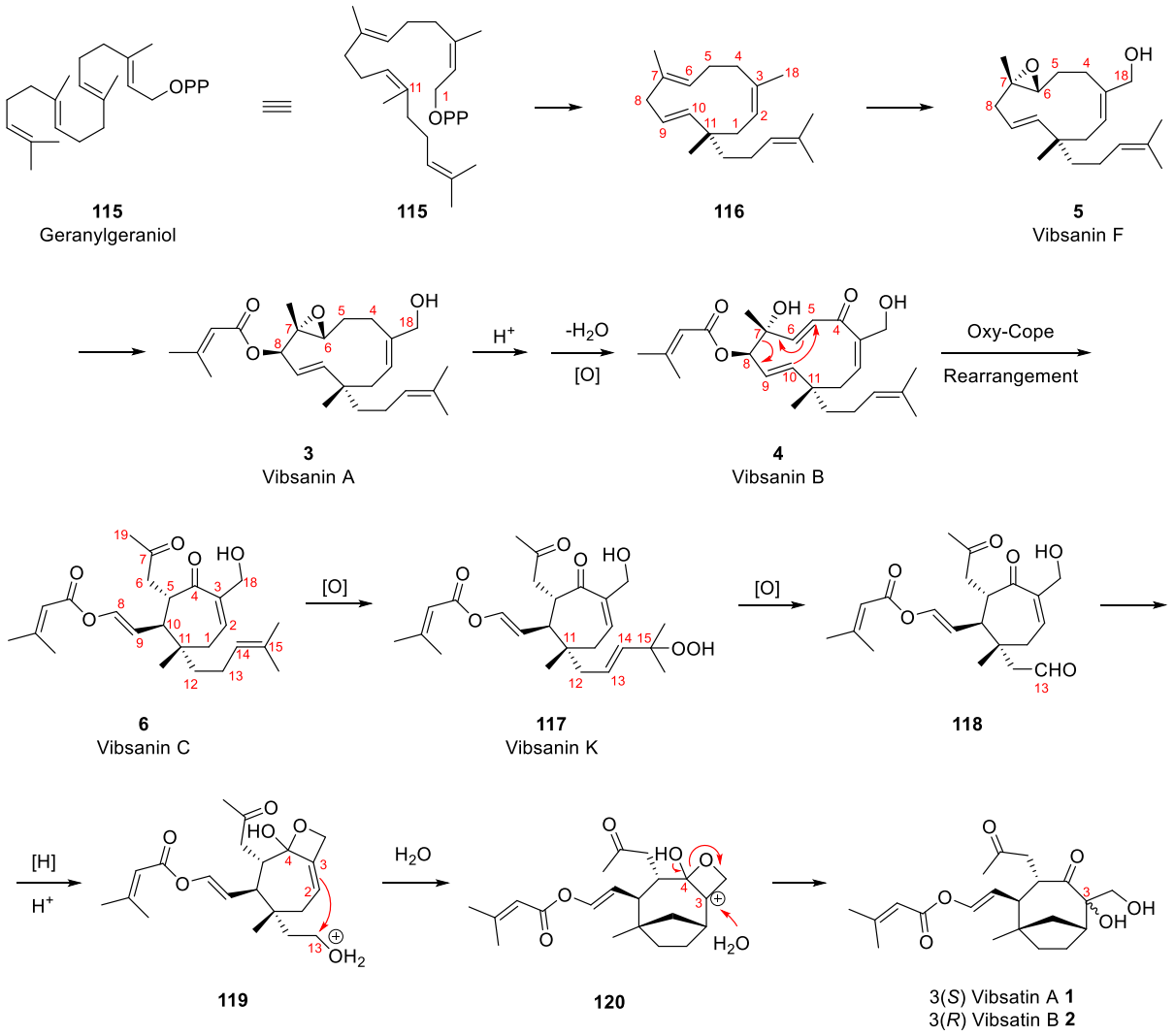


Figure 8

A biogenetic pathway starting from geranylgeraniol **115** (Scheme 23) was proposed. It was suggested that geranylgeraniol pyrophosphate cyclizes to afford the humulene-type 11-membered skeleton of vibsanins **116**. Vibsanin F **5** arises from epoxidation of the olefin between C6 and C7 and allylic oxidation at C18 of **116**. Another allylic oxidation followed by esterification onto C8 of vibsanin F provides vibsanin A **3.** Subsequent opening of the oxirane ring and oxidation at C4 afford vibsanin B **4**. The previously described Oxy-Cope rearrangement transforms vibsanin B **4** into vibsanin C **6** and consecutive oxidation of the side chain at C15 furnishes vibsanin K **117**, which features a peroxide group in its structure. Oxidative cleavage of the double bond between C14 and C15 then forms intermediate **118**. At this point, after reduction at C13, an hemiacetal **119** is generated and protonation of the newly formed primary alcohol allows attack from the C2-C3 double bond leading to the characteristic bicyclo[4.2.1]nonane scaffold of vibsatins **120**. The resulting carbocation is finally quenched by water and the ketone at C4 was restored by ring opening of the oxetane providing vibsatin A **1** or vibsatin B **2**.



Scheme 23

2.2 Neurotrophins and neurotrophic activity

As mentioned earlier in section 1.3, in 2010, neovibsanins were found to display important neurite outgrowth activity by Fukuyama, suggesting that several vibsane-type diterpenoids may be promising candidates for the development of novel therapeutic agents to treat neurodegenerative diseases. More recently (in 2014), first biological studies achieved by He and Zhao showed that vibsatins A and B also induced significant neurite outgrowth. These promising biological results associated with the unique structure of these vibsane family diterpenoids have logically attracted our attention.

Before clarifying these features, an introduction concerning neurodegenerative diseases (NDDs), is mandatory. Neurotrophins, a family of related factors involved in neuronal development and maintenance, will be also presented, taking into account that NDDs often display with neurotrophin imbalance.

Neurodegenerative disease (NDD) is a general term for indicating heterogeneous and often sporadic maladies that are characterized by progressive dysfunction of the nervous system, resulting from loss of neural structure and function as well as from brain-death.[31] Alzheimer, Parkinson and Huntington diseases are notable examples of these disorders.[32] Nowadays, these diseases affect approximately 50 million people worldwide, bringing the total healthcare cost to over 600 billion per year.[33] Efforts to understand their progression point to various molecular and cellular events, like accumulation of misfolded proteins, protofibril formation, dysfunction of the ubiquitin-proteasome system, mitochondrial damage, oxidative stress, and synaptic failure.[34] However, the etiologies of these diseases still remain under investigation and, noteworthy, very limited treatment options are currently available.

The neurotrophin family (NTF) forms a class of functionally and structurally related proteins that regulates growth, differentiation and survival of central and peripheral neurons. NTF includes Nerve Growth Factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 4/5 (NT-4/5) and neurotrophin-3 (NT-3). NTF acts through two distinct receptors: a high-affinity and selective receptor tyrosine kinase called Trk and a low affinity receptor called p75. NGF binds TrkA, BDNF and NT-4 bind TrkB, whereas NT-3 prefers TrkC but also binds TrkA and TrkB, noteworthy all neurotrophins bind to p75.[35]

The imbalance in neurotrophin receptor activity described to occur in neurodegenerative diseases may constitute a promising target for therapy.

Trk-signals are normally required for neuronal maintenance and function, and defects in Trk-receptor tyrosine kinase activation (e.g. reduced receptor expression, impaired cellular transport, agonist deficiency) are associated with early stages of neurodegeneration. This supports the view that Trk-agonism may be therapeutic (Figure 9).

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[31] (a) Thompson, L.M. *Nature* **2008**, *452*, 707–708. (b) Palop, J.J.; Chin, J.; Mucke, L. *Nature* **2006**, *443*, 768-773; (c) Martin, J.B. *N. Engl. J. Med.* **1999**, *340*, 1970-1980.

[32] (a) Thuret, S.; Moon, L.D.; Gage, F.H. *Nat. Rev. Neurosci.* **2006**, *7*, 628-643. (b) Cadotte, D.W.; Fehlings, M.G. *Clin. Orthop.* **2011**, *469*, 732-741.

[33] (a) Querfurth, H.W.; LaFerla, F.M. *N. Engl. J. Med.* **2010**, *362*, 329-344. (b) Meissner, W.G.; Frasier, M.; Gasser, T. ; Goetz, C.G.; Lozano, A.; Piccini, P.; Obeso, J.A.; Rascol, O.; Schapira, A.; Voon, V.; Weiner, D.M.; Tison, F.; Bezard, E. *Nat. Rev. Drug Discovery* **2011**, *10*, 377-393 (c) World Alzheimer Report 2013: An analysis of long-term care for dementia; Executive Summary; Published by Alzheimer's Disease International, London, **2013**.

[34] Bossy-Wetzel, E.; Schwarzenbacher, R.; Lipton, S.A. *Nat. Med.* **2004**, *10*, S2-S9.

[35] Josephy-Hernande, S.; Jmaeff, S.; Pirvulescu, I.; Aboulkassima, T.; Saragovi, H.U. *Neurobiol. Dis.* **2017**, *97*, 139-155.

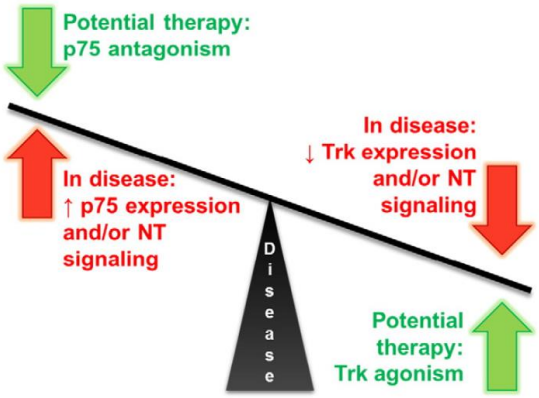


Figure 9

The p75 receptors, which are members of the TNFα receptor superfamily, are implicated in normal developmental pruning and neuronal death. When upregulated and activated in certain tissues, they can cause neurotoxicity associated with neurodegenerative diseases. Notably, the p75 receptors are commonly upregulated in neurodegenerative states. This supports the view that p75-antagonism may be therapeutic.

In summary, the neurotrophin imbalance underlying neurodegenerative diseases can be a disease-modifying therapeutic target. The pathogenic mechanisms of increased p75 expression and/or signaling can be counteracted by p75 antagonism. A decrease in Trk expression and/or signaling can be therapeutically corrected by Trk agonism.

While the rationale for targeting Trk and p75 is robust, clinical validation is mostly absent because it requires the use of disease-modifying drugs acting through these receptors. The use of the neurotrophins themselves as drugs has mostly failed despite significant efforts and growingly sophisticated –yet risky– delivery methods (these molecules must be administered directly into the central nervous system). The poor pharmacological profile of these large proteins, short half-lives, inability to penetrate tissue barriers, undesirable high potency and pleiotropic effects, and the activation of multiple receptors (where p75 activity can negate the benefit of Trk activity) may significantly reduce the therapeutic benefit. Thus, there is an urgent need for drugs without such setbacks.

The development of small molecule drugs that target neurotrophin receptors could overcome these obstacles. Currently, a number of clinical trials are being carried out using neurotrophic factor mimetics. Results from these trials, especially concerning side effects and efficacy,

will broaden and enhance neurotrophic factor-based therapy for treating neurodegenerative disorders.[36]

In this field, natural products displaying neurotrophic activity hold significant promise as tools for biological studies and as original and privileged structures; presently, several compounds are in clinical trials. However, often, the chemical biology of neurotrophic natural products has not been methodically explored. This could be due to the complexity of pathways that account for neural degeneration and the difficulties related to conducting biological experiments in primary neural cells.

The readily available rat pheochromocytoma (PC-12) cell line offers an attractive and reliable alternative to the primary cell cultures and has been used as a good *in vitro* model of neuronal differentiation. After stimulation with NGF, PC-12 cells differentiate to extend neurites and develop the characteristics of sympathetic neurons.[37]

It has been found that neovibsanin **21**, neovibsanin A **19** and neovibsanin B **20** possess neurotrophic properties. Namely, they promote neurite outgrowth of NGF-mediated PC-12 cells at concentrations ranging from 10 to 40 μM.[38] As shown in Figure 10, neovibsanin (Figure 10B), neovibsanin A (Figure 10C), and neovibsanin B (Figure 10D) significantly promoted neurite outgrowth from NGF (10 ng/mL)-treated PC-12 cells at 40 μM (Figure 10A is the control experiment). Among these three compounds, neovibsanin A seems less potent than neovibsanin and neovibsanin B. However, all of them had no effect on morphology of PC-12 cells in the absence of NGF. Additionally, other vibsane-type diterpenoids such as 7-membered and 11-membered ring subtypes have not been found to show neurotrophic activity in PC-12 cells so far.

[36] (a) Xu, J.; Lacoske, M.H.; Theodorakis, E.A. *Angew. Chem. Int. Ed*. **2013**, *52*, 2-34. (b) Chen, A.P.-J.; Müller, C.C.; Cooper, H.M.; Williams, C.M. *Tetrahedron* **2010**, *66*, 6842-6850. (c) Weissmiller, A.M.; Wu, C. *Translational Neurodegeneration* **2012**, 1-14. (d) Price, R.D.; Milne, S.A., Sharkey, J.; Matsuoka, N. *Pharmacol. Ther*. **2007**, *115*, 292-306.
[37] Pradines, A.; Magazin, M.; Schiltz, P.; Fur, G.L.; Caput, D.; Ferrara, P.; *J. Neurochem.* **1995**, 64, 1954-1964.
[38] (a) Kishimoto, Y.; Maeda, S.; Fukuyama, Y. The 126th Annual Meeting of Pharmaceutical Society of Japan, Sendai, **2006**. (b) Kubo, M.; Kishimoto, Y.; Harada, K.; Hioki, H.; Fukuyama, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2566-2571.

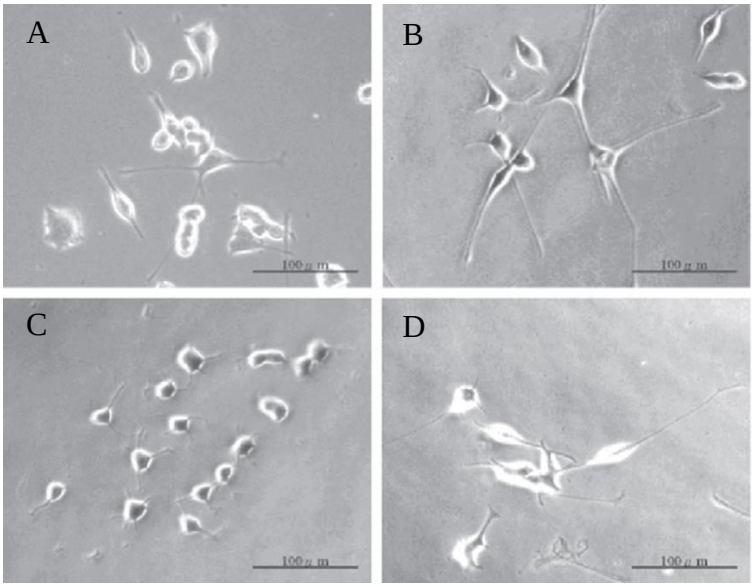


Figure 10

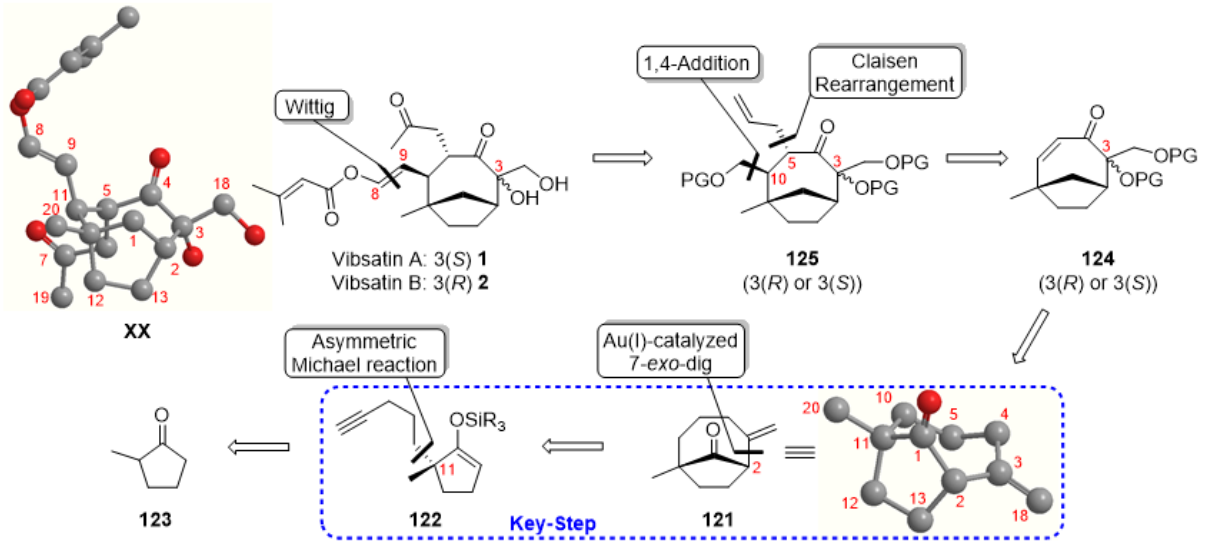
In the course of the investigation concerning *Viburnum tinus cv. variegatus*, the ability to stimulate the nerve growth factor (NGF) mediated neurite outgrowth on PC-12 cells was examined for all the various resulting isolated fractions. From these studies, it was reported that vibsatin A **1** increased the neuronal differentiation in 72h at a concentration of 10 μM, in the presence of 5 ng/mL of NGF.

Because of this promising biological activity and the challenging structural core of vibsatins A and consequently B, our group cultivated interest for the total synthesis of these two novel diterpenoids in order to provide a better understanding of the mechanism of neurotrophic action as well as to lead to the synthesis of analogues with promising neurotrophic activity.

2.3 Synthetic strategy

To this aim, it was developed a retrosynthetic pathway in which, after having asymmetrically configured one stereocenter, all the others would be controlled by chirality induction exploiting the bicyclic shape of the molecule. Accessing the bicyclo[4.2.1]nonane skeleton of vibsatins appeared as the most challenging step of this synthesis. In the last years, gold chemistry demonstrated to be a powerful tool in carbocyclizations. Thus, it has been foreseen to employ a Conia-ene derived 7-*exo*-dig cyclization catalysed by a gold(I) complex in order to access to **121** starting from enantiomerically enriched silyl enol ether **122** (Scheme 24). An asymmetric Michael addition starting from 2-methylcyclopentanone **123** would provide the 2(*R*) configuration at C11 required for the precursor **122**. This Conia-ene derived reaction was identified as the key-point of the strategy since in one single reaction, the challenging

bridged bicyclic backbone would be set up in the right configuration (2*R*). Oxidations and deoxygenation of this bicycle would allow to obtain of the α,β-unsaturated ketone **124**. Further 1,4-addition was expected to functionalize the Si-face of the double bond leading to a 10*S* configuration. Subsequent Claisen rearrangement would provide C5 allylation in a *trans*-fashion leading to **125** and to the setting of the last stereogenic center present in the vibsatins. The synthesis of vibsatins A **1** or B **2** would then be concluded by installing the lateral chain through a Wittig reaction which would build a (*E*)-double bond between C8 and C9.



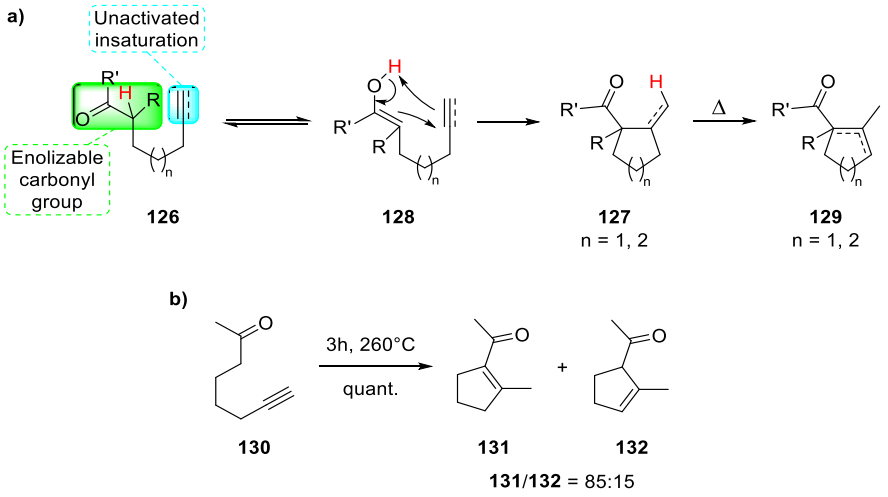
Scheme 24

2.4 Conia-ene reaction, a brief overview

The key stage, as specified before, relies on a transformation derived from the renowned Conia-ene reaction. As described by Conia and Le Perchec in their in-depth review in 1975,[39] the original version of this reaction refers to the thermal intramolecular cyclization of enolizable carbonyl compounds **126** with a tethered alkyne or alkene moiety leading to valuable five- or six-membered carbocycles **127** (Scheme 25a). In this reaction, the enol tautomer of the ketone **128** undergoes an Alder-ene type rearrangement delivering the cyclic product. Nevertheless, without extra-stabilization effects that favour the enol form, the available amount of this nucleophilic form is scarce and the use of high temperatures (usually between 250°C and 350°C) is required to trigger the cyclization. For this reason, the tolerance of functional group is restricted and decomposition of the substrate is often produced severely limiting the synthetic utility of the reaction. In the case of carbonyl compounds with a tethered alkyne, a direct consequence regards the isomerization of the

[39] Conia, J.M.; Le Perchec, P. *Synthesis* **1975**, 1-19

newly formed double bond, which, at these temperatures, shifts from *exo*-position to thermodynamically favoured *endo*-position **129**. This shows that, obviously, conjugation effects influence the transformation. Indeed, the isomerized compound **129** is usually obtained from a thermal Conia-ene reaction, as in the case of oct-7-yn-2-one **130** which, if heated to 260°C, provides a mixture of **131** and **132** in 85:15 *ratio* (Scheme 25b).[40]



Scheme 25

Because of the harsh reaction conditions and the lack of selectivity of the reaction, various modifications have been accomplished during the years. One approach utilised to overcome these problems was the utilization of β-dicarbonyl compounds as substrates. Indeed, carbonyl compounds providing an extra stabilizing group in the β-position offer various advantages: the presence of an extra electron-withdrawing group is beneficial for the acidity and enolization rate. Moreover, the enol is stabilized by hydrogen-bonding between the OH of the enol and the basic oxygen of the β-functionality. Additionally, these compounds can act as efficient chelate ligands for hard Lewis acids. Upon coordination, the substrates experience an increase in acidity thus facilitating deprotonation and metal enolate formation (Figure 11). Notably, the introduction of an additional carbonyl function in the β-position of the original carbonyl moiety allowed the development of catalytic conditions; in this topic, a recapitulatory review on catalyzed Conia-ene cyclizations of β-dicarbonyl compounds has been recently published by Enders *et al*.[41]

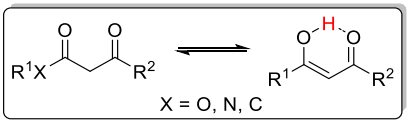


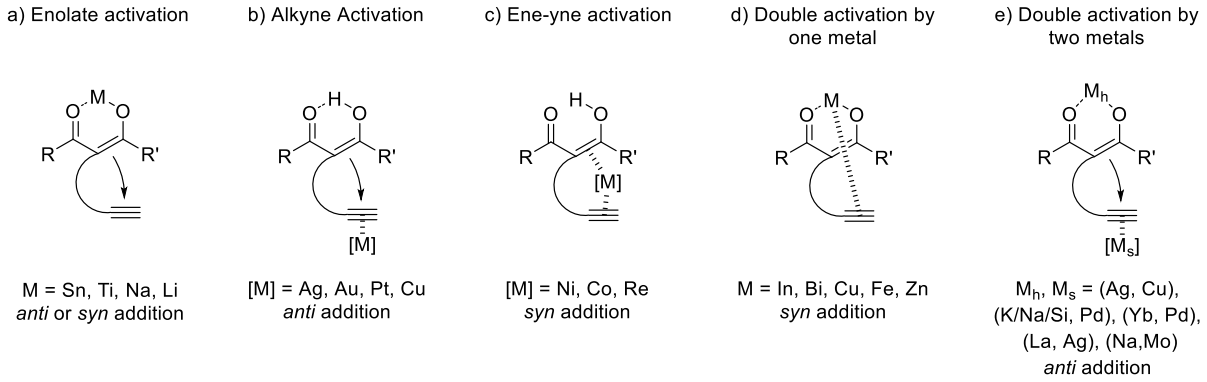
Figure 11

[40] Rouessac, F.; Le Perchec, P.; Bouket, J.L.; Conia, J.M. *Bull. Soc. Chim. France* **1967**, 3554.
[41] Hack, D.; Blumel, M.; Chauhan, P.; Philipps, A.R.; Enders, D. *Chem. Soc. Rev.* **2014**, *44*, 6059-6093.

Different catalytic systems have been developed in order to catalyse Conia-ene reactions. These systems are divided into five different subtypes depending on the activation mode (Scheme 26).[42]

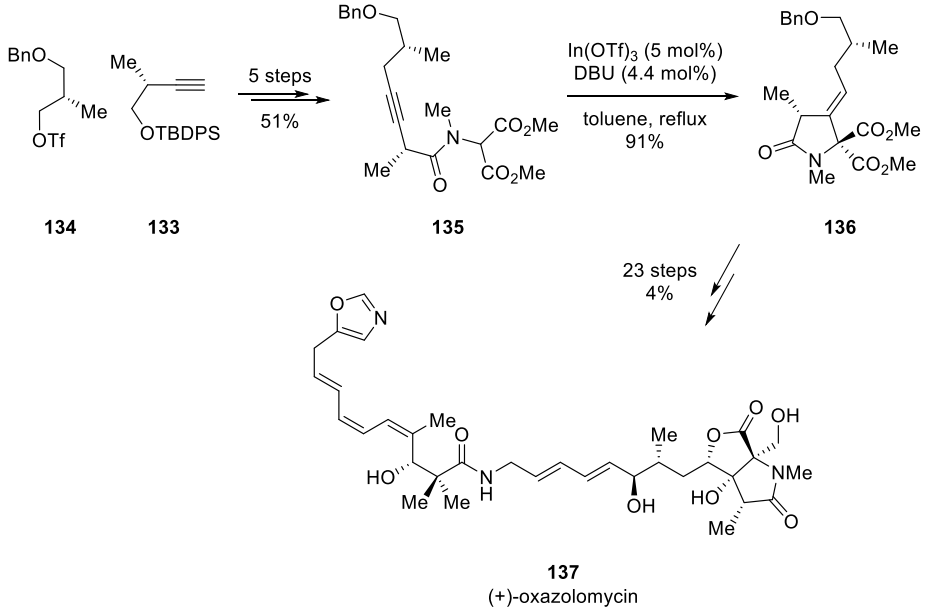
a) The first method regards the enolate activation by a metal, however, there are only a few examples of this kind of activation due to the fact that the involved carbocyclization is an endothermic process. Interestingly, the addition onto the triple bond occurs in an *anti*-fashion for metals like Na and Li and in a *syn*-fashion for Ti and Sn (Scheme 26a).
b) Activation of the alkyne moiety, instead, is a more common and more studied type. Generally, late-transition metals trigger carbocyclization in this way thank to their soft carbophilic Lewis acid character. The addition takes place in an *anti*-fashion (Scheme 26b).
c) Ene-yne activation is related with transition metals that usually catalyse [2+2+2] cycloadditions such as Co and Ni. In this case, even if products seem to be issued from a simple Conia-ene reaction, the process includes oxidative addition, β-hydride elimination and reductive elimination. For this reason, the addition of the enol onto the alkyne is realized in a *syn*-fashion (Scheme 26c).
d) Recently, methods for activating the enol and the alkyne moieties have been the subject of various researches. It has been found that some metals possess the ability to catalyse the cyclization of β-dicarbonyl compounds acting on both the enol and the triple bond if combined with external factors (bases, microwaves, etc.) and the addition follows a *syn*-addition pathway. Interestingly, some of these metals are not particularly known for their capability to activate alkynes (Scheme 26d).[43]
e) The usage of a hard metal ion able to chelate the enol moiety together with a softer carbophilic Lewis acid capable to activate the triple bond constitutes the fifth method, in which two metals activate two different moieties of the substrate. Notably, this method allows the development of asymmetric version as the hard metal ion easily coordinates chiral phosphines. The attack proceeds through an *anti*-fashion manner (Scheme 26e).

[42] Itoh, Y.; Tsuji, H.; Yamagata, K.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, 130, 17161-17167.
[43] Fürstner, A.; Davies, P.V. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.



Scheme 26

To this aim, a few examples of the exploitation of this chemistry in total synthesis are reported below. One elegant total synthesis realized through a key Conia-ene reaction of a malonate moiety, is the total synthesis of (+)-oxazolomycin, published by Hatakeyama in 2011.[44] Starting from homopropargylic alcohol **133** and triflate derivative **134** the amidomalonate **135** was synthesised in five steps (Scheme 27). Indium(III) triflate ($In(OTf)_3$) proved to be able to catalyse the cyclization of **135** into pyrrolidone derivative **136**. In this case, the catalyst activates either the triple bond or the enol moiety. A strong base is required and high temperatures are needed. Subsequently, 23 more steps were required to access to (+)-oxazolomycin **137**.

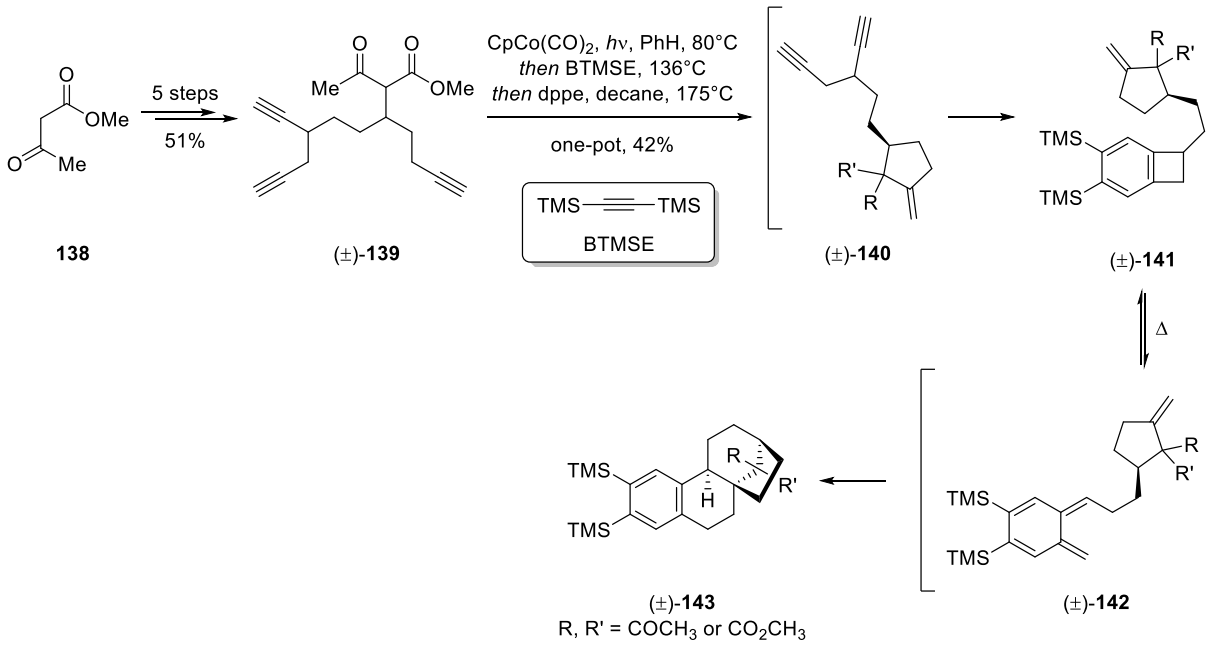


Scheme 27

One impressive synthesis of phyllocladane skeleton was reported by Malacria in 1996 exploiting ene-yne activation of a cobalt(I) catalyst to a β-ketoester followed by [2+2+2] and

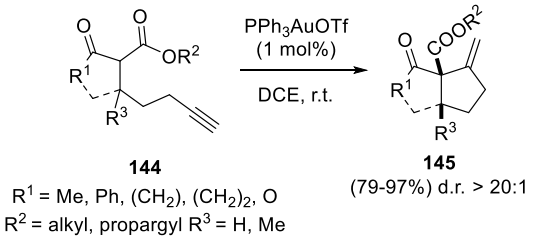
[44] Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2011**, *13*, 5398-5401.

[4+2] cycloaddition reactions (Scheme 28).[45] Starting from methyl acetoacetate **138**, the precursor of the cyclization (±)-**139** was synthesized in 5 steps. Treating this compound with dicarbonylcyclopentadienyl cobalt(I) ($CpCo(CO)_2$) under UV irradiation at 80°C afforded the cyclized intermediate (±)-**140**. The subsequent change of solvent, temperature and addition of *bis*(trimethylsilyl)ethyne (BTMSE), triggered a [2+2+2] cycloaddition that formed benzocyclobutane (±)-**141**. Electrophilic ring opening of (±)-**141** into (±)-**142** took place by raising the temperature to 175°C and the newly formed compound underwent a [4+2] Diels-Alder rearrangement providing the tetracyclic diterpene backbone (±)-**143,** typical of phyllocladane.



Scheme 28

In some cases, the developed catalytic conditions are extremely performing, leading to the utilization of about 1 mol% of catalytic charge. In this field, the cyclization of linear or cyclic β-ketoesters **144** to access cyclopentenes **145** catalysed by Au(I), reported by Toste in 2004, is depicted in Scheme 29.[46]

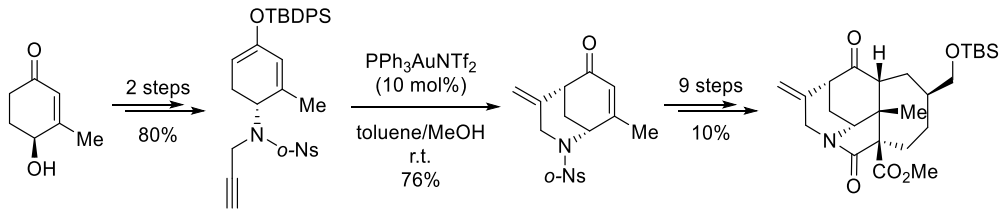


Scheme 29

[45] Cruciani, P.; Stammler, R.; Aubert C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699-2708.
[46] Kennedy-Smith, J.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.

Although broadly applicable to the diastereoselective formation of a variety of cyclic and bicyclic systems, these methods are limited to the synthesis of quaternary carbon atoms that bear two carbonyl functionalities. Therefore, it has been envisioned to take advantage of the nucleophilicity of silyl enol ethers as 'frozen enol equivalents". However, unlike for enol nucleophiles, an external proton source is required in order to protodemetallate the intermediate vinyl-metal adduct and, thus, to complete the catalytic cycle. Nevertheless, despite some examples in which Pd catalysed 5-*exo*-dig cyclizations of alkyne-tethered silyl enol ethers have been reported,[47] in most of the reports dealing with the use of silyl enol ethers, a Au(I)-based cationic complex was selected as catalyst. The mechanism of this kind of reactions will be discussed in section 3.2.6. Remarkably, in synthetic chemistry field, employing silyl enol ethers as nucleophiles in Conia-ene carbocyclizations is generally seen as a more elegant solution, although it is necessary to stoichiometrically install the silyl enol ether function.

One example is the synthesis of the [6-6-5-7] tetracyclic core of daphnilongeranin B reported in 2014 by Shao and Li (Scheme 30).[48] Cyclohexenone **146** was transformed into silyl enol ether **147** in two steps. Alkyne activation was exploited by using triphenylphosphino gold(I) bistriflimide complex (PPh_3AuNTf_2) in order to perform a 6-*exo*-dig cyclization and afford the [6-6] bicyclic compound **148**. The [6-6-5-7] tetracyclic core of daphnilongeranin B **149** was synthesized then in 9 steps.



146 **147** **148** **149**

Scheme 30

[47] (a) Chuang, S-Y.; Isobe, M. *J. Org. Chem.* **2017**, *82*, 2045-2058. (b) Brazeau, J-F.; Zhang, S.; Colomer, I.; Corkey, B.K.; Toste, F.D. *J. Am. Chem. Soc.* **2012**, *134*, 2742-2749.
[48] Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294-5297.

2.5 Conclusions

In this chapter, Vibsatin A **1** and vibsatin B **2** were introduced (Figure 12). Their unique bridged [5,7] bicyclic structures were elucidated along with a biosynthesis proposed by He and Zhao. Then, an introduction on neurodegenerative diseases followed by a disclosure of neurotrophins and neurotrophic activity was presented. Thus, the preliminary biological essays on vibsatin A **1** explaining the deriving interest in these molecules were illustrated.

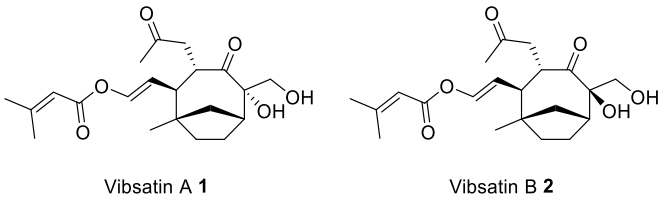
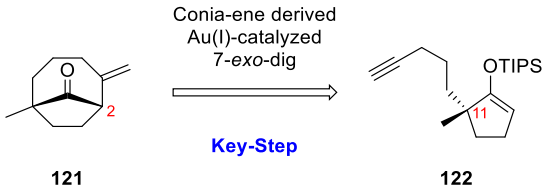


Figure 12

The retrosynthetic pathway elaborated by our group was described along with a focus on the involved key-step reaction type (Scheme 31). The general characteristics of the metal catalysed Conia-ene reaction were reported, highlighting the most important keypoints relative to substrates, mechanisms and activation modes. Selected examples of applications in total synthesis complete the chapter and provide an overview on the practical utilization of these processes.



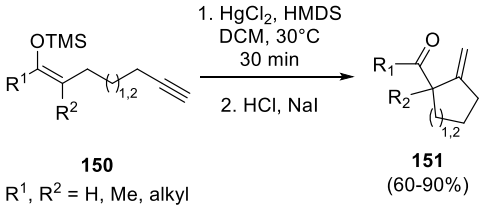
Scheme 31

3. Carbocyclization of alkynes: gold(I) catalysis and double activation

In this chapter, the gold(I)-catalysed reactions of alkenes with alkynes for the synthesis of carbocycles will be discussed and a special attention will be devoted to silyl enol ethers. At the beginning, the most relevant historical examples of these carbocyclizations will be reviewed giving a brief overview over the activation methods reported in the last century. Then the emerging technologies will be examined and a particular focus will be paid to the Conia-ene reaction, that will further constitute the key-step of our strategy towards the total synthesis of Vibsatins A and B. In the final part, combination of organo- and metal- catalysis will be examined as a novel area in carbocyclization chemistry.

3.1 Pioneeristic works

The first example of guided carbocyclization between a silyl enol ether and a triple bond moiety was reported by Conia and his group in 1985.[49] They were searching a method capable to catalyse thermal Conia-ene cyclizations in order to perform this kind of transformations at lower temperature.[39] It was found that the use of stoichiometric mercury(II) salts was efficient to catalyse the cyclization of easily enolizable alkynyl-β-diketones.[50] They then exploited $HgCl_2$ in order to perform 5-*exo*-dig and 6-*exo*-dig cyclizations of acetylenic carbonyl compounds through their trimethylsilyl enol ether derivatives **150** affording cyclic derivatives **151** (Scheme 32).

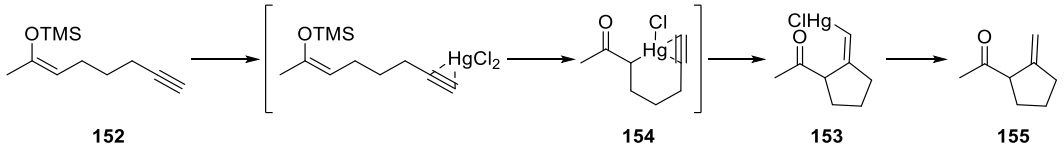


Scheme 32

Mechanistically, starting from simple silyl enol ether **152**, it was demonstrated that mercury(II) forms a Z-vinylmercurial intermediate **153** through a rearrangement of a transient α-mercury ketone **154**. Hydrolysis of the intermediate delivers the homoallylic ketone **155** (Scheme 33). Notably, this reaction was reported on cyclic and acyclic substrates and 5- or 6-membered rings were synthesized. The main drawback of this method was, obviously, the

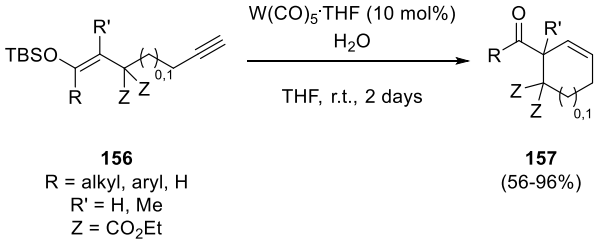
[49] Drouin, J.; Boaventura, M.A.; Conia, J.M. *J. Am. Chem. Soc.* **1985**, *107*, 1726-1729.
[50] Boaventura, M.A.; Drouin, J. ; Conia, J.M. *Synthesis* **1983**, 801-804.

stoichiometric utilization of mercury salt. Moreover, cyclization of α'-silyl enol ethers or internal alkynes were ineffective under these conditions.



Scheme 33

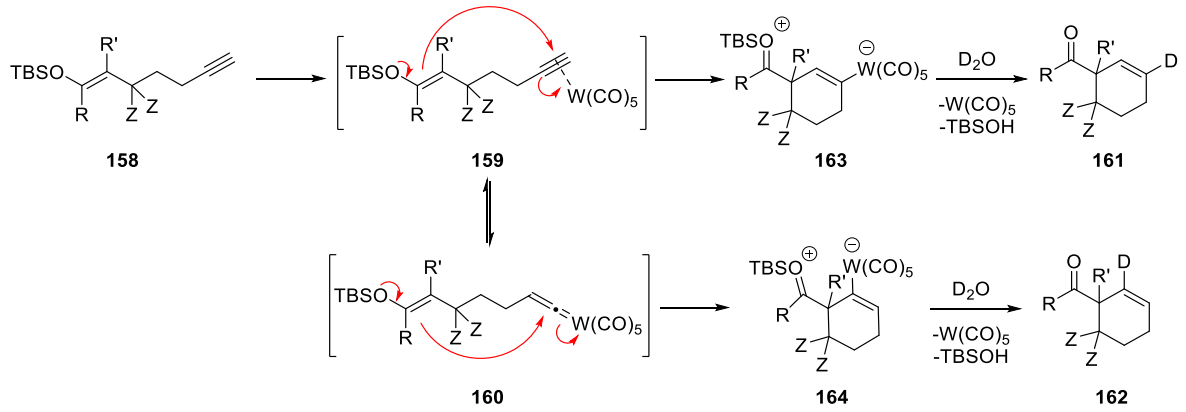
The subsequent example of activation of triple bonds toward C-alkylation of a silyl enol ether was described in 1998 by Iwasawa and his group.[51] Their objective was to exploit the tendency of triple bonds to form vinylidene and/or η^2-complexes with carbonyl adducts of group 6 metals like Cr, Mo or W with general formula $M(CO)_5{\cdot}L$ (where L = THF, Et_3N, etc.). Hence, it was found that TBS-based acetylenic silyl enol ethers like **156** undergo 5- and 6-*endo*-dig cyclization to give cyclohexenes **157** in the presence of stoichiometric or catalytic quantities of $W(CO)_5{\cdot}THF$ and a proton source like water or methanol (Scheme 34). Other metals like Cr and Mo were not effective for this kind of transformation. Finally, whereas internal alkynes were found to be inert, in this case α'-silyl enol ethers were shown to be reactive under these conditions.



Scheme 34

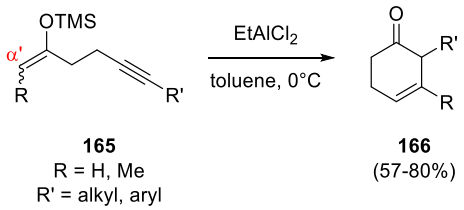
After extensive deuteration studies on simple silyl enol ethers like **158**, the same group proposed that the reaction proceeds through both a η^2-complex **159** and a vinylidene complex **160** (Scheme 35). Replacing one equivalent of water by 10 equivalents of D_2O, a 1:1 mixture of monodeuterated products **161** and **162**, deriving from **163** and **164**, was obtained.

[51] Maeyama, K.; Iwasawa N. *J. Am. Chem. Soc.* **1998**, *120*, 1928-1929.



Scheme 35

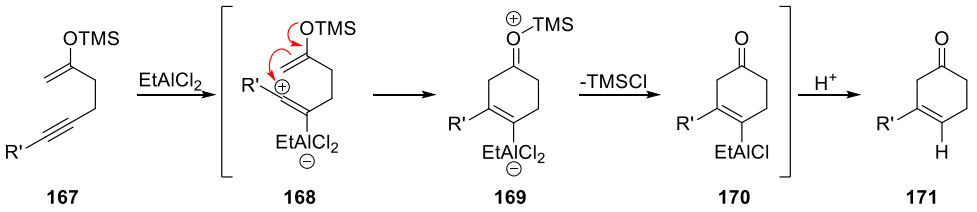
Yamamoto and his group, in 1999, described a similar reaction using an aluminium complex.[52] One year before, the same group reported an *endo*-selective Lewis-acid catalysed intramolecular allylsilylation of internal triple bonds and they decided to apply the same methodology to silyl enol ethers.[53] They found that treatment of alkynyl α-trimethylsilyl or alkynyl α'-trimethylsilyl enol ethers such as **165** with a stoichiometric amount of $EtAlCl_2$ afforded the 6-*endo*-cyclized products **166** in good to excellent yields (Scheme 36). The importance of this methodology relies on the possibility to react even internal alkynes, although a stoichiometric quantity of Lewis acid is still required.



Scheme 36

This reaction proceeds through a different pathway from those seen before. Indeed, the Lewis acid coordinates onto the triple bond of **167** and a vinyl metallate **168** is formed. Attack from the nucleophilic carbon of the silyl enol ether moiety on the newly formed carbocation provides the carbocycle **169** that, after elimination of TMSCl (**170**) and protodemetallation, affords the 6-*endo*-dig cyclized ketone **171** (Scheme 37).

[52] Imamura, K.I.; Yoshikawa E.; Gevorgyan V.; Yamamoto Y. *Tetrahedron Lett.* **1999**, *40*, 4081-4084.
[53] Imamura, K.I.; Yoshikawa E.; Gevorgyan V.; Yamamoto Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339-5340.



Scheme 37

3.2 Gold mediated carbocyclizations of alkynes

The use of gold complexes in homogeneous catalysis is a fascinating story full of unforeseen developments. Although some reports regarding the chlorination of arenes mediated by AuCl or $AuCl_3$ were already published, it is possible to state the discovery of the potential of this kind of catalysts in the last decade of the 20th century. The first application of gold in homogeneous catalysis is usually attributed to the report of Teles in 1998[54] in which the author introduce the activity of phosphine-gold cationic complexes. However, preliminary results regarding the activation of triple bonds using gold were reported by Hayashi in 1986.[55] Since then, homogeneous gold catalysis has seen an exponential growth leading to the development of many synthetic transformations of considerable importance for the building of complex molecular systems. Gold-based catalysts have been utilised to activate alkenes, allenes, alkynes, diazocompounds, nitriles etc.. Herein, we will only discuss the transformations regarding alkynes and their derivatives.

3.2.1 General considerations on Gold and its reactivity

Gold, along with silver and copper, is part of the 11th group in the periodic table and shows the following electronic configuration $4f^{14}5d^{10}6s^{1}$. However, gold possesses characteristics that makes it differ from the other late-transition metals, for example the high red-ox potential and the relative inertness toward elementary organometallic reactions (*i.e.* oxidative insertion, reductive elimination and so on). Although both +1 and +3 oxidation states are catalytically active, Au(I) species have seen a broader utilization making them the most studied forms. Cationic gold(I) complexes, moreover, attracted interest from synthetic chemists all around the world due to their unique reactivity given by a strong Lewis acidity coupled with a great ability to stabilize cationic intermediates. Indeed, the widest application that Au(I) complexes have found is the activation of alkynes toward nucleophilic addition (Figure 13).

[54] Teles, J.H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.
[55] Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.

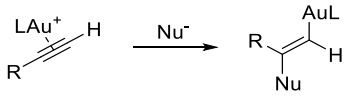


Figure 13

Gold(I) complexes selectively activate π-bonds of alkynes in complex molecular settings, this specificity has been related to relativistic effect. Before taking into account the general alkynyl activation methods reported with the usage of gold complexes, some key-points explaining why the behaviour of gold is so different compared to other metals and why gold is alkynophilic should be briefly explained from a theoretical point of view.

The relativistic effect arises from the confluence of quantum mechanics and special relativity. The term "relativistic effect" refers to any phenomena resulting from the need to consider velocity as significant relative to the speed of light (c), indeed, this is the case of electrons. A primary issue of the special theory of relativity is that mass increases towards infinity as a body's velocity approaches c, which can be mathematically described as $m = m_0/\sqrt{[1-(v/c)^2]}$ where v is the velocity of the body, m is its mass and m_0 is its non-relativistic mass. In the case of atoms, the average radial velocity of a 1s electron $Vr = Z$, where Z is the atomic number and the expression can be calculated as $c = 137$. In this way, the relative mass of electrons can be weighted. The atomic number of gold is 79, and the resolved equation states $m = m_0 / 0.81$ that equals to $m = 1.22\ m_0$. This means that the recalculated relative mass of an electron is 22% heavier than the non-relative. At the same time, it is known that the Bohr radius of orbitals is inversely proportional to the mass of electrons, thus, the orbitals of gold are more contracted. This effect also applies to all other orbitals, not only the $1s^2$, putting the electrons closer to the nucleus and consequently enhancing the ionization potential.[56] The effects of this contraction are various, one of the most pronounced is that 6s orbital results in a greatly strengthened Au-L bonds, where L is a ligand.[57] Moreover, the relativistic contraction is responsible for the superior Lewis acidity of cationic Au(I) complexes compared with other metals of the 11th group. The contraction makes the valence s and p orbitals correspond to a lower "lowest unoccupied molecular orbital" (LUMO) and therefore a strong Lewis acidity is resulting.

The last key-point that needs to be elucidated is the superior reactivity of Au-alkyne towards nucleophilic addition. Studies on Au^+-ethylene and Au^+-ethyne bonding indicate a ≈10 kcal

[56] Gorin, J.D.; Toste, F.D. *Nature* **2007**, *446*, 395-403.
[57] Desclaux, J.P.; Pyykko, P. *Chem. Phys. Lett.* **1976**, *39*, 300–303.

mol^{-1} greater stabilization for the ethylene complex over the ethyne complex.[58] Since Au(I) apparently does not complex selectively alkynes over other π-systems, the observed reactivity may be due to discrimination by the nucleophile in selecting between Au(I)-activated electrophiles.

3.2.2 Synthesis using gold catalysts: a broad overview

Despite the fact that simple gold salts such as $NaAuCl_4$ or AuCl are active enough to catalyze numerous transformations, linear two-coordinate 14-electrons gold(I) complexes bearing phosphines or *N*-heterocyclic carbenes as ligands have found more wide-ranging applications. The active species are often generated *in situ* by chloride abstraction from [LAuCl] upon treatment with a silver salt bearing a weakly coordinating anion. Complexes [LAuY] only exist as neutral species when Y^- is a coordinating anion (halides, carboxylates, sulfonates, and triflimides). The corresponding complexes with less coordinating anions, such as SbF_6^-, PF_6^-, or BF_4^-, are in most cases not stable. In this document it is implied that all the catalysts written as [LAuY] (PPh_3AuSbF_6 for example) are synthesized mixing phosphine gold(I)chloride (PPh_3AuCl) and the silver salt ($AgSbF_6$) unless when specified. Although $[AuL]^+$ species are often suggested in mechanistic proposals, structural proof for their existence as stable, isolable species is still lacking. The properties of gold(I) complexes can be easily tuned sterically or electronically depending on the ligand, consequently modulating their reactivity towards the activation of alkynes, alkenes, and allenes. Thus, complexes containing more donating N-heterocyclic carbenes **172** are less electrophilic than those bearing phosphine ligands **173** (Figure 14). Complexes with less donating phosphite ligands **174** and related species are the most electrophilic catalysts.[59]

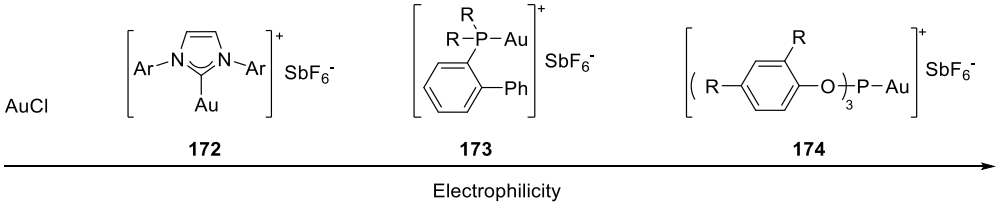


Figure 14

[58] (a) Hertwig, R.H.; Koch, W.; Schröder, D.; Schwarz, H.; Hrušák, J.; Schwerdtfeger, P. *J. Phys. Chem.* **1996**, *100*, 12253-12260. (b) Nechaev, M.S.; Rayon, V.M.; Frenking, G. *J. Phys. Chem. A* **2004**, *108*, 3134-3142.
[59] Dorel, R.; Echavarren, A.M. *Chem. Rev.* **2015**, *115*, 9028-9072.

In chemical synthesis, gold(I) complexes have been utilised to majorly perform four classes of transformation:

1. hydroarylation and hydroheteroarylation of alkynes,
2. reactions implying propargylic carboxylates,
3. addition of heteronucleophiles to alkynes,
4. and the most important, reactions involving alkenes with alkynes

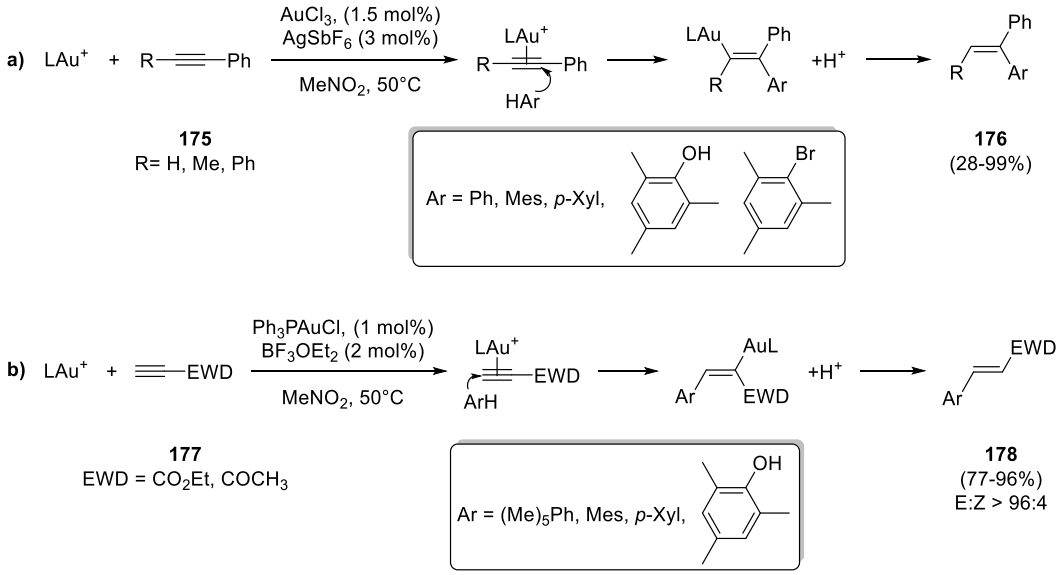
3.2.3 Hydroarylation and hydroheteroarylation of alkynes

The direct auration of electron-rich arenes and heteroarenes by gold(I) and gold(III) is a well-known process, but the resulting aryl-gold complexes are apparently not involved in subsequent C–C bond forming reactions with alkynes.[60] Indeed, aryl-gold(I) complexes only react with alkynes combined to a palladium(0) catalyst, or a palladium(II) precatalyst.[61] In the presence of triple bonds, electrophilic metal catalysts form, upon coordination to an alkyne, electrophilic complexes that undergo electrophilic aromatic substitution reactions with arenes. Gold(I) and gold(III)-complexes generally promote reactions according to this pathway. In the case of intermolecular hydroarylation, Sommer and Reetz demonstrated that terminal or internal aryl-substituted alkynes **175** provide 1,1-disubstituted alkenes **176** when treated with $AuCl_3$ and $AgSbF_6$ (Scheme 38a). It was additionally found that terminal electron poor alkynes **177** undergo hydroarylation affording 1,2-disubstituted alkenes **178** in the presence of Au(I)-complexes, although internal electron-poor alkynes revealed to be unreactive (Scheme 38b).[62] Usually, in this kind of reaction, gold catalysis provides better yields and milder reaction conditions compared to other metals. Finally, it is possible to control the regioselectivity of the formed double bond but not the substituting position of the arene counterpart.

[60] (a) Kharasch, M.S.; Isbell, H.S. *J. Am. Chem. Soc.* **1931**, *53*, 3053-3059. (b) Fuchita, Y.; Ieda, H.; Yasutake, M. *J. Chem. Soc. Dalton Trans.* **2000**, 271-274. (c) Porter, K.A.; Schier, A.; Schmidbaur, H. *Organometallics* **2003**, *22*, 4922-4927.

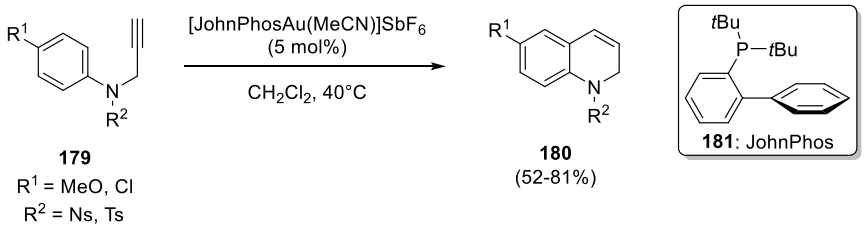
[61] Shi, Y.; Ramgren, S.D.; Blum, S.A. *Organometallics* **2009**, *28*, 1275-1277.

[62] (a) Nevado, C.; Echavarren, A.M. *Synthesis* **2005**, 167-182. (b) Yamamoto, Y.; Gridnev, I.D.; Patil, N.T.; Jin, T. *Chem. Commun.* **2009**, 5075-5084. (c) de Mendoza, P.; Echavarren, A.M. *Pure Appl. Chem.* **2010**, *82*, 801-820. (d) Reetz, M.T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485-3496.



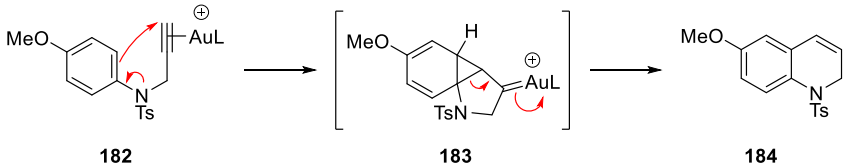
Scheme 38

A wider applicability is attributed to intramolecular hydroarylations, as the problems of selectivity of the nucleophilic arylic position can be avoided by various methods. In this area, *N*-propargyl-*N*-sulfonylaniline **179** undergoes intramolecular hydroarylation in the presence of 5% of [JohnPhosAu(MeCN)]SbF_6 (**181**) affording dihydroquinoline derivative **180** (Scheme 39). [63]



Scheme 39

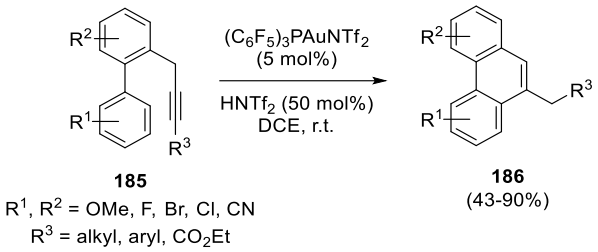
In this reaction, the mechanism has been elucidated and, starting from anisole derivative **182**, it foresees the nucleophilic attack of an aromatic carbon onto the Au(I)-alkyne adduct to form the cyclopropyl carbene **183** (Scheme 40). The latter subsequently rearranges and, after protodeauration, bicyclic compound derived from a 6-*endo*-dig cyclization **184** is provided.



Scheme 40

[63] (a) Martín-Matute, B.; Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc*. **2003**, *125*, 5757-5766. (b) Menon, R.S.; Findlay, A.D.; Bissember, A.C.; Banwell, M.G. *J. Org. Chem.* **2009**, *74*, 8901-8903.

Generally, cyclizations which follow the 5-*exo* and 6-*endo* pathway are common, 6-*exo* transformations, instead, are less frequent. An interesting example of 6-*exo*-dig cyclization consists in the use of Au(I) catalysis for hydroarylation of *o*-propargylbiphenyls to afford phenanthrenes (Scheme 41).[64] Indeed, diphenyl derivatives like **185** cyclize in the presence of a catalytic quantity of $(C_6F_5)_3PAuNTf_2$ and a half equivalent of bistriflimide ($HNTf_2$) to give phenanthrene **186**.

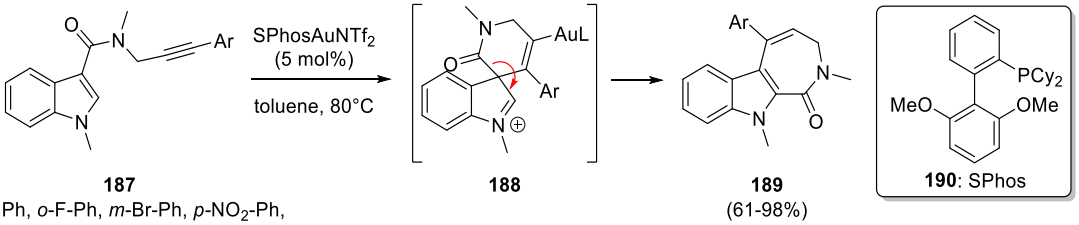


185
R^1, R^2 = OMe, F, Br, Cl, CN
R^3 = alkyl, aryl, CO_2Et

186
(43-90%)

Scheme 41

Pyrroles and indoles, as well, undergo Au(I)-catalysed hydroarylation with alkynes. An interesting example is the recently reported synthesis of dihydroindoloazepinones from indole-3-carboxamides (Scheme 42).[65] *N*-propargylindoles **187** undergo 6-*endo*-dig cyclization in the presence of $SPhosAuNTf_2$ to provide spiro-intermediates **188**, which instead of passing through a cyclopropyl carbene, rearrange to form azepinone derivatives **189**.



187
Ar = Ph, *o*-F-Ph, *m*-Br-Ph, *p*-NO_2-Ph, *p*-OMe-Ph, *p*-tol, *m*-CO_2Me-Ph, thiophene,

188

189
(61-98%)

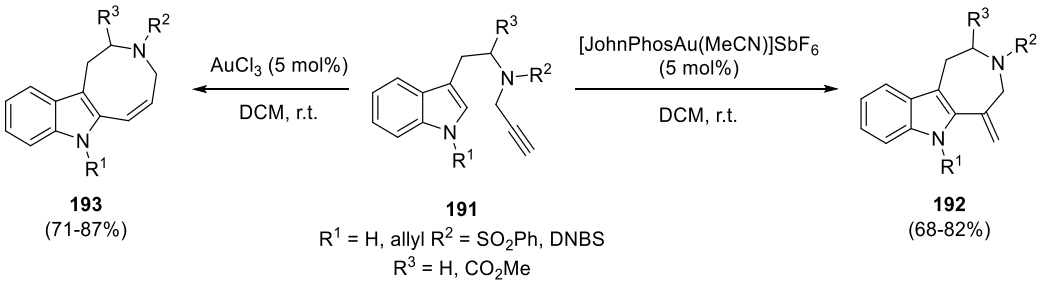
190: SPhos

Scheme 42

The synthesis of medium size rings is usually challenging. In this field, the synthesis of 8-membered rings through a 8-*endo*-dig hydroarylative cyclization has never been observed prior to 2006. The first example has been reported by Echavarren and his group, who developed a method for the synthesis of 7- and 8-membered indole condensed rings exploiting Au(III) and Au(I)-complexes. *N*-propargyl tryptophans or *N*-propargyl tryptamines **191**, undergo 7-*exo*-dig cyclization affording **192** if exposed to cationic Au(I)-complex

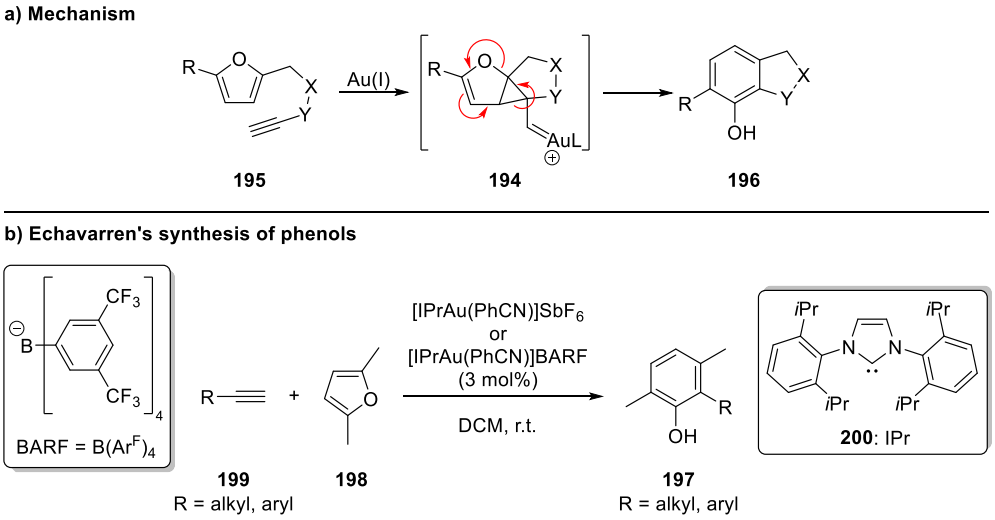
[64] Shu, C.; Li, L.; Chen, C.B.; Shen, H.C.; Ye, L.W. *Chem. Asian J.* **2014**, *9*, 1525-1529.
[65] Hashmi, A.S.K.; Yang, W.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 1273-1279.

[JohnPhosAu(MeCN)]SbF_6 (Scheme 43). Otherwise, when more electrophilic $AuCl_3$ is used, 8-*endo*-dig pathway is preferred and tricyclic compounds **193** are obtained.[66]



Scheme 43

In the case of furans, the mechanism is slightly different (Scheme 44a): once the cyclopropyl carbene **194** is formed using Au(I) or Au(III) from general furane **195**, it usually rearranges to give phenols **196**. This mechanism has been validated for the intra- and intermolecular furane hydroarylation of alkynes. Indeed, the synthesis of phenols **197** starting from 2,5-dimethylfuran **198** and alkynes **199** using gold(I) complexes bearing NHC ligands such as IPr **200** reported by Echavarren is a representative example of this chemistry (Scheme 44b).[67]

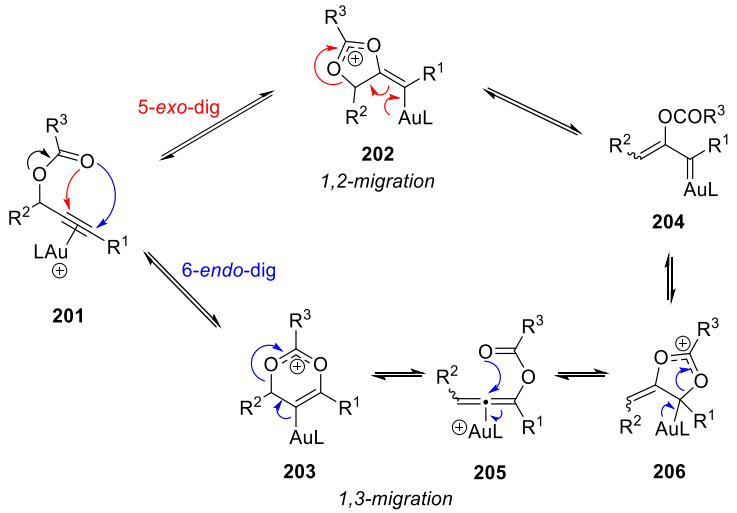


Scheme 44

[66] Ferrer, C.; Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105-1109.
[67] (a) Hashmi, A.S.K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.-Eur. J.* **2010**, *16*, 9846-9854. (b) Hashmi, A.S.K.; Weyrauch, J.P.; Rudolph, M.; Kurpejović, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6545-6547. (c) Hashmi, A.S.K.; Rudolph, M.; Weyrauch, J.P.; Wölfle, M.; Frey, W.; Bats, J.W. *Angew. Chem., Int. Ed.* **2005**, *44*, 2798-2801.

3.2.4 Reaction of propargylic carboxylates

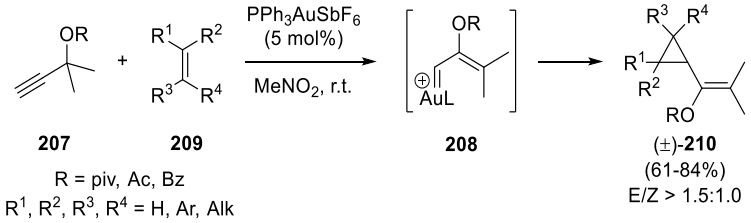
Propargylic carboxylates such as **201** are interesting scaffolds in organic synthesis as they undergo 5-*exo*-dig or 6-*endo*-dig cyclization affording intermediates **202** and **203**. Intermediate **202** is subjected to 1,2-acyloxy migration affording carbene **204**. On the other hand, 1,3-acyloxy migration delivers allene **205** from intermediate **203**. Notably, allene **205** and carbene **204** are in equilibrium through another 1,2-acyloxy migrative intermediate **206** (Scheme 45).[68] Carbene **204**, however, was reacted with alkenes, ynamides, carbon nucleophiles, imines and sulphides.[69]



Scheme 45

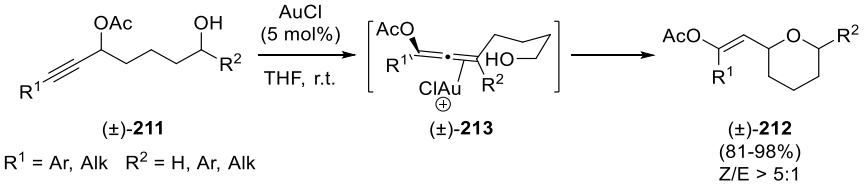
In 2005, Toste and his group reported the cyclopropanation of propargylic esters in the presence of gold(I).[70] Various propargylic esters **207** were transformed into the corresponding carbene **208**, which directly undergoes cyclopropanation onto the alkene **209** to afford the cyclopropane (±)-**210** (Scheme 46)**.** In the same paper, employing chiral phosphines, an asymmetric version of this reaction was also proposed.

[68] Xi, Y.; Wang, Q.; Su, Y.; Li, M.; Shi, X. *Chem. Commun.* **2014**, *50*, 2158-2160.
[69] (a) Rettenmeier, E.; Schuster, A.M.; Rudolph, M.; Rominger, F.; Gade, C.A.; Hashmi, A.S.K. *Angew. Chem., Int. Ed.* **2013**, *52*, 5880-5884. (b) Amijs, C.H.M.; López-Carrillo, V.; Echavarren, A.M. *Org. Lett.* **2007**, *9*, 4021-4024. (c) Iqbal, N.; Fiksdahl, A. *J. Org. Chem.* **2013**, *78*, 7885-7895. (d) Davies, P.W.; Albrecht, S.J.-C. *Chem. Commun.* **2008**, 238-240. (e) Davies, P.W.; Albrecht, S.J.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8372-8375. (f) Davies, P.; Albrecht, S. *Synlett* **2012**, 70-73.
[70] Johansson, M.J.; Gorin, D.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.



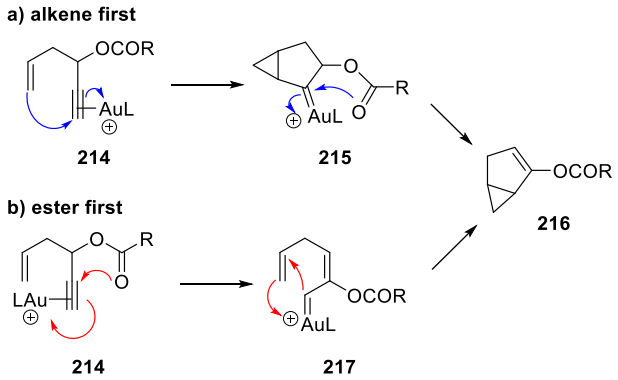
Scheme 46

Propargylic esters can react even through their allenic form. Indeed, in 2008, De Brabander reported a cycloetherification of ω-hydroxy propargylic acetates (Scheme 47).[71] Exposing (±)-**211** to AuCl delivered the tetrahydropyran derivative (±)-**212** throughout the allenic intermediate (±)-**213**. Notably, this method is limited to internal alkynes.



Scheme 47

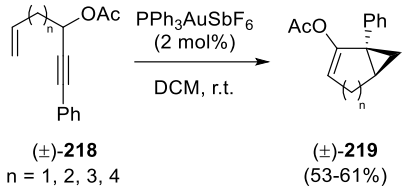
In the presence of gold(I), enynes bearing propargylic carboxylates such as **214** can react in two parallel ways (Scheme 17). Depending upon the order of reaction of the different moieties, *i.e.*, the reaction of the ester or the alkene function onto the alkyne. This transformation is well known as the Ohloff-Rautenstraucht rearrangement. [72] when the alkene reacts first the propargylic ester **214** undergoes cyclopropanation giving the intermediate **215**, which after 1,2-acyloxy migration delivers the allylic cyclopropane **216** (Scheme 48a). On the contrary, when the ester reacts first the allylic carbene **217** is provided and subsequent cyclopropanation affords **216** (Scheme 48b).



Scheme 48

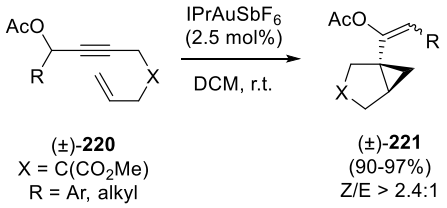
[71] De Brabander, J.K.; Liu, B.; Qian, M. *Org. Lett.* **2008**, *10*, 2533-2536.
[72] (a) Strickler, H.; Davis, J.B.; Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1328-1332. (b) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950-952.

1,5-Enynes bearing propargylic acetates undergo this transformation through ester function first.[73] 1,6-, 1,7- and 1,8-enynes such as (±)-**218** behave similarly to afford analogous products, allowing the synthesis of 6-, 7- and 8-membered ring (±)-**219** (Scheme 49).[74]



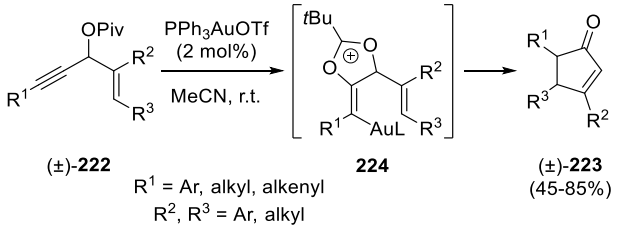
Scheme 49

1,6-Enynes such as (±)-**220**, instead, proceed through an "alkene first" pathway and deliver the exocyclic enol ether (±)-**221** (Scheme 50).[75]



Scheme 50

In the case of 1,4-enynes bearing propargylic carboxylates (±)-**222** (Scheme 51), the delivered products are simple cyclopentenones (±)-**223** as a pericyclic transformation on the intermediate **224** takes place instead of the cyclopropanation step.[76]



Scheme 51

3.2.5 Addition of heteronucleophiles to alkynes

As previously mentionned, the first example of gold-complex catalysed addition of a nucleophile into an alkyne was reported by Teles in 1998, aiming to the addition of alcohols

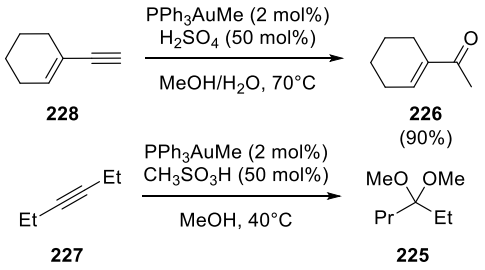
[73] (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655. (b) Marion, N.; de Frémont, P.; Lemière, G.; Stevens, E.D.; Fensterbank, L.; Malacria, M.; Nolan, S.P. *Chem. Commun.* **2006**, 2048-2050.

[74] Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; López-Romero, J.M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43-48.

[75] Gung, B.W.; Bailey, L.N.; Craft, D.T.; Barnes, C.L.;Kirschbaum, K. *Organometallics* **2010**, *29*, 3450-3456.

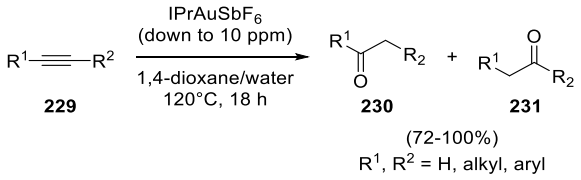
[76] (a) Shi, X.; Gorin, D.J.; Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 5802-5803. (b) Nieto Faza, O.; Silva López, C.; Álvarez, R.; de Lera, A. *J. Am. Chem. Soc.* **2006**, *128*, 2434-2437.

and water onto a triple bond following the Markovnikov rule.[7] They employed the air stable [AuMe(L)] (L = phosphine, phosphite or arsine) activated *in situ* by protic acids to form acetals such as **225** or ketones **226** starting from simple alkynes, respectively **227** and **228** (Scheme 52).



Scheme 52

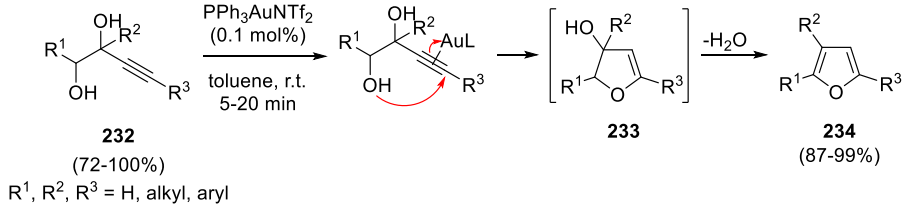
Despite its efficiency, this method suffered from various drawbacks like the use of stoichiometric quantities of protic acids. Over the years, significant improvements have been accomplished: one good witness of this evolution was reported by Nolan and his group in 2009.[77] They employed *N*-heterocyclic carbenes (NHC) as ligands for gold(I) in order to accomplish the hydration of terminal or internal alkynes **229** in acid free conditions with a catalyst loading lowered down to 10 ppm (Scheme 53). The main drawback consists in the lack of regioselectivity, leading to a mixture of two compounds **230** and **231**.



Scheme 53

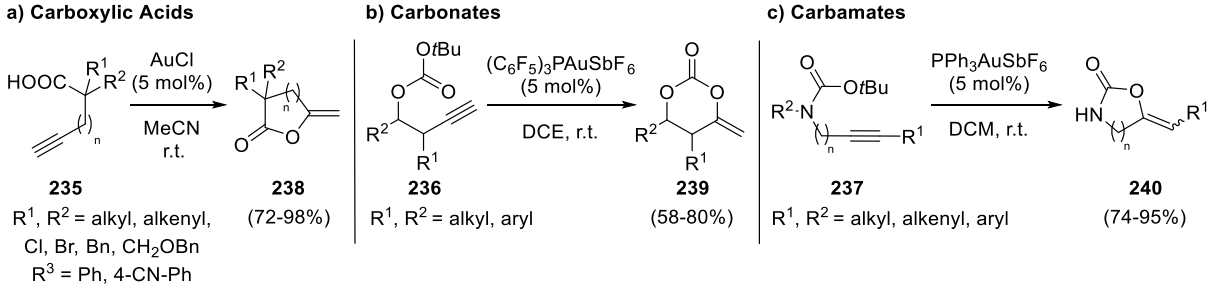
The activity of gold complexes has been widely employed for intra- and intermolecular C-O bond formation. The most studied transformations exploiting this kind of reactivity are the reactions aiming to the synthesis of *O*-containing heterocycles. For example, alkynediols **232** (Scheme 54) undergo 5-*endo*-dig cyclization to form the dihydro-3-furanol intermediates **233** which in turn, provide the furane derivatives **234** after dehydration.[78]

[77] Marion, N.; Ramón, R.S.; Nolan, S.P. *J. Am. Chem. Soc*. **2009**, *131*, 448-449.
[78] (a) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624-4627. (b) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002-5005.



Scheme 54

These transformations also take place in the case of propargylic epoxides (by ring opening)[79] or propargylic ketones and in both cases a furane is generally delivered.[80] Carboxylic acids **235** (Scheme 55a), carbonates **236** (Scheme 55b) and carbamates **237** (Scheme 55c) react with alkynes in the presence of Au(I) to give respectively lactones **238**, cyclic carbonates **239** and cyclic carbamates **240**.[81]



Scheme 55

Nowadays, a great number of tandem sequences have been developed starting from these simple nucleophilic addition reactions onto a triple bond. In this report they will not be treated as not directly related to the synthesis of vibsatins A and B.

Amines are capable to add onto a triple bond. The first to discover the hydroamination reactivity of amines was Nozaki in 1987 using Au(III),[82] but, it was much more recently (2003) that Hayashi and Tanaka developed the first Au(I)-catalysed intermolecular amination of alkynes **241** using anilines to form imines **242** and **243** in a 1:1 mixture (Scheme 56).[83]

---

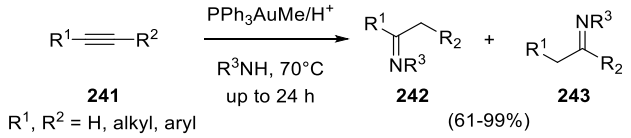
[79] (a) Dai, L.-Z.; Shi, M. *Tetrahedron Lett.* **2008**, *49*, 6437-6439. (b) Blanc, A.; Alix, A.; Weibel, J.-M.; Pale, P. *Eur. J. Org. Chem.* **2010**, 1644-1647. (c) Blanc, A.; Tenbrink, K.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342-5348.

[80] (a) Oh, C.H.; Lee, S.J.; Lee, J.H.; Na, Y.J. *Chem. Commun.* **2008**, 5794-5796. (b) Belting, V.; Krause, N. *Org. Biomol. Chem.* **2009**, *7*, 1221-1225. (c) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814-1815. (d) Gao, H.; Zhao, X.; Yu, Y.; Zhang, J. *Chem. - Eur. J.* **2010**, *16*, 456-459.

[81] Genin, E.; Toullec, P.Y.; Antoniotti, S.; Branour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112-3113. (b) Yang, T.; Campbell, L.; Dixon, D.J. *J. Am. Chem. Soc.* **2007**, *129*, 12070-12071. (c) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515-518. (d) Oppedisano, A.; Prandi, C.; Venturello, P.; Deagostino, A.; Goti, G.; Scarpi, D.; Occhiato, E.G. *J. Org. Chem.* **2013**, *78*, 11007-11016. (e) Kang, J.-E.; Shin, S. *Synlett*. **2006**, 717-720. (f) Buzas, A.; Gagosz, F. *Synlett.* **2006**, 2727-2730.

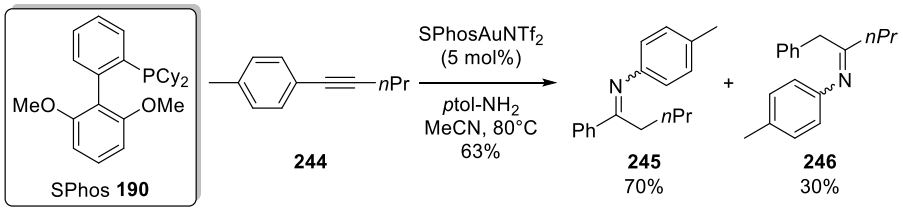
[82] Fukuda, Y.; Utimoto, K.; Nozaki, H. *Heterocycles* **1987**, *25*, 297-300.

[83] Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349-3352.



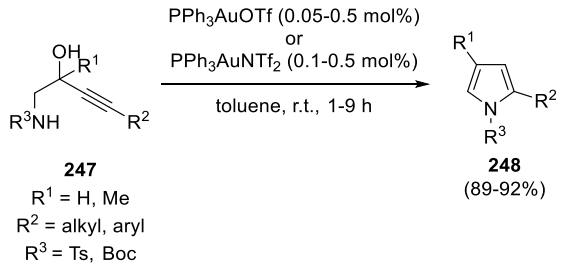
Scheme 56

A nice example of this chemistry appeared in 2009 from the hands of Corma and Leyva.[84] They exploited the reactivity of a Au(I)-based catalyst made from a low coordinating (trifluoromethane)imidate counteranion (-NTf_2) and a dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (SPhos **190**) as ligand in order to carry out this reaction. The resulting complex is active under mild conditions and displays a regioselectivity based on electronic rather than steric factors leading to a higher preference for one of the two isomers. In Scheme 23, for instance, dissymmetric alkyne **244** (Scheme 57) undergoes hydroamination under these conditions affording the two imines **245** and **246** in a 70:30 *ratio* respectively.



Scheme 57

The intramolecular version possesses a wider applicability as it permits to synthesize 5 and 6-membered nitrogen-containing heterocyclic rings. In this area, an efficient method for the synthesis of pyrroles was reported by Akai in 2009.[85] General amino-3-alkyn-2-ols **247** (Scheme 58) undergo 5-*endo*-dig cyclization followed by dehydration providing the pyrrole derivatives **248**. Good results were obtained using PPh_3AuOTf and also with PPh_3AuNTf_2.

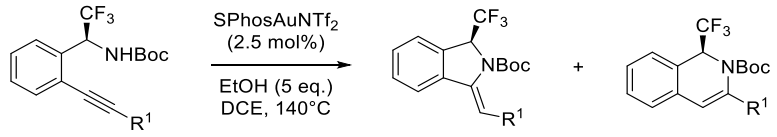


Scheme 58

The electronic properties of the alkyne substituents play a crucial role in the control of regioselectivity. Indeed, electron-donating substituents tend to favor 6-*endo*-dig cyclization

[84] Leyva, A.; Corma, A. *Adv. Synth. Catal.* **2009**, *351*, 2876-2886.
[85] (a) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E.F. *Org. Lett.* **2009**, *11*, 4624-4627. (b) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002-5005. (c) Iqbal, A.; Sahraoui, E.H.; Leeper, F.J. *Beilstein J. Org. Chem.* **2014**, *10*, 2580-2585.

pathway, whereas electron-withdrawing substituents favour the 5-*exo*-dig cyclization. An example of the electronic effects on the regioselectivity was reported by Catalan in 2013 aiming the cyclization of *o*-alkynylbenzyl carbamates.[86] It was found that modifying the alkynyl substituent of **249** inverted the regiochemistry of the cyclization (Scheme 59). **250** arised from a 5-*exo*-dig cyclization in the presence of an electron donor substituent on the alkyne. On the contrary, as the substituent possesses an electron withdrawal character, product **251** generated through a 6-*endo*-dig cyclization was delivered. However, steric factors must still be taken into account when predicting the regiochemical outcome of such kind of cyclization as these factors provide an explanation on the selectivities reached in the two extreme cases. Hence, anisole-substituted alkyne provides only 3:1 *ratio* in favour of the 6-*endo*-dig cyclized product, whereas the formation of the 5-*exo*-dig derived product is sterically favoured and the *ratio* turns to > 30:1.



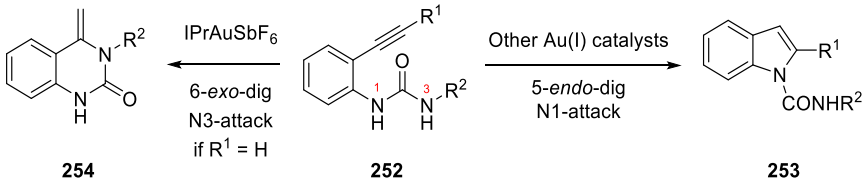
249 **250** **251**

R^1	5-*exo* -dig **250**	6-*endo* -dig **251**
4-$MeOC_6H_4$	1	3
3-$CF_3C_6H_4$	>30	1

Scheme 59

Cyclic alkynylureas are also suitable substrates for intramolecular hydroamination catalysed by gold(I). Whereas acyclic ureas follow a *O*-alkylation pathway, cyclic ureas selectively react following *N*-alkylation mode. An elegant example was reported by Cuenca and his group in 2009. In this paper, 3-substituted 1-(*o*-alkynylphenyl)ureas **252** (Scheme 60) was reacted with various gold(I) complex.[87] Generally, if gold(I)-based catalysts are used, ureas bearing an internal alkyne follow the 5-*endo*-dig pathway in which nitrogen N1 behave as the nucleophile and indolic derivative **253** is afforded. The regiochemistry can be inverted by tuning the employed gold(I) complex. Hence, it was found that NHC-based catalyst IPrAuSbF$_6$ favoured the N3-attack of the urea onto terminal alkynes leading to a 6-*exo*-dig cyclization. Under these conditions, quinazoline derivative **254** is delivered.

[86] Fustero, S.; Ibáñez, I.; Barrio, P.; Maestro, M.A.; Catalán, S. *Org. Lett.* **2013**, *15*, 832-835.
[87] Gimeno, A.; Medio-Simon, M.; Ramirez de Arellano, C.; Asensio, G.; Cuenca, A.B. *Org. Lett.* **2010**, *12*, 1900-1903.



Scheme 60

Noteworthy, other nucleophiles are able to insert onto triple bonds in the presence of Au(I) or Au(III), this is the case of thiols, thioethers or boronates, but these topics will not be described in this manuscript.

3.2.6 Reactions of alkene with alkynes

Cycloisomerization of [1,*n*]-enynes is probably one of the most studied reaction of the first decade of the 21th century. This transformation showed to be extremely powerful for the elaboration of complex molecular architectures from simple starting materials. The first examples of electrophilic activation of enynes were reported using Pd(II) and Pt(II)[88] and only several years later, in the mid 2000's, the potential of Au(I) catalysed cycloisomerization of enynes was discovered.[89]

From a mechanistic point of view, a particular focus has been undoubtedly put on the cycloisomerizations of 1,6-enynes. Generally, gold(I) complexes are assumed to form a η^2-alkyne-complex on the triple bond like **255** (Scheme 61). The Au(I)-alkyne complex then reacts with the double bond through a 5-*exo*-dig or a 6-*endo*-dig pathway to form the corresponding carbene **256** or **257**. If internal or external nucleophiles are not present in the reaction mixture, the latter carbenes rearrange in different ways affording various complex molecular architectures. These systems exhibit a high delocalization degree, which means that their structures are intermediates between cyclopropyl gold(I) carbenes and gold(I)-stabilized carbocations (Figure 15).

[88] (a) Trost, B.M. *Acc. Chem. Res.* **1990**, *23*, 34-42. (b) Trost, B.M.; Doherty, G.A. *J. Am. Chem. Soc.* **2000**, *122*, 3801-3810. (c) Méndez, M.; Muñoz, M.P.; Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520.

[89] (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M.P.; Cárdenas, D.J.; Buñuel, E.; Nevado, C.; Echavarren, A.M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146-6148. (b) Soriano, E.; Marco-Contelles, J. *Acc. Chem. Res.* **2009**, *42*, 1026-1036.

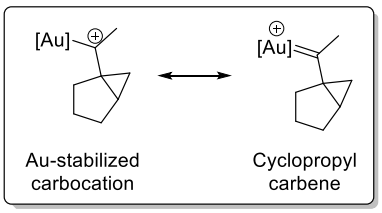


Figure 15

The mechanism of these transformations has been extensively studied *via* DFT. Kinetically 5-*exo*-dig cyclization is frequently favoured, but the discrimination between 5-*exo*-dig or 6-*endo*-dig pathway is usually related to the substituents on the two unsaturations. Indeed, according to DFT, once the cyclopropyl carbene **256** derived from a 5-*exo*-dig cyclization is formed, it can undergo three different rearrangements. The first foresees the cleavage of a single bond of the cyclopropane concomitantly with the 1,3-migration of the terminal carbon of the alkene into the carbenic carbon. After the elimination of the catalyst, a β-diene **258** is formed (Scheme 61, pathway c). An alternative *endo*-type single cleavage rearrangement provides the 6-membered ring diene **259** (Scheme 61, pathway b). The last transformation that carbene **256** can undergo, only occurs when the terminal position of the original double bond is not fully substituted (R^4=H). In this rearrangement, a formal migration of the terminal carbon of the original double bond onto the carbenic carbon followed by a cleavage of the ex-acetylenic σ-bond provides the gold(I)-carbene **260**. A 1,2-hydride shift on the latter affords then the β-diene **261** (Scheme 61, pathway a).[90]

On the other hand, the carbene deriving from the 6-*endo*-dig cyclization **257** can provide the bicyclic structure **262** through a 1,2-hydride shift (Scheme 61, pathway d). Alternatively, it can rearrange through a single cleavage of the cyclopropyl ring delivering the condensed cyclobutenic intermediate **263** (Scheme 61, pathway e). Moreover, if the terminal position of the original double bond is not fully substituted, **263** can undergo isomerization to give the cyclobutene derivative **264** (Scheme 61, pathway g). Finally, if an additional substituent is present, intermediate **263** rearranges and delivers diene **258** (Scheme 61, pathway f). [91]

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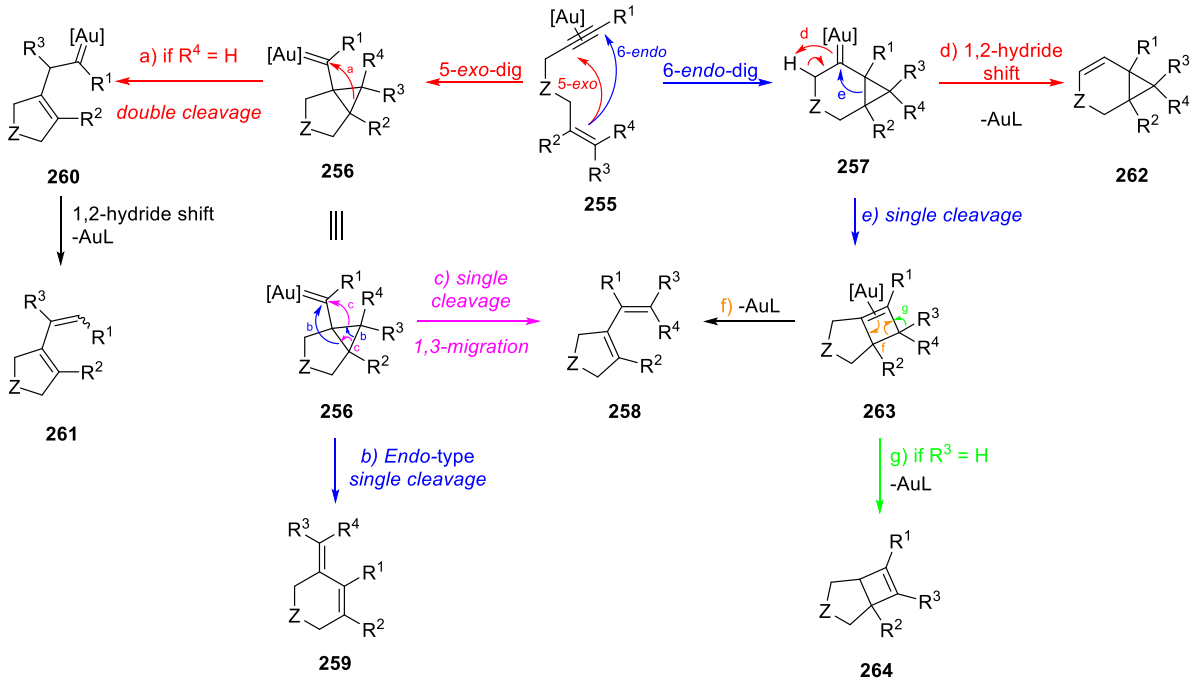
[90] (a) Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A.A.C.; Maseras, F.; Echavarren, A.M. *Org. Biomol. Chem.* **2012**, *10*, 6105-6111. (b) Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D.J.; Echavarren, A.M. *Eur. J. Org. Chem.* **2007**, 4217-4223.

[91] (a) Nieto-Oberhuber, C.; Muñoz, M.P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A.M. *Chem. - Eur. J.* **2006**, *12*, 1677-1693. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M.P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D.J.; Echavarren, A.M. *Chem. - Eur. J.* **2006**, *12*, 1694-1702. (c) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279. (d) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A.M. *Chem. - Eur. J.* **2006**, *12*, 5916-5923. (e) Lee, S.I.; Kim, S.M.; Choi, M.R.; Kim, S.Y.; Chung, Y.K. *J. Org. Chem.* **2006**, *71*, 9366-9372. (f) Ma, S.; Yu,



Scheme 61

1,6-Enynes react through one of these six pathways, the preference toward one or another route is highly influenced by the substitution pattern. Enyne **265** (Scheme 62a) bearing terminal alkyne and terminal alkene follows a single cleavage rearrangement to give diene **266** in which the *exo* double bond shows *E*-stereoconfiguration.[42] In most cases, these rearrangements are stereospecific and the original configuration of the alkene is retained. On the contrary, 1,6-enynes bearing an electron-donating group on the alkene such as **268** usually afford *Z*-1,3-dienes **267** (Scheme 62b).[92] Enynes featuring an internal alkynes **269** prefer a double cleavage pathway leading to 1,3-dienes **266** (Scheme 62c).[42,43] 1,6-Enynes bearing an heteroatom tend to undergo *endo*-type single cleavage rearrangement. Thus, from tosyl amine **270**, a mixture of **271** and **272** is obtained in 10:1 *ratio* in favour of **271** (Scheme 62d).[42,43] The formation of the 6-membered ring **271** is favoured with respect to the formation of single cleavage product **272**, but it is usually possible to invert the selectivity toward one of the two products by modifying steric and electronic character of the catalyst. However, the tendency of tosyl amines to deliver 6-membered rather than 5-membered rings is underlined in the cyclization of **273** (Scheme 62e).[93] The product (±)-**274,** resulting of a 6-*endo*-dig

S.; Gu, Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 200-203 (g) Lopez-Carrillo, V.; Echavarren, A.M. *J. Am. Chem. Soc.* **2010**, *132*, 9292-9294.

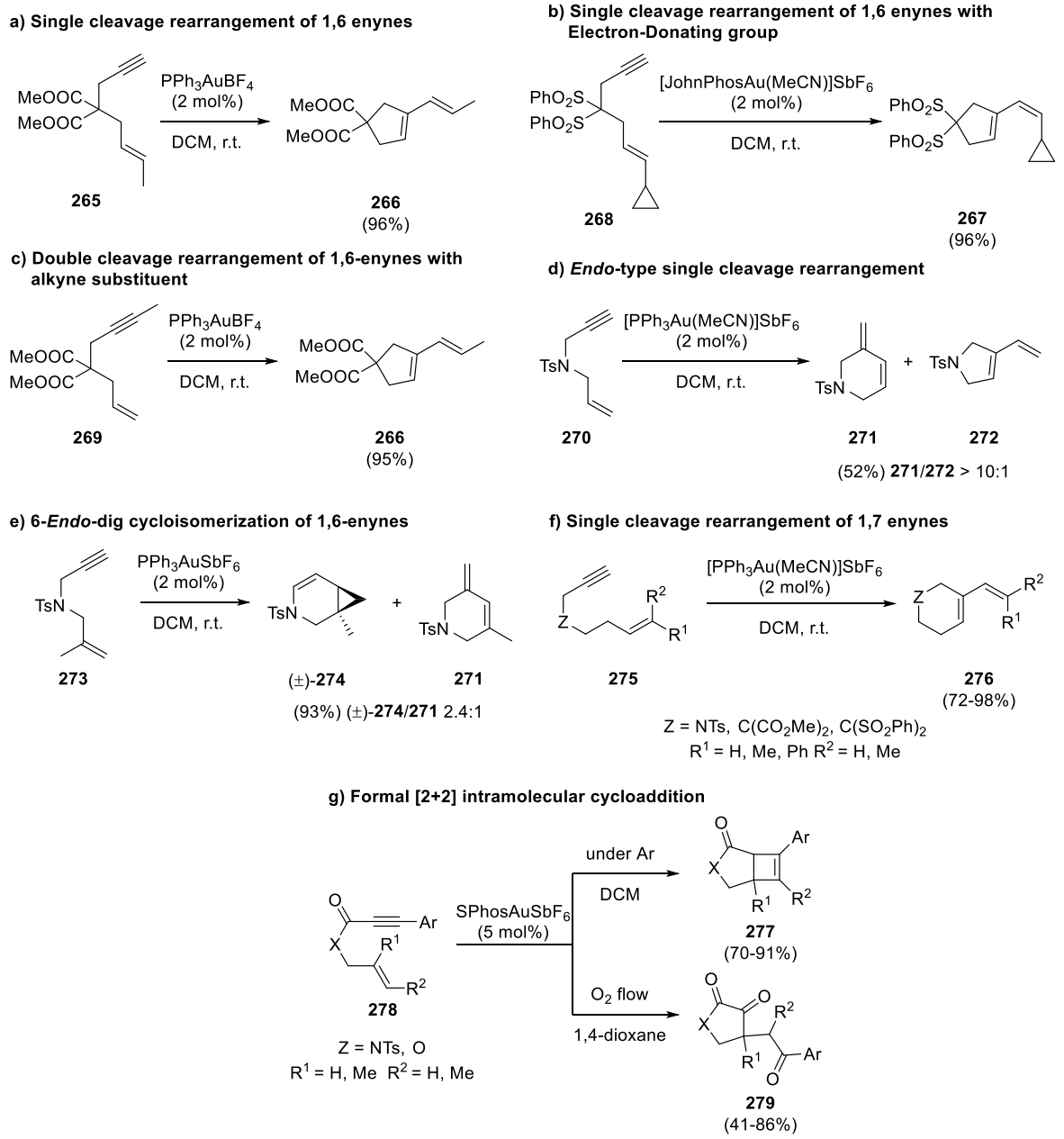
[92] Jiménez-Núñez, E.; Claverie, C.K.; Bour, C.; Cárdenas, D.J.; Echavarren, A.M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7892-7895.

[93] (a) Harrak, Y.; Simonneau, A.; Malacria, M.; Gandon, V.; Fensterbank, L. *Chem. Commun.* **2010**, *46*, 865-867. (b) Fourmy, K.; Mallet-Ladeira, S.; Dechy-Cabaret, O.; Gouygou, M. *Organometallics* **2013**, *32*, 1571-1574. (c) Dubarle-Offner, J.; Barbazanges, M.; Augé, M.; Desmarets, C.; Moussa, J.; Axet, M.R.; Ollivier, C.;

cyclization is favoured with respect to **271,** derived from an *endo*-type cleavage. 1,7-Enynes such as **275** have been much less studied. However, it has been shown that gold(I) complexes catalyse the 6-*endo*-dig single cleavage rearrangement providing 1,3-dienes **276** (Scheme 62f).[43] In 2013, Chung and his group reported the synthesis of bicyclo[3.2.0]hept-6-enes **277** from amides or esters **278** exploiting gold(I) catalysis (Scheme 62g). This reaction can be described as a formal [2+2] intramolecular cycloaddition between the alkene and the alkyne. Notably, in the presence of oxygen tricarbonyl compounds **279** are formed.[94]

Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M.; Gontard, G.; Amouri, H. *Organometallics* **2013**, *32*, 1665-1673. (d) Zhang, D.-H.; Wei, Y.; Shi, M. *Chem. - Eur. J.* **2012**, *18*, 7026-7029.

[94] (a) Lee, Y.T.; Kang, Y.K.; Chung, Y.K. *J. Org. Chem.* **2009**, *74*, 7922-7934. (b) Patil, D.V.; Park, H.-S.; Koo, J.; Han, J.W.; Shin, S. *Chem. Commun.* **2014**, *50*, 12722-12725.



Scheme 62

1,5-Enynes react through endocyclic rather than exocyclic pathways. This behaviour is easily explainable considering the deriving carbenes (Figure 16). A 4-*exo*-dig cyclization would lead to the bicyclic carbene **280**. Such structure would suffer from strong ring strain due to the cyclobutane ring, thus, 5-*endo*-dig derived carbene **281** is favoured.[95]

[95] Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *Chem. - Eur. J.* **2003**, *9*, 2627-2635.

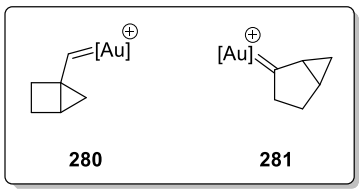
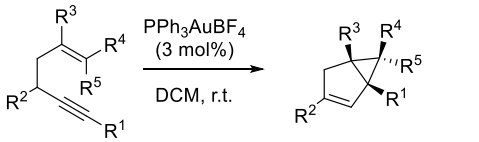


Figure 16

Alkyl- and aryl-substituted 1,5-enynes **282** (Scheme 63) undergo cycloisomerization to give bicycle[3.1.0]hexane derivatives **283**.[96]

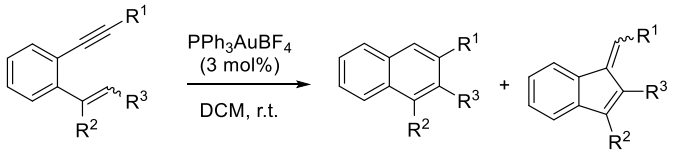


282
R^1 = H, Ph R^2 = H, aryl
R^3, R^4, R^5 = H, alkyl

(±)-**283**
(61-99%) *d.r.* 10:1 to >99:1

Scheme 63

O-alkynylstyrenes **284** (Scheme 64) react in the presence of gold(I) complexes to afford preferentially naphtalenes **285** through a 6-*endo*-dig pathway. Nevertheless, compounds **286** resulting from a 5-*exo*-dig cyclization are also delivered as side products.[97]



284
R^1 = H, I, Ph, CH_2OR, CH_2NMeTs, *n*Bu
R^2 = Me, Ph R^3 = H, Me

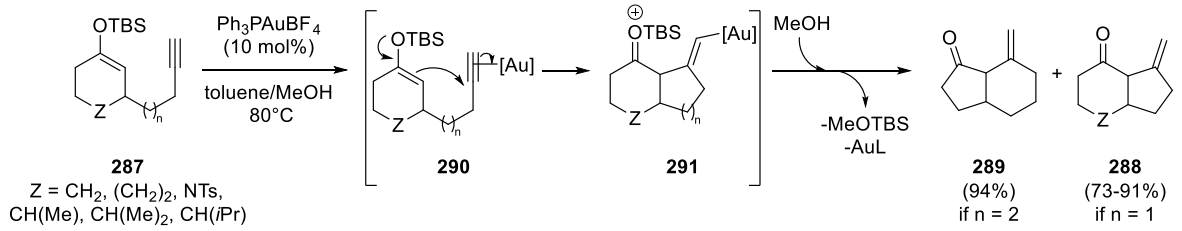
285 **286**
(71-97%)
285:**286** = 2:1 to >20:1

Scheme 64

Silyl enol ethers have been utilised as nucleophiles in the presence of an alkyne in gold(I)-catalysed cyclization reactions. In 2001, Dankwardt *et al.* reported the first paper concerning the reaction of silyl enol ethers catalysed by Au(III).[98] Toste in 2006 developed the synthesis of 5- and 6-membered rings exploiting the nucleophilic character of silyl enol ether in the presence of gold(I) complexes.[99] 1,6- and 1,7- alkynyl silyl enol ethers **287** respectively undergo 5-*exo*-dig and 6-*exo*-dig cyclization in the presence of PPh_3AuBF_4 to afford fused-

[96] Luzung, M.R.; Markham, J.P.; Toste, F.D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.
[97] (a) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 411-414. (b) Michon, C.; Liu, S.; Hiragushi, S.; Uenishi, J.; Uemura, M. *Tetrahedron* **2008**, *64*, 11756-11762. (c) Aziz, J.; Frison, G.; Le Menez, P.; Brion, J.-D.; Hamze, A.; Alami, M. *Adv. Synth. Catal.* **2013**, *355*, 3425-3436.
[98] Dankwardt, J.W. *Tetrahedron Lett.* **2001**, *42*, 5809-5812.
[99] Staben, S.T.; Kennedy-Smith, J.J.; Huang, D.; Corkey, B.K.; LaLonde, R.L.; Toste, F.D. *Angew. Chem. Int. Ed.*. **2006**, *45*, 5991-5994.

bicyclic products **288** and **289** (Scheme 65). The mechanism involves the addition of the silyl enol ether onto the η^2-complex **290** formed between the Au(I) catalyst and the alkyne moiety. Subsequent protonolysis of the resulting vinyl-gold(I) species **291** delivers the product, for this reason an external proton source like MeOH is of mandatory use. However, competitive reactions between the proton source and the electrophilic cationic Au(I) species with the highly nucleophilic silyl enol ether must be avoided. In this field, the nature of the counterion in the gold complex proved to be the key-factor.



Scheme 65

This reaction proved to be really powerful. Hence, silyl enol ethers coming from amides, aldehydes or ketones were reacted onto terminal or internal alkynes.[100] Linear, cyclic, conjugated and benzylic silyl enol ethers were found to be suitable substrates (Figure 17).[101] In the case of carbocycles, it was demonstrated that the relationship between the silyl enol ether and the alkynylic side-chain can be 1,2- for the synthesis of spirocyclic products, 1,3- and 1,4- affording bicyclic [n.3.1] bridged compounds[102] and 1,2'-.[103]

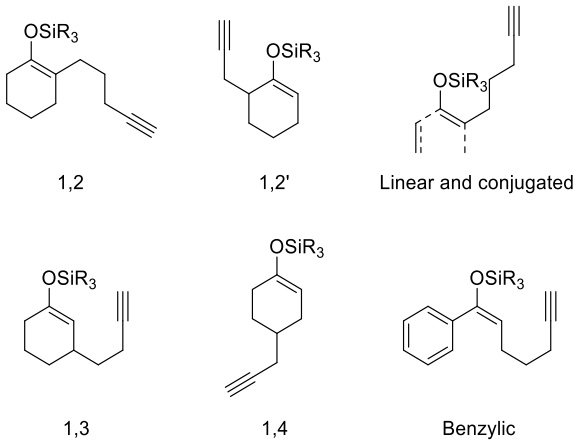


Figure 17

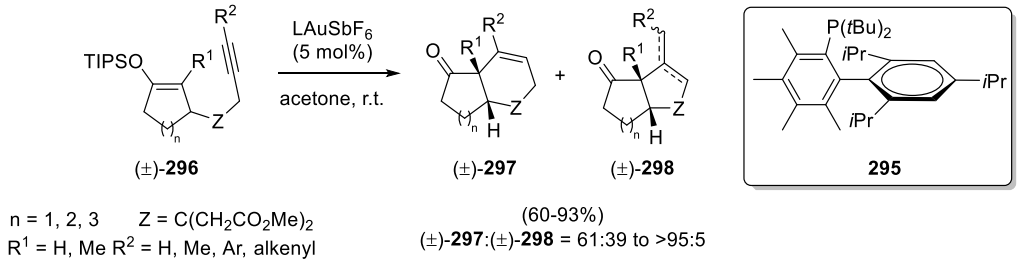
Recently, Michelet and her group reported the synthesis of α,β-unsaturated bicyclo[3.2.1]octenones using JohnPhosAuSbF$_6$.[55] Under these conditions, conjugated silyl

[100] Minnihan, E .C.; Colletti, S.L.; Toste, F.D.; Shen H.C. *J. Org. Chem.* **2007**, *72*, 6287-6289.
[101] Kusuma, H.; Karibe, Y.; Onizawa, Y.; Iwasawa N. *Angew. Chem. Int. Ed.* **2010**, *49*, 4269-4272.
[102] Carrer, A.; Péan, C.; Perron-Sierra, F.; Mirguet, O.; Michelet, V. *Adv. Synth. Cat.* **2016**, *358*, 1540-1545.
[103] Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236-4238.

enol ethers (±)-**292** undergo 5-*exo*-dig cyclization affording bicyclic compounds (±)-**293** (Scheme 66) . Notably, electron-rich aromatic substituents on the triple bond influence the mechanism of the reaction. As an example, in the case of anisole substituted alkyne the 6-*endo*-dig resulting bicycle (±)-**294** is obtained.

Scheme 66

In 2011 Barriault *et al.* reported the 6-*endo*-dig cyclization of alkynyl silyl enol ethers.[104] In order to switch from a 5-*exo*-dig selectivity to a thermodynamically unfavoured 6-*endo*-dig process, the steric and electronic nature of the Au(I) catalyst was tuned by the use of sterically demanding phosphine **295** (Scheme 67). To this extent, cyclopentanone-derived silyl enol ethers (±)-**296** were easily converted to a mixture of fused bicycles (±)-**297** and (±)-**298**, compound (±)-**297** deriving from a 6-*endo*-dig pathway was always found as the major product.



Scheme 67

The synthesis of medium size carbocycles like 7- and 8-membered rings is renowned to be more challenging than the elaboration of smaller rings. Indeed, in numerous total synthesis, a ring expansion strategy starting from cyclohexanone derivative is used in order to access such scaffolds. In 2006, the group of Sawamura developed a class of bulky semihollow phosphines[105] **299** to **301** (Figure 18). In association with gold(I), these phosphines allow the

[104] Barabé, F.; Levesque, P.; Korobkov, I.; Barriault, L. *Org. Lett.* **2011**, *13*, 5580-5583.
[105] Otchida, O.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486-16487.

unprecedent gold catalysed cyclization of large substrates through 7-*exo*-dig[106] and 8-*exo*-dig processes.[107]

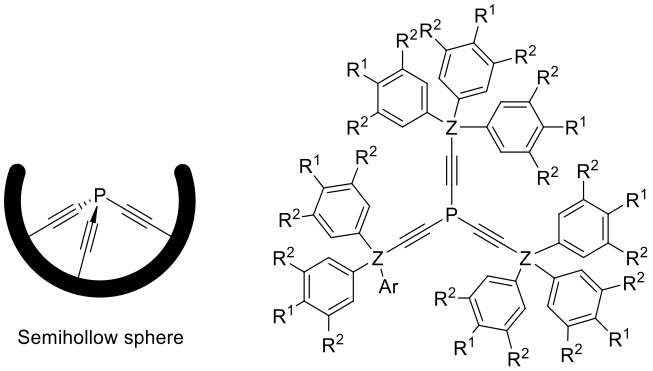
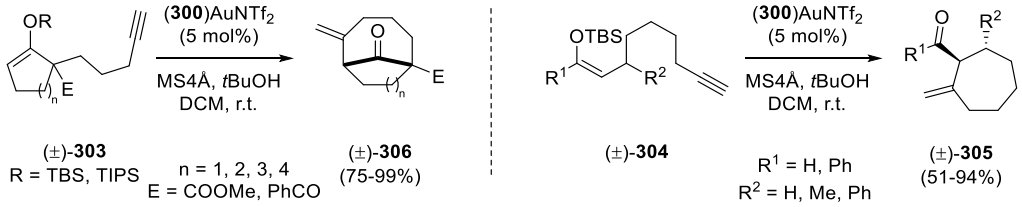


Figure 18

It was proposed that the cavity of the phosphine forces the nucleophilic center of the silyl enol ether to be closer to the gold-activated alkyne, rendering ring-closing feasible. Cyclic and acyclic silyl enol ethers (±)-**303** and (±)-**304** (Scheme 68) underwent 7-*exo*-dig cyclization to afford monocyclic product (±)-**305** or bicyclic product (±)-**306**. Silicon-based phosphines **299** and **300** both proved to be effective for this transformation, however, **300** afforded slightly better results. The scope remains however restricted to terminal alkynes.

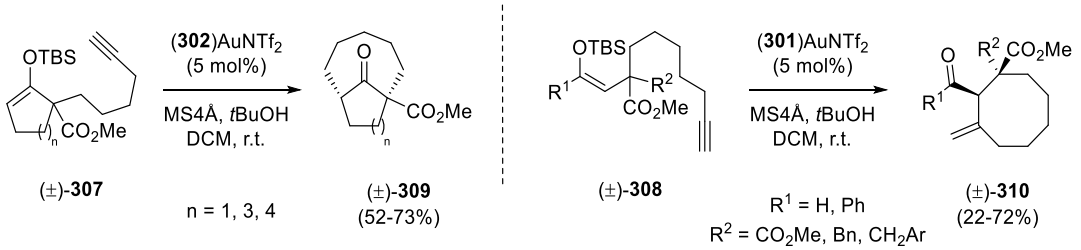


Scheme 68

With regard to silicon-based phosphine, carbon-based phosphines **301** and **302** demonstrated a higher activity toward 8-*exo*-dig cyclization of silyl enol ethers (±)-**307** and (±)-**308** (Scheme 69). Although disfavoured kinetically, the gold(I) catalysed formation of 8-membered rings has appeared as a powerful tool. Phosphine **302** exhibited a major activity with cyclic substrates (±)-**307** affording bicyclic ketones (±)-**309** and phosphine **301** was more suitable for linear substrates providing 8-membered ring compounds (±)-**310**. Again,

[106] Ito, H.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 4380-4383.
[107] Iwai, T.; Okochi, H.; Ito, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4239-4242.

the scope is limited to terminal alkynes and yields are lower if compared to the reaction leading to 7-membered cycles.



Scheme 69

3.2.7 Conclusive overview

The general characteristics of gold(I)-catalysed activation of alkynes have been discussed: after a brief historical review, the reasons why gold possesses its astonishing behaviour have been elucidated. The four major transformations: hydroarylation and hydroheteroarylation of alkynes, reactions of propargylic carboxylates, addition of heteronucleophiles to alkynes, and the most important, reactions of alkenes with alkynes have clearly widened the chemical toolbox of synthetic chemists. Remarkable is the difference in the reactivity of the various substrates. Hence, for the purpose of the synthesis of vibsatins, it is important to note that alkyne-tethered indoles undergo 7-*exo*-dig and 8-*endo*-dig cyclization by simple employment of classic Au(I)-catalysts. On the contrary, for most other substrates, cyclization leading to medium size rings (7, 8), are very difficult or even impossible to accomplish. To date, this transformation shows several restrictions since it remains limited to silyl enol ethers and a special commercially unavailable phosphine is of mandatory use.

Finally, enyne cycloisomerizations have significantly expanded the synthesizable scaffold array opening new possibilities in the synthesis of complex molecular architectures. Noteworthy, from its discovery, the field of gold catalysis has emerged as one of the top subjects in organic chemistry. If the activity in gold catalysis had followed a normal “life cycle”, a slow decay would have been expected in the numbers of publications after about a decade. After 20 years from the publishing of the pioneeristic paper of Teles, is the opposite situation that is observed, meaning that the interest is not decreasing but rather continues to grow.

3.3 Dual activation catalysis for the cyclization of alkynes

In the second part of the 20th century, the main evolution that concerned organic chemistry has undoubtedly been the area of transition metal catalysis. This field led to four Nobel prices and enabled discoveries that practically changed the every-day life all over the world. At the same time, organocatalysis has been part of the chemical research since the founding of organic chemistry. However, this is only in the end of the 20th century that the number of articles dealing with organocatalysis significantly increased. Despite the demonstrated power and wide applicability, these two fields still present drawbacks and limitations. One way of broadening their spectra of application is the use of multicatalysis strategy. Together, they can display different activation modes, allowing for new reactivity generally not accessible with a single catalyst. Here both fields can profit from one another and jointly strengthen their capacity. Generally, it is possible to rationalise the concomitant use of two catalytic sites in three different types of strategies: cooperative dual catalysis (Figure 19a), bifunctional catalysis (Figure 19b) and double activation catalysis (Figure 19c).

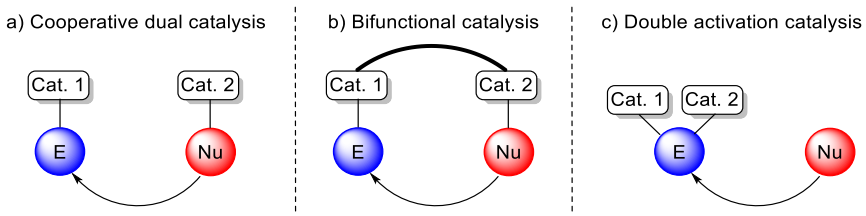


Figure 19

In cooperative dual catalysis, the two separate catalysts activate two different reactive species: one lowers the LUMO energy of the electrophile and the other raises the HOMO energy of the nucleophile. Bifunctional catalysis is accomplished by a single catalyst in which two catalytic moieties are joined together. In double activation catalysis, instead, two catalysts activate either the electrophile or the nucleophile.

Multiple catalysts are employed one-pot in one, separated, coupled or sequential catalytic cycles (Figure 20). However, in this thesis only cooperative systems will be discussed. These systems are made of a single catalytic cycle in which both substrates are activated by the two catalysts.

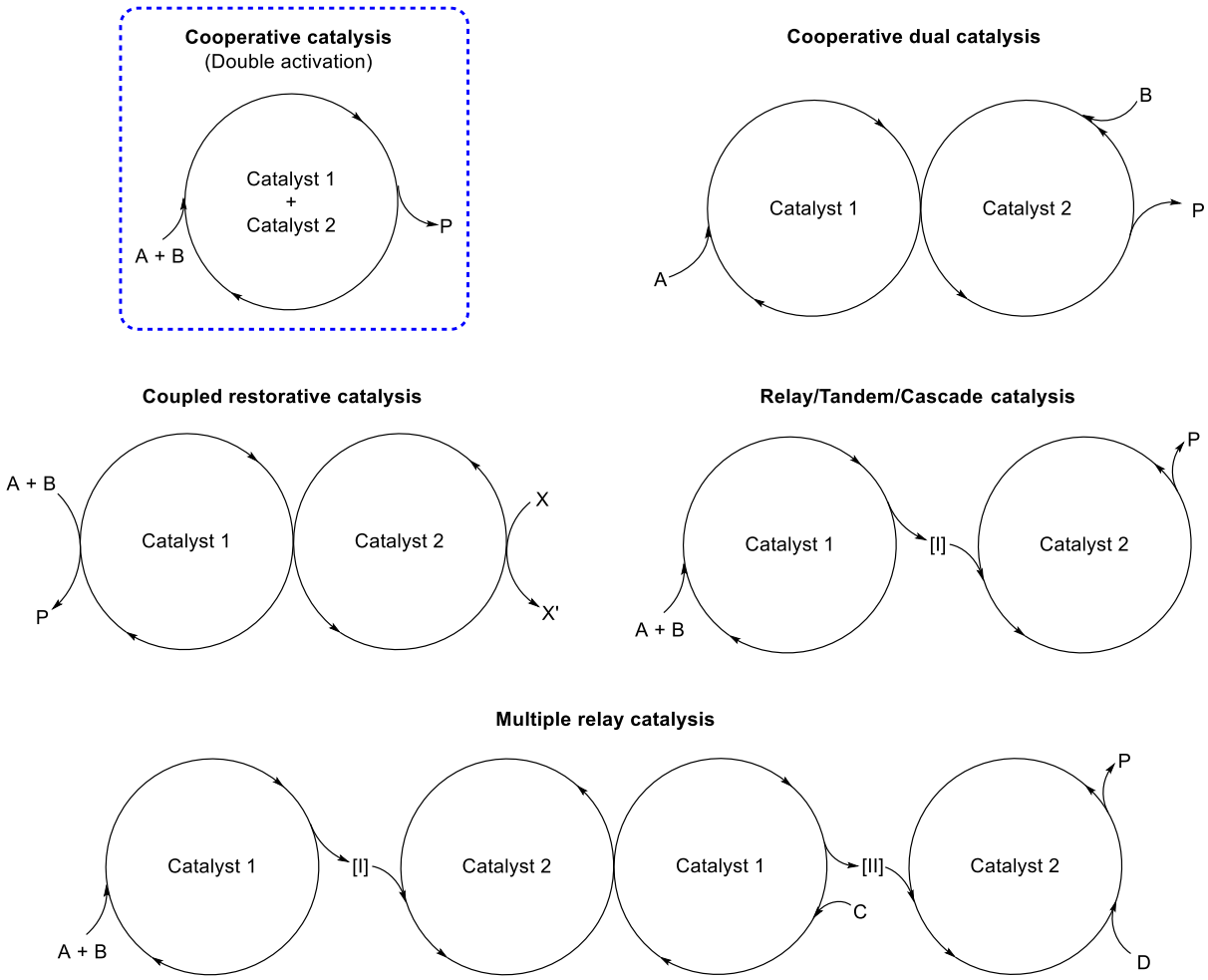
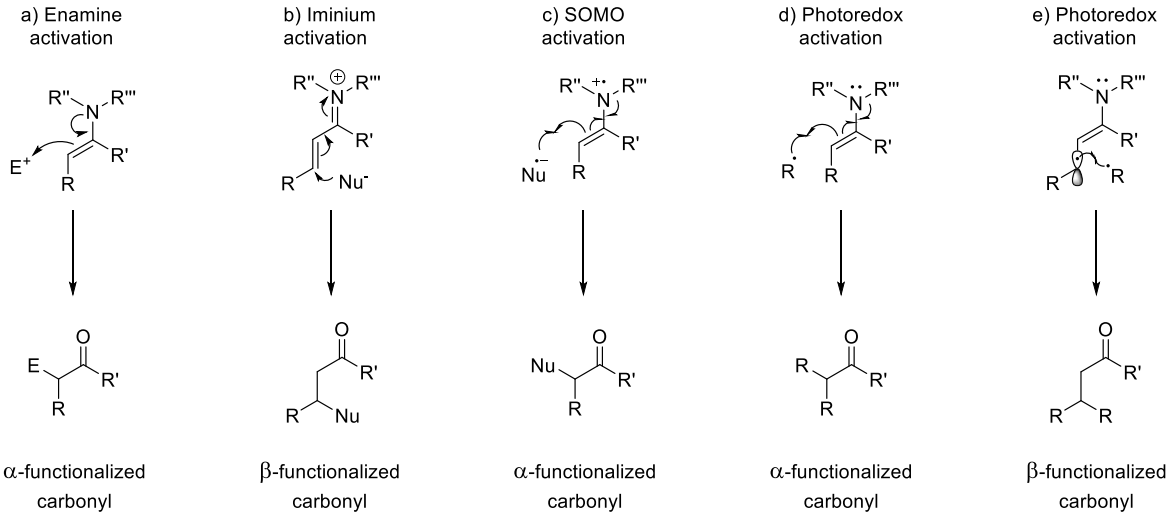


Figure 20

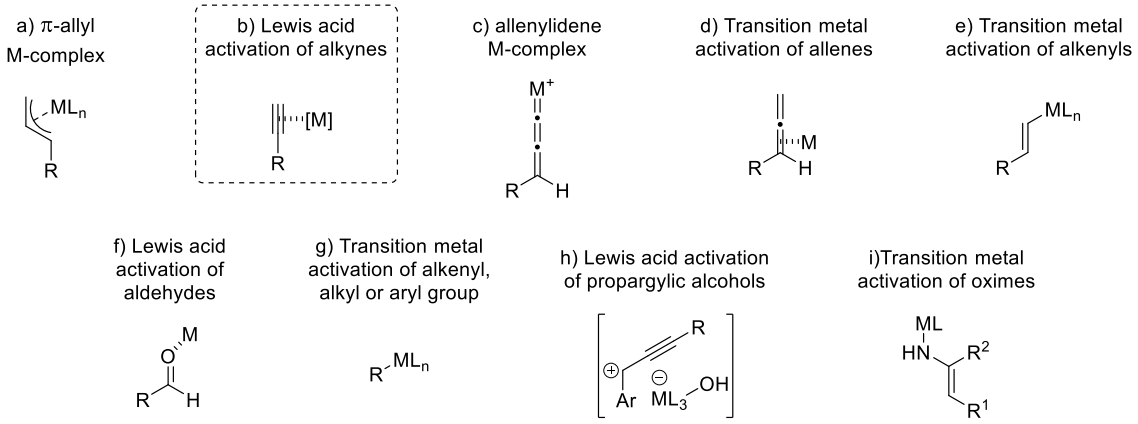
Usually, the organic catalyst is a primary or secondary amine which activates a carbonyl group in five different manners.[108] The first activation mode foresees the formation of a nucleophilic enamine which reacts with an electrophile to afford an α-functionalized carbonyl compound (Scheme 70a). Exploitation of the electrophilic character of an iminium ion by a nucleophile represents the second method (Scheme 70b). A β-functionalized carbonyl compound is delivered. In the SOMO activation, the reactive species are electrophilic radical cations deriving from enamine oxidation (Scheme 70c). Photoredox activation occurs through enamine activation catalysis (Scheme 70d) or *via* the formation of a β-enaminyl radical cation (Scheme 70e).

[108] (a) Cheong, P.H.-Y.; Legault, C.Y.; Um, J.M.; Çelebi-Ölçüm, N.; Houk, K.N. *Chem. Rev.* **2011**, *111*, 5042-5137. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724. (c) Moyano, A. Activation Modes In Asymmetric Organocatalysis. In Stereoselective Organocatalysis: Bond Formation Methodologies and activation Modes, 1st ed.; Torres, R. R., Ed.; John Wiley & Sons, Inc.; Hoboken, NJ, 2013; Chapter 2, pp 11-80.



Scheme 70

On the other hand, metals activate various functional groups following different pathways. The major activation modes observed for metals in combination with aminocatalysts are depicted in Scheme 71. For our purpose, only umpolung activation of alkynes through Lewis acid activation will be considered (Scheme 71b).[109]



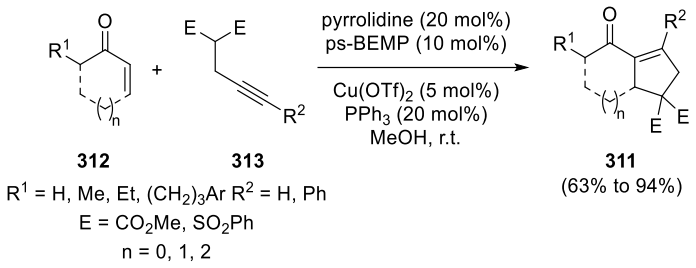
Scheme 71

3.3.1 Kirsch, Dixon and Michelet

Before discussing the various alkyne activation methods through dual cooperative activation, it must be noted that numerous publications have been reported recently aiming the activation of alkynes. In this document, only seminal reports and latest important achievements in this field will be treated introducing the concept of carbocyclization of alkynes through dual activation.

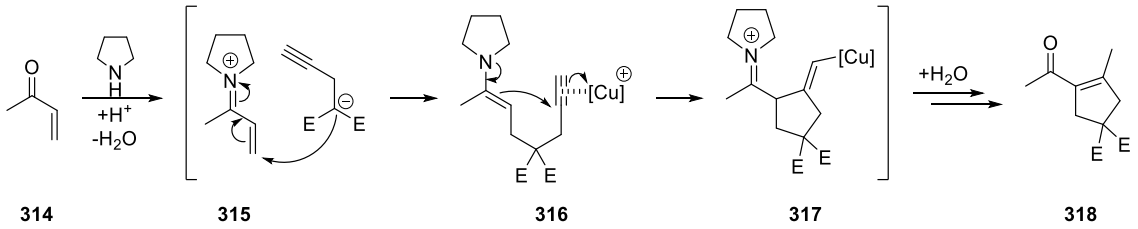
[109] Afewerki, S.; Cordova, A. *Chem. Rev.* **2016**, *116*, 13512-13570.

In 2008 Dixon and co-workers reported the development of a tandem reaction aiming to the synthesis of cyclopentenes featured with an exocyclic ketone **311** starting from an α,β-unsaturated ketone **312** and a homopropargylic malonate **313** (Scheme 72).[110,111]



Scheme 72

Pyrrolidine was elected as the organic catalyst and copper(II) triflate ($Cu(OTf)_2$) as the metallic counterpart. Various linear and cyclic ketones were suitable substrates for this reaction, nevertheless, only one example of internal alkyne was reported. Mechanistically, the pyrrolidine reacts with the ketone function of **314** and forms the iminium ion **315** (Scheme 73). A Michael addition of the homopropargylic malonate subsequently delivers the enamine **316** and the metal concomitantly activates the alkyne allowing for the cyclization to take place affording the intermediate **317**. The latter undergoes elimination of the metallic catalyst and regeneration of the carbonyl function **318**. An *exo*-homoallylic ketone should be obtained but the newly formed double bond is isomerized. Notably, PPh_3 was reported to be necessary for this reaction in order to reduce Cu(II) into Cu(I) species.

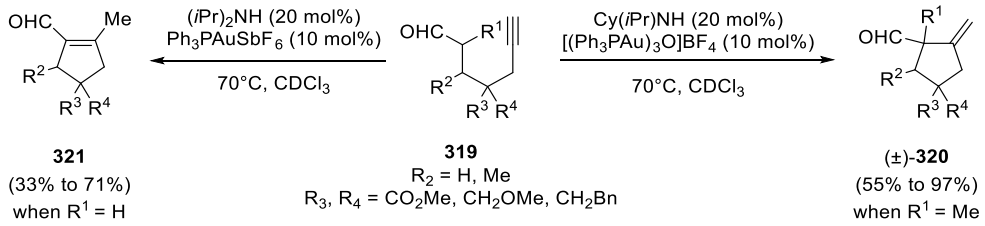


Scheme 73

Kirsch and his group reported in 2008 the first dual activation reaction in which Au(I) catalysis was used together with organocatalysis.[112] ε-Alkynyl aldehydes and α-methyl ε-alkynyl aldehydes **319** (Scheme 74) undergo 5-*exo*-dig cyclization in the presence of a secondary amine and a gold catalyst. α-Substituted aldehydes (R^1 = Me) afford exocyclic alkenes (±)-**320**, otherwise, α,β-unsaturated compounds **321** are delivered. Both $[(Ph_3PAu)_3O]BF_4$ and PPh_3AuSbF_6 are suitable catalysts, but as the cyclization of α-

[110] Yang, T.; Ferrali, A.; Campbell, L.; Dixon, D.J. *Chem. Commun.* **2008**, 2923-2925.
[111] Ps-BEMP is added in order to quench any residual protic acids present in the commercial $Cu(OTf)_2$.
[112] Binder, J.T.; Crone, B.; Haug, T.T.; Henz, H.; Kirsch S.T. *Org. Lett* **2008**, *10*, 1025-1028.

substituted aldehydes is usually longer in terms of time, $[(Ph_3PAu)_3O]BF_4$ proved to be more resistant to decomposition and thus more appropriate.



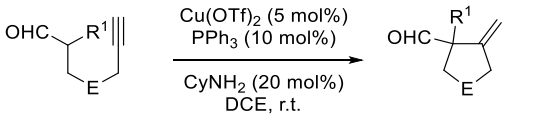
321
(33% to 71%)
when R^1 = H

319
R_2 = H, Me
R_3, R_4 = CO_2Me, CH_2OMe, CH_2Bn

(±)-**320**
(55% to 97%)
when R^1 = Me

Scheme 74

Evolution of the development of a dual activation catalysis system is observed in a series of papers published by the group of Michelet regarding the concomitant use of a copper catalyst with a primary amine. In 2011, the cyclization of α-substituted ε-alkynylaldehydes **322** into homoallylic exocyclic products (±)-**323** was reported (Scheme 75).[113]



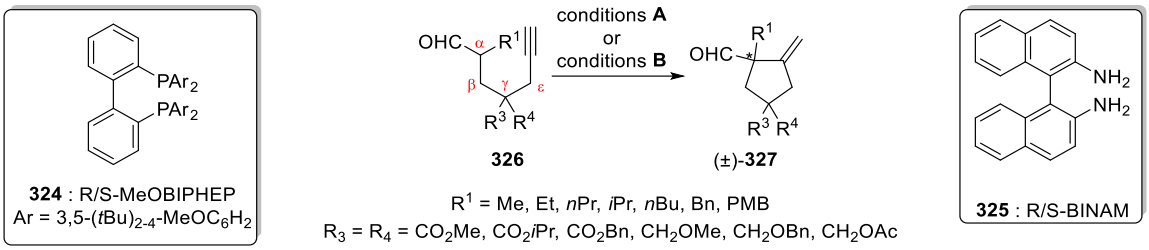
322
R^1 = Me, Et, *n*Bu, Bn, Ph
E = $C(CO_2Me)_2$, $C(CH_2OMe)_2$, $C(CH_2Bn)_2$, NTs, O

(±)-**323**
(62% to 95%)

Scheme 75

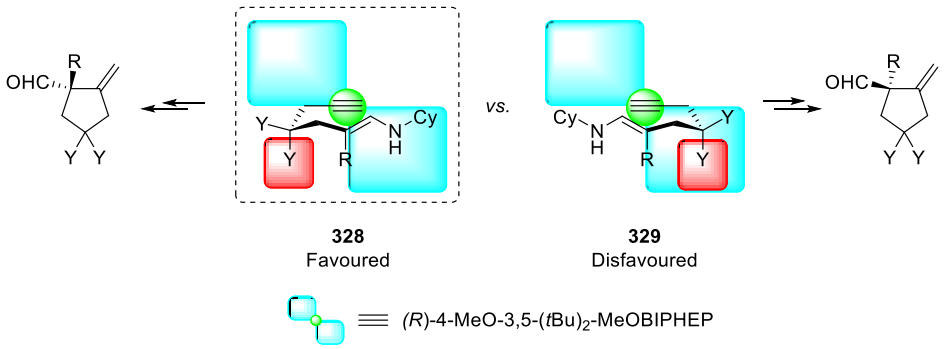
After extensive studies, the best conditions were identified. Along with the use of cyclohexyl amine ($CyNH_2$), copper(I) catalyst was generated *in situ* by reduction of copper(II) triflate ($Cu(OTf)_2$) by PPh_3. The same year, the group turned the reaction asymmetric by using chiral phosphines and reaching enantiomeric excess up to 94%.[114] One year after, it was found that indium(III) chloride ($InCl_3$) was also capable to catalyse this transformation.[115] In this report, a model explaining the enantioselectivities was also proposed (Scheme 76).

[113] Montaignac, B.; Ostlund, V.; Vitale, M.R.; Vidal, V.R.; Michelet, V. *Org. Biomol. Chem.* **2012**, *10*, 2300-2306.
[114] Montaignac, B.; Praveen, C.; Vitale, M.R.; Michelet, V.; Vidal, V.R. *Chem. Commun*. **2012**, *48*, 6559-6561.
[115] Praveen, C.; Montaignac, B.; Vitale, M.R.; Vidal, V.R.; Michelet, V. *ChemCatChem* **2013**, *5*, 2395-2404.



Scheme 76

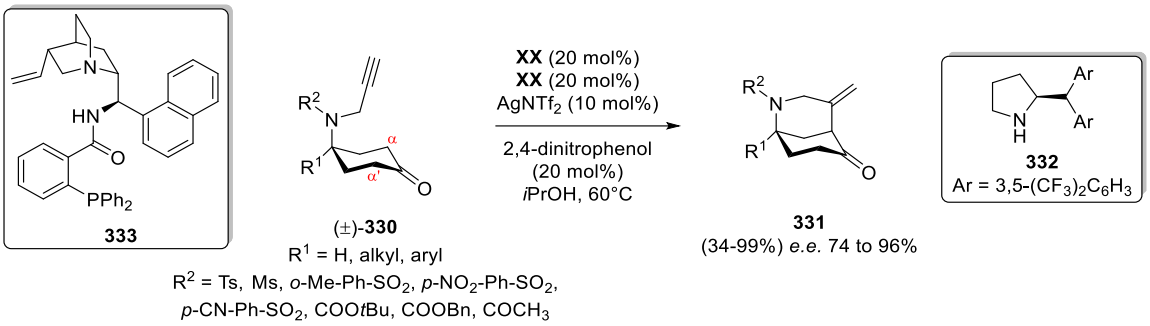
Conditions **A** ($InCl_3$) afforded either good yields of (±)-**327** and low enantiomeric excess or low yields and high enantioselectivities. Conditions **B** ($Cu(OTf)_2$), on the other hand, delivered yields of (±)-**327** up to 88% along with moderate to good enantiomeric excess (up to 90%). In this latter case, it is possible to rationalise such results by focusing on the chair-like transition states (TS) **328** and **329** (Scheme 77). Hence, the bulky ligand imposes a quadrant like steric environment around the triple bond. Pseudo axial γ-substituents (Y) are responsible for the promotion of one or the other TS and, for steric reasons, transition state **328** is favoured.



Scheme 77

Very recently Dixon and co-workers developed a desymmetrizing cycloisomerization of alkyne-linked cyclohexanones.[116] Ketones (±)-**330** undergo 6-*exo*-dig cyclization affording asymmetric bicycles **331** in the presence of silver bistriflimide ($AgNTf_2$), chiral pyrrolidine **332** and the cinchonidine-derived aminophosphine **333** (Scheme 78). Notably, a catalytic quantity of an acidic additive 2,4-dinitrophenol is also required in order to enhance the catalytic turnover.

[116] Manzano, R.; Datta, S.; Paton, R.S.; Dixon, D.J. *Angew. Chem. Int. Ed.* **2017**, 56, 5834-5838.



Scheme 78

An explanation for the asymmetric selective alkenylation at the α-position was researched by performing DFT computations on the competing transition states of this transformation (Figure 21). The aminophosphine-silver complex is likely to be rapidly formed by coordination of the quinuclidine nitrogen, the phosphorous atom and the amide nitrogen to the silver center. Concomitantly, it was demonstrated that pyrrolidines bearing bulky groups as substituents preferentially form *s-cis* enamines.[117] The matching effect of the chiralities between these two moieties provides a single α-alkenylation product enantiomerically enriched.

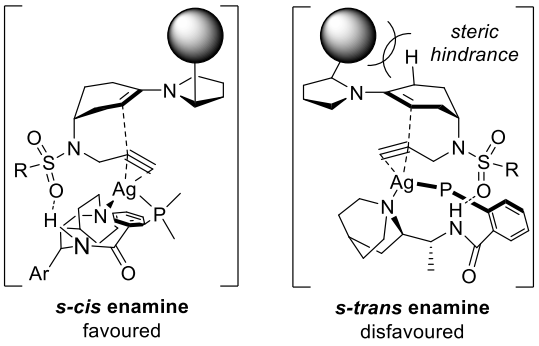


Figure 21

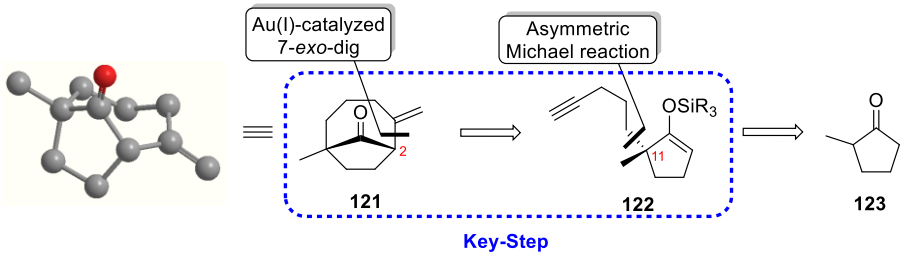
[117] (a) Arnl, M.; Zaragozà, R.J.: Domingo, L.R.; *Tetrahedron: Asymmetry* **2007**, *18*, 157–164; (b) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321–4332; (c) Cao, Y.-J.; Lu, H.-H.; Lai, Y.-Y.; Lu, L.-Q.; Xiao, W.-J., *Synthesis* **2006**, 3795–3800.

3.3.2 Conclusive remarks

The aim of this part was to introduce the concept of dual activation catalysis through selected relevant examples. Double-activation carbocyclizations involving a carbonyl moiety and a triple bond are still a merging field in organic chemistry, indeed, nowadays only systems leading to 5- and 6-membered rings have been developed. With respect to the use of silyl enol ethers, these systems offer the possibility to avoid the stoichiometric installation of the nucleophilic site. In section 3.2.6, the utilization of a bulky phosphine as an essential requirement for the execution of 7-*exo*-dig or 8-*exo*-dig carbocyclizations is described. However, for this purpose, and most specifically for the purpose of vibsatins syntheses, the development of a double activation system which would allow access to medium size rings like 7- or 8-membered carbocycles it would be of great interest. Compared to the amount of developed methodologies exploiting transition metal catalysis, dual activation cooperative catalysis is still a partially unexplored area of organic chemistry that offers great potential for improvement, while respecting sustainability concepts, *i.e.* greener and cheaper conditions.

4. Synthesis of the bicyclic key intermediate

In this chapter, the investigations upon the Au(I)-catalyzed 7-*exo*–dig cyclization leading to the bicyclic key intermediate **121** of vibsatins will be presented (Scheme 79). The first purpose, in order to get access to the bicyclo[4.2.1]nonane skeleton of the key-intermediate **121**, was the synthesis of the precursor **122**, which will start from 2-methylcyclopentanone **123**.



Scheme 79

At the beginning, the synthetic approach leading to the substrates **122** engaged in the studies of the key-step reaction will be introduced. A practical explanation on the Au(I)-catalysed methodology will be the subsequent topic followed by the synthesis of the employed phosphine.

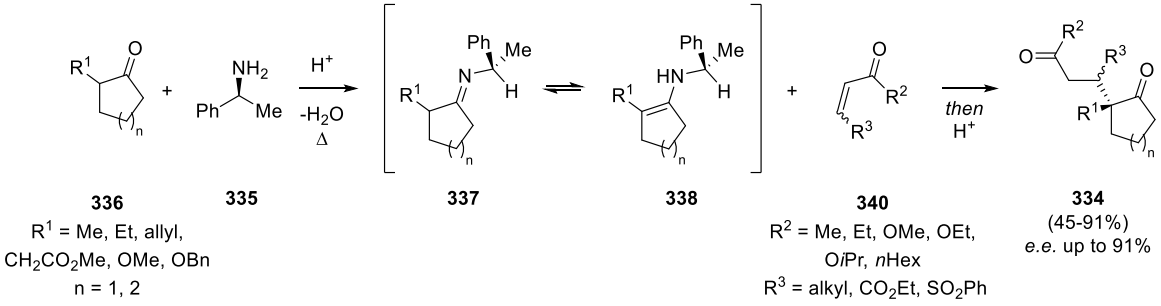
An important optimization process upon the best conditions utilised in the key-step reaction was realized and explained. To this aim, various model substrates related to the molecules originally reacted in the Sawamura's report were synthesized in order to reproduce the transformation and to evaluate its feasibility. The analysis of the essays leading to the optimization of the cyclization on the precursor **122** will be discussed. The chapter will then be closed by the investigation of various cyclization reactions exploiting double activation catalysis.

4.1 Synthesis of the precursor 122

In order to control the quaternary stereocenter at C11, it was decided to take inspiration from the works of d'Angelo and Desmaële.[118] The synthesis of enantiomerically enriched 2,2-disubstituted cyclic ketones **334** was developed employing (*S*)- or (*R*)-phenylethylamines **335** (Scheme 80). This procedure was composed of two successive reactions: first, the condensation of the chiral amine **335** onto the ketone **336** to afford imine **337** and the

[118] (a) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273-274. (b) D'Angelo, J.; Desmaële, D. *Tetrahedron lett.* **1990**, *31*, 879-882. (c) D'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459-505.

Michael addition involving the enaminic tautomer **338** and the α,β-unsaturated carbonyl compound **340**. In this manner, the enantioenriched ketone **334** is finally delivered after an acid hydrolysis.

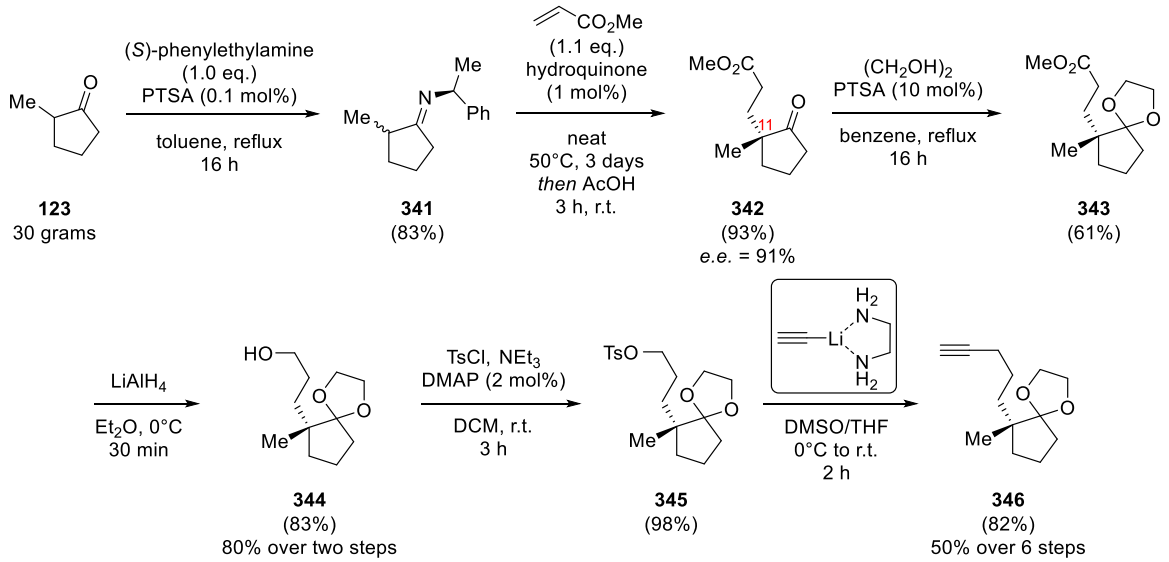


Scheme 80

The substrate suitable for the cationic gold(I) catalysed cyclization was synthesized in a eight steps sequence starting from 30 grams (0.3 mol) of 2-methylcyclopentanone **123** (Scheme 81). *p*-Toluene sulfonic acid (10 mol%) catalysed condensation of (*S*)-(-)-phenylethylamine onto **123** afforded the corresponding imine **341** in 83% yield.[119] The latter was purified by direct distillation from the reaction mixture and, due to its sensitivity to water and moisture, it was immediately reacted with methyl acrylate. After an acidic hydrolysis of the resulting adduct, enantioenriched ketoester **342** was provided in 93% yield and 91% *e.e.*. Noteworthy, the reaction time was about three days and hydroquinone was added in order to avoid the radical polymerization of the acrylate.

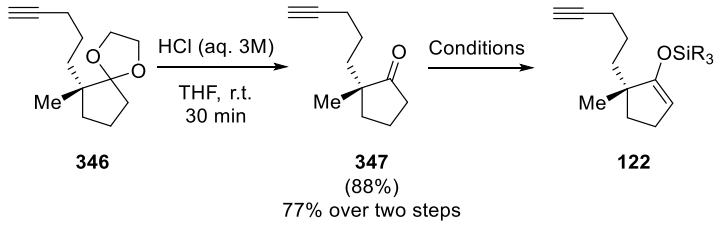
A classical chemistry based sequence, inspired from a previous work reported by Miesch and her group, was next employed for the functionalization of the newly obtained ketoester **342**.[120] Firstly, the ketone function was protected as a ketal **343** and the ester was reduced to alcohol **344** employing lithium aluminium hydride ($LiAlH_4$) in 51% yield over two steps. Notably, if the ketal is directly engaged in the reduction step without purification, the global yield increases to 80%. The primary alcohol was then transformed into its tosylate derivative **345** in quantitative yield and the newly formed functional group was displaced by lithium-acetylide delivering terminal alkyne **346** in 82% yield. The six step sequence resulted in 50% overall yield and 32 grams (0.15 mol) of acetonide **346** were obtained starting from 30 grams (0.3 mol) of 2-methylcyclopentanone.

[119] In $CDCl_3$ solvent, 1H-NMR analysis confirmed that compound **341** is found as an imine.
[120] Schafer, C.; Miesch, M.; Miesch, L. *Org. Biomol. Chem.* **2012**, *10*, 3253-3257.



Scheme 81

The ketone **347** was regenerated under acidic conditions making the installation of the silyl enol ether functionality to be the last step (Scheme 82). In the purpose of studying the 7-*exo*-dig cyclization reaction, two different silyl groups were introduced. Noteworthy, the TBS-based silyl enol ether **348** and the bulkier TIPS-derivative **349** were both synthesized in excellent yields.

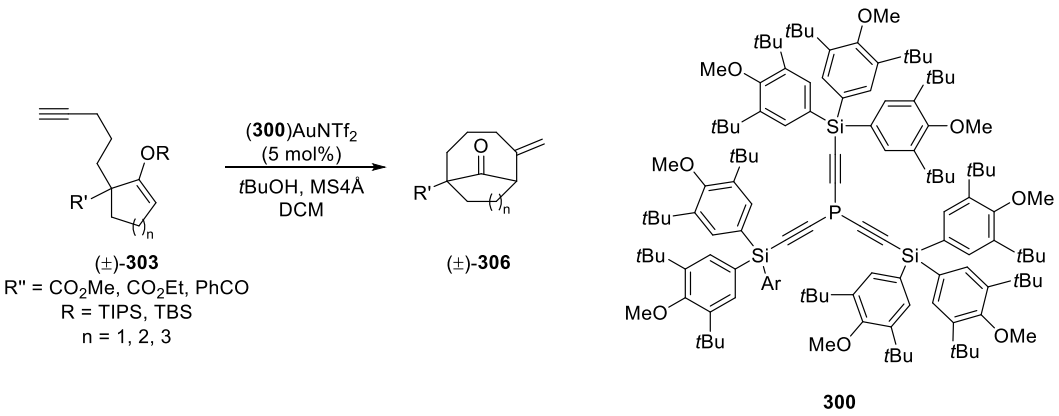


Product	R	Conditions	Yield (%)
348	TBS	TBSOTf, NEt_3 DCM, 1h, r.t.	98%
349	TIPS	TIPSOTf, 2,6-lutidine DCM, 2h30, r.t.	95%

Scheme 82

4.2 Au(I)-catalysed 7-*exo*-dig cyclization

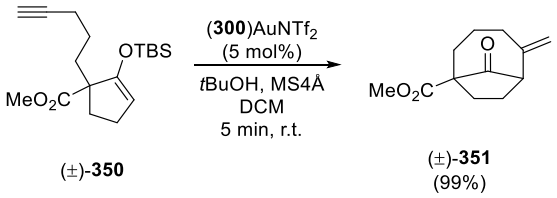
In 2010, Sawamura and his group reported the 7-*exo*-dig cyclization of alkyne-tethered silyl enol ethers.[106] As explained in section 3.2.6, a gold(I) complex formed using a non-commercial bulky phosphine catalyses the cyclization of alkyne-tethered silyl enol ethers providing 7-membered ring compounds (Scheme 83). Notably, among various different phosphines developed by Sawamura, **300** was individuated to be the most active for the set-up of 7-*exo*-dig cyclizations. Temperatures and reaction times were tuned for each substrate.



Scheme 83

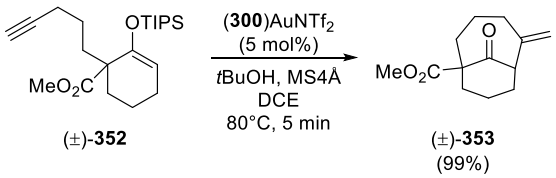
Technically, those transformations were reported under strict oxygen- and water-free conditions by using a glove-box and, moreover, on a very small 0.1 mmol scale (≈ 20 mg), which is not acceptable in the context of a total synthesis project. Based on these considerations, an adaptation of this methodology to glove-box free conditions was our primary objective. Also, the second objective was represented by the scale up of the process until reaching the possibility to engage about 10 grams of substrate.

As reported by Sawamura, TBS-based silyl enol ether (±)-**350** underwent 7-*exo*-dig cyclization to provide racemic bicyclic ketone (±)-**351** in quantitative yield at room temperature in five minutes (Scheme 84). *t*BuOH was employed as a proton source and molecular sieve was added in order to trap the putative remaining traces of water. MeOH or *t*BuOH were indicated as totally interchangeable, the choice of using *t*BuOH was probably due to easier purification and storage practical protocols.



Scheme 84

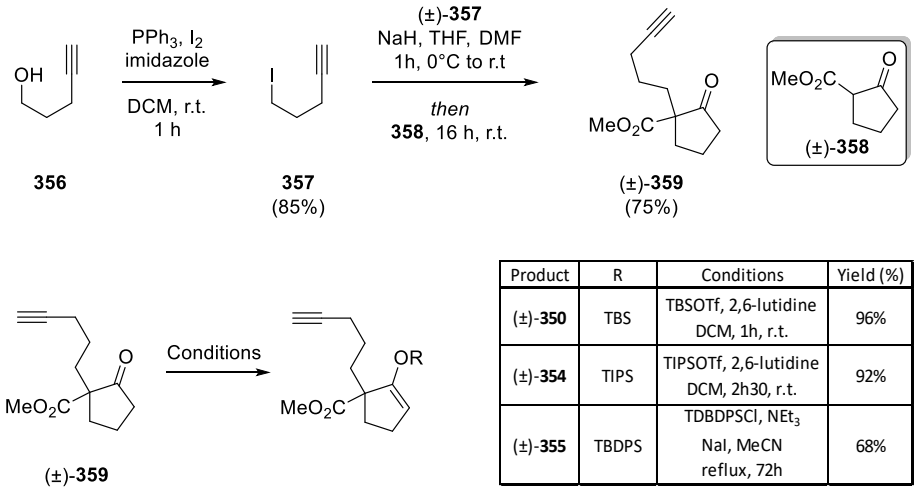
Notably, in the same report, the cyclization of a TIPS-derived silyl enol ether required stronger conditions. Indeed, silyl enol ether (±)-**350** underwent cyclization affording bicyclic ketone (±)-**351** in five minutes in quantitative yields (Scheme 85). In this case, the temperature was set to 80°C instead of room temperature, demonstrating that bulkier TIPS-based substrates were less reactive compared to TBS-based ones.



Scheme 85

4.3 Synthesis of the model substrates and phosphine 300

In order to optimize the cyclization process without using glove-box techniques, it was decided to start the investigations on the model substrate (±)-**350** along with two other similar racemic silyl enol ethers (±)-**354** and (±)-**355** (Scheme 86). These three silyl enol ethers were first synthesized in three steps starting from 5-pentyn-1-ol **356**. The alcohol **356** was transformed into its corresponding iodide derivative **357** in 85% yield and it was reacted with methyl cyclopentanone-2-carboxylate (±)-**358** affording alkyne-tethered ketoester (±)-**359** in 75% yield. Subsequent treatment with a silyl-source completed the synthesis. The TBS derived silyl enol ether (±)-**350** and the TIPS based silyl enol ether (±)-**354** were both respectively obtained in 96% and 92% yields, on the other hand, TBDPS derivative (±)-**355** was afforded in a lower 68% yield.

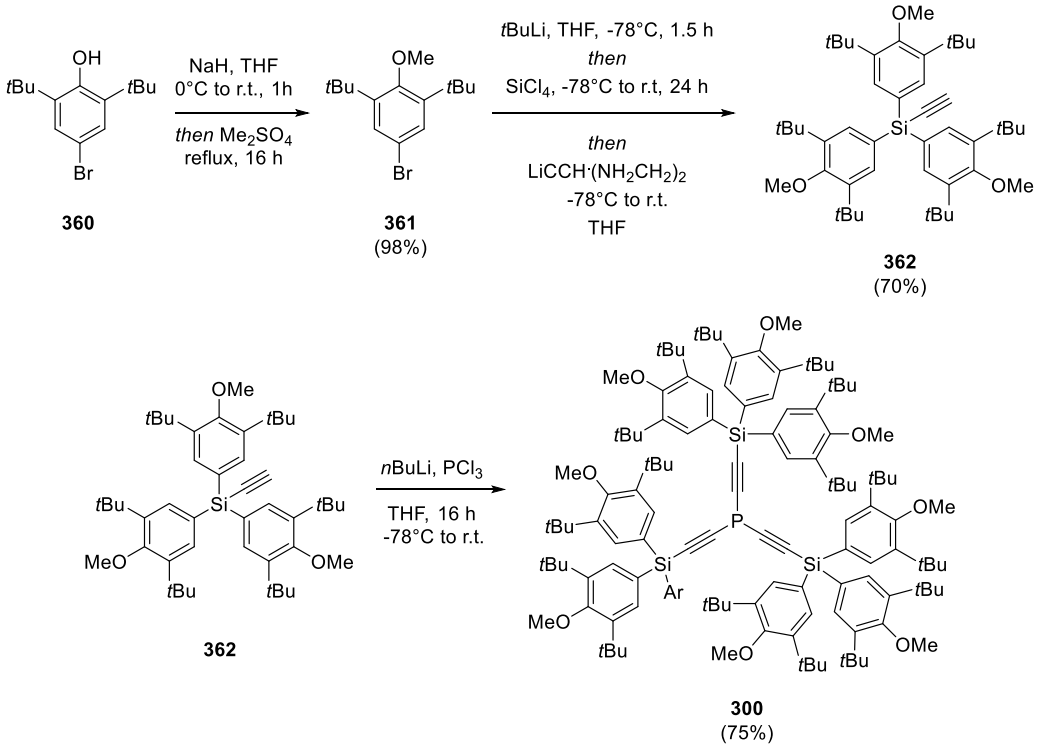


Product	R	Conditions	Yield (%)
(±)-**350**	TBS	TBSOTf, 2,6-lutidine DCM, 1h, r.t.	96%
(±)-**354**	TIPS	TIPSOTf, 2,6-lutidine DCM, 2h30, r.t.	92%
(±)-**355**	TBDPS	TDBDPSCl, NEt_3 NaI, MeCN reflux, 72h	68%

Scheme 86

The synthesis of the phosphine **300** was realized as reported by Sawamura, in three steps starting from 30 grams of bromophenol derivative **360** (Scheme 87).[105] The latter was quantitatively transformed into its anisole derivative **361**, then a one-pot process made of three distinct steps leaded to silane **362**. **361** (3 eq.) was exchanged with *tert*-butyllithium and the resulting anion was reacted with one equivalent of $SiCl_4$. Lithium acetylide was then added to the resulting adduct in order to provide alkyne-tethered silane **362** in 70% yield. Phosphine **300** was finally obtained in 75% yield by reaction of intermediate **362** with *n*-

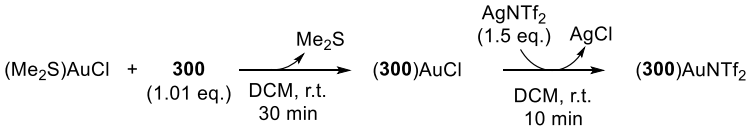
butyllithium and PCl_3. The overall yield was calculated to be 53% starting from 5.5 grams of $SiCl_4$.



Scheme 87

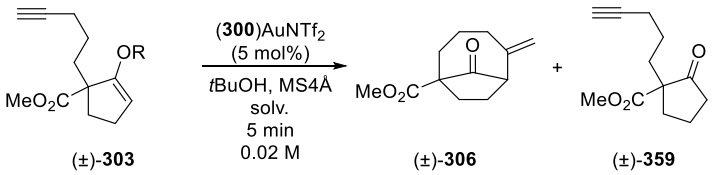
4.4 Cyclization studies

With the substrates and the phosphine in hands, we started to examine the 7-*exo*-dig cyclization reaction. It is important to notice that the side reaction of this process regarded the electrophilic cleavage of the silyl enol ether which regenerated the original ketone. Oxygen and moisture-free conditions were described as mandatory when performing these transformations. Consequently, in order to run these reactions on a simple vacuum line, special Schlenk tubes were tailor-made and employed (see experimental part for a picture). The catalyst was synthesized *in-situ* for each tested substrate. In this aim, $(Me_2S)AuCl$ was stirred in DCM with a slight excess of phosphine **300** (1.01 equivalents) and, after 30 minutes, the volatiles were evaporated in order to afford intermediate (**300**)AuCl and to eliminate the remaining Me_2S (Scheme 88). Solubilisation with DCM and addition of 1.5 equivalent of $AgNTf_2$ led to the precipitation of AgCl and to the concomitant generation the active species $[(\mathbf{300})Au]NTf_2$ over 10 minutes. Filtering the suspension under inert atmosphere through a pad of Celite$^{(R)}$ directly into the reaction vessel delivered the active catalyst.



Scheme 88

Our studies started by investigating the cyclization on 0.3 mmol (≈50 mg) of silyl enol ethers (±)-**303** derived from β-ketoesters in the presence of 5 mol% catalyst and one equivalent of *t*BuOH in dichloromethane at room temperature, the concentration of the substrate resulted to be 0.02 mol/L (Scheme 89). The first attempts employing the TBS-based substrates (±)-**350** resulted mostly in the cleavage of the silyl enol ether affording ketone (±)-**359** (Table 1, entry 1). Moreover, TBS-based substrates proved to be very sensitive to environmental-induced differences in the preparation of the catalyst and the reaction was hardly reproducible leading to a maximum 12% of isolated yield in desired product (Table 1, entries 2 and 3). TBDPS-derived silyl enol ether (±)-**355** exhibited a greater resistance toward electrophilic cleavage but at the same time a slight reluctance to react as well, however, from this essay the isolated yield raised to 31% (Table 1, entry 4). Triisopropylsilyl enol ether based substrate (±)-**354** displayed to be the most inert, since after three hours, only 38% of the starting product was consumed (Table 1, entry 5). However, following the guidelines mentioned in the original Sawamura's paper, TIPS-derived substrate was refluxed in DCE providing total conversion of the departing product, but the amount of cleavage was still prevailing (Table 1, entry 6). On the other hand, refluxing the TIPS-based silyl enol ether (±)-**354** in DCM for five minutes provided a 82:18 *ratio* and bicyclic ketone (±)-**306** was isolated in 68% yield. Notably, in order to investigate the mandatory utilization of the phosphine **300** in the execution of 7-*exo*-dig cyclization reactions, a phosphine classically used in Au(I) catalysis such as JohnPhos **181** was utilized instead of **300**.[121] Under these conditions, the same TIPS-based silyl enol ether (±)-**354** underwent cyclization at room temperature displaying a low conversion of 10% but interestingly without formation of the side product (±)-**359** (Table 1, entry 8).



Scheme 89

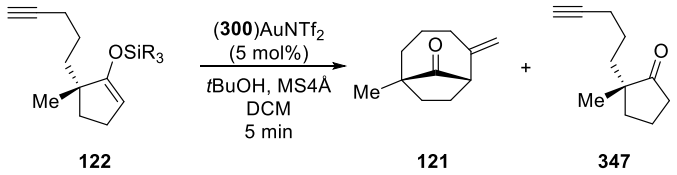
[121] Huwyler, N.; Carreira, E.M. *Angew. Chem. Int. Ed.* **2012**, *51*, 13066–13069.

Entry	Substrate	R	T	Solv.	Conv.[a]	(±)-306/(±)-359[a]	Isolated
1	(±)-**350**	TBS	r.t.	DCM	100%	15:85	/
2	(±)-**350**	TBS	r.t.	DCM	100%	0:100	/
3	(±)-**350**	TBS	r.t.	DCM	100%	22:88	12%
4	(±)-**355**	TBDPS	r.t.	DCM	70%	48:52	31%
5[b]	(±)-**354**	TIPS	r.t.	DCM	38%	30:70	/
6	(±)-**354**	TIPS	80°C	DCE	100%	35:65	30%
7	(±)-**354**	TIPS	40°C	DCM	100%	82:18	68%
8[c]	(±)-**354**	TIPS	r.t.	DCM	10%	100:0	/

[a] Calculated via NMR. [b] Reaction time 3 h. [c] JohnPhos utilised instead of **300.**

Table 1

Starting from these results, we then decided to turn our attention toward enantiomerically enriched silyl enol ethers derived from ketones **122** (Scheme 90). The TBS-derived substrate **348** was first tested and, also in this case, it resulted in mostly total cleavage of the silyl enol ether function (Table 2, entry 1). However, moving toward the TIPS-based silyl enol ether **349** provided better results. The first trial, realized in refluxing at 40°C, majorly afforded desilylated product **347** (Table 2, entry 2).The second test at room temperature surprisingly resulted in the total conversion of the substrate into the bicyclic target molecule **121** and an isolated yield of 80% was reached (Table 2, entry 3). With this good result in hands, concentration was raised to 0.05 M affording 92% of isolated product (Table 2, entry 4) and, the last essay, conducted with a concentration of 0.1 M finally afforded the best result in terms of isolated yield (95%) (Table 2, entry 5).



Scheme 90

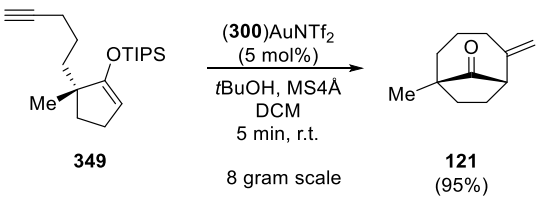
Entry	Substrate	R	[M]	T	Conversion[a]	121:347[a]	Isolated
1	**348**	TBS	0.02 M	r.t.	100%	8:92	/
2	**349**	TIPS	0.02 M	40°C	100%	22:88	/
3	**349**	TIPS	0.02 M	r.t.	100%	>95:5	80%
4	**349**	TIPS	0.05 M	r.t.	100%	>95:5	92%
5	**349**	TIPS	0.10 M	r.t.	100%	>95:5	95%

[a] Calculated *via* ^{1}H-NMR

Table 2

Comparing the results of Table 1 and Table 2, it is possible to notice the higher reactivity towards both cleavage and cyclization of the ketone-derived silyl enol ethers (R = Me) compared to ketoesters-derived silyl enol ethers (R = COOMe). This is especially well displayed for TIPS-silyl enol ether derivatives: **349** reacted properly and quantitatively at room temperature, whereas raising the temperature only promoted the cleavage of the silyl group. On the other hand, a temperature of 40°C was mandatory for the cyclization of (±)-**354**.

Once the best conditions for the synthesis of the key-intermediate **121** determined, scale up was realized until the transformation could be performed on more than 8 g (25 mmol) of TIPS-based substrate **349** (Scheme 91).



Scheme 91

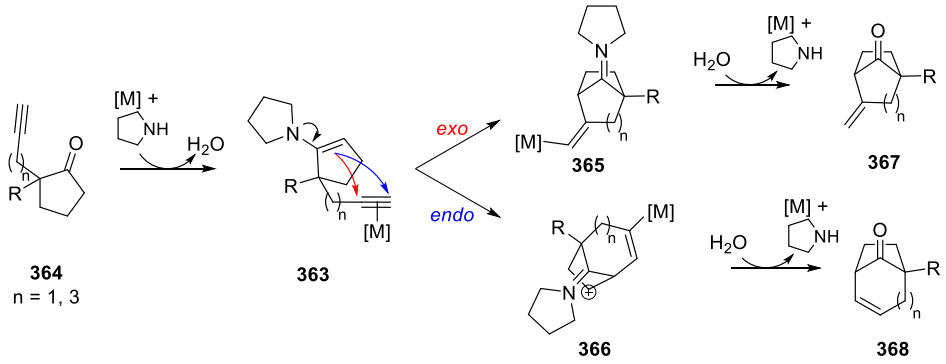
To this aim, the purification step plays a special role in this reaction. The quench was done by a simple filtration on a silica pad in order to remove the catalyst, but the total removal of the phosphine from the product revealed to be a difficult task. Phosphine **300**, indeed, showed the tendency to partially co-eluate with the bicyclic ketone **121**. Purification by column chromatography usually afforded ketone **121** along with traces (2-3%) of the phosphine. During the scale-up phase, this problem was overcome by precipitation and subsequent filtration of the phosphine employing EtOH. In this way, the following column chromatography purification afforded pure product and, moreover, the solid phosphine was recovered. The recycled phosphine, usually around 60% of the original engaged quantity, exhibited the same reactivity of the freshly synthesised one.

4.5. Double activation catalysis

In parallel to the synthesis of the vibsatins, it was investigated an alternative route in order to get access to the bicyclo[4.2.1]nonane scaffold. As explained in the last Section, the key step of our synthesis of the vibsatins relied on a 7-*exo*-dig cyclization catalysed by gold(I). Three major drawbacks are associated with this reaction: the stoichiometric utilization of a silyl source for the synthesis of the silyl enol ether substrate, the strong oxygen- and moisture-free conditions and the utilization of the non-commercial bulky phosphine. Starting from these assumptions, we aimed to overcome these drawbacks by the use of double activation catalysis. In Section 3.3, the general characteristics of double activation catalysis were previously discussed. In our case, the substitution of a preformed silyl enol ether by an *in situ* formed enamine and the usage of commercially available cheaper metal catalysts based on Ag or Cu will be discussed.

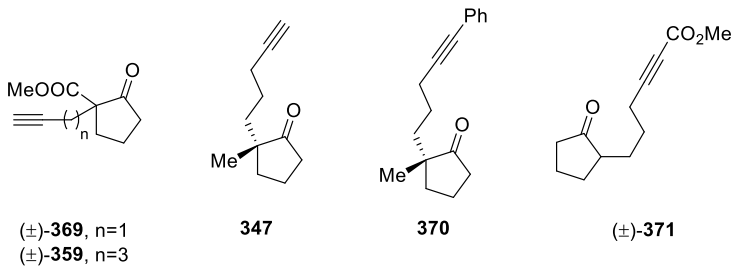
4.5.1 Concept and substrates syntheses

Our original idea regarded the execution of cyclization reactions by using a secondary amine coupled to a metal catalyst. To this aim, pyrrolidine was elected as the secondary amine and different silver and copper catalysts were tested. The foreseen mechanism would be divided into three steps. In the first step, enamine **363** would be *in-situ* synthesised starting from the starting ketone **364** (Scheme 92). The metal catalyst would then complex the triple bond moiety and allow the cyclization of the enamine affording iminium compounds **365** or **366** depending upon the *exo*- or *endo*-pathway followed. Hydrolysis of the iminium ion and protodemetallation would then provide the bicyclic ketones **367** or **368**.



Scheme 92

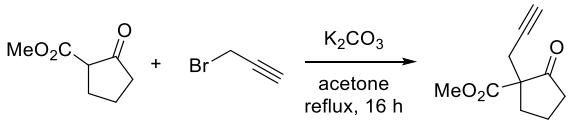
We started our investigations on six different substrates depicted in Figure 22. Ketoester (±)-**359** and ketone **347** were already available and their achievement was previously detailed in Section 4.3 and 4.1.



(±)-**369**, n=1
(±)-**359**, n=3 **347** **370** (±)-**371**

Figure 22

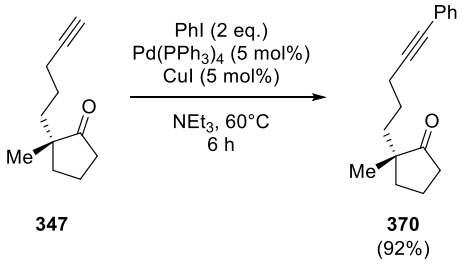
Ketoester (±)-**369** was easily synthesized as reported in the literature starting from cyclopentanone-2-carboxylate and propargyl bromide **372** (Scheme 93).[122] A mild base such as K_2CO_3 in acetone was used and compound (±)-**369** was obtained in 73%.



(±)-**358** **372** (±)-**369** (73%)

Scheme 93

Internal alkyne **370** was obtained starting from formerly synthesized terminal alkyne **347** by exploitation of classic Sonogashira protocols (Scheme 94). The use of phenyl iodide together with a catalytic quantity of palladium tetrakis ($Pd(PPh_3)_4$) and copper iodide in a mild base like NEt_3 as solvent, readily provided arylation of the triple bond affording **370** in 92% yield.



347 **370** (92%)

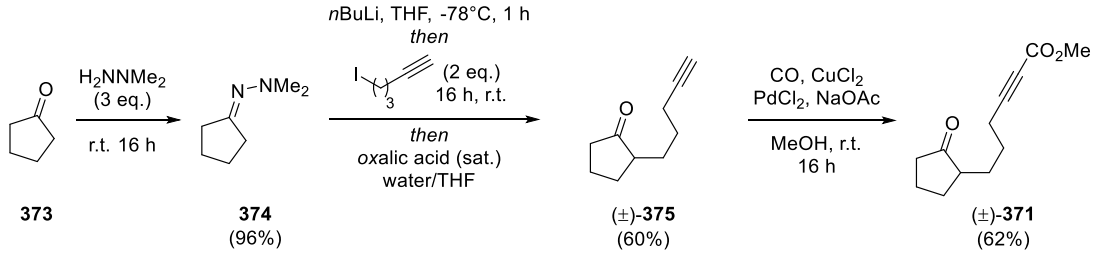
Scheme 94

The ester (±)-**371** was instead synthesized in three steps starting from cyclopentanone **373** (Scheme 95). The latter was reacted with 1,1-dimethylhydrazide affording hydrazone **374** quantitatively. Alkylation using 5-iodopent-1-yne and acidic cleavage of the hydrazone afforded alkyne tethered ketone (±)-**375** in 60% yield.[123] Installation of the methylester on the alkyne moiety was tested, at the beginning, by the use of a strong base (LDA) and $ClCO_2Me$

[122] (a) Teixeira, L.H.P.; Barreiro, E.J.; Fraga, C.A.M. *Synthetic Comm.* **1997**, *27*, 3241-3257. (b) Belotti, D.; Cossy, J.; Pete, J.P.; Portella, C. *J. Org. Chem.* **1986**, *51*, 4196-4200.

[123] Leboeuf, D.; Simonneau, A.; Aubert, C.; Malacria, M.; Gandon, V.; Fensterbank, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 6868-6871.

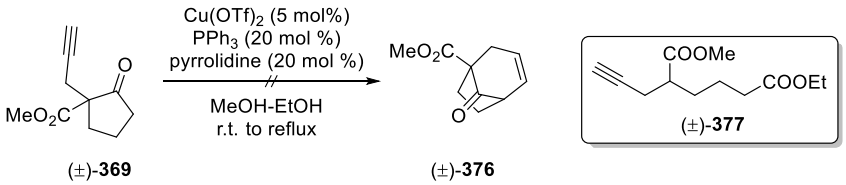
but surprisingly failed.[124] Palladium mediated solvocarbonylation, on the other hand, afforded the desired terminal ketoester (±)-**371** in 62% yield.[125]



Scheme 95

4.5.2 Cyclizations essays

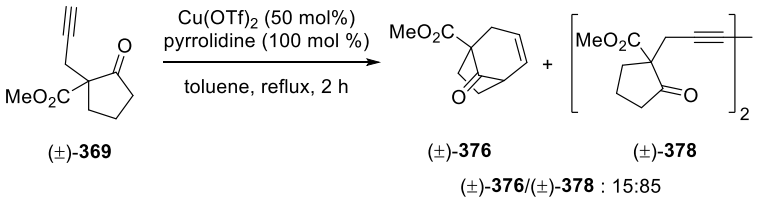
Once the substrates synthesized, we then started to investigate the cyclization reactions. We started our essays with ketoester (±)-**369** exploiting the conditions reported by Dixon and his group (Scheme 96).[109126] Various temperatures were tested but cyclized product (±)-**376** was never observed. On the other hand, switching from methanol to ethanol and heating to reflux, delivered product (±)-**377** deriving from the ethanol addition onto the ketone and ring opening.



Scheme 96

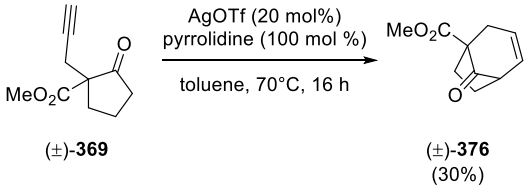
Increasing the catalytic charge to sub-stoichiometric quantities, however, permitted to obtain a bicyclo[3.2.1]octane (±)-**376** resulting from a 6-*endo*-dig cyclization in only 15% yield along with 85% of dimerized alkyne (±)-**378**, probably resulting from a Glaser-Hay coupling (Scheme 97).[127]

[124] MacKay, J.A.; Landis, Z.C.; Motika, S.E., Kench, M.H. *J. Org. Chem.* **2012**, *77*, 7768-7774.
[125] Yanagita, Y.; Suto, T.; Matsuto, N.; Kurosu, Y.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 1946-1949.
[126] For the discussion upon the Dixon's reported dual activation cyclizations, see Section 3.3.1
[127] (a) Balaraman, K.; Kesavan, V. *Synthesis* **2010**, *20*, 3461-3466. (b) Eglinton, G.; Galbraith, A.R. *Chem. Ind.* (London) 1956, 737 (c) Hay, A.S. *J. Org. Chem.* **1960**, *25*, 1275-1276. (b) Hay, A.S. *J. Org. Chem.* **1962**, 27, 320-320.



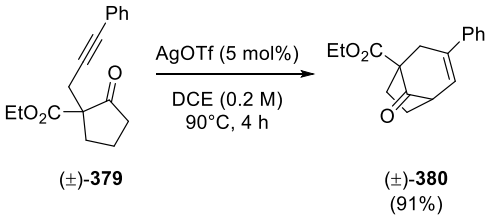
Scheme 97

Various conditions were then explored in order to contrast the formation of the dimeric product (dilution, degased solvent, lower temperatures) but it mostly resulted in the same unfavourable *ratio*. Various metal catalysts were then tested in order to avoid the Glaser-Hay coupling, including: $AgNTf_2$, $AgSbF_6$,[109] PPh_3AuSbF_6,[112] $In(OTf)_3$,[41] $Fe(OTf)_3$[128] and the best result to date was obtained using AgOTf. Indeed, heating at 70°C in toluene (±)-**369** in the presence of one equivalent of pyrrolidine and a catalytic quantity of AgOTf, delivered bicyclic product (±)-**376** in 30% yield (Scheme 98).



Scheme 98

A very similar cyclization using the same silver complex was reported by Chegondi and his group in late 2015 (Scheme 99).[129] For instance, internal alkyne (±)-**379** underwent 6-*endo*-dig cyclization affording bicyclooctene (±)-**380** in 91% yield. Notably, the only presence of AgOTf was capable to catalyse the formation of the nucleophilic enol concomitantly to the activation of the triple bond moiety. This report raised doubts about the real necessity to use pyrrolidine in the studied reactions, however, only internal alkynes were suitable in this process.

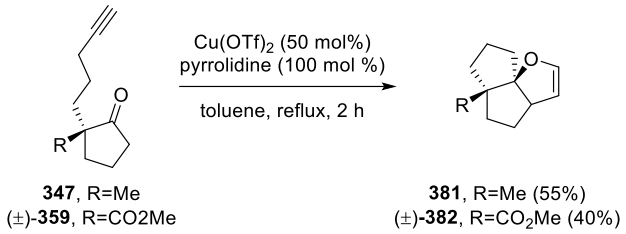


Scheme 99

We then turned our attention to suitable substrates for 7-*exo*- or 8-*endo*-dig cyclizations. From first essays, it was demonstrated that simple ketone **347** and ketoester (±)-**359** reacted

[128] Jalal, S.; Paul, K.; Jana, U. *Org. Lett.* **2016**, *18*, 6512-6515.
[129] Kallepu, S.; Gollapelli, K.K.; Nanubolu, J.B.; Chegondi, R. *Chem. Commun.* **2015**, *51*, 16840-16843.

with stoichiometric amount of pyrrolidine and substoichiometric quantity of $Cu(OTf)_2$ to give surprisingly condensed tricycles **381** and (±)-**382** in respectively 55% and 40% yield (Scheme 100).

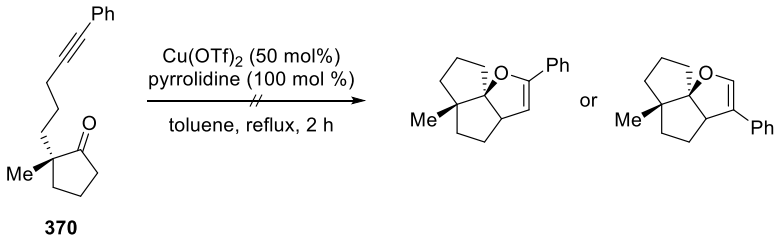


347, R=Me
(±)-**359**, R=CO2Me

381, R=Me (55%)
(±)-**382**, R=CO_2Me (40%)

Scheme 100

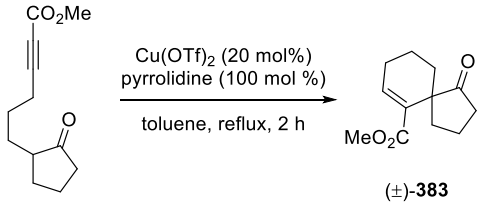
At the beginning, it appeared that yields follow the amount of utilised $Cu(OTf)_2$, but lowering or enhancing the percentage of copper catalyst resulted in lower yields. The same results were observed concerning of pyrrolidine: the utilization of two equivalents or half equivalent of pyrrolidine lowered the yields. Other metals were also tested but only $Cu(OTf)_2$ provided the formation of this type of tricyclic products. However, on the other hand, aryl-tethered alkyne **370** showed no reactivity in the same conditions and the starting product was recovered (Scheme 101).



370

Scheme 101

The concomitant application of 20 mol% of copper(II) triflate and one molar equivalent of pyrrolidine to (±)-**371**, delivered the spiro-ketone (±)-**383** in 31% yield instead of a condensed tricycle (Scheme 102). In this case, the 6-*endo*-dig cyclization pathway was preferred.



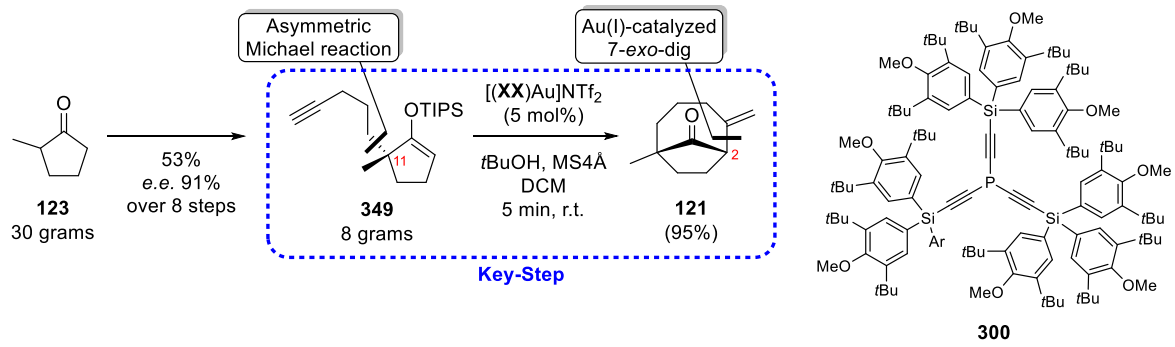
(±)-**371**

(±)-**383**
(38%)

Scheme 102

4.6 Conclusions

In the course of the synthesis of vibsatins, the bicyclic ketone key-intermediate **121** was synthesized (Scheme 103). The configuration at C11 was controlled by using a reported method exploiting an asymmetric Michael reaction and, starting from 30 grams of 2-methylcyclopentanone **123**, the cyclization precursor **349** was obtained in 53% yield over eight steps with an enantiomeric excess of 91%.

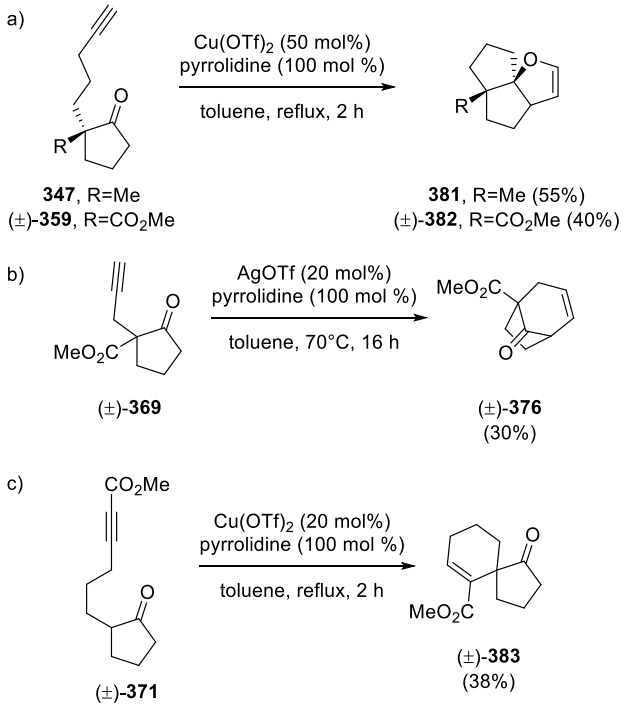


Scheme 103

A study upon the 7-*exo*-dig cyclization was first engaged on a model substrate. This study demonstrated the superior reactivity outcome of the TIPS-based silyl enol ether (±)-**354**. The various trials of this study suggest that the two competitive reactions (7-*exo*-dig cyclization and the electrophilic cleavage) possess different kinetic profiles and tuning the operative conditions results in the promotion of one of the two processes. Notably, the utilization of a JohnPhos based catalyst resulted only in the formation of the bicyclic ketone and, even if the conversion was low, it represents an interesting departing point for a study aiming to the substitution of the bulky ligand **300** with commercially available phosphines. Once the best conditions tuned, the desired key-intermediate **121** was obtained in 92% yield and the subsequent scale up allowed to run this 7-*exo*-dig gold(I)-catalysed cyclization on up to 8 grams of substrate in glove-box free conditions.

In parallel to these studies, an investigation upon alternative medium size ring cyclizations exploiting dual activation was engaged in order to overcome the drawbacks relative to this gold(I) developed methodology. The stoichiometrically installed silyl enol ether moiety was replaced by the *in-situ* preparation of an enamine using pyrrolidine and AgOTf or $Cu(OTf)_2$ complexes were used instead of a gold(I)-based catalyst. At the present time, we were not able to reach the synthesis of 7- or 8-membered ring under these conditions. However, from preliminary studies some interesting results were observed, for instance, the reaction of 2,2-disubstituted ketones bearing long alkynylic side-chains such as (±)-**359** and 3**47** providing

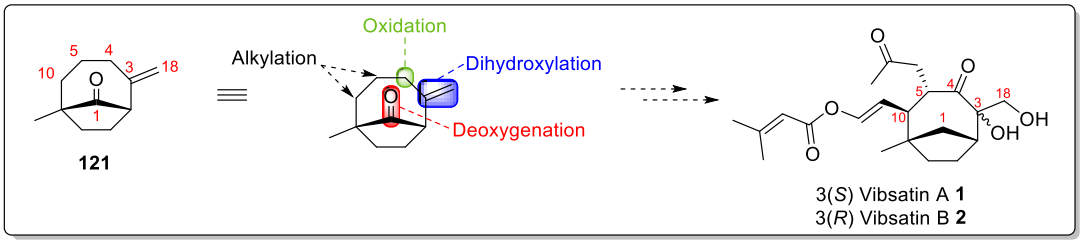
unprecedented condensed tricyclic compounds (±)-**352** and 3**81** (Scheme 104a). On the other hand, propargyl-tethered ketoester (±)-**369** undergo 6-*endo*-dig cyclization reaction to afford bicyclo[3.2.1]octane (±)-**376** (Scheme 104b) and monosubstituted ketone (±)-**371** provides the spiro-compound (±)-**383** (Scheme 104c).



Scheme 104

5. Towards the total syntheses of Vibsatins A and B

The main topic of this chapter will be the functionalization of the bicyclic skeleton **121**. The requisite transformations for the synthesis of the vibsatin A and B are depicted in Scheme 105. C4 carbon would be oxidized and the double bond between C3 and C18 would be dihydroxylated. Two stereoselective alkylation reactions would be executed at C5 and C10 and the deoxygenation at C1 would be done at the best stage of the synthesis.



Scheme 105

At the beginning of this project, the deoxygenation of the ketone at C1 was assumed to be of easy realization through classical reported methodologies. Unfortunately, this transformation, which appeared to be a highly challenging step of the synthesis, will be discussed in the next chapter. Remarkably, various deoxygenation essays on early intermediate ketone **121** failed. For this reason, three different functionalization sequences of the bicyclic backbone have been realized to overcome this problem. To this aim, deoxigenative tests were conducted on almost all the intermediates presented in this unit.

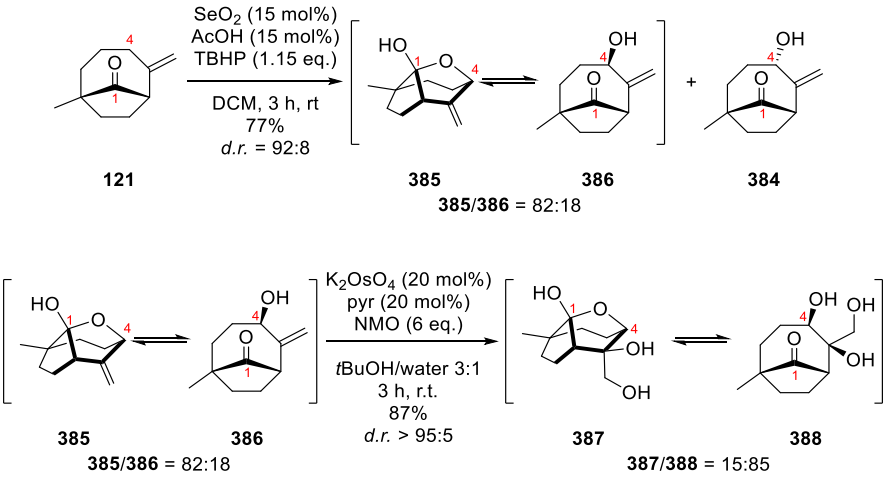
This chapter is divided into three sections, each one devoted to a particular strategy. At the beginning, the direct functionalization of ketone **121** leading to vibsatin B, C3 epimer of vibsatin A, will be presented. A strategy based on a transthioketalization will then follow and the chapter will be closed by a discussion upon the C1-alcohol series which represents the up to date ongoing synthesis. These two last approaches would lead to a vibsatin A derived C3 epimer.

N.B. In some cases, the configuration of the newly formed stereocenters is anticipated in the schemes, but the confirmation of such geometries will be immediately discussed.

5.1 Direct functionalization strategy

Direct functionalization of the unprotected bicyclic ketone **121** was initially envisaged. It was decided to perform an allylic oxidation at C4 followed by a dihydroxylation of the C3-C18 alkene. At the beginning, reported copper and palladium catalysed methods for the allylic

oxidation were tested, but they mostly resulted in the decomposition of the substrate.[130] Oxidation through the use of a catalytic quantity of selenium oxide (SeO_2) in the presence of *tert*-butyl hydroperoxyde (TBHP) and acetic acid, on the other hand, readily provided allylic oxidation in 77% yield in a diastereomeric *ratio* of 92:8 (Scheme 106).[131] After purification, minor isomer **384** was obtained in 5% yield and the major diastereomer was afforded in 70% yield. This latter compound revealed to be an inseparable mixture of two forms **385** and **386** in a 82:18 *ratio* due to a hemiketalic equilibrium between the C4 alcohol and the C1 ketone. The hemiketalic tricyclic form **385** was favoured and this behaviour demonstrated the spatial close proximity between C4 and C1 and, thus, confirmed the configuration of C4. The dihydroxylation reaction at the C3-C18 double bond of **385** and **386** was performed exploiting a catalytic quantity of potassium osmate dihydrate ($K_2OsO_4{\cdot}2H_2O$) in the presence of NMO and pyridine.[132] The reaction smoothly delivered a mixture of triols **387** and **388** in 87% yield ascribable to the hemiketalic equilibrium. Notably, this equilibrium is totally inversed toward the open form **388** (**387**/**388** = 15:85). No C3-epimers were observed (diasteromeric *ratio* higher than 95:5).



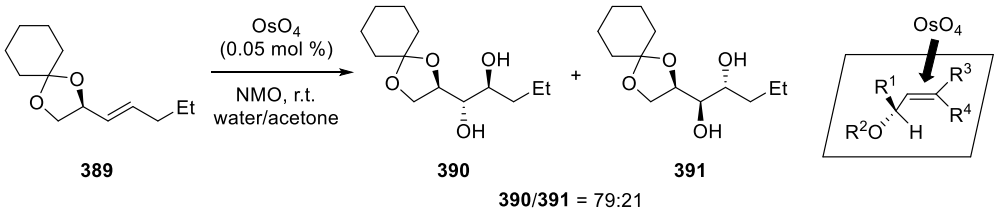
Scheme 106

[130] (a) Chen, M.S.; Prabagaran, N.; Labenz, N.A.; White, C.M. *J. Am. Chem. Soc.* **2005**, *127*, 6970-6971. (b) García-Cabeza, A.; Marín-Barrios, R.; Azarken, R.; Moreno-Dorado, F.J.; Ortega, M.J.; Vidal, H.; Gatica, J.M.; Massanet, G.M.; Guerra, F.M. *Eur. J. Org. Chem.* **2013**, 8307-8314. (c) García-Cabeza, A.; Marín-Barrios, R.; Moreno-Dorado, F.J., Ortega, M.J.; Massanet, G.M.; Guerra, F.M. *Org. Lett.* **2014**, *16*, 1598-1601.

[131] For recent reviews upon allylic oxidation see: (a) Weidmann, V.; Maison, W. *Synthesis* **2013**, *45*, 2201–2221. (b) Nakamura, A.; Nakada, M. *Synthesis* **2013**, *45*, 1421–1451.

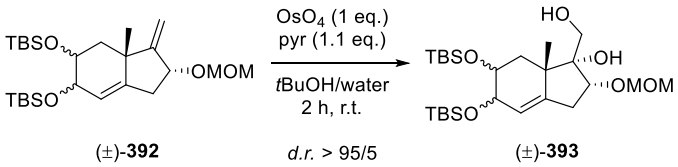
[132] Martín Hernando, J.I.; Rico Ferreira, M.d-R.; Candela Lena, J.I.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron: Asymmetry* **2000**, *11*, 951-973.

In 1983, Kishi and co-workers reported an empirical rule for the stereochemical outcome of the dihydroxylation reactions of allylic alcohols.[133] It was demonstrated, on a series of enantioenriched linear allylic alcohols, that the relative stereochemistry between the preexisting hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major diastereomer in all cases was *anti*. One example is depicted in Scheme 107, olefin **389** is dihydroxylated in the presence of OsO_4 and NMO affording mainly diastereomer **390** (**390**/**391**, *d.r.* 79:21), which presents an *anti*-relationship between the newly formed stereocenter and the adjacent pre-existing one.



Scheme 107

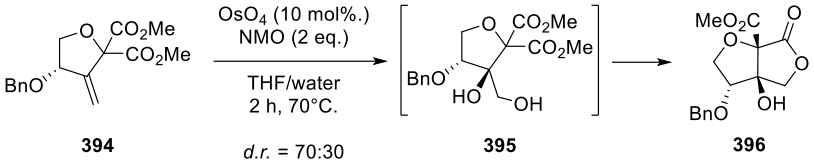
However, this *anti*-relationship is only an empirical rule. Hence, very often, the observed diastereoselectivities were modest and at the same time, for instance, exceptions were found. On cyclic substrates the situation appeared relatively more complex. Arseniyadis in 2007, investigated dihydroxylative reactions starting from an *exo*cyclic allylic alcohol in the course of the synthesis of iridal's core structure.[134] Condensed bicycle (±)-**392** underwent osmylation providing the *cis*-triol (±)-**393** as single diastereomer (Scheme 108).



Scheme 108

On the other hand, in the Hatakeyama's synthesis of the (-)-cinatrin C_1, it was found that, on a 5-membered ring *exo*cyclic allylic benzyl ether **394**, the dihydroxylation reaction afforded a mixture of two diastereomers relative to a 70:30 *ratio* in favour of the *trans* related diol **395**, which underwent lactonisation to provide the bicyclic structure **396** (Scheme 109).[135]

[133] (a) Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943-3946. (b) Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247-2255.
[134] Corbu, A.; Gauron, G.; Castro, J.M.; Dakir, M.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 4745-4748.
[135] Urabe, F.; Nagashima, S.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2013**, *78*, 3847-3857.



Scheme 109

In order to obtain accurate structural informations on compounds **385**/**386** and **387**/**388**, crystals suitable for X-ray diffraction analysis were obtained from mixtures of cyclohexane and Et_2O. Moreover, upon the four structures, only crystals from the hemiketalic forms were obtained and analysed. In Figure 23 is shown the X-ray diffraction analysis representation of compound **385**. From this figure, it is clearly evidenced that the faces of the double bond differ in accessibility. The *Si*-face is expected to be less hindered and consequently preferred in the case of dihydroxylation reaction.

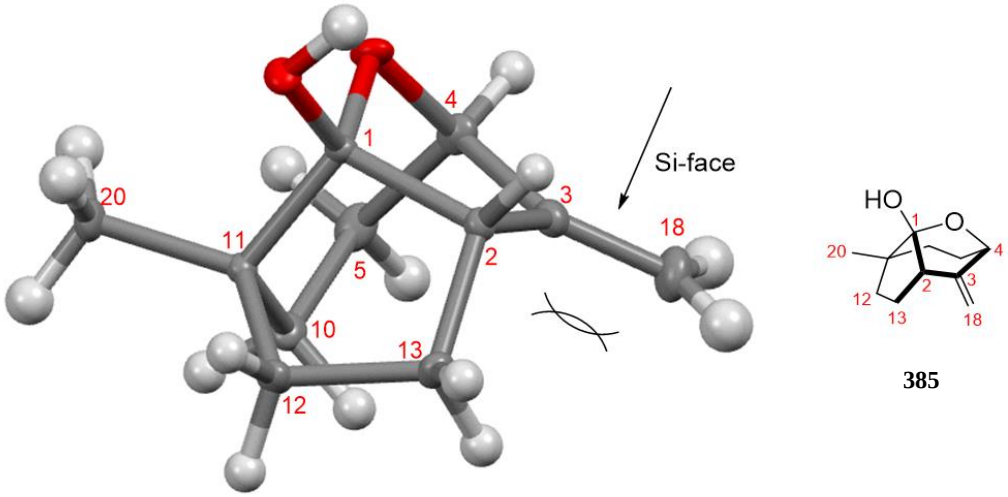
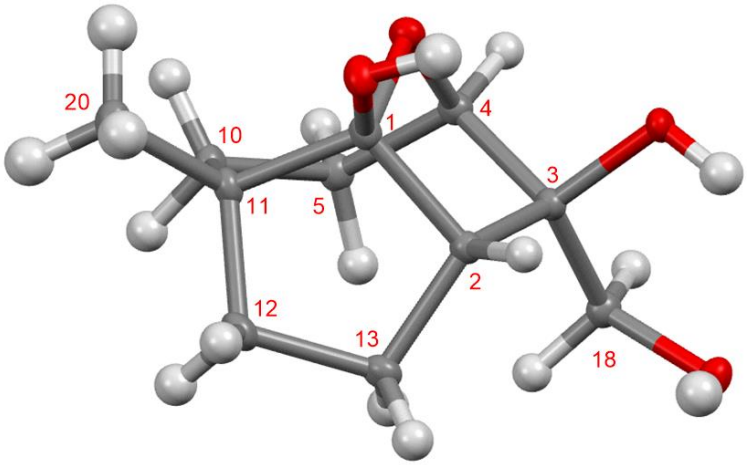
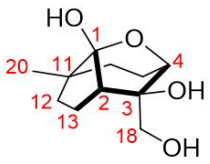


Figure 23

This hypothesis was in good agreement with the reaction involving **385**, **386** and potassium osmate to produce triols **387** and **388**. The hemiketalic form **387** crystallized and its X-ray diffraction structure is shown in Figure 24. Moreover, the configuration at the C3 resulted to be directly related to vibsatin B, meaning a *cis*-relationship between C3 and C4 alcohols.

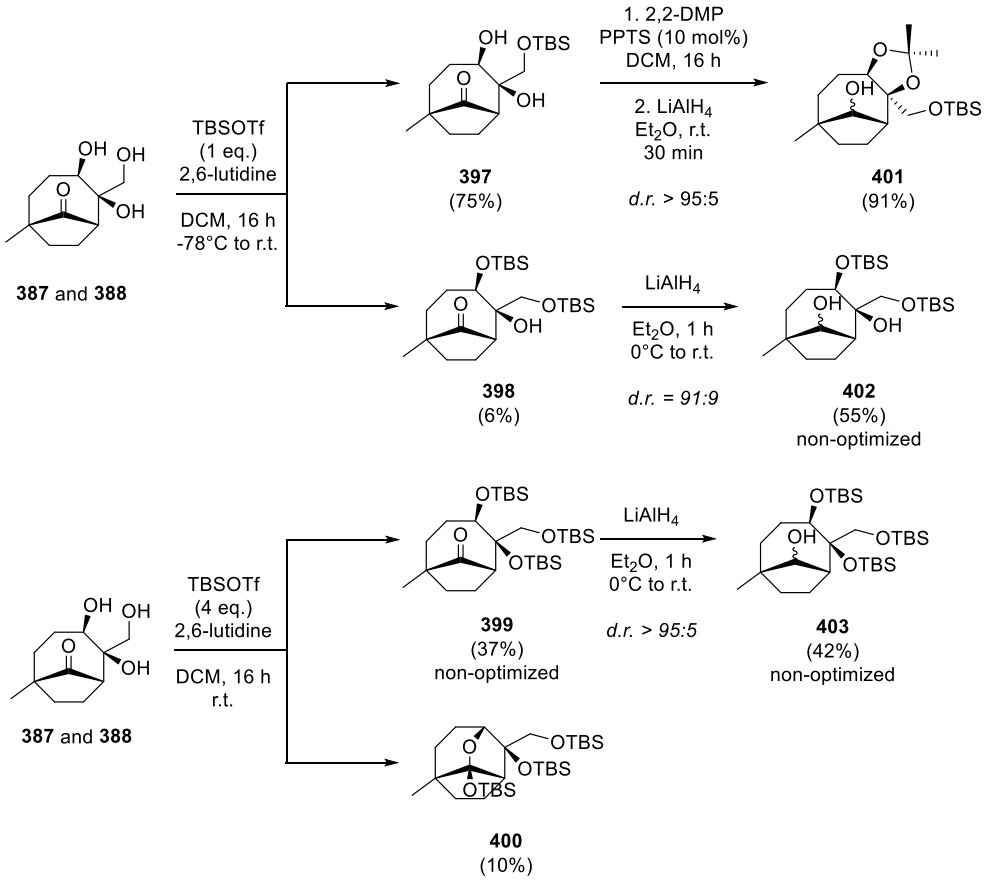




387

Figure 24

Ketotriol **388** was then protected employing TBSOTf. The use of a single equivalent of TBSOTf provided a mixture of monoprotected and *bis*protected ketone **397** and **398** in respectively 75% and 6% yield (Scheme 110). Four equivalents of TBS-triflate, instead, afforded ketone **399** in 37% yield along with 10% of protected hemiketal **400**. Diol **397** was next transformed into an acetonide and subsequent reduction of the ketone function afforded compound **401** stereoselectively in 91% yield (*d.r.* > 95:5). On the other hand, ketones **398** and **399** were reduced to their corresponding alcohols **402** and **403** in respectively 55% and 42% yield, **399** was stereoselectively reduced but **398** exhibited a diastereomeric *ratio* of 91:9. The configuration of the newly formed stereocenter at C1 was not proven but the reduction step for these three compounds is likely to follow the same stereochemical outcome undertaken by ketone **418**, as formerly explained in section 5.3, relative to a 1(*R*) configuration, *i.e.* vibsatin B series.



Scheme 110

Each intermediate synthesised in this Section, represented below in Figure 25, has been tested in various deoxygenative conditions and this will be the subject of the next chapter.

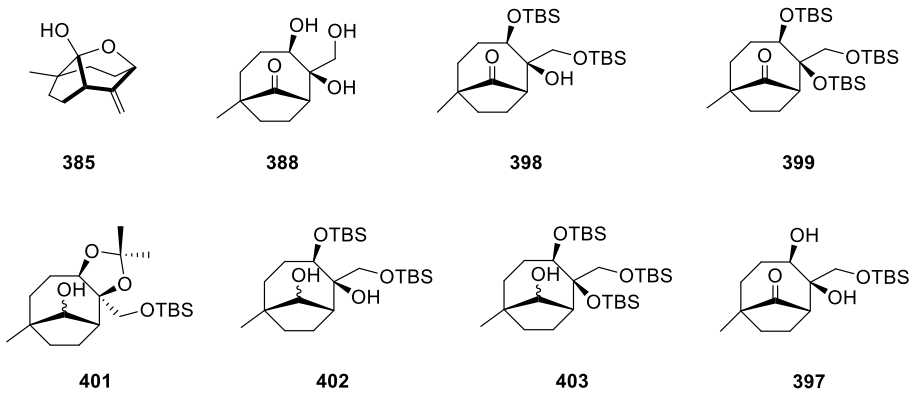
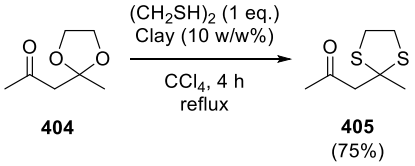


Figure 25

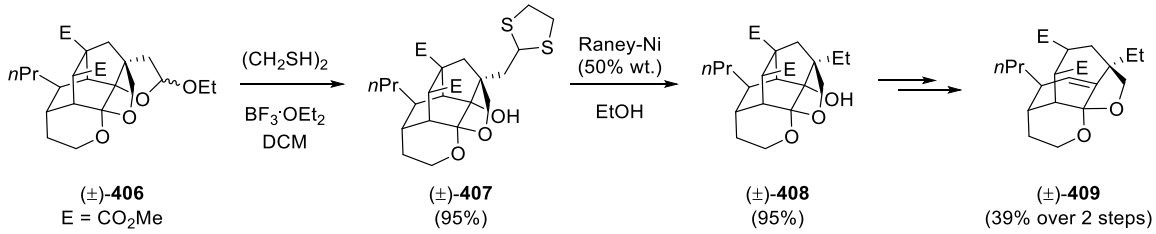
5.2 Transthioketalization strategy

In order to pursue the study of the deoxygenation reaction at C1, it was concomitantly then decided to investigate the possibility to exchange an acetal group by a thioacetal scaffold in the presence of ketones or other functional groups. Indeed, kinetically, the acid catalysed transformation of a ketal into a thioketal is faster than the direct conversion of a ketone into a thioketal. This difference allows for the selective synthesis of thioketals in the presence of free carbonyl groups. For instance, mildly acidic kaolinitic clay catalyses the selective transthioketalization of ketal monoprotected pentanedione **404**, affording thioketal **405** in 75% yield (Scheme 111).[136]



Scheme 111

This transthioketalization strategy was formerly employed in many total synthesis. Wood and his group, for instance, exploited this reaction in the synthesis of the core of phomoidride B.[137] Intermediate (±)-**406**, synthesized in a 6 steps sequence, was treated with ethanedithiol in the presence of a stoichiometric quantity of $BF_3{\cdot}OEt_2$ affording dithiolane (±)-**407** (Scheme 112). Hydrogenation by Raney-Ni (50% weight in water) then delivered intermediate (±)-**408** which was converted in the target molecule (±)-**409** over two steps.



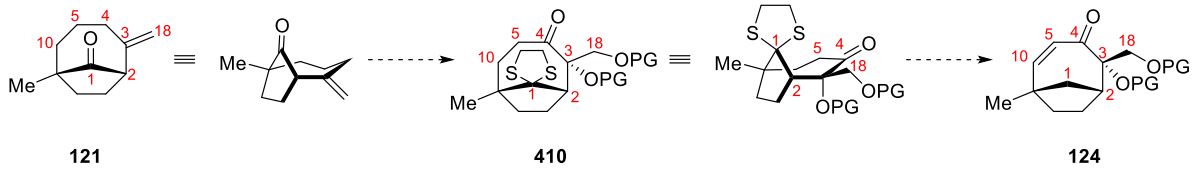
Scheme 112

This above mentioned application to the synthesis of a complex structure, constituted a reliable basis for our work. A synthetic route based on the transthioketalization was devised including successive installation of a ketal at C1 position, oxidation at C4 and

[136] Jnaneshwara, G.K.; Barhate, N.B.; Sudalai, A.; Deshpande, V.H.; Wakharkar, R.D.; Gajare, A.S.; Shingare, M.S.; Sukumar, R. *J. Chem. Soc. Perkin Trans.* **1998**, *1*, 965-968.

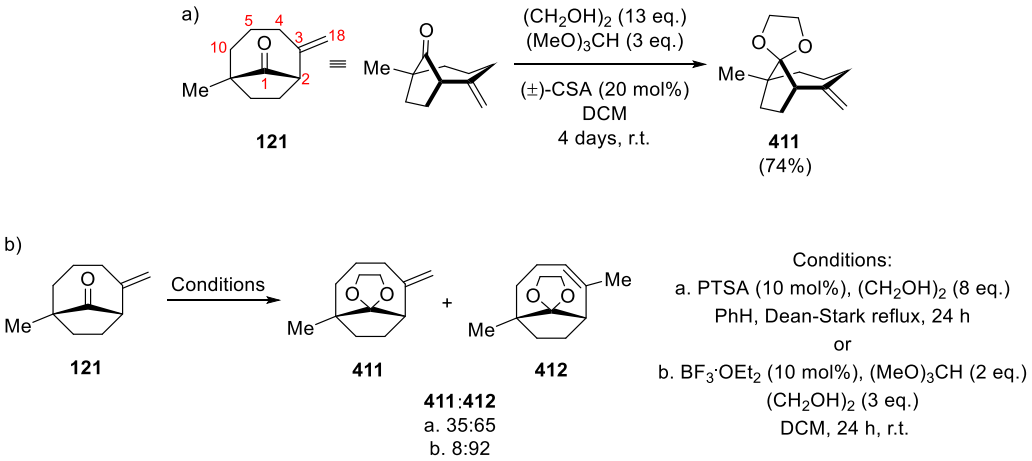
[137] (a) Njardarson, J.T., Wood, J.L. *Org. Lett.* **2001**, *3*, 2431-2434. (b) Murphy, G.K.; Hama, N.; Bedermann, A.; Dong,P.; Schneider, C.M.; McMahon, T.C.; Tao, R.N.; Twenter, B.M.; Spiegel, D.A.; Wood J.L. *Org. Lett.* **2012**, *14*, 4544-4547. (c) Njardason, J.T., McDonald, I.M.; Spiegel, D.A.; Inoue, M.; Wood, J.L. *Org. Lett.* **2001**, *3*, 2435-2438.

dihydroxylation of the double bond at C3-C18 (Scheme 113). The ketal at C1 would then be transformed into its thioketal derivative **410** and subsequent application of Raney-Ni would complete the deoxygenation at C1 center. Final formation of the alkene moiety at C5-C10 would then allow access to α,β-unsaturated ketone **124**.



Scheme 113

To this aim, bicyclic ketone **121** was treated with ethylene glycol in the presence of trimethoxy methane [$(MeO)_3CH$] and 10 mol% camphorsulfonic acid [(±)-CSA] affording ketal **411** in 74% yield (Scheme 114a). Notably, the reaction time for this transformation resulted to be longer when compared to other ketalization protocols. Alternatively, Dean-Stark and Lewis-acid employing conditions were also tested, but in both cases, the *exo* double bond shifted to the *endo* position mainly providing ketal **412** (Scheme 114b).

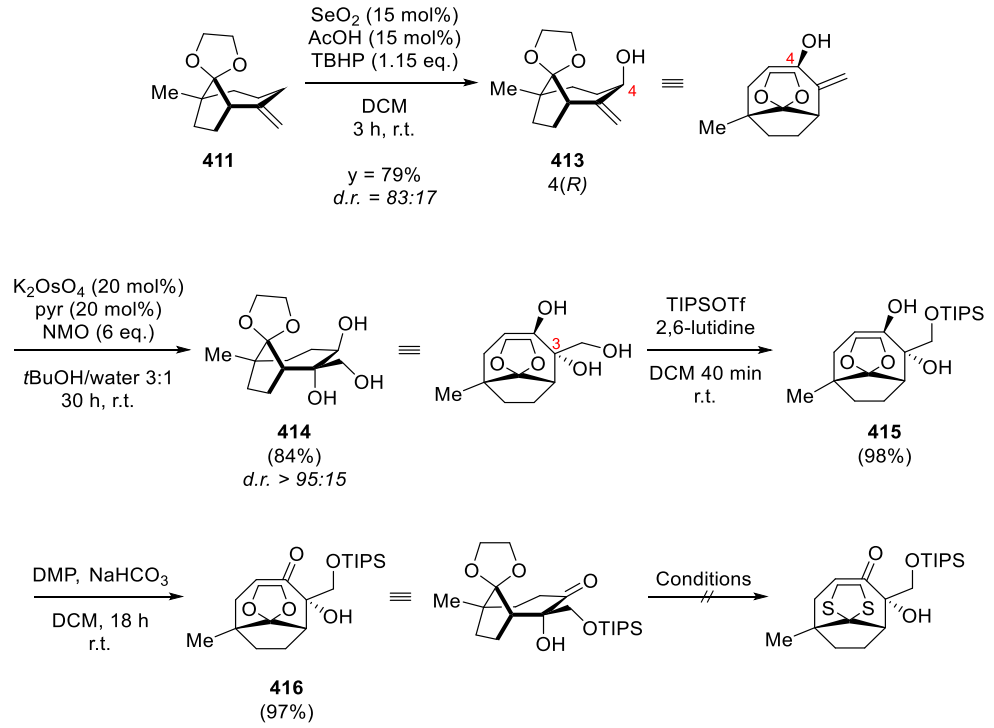


Scheme 114

Allylic oxidation at C4 position was then envisaged. Application of catalytic selenium oxide (15 mol%) in the presence of *t*BuOH and AcOH in DCM for three hours to acetal **411**, afforded the allylic alcohol **413** in 79% yield with a 83:17 diastereomeric *ratio* (Scheme 115). This mixture was directly engaged in the dihydroxylation reaction. This transformation was performed using catalytic potassium osmate (20 mol%) together with NMO and pyridine and resulted to be highly stereoselective since only 3(*S*)-triol **414** was isolated in 84%.[138] The primary alcohol of triol **414** was protected as a TIPS-derivative **415** in 98% yield and the

[138] By NMR analysis on the crude, it was observed also the dihydroxylation product deriving from the minor diastereomer produced in the allylic oxidation step but during the purification stage it was not recovered.

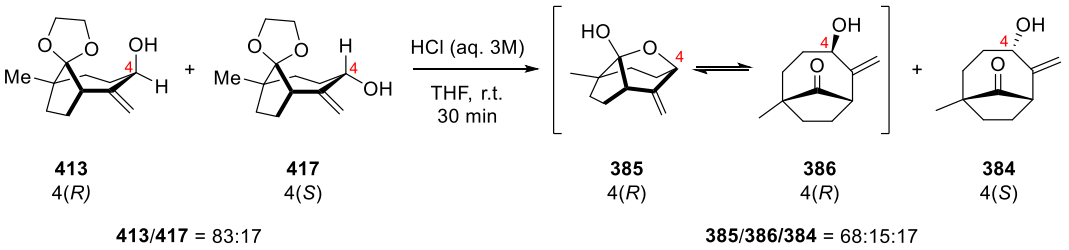
secondary alcohol underwent subsequent Dess-Martin oxidation to afford ketoalcohol **416** in 97% yield. In order to run the transthioketalization of the ketal function of **416**, several catalysts were tested in the presence of ethanedithiol in various conditions. Lewis acid catalysts such as $InCl_3$,[139] $SiO_2/SOCl_2$,[140] nBu_4NBr_3[141] and $TiCl_4$[142] together with non-acidic *in-situ* prepared $(Me_3AlSCH_2)_2$[143] failed to catalyse the reaction. On the other hand, treatment with I_2[144] and $BF_3{\cdot}OEt_2$[5] delivered complex mixtures of products.



Scheme 115

It has not been possible to prove the C4 configuration of the major diastereomer **413** deriving from allylic oxidation through NOESY analysis. However, submitting the mixture of **413** and its epimer **417** to aqueous HCl (3M in THF) for 30 minutes at room temperature, yielded a mixture of three components in which the prevailing form was the tricyclic hemiketalic product **385** presented in Section 5.1 (Scheme 116). On the basis of these results, it was possible to attribute the origin of the hemiketal **385** to alcohol **413**, thus, the configuration at C4 of the predominant diastereomer after allylic oxidation was assumed to be 4(*R*).

[139] Ranu, B.C.; Das, A.; Samanta, S. *Synlett.* **2002**, *5*, 727-730.
[140] Firouzabadi, H.; Iranpoor, N.; Karimi, B.; Hazarkhani, H. *Synlett.* **2000**, *2*, 263-265.
[141] Naik, S.; Gopinath, R.; Goswami, M.; Patel, B.K. *Org. Biomol. Chem.* **2004**, *2*, 1670-1677
[142] Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, *24*, 1289-1292.
[143] Snyder, S.A.; Corey, E.J. *J. Am. Chem. Soc.* **2006**, *128*, 740-742.
[144] Firouzabadi, H.; Iranpoor, N.; Karimi, B.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527-7529.



Scheme 116

The stereochemical outcome of the dihydroxylation reaction at C3 was determined by running NOESY analysis. Due to the overlap of the diastereotopic proton signals resonating in the alkylic spectral zone (1-2 ppm), it was impossible to clearly conclude about the stereochemistry at C3 of triol **414**. On the contrary, on ketone **416**, a strong NOE interaction was found between the C3 hydroxyl group and the C13 proton confirming the 3(*S*) configuration at C3 (Figure 26 and Figure 27), namely vibsatin A series. In this synthetic scheme, the installation of a ketalic group at C1 appeared to be responsible for the inversion of the stereochemistry relative to the dihydroxylation step. Together with the results obtained for the unprotected ketone in the precedent section, it is suggested that, on this type of bridged bicyclic structures, the substituent at C1 is at the origin of the facial selectivity, regardless the configuration of the allylic alcohol.

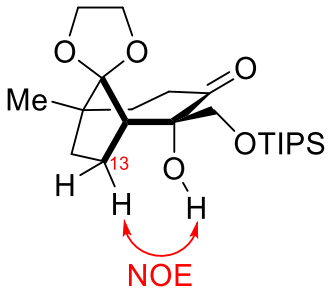


Figure 26

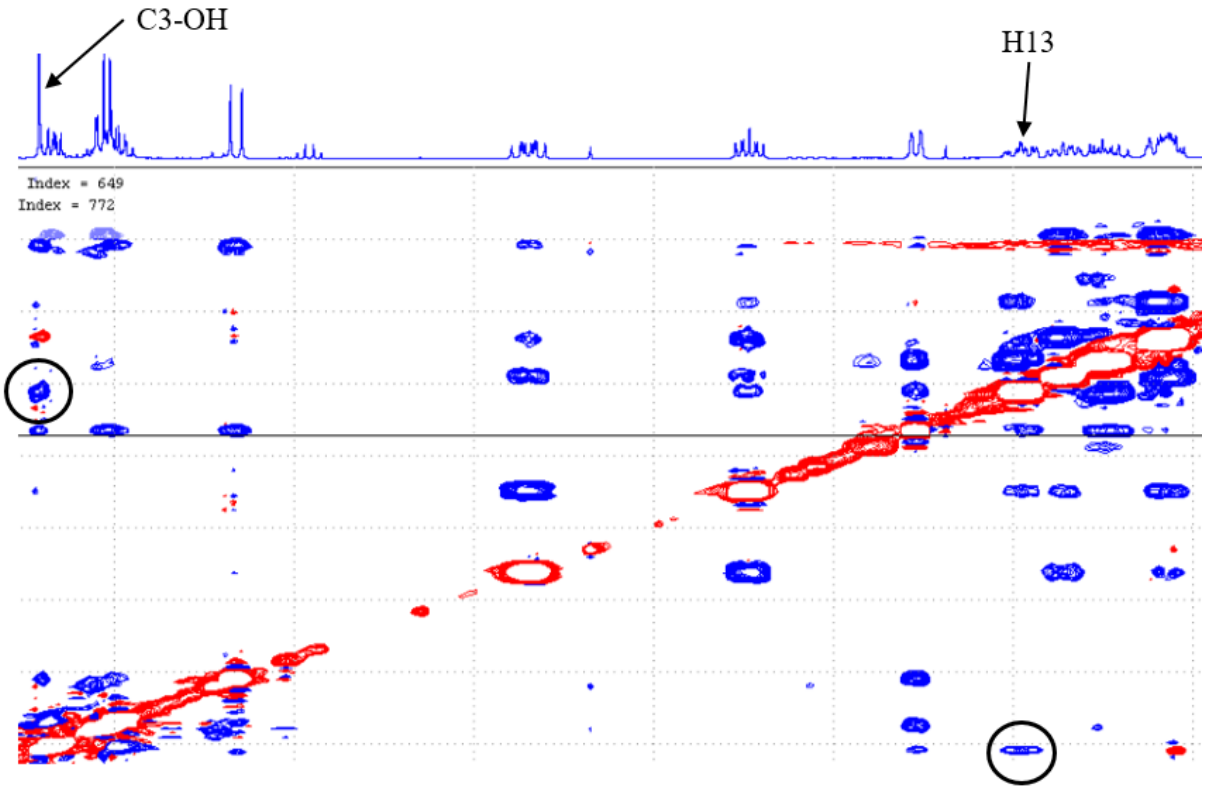
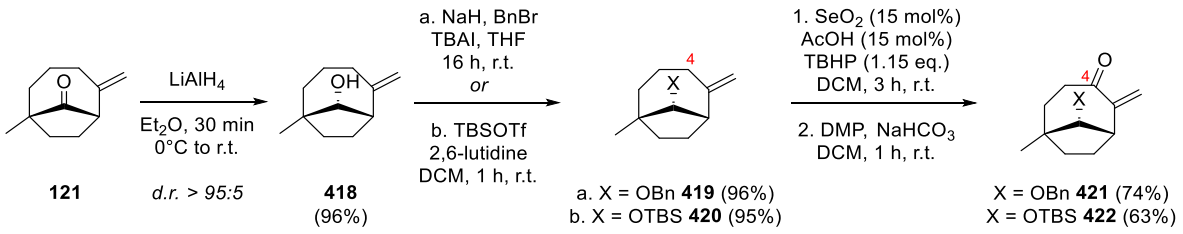


Figure 27

5.3 C1 alcohol series: ongoing synthesis

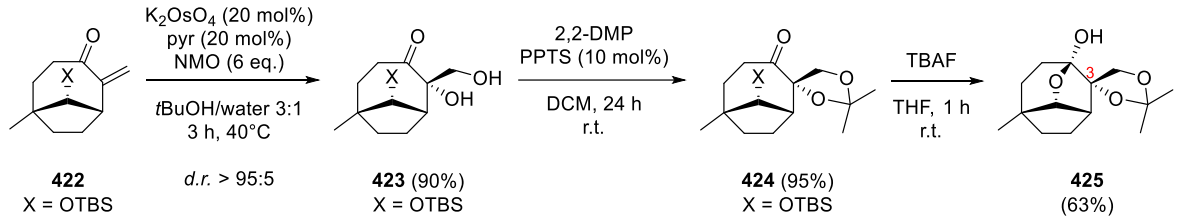
This last part of Chapter 5 will describe the ongoing synthesis that should hopefully lead to the total synthesis of the vibsatin A. To this aim, ketone **121** was reduced to alcohol **418** in quantitative yields and it was then decided to protect the hydroxyl function in two different forms: benzyl ether **419** and TBS ether **420**. These products were respectively obtained in 96% and 95% yields (Scheme 117). Both compounds readily underwent allylic oxidation promoted by SeO_2 and subsequent Dess-Martin oxidation, affording α,β-unsaturated ketones **421** in 74% yield and **422** in 63% yield, respectively for benzyl and TBS series. Noteworthy, it was decided to oxidize the C4-alcohol to ketone in order to investigate about the driving factor of the stereoselection during the subsequent dihydroxylative osmylation.



Scheme 117

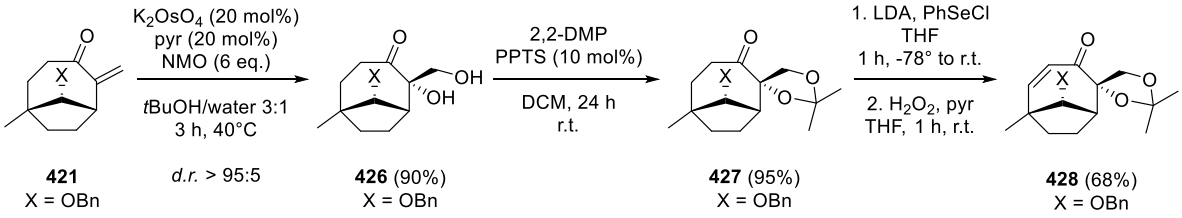
Thus, TBS ether **422** was treated with potassium osmate in the aforementioned conditions stereoselectively delivering the vibsatin A type diol **423**. This result finally validates our hypothesis regarding the shape-induction of the substrate toward functionalization of the double bond (Scheme 118).

Compound **424** was then obtained in quantitative yield after acetonide protection of the diol **423**. Noteworthy, TBAF mediated deprotection of the TBS-group immediately produced another hemiketalic product **425** confirming the (*R*)-configuration of the alcohol at the bridge position (C1). Based on this observation, another evidence arised upon the steric hindrance on the *Re*-face of the ketone of compound **121**.



Scheme 118

Benzyl ether **421** followed a similar synthetic route: stereoselective dihydroxylation provided diol **426** in 90% yield and protection of the latter with dimethoxypropane afforded compound **427** in 95% yield (Scheme 119). The introduction of a phenylselenyl group at C10 and subsequent selenoxide elimination through H_2O_2 in the presence of pyridine, produced the desired α,β-unsaturation in 68% yield over two steps furnishing the substrate **428** suitable for 1,4-addition.



Scheme 119

Once more, in this series, the C3 configuration of **426** was elucidated by NOESY analysis. This time, NOE effect between C3-OH and C13 was observed (Figure 28 and Figure 29).

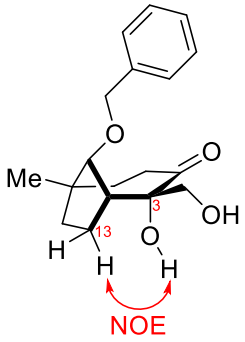


Figure 28

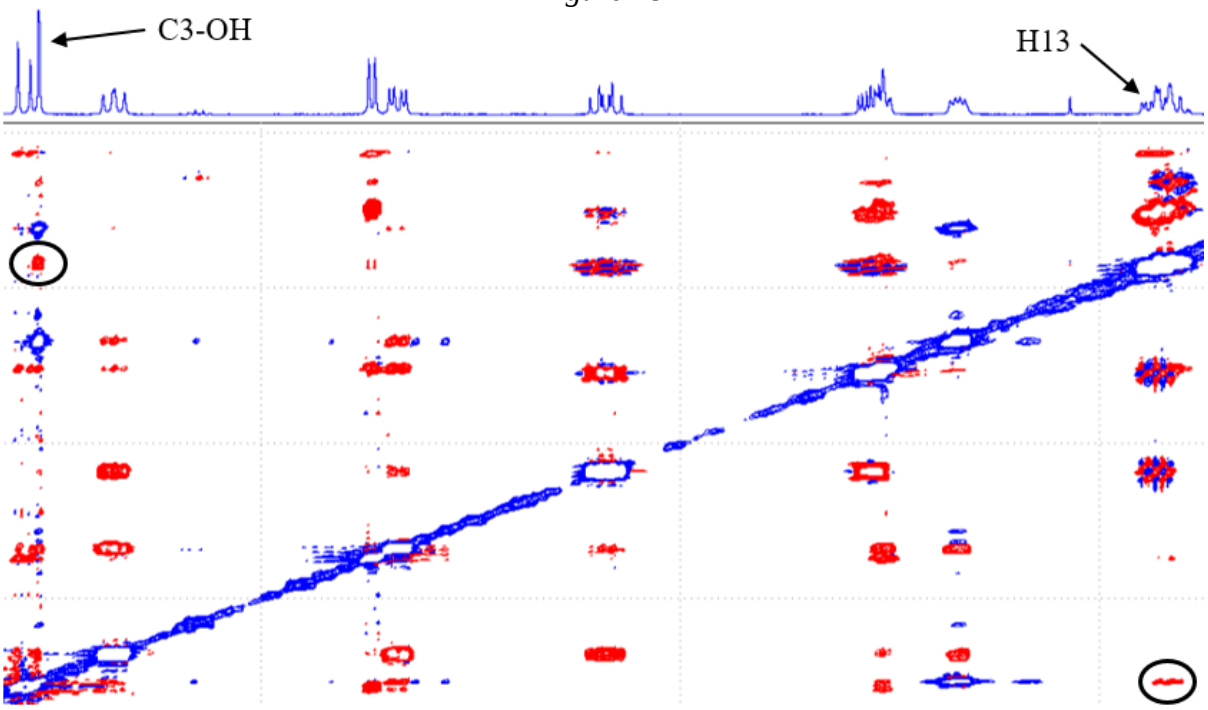
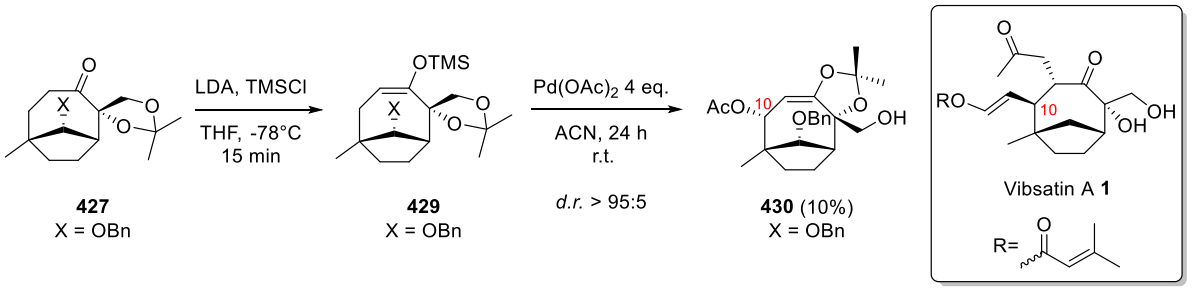


Figure 29

Notably, in order to install the α,β-unsaturation, various methods were examined before the utilization of PhSeCl. The activity of Nicolaou's dehydrogenative methods employing coupled IBX/*N*-oxide reactants proved to be ineffective on both ketone **427** and *in-situ* made silyl enol ether **429** (Scheme 120).[145] Stoichiometric $Pd(OAc)_2$ foreseen in the Saegusa-Ito reaction was then tested and, surprisingly, direct addition of an acetate group onto C10 was observed, delivering product **430**. The configuration of the stereocenter at C10 resulted to be inverted compared to the vibsatins A and B. However, this test proved to be promising for the successive steps of the synthesis. Various modifications of the Saegusa-Ito reaction

[145] (a) Nicolaou, K.C.; Montagnon, T.; Baran P.S. *Angew. Chem. Int. Ed.* **2002**, *41*, 993-996. (b) Nicolaou, K.C.; Gray, D.L.F.; Montagnon, T.; Harrison S.T. *Angew. Chem. Int. Ed.* **2002**, *41*, 996-1000.

exploiting a catalytic quantity of palladium were performed. Shibasaki's, Larock's and Tsuji conditions were employed but only starting material was recovered in cases.[146]



427
X = OBn

429
X = OBn

430 (10%)
X = OBn

Scheme 120

The configuration at C10 of **430** was disclosed by NOESY analysis. A weak NOE interaction was detected between one of the two diastereotopic protons at C18 and the C10 proton (Figure 30 and Figure 31)

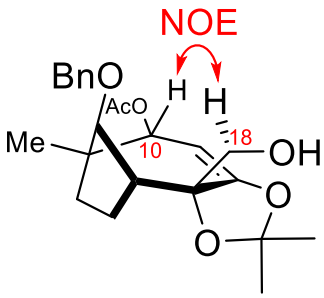


Figure 30

[146] (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5635-5638. (b) Larock, R.C.; Hightower, T.R.; Kraus, G.A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423-2426. (c) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546-14547.

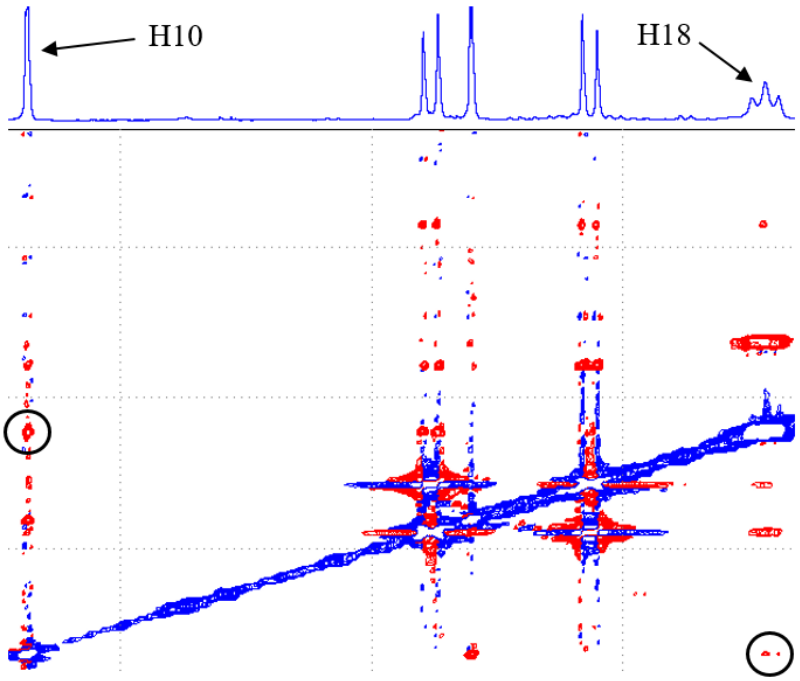
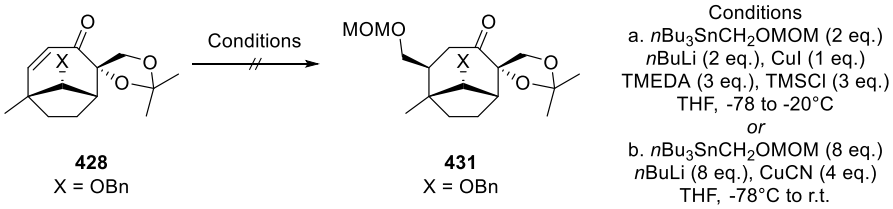


Figure 31

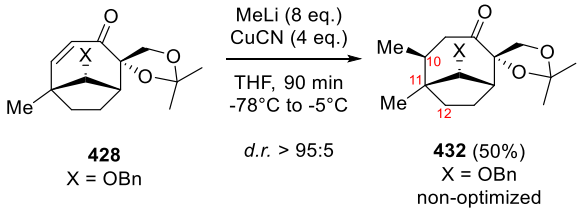
At the present time, the 1,4-addition step is currently under investigation. Initial attempts of insertion of a $MOMOCH_2$- group employing the methodology previously described by Williams in the total synthesis of vibsanin E (**8**, Chapter 1) proved to be unsuccessful.[16] In this method, the -CH_2OMOM group was insalled by reaction of an *in-situ* made cuprate starting from *n*Bu_3SnCH_2OMOM precedently synthesized in two steps as reported in the literature (Scheme 121).[147] Initially, two equivalents of stannane were transmetallated with *n*BuLi and reacted with a single equivalent of copper iodide in the presence of TMEDA and TMSCl to form the Gilman type cuprate (Scheme 121, conditions a), however the latter demonstrated to be ineffective in the alkylation at C10 position of **428** and failed to deliver compound **431**. A modified procedure was then utilized. This time, a more reactive Lipshutz-type cuprate was used. Practically, four equivalents of cyanocuprate were reacted with **428** in previously described conditions, but this approach only afforded the total recovery of the starting material (Scheme 121, conditions b).

[147] Danheiser, R.L.; Romines, K.R.; Koyama, H.; Gee, S.K.; Johnson, C.R.; Medich, J.R. *Org. Synth.* **1993**, *71*, 133-137.



Scheme 121

Considering the bulkiness of $(MOMCH_2)_2CuCN{\cdot}LiCN$ reagent or of $MOMOCH_2$-cuprate, a test reaction was next conducted in order to investigate the reactivity of cyanocuprates for alkylation of the C10 position. To this aim, four equivalents of methyl cyanocuprate were reacted with **428** and, surprisingly, smoothly delivered the desired ketone **432** in 50% yield as a single diastereomer (Scheme 122).



Scheme 122

Moreover, the configuration of the newly formed C10 stereocenter of **432** was confirmed to be 10(*S*), *i.e.* the same configuration as the vibsatins. This assumption was verified through NOESY analysis, which are depicted in Figure 33. A strong NOE correlation between the C10-hydrogen and one proton at C12 was found, validating the 10(*S*) configuration of the newly formed stereocenter (Figure 32).

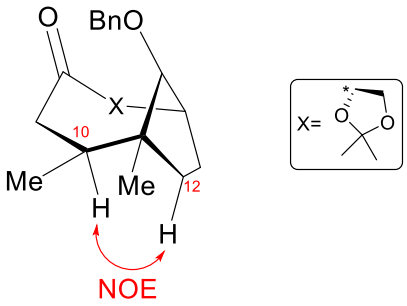


Figure 32

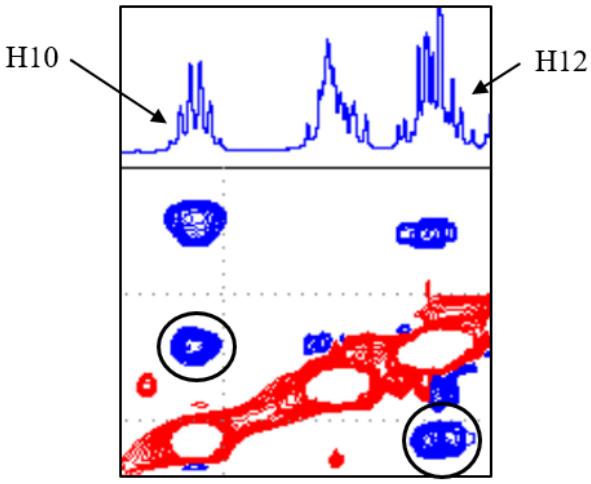
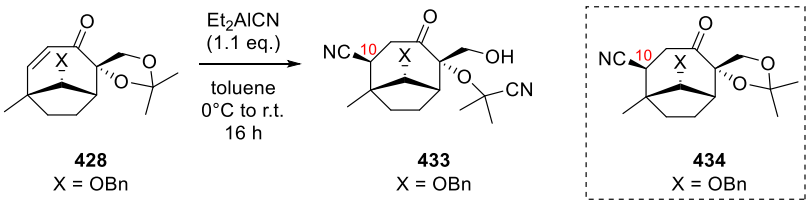


Figure 33

Regarding the low reactivity of alkylcyanocuprates, the insertion of a cyanide group was foreseen as a good alternative to the -CH_2OMOM group. Indeed, based on the work on pyrrocidines described by Kobayashi, α,β-unsaturated ketone **428** was treated with 1.1 eq. Et_2AlCN (1M sol. in toluene).[148] Noteworthy, this reaction was performed on a very small scale (0.1 mmol) and two products were obtained after purification. Surprisingly, the major fraction resulted to be **433** and from preliminary NMR analysis it appeared that the minor fraction should contain the desired compound **434** (Scheme 123).



Scheme 123

433 was subjected to NOESY experiment, two NOE interactions were found between the C10 and the C12 proton and also between the C10 and the C13 (Figure 34 and 35). Once again, this analysis confirmed the 10(*S*) configuration of the C10 center relative to the vibsatin structures.

[148] Tanaka, R.; Ohishi, K.; Takanashi, N.; Nagano, T.; Suizu, H.; Suzuki, T.; Kobayashi, S. *Org. Lett.* **2012**, *14*, 4886-4889.

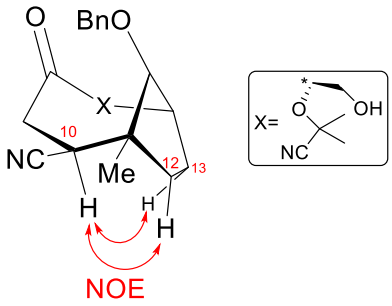


Figure 34

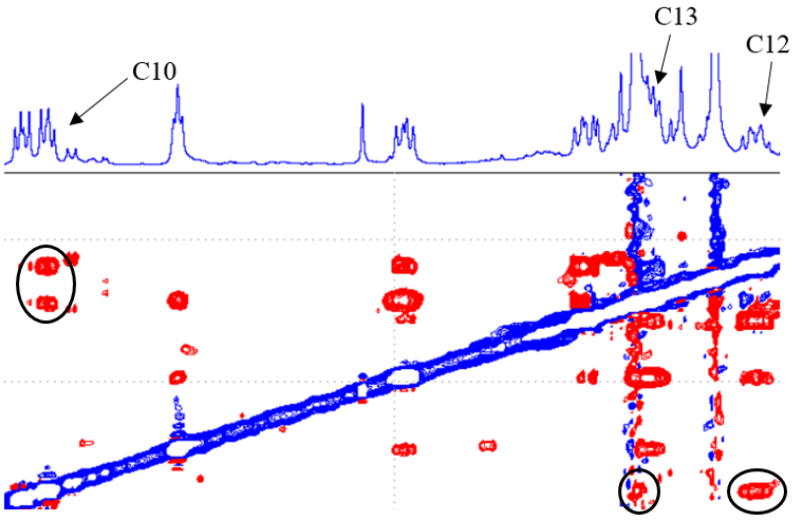
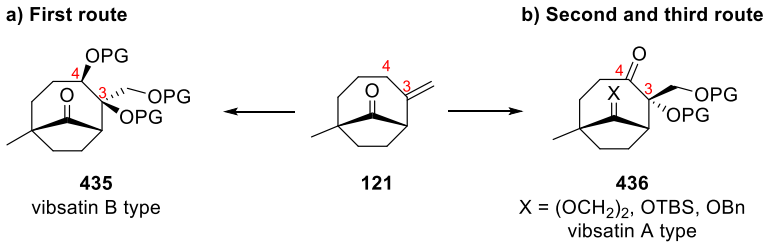


Figure 35

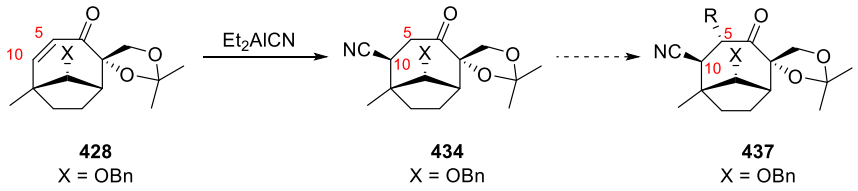
5.4 Conclusion and perspectives

The up to date functionalizations of the bicyclic framework of ketone **121** were presented in this chapter. The first strategy was undertaken starting from unprotected ketone **121** at C1 leading to 3(*R*) vibsatin B type intermediates **435** (Scheme 124a). An inverted stereochemical outcome leading to vibsatin A type 3(*S*) configuration such as **436** was observed when C1 ketal and C1 benzyl or silyl ether substrates were used. These synthetic routes were presented respectively in the second and third part of the chapter (Scheme 124b). Noteworthy, common transformations between the various strategies regarded the allylic oxidation using selenium oxide followed by a dihydroxylation step employing potassium osmate and the Dess-Martin oxidation at C4 providing a carbonyl group. Moreover, the stereochemistry of the dihydroxylation reactions demonstrated to be dependent on the substituent present at C1, whereas the C4 configuration appeared to be irrelevant.



Scheme 124

The conjugate addition at C10 of the α,β-unsaturated ketone **428** is still under investigation (Scheme 125). Notably, among the various methods, the insertion of a cyanide group already provided promising results but, at the moment, it was only performed on a small scale and further optimization of the reaction is required in order to afford C10 alkylation product **434** in larger scales. Once the alkylation at C10 validated, our attention will be turned to the alkylation at the C5 position in order to complete the installation of all the five stereocenters of the vibsatin skeleton such as in **437**.

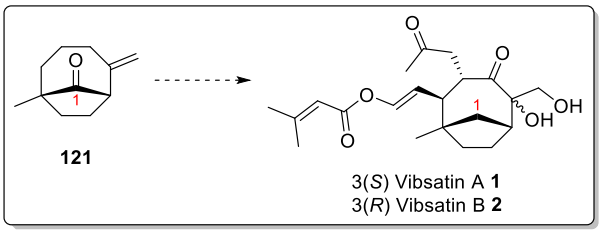


Scheme 125

Noteworthy, most of the synthesized compounds underwent various deoxygenative tests presented in the next chapter.

6. Deoxygenation

Once the bicyclic scaffold was set-up, the removal of the oxygen at the C1 carbon was of mandatory importance. In this context, first deoxygenation tests were conducted on bicyclic ketone **121** depicted in Scheme 126. Despite the various powerful chemical techniques employed in this aim, the deoxygenation at C1 appeared to be a critical step. For this reason, the numerous intermediates synthesised in Chapter 5, bearing an alcohol or a ketone function at C1, were engaged. Notably, in the literature, examples of successful deoxygenation reactions applied on bridged bicyclic-[n.m.1] molecules are scarce but further investigation are currently in progress.



Scheme 126

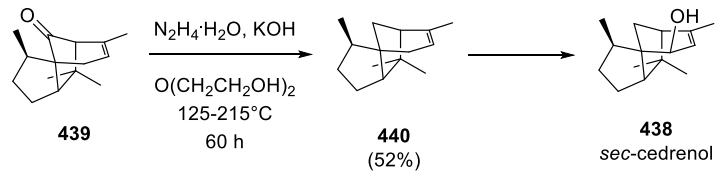
In this chapter, the various employed techniques will be briefly introduced followed by the analysis of all the trials performed on the different substrates. The chapter is divided in four parts, depending on the type of chemistry employed. Wolff-Kishner based reactions will be the topic of the first part and Mozingo type reductions will be explained in the second subchapter along with a brief introduction upon Clemmensen based deoxygenation. Discussion upon hydride displacement transformations will be gathered in the fourth part and Barton-McCombie reductions will also be discussed. Finally, a ring opening metathesis approach will close then the chapter.

6.1 Wolff-Kishner type reductions

The Wolff-Kishner reduction reaction is one of the oldest chemical transformation discovered, originally reported in 1911 by Nikolai Kishner and Ludwigg Wolff. The primary reported harsh procedures involved the addition of the preformed hydrazone or semicarbazone to hot potassium hydroxide.[149] Over the years, various modification have been accomplished aiming to the execution of the transformation under milder conditions. The most famous is the Huang-Minlon modification, which employs hydrazine hydrate and a base

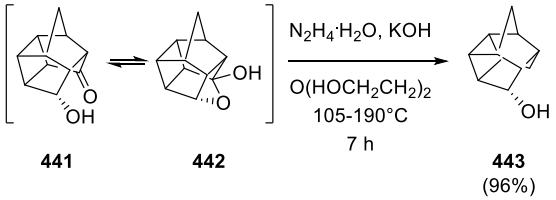
[149] (a) Kishner, N.J. *Russ. Phys. Chem. Soc.* **1911**, *43*, 582-595. (b) Wolff, L. *Justus Liebigs Ann. Chem.* **1912**, *394*, 86-108.

in a one-pot tandem sequence in high boiling point solvents.[150] This methodology foresees the formation of the hydrazone around 120°C, subsequent addition of the base and final distillation of the excess of hydrazine and water at 160°C. The expulsion of nitrogen gas is then afforded at temperatures over 190°C. One recent example is represented by the synthesis of *sec*-cedrenol **438** reported by Pettus in 2011 in which ketone **439** undergoes deoxygenation affording **440** in 52% (Scheme 127).[151] Notably, the hydrazone formation was performed at 120°C over 48 hours, the temperature was then raised to 185°C for 6 hours in order to eliminate the hydrazine excess and finally the expulsion of the nitrogen molecule was realized at 215°C over 6 hours.



Scheme 127

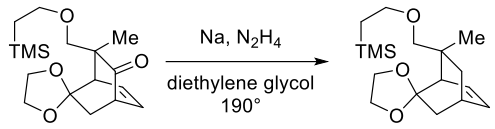
Moreover, during the same year, Kassiou and his group demonstrated the successful applicability of the procedure on hemiacetalic centers during their synthesis of homocubanes.[152] Intramolecular hemiacetal **442** and its open form **441** underwent deoxygenation in quantitative yields affording alcohol **443** (Scheme 128).



Scheme 128

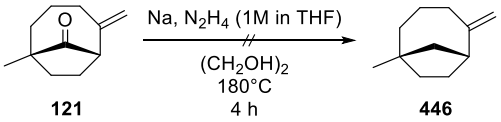
Metallic sodium was also used as a base in protic solvents. Paquette and his group, for instance, reported the deoxygenation of a bicyclo[2.2.2]octenone derivative **444** employing metallic sodium and hydrazine in diethylene glycol affording bicyclic octene **445** in 71% yield (Scheme 129).[153]

[150] Huang-Minlon. *J. Am. Chem. Soc.* **1946**, *68*, 2487-2488.
[151] Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603-1608.
[152] Banister, S.D.; Moussa, I.A.; Beinat, C.; Reynolds, A.J.; Schiavini, P.; Jorgensen, W.T.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 38-41.
[153] Paquette, L.A.; Ra, C.S.; Silvestri, T.W. *Tetrahedron* **1989**, *45*, 3099-3106.



Scheme 129

In our case, the first attempt exploiting this chemistry was performed on ketone **121** using metallic sodium and hydrazine (1M sol. in THF) in ethylene glycol (Scheme 130).[154] The expected product **446** would have been relatively volatile and, due to the high temperatures required in this transformation, this reaction was performed in a sealed tube in order to avoid the possible loss of the product. The use of high boiling point polar solvents resulted in problematic work-up stages. However, in this case, only starting product was recovered.



Scheme 130

Our attention then turned to three different less volatile substrates illustrated in Figure 36. Various conditions were investigated and triols **388** and **397** both provided a complex mixture of degradation products. Hemiacetal **385**, on the other hand, demonstrated to be inert toward hydrazine in the presence of various bases also at temperatures above 200°C and the starting material was systematically recovered.[155]

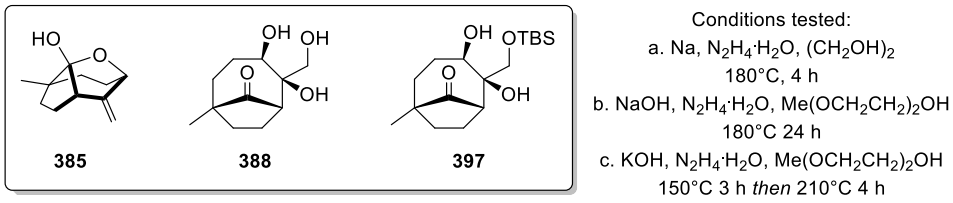
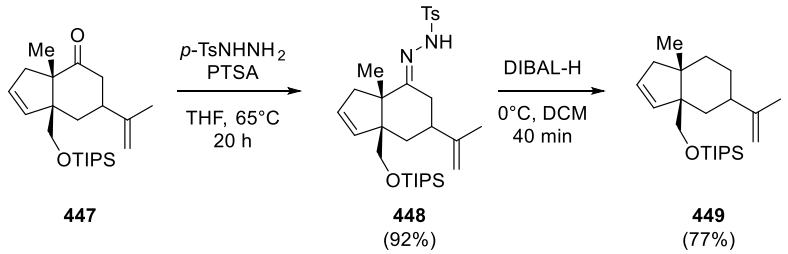


Figure 36

In 1963, Caglioti and his group developed a two-step process for the deoxygenation of ketones or aldehydes derived from the classical Wolff-Kishner procedure.[156] This represents one of the mildest methodology as it allows to execute the deoxygenation of carbonyl compounds at lower temperatures. On the other hand, this modification foresees the isolation of the intermediate hydrazone. Indeed, in the first step, a tosyl hydrazone is generated and subsequent reduction of the latter completes the deoxygenation. This method became

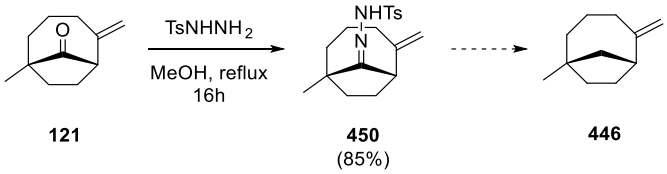
[154] Nickon, A.; Zurer, P.S. *J. Org. Chem.* **1981**, *46*, 4685-4694.
[155] Acherar, S.; Audran, G.; Cecchin, F.; Monti, H. *Tetrahedron* **2004**, 5907-5912.
[156] (a) Caglioti, L.; Magi, M. *Tetrahedron* **1963**, *19*, 1127-1131. (b) Caglioti, L. *Tetrahedron* **1966**, *22*, 487-493.

relatively popular and is still employed in various synthetic reports. For instance, it was used in the total synthesis of (+)-cyperolone by Kirsch in 2012.[157] Ketone **447** was reacted with *p*-$TsNHNH_2$ affording hydrazone **448** in 92% yield, further reduction of the latter by DIBAL-H then delivered the deoxygenated cyclohexane **449** in 77% yield (Scheme 131).



Scheme 131

The Caglioti modification was employed for our deoxygenation essays. The first test was conducted using ketone **121** by treatment with tosyl-hydrazide in MeOH affording hydrazone **450** in 85% yield (Scheme 132).



Scheme 132

The resulting tosyl hydrazone was reacted with an array of reducing agents, including: $LiAlH_4$,[158] DIBAL-H,[159] $NaBH_3CN$,[160] $NaBH_3CN/ZnCl_2$,[161] catecholborane/NaOAc[162] and $CeCl_3/LiEt_3BH$. When hydrides like $NaBH_3CN$ were used, the departing product was systematically recovered, otherwise $LiAlH_4$ and DIBAL-H induced the cleavage of the hydrazone and provided the starting ketone **121**.

The condensation of the tosyl hydrazide was tested onto various carbonyl compounds, which are depicted in Figure 37. Notably, the substrates were heated in MeOH in the presence of tosyl hydrazine and, when **385** and **388** were reacted, catalytic PTSA. However, in all cases the departing product was recovered.

[157] Klahn, P.; Duschek, A.; Liébert, C.; Kirsch, S.F. *Org. Lett.* **2012**, *14*, 1250-1253.
[158] Tkachev, A.V.; Rukavishnikov, A.V.; Gatilov, Y.V.; Bagrjanskaja, I.Y. *Tetrahedron: Asymmetry* **1992**, *3*, 1165-1187.
[159] Lightner, D A.; Gawroński, J.K.; Bouman, T.D. *J. Am. Chem. Soc.* **1980**, *102*, 1983-1990.
[160] Frey, B.; Schnaubelt, J.; Reiβig, H.U. *Eur. J. Org. Chem.* **1999**, 1385-1393.
[161] Kim, S.; Oh, C.H.; Ko, J.S.; Ahn, K.H.; Kim, Y. *J. Org. Chem.* **1985**, *50*, 1927-1932.
[162] Kabalka, G.W.; Baker Jr., J.D. *J. Org. Chem.* **1975**, *40*, 1834-1835.

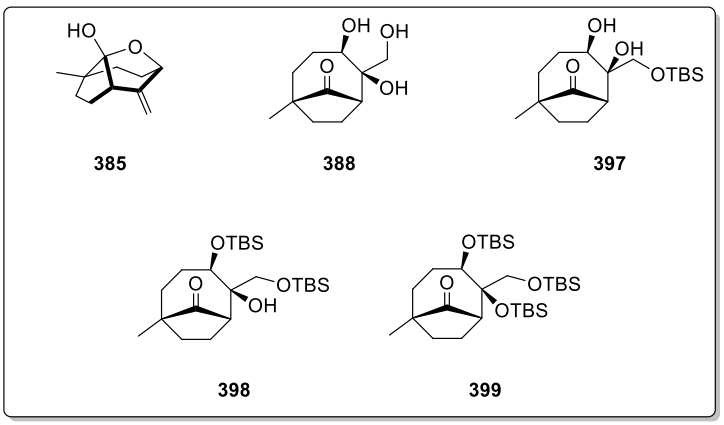


Figure 37

6.2 Mozingo type reductions and sulphur chemistry

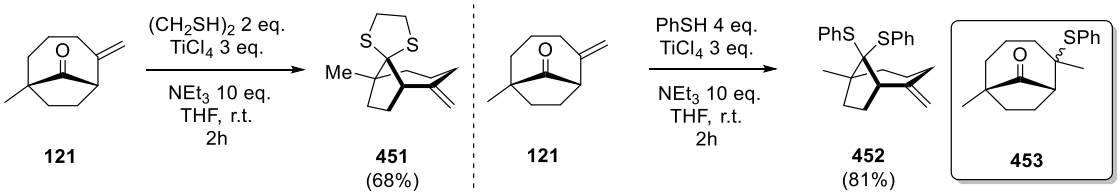
As previously explained in section 5.2, the thioacetalization strategy at an advanced stage of the synthesis failed. Nevertheless, the installation and subsequent desulfurization of a thioacetal remain methodologies that are still exploited in much reported synthesis and represent a classical method for the deoxygenation of carbonyl compounds.[163,164]

It was interesting to test the possibility to synthesize and reduce some dithianes and thus reducing the C1 ketonic carbon to methylene. To this aim, our objective was to test the feasibility of the process, not the chemoselectivity. Ketone **121** was reacted with ethanedithiol and with phenylthiol affording compounds **451** and **452** respectively in 68% and 81% yield (Scheme 133). The conditions employed for the syntheses of these dithianes foresee the stoichiometric utilization of $TiCl_4$ and a large excess of NEt_3. Triethylamine was utilized in order to prevent the shift of the double bond from the *exo*- to the *endo*-position.[165] Notably, other Lewis acid were tested: both $BF_3{\cdot}OEt_2$ and $SnCl_4$ caused the addition of the thiol onto the double bond affording **453**.

[163] References relative to Raney-Ni: (a) Paquette, L.A. ; Ham, W.H. *J. Am. Chem. Soc.* **1987**, *109*, 3025-3036. (b) Meng, X-L.; Liu, T.; Sun, Z-W.; Wang, J-C.; Peng, F-Z.; Shao, Z-H. *Org. Lett.* **2014**, *16*, 3044−3047 (c) Pal, S.K.; Gupta, P.D.; Mukherjee, D. *Tetrahedron* **2002**, *58*, 1765-1771. (d) Padwa, A.; Brodney, M.A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119-3128.

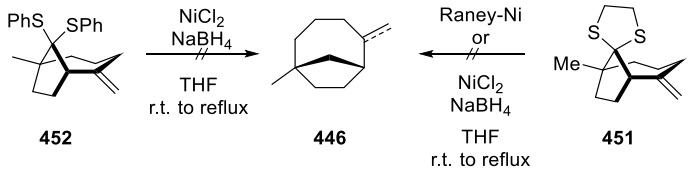
[164] References relative to $NiCl_2/NaBH_4$: (a) Clark, J.; Grantham, R.K.; Lydiate, J. *J. Chem. Soc.* **1968**, 1122-1124. (b) Paul, R.; Buisson, P.; Joseph, N. *Ind. Eng. Chem.* **1952**, *44*, 1006-1010. (c) Truce, W.E.; Perry, F.M. *J. Org. Chem.* **1965**, *30*, 1316-1317.

[165] The utilization of Lewis acids usually catalyse the shift of the double bond from an *exo*- position toward an *endo* position. See Section 6.6 for an accurate explanation.



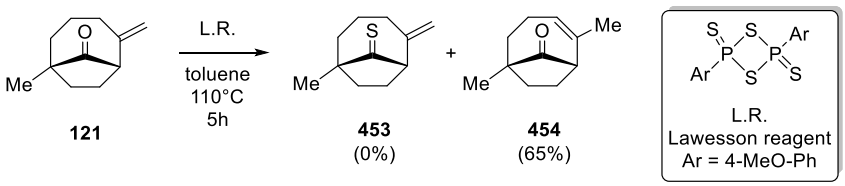
Scheme 133

The presence of the *exo*-double bond was taken into account when executing these reactions and, as formerly said, an eventual hydrogenation of the unsaturation was irrelevant. The synthesised dithianes were subsequently engaged in desulfurization tests: **451** and **452** were treated with Raney-Ni or with $NaBH_4/NiCl_2$ in various conditions (Scheme 134). Compound **446** was never observed and the various reactions mostly resulted in the recovery of the starting products or in the hydrogenation of the double bond.



Scheme 134

The possibility to synthesize and then reduce a thiocarbonyl group was then explored. Lawesson's reagent is renowned to be a powerful reagent for thionation of oxygen containing functional groups. Indeed, Lawesson's reagent demonstrated to be more effective on hindered substrate and to necessitate shorter reaction times compared to P_4S_{10}.[166] Otherwise, it is not selective for oxygenated groups and usually the order of reactivity is: alcohol > amides > ketones > esters.[167] However, the application of the Lawesson's reagent to ketone **121** at 110°C in toluene for five hours failed to afford **453** deriving from thionation of the carbonyl function (Scheme 135). On the other hand, compound **454**, in which the double bond shifted to a more stable *endo*-position, was obtained in 65% yield.



Scheme 135

[166] Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210-5278.
[167] Ori, M.; Nishio, T. *Heterocycles* **2000**, *52*, 111-116.

6.3 Clemmensen reaction

The Clemmensen reaction is one of the oldest deoxygenative transformation published.[168] The originally reported conditions employ zinc amalgam and gaseous hydrochloric acid. Various modifications aiming to avoid the use of mercury and to execute this reduction in organic solvents were reported over the years. The exact mechanism of the reaction has not been fully elucidated although it is known that alcohols are not intermediates.[169] It was decided to test the reactivity of our compounds in the acidic conditions related to the reaction.

Because of the aforementioned acidity, only a small array of three compounds represented in Figure 38 were thought as suitable substrates. Two different sets of conditions corresponding to different degrees of reactivity were tested. We started examining the behaviour of Zn powder and TMSCl in a mixture of *i*PrOH and DCM then we switched to harsher aqueous hydrochloric acid and Zn powder refluxed in ethanol.[170] In all cases the starting material was recovered.

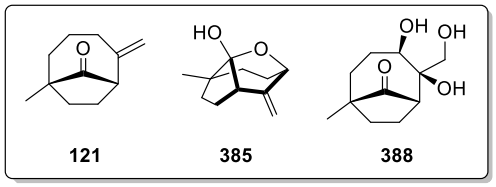


Figure 38

6.4 Hydride displacement

Once the difficulty of deoxygenating the C1 carbon in the form of sp^2 carbon stated, the latter was reduced to sp^3 carbon and various attempts to eliminate the resulting alcohol were conducted. The transformation of an alcohol function to a leaving group followed by a nucleophilic substitution by an hydride is a common method for the deoxygenation of alcohols.[171] To this aim, the precedently synthesised alcohol **418** was transformed into its mesyl derivative **455** (Scheme 136). This compound demonstrated to be unstable towards usual operative conditions and the crude mixture was obtained by simple evaporation of the solvent from the reaction flask using a flush of argon followed by vacuum. The solvent was added and the hydride displacement tests were accomplished.

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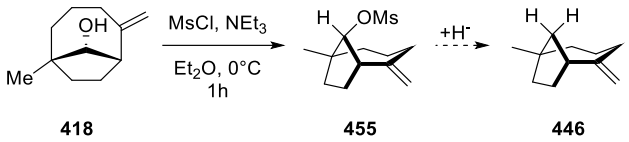
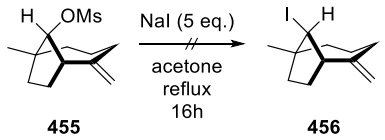
[168] Clemmensen, E. *Chemische Berichte* **1913**, *46*, 1837-1843.
[169] Saji, T.; Hoshino, K.; Ishii, Y.; Goto, M. *J. Am. Chem. Soc.* **1991**, *113*, 450-456.
[170] For Zn/TMSCl see: (a) Xu, S.; Toyama, T.; Nakamura, J.; Arimoto, H. *Tetrahedron Lett.* **2010**, *51*, 4534-4537. For Zn/HCl see: (b) Kraft, P.; Eichenberger, W. *Eur. J. Org. Chem.* **2003**, 3735-3743.
[171] (a) Mortimore, M.; Cockerill, G.S.; Kocienski, P.; Treadgold, R. *Tetrahedron Lett.* **1987**, *28*, 3747-3750. (b) Hanessian, S.; Murray, P.J.; Sahoo, S.P. *Tetrahedron Lett.* **1985**, *26*, 5623-5626.



Scheme 136

In order to get access to alkene **446**, various hydride sources were examined, including: $LiAlH_4$, DIBAL-H, $NiCl_2/NaBH_4$ and $LiEt_3BH$. In most cases, the attack of the reducing agent occurred on the sulphur atom and the corresponding alcohol **418** was regenerated.

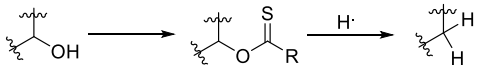
However, in order to investigate about the possibility to invert the configuration at C1, a Finkelstein reaction was also tested on the mesylate **455** in order to get access to iodo derivative **456**. Refluxing **455** over 16 h in acetone resulted only in the recovery of the starting alcohol **418** (Scheme 137).[172]



Scheme 137

6.5 Barton-McCombie reaction

In 1975, British chemists Derek Barton and Stuart McCombie, developed a new radical method for the deoxygenation of alcohols.[173] The method states the transformation of the alcohol into a thiocarbonyl-derivative and subsequent deoxygenation by the using a radical source such as nBu$_3$SnH and a radical initiator, for example AIBN (Scheme 138).

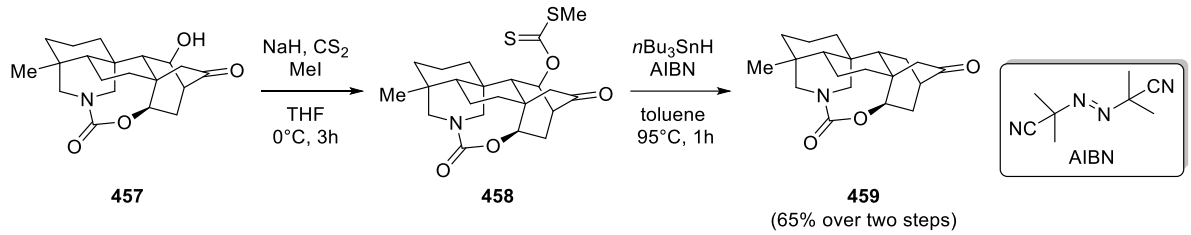


Scheme 138

Although various modifications aiming to avoid the utilization of tin derivatives were described, this method is still one of the most powerful and reliable.[174] Nowadays it is still utilised in a variety of the total synthesis reports in which an alcohol must be reduced. For instance, Sarpong and his group applied this approach in the course of the synthesis of the hetidine and atisine skeletons.[175] Ketoalcohol **457** was transformed into xanthate **458** by

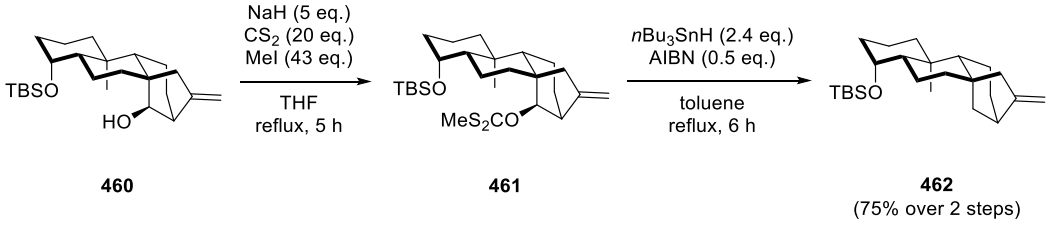
[172] Baughman, T.W.; Sworen, J.C.; Wagener, K.B. *Tetrahedron* **2004**, *60*, 10943-10948
[173] Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *0*, 1574-1585.
[174] (a) Chatgilialoglu, C. *Acc. Chem. Res.***1992**, *25*, 188-194. (b) Postigo, A.; Kopsov, S.; Ferreri, C.; Chatgilialoglu, C. *Org. Lett.* **2007**, *9*, 5159-5162. (c) Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron Lett.* **1991**, *32*, 2569-2572. (d) Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Synlett* **1991**, 6, 435-438.
[175] Hamlin, A.M.; Lapointe, D.; Owens, K.; Sarpong, R. *J. Org. Chem.* **2014**, *79*, 6783-6800.

sequential addition of: NaH, CS_2 and MeI (Scheme 139). Heating **458** in toluene at 95°C for one hour in the presence of nBu$_3$SnH and AIBN afforded 65% of deoxygenated compound **459**.



Scheme 139

Another example of this method regards the total synthesis of (±)-cafestol reported by Hong and co-workers.[176] Notewothy, in this case, the deoxygenation was run in the presence of an *exo*-unsaturation. Indeed, alcohol **460** was transformed into xanthate **461** and radical deoxygenation was accomplished providing alkene **462** in 75% yield (Scheme 140). This example was particularly relevant because of the similarity between substrate **460** and the bicyclic alcohol **418**.



Scheme 140

Various thiono-derivatives are capable to undergo radical deoxygenation, two of the most utilised are the methyl xanthate and the imidazol-1-ylthiocarbonyl (Figure 39).[177]

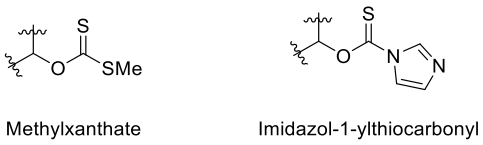
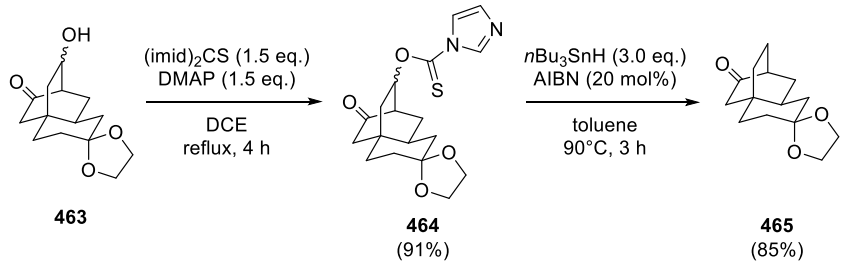


Figure 39

A imidazol-1-ylthiocarbonyl derivative, for instance, was successfully employed in the synthesis of Platencin reported by Yadav and his group.[178] Alcohol **463** was transformed into

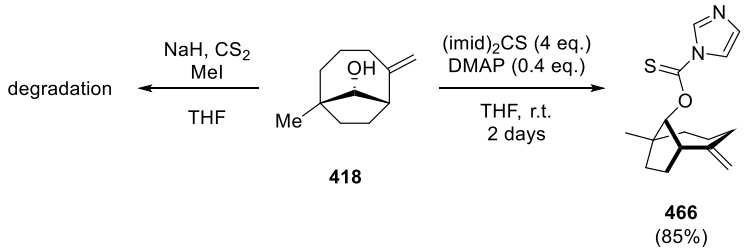
[176] Zhu, L.; Luo, J.; Hong, R. *Org. Lett.* **2014**, *16*, 2162−2165.
[177] McCombie, S.W.; Motherwell, W.B.; Tozer, M.J. *Organic Reactions* (Hoboken, NJ, United States) **2012**, 77, 161-591.
[178] Yadav, J.S.; Goreti, R.; Pabbaraja, S.; Sridhar, B. *Org. Lett.* **2013**, *15*, 3782-3785.

thionocarbamate **464** and subsequent application of *n*Bu_3SnH and AIBN delivered the deoxygenated product **465** (Scheme 141)



Scheme 141

Therefore, it was decided to test our substrates under these conditions. We started our investigations by the synthesis of the thiono-derivative from alcohol **418** (Scheme 142). Various conditions were tested but the utilization of NaH, CS_2 and MeI on this substrate demonstrated to mainly deliver degradation products. Otherwise, the synthesis of the imidazolyl derivative was accomplished affording **466** in 85% yield by using thiocarbonyldiimidazole ((imid)$_2$CS) and DMAP.



Scheme 142

Unfortunately, the application of *n*Bu_3SnH/AIBN to derivative **466** in refluxing THF leaded to the rapid degradation of the substrate independently from the amount of stannane employed. Thus, this result drove us to investigate the reactivity of thiono-derivatives derived from other alcoholic substrates. To this aim, derivatization to thiono-compounds was tested onto the three alcohols represented in Figure 40 in various conditions, however, xanthate or a thiono-derivatives were never obtained.[179]

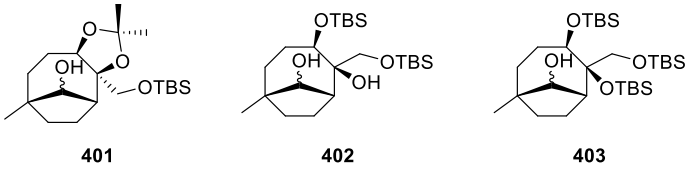
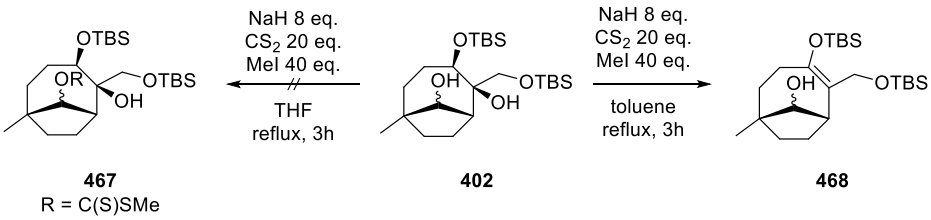


Figure 40

[179] Another substrate underwent such tests: the acetonide of **401** was replaced by –MEM groups, but also in this case it was recovered only the departing product.

It was observed that these substrates underwent various side reactions. When reacted with CS_2 and MeI in the presence of NaH in refluxing THF, *bis*protected triol **402** did not show any reactivity and the starting material is recovered (Scheme 143). Alternatively, when toluene was used as solvent, instead of affording **467**, elimination of the tertiary alcohol occurred and silyl enol ether **468** was retrieved.



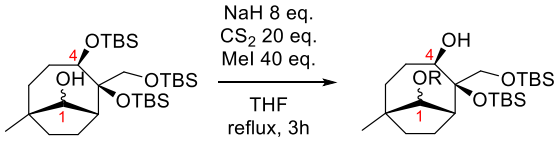
467
R = C(S)SMe

402

468

Scheme 143

Compound **403** was also submitted to similar conditions. In this case, refluxing **403** in THF afforded a TBS-group shift from C4 alcohol to C1 alcohol leading to structure **469** (Scheme 144).



403

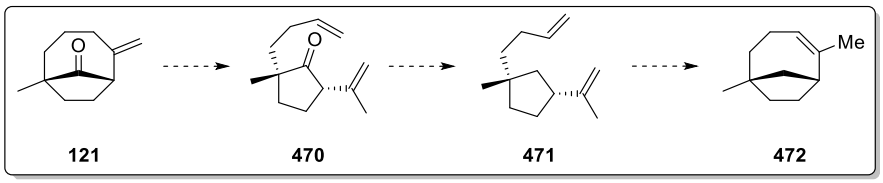
469
(21%)
R = TBS

Scheme 144

However, the treatment of the three above mentioned compounds with thiocarbonyldiimidazole resulted in the recovery of the starting material.

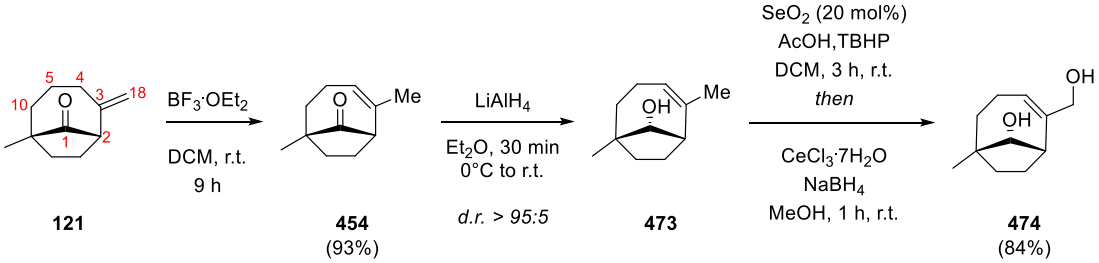
6.6 Ring Opening Metathesis strategy

Once the difficulties related to the reduction of the C1 oxygen established, another synthetic scheme was devised to circumvent this problem. Our hypothesis regarded the steric hindrance induced by the bicycle itself as one of the plausible explanation for the inertness of the C1-oxygen towards reduction conditions. Thus, starting from **121**, it was envisaged to open the 7-membered ring through ring opening metathesis and run a deoxygenation reaction on **470** to get access to cyclopentane derivative **471** (Scheme 145). Ring closing metathesis would then deliver bicyclic compound **472**.



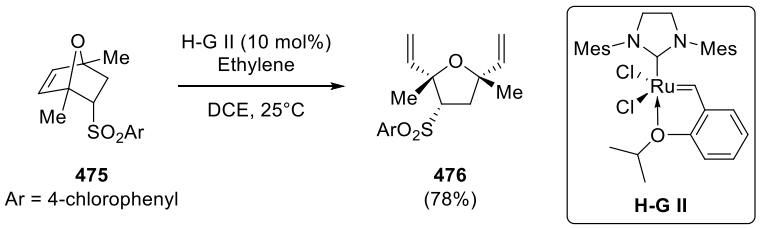
Scheme 145

Starting from ketone **121** (Scheme 146), the C3-C18 *exo*-double bond was shifted into C3-C4 *endo* position by stoichiometric $BF_3{\cdot}OEt_2$ affording **454** in 93% yield. The ketone function was reduced to alcohol **473** and allylic oxidation performed on the latter compound delivered a mixture of primary allylic alcohol and α,β-unsaturated aldehyde.[180] Luche reduction executed directly on the crude mixture allowed to obtain diol **474** in 84% yield.



Scheme 146

With substrates **454**, **473** and **474** in hands, we then turned our attention to the search for most suitable catalyst for ring opening metathesis with ethylene. The choice was based on the reported works of Martin and Aubé in which Hoveyda-Grubbs 2nd generation catalyst (H-G II) was employed for the opening of a strained ring in the presence of gaseous ethylene.[181] Under these conditions, bicyclic compound **475** underwent ring opening metathesis, affording tetrahydrofuran derivative **476** in 78% yield (Scheme 147).



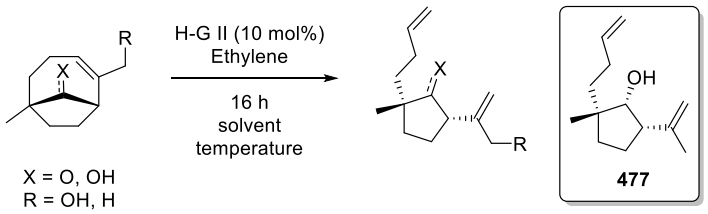
Scheme 147

Various substrates were next submitted to these reaction conditions (Scheme 148). Notably, ketone **454** reacted poorly with ethylene both at 25°C or 110°C (Table 3, entries 1 and 4).

[180] The configuration of the C1 center was not proved but it was assumed to possess a similar stereochemistry as alcohol **418** showed in Section 5.3.

[181] (a) Ghosh, P.; Judd, W.R.; Ribelin, T.; Aubé, J. *Org. Lett.* **2009**, *11*, 4140-4142. (b) Benjamin, N.M.; Martin, S. *Org. Lett.* **2011**, *13*, 450-453.

Diol **474** mostly exhibited the same reactivity (Table 3, entries 2 and 5). On the other hand, alcohol **473** demonstrated to be slightly more reactive, delivering the corresponding cyclopentanol **477** in 28% yield (Table 3, entry 3). Additionally, microwave irradiation proved to be ineffective in enhancing the yields of this transformation (Table 3, entry 6).



Scheme 148

Entry	Substrate	X	R	Solvent	Temperature	Yield
1	**454**	=O	H	DCM	25°C	7%
2	**474**	OH	OH	DCE	60°C	5%
3	**473**	OH	H	toluene	110°C	28%
4	**454**	=O	H	toluene	110°C	8%
5	**474**	OH	OH	toluene	110°C	9%
6[a]	**473**	OH	H	toluene	MW, 110°C	6%

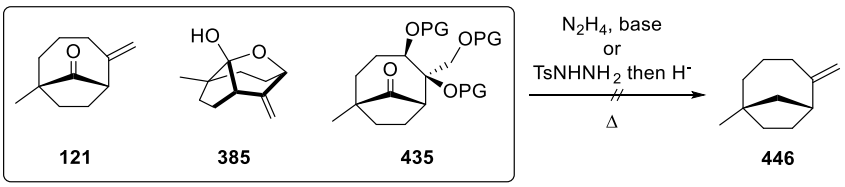
[a] Reaction time: two hours

Table 3

When this alternative strategy was planned, we were conscious of the substantial extension of the synthetic scheme it may involve, however, it was mandatory to find a method capable to overcome the deoxygenation problem. Opening the bicyclic scaffold would undoubtedly permit to enhance the reactivity at C1 center toward various deoxygenation techniques, however, the modest yields obtained in these preliminary essays did not allow to pursue the investigations following this route.

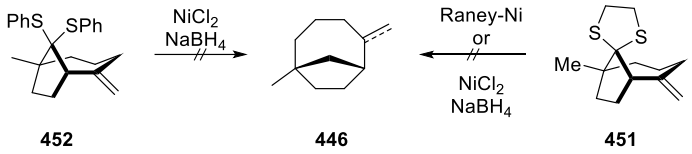
6.7 Conclusion

In this chapter all the various deoxygenation essays have been reviewed in a bibliographic point of view and the main results have been presented. In the Wolff-Kishner related reactions, among the various substrates engaged, deoxygenation was never achieved. Only tosyl hydrazone **450** was isolated and subsequent reduction regenerated the starting alcohol or the intermediate hydrazone (Scheme 149).



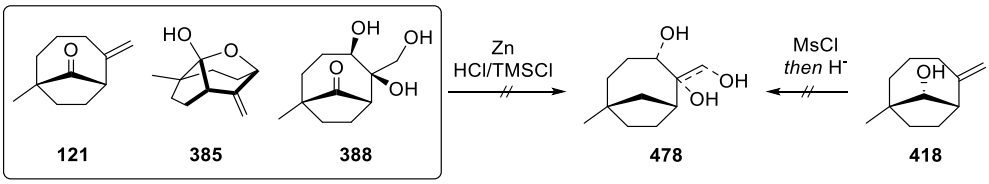
Scheme 149

The feasibility of the Mozingo desulfurization process was next studied. Two different thioketals **451** and **452** were synthesized and desulfurization was tested using $NiCl_2$ or Raney-Ni (Scheme 150). Both catalysts resulted to be ineffective in delivering **446**. However, these essays provided a preliminary idea about the reluctance of the C1 to undergo total reduction to methylene.



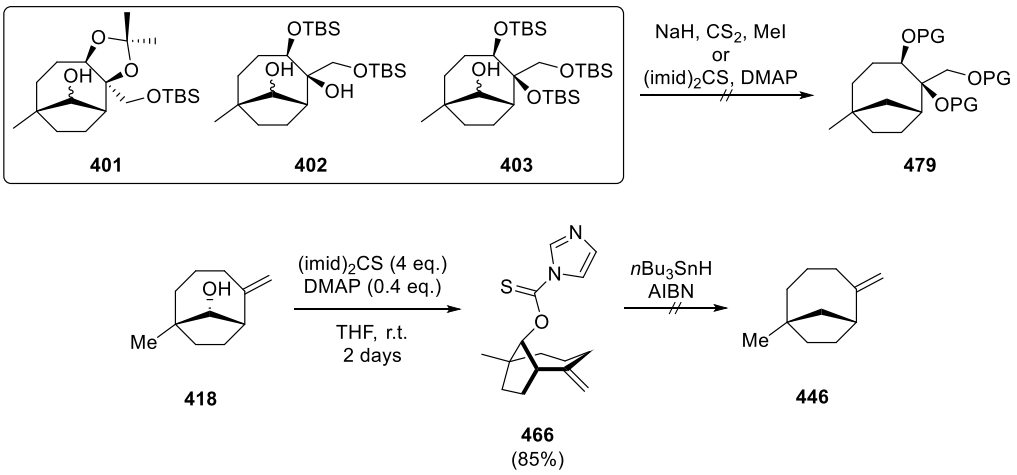
Scheme 150

The Clemmensen-based tests conducted on the free carbonyl compounds **121**, **385** and **388**, provided only the recovery of the starting materials even in harsh conditions (Scheme 151). The same results were observed when hydride displacement was investigated from alcohol **418**.



Scheme 151

It was then demonstrated that thiocarbonyl compounds suitable for Barton-McCombie reaction were hardly synthesizable and only the imidazolyl thiocarbonyl derivative **466** was obtained (Scheme 152). Radical deoxygenation essays on the latter were tested and unfortunately led to the decomposition of the substrate.



Scheme 152

At the moment, we are not able to provide a reliable explanation for the failure of such number of deoxygenation strategies, however, one of the most plausible hypothesis regards the steric hindrance at C1 induced by the bicycle, especially well highlighted by the totally diastereoselective reduction of the ketone at C1. The ROM-based strategy tends to prove the accuracy of the last affirmation even if further investigation on the metathesis step are nonetheless needed.

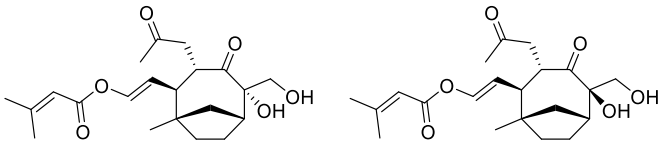
In order to circumvent this putative problem of steric hindrance, it was next envisioned to pursue the synthesis of vibsatin A and B while protecting the alcohol at C1. Functionalization of the bicyclic skeleton would then be targeted and the deoxygenation would be envisaged at a later stage of the synthesis. Hence, steric and electronic factors may be significantly different once the functions installed at C3, C4, C5, C10 and C18.

7. General Conclusion

Neurodegenerative disorders still represents an unsolved worldwide problematic for the healthcare system. Nervous system growth factors, i.e., neurotrophins, constitute a promising solution to these disorders. To this aim, natural products displaying neurotrophic activity such as some vibsane-type diterpenoids hold significant potential as tools for biological studies.

Vibsatin A **1** and vibsatin B **2,** two vibsane derivatives isolated as very minor metabolites in 2014, attracted our attention as these compounds were found to greatly enhance neurite outgrowth (Figure 1). Moreover, vibsatins reveal a structurally dense architecture featuring an unprecedented bicyclo[4.2.1]nonane framework.

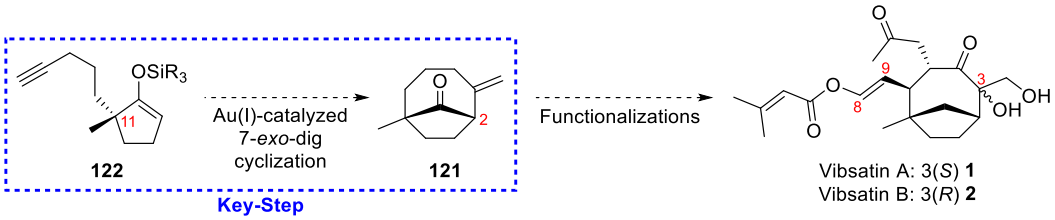
If various synthetic studies were accomplished towards the elaboration of vibsane-type natural substances, no total synthesis of vibsatins A **1** and B **2** were reported to date (Figure 41). Therefore, it was important to develop a straightforward chemical route to evaluate and optimize the biological properties of these natural products. In this context, the total synthesis of vibsatin A and vibsatin B constitutes the aim of this thesis work.



Vibsatin A **1** Vibsatin B **2**

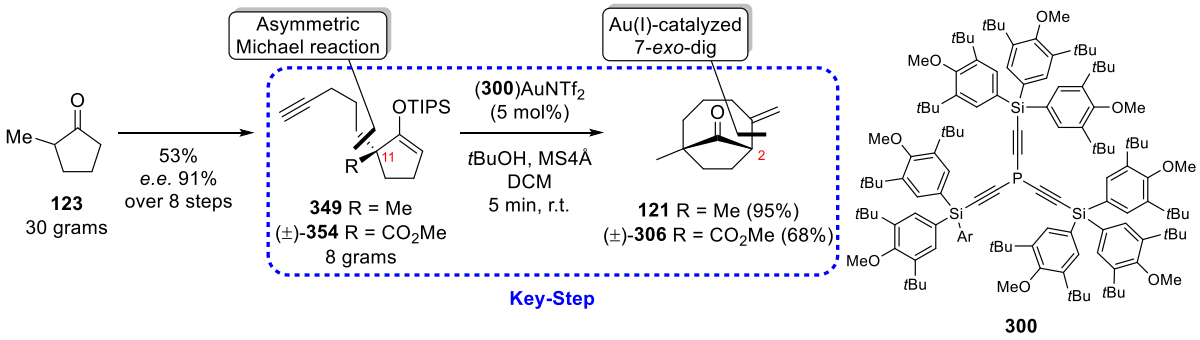
Figure 41

The key-step of the synthesis was identified as the cyclization reaction. Thus, the retrosynthetic pathway elaborated by our group was mainly divided in two parts. The access to the bridged bicyclo[4.2.1]nonane skeleton of the vibsatins **121** through a 7-*exo*-dig Au(I)-catalysed cyclization reaction was intended at an early stage of the synthesis starting from an enantioenriched precursor **122** synthesized in a few steps (Scheme 153). Once the bicyclic framework obtained, various functionalizations on the latter conducted towards the elaboration of both molecules. In this field, latest development towards installation of C3, C4 and C10 centers are presented, along with the strategies envisioned to remove the C1 oxygen.



Scheme 153

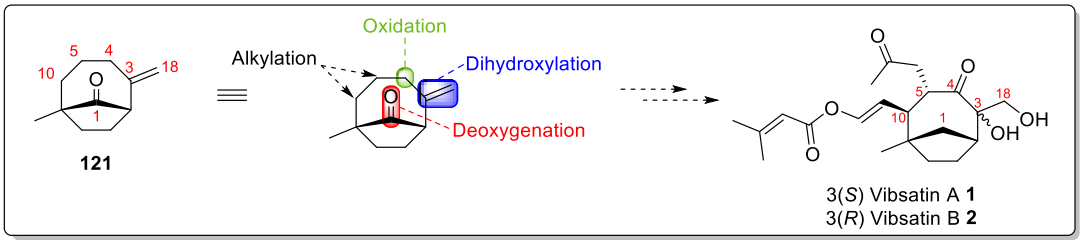
The enantioenriched precursor **122** was first synthesized in 53% yield over eight steps and with 91% enantiomeric excess (Scheme 154). The configuration at C11 was controlled by exploiting an asymmetric Michael reaction starting from 30 grams of 2-methylcyclopentanone **123**. A study upon the 7-*exo*-dig cyclization was first engaged on a model substrate employing phosphine **300**. This study demonstrated the superior reactivity outcome of the TIPS-based silyl enol ether (±)-**354**. The numerous trials peformed in the course of this study, suggested that the two competitive reactions (7-*exo*-dig cyclization and electrophilic cleavage) possess different kinetic profiles and tuning the operative conditions results in the promotion of one out of the two processes. Once the best conditions defined, the desired bicyclo[4.2.1]nonane vibsatin's derived skeleton **121** was obtained in 95% yield from **349** and the subsequent scale up allowed to run this 7-*exo*-dig gold(I)-catalysed cyclization on 8 grams of substrate.



Scheme 154

Starting from the key-intermediate **121**, direct functionalization on the skeleton were foreseen and depicted in Scheme 155. Main steps would be:

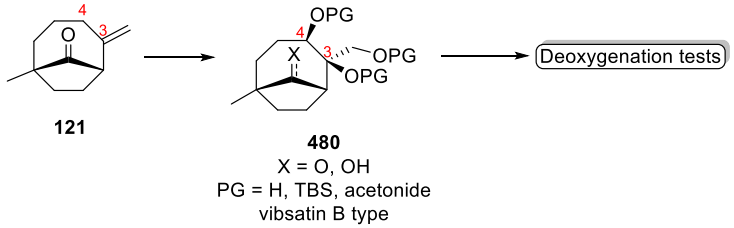
- oxidation at C4
- dihydroxylation at C3-C18 alkene
- two diastereoselective alkylation reactions at C5 and C10
- deoxygenation at C1, this reaction being performed at the most accurate stage of the synthesis



Scheme 155

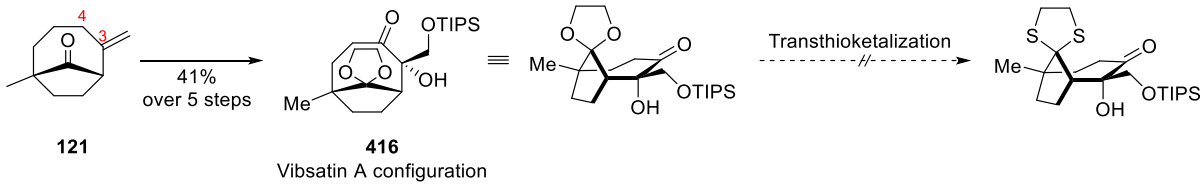
The deoxygenation of the ketone at C1 resulted to be one of the most challenging step of the whole synthesis. Moreover, due to the failure of various deoxygenation essays on simple unfunctionalized **121**, three different functionalization sequences of the bicyclic backbone have been realized aiming to overcome this problem at a later stage of the sequence.

The first strategy was undertaken starting directly from ketone **121**. After oxidation at C4 and dihydroxylation of the double bond, the afforded ketotriol possessed a *R* configuration at C3; relative to vibsatin B. This latter compound was protected under various forms and its derivatives **480** underwent several deoxygenative essays (Scheme 156).



Scheme 156

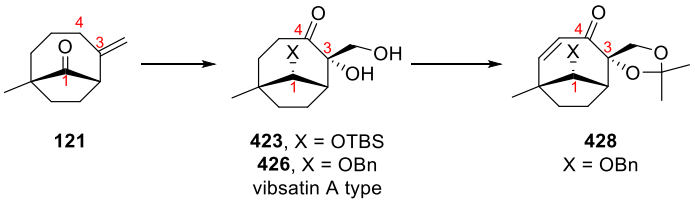
The second approach was based on the installation of a ketal at C1 in order to perform a transthioketalization and subsequent desulphurization reaction at a further stage (Scheme 157). This synthetic line provided an inverted stereochemical outcome at the dihydroxylation step leading to vibsatin A type, 3(*S*) configuration. A wide array of catalysts were tested in order to perform a transthioketalization reaction on compound **416**, previously synthesized in 41% yield over 5 steps starting from ketone **121**. However, the desired C1 thioketal was never obtained.



Scheme 157

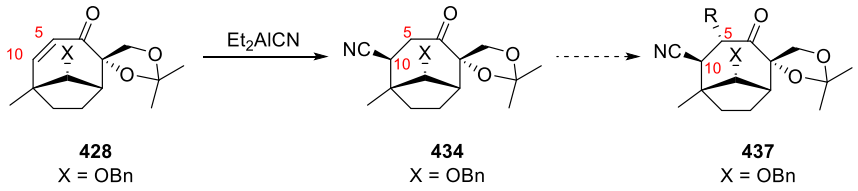
In the third strategy, the ongoing one, it was decided to reduce the C1 oxygen to alcohol and to protect it as an ether (Scheme 158). Following roughly the same synthetic route, as

previously described, a vibsatin A derived, 3(*S*) compounds **423** and **426** were afforded, demonstrating that the stereochemistry of the dihydroxylation reactions only depended on the substituents present at C1 and proving the irrelevance of the C4 configuration at this stage. The synthesis was next pursued through simple chemical transformations until the α,β-unsaturated compound **428** was reached.



Scheme 158

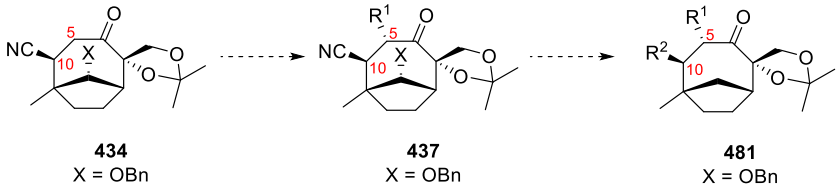
At the present time, the conjugate addition at C10 of the α,β-unsaturated ketone **428** is under investigation and, after preliminary studies, the insertion of a cyanide group exploiting Et_2AlCN appeared to be the most effective method, affording compound **434**. Further optimization of this reaction is required in order to afford C10 alkylation on larger scales, interestingly, the configuration at C10 resulted to be 10(*S*), *i.e.* in accordance with vibsatin A and B. With four stereocenters controlled out of five, our attention will next be turned to the alkylation at the C5 position in order to achieve the set-up of the last stereocenter of the vibsatin skeleton such as in **437** (Scheme 159).



Scheme 159

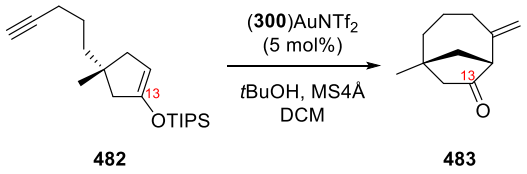
All the intermediates synthesized in these last three strategies underwent deoxygenation essays. Clemmensen, Wolff-Kishner, Barton-McCombie, hydride displacement and sulphur chemistry based methodologies were employed, however, the removal of the C1 oxygen was, to date, never obtained.

In the period ahead, our work will aim to pursue the ongoing strategy. Achieving the installation of all the five stereocenters of the vibsatins will be the first objective and, starting from this point, our efforts will be directed toward finding a better stage for performing a successful deoxygenation at C1 (Scheme 160).



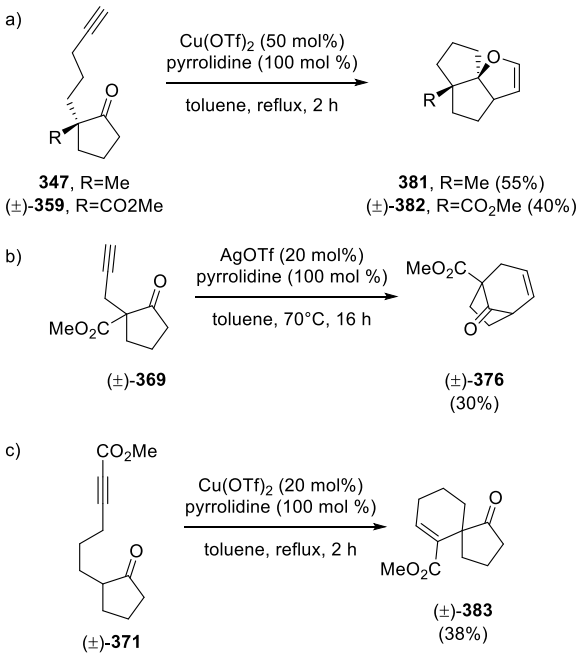
Scheme 160

Otherwise, one alternative approach would consist in the possibility to shift the carbonyl from C1 to C13 by synthesizing silyl enol ether **482** (Scheme 161). The cyclized product **483** bearing a carbonyl at C13 should exhibit a different reactivity allowing the deoxygenation to occur.



Scheme 161

In parallel to the studies on gold(I) catalysed cyclization, an investigation upon alternative medium size ring cyclizations was engaged. Replacing the stoichiometrically installed silyl enol ether moiety and the gold(I)-based catalyst by an *in-situ* prepared enamine and readily available metal complexes (AgOTf or $Cu(OTf)_2$) leads to a different reactivity and products (±)-**382** and **381** featuring an unprecedented tricyclic structure were isolated along with bicyclo[3.2.1]octane (±)-**376** and spiro-compound (±)-**383** (Scheme 162).



Scheme 162

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9. Experimental Part

9.1 Usual procedures

Unless otherwise stated, all commercially available reagents and solvents were used without further purification.

All reactions were carried out in oven or flame-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. For reactions requiring anhydrous conditions, dry solvents were freshly distillated prior to use (THF, diethyl ether and toluene over sodium/benzophenone system, CH_2Cl_2 and DMSO over calcium hydride and MeOH and EtOH over magnesium turnings).

Reactions were magnetically stirred and monitored by thin layer chromatography with 0.20 mm Merck $60F_{254}$ pre-coated silica gel plates. Visualization was accomplished with UV light and subsequent treatment with a 10% ethanolic phosphomolybdic acid solution followed by heating at 100-110 °C.

Flash chromatography was performed with silica gel 60 (particle size 0.040-0.063 μm) supplied by SDS Carlo Erba. Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted.

Whenever "deactivated silica gel" is mentioned, the corresponding flash chromatography was performed using solvents containing 3% of triethylamine.

Physical data and spectroscopic measurements

NMR Spectra were recorded on Bruker Avance 300 MHz, 400 MHz or 600 MHz spectrometers.

^{1}H NMR spectra were recorded using an internal deuterium lock at ambient temperature. Internals references of δ_H 7.26 and 3.35 were used respectively for $CDCl_3$ and methanol-d_4 (MeOD).. Data are represented as follows: chemical shift (in ppm), multiplicity (s = single, d = doublet, t = triplet, q = quartet and *br.* = broad), integration, coupling constant (*J*), expressed in Hz, attribution. ^{13}C-NMR spectra were recorded at 75 MHz, 100 MHz or 125 MHz. Internals references of δ_C 77.00 and 49.8 were used respectively for $CDCl_3$ and methanol-d_4 (MeOD). ^{13}C NMR assignments were confirmed by 2D COSY, HSQC and HMBC spectra.

Mass spectra were recorded on a GC/MS coupling unit with a MSD 5973 spectrometer and a Hewlett-Packard HP-GC 6890 chromatograph. Ionization was obtained either by electronic impact (EI) or chemical ionization with methane (CI, CH_4). Mass spectral data are reported as m/z.

High-resolution mass-spectra were obtained on a Thermo-Electron MAT-95 or Q-TOF1 spectrometer (Waters). Ionization was obtained by electrospray (ES) using Na, K or Li. Mass spectral data are reported as *m/z*.

Optical rotations were recorded on a Perkin Elmer Model 341 polarimeter at 589 nm and reported as follows: $[\alpha]_D$, concentration (c in g/100 mL) and solvent.

Organometallic titration

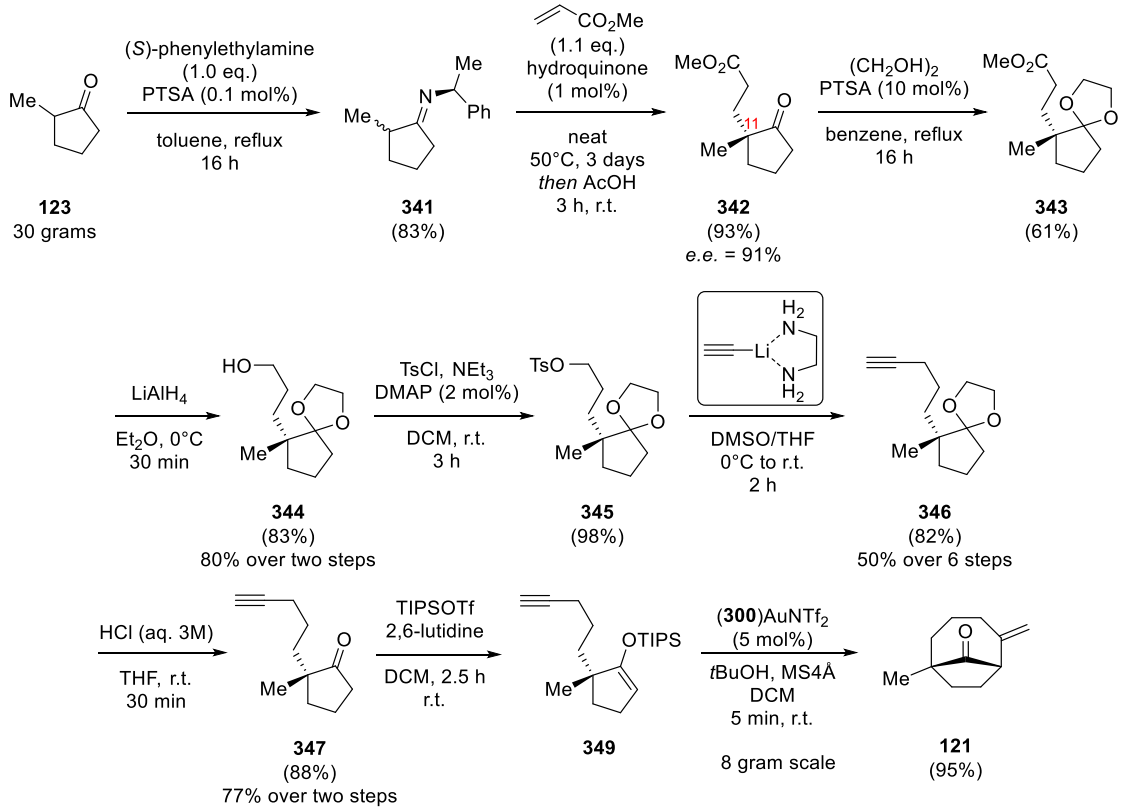
The procedure of S.C. Watson and J.F. Eastham was used.[182] The solution of organolithium or organomagnesium compound to be titrated was slowly added at 0 °Cto a solution of benzylalcohol (500 µL, 4.83 mmol, 1.0 equiv) in dry diethyl ether or THF containing a small amount of 2,2-biquinoline or 1,10-phenanthroline. The addition was stopped when the colourless solution became red.

Nomenclature

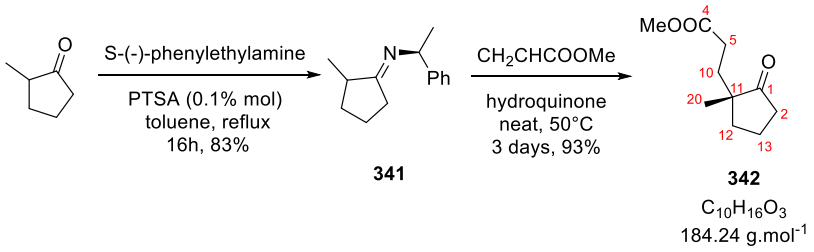
IUPAC nomenclature was used for all the compounds.

[182] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

9.2 Synthesis of bicyclic ketone 121



Methyl (*R*)-3-(1-methyl-2-oxocyclopentyl)propanoate **342**



Step 1

In a round-bottomed flask equipped with a Dean–Stark apparatus were placed 2-methylcyclopentanone, (7.42 g, 75.7 mmol), (*S*)-1-phenylethylamine (9.17 g, 75.7 mmol) and *p*-toluenesulfonic acid (14.5 mg, cat.) in toluene (50 mL). The reaction mixture was heated at reflux for 16 h then concentrated under reduced pressure. The residue was distilled (b.p. 110°C, 2 mBar) to give the intermediary imine **341** as a greenish oil (1.1 diastereomeric mixture, 12.23 g, 83%). IR (film): $\tilde{\nu}$ = 1673 cm^{-1} (C=N).

Step 2

To the imine **341** (12.23 g, 60.8 mmol) was added freshly distilled methyl acrylate (5.23 g, 60.8 mmol) and hydroquinone (67 mg, cat.). The mixture was stirred at 50 °C for 3 days and concentrated under reduced pressure. To the residue was added 20% aqueous acetic acid (18 mL) and THF (30 mL). After being stirred for 24 h at 20 °C, the mixture was concentrated *in vacuo* and 3M hydrochloric acid (20 mL) was added. The aqueous layer was extracted with diethylether (4 × 50 mL) and the organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification over silica gel (cyclohexane/AcOEt, 50:50) afforded (*R*)-3-(1-methyl-2-oxocyclopentyl)propanoate **342** as a colourless oil (9.8 g, *ee* = 70% from 2-methylcyclopentanone).

RN: 94089-46-0.

$[\alpha]_D^{20}$ = + 36.4 (*c* 1.0, $CHCl_3$).

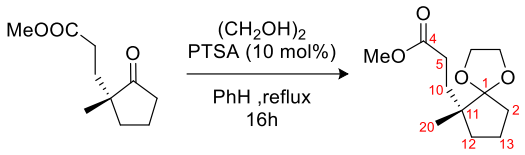
^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.62 (s, 3H, OCH_3), 2.36–2.12 (m, 4H, H-2, H-5), 1.93–1.63 (m, 6H, H-10, H-12, H-13), 0.97 (s, 3 H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 222.3 (C, C-1), 173.8 (C, C-4), 51.6 (CH_3, OCH_3), 47.5 (C, C-11), 37.4 (CH_2, C-2), 36.1 (CH_2, C-12), 31.4 (CH_2, C-10), 29.3 (CH_2, C-5), 21.4 (CH_3, C-20), 18.6 (CH_2, C-13) ppm.

FTIR (neat): ν = 2957, 1731, 1436, 1374, 1199, 1164 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{10}H_{16}O_3Na^+$: $[M+Na]^+$: 207.0992; found: 207.0993.

Methyl (*R*)-3-(6-methyl-1,4-dioxaspiro[4.4]nonan-6-yl)propanoate **343**



342 **343**

$C_{12}H_{20}O_4$

228.29 g.mol^{-1}

In a round-bottomed flask equipped with a Dean–Stark apparatus was placed ketoester **342** (20.0 g, 109 mmol), ethylene glycol (54.2 g, 0.87 mol, 8 equiv.) and *p*-toluenesulfonic acid (2.07 g, 10.9 mmol, 0.1 equiv.) in benzene (650 mL). The reaction mixture was reflux for 16 h and a saturated solution of $NaHCO_3$ (300 mL) was added. The organic layer was separated. The aqueous layer was extracted with Et_2O (x3). The organic layers were then dried over $MgSO_4$, filtered and concentrated under reduced pressure. **343** was obtained as a brown oily residue (27.0 g, quantitative yield) and was directly engaged in the next reaction without further purification.

RN: 197163-97-6.

$[\alpha]_D^{20}$: -4.11 (c 1.0, $CHCl_3$).

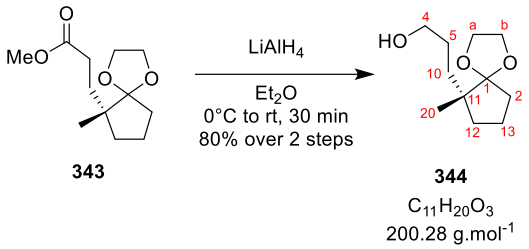
^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.92-3.80 (m, 4H, O-CH_2-CH_2), 3.66 (s, 3H, OCH_3), 2.20–2.40 (m, 2H, H-5), 1.87-1.77 (m, 2H, H-2), 1.72 (t, *J* = 8.4 Hz, 2H, H-10), 1.68-1.56 (m, 3H, H-12, Ha-13), 1.52-1.43 (m, 1H, Hb-13), 0.95 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 175.0 (C, C-4), 119.5 (C, C-1), 64.9 (CH_2, O-CH_2), 64.7 (CH_2, O-CH_2), 51.7 (CH_3, OCH_3), 45.4 (C, C-11), 35.6 (CH_2, C-13), 33.5 (CH_2, C-2), 30.4 (CH_2, C-10), 30.2 (CH_2, C-5), 20.1 (CH_3, C-20), 18.0 (CH_2, C-12) ppm.

FTIR (neat): ν = 2950, 2875, 1735, 1435, 1374, 1033 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{12}H_{20}O_4Na^+$: $[M+Na]^+$: 223.1310; found: unstable.

(*R*)-3-(6-methyl-1,4-dioxaspiro[4.4]nonan-6-yl)propan-1-ol **344**



Diethyl ether (100 mL) was added to a round-bottom flask containing crude **343** (27.0 g) and the mixture was cooled down to 0°C. The solution was slowly added to a suspension of $LiAlH_4$ (4.14 g, 109 mmol, 1 equiv.) in diethyl ether (250 mL) at 0°C. The mixture was then allowed to warm up to room temperature. After 30 min the reaction was quenched by successive addition of water (5 mL), 2M solution of NaOH (5 mL) and water (15mL). After stirring for 30 min, a white precipitate appears and the suspension was filtered on celite and the solvent was removed under reduced pressure. Flash purification over silica gel (cyclohexane/AcOEt: 70:30 to 40:60) afforded the alcohol **344** as a colorless oil (17.4 g, 80% yield over two steps).

RN: 211235-36-8.

$[\alpha]_D^{20}$: -6.81 (c 1.0, $CHCl_3$).

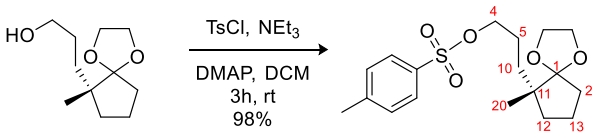
^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.89 (s, 4H, O-CH_2-CH_2), 3.61 (t, *J* = 6.8 Hz, 2H, H-4), 1.88-1.75 (m, 2H, H-2), 1.67-1.31 (m, 8H, H-5, H-10, H-12, H-13), 0.95 (s, 3H, 20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 119.8 (C, C-1), 64.9 (CH_2, O-CH_2), 64.7 (CH_2, O-CH_2), 64.1 (CH_2, C-4), 45.7 (C, C-11), 35.5 (CH_2, C-12), 33.6 (CH_2, C-2), 31.0 (CH_2, C-10), 28.3 (CH_2, C-5), 20.2 (CH_3, C-20), 18.0 (CH_2, C-13) ppm.

FTIR (neat): ν = 3394, 2947, 2872, 1137, 1052, 948 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{11}H_{20}O_3Na^+$: $[M+Na]^+$: 223.1310; found: 223.1307.

(*R*)-2-(6-methyl-1,4-dioxaspiro[4.4]nonan-6-yl)ethyl 4-methylbenzenesulfonate **345**



344

345

$C_{18}H_{26}O_5S$

354.46 g.mol^{-1}

To a solution of **344** (4.07 g, 20.35 mmol, 1 equiv.), triethylamine (7.1 mL, 50.9 mmol, 2.5 equiv.) and 4-dimethylaminopyridine (50 mg, 0.41 mmol, 0.02 equiv.) in DCM (40 mL) at 0°C was added tosyl chloride (4.08 g, 21.4 mmol, 1.05 equiv.) portionwise. Ice bath was removed after 30 min and the solution was stirred for 3 h at room temperature. A saturated solution of $NaHCO_3$ (100 mL) was then added. The organic layer was separated and the aqueous layer was extracted with DCM (2x). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash Purification over silica gel (cyclohexane/AcOEt: 50:50) afforded **345** (7.04 g, quantitative yield) as a colourless oil.

RN: 1215086-63-7.

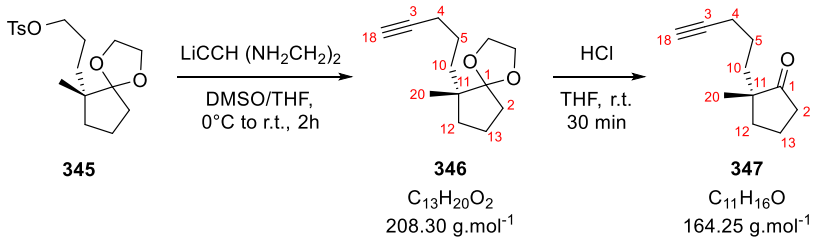
$[\alpha]_D^{20}$ = + 1.2 (c 1.0, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.0 Hz, 2H, H-ar), 7.32 (d, *J* = 8.0 Hz, 2H, H-ar), 3.98 (t, *J* = 6.4 Hz, 2H, C-4), 3.89-3.77 (m, 4H, O-CH_2-CH_2), 2.42 (s, 3H, Ar-CH_3), 1.83-1.45 (m, 7H, H-2, H-5, Ha-12, H-13), 1.45-1.35 (m, 1H, Hb-12), 1.30 (m, 2H, H-10), 0.87 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 144.6 (C, C-ar), 133.4 (C, C-ar), 129.8 (2CH, C-ar), 127.9 (2CH, C-ar), 119.4 (C, C-1), 71.7 (CH_2, C-4), 64.8 (CH_2, O-CH_2), 64.5 (CH_2, O-CH_2), 45.4 (C, C-11), 35.5 (CH_2, C-12), 33.4 (CH_2, C-2), 30.8 (CH_2, C-10), 24.6 (CH_2, C-5), 21.7 (CH_3, C-ar-C$\underline{H_3}$), 20.1 (CH_3, C-20), 17.9 (CH_2, C-13) ppm.

HRMS (ESI): *m/z* calcd for $C_{18}H_{26}O_5SNa^+$: $[M+Na]^+$: 377.1399; found: 377.1392.

(*S*)-6-methyl-6-(pent-4-yn-1-yl)-1,4-dioxaspiro[4.4]nonane **346** and (S)-2-methyl-2-(pent-4-yn-1-yl)cyclopentan-1-one **347**



345

346
$C_{13}H_{20}O_2$
208.30 g.mol^{-1}

347
$C_{11}H_{16}O$
164.25 g.mol^{-1}

To a suspension of lithium acetylide, ethylenediamine complex (7.0 g, 68.2 mmol, 1.5 equiv.) in DMSO/THF (2:1, 85 mL) at 0°C, a solution of **345** (16.1 g, 45.5 mmol, 1 equiv.) in DMSO/THF (2:1, 50 mL) was added dropwise and the temperature was warmed to room temperature over 2 h. A saturated solution of NH_4Cl (150 mL) was then added and the mixture was extracted with Et_2O (x4). The organic layers were washed with brine (x2), dried over $MgSO_4$, filtered and removal of the solvent under reduced pressure provided **346** as a crude brown oil that was directly engaged in the next step.

$[\alpha]_D^{20}$: -4.12 (c 1.0, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$): δ = 3.95-3.86 (m, 4H, O-CH_2-CH_2), 2.17 (td, *J* = 6.9, 2.6 Hz, 2H, H-4), 1.95 (t, *J* = 2.6 Hz, 1H, H-18), 1.90-1.78 (m, 2H, H-2), 1.68-1.57 (m, 3H, H-13, Ha-10), 1.57-1.40 (m, 5H, Hb-10, H-12, H-5), 0.96 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$): δ = 119.7 (C, C-1), 84.9 (C, C-3), 68.2 (CH, C-18), 64.9 (CH_2, O-CH_2), 64.7 (CH_2, O-CH_2), 45.9 (C, C-11), 34.4 (CH_2, C-10), 34.4 (CH_2, C-12), 33.5 (CH, C-2), 24.3 (CH_2, C-5), 20.2 (CH_3, C-20), 19.6 (CH_2, C-4), 18.0 (CH_2, C-13) ppm.

FTIR (neat): ν = 3295, 2951, 2876, 1736, 1463, 1376, 1312, 1151, 1133, 1068, 948 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{13}H_{20}O_2Na^+$: $[M+Na]^+$: 231.1356; found: unstable.

The crude alkyne **346** (10 g) was dissolved in a mixture of THF (60 mL) and HCl (3M in water, 20 mL) was added. After 30 min, THF is removed under reduced pressure and the aqueous residue was neutralized with a 1M solution of NaOH. The aqueous layer was then extracted with Et_2O (x3) and the organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash purification over silica gel (cyclohexane/AcOEt, 100:0 to 80:20) provided **347** (6.1 g, 82% yield over two steps).

$[\alpha]_D^{20}$: +56,71 (c 1.0, $CHCl_3$).

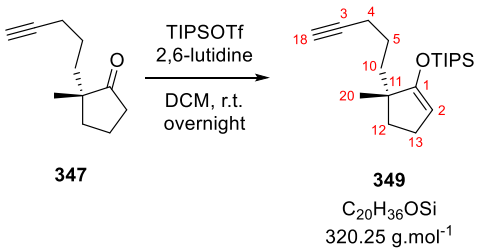
^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.35-2.20 (m, 2H, H2), 2.19-2.16 (m, 2H, H-4), 1.94 (t, *J* = 2.6 Hz, 1H, H-18), 1.92-1.82 (m, 3H, H-13, Ha-10), 1.80-1.69 (m, 1H, Hb-10), 1.62-1.35 (m, 4H, H-5, H-12), 0.97 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$): δ = 223.3 (C, C-1), 84.2 (C, C-3), 68.6 (CH, C-18), 48.1 (C, C-11), 37.7 (CH_2, C-2), 35.9 (CH_2, C-10), 35.8 (CH_2, C-12), 23.6 (CH_2, C-5), 21.8 (CH_3, C-20), 19.0 (CH_2, C-4), 18.8 (CH_2, C-13) ppm.

FTIR (neat): *v* = 3290.62, 2957.79, 1870.11, 1732.20, 1459.44, 1162.26, 1075.14 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}ONa^{+}$: $[M+Na]^{+}$: 187.1093; found: 187.1091.

(*S*)-triisopropyl((5-methyl-5-(pent-4-yn-1-yl)cyclopent-1-en-1-yl)oxy)silane **349**



In a round-bottom flask containing ketone **347** (5.66 g, 34.5 mmol, 1 equiv.) dissolved in DCM (170 mL) at 0°C, were successively added 2,6-lutidine (7.38 g, 69 mmol, 2 equiv.) and TIPSOTf (13.9 mL, 51.7 mmol, 1.5 equiv.). The ice bath was removed and the mixture was stirred overnight. DCM was removed under reduced pressure and the oily residue was purified by flash chromatography over silica gel (cyclohexane/AcOEt, 98:2 to 90:10) to afford pure **349** (10.5 g, quantitative yield).

$[\alpha]_D^{20}$ = -2.20 (c 1.0, $CHCl_3$).

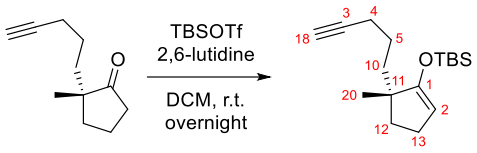
^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.24 (t, *J* = 2.1 Hz, 1H, H-2), 2.20-2.06 (m, 4H, H-4, H-13), 1.92 (t, *J* = 2.6 Hz, 1H, H-18), 1.78 (ddd, *J* = 12.7, 8.4, 5.7 Hz, 1H, Ha-12), 1.57 (ddd, *J* = 12.7, 8.7, 5.2 Hz, 1H, Hb-12), 1.55-1.38 (m, 4H, H-5, H-10), 1.20 (sext, *J* = 7.2 Hz, 3H, Si-CH), 1.08 (d, *J* = 7.2 Hz, 18 H, Si-CH-CH_3), 1.05 (s, 3H, 20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ =159.6 (C, C-1), 98.0 (CH, C-2), 85.0 (C, C-3), 68.1 (CH, C-18), 56.8 (C, C-11), 38.42 (CH_2, C-10), 34.5 (CH_2, C-12), 25.6 (CH_2, C-13), 25.4 (CH_3, C-20), 24.3 (CH_2, C-5), 19.3 (CH_2, C-4), 18.2 (6CH_3, Si-CH-(C$\underline{H}_3$)$_2$), 12.7 (3CH, Si-CH) ppm.

FTIR (neat): *v* = 3315, 2944, 2866, 1643, 1462, 1340, 1249, 881 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{20}H_{36}OSiNa^+$: $[M+Na]^+$: 343.2433; found: 343.2428.

(S)-tert-butyldimethyl((5-methyl-5-(pent-4-yn-1-yl)cyclopent-1-en-1-yl)oxy)silane **348**



347 **348**

$C_{17}H_{30}OSi$

278.51 g.mol^{-1}

In a round-bottom flask containing ketone **347** (645 mg, 3.93 mmol, 1 equiv.) dissolved in DCM (170 mL) at 0°C, were successively added 2,6-lutidine (1.37 mL, 11.8 mmol, 3 equiv.) and TBSOTf (1.08 mL, 4.72 mmol, 1.2 equiv.). The ice bath was removed and the mixture was stirred overnight. DCM was removed under reduced pressure and the oily residue was purified by flash chromatography over silica gel (cyclohexane/AcOEt, 98:2 to 90:10) to afford pure **348** (10.5 g, quantitative yield).

$[\alpha]_D^{20}$ = -2.20 (c 1.0, $CHCl_3$).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.43 (t, *J* = 2.2 Hz, 1H, H-2), 2.20-2.08 (m, 4H, H-4, H-13), 1.92 (t, *J* = 2.6 Hz, 1H, H-18), 1.76 (ddd, *J* = 12.6, 8.4, 5.5 Hz, 1H, Ha-12), 1.55-1.38 (m, 5H, H-5, H-10, Hb-12), 1.09 (s, 3H, H-20), 0.92 (s, 9H, Si-C-CH_3), 0.15 (s, 3H, Si-CH_3), 0.14 (s, 3H, Si-CH_3) ppm.

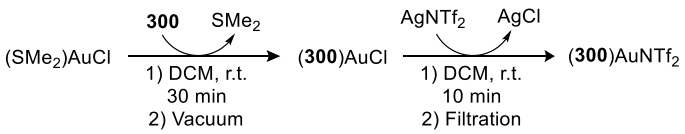
^{13}C-NMR (100MHz, $CDCl_3$) δ =159.6 (C, C-1), 98.5 (CH, C-2), 85.0 (C, C-3), 68.2 (CH, C-18), 46.4 (C, C-11), 38.5 (CH_2, C-10), 34.5 (CH_2, C-12), 25.8 ($3CH_3$, Si-C-CH_3), 25.6 (CH_2, C-13), 25.3 (CH_3, C-20), 24.2 (CH_2, C-5), 19.3 (CH_2, C-4), 18.2 (C, Si-C), -4.6 (CH_3, Si-CH_3), -4.9 (CH_3, Si-CH_3) ppm.

General procedure for Au^{I} mediated 7-*exo-dig* cyclization

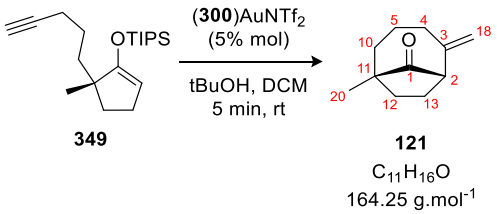
1. Dry Hamilton gas-tight syringes are preferred however plastic syringes can be used if properly dried under vacuum at r.t. before a single and unique usage.
2. When large volumes are required, a dry canula is used for the transfer (dried at 120°C at first and then cooled down under vacuum in a big round-bottom flask before quench with Ar).
3. $(Me_2S)AuCl$ is light sensitive, water sensitive but air stable
4. $AgNTf_2$ is particularly light sensitive but air and water stable (but has to be treated as water sensitive as well)
5. Molecular sieves is activated for 16h at 400°C under vacuum then for 20 min under vacuum in the reaction vessel prior to the reaction.
6. Celite® must be stored in the oven at 120°C.
7. During the preparation of the catalyst, direct sun or artificial light irradiation must be avoided.
8. When silver complex is added, the solution can turn different colors depending upon the presence and the concentration of Au^{0} nanoparticles that comes from the disproportionation of Au^{I}.

   The presence of this particles depends upon: the age of gold and silver complexes, the attention paid to moisture and light in the course of the synthesis and the possible presence of triflic acid. Depending on the quality of the catalyst, the precipitate can range from white (good) to bright/dark violet for good (efficient) to black/brown (much less efficient).
9. N.B.: the catalyst's intermediate, $[L_1AuCl]$, is more stable against disproportionation compared with $(Me_2S)AuCl$.

Operative method



(1*S*,6*S*)-1-methyl-5-methylenebicyclo[4.2.1]nonan-9-one **121**



349

121

$C_{11}H_{16}O$

164.25 g.mol^{-1}

In a dry aluminum foil wrapped vial, were placed $(Me_2S)AuCl$ (0.05 equiv.) and **300** (>0.05 equiv.) dissolved in DCM (≈0.01 M) and the mixture was stirred in the dark for at least 30 min. The solvent was removed under successively an argon flow and vacuum. The vial was refilled with DCM and $AgNTf_2$ (≈0.075 equiv.) was subsequently added, the resulting suspension was stirred for 10 min.

Concomitantly, A 2-neck-schlenk containing dry MS4Å was fitted with a glass filter system equipped of a glass or young® tap. The filter was covered with dry celite® (see figure below) and the whole system was carefully flame-dried and flushed with argon (x3 vacuum-argon cycles) then wrapped in an aluminum foil.

The solution was transferred *via* cannula onto the filtration system and the filter was washed several times with DCM. One equivalent of *t*-BuOH was added in the reaction vessel and dry DCM was added until the concentration of the catalyst reached 0.003M. The substrate **349** (8 g, 25 mmol, 1 eq.) was solubilized in dry DCM (0.6M) and the resulting solution was added dropwise to the reaction vessel. After 10 min, the resulting solution was filtered on a pad of silica gel and the solvent was removed under reduced pressure. Precipitation and filtration of the phosphine in EtOH followed by purification over silica gel (pentane/Et_2O, 100:0 to 95:5) afforded the bicyclic ketone **121** (3.9 g, 95% yield).

$[\alpha]_D^{20}$ = +122.4 (c 1.0, CHC).

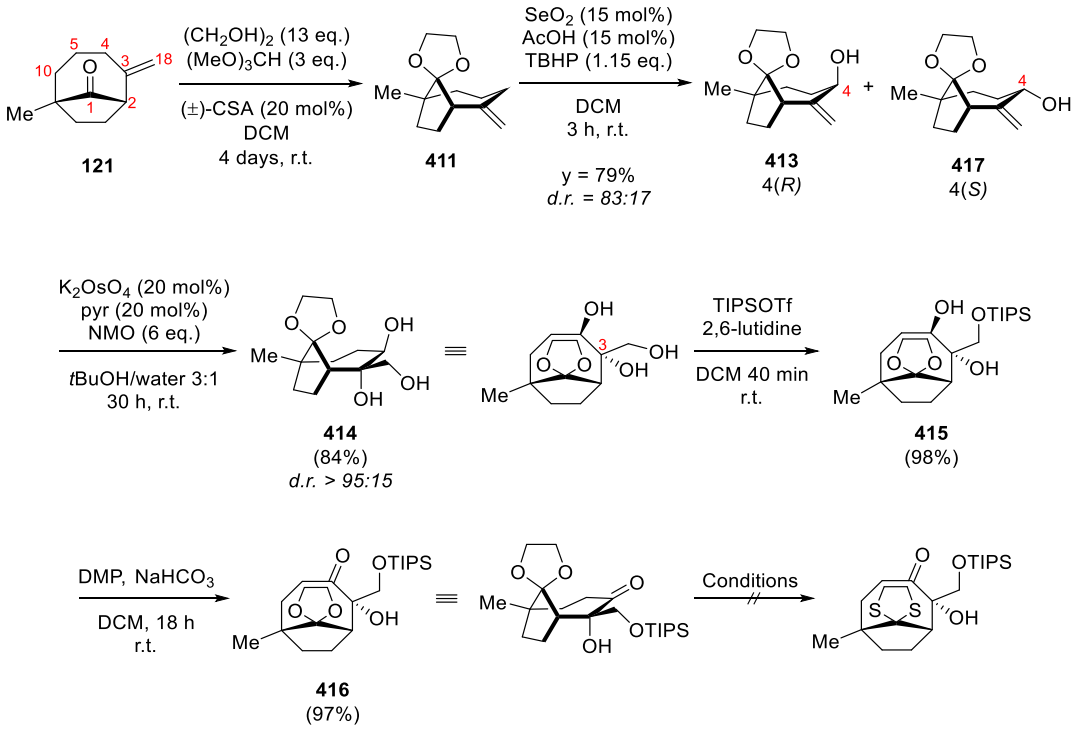
^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.79 (s, 1H, H-18), 4.74 (s, 1H, H-18), 3.15 (dd, *J* = 9.7, 3.0 Hz, 1H, H-2), (dd, *J* = 15.6, 6.9 Hz, 1H, Ha-4), 2.26 (dtd, *J* = 13.4, 10.1, 5.0 Hz, 1H, Ha-5), 2.15-2.05 (m, 1H, Hb-4), 2.01 (ddd, *J* = 12.9, 8.8, 3.7 Hz, Ha-12), 1.89-1.62 (m, 4H, Hb-12, Hb-5, H-13), 1.58 (dt, *J* = 13.7, 4.4 Hz, 1H, 10), 1.42 (ddd, *J* = 11.9, 12.6, 4.4 Hz, 1H, 10), 1.09 (s, 3H, 20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 221.8 (C, C-1), 147.1 (C, C-3), 112.1 (CH_2, C-18), 54.6 (CH, C-2), 49.0 (C, C-11), 41.2 (CH_2, C-10), 35.3 (CH_2, C-4), 33.0 (CH_2, C-12), 27.2 (CH_2, C-5), 24.3 (CH_2, C-13), 23.3 (CH_2, C-20) ppm.

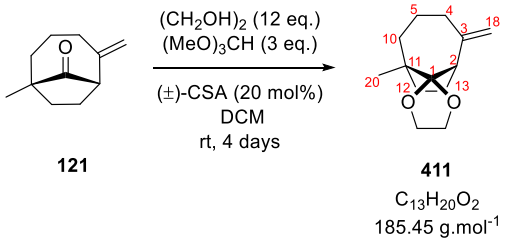
FTIR (neat): ν = 3075, 2961, 2927, 1737, 1636, 1451, 1374, 1309, 1167, 1075, 895, 892 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}ONa^+$: $[M+Na]^+$: 187.1099; found: 187.1102.

9.3 Synthesis of ketone 416



(1*S*,6*S*)-1-methyl-5-methylenespiro[bicyclo[4.2.1]nonane-9,2'-[1,3]dioxolane] **411**



To a solution of **121** (200 mg, 1.22 mmol, 1equiv.), ethylene glycol (905 mg, 14.6 mmol, 12 equiv.) and $(MeO)_3CH$ (388 mg, 3.66 mmol, 3 equiv.) in dry dichloromethane (12 mL) was added camphorsulfonic acid (51 mg, 0.220 mmol, 0.18 equiv.) and the solution was stirred for 4 days at room temperature. A saturated $NaHCO_3$ solution was added and the aqueous layer was extracted with DCM (x3). The organic layers were washed with water, dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (pentane/Et_2O, 100:0 to 95:5) to afford **411** as a colorless oil (188 mg, 74% yield).

$[\alpha]_D^{20}$ = +12.69 (c 1.0, $CHCl_3$).

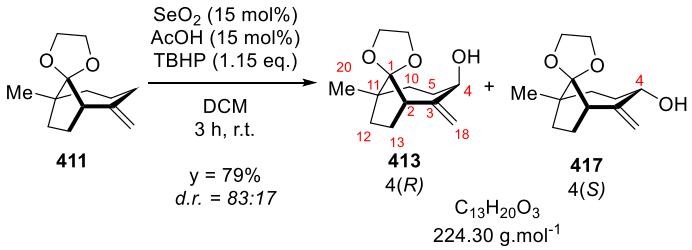
^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.61 (s, 1H, Ha-18), 4.55 (s, 1H, Hb-18), 3.96-3.86 (m, 4H, O-CH_2), 2.85-2.80 (dd, *J* = 10.7, 2.2 Hz, 1H, H-2), 2.57-2.36 (m, 2H, H-4), 2.18 (dddd, *J* = 13.8, 10.8, 10.7, 2.5 Hz, 1H, Ha-13), 1.70-1.48 (m, 7H, H-5, H-10, H-12, Hb-13), 0.93 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 151.6 (C, C-3), 118.7 (C, C-1), 110.4 (CH_2, C-18), 65.94 (CH_2, O-CH_2), 63.72 (CH_2, O-CH_2), 53.2 (CH, C-2), 46.44 (C, C-11), 39.5 (CH_2, C-10), 34.8 (CH_2, C-5), 33.9 (CH_2, C-12), 29.5 (CH_2, C-13), 23.4 (CH_2, C-4), 22.7 (CH_3, C-20) ppm.

FTIR (neat): *ν* = 3067, 2954, 2924, 1629, 1469, 1212, 1150, 1077, 1049, 1038, 1007, 878 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{13}H_{20}O_2Na^+$: $[M+Na]^+$: 208.1463; found: unstable.

Methyl (1*R*,4*R*,6*S*)-1-methyl-5-methylenespiro[bicyclo[4.2.1]nonane-9,2'-[1,3]dioxolan]-4-ol **413** and **417**



In a round-bottomed flask was placed **411** (500 mg, 2.4 mmol, 1 equiv.) in DCM (12 mL). selenium dioxide (40 mg, 0.36 mmol, 0.15 equiv.), TBHP (5.5M in decane, 0.48 mL, 2.66 mmol, 1.15 equiv.) and dry acetic acid (21 µL, 0.36 mmol, 0.9 equiv.) were successively added and the mixture was stirred for 3 h. Saturated $NaHCO_3$ (10 mL) was added, the aqueous layer was extracted with DCM (x3) and the organic layers were dried over $MgSO_4$ and filtered. Removal of the solvent under reduced pressure provided a brown oil. Purification by flash chromatography over silica gel (pentane/Et_2O, 80:20 to 50:50) afforded **413** and **417** (*d.r. :* 83 : 17, 480 mg, 79% yield) as an inseparable mixture (white solid).

$[\alpha]_D^{20}$: 15.5 (c 1.0, $CHCl_3$).

FTIR (neat): ν = 3496, 3070, 2928, 1631, 1155, 1046 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{13}H_{20}O_3Na^+$: $[M+Na]^+$: 247.2892; found: 247.2896.

Major diastereoisomer 413

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.06 (d, *J* = 1.6 Hz, 1H, Ha-18), 4.89 (d, *J* = 1.8 Hz, 1H, Hb-18), 4.28 (dd, *J* = 10.8, 5.3 Hz, 1H, Ha-4), 4.09 (d, *J* = 10.8 Hz, 1H, OH), 4.01-3.91 (m, 4H, O-CH_2), 2.92 (dd, *J* = 10.7, 2.3 Hz, 1H, H-2), 2.28-2.14 (m, 1H, Ha-13), 2.03-1.86 (m, 2H, Ha-10, Hb-13), 1.86-1.75 (m, 1H, Ha-5), 1.75-1.57 (m, 2H, H-12), 1.53-1.41 (m, 1H, Hb-5), 1.30-1.23 (m, 1H, Hb-10), 0.94 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 152.0 (C, C-3), 118.6 (C, C-1), 118.0 (CH_2, C-18), 72.4 (CH, C-4), 65.6 (CH_2, O- CH_2), 64.1 (CH_2, O-CH_2), 53.3 (CH, C-2), 46.5 (C, C-11), 33.9 (CH_2, C-12), 31.4 (CH_2, C-10), 29.9 (CH_2, C-5), 29.5 (CH_2, C-13), 22.2 (CH_3, C-20) ppm.

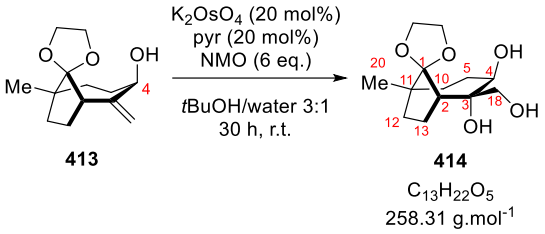
Minor diastereoisomer 417

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.09 (t, *J* = 1.6 Hz, 1H, Ha-18), 4.79 (t, *J* = 2.0 Hz, 1H, Hb-18), 4.44 (d, *J* = 7.2 Hz, 1H, H-4), 3.90-3.80 (m, 4H, O-CH_2) ppm. *The other proton signals are overlapped with the signals of the major diastereoisomer*.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 153.9 (C, C-3), 118.5 (C, C-1), 110.1 (CH_2, C-18), 72.7 (CH, C-4), 65.9 (CH_2, O-CH_2), 63.9 (CH_2, O-CH_2), 52.1 (CH, C-2), 45.9 (C, C-11), 36.6 (CH_2, C-12), 33.9 (CH_2, C-10), 33.5 (CH_2, C-5), 30.0 (CH_2, C-13), 22.0 (CH_3, C-20).

(4*R*,5*S*)-5-(hydroxymethyl)-1-methylspiro[bicyclo[4.2.1]nonane-9,2'-[1,3]dioxolane]-4,5-diol

414



$C_{13}H_{22}O_5$
258.31 g.mol^{-1}

In a round-bottomed flask were placed **413** (240 mg, 1.07 mmol, 1 equiv.) and *N*-methylmorpholine-*N*-Oxide (752 mg, 6.43 mmol, 6 equiv.) in a 3:1 (v/v) solution of *t*-BuOH/H_2O (11 mL). Pyridine (86 µL, 1.07 mmol, 1 equiv.) and potassium osmate dihydrate (79 mg, 0.214 mmol, 0.2 equiv.) were added. The mixture was stirred for 3 h at room temperature. A 20% m/m% solution of $NaHSO_3$ (22 mL) was added and the mixture was stirred for an additional hour. The mixture was then extracted with AcOEt (x5) and the organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Purification by flash chromatography over silica gel (AcOEt/MeOH, 100:0 to 80:20) provided **414** as white solid (234 mg, 85% yield).

$[\alpha]_D^{20}$: -21.18 (c 1.0, $CHCl_3$).

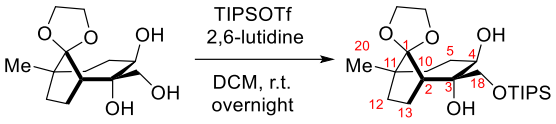
^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.19 (d, *J* = 11.9 Hz, 1H, C-4-OH), 4.06 (d, *J* = 10.9 Hz, 1H, Ha-18), 4.03-3.86 (m, 4H, O-CH_2), 3.69 (dd, *J* = 11.9, 6.5 Hz, 1H, H-4), 3.20 (t, *J* = 10.9 Hz, 1H, Hb-18), 2.54 (d, *J* = 10.9 Hz, C-18-OH), 2.51 (s, 1H, C-3-OH), 2.21-2.32 (m, 1H, Ha-5), 2.05-1.93 (m, 2H, H-2, Ha-13), 1.87-1.69 (m, 3H, Hb-5, Ha-10, Hb-13), 1.69-1.50 (m, 2H, H-12), 1.29-1.22 (m, 1H, Hb-10), 0.92 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 119.0 (C, C-1), 75.3 (CH, C-4), 75.1 (C, C-3), 70.2 (CH_2, C-18), 66.6 (O-CH_2), 64.0 (O-CH_2), 50.2 (CH, C-2), 46.8 (C, C-11), 33.1 (CH_2, C-12), 31.6 (CH_2, C-10), 26.2 (CH_2, C-13), 22.3 (CH_3, C-20), 20.9 (CH_2, C-5) ppm.

FTIR (neat): ν = 3412, 2928, 2890, 1664, 1456, 1122.22, 1050 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{13}H_{22}O_5Na^+$: $[M+Na]^+$: 281.1359 ; found: 281.1351.

(4*R*,5*S*)-1-methyl-5-(((triisopropylsilyl)oxy)methyl)spiro[bicyclo[4.2.1]nonane-9,2'-[1,3]dioxolane]-4,5-diol **415**



414

415
$C_{22}H_{42}O_5Si$
414.66 g.mol^{-1}

In a round-bottomed flask were placed **414** (150 mg, 0.58 mmol, 1 equiv.) and 2,6-lutidine (135 µL, 1.16 mmol, 2 equiv.) dissolved in DCM (5 mL) at 0°C. TIPSOTf (156 µL, 0.58 mmol, 1 equiv.) was added dropwise and the mixture was stirred overnight. Water (5 mL) was added, the aqueous layer was extracted with DCM (x3), the organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The oily residue was purified by flash chromatography over silica gel (pentane/Et_2O, 90:10 to 70:30) affording **415** (235 mg, quantitative yield)

$[\alpha]_D^{20}$: 36.4 (c 1.0, $CHCl_3$).

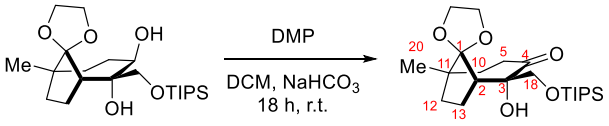
^{1}H-NMR (400MHz, $CDCl_3$)) δ = 4.03-3.88 (m, 6H, O-CH_2, Ha-18, C-4-OH), 3.72-3.64 (m, 2H, H-4, Hb-18), 2.86 (s, 1H, C-3-OH), 2.37 (dd, *J* = 10.2, 2.2 Hz, 1H, H-2), 2.25 (dddd, *J* = 2.8, 6.7, 11.1, 14.0 Hz, 1H, Ha-13), 1.93 (ddd, *J* = 15.3, 12.4, 3.6 Hz, 1H, Ha-5), 1.82-1.69 (m, 3H, Hb-5, Hb-13, Ha-10), 1.69-1.49 (m, 2H, H-12), 1.25 (ddd, *J* = 14.9, 5.6, 4.1 Hz, 1H, Hb-10), 1.20-1.11 (m, 3H, Si-CH), 1.10-1.05 (m, 18H, Si-(CH(CH_3)$_2$), 0.92 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 119.4 (C, C-1), 75.2 (CH, C-4), 74.3 (C, C-3), 68.3 (CH_2, C-18), 66.5 (CH_2, O-CH_2), 63.9 (CH_2, O-CH_2), 48.9 (CH, C-2), 46.7 (C, C-11), 33.5 (CH_2, C-12), 32.1 (CH_2, C-10), 27.2 (CH_2, C-5), 22.6 (CH_3, C-20), 21.6 (CH_2, C-13), 18.1 (6CH_3, Si-CH(CH_3)$_2$), 12.1 (3CH, Si-CH) ppm.

FTIR (neat): ν = 2957, 1731, 1436, 1374, 1199, 1164 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{22}H_{42}O_5SiNa^+$: $[M+Na]^+$: 437.2702 ; found: 437.2685.

(5*S*)-5-hydroxy-1-methyl-5-(((triisopropylsilyl)oxy)methyl)spiro[bicyclo[4.2.1]nonane-9,2'-[1,3]dioxolan]-4-one **416**



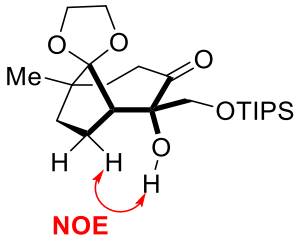
415

416
$C_{22}H_{40}O_5Si$
412.64 g.mol^{-1}

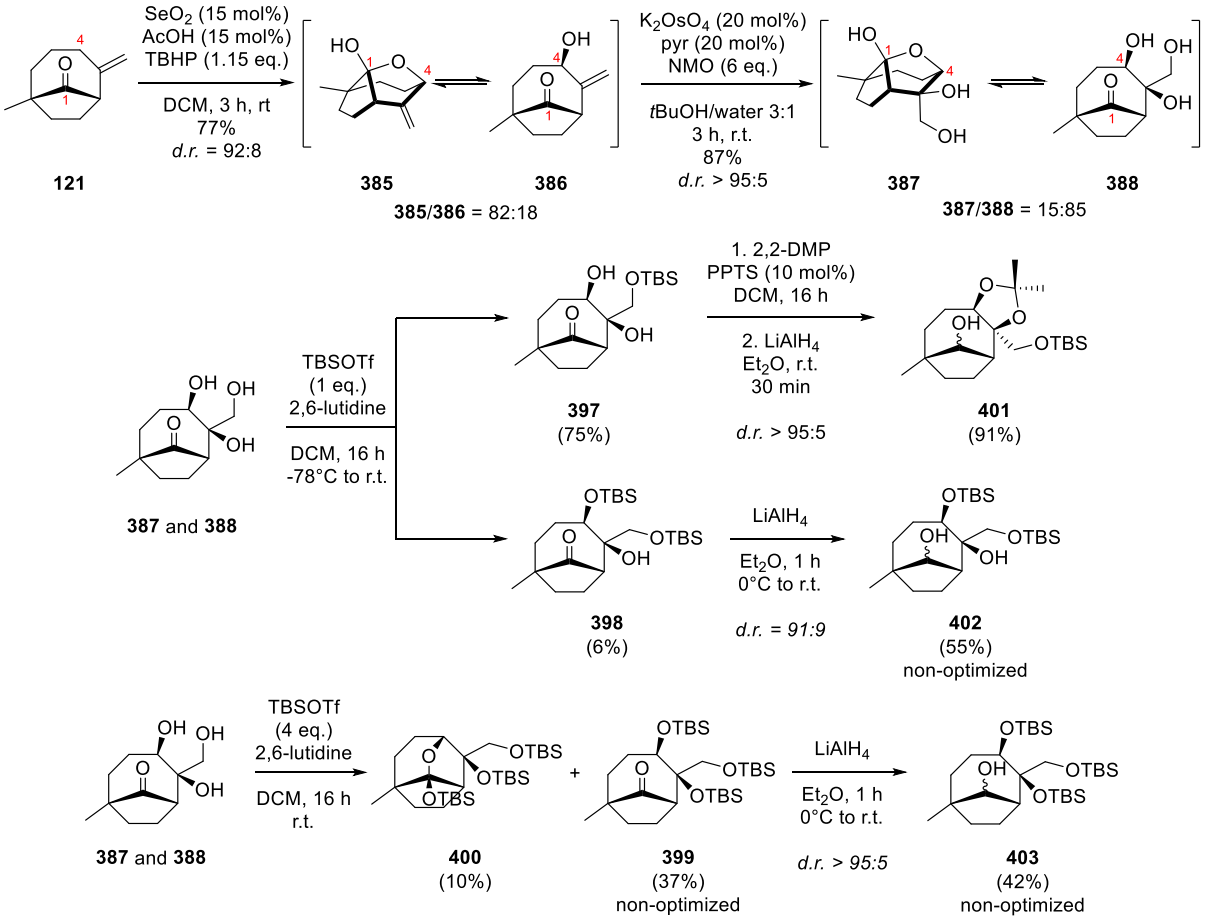
To a stirred solution of Dess-Martin Periodinane (327 mg, 0.77 mmol, 1.5 equiv.) and $NaHCO_3$ (136 mg, 1.54 mmol, 3 equiv.) in DCM (10 mL) was added a solution of **415** (213 mg, 0.51 mmol, 1 equiv.) in DCM (3 mL) and the mixture was stirred for 18 h. A saturated solution of $Na_2S_2O_3$ (15 mL) was added, the aqueous layer was extracted with DCM (x3) and the organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 9:1 to 7:3) afforded ketone **416** (203 mg, quantitative yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.59 (d, *J* = 9.8 Hz, 1H, Ha-18), 4.06 (s, 1H, C-3-OH), 4.05-3.87 (m, 4H, O-CH_2), 3.63 (d, *J* = 9.8 Hz, 1H, Hb-18), 2.99 (ddd, *J* = 12.1, 9.5, 7.6 Hz, 1H, Ha-5), 2.51 (ddd, *J* = 12.1, 6.8, 5.0 Hz, 1H, Hb-5), 2.15 (d, *J* = 8.1 Hz, 1H, H-2), 1.92 (dddd, *J* = 14.0, 10.0, 3.5, 1.4 Hz, 1H, Ha-13), 1.83 (ddd, *J* = 13.7, 7.6, 5.0 Hz, 1H, Ha-10), 1.74 (ddd, *J* = 13.7, 9.6, 6.8 Hz, 1H, Hb-13), 1.65-1.56 (m, 2H, Hb-10, Ha-12), 1.38 (ddd, *J* = 13.9, 10.0, 7.6 Hz, 1H, Hb-12), 1.09-1.01 (m, 21H, Si-CH-(CH_3)$_2$), 0.98 (s, 3H, H-20) ppm.

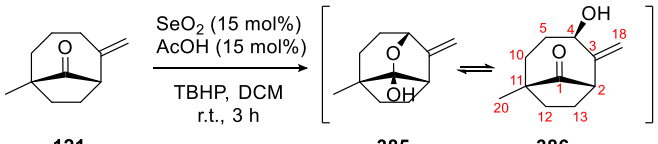
^{13}C-NMR (100MHz, $CDCl_3$) δ = 212.1 (C, C-4), 118.6 (C, C-1), 80.0 (C, C-3), 69.0 (CH_2, C-18), 66.2 (CH_2, O-CH_2), 64.1 (CH_2, O-CH_2), 49.3 (CH, C-2), 45.4 (C, C-11), 37.8 (CH_2, C-10), 36.0 (CH_2, C-5), 35.1 (CH_2, C-12), 23.8 (CH_3, C-20), 21.3 (CH_2, C-13), 18.06 (6CH_3, Si-CH-(CH_3)$_2$), 12.1 (3CH_2, Si-CH) ppm.



9.4 Direct functionalization



(2*R*,4a*R*,7*S*,7a*S*)-4a-methyl-8-methylenehexahydro-2,7-methanocyclopenta[b]pyran-7a(2*H*)-ol **385** and **386**



$C_{11}H_{16}O_2$
180.25 g.mol^{-1}

To a stirred solution of **121** (400 mg, 2.44 mmol, 1 equiv.), TBHP (5.5 M in heptane, 0,51 mL, 1.15 equiv.) and dry acetic acid (22 µL, 0.366 mmol, 0.15 equiv.) in DCM (11 mL), was added selenium dioxide (40 mg, 0.366 mmol, 0.15 equiv.). The mixture was stirred for 5 h at room temperature and then quenched with a saturated solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with DCM (x3). The organic layers were dried over $MgSO_4$,

filtered and concentrated under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 95:5 to 70:30) afforded an inseparable mixture of **385** and **386** (310 mg, 70% yield calculated over 81% of conversion).

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}O_2Na^+$: $[M+Na]^+$: 203.1048 ; found: 203.1038.

Major Isomer 385

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.92 (dd, *J* = 2.3, 1.3 Hz, 1H, Ha-18), 4.90 (dd, *J* = 2.8, 1.3 Hz, 1H, Hb-18), 4.69 (broad s, 1H, H-4), 3.02 (s, 1H, C1-OH), 2.62 (ddd, *J* = 9.0, 5.2, 2.9 Hz, 1H, H-2), 2.10-2.21 (m, 1H, Ha-5), 1.92-2.07 (m, 2H, H-13), 1.62-1.90 (m, 3H, Hb-5, Ha-10, Ha-12), 1.42-1.59 (m, 3H, Hb-10, Hb-12, Hb-13), 1.06 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 157.2 (C, C-3), 113.9 (C, C-1), 105.5 (CH_2, C-18), 80.0 (CH, C-4), 51.3 (CH, C-2), 41.6 (C, C-11), 39.0 (CH_2, C-12), 31.4 (CH_2, C-10), 30.4 (CH_2, C-13), 27.1 (CH_2, C-5), 19.4 (CH_3, C-20) ppm.

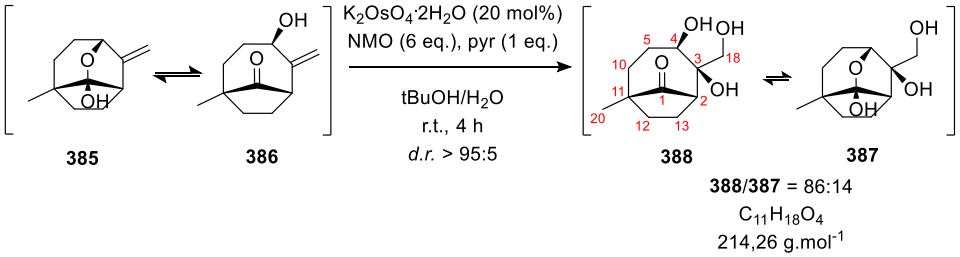
Minor Isomer 386

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.08 (s, 1H, Ha-18), 4.96 (s, 1H, Hb-18), 4.45 (broad s, 1H, H-4), 3.14 (dd, *J* = 10.1, 2.8 Hz, 1H, H-2), 2.36-2.25 (m, 1H, H-5), 1.11 (s, 3H, H-20) ppm.

The other proton signals are overlapped with the signals of the major diastereoisomer.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 220.1 (C, C-1), 149.8 (C, C-3), 115.5 (CH_2, C-18), 73.4 (CH, C-4), 52.7 (CH, C-2), 49.1 (C, C-11), 33.9 (CH_2, C-10, C-12 or C-13), 33.1 (CH_2, C-10, C-12 or C-13), 29.9 (CH_2, C-10, C-12 or C-13), 27.1 (CH_2, C-5), 23.1 (CH_3, C-20) ppm.

(1*R*,4*R*,5*R*,6*S*)-4,5-dihydroxy-5-(hydroxymethyl)-1-methylbicyclo[4.2.1]nonan-9-one **387** and **388**



388/**387** = 86:14
$C_{11}H_{18}O_4$
214,26 g.mol^{-1}

To a stirred solution of **385** and **386** (300 mg, 1.67 mmol, 1 equiv.) in *t*-BuOH/water (3:1, 17 mL), NMO (1.17 g, 10 mmol, 6 equiv.), pyridine (134 µL, 1.67 mmol, 1 equiv.) and potassium osmate dihydrate (184 mg, 0.50 mmol, 0.3 equiv.) were successively added. After 4h stirring at room temperature, a 20% (m/m) aqueous solution of $NaHSO_3$ (20 mL) was added and the mixture was stirred for an additional hour. Sodium chloride was added (2 g) and the mixture was extracted with AcOEt (x5). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (AcOEt/MeOH, 10:0 to 80:20) afforded **388** and **387** as an unseparable mixture (310 mg, 87% yield).

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O_4Na^+$: $[M+Na]^+$: 237.1103 ; found: 237.1097.

Major isomer 388

^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.87 (d, *J* = 12 Hz, 1H, Ha-18), 3.76 (s, 1H, OH), 3.64 (d, *J* = 9.6 Hz, 1H, H-4), 3.44 (d, *J* = 11.6 Hz, 1H, Hb-18), 3.01 (broad s, 2H, OH), 2.63 (dd, *J* = 9.9, 6.0 Hz, 1H, H-2), 2.10-1.95 (m, 1H, Ha-13), 1.90-1.78 (m, 1H, Ha-12), 1.75-1.61 (m, 4H, Ha-5, Ha-10, Hb-12, Hb-13), 1.59-1.48 (m, 2H, Hb-5, Hb-10), 1.08 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 226.2 (C, C-1), 75.3 (C, C-3), 73.0 (CH, C-4), 65.8 (CH_2, C-18), 49.1 (CH, C-2), 49.0 (C, C-11), 36.7 (CH_2, C-12), 35.3 (CH_2, C-10), 30.3 (CH_2, C-5), 21.8 (CH_3, C-20), 19.1 (CH_2, C-13) ppm.

Minor Isomer 387

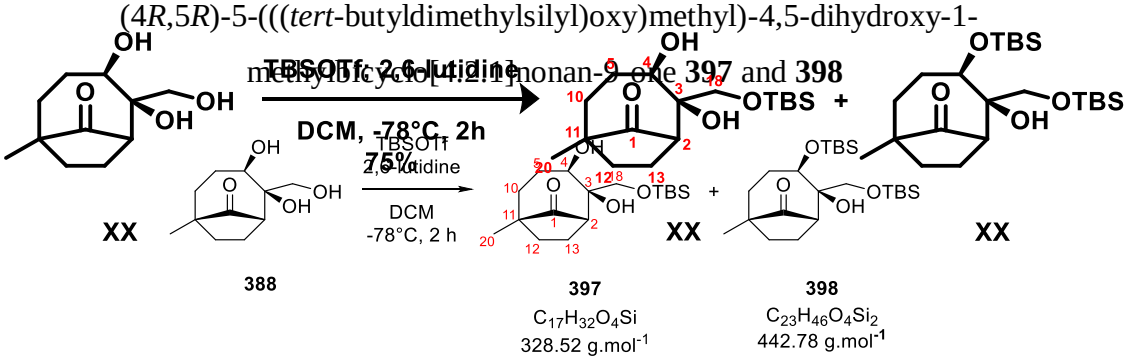
*Some of the ^{1}H-NMR signals of **387** are not distinguishable from the signals of **388**. This renders uncomplete the assignement of the ^{13}C-NMR signals of **387**.*

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.88 (s, 1H, C3-OH), 4.16 (d, *J* = 7.2 Hz, 1H, H-4), 3.76 (dd, 2H, *J* = 22.3, 12.6 Hz, 2H, H-18), 2.26 (dd, 1H, *J* = 10.5, 5.4 Hz, C-2), 1.05 (s, 3H, C-

20) ppm. *The other proton signals are overlapped with the signals of the major diastereoisomer*

^{13}C-NMR (100MHz, $CDCl_3$) δ = 115.3 (C, C-1), 83.6 (C, C-3), 82.8 (CH, C-4), 62.7 (CH_2, C-18), 57.4 (CH, C-2), 49.0 (C, C-11), 42.8 (CH_2, C-12), 39.2 (CH_2, C-10), 31.5 (CH_2, C-5), 22.8 (CH_2, C-13), 20.9 (CH_3, C-20) ppm.

(4*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5-dihydroxy-1-methylbicyclo[4.2.1]nonan-9-one **397** and **398**



To a stirred solution of **388** (420 Mg, 1.96 mmol, 1 equiv.) and 2,6-lutidine (420 mg, 456 µL, 3.92 mmol, 2 equiv.) in dichloromethane (18 mL) at -78°C, was added TBSOTf (517 mg, 450 µL, 1.96 mmol, 1 equiv.) over 30 min and the mixture was stirred at -78°C for 90 min. The reaction was quenched with a saturated solution of $NaHCO_3$ (25 mL), the aqueous layer was extracted with dichloromethane (x3). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 100:0 to 90:10) afforded **397** as a light yellow oil (480 mg, 75% yield) along with **398** (50 mg, 6% yield).

397

^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.79 (d, *J* = 10.2 Hz, 1H, Ha-18), 3.70 (ddd, *J* = 9.7, 8.4, 3.3 Hz, 1H, H-4), 3.59 (d, *J* = 10.2 Hz, 1H, Hb-18), 3.15 (s, 1H, C3-OH), 2.83 (d, *J* = 8.4 Hz, 1H, C4-OH), 2.56 (dd, *J* = 10.4, 5.8 Hz, 1H, H-2), 2.01-1.91 (m, 1H, Ha-13), 1.84-1.52 (m, 7H, H-5, H-10, H-12, Hb-13), 1.10 (s, 3H, H-20), 0.90 (s, 9H, Si-C(CH_3)$_3$), 0.09 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 220.1 (C, C-1), 74.7 (C, C-3), 13.0 (CH, C-4), 67.4 (CH_2, C-18), 49.9 (CH, C-2), 48.7 (C, C-11), 36.8 (CH_2, C-12), 35.5 (CH_2, C-10), 30.3 (CH_2, C-5), 26.0 (3CH_3, Si-C(CH_3)$_3$), 22.2 (CH_3, C-20), 19.2 (CH_2, C-13), 18.4 (C, Si-C(CH_3)$_3$), -5.2 (CH_3, Si-CH_3), -5.4 (CH_3, Si-CH_3) ppm.

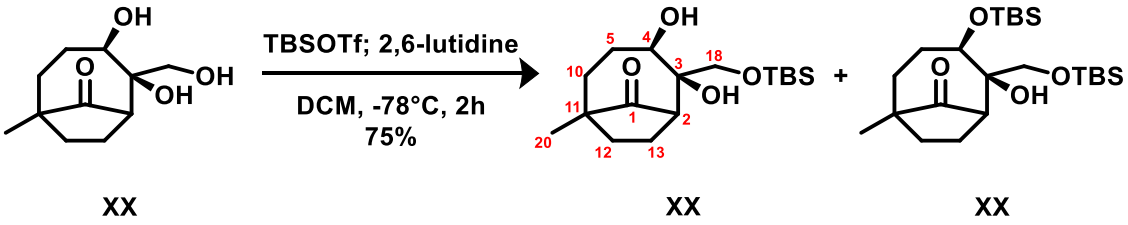
HRMS (ESI): *m/z* calcd for $C_{17}H_{32}O_4SiNa^+$: $[M+Na]^+$: 351.1970; found: 351.1964.

398 (Side product)

^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.79 (dd, *J* = 9.4, 1.3 Hz, 1H, H-4), 3.57 (s, 2H, H-18), 2.89 (s, 1H, C3-OH), 2.61 (dd, *J* = 10.3, 5.6 Hz, 1H, H-2), 1.57-2.00 (m, 7H, Ha-10, H-5, H-12, H-13), 1.41 (ddd, *J* = 12.8, 8.6, 2.6 Hz, 1H, Hb-10), 1.06 (s, 3H, H-20), 0.89 (s, 9H, C18-O-Si-$C(CH_3)_3$), 0.88 (s, 9H, C4-O-Si-$C(CH_3)_3$), 0.07 (s, 3H, C18-O-Si-CH_3), 0.06 (s, 3H, C18-O-Si-CH_3), 0.05 (s, 6H, C4-O-Si-$(CH_3)_2$) ppm

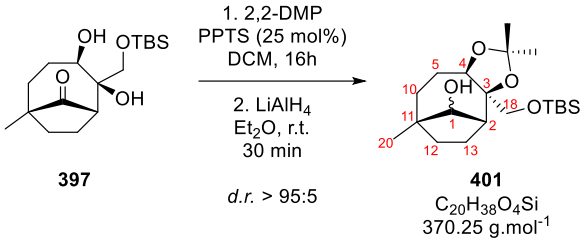
^{13}C-NMR (100MHz, $CDCl_3$) δ = 219.0 (C,C-1), 74.8 (C, C-3), 73.1 (C, C-4), 68.4 (CH_2, C-18), 51.2 (CH, C-2), 48.5 (C, C-11), 35.6 (CH_2, C-12), 35.0 (CH_2, C-10), 29.4 (CH_2, C-5), 26.1 (3 CH_3, C18-O-Si-$C(CH_3)_3$), 25.9 (3CH_3, C4-O-Si-$C(CH_3)_3$), 22.7 (CH_3, C-20), 20.0 (CH_2, C-13), 18.4 (C, C18-O-Si-C), 18.2 (C, C4-O-Si-C), -4.2 (CH_3, C-4-O-Si-CH_3), -4.8 (CH_3, C4-O-Si-CH_3), -5.2 (CH_3, C18-O-Si-CH_3), -5.4 (CH_3, C18-O-Si-CH_3) ppm.

HRMS (ESI): *m/z* calcd for $C_{23}H_{46}O_4Si_2Na^+$: $[M+Na]^+$: 465.2835; found: 465.2829.



XX XX XX

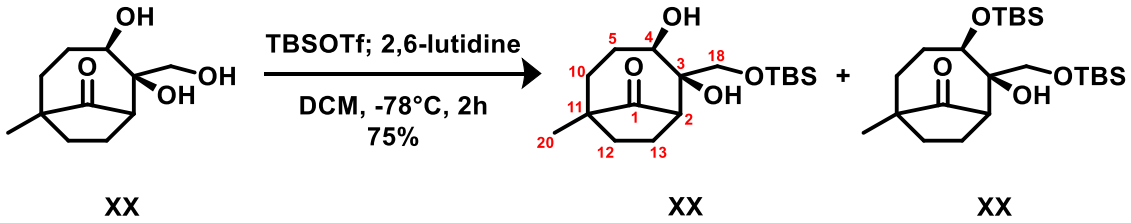
(3aR,4R,7R,9aR)-3a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2,7-trimethyloctahydro-4,7-methanocycloocta[d][1,3]dioxol-10-ol **401**



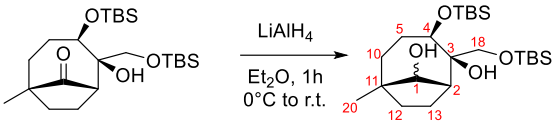
Monoprotected diol **397** (180 mg, 0.55 mmol, 1 eq.) was solubilized in DCM (9 mL), 2,2-dimethoxymethane (9 mL) and PPTS (34 mg, 0.137 mmol, 0.25 eq.) were added and the mixture was stirred for 16 hours. Solvent was then evaporated under reduced pressure and Et_2O (25 mL) was added to the residue. The mixture was cooled to 0°C and $LiAlH_4$ (31 mg, 0.82 mmol, 1.5 eq.) was portionwise inserted. After 30 minutes the reaction was quenched by sequential addition of H_2O (30 µL), 2M aqueous NaOH (30 µL) and again water (90 µL). White aluminium salts were filtered over a celite pad and the filtrate was reduced under reduced pressure. Purification on silica gel (Pentane/Et_2O 80:20) afforded **401** in 91 % yield (185 mg).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.06 (d, J = 4.8 Hz, 1H, H-4), 3.71 (t, J = 8.6 Hz, 1H, H-1), 3.66 (dd, J = 12.7, 11.2 Hz, 2H, H-18), 3.50 (d, J = 9.0 Hz, 1H, C-1-OH), 2.68 (ddd, J = 10.0, 8.6, 2.0 Hz, 1H, H-2), 2.11-2.04 (m, 1H, Ha-5), 1.99 (td, J = 14.3, 1.9 Hz, 1H, Ha-10); 1.85-1.74 (m, 2H, Hb-5, Ha-13), 1.66-1.60 (m, 1H, Hb-13), 1.59 (s, 3H, O-C-CH_3), 1.50-1.58 (m, 1H, Ha-12), 1.34-1.46 (m, 1H, Hb-12), 1.39 (s, 3H, O-C-CH_3), 1.14-1.07 (m, 1H, H-10), 1.03 (s, 3H, H-20), 0.89 (s, 9H, Si-C(CH_3)$_3$), 0.06 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$) ppm.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 107.0 (C, O-C-CH_3), 86.9 (C, C-3), 82.1 (CH, C-1), 77.7 (CH, C-4), 70.0 (CH_2, C-18), 44.0 (CH, C-2), 43.9 (C, C-11), 32.3 (CH_2, C-12), 28.7 (CH_2, C-10), 28.0 (CH_3, C-20), 26.6 (CH_3, O-C-CH_3), 26.0 (3CH_3, Si-C(CH_3)$_3$), 25.8 (CH_3, O-C-CH_3), 25.5 (CH_2, C-5), 21.8 (CH_2, C-13), 18.4 (C, Si-C(CH_3)$_3$), -5.3 (CH_3, Si(CH_3)$_2$), -5.4 (CH_3, Si(CH_3)$_2$) ppm.



(2*R*,3*R*)-3-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methylbicyclo[4.2.1]nonane-2,9-diol **402**



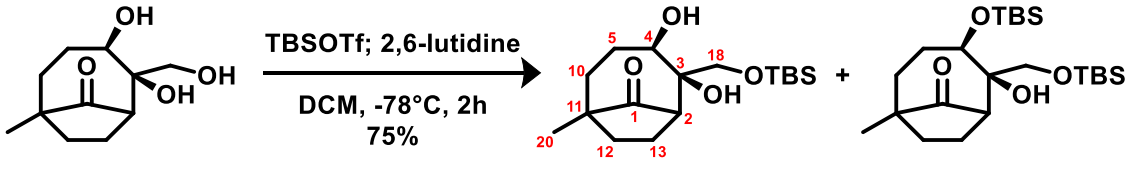
398 *d.r. = 91:9* **402**

$C_{23}H_{48}O_4Si_2$
444.80 g.mol^{-1}

Ketone **398** (90 mg, 0.20 mmol, 1 eq.) was solubilized in Et_2O (2 mL), and the mixture was cooled to 0°C. $LiAlH_4$ (8 mg, 0.21 mmol, 1.05 eq.) was added and the ice bath was removed. After one hour the reaction was quenched by sequential addition of H_2O (10 µL), 2M aqueous NaOH (10 µL) and again water (30 µL). White aluminium salts were filtered over a celite pad and the filtrate was reduced under reduced pressure. Purification on silica gel (Pentane/Et_2O 80:20) afforded **402** in 55 % yield (50 mg).

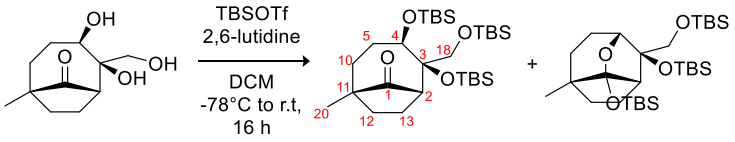
^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.64 (d, *J* = 11.6 Hz, 1H, C-1-OH), 3.77 (d, *J* = 6.4 Hz, 1H, H-4), 3.73 (dd, *J* = 11.6, 8.0 Hz, 1H, H-1), 3.48 (dd, *J* = 10.0, 17.6 Hz, 2H, H-18), 2.93 (s, 1H, C-3-OH), 2.49 (ddd, *J* = 10.5, 7.8, 2.6 Hz, 1H, H-2), 1.86 (ddd, *J* = 14.3, 13.8, 3.3 Hz, 1H, Ha-10), 1.68-1.81 (m, 3H, H-5, Ha-13), 1.56-1.67 (m, 1H, Hb-13), 1.50-1.44 (m, 1H, Ha-12), 1.44-1.36 (m, 1H, Hb-12), 1.14 (dt, *J* = 14.3, 3.9 Hz, 1H, Hb-10), 1.03 (s, 3H, H-20), 0.94 (s, 9H, Si-C$(CH_3)_3$), 0.90 (s, 9H, Si-C$(CH_3)_3$), 0.14 (s, 3H, Si$(CH_3)_2$), 0.11 (s, 3H, Si$(CH_3)_2$), 0.08 (s, 3H, Si$(CH_3)_2$), 0.06 (s, 3H, Si$(CH_3)_2$) ppm.

^{1}H-NMR (400MHz, $CDCl_3$) δ= 82.9 (CH, C-1), 77.6 (C, C-3), 72.7 (CH, C-4), 69.0 (CH_2, C-18), 48.7 (CH, C-2), 44.1 (C, C-11), 34.2 (CH_2, C-12), 30.4 (CH_2, C-10), 28.2 (CH_2, C-5), 27.9 (CH_3, C-20), 26.1 ($3CH_3$, Si-C$(CH_3)_3$), 25.9 ($3CH_3$, Si-C$(CH_3)_3$), 22.0 (CH_2, C-13), 18.6 (C, Si-C$(CH_3)_3$), 18.4 (C, Si-C$(CH_3)_3$), -4.7 (CH_3, Si$(CH_3)_2$), -4.9 (CH_3, Si$(CH_3)_2$), -5.2 (CH_3, Si$(CH_3)_2$), -5.4 (CH_3, Si$(CH_3)_2$) ppm.



XX **XX** **XX**

(1*R*,4*R*,5*R*,6*S*)-4,5-*bis*((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methylbicyclo[4.2.1]nonan-9-one **399**



388 and **387** | **399** | **400**

$C_{29}H_{60}O_4Si_3$
557.05 g.mol^{-1}

In a round-bottomed flask containing a solution of **388** (120 mg, 0.56 mmol, 1 equiv.) and 2,6-lutidine (450 mg, 490 µL, 4.2 mmol, 7.5 equiv.) in dichloromethane (6 mL) at -78°C, was added TBSOTf (475 mg, 413 µL, 1.8 mmol, 3.2 equiv.). The mixture was stirred overnight, then quenched with a saturated solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with dichloromethane (x3) and the organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 99:1 to 90:10) afforded triol **399** (110 mg, 37% yield) along with hemiacetal **400** (60 mg, 10% yield).

Ketone 399

^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.89 (d, *J* = 10.9 Hz, 1H, Ha-18), 3.75 (d, *J* = 10.3 Hz, 1H, H-4), 3.55 (d, *J* = 10.9 Hz, 1H, Hb-18), 2.73 (d, *J* = 9.1, 3.7 Hz, 1H, H-2), 2.11 (dddd, *J* = 14.9, 14.0, 10.7, 4.8 Hz, 1H, Ha-5), 1.87-1.71 (m, 3H, H-12, Ha-13), 1.65-1.55 (m, 2H, Ha-10, Hb-13), 1.49 (td, *J* = 13.7, 4.8 Hz, 1H, Hb-10), 1.35-1.24 (m, 1H, Hb-5), 1.05 (s, 3H, H-20), 0.91 (s, 9H, Si-C(CH_3)$_3$), 0.89 (s, 9H, Si-C(CH_3)$_3$), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.23 (s, 3H, Si(CH_3)$_2$), 0.08 (s, 3H, Si(CH_3)$_2$), 0.07 (s, 3H, Si(CH_3)$_2$), 0.06 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 218.2 (C, C-1), 79.7 (C, C-3), 74.8 (CH, C-4), 67.1 (CH_2, C-18), 50.5 (CH, C-2), 47.2 (C, C-11), 38.2 (CH_2, C-10), 37.2 (CH_2, C-12), 30.5 (CH_2, C-5), 26.4 (3CH_3, Si-C(CH_3)$_3$), 26.2 (3CH_3, Si-C(CH_3)$_3$), 25.9 (3CH_3, Si-C(CH_3)$_3$), 24.4 (CH_3, C-20), 19.7 (CH_2, C-13), 19.1 (C, Si-C(CH_3)$_3$), 18.6 (C, Si-C(CH_3)$_3$), 18.2 (C, Si-C(CH_3)$_3$), -2.5 (CH_3, Si(CH_3)$_2$), -2.6 (CH_3, Si(CH_3)$_2$), -4.2 (CH_3, Si(CH_3)$_2$), -4.7 (CH_3, Si(CH_3)$_2$), -5.0 (CH_3, Si(CH_3)$_2$), -5.4 (CH_3, Si(CH_3)$_2$) ppm.

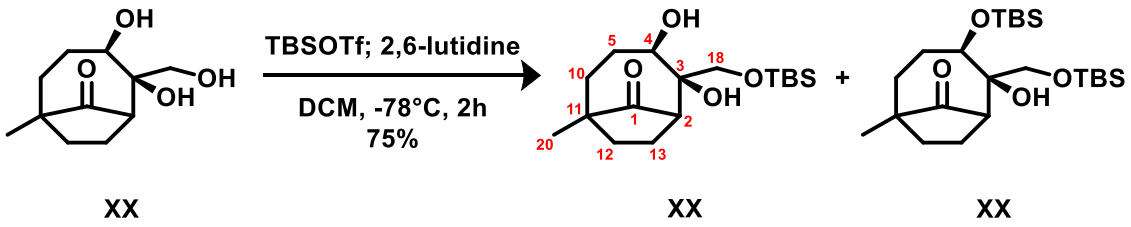
HRMS (ESI): *m/z* calcd for $C_{29}H_{60}O_4Si_3Na^+$: $[M+Na]^+$: 579.3692; found: 579.3693.

Hemiacetal 400

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.02 (d, *J* = 5.2 Hz, 1H, H-4), 3.98 (d, *J* = 9.3 Hz, 1H, Ha-18), 3.42 (d, *J* = 9.3 Hz, 1H, Hb-18), 2.90 (dd, *J* = 9.3, 1.9 Hz, 1H, H-2), 2.30 (td, *J* = 13.3, 2.3 Hz, 1H, Ha-10), 2.16 (dddd, *J* = 15.0, 14.4, 5.2, 2.7 Hz, 1H, Ha-5), 1.78-1.61 (m, 5H, Hb-5, H-12, H-13), 1.17 (ddd, *J* = 13.3, 3.8, 3.2 Hz, 1H, Hb-10), 0.95 (s, 3H, H-20), 0.90 (s, 9H, Si-C$(CH_3)_3$), 0.89 (s, 9H, Si-C$(CH_3)_3$), 0.87 (s, 9H, Si-C$(CH_3)_3$), 0.20 (s, 3H, Si$(CH_3)_2$), 0.18 (s, 3H, Si$(CH_3)_2$), 0.06 (s, 6H, Si$(CH_3)_2$), 0.05 (s, 6H, Si$(CH_3)_2$) ppm.

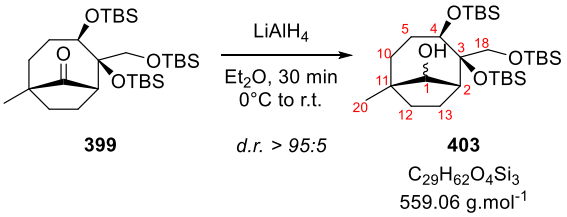
^{13}C-NMR (100MHz, $CDCl_3$) δ = 110.9 (C, C-1), 80.7 (C, C-3), 67.4 (CH_2, C-18), 67.0 (CH, C-4), 54.2 (CH, C-2), 49.7 (C, C-11), 39.2 (CH_2, C-12), 33.8 (CH_2, C-10), 31.8 (CH_2, C-5), 26.2 ($3CH_3$, C18-O-Si-C$(CH_3)_3$), 26.1 ($3CH_3$, C1-O-Si-C$(CH_3)_3$), 26.0 ($3CH_3$, C3-O-Si-C$(CH_3)_3$), 24.4 (CH_3, C-20), 19.7 (CH_2, C-13), 18.4 (C, C18-O-Si-C), 18.3 (C, C1-O-Si-C), 18.2 (C, C3-O-Si-C), -2.3 (CH_3, Si$(CH_3)_2$), -2.6 (CH_3, Si$(CH_3)_2$), -4.0 (CH_3, Si$(CH_3)_2$), -4.5 (CH_3, Si$(CH_3)_2$), -4.8 (CH_3, Si$(CH_3)_2$), -5.1 (CH_3, Si$(CH_3)_2$) ppm. 

HRMS (ESI): *m/z* calcd for $C_{29}H_{60}O_4Si_3Na^+$: $[M+Na]^+$: 579.3692; found: 579.3681.



XX XX XX

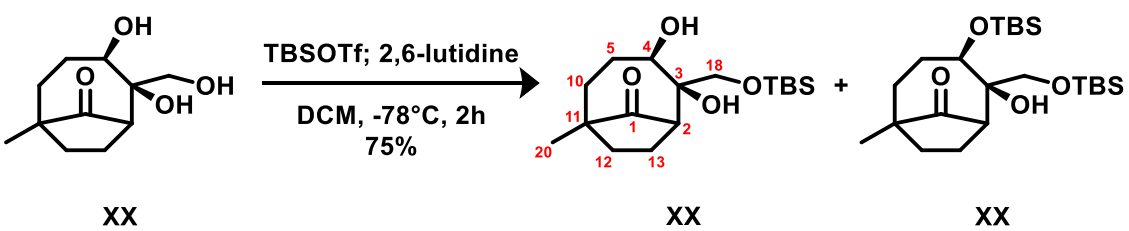
(4*R*,5*R*)-4,5-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-methylbicyclo[4.2.1]nonan-9-ol **403**



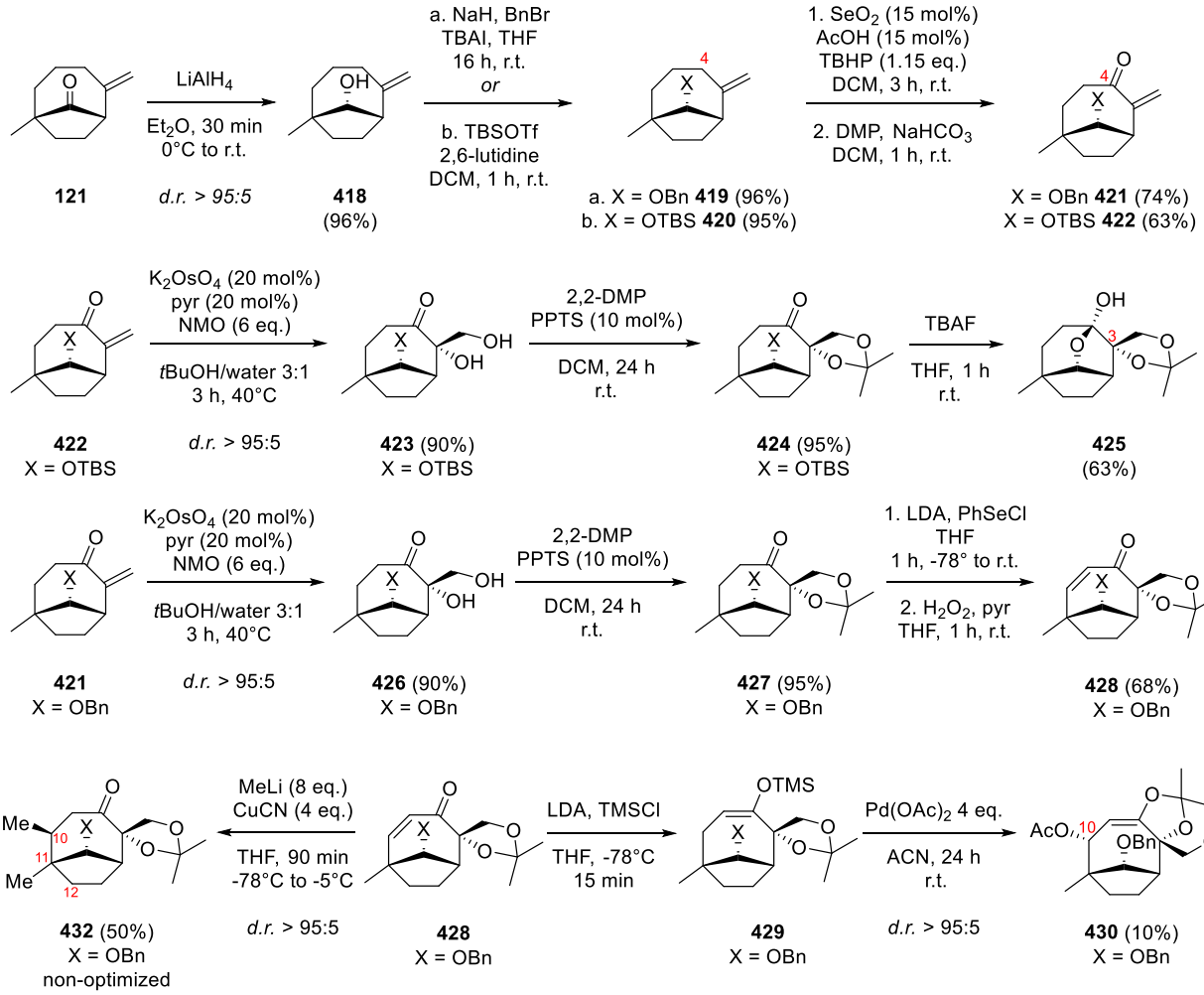
Ketone **399** (100 mg, 0.18 mmol, 1 eq.) was solubilized in Et_2O (2 mL), and the mixture was cooled to 0°C. $LiAlH_4$ (7 mg, 0.18 mmol, 1 eq.) was added and the ice bath was removed. After 30 minutes the reaction was quenched by sequential addition of H_2O (10 µL), 2M aqueous NaOH (10 µL) and again water (30 µL). White aluminium salts were filtered over a celite pad and the filtrate was reduced under reduced pressure. Purification on silica gel (Pentane/Et_2O 95:5) afforded **403** in 42 % yield (42 mg).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.72 (d, *J* = 6.0 Hz, 1H, C-1-OH), 3.91 (d, *J* = 11.5 Hz, 1H, Ha-18), 3.82 (dd, *J* = 7.0, 6.0 Hz, 1H, H-1), 3.69 (dd, *J* = 11.6, 1.2 Hz, 1H, H-4), 3.51 (d, *J* = 11.6 Hz, 1H, Hb-18), 2.77 (t, *J* = 7.0 Hz, 1H, H-2), 2.48 (dddd, *J* = 11.0, 14.6, 11.6, 7.3 Hz, 1H, Ha-5), 1.72-1.60 (m, 2H, Ha-13, Ha-10), 1.57-1.52 (m, 1H, Ha-12), 1.50-1.40 (m, 2H, Hb-5, Hb-12), 1.37-1.27 (m, 2H, Hb-13, Hb-10), 1.09 (s, 3H, H-20), 0.92 (s, 9H, Si-C$(CH_3)_3$), 0.91 (s, 9H, Si-C$(CH_3)_3$), 0.90 (s, 9H, Si-C$(CH_3)_3$), 0.23 (s, 3H, Si$(CH_3)_2$), 0.19 (s, 3H, Si$(CH_3)_2$), 0.07 (s, 3H, Si$(CH_3)_2$), 0.06 (s, 3H, Si$(CH_3)_2$), 0.05 (s, 6H, Si$(CH_3)_2$) ppm.

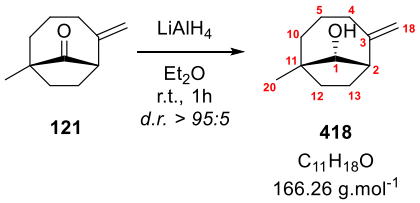
^{1}H-NMR (400MHz, $CDCl_3$) δ = 86.7 (C, C-3), 83.8 (CH, C-1), 73.4 (CH, C-4), 67.1 (CH_2, C-18), 43.0 (CH, C-2), 42.4 (C, C-11), 38.5 (CH_2, C-12), 35.7 (CH_2, C-10), 30.9 (CH_3, C-20), 29.9 (CH_2, C-5), 26.5 ($3CH_3$, Si-C$(CH_3)_3$), 26.1 ($6CH_3$, Si-C$(CH_3)_3$), 22.0 (CH_2, C-13), 19.1 (C, Si-C$(CH_3)_3$), 18.6 (C, Si-C$(CH_3)_3$), 18.4 (C, Si-C$(CH_3)_3$), -2.1 (CH_3, Si$(CH_3)_2$), -2.3 (CH_3, Si$(CH_3)_2$), -4.3 (CH_3, Si$(CH_3)_2$), -4.5 (CH_3, Si$(CH_3)_2$), -4.9 (CH_3, Si$(CH_3)_2$), -5.3 (CH_3, Si$(CH_3)_2$) ppm.



9.5 Ongoing strategy



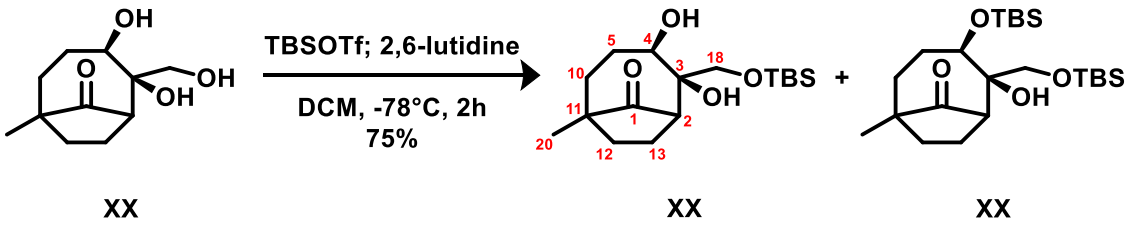
(9*R*)-1-methyl-5-methylenebicyclo[4.2.1]nonan-9-ol **418**



To a stirred solution of **121** (750 mg, 4.57 mmol, 1 equiv.) in Et_2O (13 mL) was portionwise added $LiAlH_4$ (174 mg, 4.57 mmol, 1 equiv.). After 1 h, water (200 µL), aqueous 2M NaOH (200 µL) and water (600 µL) were successively added and the mixture was then stirred for 30 min. Filtration over celite® and removal of the solvent under reduced pressure afforded **418** (730 mg, quantitative yield) as a single diastereoisomer without further purification.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.72 (dd, *J* = 3.1, 2.3 Hz, 1H, Ha-18), 4.68 (t, *J* = 2.3 Hz, 1H, Hb-18), 3.77 (d, *J* = 7.8 Hz, 1H, H-1), 3.01 (ddd, *J* = 10.0, 7.8, 2.0 Hz, 1H, H-2), 2.56-2.40 (m, 2H, H-4), 2.03 (dddd, *J* = 14.1, 11.6, 9.8, 3.7 Hz, 1H, Ha-13), 1.70-1.52 (m, 5H, H-5, Ha-10, Ha-12, Hb-13), 1.50-1.41 (m, 1H, Hb-12), 1.39-1.31 (m, 1H, Hb-10), 1.06 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 152.4 (C, C-3), 112.2 (CH_2, C-18), 81.8 (CH, C-1), 50.3 (CH, C-2), 44.4 (C, C-11), 37.0 (CH_2, C-10), 35.6 (CH_2, C-4), 34.4 (CH_2, C-12), 28.8 (CH_3, C-20), 28.4 (CH_2, C-13), 23.7 (CH_2, C-5) ppm.



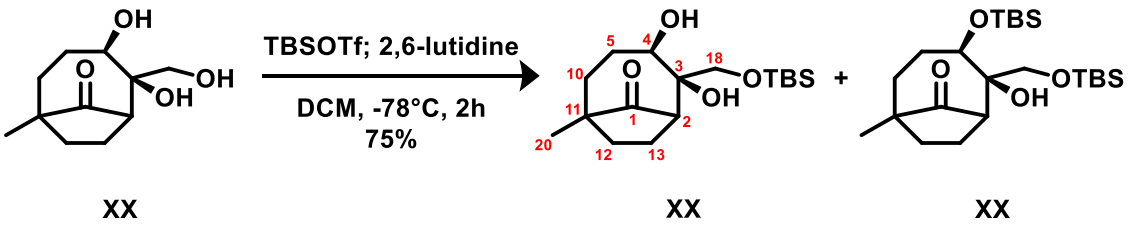
Tert-butyldimethyl(((9*R*)-1-methyl-5-methylenebicyclo[4.2.1]nonan-9-yl)oxy)silane **420**

418 (200 mg, 1.2 mmol, 1equiv.) was solubilized in dry DCM (3 mL), triethylamine (364 mg, 501 µL, 3.6 mmol, 3 equiv.) was then added followed by TBSOTf (477 mg, 414 µL, 1.8 mmol, 1.5 equiv.). The mixture was stirred for 30 min and a saturated solution of $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with DCM (x3), the organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (Pentane/Et_2O, 100:0 to 95:5) and **420** (320 mg, quantitative yield) was obtained.

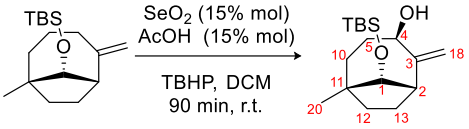
^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.56 (t, *J* = 2.3 Hz, 1H, Ha-18), 4.52 (t, *J* = 2.6 Hz, 1H, Hb-18), 3.71 (d, *J* = 7.9 Hz, 1H, H-1), 2.87 (ddd, *J* = 9.9, 8.2, 2.1 Hz, 1H, H-2), 2.55 (dddd, *J* = 15.5, 12.0, 5.5, 2.6 Hz, 1H, Ha-4), 2.45-2.39 (m, 1H, Hb-4), 2.03 (dddd, *J* = 14.0, 11.6, 10.3, 3.4 Hz, 1H, Ha-13), 1.70-1.45 (m, 4H, Hb-13, H-5, Ha-10, Ha-12), 1.44-1.35 (m, 1H, Hb-12), 1.28-1.22 (m, 1H, Hb-10), 0.97 (s, 3H, H-20), 0.89 (s, 9H, Si-C(CH_3)$_3$), 0.02 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 154.5 (C, C-3), 110.1 (CH_2, C-18), 82.4 (CH, C-1), 50.3 (CH, C-2), 44.9 (C, C-11), 37.6 (CH_2, C-10), 36.2 (CH_2, C-4), 33.5 (CH_2, C-12), 29.6 (CH_2, C-13), 29.0 (CH_3, C-20), 26.0 (3 CH_3, Si-C(CH_3)$_3$), 23.9 (CH_2, C-5), 18.3 (C, Si-C(CH_3)$_3$), -4.4 (CH_3, Si-C(CH_3)$_3$), -4.9 (CH_3, Si-C(CH_3)$_3$) ppm.

HRMS (ESI): *m/z* calcd for $C_{17}H_{32}OSiNa^+$: $[M+Na]^+$: 303.2115, found: 303.2126.



(9*R*)-9-((*tert*-butyldimethylsilyl)oxy)-6-methyl-2-methylenebicyclo[4.2.1]nonan-3-one and (1*R*,2*S*,6*R*,9*R*)-9-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-(hydroxymethyl)-6-methylbicyclo[4.2.1]nonan-3-one **422**

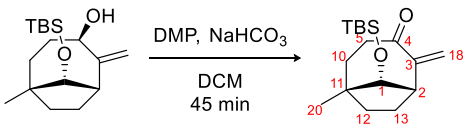


420 **420b**
$C_{17}H_{32}O_2Si$
296.53 g.mol^{-1}

To a solution of **420** (300 mg, 1.07 mmol, 1 equiv.) in DCM (5 mL) were successively added selenium dioxide (18 mg, 0.16 mmol, 0.15 equiv.), TBHP (5.5M in decane, 0.22 mL, 1.23 mmol, 1.15 equiv.) and dry acetic acid (9 µL, 0.15 mmol, 0.2 equiv.). The mixture was stirred for 90 min and a saturated solution of $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with DCM (x3). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 90:10 to 50:50) afforded **420b** (200 mg, 65% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.06 (t, *J* = 2.1 Hz, 1H, Ha-18), 4.79 (t, *J* = 2.1 Hz, 1H, Hb-18), 4.45 (d, *J* = 8.3 Hz, 1H, H-4), 3.71 (d, *J* = 7.9 Hz, 1H, H-1), 3.01 (ddd, *J* = 10.3, 8.3, 2.1 Hz, 1H, H-2), 2.13-2.03 (m, 1H, Ha-5), 1.70-1.83 (m, 2H, H-12), 1.64-1.34 (m, 3H, Hb-5, H-10), 1.34-1.18 (m, 2H, H-13), 0.96 (s, 3H, H-20), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.03 (s, 3H, Si(CH_3)$_2$), 0.01 (s, 3H, Si(CH_3)$_2$) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 156.2 (C, C-3), 109.7 (CH_2, C-18), 81.9 (C, C-1), 73.6 (CH, C-4), 49.1 (CH, C-2), 44.0 (C, C-11), 34.3 (CH_2, C-12), 33.6 (CH_2, C-13), 33.0 (CH_2, C-10), 29.8 (CH_2, C-5), 28.1 (CH_3, C-20), 25.9 (3CH_3, Si-C(CH_3)$_3$), 18.1 (C, Si-C(CH_3)$_3$), -4.6 (CH_3, Si(CH_3)$_2$), -5.0 (CH_3, Si(CH_3)$_2$) ppm.



420b **422**
$C_{17}H_{30}O_2Si$
294.51 g.mol^{-1}

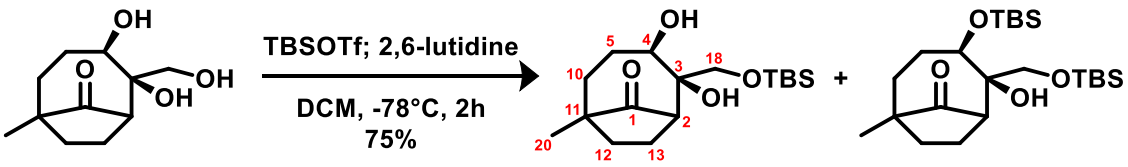
To a stirred solution of **420b** (180 mg, 0.61 mmol, 1 equiv.) and $NaHCO_3$ (161 mg, 1.83 mmol, 3 equiv.) in DCM (10 mL) was added Dess-Martin periodinane (385 mg, 0.91 mmol, 1.5 equiv.). The mixture was stirred for 45 min and a saturated solution of $Na_2S_2O_3$ (10 mL)

was added. The aqueous layer was extracted with DCM (x3). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 95:5 to 80:20) provided **422** (173 mg, 96% yield).

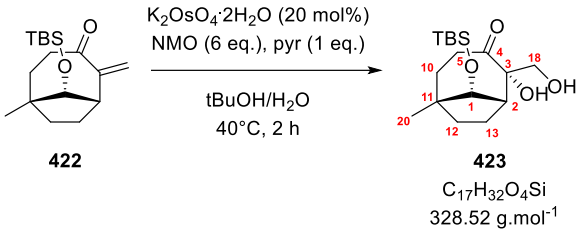
^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.76 (d, *J* = 2.4 Hz, 1H, Ha-18), 5.03 (d, *J* = 2.4 Hz, 1H, Hb-18), 3.81 (d, *J* = 8.4 Hz, 1H, H-1), 3.01 (ddd, *J* = 10.1, 8.4, 2.4 Hz, 1H, H-2), 2.61 (td, *J* = 13.7, 4.2 Hz, 1H, Ha-5), 2.47 (ddd, *J* = 13.7, 4.8, 3.5 Hz, 1H, Hb-5), 2.24-2.11 (m, 1H, Ha-13), 1.90 (tdd, *J* = 13.9, 3.2, 1.4 Hz, 1H, Ha-10), 1.82-1.67 (m, 2H, Hb-13, Ha-12), 1.65-1.55 (m, 1H, Hb-12), 1.31-1.21 (m, 1H, Hb-10), 1.01 (s, 3H, H-20), 0.82 (s, 9H, Si-C(CH_3)$_3$), 0.02 (s, 3H, Si-CH_3), -0.01 (s, 3H, Si-CH_3) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 202.5 (C, C-4), 150.0 (C, C-3), 122.0 (CH_2, C-18), 81.4 (CH, C-1), 47.8 (CH, C-2), 44.8 (C, C-11), 41.4 (CH_2, C-5), 33.6 (CH_2, C-12), 31.8 (CH_2, C-10), 28.1 (CH_3, C-20), 27.8 (CH_2, C-13), 25.8 (3CH_3, Si-C(CH_3)$_3$), 18.2 (C, Si-C(CH_3)$_3$), -4.3 (CH_3, Si(CH_3)$_2$), -4.8 (CH_3, Si(CH_3)$_2$) ppm.

HRMS (ESI): *m/z* calcd for $C_{17}H_{30}O_2SiNa^+$: $[M+Na]^+$: 317.1907 found: 317.1909.



(1R,2S,6R,9R)-9-((tert-butyldimethylsilyl)oxy)-2-hydroxy-2-(hydroxymethyl)-6-methylbicyclo[4.2.1]nonan-3-one **423**



422 **423**

$C_{17}H_{32}O_4Si$

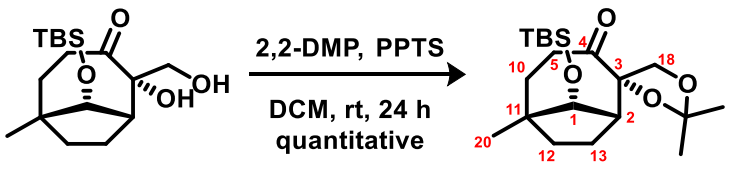
328.52 g.mol^{-1}

To a stirred solution of **422** (150 mg, 0.51 mmol, 1 equiv) in *t*-BuOH/water (3:1, 8 mL), NMO (358 mg, 3.06 mmol, 6 equiv.), pyridine (41 µL, 0.51 mmol, 1 equiv.) and potassium osmate dihydrate (37 mg, 0.10 mmol, 0.2 equiv.) were successively added and the mixture was heated to 40°C and stirred for 2 h. A 20% (m/m) aqueous solution of $NaHSO_3$ (10 mL) was added and the mixture was stirred for an additional hour at room temperature. Sodium chloride was added (1 g) and the mixture was extracted with AcOEt (x5). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (cyclohexane/AcOEt, 50:50 to 0:100) afforded **423** (150 mg, 90% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.46 (s, 1H, C3-OH), 4.42 (dd, *J* = 11.6, 9.6 Hz, 1H, Ha-18), 3.93 (d, *J* = 6.3 Hz, 1H, H-1), 3.52 (dd, *J* = 11.6, 4.7 Hz, 1H, Hb-18), 3.08 (dt, *J* = 11.9, 8.6 Hz, 1H, Ha-5), 2.53 (ddd, *J* = 11.9, 7.5, 4.3 Hz, 1H, Hb-5), 2.41 (dd, *J* = 9.6, 4.7 Hz, 1H, C18-OH), 2.19 (t, *J* = 6.3 Hz, 1H, H-2), 1.84-1.77 (m, 1H, Ha-13), 1.73 (ddd, *J* = 13.3, 8.6, 4.3 Hz, 1H, Ha-10), 1.50-1.38 (m, 3H, Hb-10, Ha-12, Hb-13), 1.34-1.28 (m, 1H, Hb-12), 1.05 (s, 3H, H-20), 0.95 (s, 9H, Si-C(CH_3)$_3$), 0.12 (s, 3H, Si(CH_3)$_2$), 0.11 (s, 3H, Si(CH_3)$_2$) ppm.

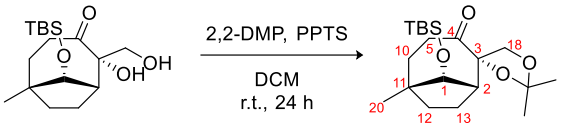
^{13}C-NMR (100MHz, $CDCl_3$) δ = 214.0 (C, C-4), 82.5 (C, C-3), 81.9 (CH, C-1), 69.3 (CH_2, C-18), 48.4 (CH,C-2), 42.2 (C, C-11), 34.9 (CH_2, C-5), 34.8 (CH_2, C-12), 34.4 (CH_2, C-10), 30.2 (CH_3, C-20), 26.15 (3CH_3, Si-C(CH_3)$_3$), 20.3 (CH_2, C-13), 18.1 (C, Si-C(CH_3)$_3$), -3.8 (CH_3, Si(CH_3)$_2$), -3.9 (CH_3, Si(CH_3)$_2$) ppm.

HRMS (ESI): *m/z* calcd for $C_{17}H_{32}O_4SiNa^+$: $[M+Na]^+$: 351.1968 found: 351.1956.



XX **XX**

(1*R*,2*S*,6*R*,9*R*)-9-((*tert*-butyldimethylsilyl)oxy)-2',2',6-trimethylspiro[bicyclo[4.2.1]nonane-2,4'-[1,3]dioxolan]-3-one **424**



423 **424**

$C_{20}H_{36}O_4Si$

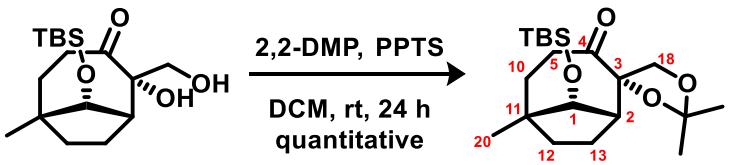
368.59 g.mol^{-1}

A mixture of **423** (86 mg, 0.26 mmol, 1 equiv.), PPTS (18 mg, 0.07 mmol, 0.27 equiv.), 2,2-DMP (4 mL) and DCM (3 mL) was stirred for 24 h. A saturated solution of $NaHCO_3$ (10 mL) was added, the aqueous layer was extracted with DCM (x3 mL) and the organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 90:10 to 70:30) to afford **424** (91 mg, quantitative yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.66 (d, *J* = 8.6 Hz, 1H, Ha-18), 3.92 (d, *J* = 8.2 Hz, 1H, H-1), 3.96 (d, *J* = 8.6 Hz, 1H, Hb-18), 2.71 (td, *J* = 12.2, 4.6 Hz, 1H, Ha-5), 2.53 (ddd, *J* = 9.8, 8.2, 2.2 Hz, 1H, H-2), 2.41 (ddd, *J* = 12.2, 5.6, 3.5 Hz, 1H, Hb-5), 2.28 (dddd, *J* = 15.0, 10.9, 7.5, 2.2 Hz, 1H, Ha-13), 1.80-1.59 (m, 3H, Ha-10, Ha-12, Hb-13), 1.56-1.45 (m, 1H, Hb-12), 1.36 (s, 3H, O-C-CH_3), 1.35-1.30 (m, 1H, Hb-10) 1.28 (s, 3H, O-C-CH_3), 0.98 (s, 3H, H-20), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.07 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$) ppm.

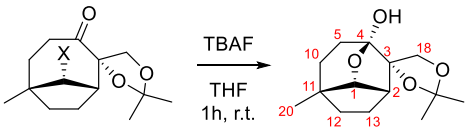
^{13}C-NMR (100MHz, $CDCl_3$) δ = 205.9 (C, C-4), 109.6 (C, O-C-CH_3), 85.0 (C, C-3), 81.8 (CH, C-1), 75.5 (CH_2, C-18), 49.1 (CH, C-2), 44.3 (C, C-11), 38.0 (CH_2, C-5), 34.0 (CH_2, C-10), 33.8 (CH_2, C-12), 28.4 (CH_3, C-20), 27.3 (CH_3, O-C-CH_3), 26.1 (CH_3, O-C-CH_3), 26.0 (3CH_3, Si-C(CH_3)$_3$), 22.1 (CH_2, C-13), 18.1 (C, Si-C(CH_3)$_3$), -3.7 (CH_3, Si(CH_3)$_2$), -4.3 (CH_3, Si(CH_3)$_2$) ppm.

HRMS (ESI): *m/z* calcd for $C_{20}H_{36}O_4SiNa^+$: $[M+Na]^+$: 391.2275, found: 391.2297



XX **XX**

(2'*R*,4*S*,4a'*R*,7'*R*,7a'*R*)-2,2,4a'-trimethylhexahydrospiro[[1,3]dioxolane-4,8'-[2,7]methanocyclopenta[b]pyran]-2'(3'H)-ol **425**



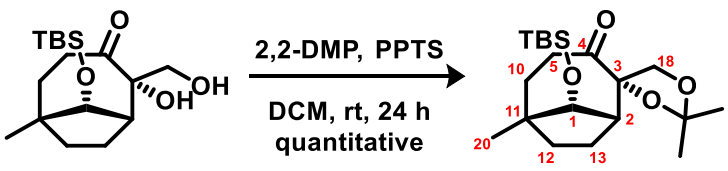
424
X = OTBS

425
$C_{14}H_{22}O_4$
254.33 g.mol^{-1}

To a solution of ketone **424** (94 mg, 0.25 mmol, 1 eq.) in THF (3 mL) was added a solution of TBAF (1M in THF, 0.5 mL, 0.5 mmol, 1 eq.). After one hour water was added (5 mL), the layers were separated and the aqueous layer was extracted with Et_2O (x3). The reunited organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification over silica gel (cyclohexane/AcOEt 7:3) afforded hemiacetal **425** in 63% yield (40 mg).

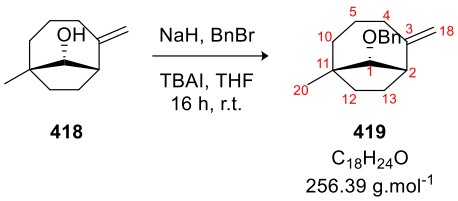
1H-NMR (400MHz, $CDCl_3$) δ = 4.52 (d, J = 9.0 Hz, 1H, Ha-18), 3.96 (d, J = 8.0 Hz, 1H, H-1), 3.63 (d, J = 9.0 Hz, 1H, Ha-18), 3.13 (br s, 1H, OH), 2.34 (ddd, J = 9.5, 8.0, 4.1 Hz, 1H, H-2), 2.12-2.01 (m, 2H, Ha-10, Ha-13), 1.67-1.46 (m, 5H, H-12, Hb-10, Hb-13, Ha-5), 1.44 (s, 3H, O-C-CH_3), 1.35 (s, 3H, O-C-CH_3), 1.32-1.22 (m, 1H, Hb-5), 1.10 (s, 3H, H-20) ppm.

13C-NMR (100MHz, $CDCl_3$) δ =110.0 (C, O-C-CH_3), 102.6 (C, C-4), 88.1 (CH, C-1), 86.4 (C, C-3), 72.8 (CH_2, C-18), 46.9 (CH, C-2), 38.5 (CH_2, C-5), 37.6 (C, C-11), 30.6 (CH_2, C-10), 30.3 (CH_2, C-12), 27.0 (CH_3, O-C-CH_3), 26.1 (CH_3, C-20), 25.6 (CH_3, O-C-CH_3), 21.9 (CH_2, C-13) ppm.



XX **XX**

(9*R*)-9-(benzyloxy)-1-methyl-5-methylenebicyclo[4.2.1]nonane **419**



418 **419**

$C_{18}H_{24}O$

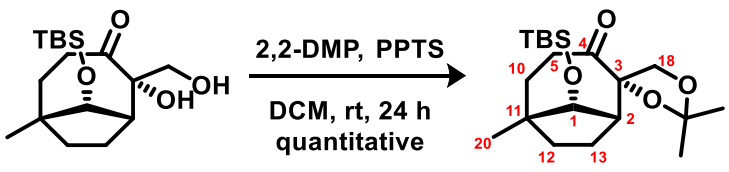
256.39 g.mol^{-1}

To a suspension of NaH (226 mg, 5.64 mmol, 1.5 equiv.) and TBAI (182 mg, 0.56 mmol, 0.15 equiv.) in THF (4 mL) was added dropwise a solution of **418** (624 mg, 3.76 mmol, 1 equiv.) in THF (4 mL). BnBr (535 µL, 771 mg, 4.51 mmol, 1.2 equiv.) was then added and the mixture was stirred for 18 h at room temperature. A saturated solution of $NaHCO_3$ was added, the aqueous layer was extracted with Et_2O (x3), the organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 100:0 to 90:10) afforded **419** (920 mg, quantitative yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.31-7.39 (m, 4H, H-ar), 7.24-7.30 (m, 1H, H-ar), 4.70 (d, *J* = 11.9 Hz, 1H, O-C<u>Ha</u>Hb-Ar), 4.65 (d, *J* = 2.3 Hz, 2H, H-18), 4.40 (d, *J* = 11.9 Hz, 1H, O-CHa<u>Hb</u>-Ar), 3.52 (d, *J* = 7.7, 1H, H-1), 3.17 (ddd, *J* = 10.2, 7.7, 2.0 Hz, 1H, H-2), 2.70-2.60 (m, 1H, Ha-4), 2.46 (dd, *J* = 15.1, 5.6 Hz, 1H, Hb-4), 2.08 (dddd, *J* = 11.9, 13.5, 10.2, 3.1 Hz, 1H, Ha-13), 1.79 (ddd, *J* = 12.5, 13.2, 4.0 Hz, 1H, Ha-10), 1.69-1.51 (m, 4H, H-5, Ha-12, Hb-13), 1.47-1.38 (m, 1H, Hb-12), 1.36-1.29 (m, 1H, Hb-10), 1.07 (s, 3H, H-20) ppm.

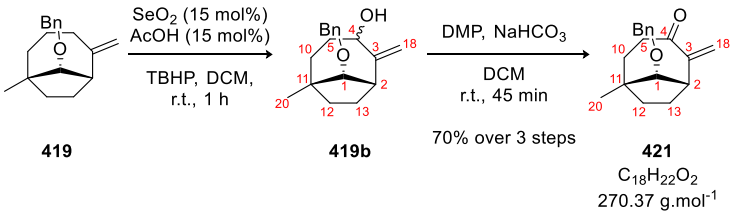
^{13}C-NMR (100MHz, $CDCl_3$) δ = 154.3 (C, C-3), 139.5 (C, C-ar), 128.3 (2CH, C-ar), 127.5 (2CH, C-ar), 127.3 (CH, C-ar), 110.3 (CH_2, C-18), 88.2 (CH, C-1), 71.6 (CH_2, O-CH_2-Ar), 47.0 (CH, C-2), 44.6 (C, C-11), 37.9 (CH_2, C-10), 36.2 (CH_2, C-4), 34.2 (CH_2, C-12), 29.9 (CH_2, C-13), 29.0 (CH_3, C-20), 23.9 (CH_2, C-5).

HRMS (ESI): *m/z* calcd for $C_{18}H_{24}ONa^+$: $[M+Na]^+$: 279.1719 found: 279.1721.



XX **XX**

(1*S*,6*R*,9*R*)-9-(benzyloxy)-6-methyl-2-methylenebicyclo[4.2.1]nonan-3-one **421**



To a stirred solution of alkene **419** (850 mg, 3.32 mmol, 1 equiv.) in DCM (12 mL) were successively added TBHP (5.5M in decane, 0.69 mL, 1.15 mmol, 1.15 equiv.), dry acetic acid (29 µL, 0.5 mmol, 0.15 equiv.) and selenium dioxide (55 mg, 0.50 mmol, 0.15 equiv.). The mixture was stirred for 1 h and a saturated solution of $NaHCO_3$ (15 mL) was added. The aqueous layer was extracted with DCM (x3). The organic layers were dried over $MgSO_4$, filtered, and removal of the solvent under reduced pressure provided desired allylic alcohol **419b** as a mixture of two epimers at C-4 (*ratio* 73:27*)* that was directly engaged in the next reaction.

HRMS (ESI): *m/z* calcd for $C_{18}H_{24}O_2Na^+$: $[M+Na]^+$: 295.1669 found: 295.1667.

Major Diastereoisomer

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.30-7.35 (m, 4H, H-ar), 7.30-7.35 (m, 1H, H-ar), 5.11 (d, *J* = 1.7 Hz, 1H, Ha-18), 5.0 (d, *J* = 1.7 Hz, 1H, Hb-18), 4.74 (d, *J* = 11.5 Hz, 1H, O-C<u>Ha</u>Hb-Ar), 4.64 (d, *J* = 10.7 Hz, 1H, C4-OH), 4.47 (d, *J* = 11.5 Hz, 1H, O-CHa<u>Hb</u>-Ar), 4.32 (dd, *J* = 11.0, 5.3 Hz, 1H, H-4), 3.53 (d, *J* = 7.6 Hz, 1H, H-1), 3.22 (ddd, *J* = 10.2, 7.6, 1.7 Hz, 1H, H-2), 2.17-2.06 (m, 1H, Ha-5), 2.01 (td, *J* = 14.1, 2.2 Hz, 1H, Hb-5), 1.95-1.73 (m, 2H, H-13), 1.70-1.60 (m, 1H, Ha-10), 1.58-1.49 (m, 1H, Ha-12), 1.49-1.39 (m, 1H, Hb-10), 1.26-1.17 (m, 1H, Hb-12), 1.08 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 154.1 (C, C-3), 137.3 (C, C-ar), 128.5 (2CH, C-ar), 128.1 (2CH, C-ar), 128.0 (CH, C-ar), 117.9 (CH_2, C-18), 87.8 (CH, C-1), 72.7 (CH, C-4), 72.3 (CH_2, O-CH_2-Ar), 47.1 (CH, C-2), 44.4 (C, C-11), 33.9 (CH_2, C-10), 30.0 (CH_2, C-13), 29.8 (CH_2, C-12), 29.7 (CH_2, C-5), 28.3 (CH_3, C-20) ppm.

Minor Diastereoisomer

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.29-7.38 (m, 5H, H-ar), 5.13 (t, *J* = 1.9 Hz, 1H, Ha-18), 4.89 (t, *J* = 1.9 Hz, 1H, Hb-18), 4.64 (d, *J* = 11.9 Hz, 1H, O-C<u>Ha</u>Hb-Ar), 4.52-4.49 (m, 1H, H-4), 4.37 (d, *J* = 11.9 Hz, 1H, O-CHa<u>Hb</u>-Ar), 3.50 (d, *J* = 7.8 Hz, 1H, H-1), 3.28 (ddd, *J* =

10.3, 7.8, 1.5 Hz, 1H, H-2), 2.07-2.18 (m, 1H, Ha-5), 1.95-1.84 (m, 1H, Ha-13), 1.82-1.76 (m, 1H, Hb-5), 1.65-1.57 (m, 2H, Hb-13, Ha-10), 1.45-1.37 (m, 1H, Hb-10), 1.32-1.24 (m, 2H, H-12), 1.05 (s, 3H, H-20) ppm.

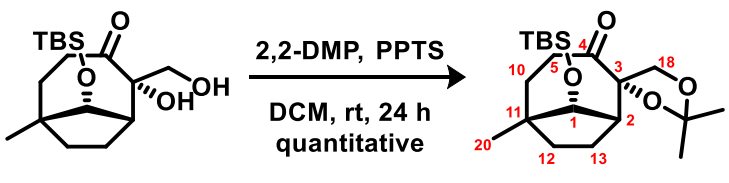
^{13}C-NMR (100MHz, $CDCl_3$) δ = 155.9 (C, C-3), 139.1 (C, C-ar), 128.4 (2CH, C-ar), 127.5 (2CH, C-ar), 127.4 (CH, C-ar), 109.9 (CH_2, C-18), 87.8 (CH, C-1), 73.5 (CH, C-4), 71.7 (CH_2, O-CH_2-Ar), 46.0 (CH, C-2), 44.0 (C, C-11), 34.4 (CH_2, C-10), 34.2 (CH_2, C-13), 33.8 (CH_2, C-12), 30.3 (CH_2, C-5), 28.3 (CH_3, C-20) ppm .

To a stirred solution of Dess-Martin Periodinane (2.1 g, 5 mmol, 1.5 equiv.) and $NaHCO_3$ (880 mg, 10 mmol, 3 equiv.) in DCM (35 mL) was added a solution of crude **419b** in DCM (35 mL) and the mixture was stirred for 45 min. A saturated solution of $Na_2S_2O_3$ (50 mL) was added, the aqueous layer was extracted with DCM (x3) and the organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 90:10 to 50:50) provided ketone **421** (627 mg, 70% yield).

HRMS (ESI): calculated for $C_{17}H_{32}O_2SiNa$: 319.2072 found: in progress

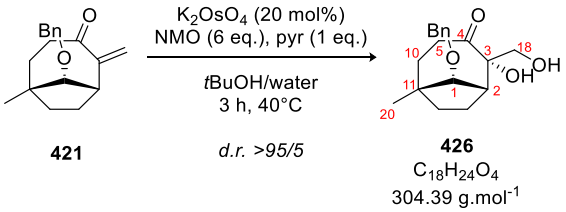
^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.29-7.34 (m, 2H, H-ar), 7.22-7.28 (m, 3H, H-ar), 5.86 (d, *J = 2.2 Hz*, 1H, Ha-18), 5.18 (d, *J* = 2.2 Hz, 1H, Hb-18), 4.57 (d, *J* = 11.7 Hz, 1H, O-CHaHb-Ar), 4.25 (d, *J* = 11.7 Hz, 1H, O-CHaHb-Ar), 3.55 (d, *J* = 8.1 Hz, 1H, H-1), 3.34 (ddd, *J* = 10.3, 8.1, 1.7 Hz, 1H, H-2), 2.68 (td, *J* = 13.8, 4.1 Hz, 1H, Ha-5), 2.53 (ddd, *J* = 13.5, 4.6, 3.5 Hz, 1H, Hb-5), 2.28-2.15 (m, 1H, Ha-13), 2.05 (tdd, *J* = 13.9, 3.3, 1.2 Hz, 1H, Ha-10), 1.85-1.72 (m, 2H, Hb-13, Ha-12), 1.64-1.52 (m, 1H, Hb-12), 1.31 (dt, *J* = 13.8, 4.4 Hz, 1H, Hb-10) 1.07 (s, 3H, 20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 202.8 (C, C-4), 149.4 (C, C-3), 138.5 (C, C-ar), 128.3 (2CH, C-ar), 127.7 (2CH, C-ar), 127.5 (CH, C-ar), 122.3 (CH_2, C-18), 86.7 (CH, C-1), 71.1 (CH_2, O-CH_2-Ar), 44.6 (CH, C-2), 44.5 (C, C-11), 41.4 (CH_2, C-5), 34.2 (CH_2, C-12), 32.1 (CH_2, C-10), 28.4 (CH_2, C-13), 27.8 (CH_3, 20) ppm.



XX XX

(1*R*,2*S*,6*R*,9*R*)-9-(benzyloxy)-2-hydroxy-2-(hydroxymethyl)-6-methylbicyclo[4.2.1]nonan-3-one **426**

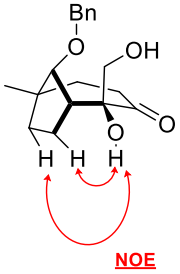


To a stirred solution of allylic alcohol **421** (2.4 g, 8.89 mmol, 1 equiv.) in *t*-BuOH/water (3:1, 88 mL), NMO (6.2 g, 53.3 mmol, 6 equiv.), pyridine (0.72 mL, 8.89 mmol, 1 equiv.) and potassium osmate dihydrate (655 mg, 1.78 mmol, 0.2 equiv.) were successively added and the mixture was heated to 40°C and stirred for 3 h. A 20% (m/m) aqueous solution of $NaHSO_3$ (100 mL) was then added and the mixture was stirred for an additional hour at room temperature. The aqueous layer was extracted with AcOEt (x6), organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Purification by flash chromatography over silica gel (cyclohexane/AcOEt, 70:30 to 50:50) provided **426** (234 mg, 90% yield) as a white solid (single diastereoisomer).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.28-7.39 (m, 5H, H-ar), 4.74 (d, *J* = 11.7 Hz, 1H, O-CHaHb-Ar), 4.54 (d, *J* = 11.7 Hz, 1H, O-CHaHb-Ar), 4.50 (s, 1H, C3-OH), 4.32 (dd, *J* = 11.4, 9.2 Hz, 1H, Ha-18), 3.71 (d, *J* = 6.2 Hz, 1H, H-1), 3.65 (dd, *J* = 11.4, 4.8 Hz, 1H, Hb-18), 3.15 (dt, *J* = 12.1, 8.9 Hz, 1H, Ha-5), 2.45-2.56 (m, 2H, Hb-5, H-2), 2.31 (dd, *J* = 9.2, 4.7 Hz, 1H, C18-OH), 1.75-1.88 (m, 2H, Ha-12, Ha-13), 1.39-1.55 (m, 3H, Ha-10, Hb-12, Hb-13), 1.23-1.31 (m, 1H, Hb-10), 1.10 (s, 3H, H-20) ppm.

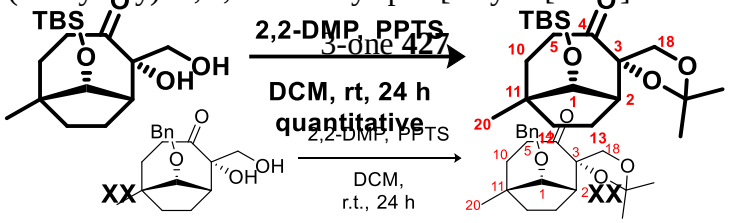
^{13}C-NMR (100MHz, $CDCl_3$) δ = 214.1 (C, C-4), 138.0 (C, C-ar), 128.6 (2CH, C-ar), 128.0 (CH, C-ar), 127.7 (2CH, C-ar), 89.0 (CH, C-1), 82.9 (C, C-3), 74.0 (CH_2, O-CH_2-Ar), 68.7 (CH_2, C-18), 44.8 (CH, C-2), 42.0 (C, C-11), 35.4 (CH_2, C-10), 35.1 (CH_2, C-5), 34.8 (CH_2, C-12), 30.4 (CH_3, C-20), 20.5 (CH_2, C-12) ppm.

HRMS (ESI): *m/z* calcd for $C_{18}H_{24}O_4Na^+$: $[M+Na]^+$: 327.1567 found: 327.1576.



NOE interaction between signal at 4.50 ppm (s, 1H, C3-OH) and another at 1.78-1.88 (m, 2H, H-12, H-13).

(1*R*,2*S*,6*R*,9*R*)-9-(benzyloxy)-2',2',6-trimethylspiro[bicyclo[4.2.1]nonane-2,4'-[1,3]dioxolan]-3-one **427**



426

427
$C_{21}H_{28}O_4$
344,45 g.mol^{-1}

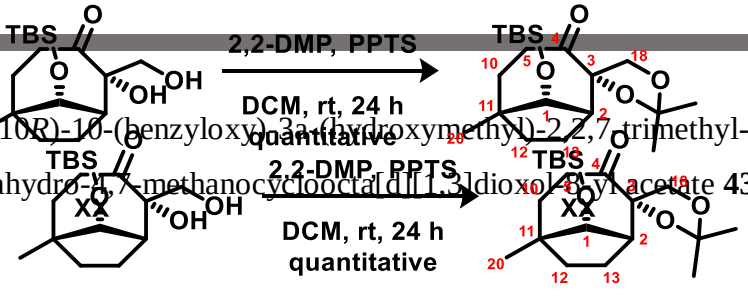
A solution of **426** (2.14 g, 7.07 mmol, 1 equiv.), 2,2-DMP (152 mL) and PPTS (670 mg, 2.7 mmol, 0.3 equiv.) in DCM (112 mL) was stirred for 24 h. A saturated solution of $NaHCO_3$ (150 mL) was added, the aqueous layer was extracted with DCM (x3) and the organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash chromatography over silica gel (pentane/Et_2O, 9:1 to 7:3) afforded **427** (2.31 g, quantitative yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.36-7.26 (m, 3H, H-ar), 7.25-7.21 (m, 2H, H-ar), 4.63 (d, *J* = 8.8 Hz, 1H, Ha-18), 4.58 (d, *J* = 11.8 Hz, 1H, O-CHa-Ar), 4.56 (d, *J* = 11.8 Hz, 1H, O-CHb-Ar), 3.72 (d, *J* = 8.1 Hz, 1H, H-1), 3.71 (d, *J* = 8.8 Hz, 1H, Hb-18), 2.79-2.70 (m, 2H, Ha-5, H-2), 2.51 (ddd, *J* = 11.6, 5.6, 4.2 Hz, 1H, Hb-5), 2.27 (dddd, *J* = 15.4, 10.4, 7.6, 2.6 Hz, 1H, Ha-13), 1.85-1.72 (m, 2H, Ha-10, Hb-13), 1.65 (ddd, *J* = 14.0, 10.4, 3.8 Hz, 1H, Ha-12), 1.56-1.47 (m, 1H, Hb-12), 1.44-1.39 (m, 1H, Hb-10), 1.37 (s, 3H, O-C-CH_3), 1.30 (s, 3H, O-C-CH_3), 1.06 (s, 3H, H-20) ppm.

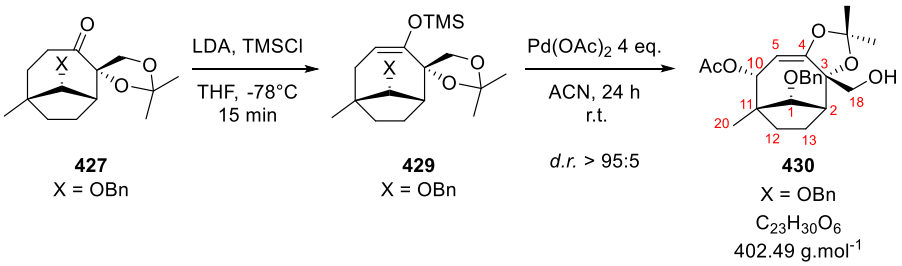
^{13}C-NMR (100MHz, $CDCl_3$) δ = 206.7 (C, C-4), 138.2 (C, C-ar), 128.5 (2CH, C-ar), 127.7 (CH, C-ar), 127.3 (2CH, C-ar), 109.9 (C, O-C-CH_3), 88.7 (CH, C-1), 85.2 (C, C-3), 73.9 (CH_2, O-CH_2-Ar), 72.4 (CH_2, C-18), 47.0 (CH, C-2), 44.1 (C, C-11), 38.3 (CH_2, C-5), 34.7 (CH_2, C-12), 34.2 (CH_2, C-10), 28.6 (CH_3, C-20), 27.4 (CH_3, O-C-CH_3), 26.0 (CH_3, O-C-CH_3), 22.14 (CH_2, C-13) ppm.

HRMS (ESI): *m/z* calcd for $C_{21}H_{28}O_4Na^+$: $[M+Na]^+$: 367.1885 found: in progress

(3a*S*,4*R*,7*S*,8*R*,10*R*)-10-(benzyloxy)-3a-(hydroxymethyl)-2,2,7-trimethyl-3a,4,5,6,7,8-hexahydro-4,7-methanocycloocta[*d*][1,3]dioxol-8-yl acetate **430**



XX **XX**

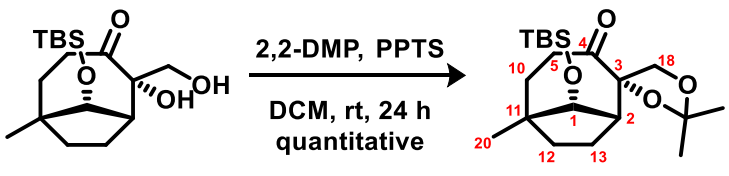


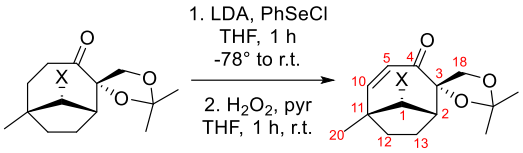
To a solution of **427** (240 mg, 0.69 mmol, 1 eq.) in THF (4 mL) cooled at -78°C was added LDA (1 mL, 1.03 mmol, 1.5 eq.) and the mixture was stirred for 10 min. TMSCl (0.26 mL, 2.07 mmol, 3 eq.) was added and the temperature was raised to r.t.. Water (4 mL) was added the aqueous phase was extracted with Et_2O (x3) and thegathered organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. To the resulting crude mixturewere added ACN (12 mL) and $Pd(OAc)_2$ (618mg, 2.76 mmol, 4 eq.) and the mixture was stirred at r.t. for 24 h. Then, the mixture was filtered on Celite® and the solvent was evaporated under reduced pressure. Flash purification over silica gel (pentane/Et_2O 95:5 to 70:30) afforded **430** (29 mg, 10% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.43-7.28 (m, 5H, H-ar), 5.66 (d, *J* = 1.4 Hz, 1H, H-10), 4.86 (d, *J* = 11.7 Hz, 1H, O-CHaHb-Ar), 4.78 (d, *J* = 1.7 Hz, 1H, H-5), 4.54 (d, *J* = 11.7 Hz, 1H, O-CHaHb-Ar), 4.19 (t, *J* = 10.8 Hz, 1H, Ha-18), 3.75 (d, *J* = 7.0 Hz, 1H, H-1), 4.19 (d, *J* = 11.7 Hz, 1H, Hb-18), 2.82 (td, *J* = 7.0, 1.3 Hz, 1H, H-1), 2.14 (br. d, *J* = 10.8 Hz, 1H, OH), 2.05 (s, 3H, C(O)-CH_3), 2.04-1.98 (m, 1H, Ha-12), 1.80-1.70 (m, 2H, H-13), 1.55 (s, 3H, O-C-CH_3), 1.45 (s, 3H, O-C-CH_3), 1.26-1.34 (m, 1H, Hb-12), 1.07 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 170.2 (C, O-C(O)), 151.1 (C, C-4), 137,7 (C, C-ar), 128.4 (2CH, C-ar), 128.1 (2CH, C-ar), 127.9 (CH, C-ar), 110.4 (C, O-C-CH_3), 102.4 (CH_2, C-5), 88.7 (CH, C-1), 87.4 (C, C-3), 73.6 (CH, C-10), 73.6 (CH_2, O-CH_2-Ar), 66.6 (CH_2, C-18), 47.1 (C, C-11), 29.5 (CH_2, C-12), 28.5 (CH_3, O-C-CH_3), 28.2 (CH_3, O-C-CH_3), 25.4 (CH_3, C-20), 22.6 (CH_2, C-13), (CH_3, C(O)-CH_3) ppm.

(1R,2S,6R,9R)-9-(benzyloxy)-2',2',6-trimethylspiro[bicyclo[4.2.1]nonane-2,4'-1,3]dioxolan]-4-en-3-one **428**





427
X = OBn

428
X = OBn
$C_{21}H_{26}O_4$
342.43 g.mol^{-1}

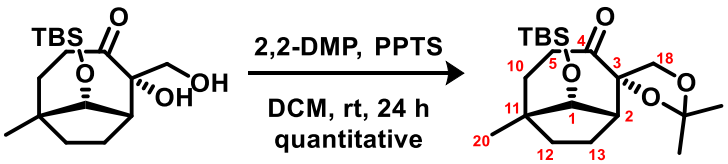
In a round bottom flask containing **427** (200 mg, 0.58 mmol, 1 eq.) in THF (14 mL) cooled to -78°C was added LDA (1.34 mL, 0.87 mmol, 1.5 eq.) and the mixture was stirred for 15 min. at -78°C. A solution of PhSeCl (331 mg, 1.73 mmol, 3 eq.) in THF (14 mL) was added, the temperature was raised to r.t. and the mixture was stirred for 30 min. A saturated solution of NH_4Cl (15 mL) was added and the aqueous layers were extracted with Et_2O (x3). The gathered organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. To the resulting crude (500 mg) were added THF (40 mL), pyridine (0.15 mL, 1.8 mmol, 3.5 eq.) and finally H_2O_2 (30% (w/w) in H_2O, 0.13 mL, 1.3 mmol, 2.5 eq.). After 30 minutes, a saturated solution of $Na_2S_2O_3$ (15 mL) was added and the aqueous phase was extracted with Et_2O (x3). The gathered organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash purification over silica gel (pentane/Et_2O 95:5 to 80:20) afforded **428** (135 mg, 68% yield) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.38-7.27 (m, 5H, H-ar), 7.24-7.20 (m, 2H, H-ar), 6.07-5.99 (m, 2H, H-5, H-10), 4.59 (s, 2H, O-CH_2-Ar), 4.35 (d, *J* = 9.2 Hz, 1H, Ha-18), 3.87 (d, *J* = 9.2 Hz, 1H, Hb-18), 3.73 (d, *J* = 9.2 Hz, 1H, H-1), 2.79 (td, *J* = 9.2, 4.5 Hz, 1H, H-2), 2.05-1.85 (m, 2H, H-13), 1.61 (ddd, *J* = 13.1, 8.6, 1.9 Hz, 1H, Ha-12), 1.52 (dd, *J* = 10.4, 9.0 Hz, 1H, Hb-12), 1.48 (s, 3H, O-C-CH_3), 1.37 (s, 3H, O-C-CH_3), 1.06 (s, 3H, H-20) ppm.

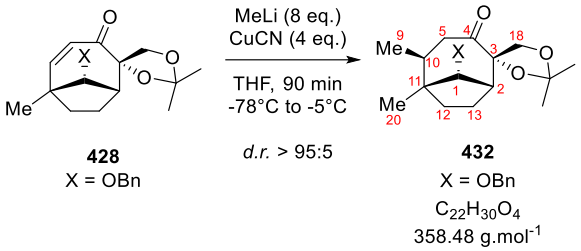
^{13}C-NMR (100MHz, $CDCl_3$) δ = 200.2 (C, C-4), 146.6 (CH, C-5), 137.8 (C, C-ar), 128.9 (CH, C-10), 128.5 (2CH, C-ar), 127.9 (CH, C-ar), 127.6 (2CH, C-ar), 110.3 (C, O-C-CH_3), 87.6 (CH, C-1), 86.9 (C, C-3), 74.1 (CH_2, O-CH_2-Ar), 74.0 (CH_2, C-18), 45.6 (CH, C-2) 40.8 (C, C-11), 36.1 (CH_2, C-12), 27.3 (CH_3, O-C-CH_3), 26.0 (CH_3, O-C-CH_3), 25.8 (CH_3, C-20), 22.8 (CH_2, C-13) ppm.

HRMS (ESI): *m/z* calcd for $C_{21}H_{26}O_4Na^+$: $[M+Na]^+$: 365.1729; found: 365.1730.

(1R,2S,5S,6R,9R)-9-(benzyloxy)-2',2',5,6-tetramethylspiro[bicyclo[4.2.1]nonane-2,4'-[1,3]dioxolan]-3-one **432**



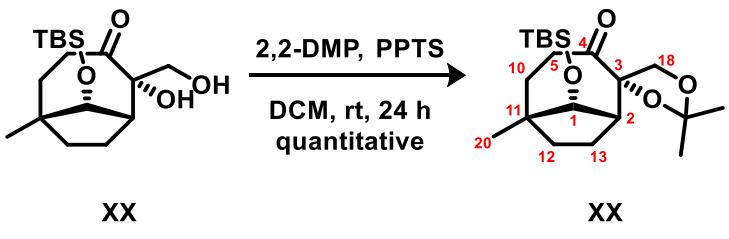
XX **XX**



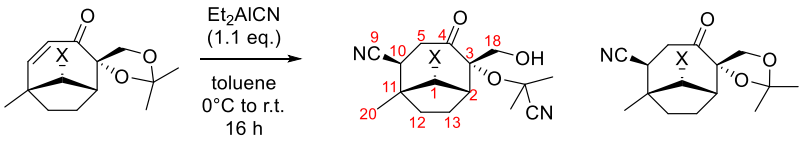
To a suspension of CuCN (6- mg, 0.74 mmol, 4 eq.) in THF (2.5 mL) at -78°C was added MeLi (0.92 mL, 1.48 mmol, 8 eq.) and the mixture was stirred 20 min before being canulated into a solution of **428** (63 mg, 0.18 mmol; 1 eq.) in THF (1 mL) at -78°C. The temperature was raised to -5°C over 2 hours and NH_4Cl (4 mL) was added and the aqueous phase was extracted with Et_2O (x3). The gathered organic layers were washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash purification over silica gel (pentane/Et_2O 95:5 to 70:30) afforded **432** (32 mg, 50% yield) as a white solid.

^{1}H-NMR (600MHz, $CDCl_3$) δ = 7.38-7.27 (m, 5H, H-ar), 4.64 (d, *J* = 11.8 Hz, 1H, O-CHa-Ar), 4.56 (d, *J* = 11.8 Hz, 1H, O-CHa-Ar), 4.39 (d, *J* = 9.1 Hz, 1H, Ha-18), 3.94 (d, *J* = 9.1 Hz, 1H, Hb-18), 3.75 (d, *J* = 7.4 Hz, 1H, H-1), 2.72 (dd, *J* = 7.0, 3.6 Hz, 2H, H-5), 2.63 (t, *J* = 7.4 Hz, 1H, H-2), 2.09 (dddd, J = 14.8, 7.9, 4.3 Hz, 1H, Ha-13), 1.78 (sex, *J* = 7.0 Hz, 1H, H-10), 1.65-1.59 (m, 1H, Hb-13), 1.53-1.45 (m, 2H, H-12), 1.40 (s, 3H, O-C-CH_3), 1.36 (s, 3H, O-C-CH_3), 1.14 (s, 3H, H-20), 1.09 (d, *J* = 7.0 Hz, 3H, H-9) ppm.

^{13}C-NMR (150MHz, $CDCl_3$) δ = 20.8 (C, C-4), 138.1 (C, C-ar), 128.6 (2CH, C-ar), 127.9 (CH, C-ar), 127.6 (2CH, C-ar), 110.3 (C, O-C-CH_3), 91.1 (CH, C-1), 88.0 (C, C-3), 74.4 (CH_2, O-CH_2-Ar), 71.8 (CH_2, C-18), 47.7 (CH, C-2), 45.6 (CH_2, C-5), 44.3 (C, C-11), 42.0 (CH, C-10), 39.0 (CH_2, C-12), 28.3 (CH_3, C-20), 27.2 (CH_3, O-C-CH_3), 25.9 (CH_3, O-C-CH_3), 22.0 (CH_2, C-13), 18.3 (CH_3, C-9) ppm.



(1R,2S,5S,6R,9R)-9-(benzyloxy)-5-((2-cyanopropan-2-yl)oxy)-5-(hydroxymethyl)-1-methyl-4-oxobicyclo[4.2.1]nonane-2-carbonitrile **433**



428
X = OBn

433
X = OBn
$C_{23}H_{28}N_2O_4$
396.48 g.mol^{-1}

434
X = OBn
$C_{22}H_{27}NO_4$
369.46 g.mol-1

Et_2AlCN (0.13 mL, 0.13 mmol, 1.1 eq.) was added dropwise to a solution of **428** (40 mg, 0.12 mmol, 1 eq.) in toluene (2 mL) at 0°C. The ice bath was removed and the mixture was stirred for 16 hours. NH_4Cl (5 mL) was added and the aqueous phase was extracted with AcOEt (x3). The gathered organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash purification over silica gel (cyclohexane/AcOEt 60:40 to 30:70) afforded **433** (17 mg, 36% yield) along with **434** (8 mg, 18% yield).

433

^{1}H-NMR (600MHz, $CDCl_3$) δ = 7.53-7.27 (m, 5H, H-ar), 4.85 (d, *J* = 11.5 Hz, 1H, O-CHa-Ar), 4.71 (d, *J* = 11.5 Hz, 1H, O-CHb-Ar), 4.53 (d, *J* = 9.2 Hz, 1H, Ha-18), 4.22 (s, 1H, C18-OH), 3.87 (d, *J* = 7.4 Hz, 1H, H-1), 3.54 (t, *J* = 11.1 Hz, 1H, Ha-5), 3.51 (d, *J* = 9.1 Hz, 1H, Hb-18), 2.81 (dd, *J* = 11.1, 7.7 Hz, 1H, H-5), 2.75 (dd, *J* = 10.5, 7.4 Hz, 1H, H-10), 2.46 (t, *J* = 5.6 Hz, 1H, H-2), 1.95 (dd, *J* = 13.7, 9.0 Hz, 1H, Ha-13), 1.58-1.50 (m, 1H, Ha-12), 1.43 (s, 3H, O-C-CH_3), 1.42 (s, 3H, O-C-CH_3), 1.41-1.37 (m, 1H, Hb-13), 1.25 (s, 3H, H-20), 1.16 (ddd, *J* = 10.7, 14.5, 10.2 Hz, 1H, Hb-12) ppm.

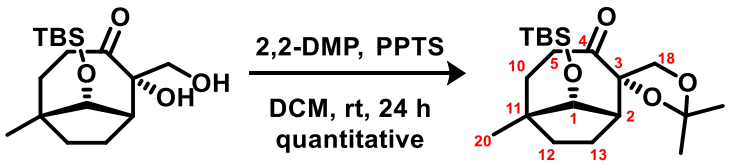
^{13}C-NMR (150MHz, $CDCl_3$) δ = 207.9 (C, C-4), 136.9 (C, C-ar), 128.8 (2CH, C-ar), 128.5 (CH, C-ar), 128.5 (2CH, C-ar), 120.1 (C, C9), 120.0 (C, CN), 88.4 (CH, C-1), 82.2 (C, C-3), 75.1 (CH_2, O-CH_2-Ar), 71.7 (CH_2, C-18), 70.9 (C, O-C), 45.4 (CH, C-2), 43.5 (C, C-11), 37.9 (CH_2, C-5), 36.9 (CH, C-10), 36.4 (CH_2, C-12), 29.3 (CH_3, O-C-CH_3), 26.7 (CH_3, O-C-CH_3), 26.1 (CH_3, C-20), 20.5 (CH_2, C-13) ppm.

434

^{1}H-NMR (600MHz, $CDCl_3$) δ = 7.41-7.31 (m, 5H, H-ar), 4.79 (d, *J* = 11.7 Hz, 1H, O-CHa-Ar), 4.62 (d, *J* = 11.5 Hz, 1H, O-CHb-Ar), 4.43 (d, *J* = 9.3 Hz, 1H, Ha-18), 3.86 (d, *J* = 9.3 Hz, 1H, Hb-18), 3.85 (d, *J* = 7.6 Hz, 1H, H-1), 3.11 (dd, *J* = 11.9, 7.2 Hz, 1H, Ha-5), 2.91 (dd, *J* = 11.9, 6.2 Hz, 1H, Ha-5), 2.75 (dd, *J* = 7.2, 6.2 Hz, 1H, H-10), 2.66 (t, *J* = 7.2 Hz, 1H,

H-2), 2.14-2.09 (m, 1H, Ha-13), 1.69-1.63 (m, 2H, H-12), 1.54-1.49 (m, 1H, Hb-13), 1.39 (s, 3H, H-20), 1.38 (s, 3H, O-C-CH_3), 1.33 (s, 3H, O-C-CH_3) ppm.

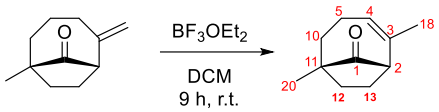
^{13}C-NMR (150MHz, $CDCl_3$) δ = 202.8 (C, C-4), 137.2 (C, C-ar), 128.7 (2CH, C-ar), 128.3 (2CH, C-ar), 128.2 (CH, C-ar), 119.9 (C, C9), 110.1 (C, O-C-CH_3), 87.8 (CH, C-1), 86.8 (C, C-3), 75.8 (CH_2, O-CH_2-Ar), 72.0 (CH_2, C-18), 48.1 (CH, C-2), 45.2 (C, C-11), 39.6 (CH_2, C-5), 36.9 (CH, C-10), 36.0 (CH_2, C-12), 28.3 (CH_3, C-20), 27.1 (CH_3, O-C-CH_3), 25.8 (CH_3, O-C-CH_3), 21.9 (CH_2, C-13) ppm.



XX XX

9.6 Miscellaneous reactions

(1*S*,6*S*)-2,6-dimethylbicyclo[4.2.1]non-2-en-9-one **454**



121 **454**
$C_{11}H_{16}O$
164.25 g.mol^{-1}

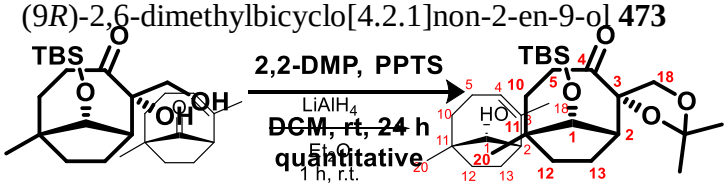
Ketone **121** (500 mg, 3.05 mmol, 1 equiv.) was dissolved in DCM (2.5 mL) and freshly distilled boron trifluoride diethyl etherate (2.16 g, 15.25 mmol, 1.88 mL, 5 equiv.) was added dropwise. Stirring was maintained for 9 h and the reaction mixture was subsequently poured into a saturated solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (x3), the organic layers were dried over $MgSO_4$, filtered and removal of the solvent under reduced pressure afforded pure **454** (474 mg, 95% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.50 (ddd, *J* = 8.4, 4.1, 1.2 Hz, 1H, H-4), 2.63 (dd, *J* = 9.6, 2.9 Hz, 1H, H-2), 2.52-2.41 (m, 1H, Ha-5), 2.26-2.15 (m, 1H, Ha-13), 2.09-1.97 (m, 3H, Hb-5, Hb-13, Ha-12), 1.81 (t, *J* = 1.2 Hz, 3H, H-18), 1.80-1.71 (m, 1H, Hb-12), 1.80-1.73 (m, 1H, Ha-10), 1.56 (dt, *J* = 13.5, 4.3 Hz, 1H, Hb-10), 1.05 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 219.8 (C, C-1), 139.9 (C, C-3), 124.7 (CH, C-4), 53.1 (CH, C-2), 49.8 (C, C-11), 42.0 (CH_2, C-10), 33.1 (CH_2, C-12), 26.3 (CH_3, C-18), 25.5 (CH_2, C-13), 23.7 (CH_2, C-5), 22.9 (CH_3, C-20) ppm.

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}ONa^+$: 187.1099 $[M+Na]^+$: found: 187.1097

(9*R*)-2,6-dimethylbicyclo[4.2.1]non-2-en-9-ol **473**



454 **473**
XX *d.r. > 95:5* XX
$C_{11}H_{18}O$
166.26 g.mol^{-1}

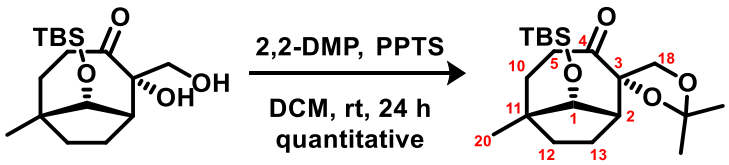
To a stirred solution of **454** (100 mg, 0.61 mmol, 1 equiv.) in Et_2O (3 mL) was portionwise added $LiAlH_4$ (34 mg, 0.92 mmol, 1.5 equiv). After 1 h, water (50 µL), aqueous 2M NaOH

(500 µL) and water (150 µL) were successively added and the mixture was then stirred for 30 min. Filtration over celite® and removal of the solvent under reduced pressure afforded **473** (85 mg, 84% yield) as a single diastereoisomer without further purification.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.65 (d, *J* = 8.9 Hz, 1H, H-4), 3.64 (dd, *J* = 11.7, 7.9 Hz, 1H, H-1), 2.65 (ddt, *J* = 9.6, 7.8, 1.7 Hz, 1H, H-2), 2.29-2.17 (m, 1H, Ha-5), 2.04-1.93 (m, 2H, Hb-5, Ha-13), 1.77 (s, 1H, C1-OH), 1.74 (s, 3H, H-18), 1.72-1.65 (m, 2H, Hb-13, Ha-12), 1.54-1.42 (m, 2H, Hb-12, Ha-10), 1.14 (dt, *J* = 14.2, 3.7 Hz, 1H, Hb-10), 1.00 (s, 3H, H-20) ppm.

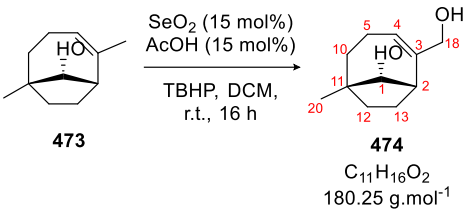
^{13}C-NMR (100MHz, $CDCl_3$) δ = 140.8 (C, C-3), 125.6 (CH, C-4), 79.7 (CH, C-1), 47.4 (CH, C-2), 44.8 (C, C-11), 34.0 (CH_2, C-12), 31.3 (CH_2, C-10), 28.6 (CH_3, C-20), 28.0 (CH_3, C-18), 36.8 (CH_2, C-13), 24.3 (CH_2, C-5) ppm.

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}ONa^+$: $[M+Na]^+$: 189.1255; found: 189.1249



XX XX

2-(hydroxymethyl)-6-methylbicyclo[4.2.1]non-2-en-9-one **474**



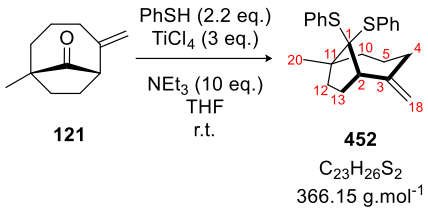
To a stirred solution of **473** (150 mg, 1.51 mmol, 1 equiv.) and dry acetic acid (17 µL, 0.30 mmol, 0.2 equiv.) in DCM (8 mL), TBHP (5.5 M in heptane, 0,27 mL, 1.0 equiv.) and selenium dioxide (33 mg, 0.30 mmol, 0.20 equiv.) were added. The mixture was stirred overnight at room temperature and then quenched with a saturated solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (x3). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was solubilized in MeOH (4 mL), cerium chloride heptahydrate (560 mg, 1.51 mmol, 1 equiv.) and $NaBH_4$ (58 mg, 1,51 mmol, 1 equiv.) were successively added. After 1 h, a saturated solution of NH_4Cl (10 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (x2). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography over silica gel (pentane/Et_2O, 80:20 to 50:50) afforded **474** (310 mg, 84% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.88 (ddd, *J* = 8.4, 1.7, 3.0 Hz, 1H, H-4), 3.95 (dd, *J* = 24.7, 12.1 Hz, 2H, H-18), 3.70 (broad s, 1H, H-1), 2.80 (ddd, *J* = 11.3, 8.3, 2.7 Hz, 1H, H-2), 2.30 (t, *J* = 14.7 Hz, 1H, Ha-5), 2.16-2.02 (m, 2H, Hb-5, Ha-13), 1.79-1.69 (m, 2H, Ha-12, Hb-13), 1.60-1.47 (m, 2H, Ha-10, Hb-12), 1.18 (dt, *J* = 14.0, 3.9 Hz, 1H, Hb-10), 1.02 (s, 3H, H-20).

^{13}C-NMR (100MHz, $CDCl_3$) δ = 143.5 (C, C-3), 128.0 (CH, C-4), 79.4 (CH, C-1), 69.4 (CH_2, C-18), 45.0 (C, C-11), 43.9 (CH, C-2), 34.0 (CH_2, C-12), 31.0 (CH_2, C-10), 28.5 (CH_3, C-20), 27.1 (CH_2, C-13), 24.0 (CH_2, C-5) ppm.

HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O_2Na^+$: $[M+Na]^+$: 205.1199 found: 205.1178.

((6*R*)-1-methyl-5-methylenebicyclo[4.2.1]nonane-9,9-diyl)bis(phenylsulfane) **452**



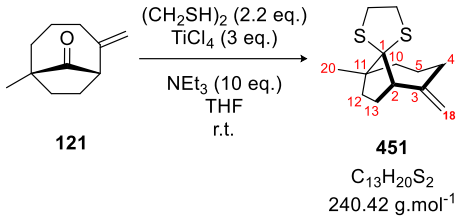
To a solution of **121** (400 mg, 2.44 mmol, 1 equiv.) in THF (27 mL) was successively added $TiCl_4$ (1M solution in THF, 7.32 mL, 7.32 mmol, 3 equiv.) and a solution of triethylamine (2.46 g, 24.4 mmol, 3.4 mL, 10 equiv.) and thiophenol (0.47 mL, 505 mg, 5.37 mmol, 2.2 equiv.) in THF (20 mL). The mixture was stirred at room temperature for 4 h and spare thiophenol was added every hour (0.47 mL, 2.2 equiv. each time). $NaBH_4$ (2g, 12.2 mmol, 5 equiv.) was then added. After 30 min, water r (50 mL) was added. The aqueous layer was extracted with Et_2O (x3) and the organic layers were dried over $MgSO_4$, filtered and the solvent was concentrated under reduced pressure. Flash chromatography over silica gel (pentane/Et_2O, 100:0 to 90:10) provided **452** (720 mg, 81% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.97 (dd, *J* = 7.6, 1.8 Hz, 2H, H-ar), 7.72 (dd, *J* = 7.0 Hz, 2H, H-ar), 7.32-7.40 (m, 6H, H-ar), 4.63 (t, *J* = 2.5 Hz, 1H, Ha-18), 4.40 (t, *J* = 2.5 Hz, 1H, Hb-18), 2.97-3.41 (m, 2H, H-2, Ha-4), 2.54 (ddd, *J* = 16.6, 3.7, 3.7 Hz, 1H, Hb-4), 2.44 (ddd, *J* = 6.7, 15.3, 6.9 Hz, 1H, Ha-10), 2.26-2.11 (m, 2H, Ha-13, Ha-12), 1.80-1.70 (m, 3H, H-5, Hb-12), 1.55-1.45 (m, 2H, Hb-13, Hb-10), 0.89 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 151.3 (C, C-3), 136.9 (2CH, C-ar), 135.1 (2CH, C-ar), 134.3 (C, C-ar), 133.0 (C, C-ar), 128.7 (2CH, C-ar), 128.6 (2CH, C-ar), 128.4 (CH, C-ar), 128.3 (CH, C-ar), 112.7 (CH_2, C-18), 80.2 (C, C-1), 57.2 (CH, C-2), 55.0 (C, C-11), 41.3 (CH_2, C-10), 37.2 (CH_2, C-12), 33.9 (CH_2, C-4), 30.7 (CH_2, C-13), 25.1 (CH_3, C-20), 23.5 (CH_2, C-5) ppm.

HRMS (ESI): *m/z* calcd for $C_{23}H_{26}S_2Na^+$: $[M+Na]^+$: 389.1374; found: 389.1359.

(6*R*)-1-methyl-5-methylenespiro[bicyclo[4.2.1]nonane-9,2'-[1,3]dithiolane] **451**



121 **451**

$C_{13}H_{20}S_2$

240.42 g.mol^{-1}

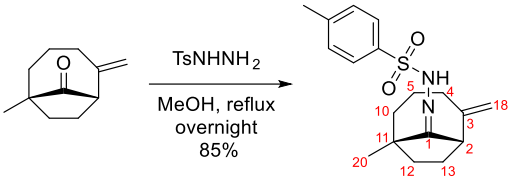
To a solution of **121** (300 mg, 1.83 mmol, 1 equiv.) in THF (22.1 mL) was successively added $TiCl_4$ (1M solution in THF, 5.49 mL, 5.49 mmol, 3 equiv.) and a solution of NEt_3 (1.85 g, 18.3 mmol, 2.55 mL, 10 equiv.) and $(CH_2SH)_2$ (338 µL, 378 mg, 4.02 mmol, 2.2 equiv.) in THF (8.5 mL). The mixture was stirred at room temperature overnight then water (30 mL) was added. The aqueous layer was extracted with Et_2O (x3) and the organic layers were dried over $MgSO_4$, filtered and the solvent was concentrated under reduced pressure. Flash chromatography over silica gel (pentane/Et_2O, 100:0 to 90:10) provided **451** (300 mg, 68% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 4.63 (t, *J* = 1.3 Hz, 2H, H-18), 3.34 (dd, *J* = 10.3, 2.2 Hz, 1H, H-2), 3.25 (ddd, *J* = 5.9, 5.3, 1.5 Hz, 2H, S-CH_2), 3.17 (ddd, *J* = 5.9, 5.3, 1.5 Hz, 2H, S-CH_2), 2.49-2.44 (m, 2H, H-4), 2.36-2.25 (m, 1H, Ha-12), 1.80-1.70 (m, 2H, H-13), 1.65-1.53 (m, 5H, H-10, H-5, Hb-12), 1.20 (s, 3H, H-20) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 153.5 (C, C-3), 111.3 (CH_2, C-18), 83.5 (C, C-1) 63.3 (CH, C-2), 50.0 (C, C-11), 43.16 (CH_2, C-10), 40.4 (CH_2, S-CH_2), 38.1 (CH_2, S-CH_2), 35.8 (CH_2, C-13), 34.7 (CH_2, VC4), 31.2 (CH_2, C-12), 26.5 (CH_3, C-20), 23.2 (CH_2, C-5) ppm.

4-methyl-*N'*-(1-methyl-5-methylenebicyclo[4.2.1]nonan-9-ylidene)benzenesulfonohydrazide

450



121 **450**

$C_{18}H_{24}N_2O_2S$

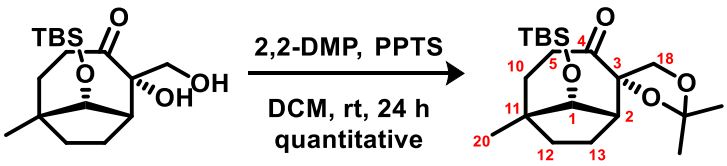
332.46 g.mol^{-1}

A solution of **121** (100 mg, 0.61 mmol, 1 equiv.) and $TsNHNH_2$ (136 mg, 0.732 mmol, 1.2 equiv.) in MeOH (4 mL) was refluxed overnight, the solvent was then concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (pentane/Et_2O, 80:20 to 50:50) providing **450** (172 mg, 85% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.0 Hz, 2H, H-ar), 7.29 (d, *J* = 8.0 Hz, 2H, H-ar), 7.07 (s, 1H, NH), 4.88 (t, *J* = 1.9 Hz, 1H, Ha-18), 4.85 (t, *J* = 1.9 Hz, 1H, Hb-18), 3.47 (dd, *J* = 10.2, 3.1 Hz, 1H, H-2), 2.42 (s, 3H, Ar-CH_3), 2.26-2.12 (m, 2H, H-4), 1.77-1.35 (m, 8H, H-5, H-10, H-12, H-13), 1.15 (s, 3H, H-20) ppm.

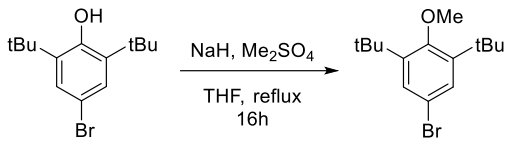
^{13}C-NMR (100MHz, $CDCl_3$) δ = 170.1 (C, C-1), 146.7 (C, C-3), 144.0 (C, C-ar), 135.6 (C, C-ar), 129.4 (2CH, C-ar), 128.2 (2CH, C-ar), 113.0 (CH_2, C-18), 47.3 (C, C-11), 46.0 (CH, C-2), 44.4 (CH_2, C-10), 35.4 (CH_2, C-12), 34.7 (CH_2, C-4), 30.7 (CH_2, C-5), 24.3 (CH_3, C-20), 23.6 (CH_2, C-13), 21.7 (CH_3, Ar-CH_3) ppm.

HRMS (ESI): *m/z* calcd for $C_{18}H_{24}N_2O_2SNa^+$: $[M+Na]^+$: 355.1456; found: 335.1461.



XX **XX**

tris((tris(3,5-di-tert-butyl-4-methoxyphenyl)silyl)ethynyl)phosphane **300**

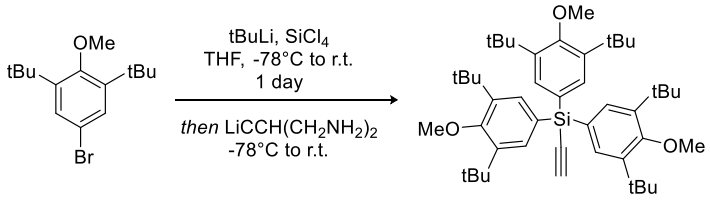


361
$C_{15}H_{23}BrO$
298.25 g.mol-1

To a suspension of NaH (8.0 g, 200 mmol, 1.5 equiv.) in THF (480 mL) at 0 °C was slowly added a solution of 4-bromo-2,6-di-*tert*-butylphenol (38 g, 134 mmol, 1 equiv.) in THF (120 mL) and the mixture was stirred for 1 h at room temperature. After cooling to 0 °C, dimethyl sulfate (18.5 g, 147 mmol, 1.1 equiv.) was added and the mixture was refluxed for 16 h. Water was added at 0 °C followed by hexane at r.t. and the organic layer was washed with water until it became a clear solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography over silica gel (hexane, 100%) delivered the title compound as a white solid in quantitative yield.

RN: 1516-96-7

Spectroscopic data were consistent with those reported in the literature.

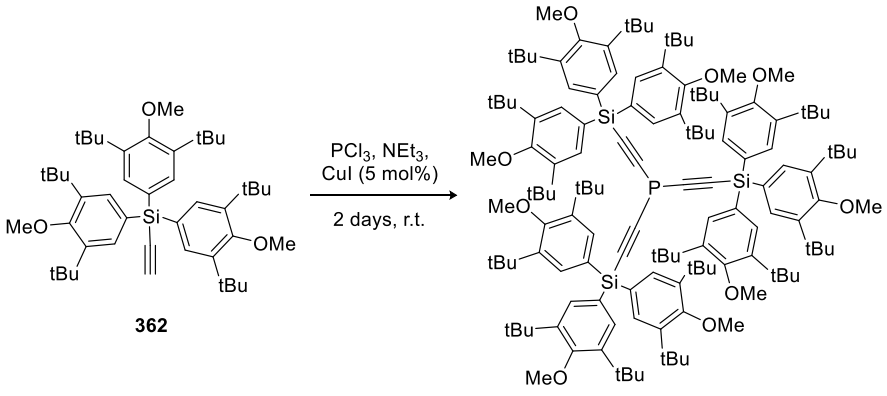


361 **362**
$C_{47}H_{70}O_3Si$
711.16 $g.mol^{-1}$

To a solution of **361** (46.4 mmol) in THF was added *t*-BuLi (2.5 M in pentane, 92.8 mmol) at -78 °C. After stirring for 1.5 h at this temperature, the mixture was warmed to room temperature, cooled again to -78 °C and silicium tetrachloride (15.5 mmol) was then added. The mixture was slowly warmed to room temperature, stirred for 1 day and subsequently transferred *via* cannula to a solution of lithium acetylide cooled at -78 °C. The resulting mixture was slowly warmed to room temperature and stirred for 6 h. An aqueous NH_4Cl solution was added and the mixture was extracted with Et_2O (x3). The combined extracts were dried over $MgSO_4$, and concentrated under a reduced pressure. Precipitation from MeOH delivered **362** (72%).

RN: 923013-73-4

Spectroscopic data were consistent with those reported in the literature.



362

300

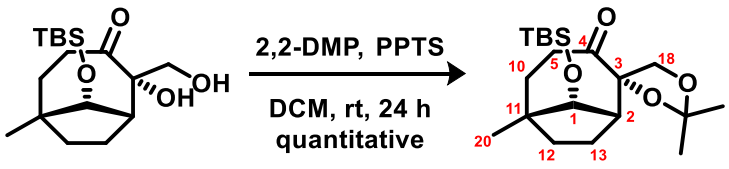
$C_{141}H_{207}O_9PSi_3$

2161.43 g.mol^{-1}

A mixture of **362** (4.97 g, 7 mmol, 3.3 eq.), PCl_3 (270 mg, 2 mmol, 1 eq.), Et_3N (1.81 g, 18 mmol, 9 eq.) and CuI (19 mg, 0.1 mmol, 0.05 eq.) in toluene was stirred for 2 days at r.t.. The mixture was filtrated over celite® and the filtrate was concentrated under a reduced pressure. Purification by flash chromatography over silica gel (hexane/CH_2Cl_2: 95:5 to 70:30) followed by recrystallization from EtOH gave **300** as colorless crystals (quantitative yield).

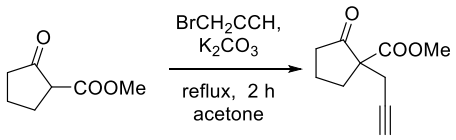
RN: 923013-74-5

Spectroscopic data were consistent with those reported in the literature.



XX **XX**

Methyl 2-oxo-1-(prop-2-yn-1-yl)cyclopentane-1-carboxylate (±)-**369**

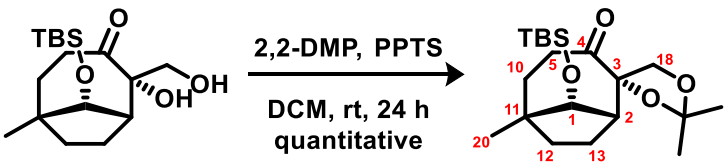


(±)-369
$C_{10}H_{12}O_3$
180.20 g.mol^{-1}

To a suspension of anhydrous potassium carbonate (10.6 g; 28.2 mmol, 4 equiv.) in dry acetone (18 ml) was added a solution of 2-carbomethoxycyclopentanone (1 g, 0.87 ml, 7 mmol, 1 equiv.) in dry acetone (9 ml). The reaction mixture displayed a characteristic yellow colour after stirring at room temperature for 15 min. Then, propargyl bromide (832 mg, 14 mmol, 2 equiv.) was added slowly and the mixture was refluxed for 2 h. The suspension was filtered over celite®, the filtrate was concentrated under reduced pressure and diluted with Et_2O and water. The aqueous layer was extracted with Et_2O (x2) and the organic layers were dried over $MgSO_4$, filtrated and the solvent was removed under reduced pressure. Flash Purification by flash chromatography over silica gel (pentane/Et_2O, 80:20 to 50:50) provided the desired product (±)-**369** (882 mg, 70% yield).

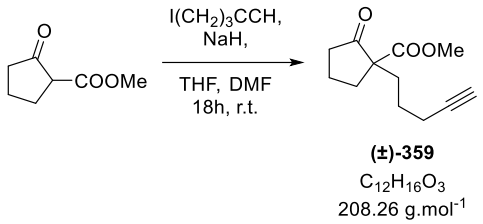
RN: 196716-62-8.

Spectroscopic data were consistent with those reported in the literature.



XX **XX**

Methyl 2-oxo-1-(pent-4-yn-1-yl)cyclopentane-1-carboxylate (±)-**359**

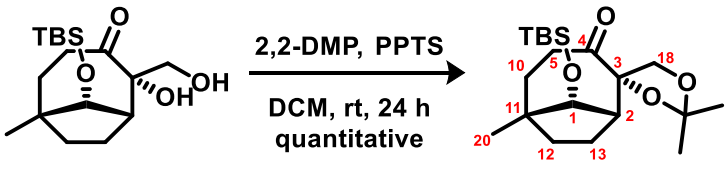


(±)-359
$C_{12}H_{16}O_3$
208.26 g.mol^{-1}

To a suspension of NaH (60 wt. %, 910 mg, 22.8 mmol) in a THF/DMF mixture (1:1, 20 mL) was added dropwise methyl 2-oxocyclohexanecarboxylate (3.28 mL, 20.0 mmol) at 0°C. The mixture was stirred at this temperature for 10 min and at room temperature for 1 h then 5-iodo-1-pentyne (4.67 g, 24.1 mmol) was added and the reaction mixture was stirred for 18 h. The resulting suspension was diluted with ether and quenched with a saturated aqueous NH_4Cl solution. The organic layer was washed with a saturated aqueous NH_4Cl (x3) solution, the aqueous layer was extracted with ether (x3), the organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography over silica gel (hexane/EtOAc 99:1 to 92:8) afforded (±)-**359** (3.12 g, 75%) as a colorless oil.

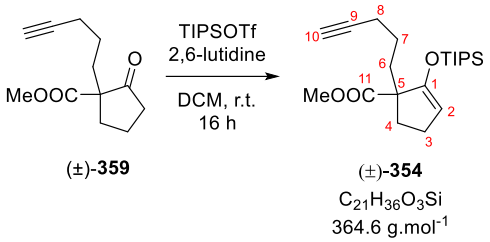
RN: 223796-03-0.

Spectroscopic data were consistent with those reported in the literature.



XX **XX**

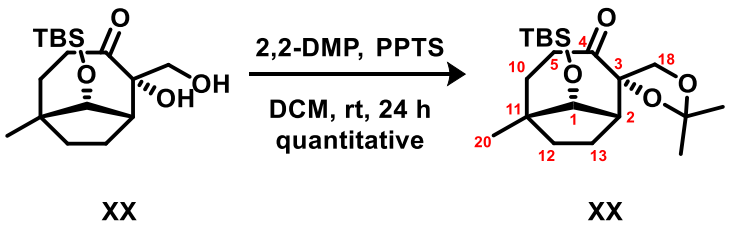
Methyl 1-(pent-4-yn-1-yl)-2-((triisopropylsilyl)oxy)cyclopent-2-ene-1-carboxylate (±)-**354**



To a stirred solution of (±)-**359** (500 mg, 2.40 mmol, 1 equiv.) in DCM (8 mL) at 0°C were successively added 2,6-lutidine (513 mg, 4.80 mmol, 2 equiv.) and TIPSOTf (0.64 mL, 2.40 mmol, 1.0 equiv.). The mixture was stirred overnight and the crude was evaporated *in vacuo*. Flash purification over silica gel (cyclohexane/AcOEt, 80:20 to 50:50) afforded pure (±)-**354** (803 mg, 92% yield).

^{1}H-NMR ($CDCl_3$) δ = 4.69 (t, *J* = 2.2 Hz, 1H, H-2), 3.64 (s, 3H, OCH_3), 2.40-2.29 (m, 2H, H-8), 2.26-2.14 (m, 3H, Ha-3, H-4), 2.02-1.91 (m, 1H, Hb-3), 1.98 (t, *J* = 2.6 Hz, 1H, H-10), 1.87-1.70 (m, 2H, H-7), 1.60-1.46 (m, 2H, H-6), 1.20 (sext, *J* = 7.2 Hz, 3H, Si-CH), 1.08 (d, *J* = 7.2 Hz, 18H, Si-($CH(CH_3)_2$) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 175.7 (C, C-11), 154.1 (C, C-1), 102.2 (CH, C-2), 84.1 (C, C-9), 68.2 (CH, C-10), 57.8 (CH_3, OCH_3), 51.4 (C, C-5), 33.5 (CH_2, C-6), 31.5 (CH_2, C-4), 26.2 (CH_2, C-3), 25.2 (CH_2, C-7), 23.6 (CH_2, C-8), 18.2 (6CH_3, Si-($CH(CH_3)_2$), 12.7 (3CH, Si-CH) ppm.



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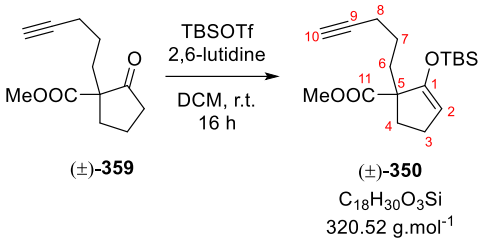
Methyl 1-(pent-4-yn-1-yl)-2-((triisopropylsilyl)oxy)cyclopent-2-ene-1-carboxylate (±)-**350**



To a stirred solution of (±)-**359** (1 g, 4.81 mmol, 1 equiv.) in DCM (10 mL) at 0°C were successively added 2,6-lutidine (1.12 mL, 9.62 mmol, 2 equiv.) and TBSOTf (1.65 mL, 7.21 mmol, 1.5 equiv.). The mixture was stirred overnight and the crude was evaporated *in vacuo*. Flash purification over silica gel (cyclohexane/AcOEt, 80:20 to 50:50) afforded pure (±)-**350** (1.2 g, 75% yield).

^{1}H-NMR ($CDCl_3$) δ = 4.70 (t, *J* = 2.2 Hz, 1H, H-2), 3.66 (s, 3H, OCH_3), 2.38-2.15 (m, 2H, H-8, H-4), 1.97-1.68 (m, 4H, H-3, H-7), 1.98 (t, *J* = 2.6 Hz, 1H, H-10), 1.87-1.70 (m, 2H, H-7), 1.60-1.46 (m, 2H, H-6), 0.91 (s, 9H, Si-C-CH_3), 0.17 (s, 3H, Si-CH_3) , 0.13 (s, 3H, Si-CH_3) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 175.6 (C, C-11), 154.0 (C, C-1), 102.2 (CH, C-2), 84.1 (C, C-9), 68.2 (CH, C-10), 57.8 (CH_3, OCH_3), 51.4 (C, C-5), 35.5 (CH_2, C-6), 31.5 (CH_2, C-4), 26.2 (CH_2, C-3), 25.2 ($3CH_3$, Si-C-CH_3), 23.5 (CH_2, C-7), 18.6 (CH_2, C-8), 17.6 (C, Si-C), -5.1 (CH_3, Si-CH_3), -5.8 (CH_3, Si-CH_3) ppm

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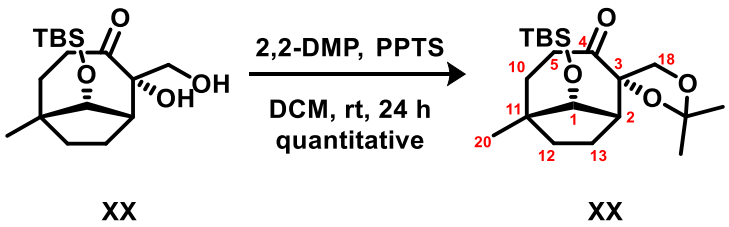
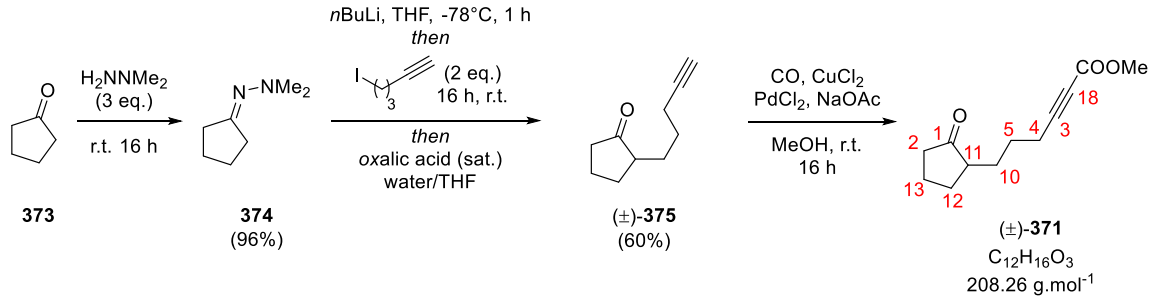


Methyl 6-(2-oxocyclopentyl)hex-2-ynoate (±)-**371**



In a round-bottomed flask, *N*,*N*-dimethylhydrazine (1.15 mL, 15 mmol, 3 equiv.) was added to cyclopentanone (5 mmol, 1 equiv.) at room temperature, the reaction mixture was stirred overnight under neat conditions then quenched with a saturated NH_4Cl solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude residue was directly engaged in the next step without further purification.

RN: 14090-60-9.

Spectroscopic data were consistent with those reported in the literature.

Hydrazone **374** (5 mmol, 1 equiv.) was placed in dry THF (5 mL) under argon, *n*-butyllithium (2.3 M in hexane, 2.4 mL, 5.5 mmol, 1.1 equiv.) was added to the solution at -78 °C. The mixture was stirred at this temperature for 1 h and 5-iodo-1-pentyne (1.45 g, 7.5 mmol, 1.5 equiv.) was added to the solution, which was allowed to stir at room temperature overnight. The reaction mixture was quenched with a saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was diluted in diethyl ether (10 mL), a saturated oxalic acid solution was added and the mixture was stirred at room temperature for 4 h then diluted with water. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Flash purification over silica gel (pentane/Et_2O, 70:30 to 50:50) provided the desired ketone (±)-**375** (408 mg, 54.4% yield).

RN: 42797-75-1.

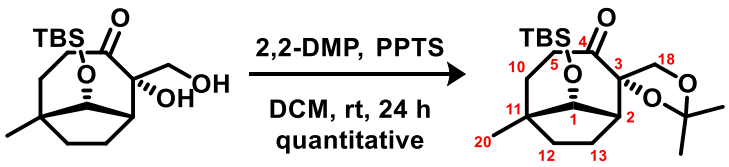
Spectroscopic data were consistent with those reported in the literature

In a round-bottomed flask, $PdCl_2$ (7.8 mg, 0.044 mmol, 0.02 equiv.), $CuCl_2$ (739 mg, 5.50 mmol, 2.5 equiv.) and NaOAc (542 mg, 6.60 mmol, 3 equiv.) were placed in MeOH (10 mL). The flask was fitted with a septa and was flushed with carbon monoxide then fitted with a balloon of gaseous carbon monoxide. A solution of (±)-**375** (330 mg, 2.20 mmol, 1 equiv.) in MeOH (10 mL) was added *via* cannula at 0°C and the mixture was stirred at 0°C for 12 h, then quenched with a saturated aqueous NH_4Cl/NH_4OH solution (9:1, 10 mL), and extracted with EtOAc/hexane = 1/4 (3x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash purification over silica gel (pentane/Et_2O, 50:50 to 0:100) afforded (±)-**371** (366 mg, 80% yield) a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ = 3.72 (s, 3H, OCH_3), 2.33 (td, *J* = 7.1, 2.1 Hz, 2H, H-8), 2.30-2.16 (m, 2H, Ha-2, Ha-4), 2.15-1.94 (m, 3H, Hb-2, Ha-3,H-5), 1.86-1.71 (m, 2H, Hb-3, Ha-6), 1.69-1.58 (m, 2H, H-7), 1.55-1.44 (m, 1H, Hb-4), 1.42-1.30 (m, 1H, Hb-6) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 220.8 (C, C-1), 154.3 (C, C-11), 89.2 (C, C-9), 73.2 (C, C-10), 52.7 (CH_3, OCH_3), 48.7 (CH, C-5), 38.1 (CH_2, C-2), 29.7 (CH_2, C-4), 29.1 (CH_2, C-6), 25.7 (CH_2, C-7), 20.8 (CH_2, C-3), 18.9 (CH_2, C-8) ppm.

HRMS (ESI): *m/z* calcd for $C_{12}H_{16}O_3Na^+$: $[M+Na]^+$: 231.0997; found: 231.0995.



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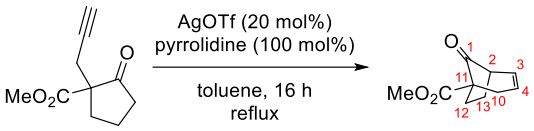
Methyl 8-oxobicyclo[3.2.1]oct-3-ene-1-carboxylate (±)-**376**



(±)-**369**

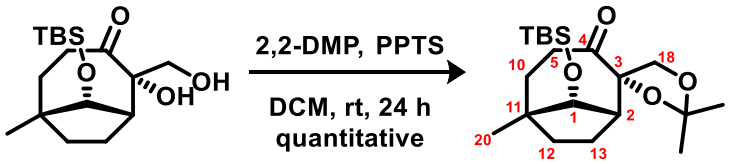
(±)-**376**
$C_{10}H_{12}O_3$
180.20 g.mol^{-1}

A mixture containing (±)-**369** (40 mg, 0.22 mmol, 1 eq.), AgOTf (11 mg, 44 µmol, 0.2 eq.) and pyrrolidine (18 µL, 0.22 mmol, 1 eq.) was refluxed in toluene (1 mL) in a sealed tube for 16 h. Water was added and the aqueous layer was extracted with Et_2O (x3). The gathered organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash purification over silica gel (pentane/Et_2O 80:20 to 50:50) afforded (±)-**376** (15 mg, 38% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.84 (dddd, *J* = 9.1, 6.7, 2.5, 0.7 Hz, 1H, H-4), 5.62 (ddd, *J* = 9.1, 4.2, 2.5 Hz, 1H, H-3), 3.77 (s, 3H, OCH_3), 3.30 (ddd, *J* = 17.5, 4.2, 2.2 Hz, 1H, H-2), 2.77-2.62 (m, 2H, H-10), 2.20-2.06 (m, 4H, H-12, H-13).

^{13}C-NMR (100MHz, $CDCl_3$) δ =211.3 (C, C-1), 171.8 (C, CO), 131.9 (CH, C-3), 125.6 (CH, C-4), 56.1 (C, C-11), 52.6 (CH_3, OCH_3), 46.4 (CH, C-2), 44.9 (CH_2, C-10), 30.8 (CH_2, C-12), 29.0 (CH_2, C-13) ppm.

HRMS (ESI): *m/z* calcd for $C_{10}H_{12}O_3Na^+$: $[M+Na]^+$: 203.0693; found: 203.0684.



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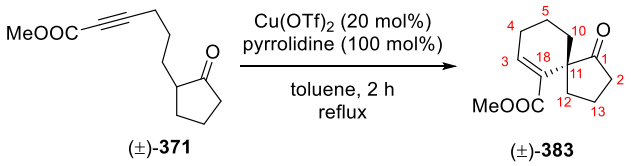
Methyl 1-oxospiro[4.5]dec-6-ene-6-carboxylate (±)-**383**



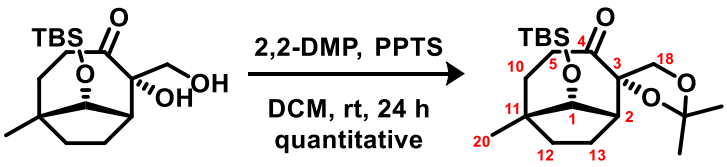
(±)-**371**

(±)-**383**
$C_{12}H_{16}O_3$
208.26 g.mol^{-1}

A mixture containing (±)-**371** (40 mg, 0.19 mmol, 1 eq.), $Cu(OTf)_2$ (14 mg, 38 µmol, 0.2 eq.) and pyrrolidine (16 µL, 0.19 mmol, 1 eq.) was refluxed in toluene (1 mL) in a sealed tube for 2 h. Water was added and the aqueous layer was extracted with Et_2O (x3). The gathered organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash purification over silica gel (pentane/Et_2O 80:20 to 50:50) afforded (±)-**383** (15 mg, 38% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 5.92 (sep, *J* = 1.2 Hz, 1H, H-3), 3.64 (s, 3H, OCH_3), 3.01 (qq, *J* = 14.8, 1.2 Hz, 2H, H-4), 2.48-2.27 (m, 3H, H-5, Ha-2), 2.24-2.00 (m, 4H, Hb-2, Ha-10, Ha-12, Ha-13), 1.89-1.73 (m, 3H, Hb-10, Hb-12, Hb-13).

^{13}C-NMR (100MHz, $CDCl_3$) δ = 221.1 (C, C-1), 171.6 (C, CO), 136.7 (C, C-18), 133.4 (CH, C-3), 64.4 (C, C-11), 52.0 (CH_3, OCH_3), 37.4 (CH_2, C-2), 37.1 (CH_2, C-4), 34.4 (CH_2, C-12), 34.4 (CH_2, C-10), 30.2 (CH_2, C-5), 20.1 (CH_2, C-13) ppm.



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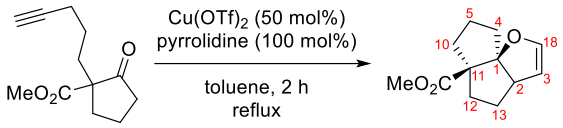
Methyl 3a,4,7,8-tetrahydro-5H-pentaleno[6a,1-b]furan-5a(6H)-carboxylate (±)-**382**



A mixture containing (±)-**359** (100 mg, 0.51 mmol, 1 eq.), $Cu(OTf)_2$ (94 mg, 0.25 mol, 0.5 eq.) and pyrrolidine (42 µL, 0.51 mmol, 1 eq.) was refluxed in toluene (2 mL) in a sealed tube for 2 h. Water was added and the aqueous layer was extracted with Et_2O (x3). The gathered organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Flash purification over silica gel (pentane/Et_2O 80:20 to 50:50) afforded (±)-**382** (42 mg, 40% yield).

^{1}H-NMR (400MHz, $CDCl_3$) δ = 6.20 (t, *J* = 2.3 Hz, 1H, H-3), 4.76 (t, *J* = 2.3 Hz, 1H, H-18), 3.70 (s, 3H, OCH_3), 3.05 (ddd, J = 10.2, 4.6, 2.3 Hz, 1H, H-2), 2.49 (dt, *J* = 13.3, 8.8 Hz, 1H, Ha-10), 2.39 (td, *J* = 12.0, 7.2 Hz, 1H, Ha-12), 2.27 (td, *J* = 12.2, 7.8 Hz, 1H, Ha-4), 1.96-1.80 (m, 3H, Hb-4, Ha-13, Ha-5), 1.71 (ddt, *J* = 12.5, 7.2, 2.6 Hz, 1H, Hb-13), 1.64-1.54 (m, 2H, Hb-5, Hb-12), 1.49-1.41 (m, 1H, Hb-10) ppm.

^{13}C-NMR (10MHz, $CDCl_3$) δ = 175.5 (C, CO), 145.1 (CH, C-3), 106.2 (C, C-1), 103.7 (CH, C-18), 63.3 (C, C-11), 53.9 (CH, C-2), 52.0 (CH_3, OCH_3), 37.6 (CH_2, C-4), 35.9 (CH_2, C-10), 33.9 (CH_2, C-12), 31.6 (CH_2, C-13), 23.2 (CH_2, C-5) ppm.

HRMS (ESI): *m/z* calcd for $C_{11}H_{16}O_3Na^+$: $[M+Na]^+$: 231.0992, found: 231.0999.