Total Synthesis of the Natural Products (±)-Symbioimine, (+)-Neosymbioimine and Formal Synthesis of Platencin.

Totalsynthese der Naturstoffe (±)-Symbioimine, (+)-Neosymbioimine und Formale Synthese von Platencin.

DISSERTATION

der Fakultät für Chemie und Pharmazie
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Publications

1. Georgy N. Varseev, Martin E. Maier "Formal Synthesis of Platencin" *Angewandte Chemie* **2009**, *121*, 3739-3742; *Angewandte Chemie Int. Ed*. **2009**, *48*, 3685-3688.

2. Georgy N. Varseev, Martin E. Maier "Enantioselective Total Synthesis of (+)-Neosymbioimine" *Org. Lett.* **2007**, *9*, 1461-1464.

3. Georgy N. Varseev, Martin E. Maier "Total Synthesis of (±)-Symbioimine" *Angewandte Chemie* **2006**, *118*, 4885-4889; *Angewandte Chemie Int. Ed.* **2006**, *45*, 4767-4771.

4. Georgy N. Varseev, Martin E. Maier "A Novel Palladium-Catalyzed Arylation-Dehydroaromatization Reaction: Synthesis of 7-Aryltetralones" *Org. Lett.* **2005**, *7*, 3881-3884.

5. Valentine G. Nenajdenko, Georgy N. Varseev, Alexey V. Shastin and Elisabeth S. Balenkova, *J. Fluorine Chem*. **2005**, *126*, 907-913.

6. Valentine G. Nenajdenko, Georgy N. Varseev, Vasily N. Korotchenko, Alexey V. Shastin and Elisabeth S. Balenkova, *J. Fluorine Chem*. **2004**, *124*, 1339-1345.

7. Valentine G. Nenajdenko, Georgy N. Varseev, Vasily N. Korotchenko, Alexey V. Shastin and Elisabeth S. Balenkova, *J. Fluorine Chem.* **2003**, *124*, 115-118.

8. A. V. Shastin, N. V. Korotchenko, G. N. Varseev, V. G. Nenajdenko, E. S. Balenkova, *Russ. J. Org. Chem*. **2003**, *39*, 433-436.

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Hare Krishna

Hare Krishna

Krishna Krishna

Hare Hare

Hare Rama

Hare Rama

Rama Rama

Hare Hare

Table of Contents

Abbreviations

abs.	absolute
Ac	Acetyl
AIBN	Azobisisobutyronitrile
aq.	aqueous
ar. (arom.)	aromatic
BBN (9-)	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
br	broad (NMR)
Boc	tert. Butoxy carbonyl
b.p.	Boiling point
Bu	Butyl
Bz	Benzoyl
c	Concentration
CAN	Cerium(IV) ammonium nitrate
Cbz	Carboxybenzyl
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
Cp'	Pentamethylcyclopentadienyl
CSA	Camphor sulfonic acid
Cy	cyclohexyl
δ	Chemical shift in ppm (NMR)
d	Doublet (NMR)
dba	*trans*,*trans*-dibenzylideneacetone
DCM	Dichloromethane
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	Di-iso-propyl azodicarboxylate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL(-H)	Diisobutylaluminium hydride

DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
dppf	1,1'-Bis(diphenylphosphino)ferrocene
E	trans
ee	Enantiomeric excess
EI	Electron impact
EOM	Ethoxymethoxymethyl
Eq.	equation
ESI	Electronspray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Fig.	Figure
Fur	Furyl
g	gram(s)
GC	Gas chromatography
h	hour(s)
HOMO	Highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IC_{50}	half maximal Inhibitory Concentration
IR	Infrared
PCC	Pyridinium chlorochromate
Piv	Pivaloyl
*i*Pr	isopropyl
J	coupling constant

L	liter(s)
LA	Lewis acid
LC	Liquid chromatography
LDA	Lithium diisopropylamide
HMDS	Hexamethyldisilazane
LUMO	Lowest unoccupied molecular orbital
m	Multiplet (NMR)
*m*CPBA	*meta*-cloroperbenzoic acid
Me	Methyl
MeOH	Methanol
mg	milligram
μg	microgram
MOM	Methoxymethyl
Ms	Methanesulfonyl
MVK	Methylvinylketone
m/z	Mass to charge ratio (MS)
NBS	N-bromosuccinimide
nM	nanomolar
NMO	N-Methylmorpholin-N-Oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
PPTS	Pyridinium *para*-toluene sulfonate
*p*TSA	*para*-Toluene sulfonic acid
Py	Pyridine
q	Quartet (NMR)
RCM	Ring-closing metathesis
R_f	Retention factor (TLC)
rt	Room temperature (ca. 23 °C)
s	Singlet (NMR)

SET	Single electron transfer
t	Triplet (NMR)
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TCAA	Trichloroacetanhydride
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TfO	Trifluoromethanesulfonate
TFAA	Trifluoroacetic acid anhydride
TMS	Trimethylsilyl
Tos (Ts)	*p*-Toluenesulfonyl
Triflate	Trifluoromethane sulfonate
UV	Ultraviolet
Z	cis

Literature Review: Biomimetic Strategies in Total Synthesis

Introduction

Synthetic realization of biogenetic pathways in total synthesis of naturally occurring compounds is one of the most impressive parts of organic chemistry. This discipline is strongly intersected with biochemistry because essentially all biological processes in living nature are based on organic reactions. Very complicated transformations of substances, like photosynthesis or the preparation of milk from grass, are not reproduced in laboratory. But many simple processes, like synthesis of peptides, DNA and, of cause, biologically active compounds, could be repeated *in vitro*. Thus, organic chemistry is firmly connected to biochemistry as well as to pharmacology and medicine. And the overall goal of all these disciplines is the preparation of biologically active compounds in the laboratory or factory. Understanding of biogenetic pathways helps chemists to achieve the total synthesis of natural compounds in a very elegant manner. The successful synthesis of many natural products often follows routes analogous to processes that occur in the living cell with less enzyme participation.

The theory of minimum enzyme participation in the biosynthesis of complex natural compounds originates from the fact that plants and bacteria produce an enormous amount of bioactive metabolites. The role of these secondary metabolites is not yet fully studied as well as their biosynthesis, and this theory says that most of these compounds are formed in living cells as side products of their metabolism. [1] Some typical functions of that metabolites include defence against other species or communication between species (ct. pheromones).

Another theory considers that the huge structural diversity of biological metabolites produced by nature was formed during the evolution of enzymes, and that all metabolites play a certain role in the internal economy of the producing organism. D. Williams in his article "Why are secondary metabolites (natural products) biosynthesized?"[2] wrote: *"We propose that all such structures serve the producing organisms by improving their survival fitness. We argue that this conclusion is necessitated by the fact that natural products are normally complex structures, whose biosynthesis is programmed by many kilobases of DNA. If it were*

otherwise, the pressures of Darwinian natural selection would have precluded the expenditure of so much metabolic energy in their construction and the development of such complexity."

Vedic knowledge about nature tells us that all living organisms were created according to the plan of supreme intelligence, and all plants play a certain role in the interactions between organisms. Bioactive chemical substances, respectively, also have influence on certain functions of human organism and mind and these compounds are synthesized by the aid of plants specially for utilizing them in medicine and nourishment. Vedic scriptures say that all plants were applied in people's everyday life, but in the age of *Kali-yuga* this science was forgotten, and some traces of that knowledge still remain in some countries as folk medicine. The folk medicine often helps modern scientists to find bioactive compounds in plants, and to synthesize their analogs with a view towards development of new drugs.

Perhaps the most appealing facet of a biomimetic strategy is that it pursues the development of synthetic methodology inspired by biogenesis, even if the mimicked biogenetic route is only hypothetical. The importance of biomimetic synthesis can be emphasized by words of Skyler and Heathcock who have written that "*a truly biomimetic total synthesis represents a general solution not to the preparation of a compound but to the preparation of all similarly derived natural products (discovered and undiscovered).*"[3]

We can determine biomimetic total synthesis as a straightforward and efficient preparation of complex natural products and their analogs from simple natural compounds or their derivatives using typical biogenetic reactions. Biogenetic reactions we can determine as reactions involved in the conversion of metabolites, catalyzed with enzymes or uncatalyzed, which take place in living cells, or similar to them. We should note that some enzyme catalyzed reactions could be mimicked in the laboratory by using appropriate catalysts, activation by light or by improving of basic conditions like reagents, solvent, temperature, pressure or concentration. Those reactions we should determine as biomimetic. The scope of biomimetic reactions consists of few types of simple transformations like aldol, Michael or Diels-Alder reactions. Sometimes one simple reaction initiates a cascade of reactions leading to selective formation of products containing complex polycyclic skeletons and several new stereocenters. Skeletal rearrangement of metabolites, catalysed with enzymes, could be mimicked by analogues transformations of carbocations or radicals. This review is an attempt to summarize and classify the knowledge about biomimetic total synthesis.

All the scope of biomimetic syntheses we divided by its key reactions. This division is not very punctual, because some syntheses coud include several different types of key reactions, but such classification of literature reported syntheses could simplify the information and make the studying and reviewing of it more clearly. Thus, the review would consist of following parts:

1) Biomimetic Mannich, Michael and aldol reactions.

2) Biomimetic cyclization of polyketides, which both could be related to a polyketide biosynthetic pathway.

3) Cation-π cyclizations.

4) Radical-π cyclizations, which both relate to the terpene cyclization pathway.

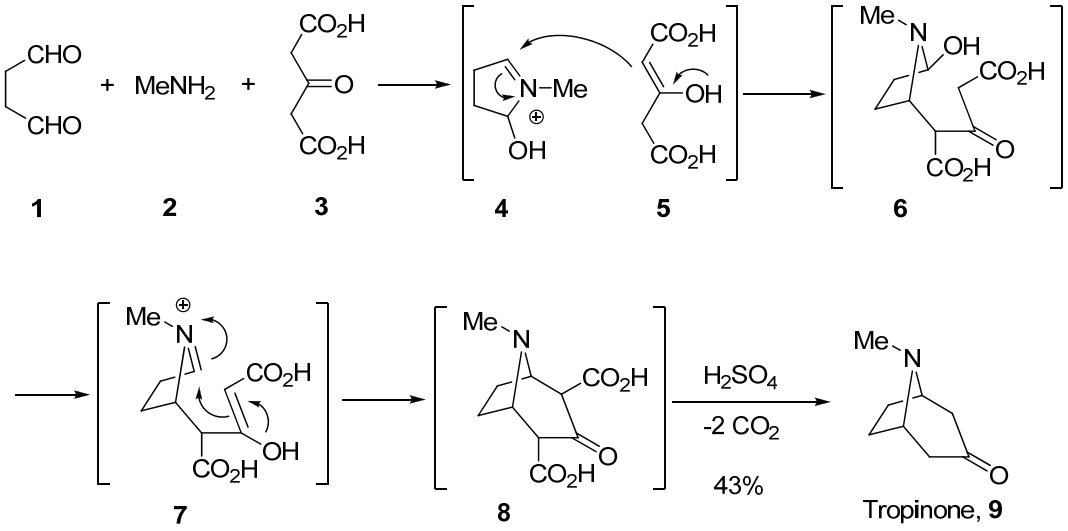
5) Synthesis of polyethers, which could reflect the biogenetic formation of C-O bonds, especially in tetrahydrofurans and other oxa-cycles.

6) Oxidative aromatic coupling and dimerizations, which usually followes the biogenetic pathway of formation C-C bonds between aromatic units.

7) Pericyclic reactions, which is the most common biogenetic pathway for the synthesis of complex polycyclic natural products.

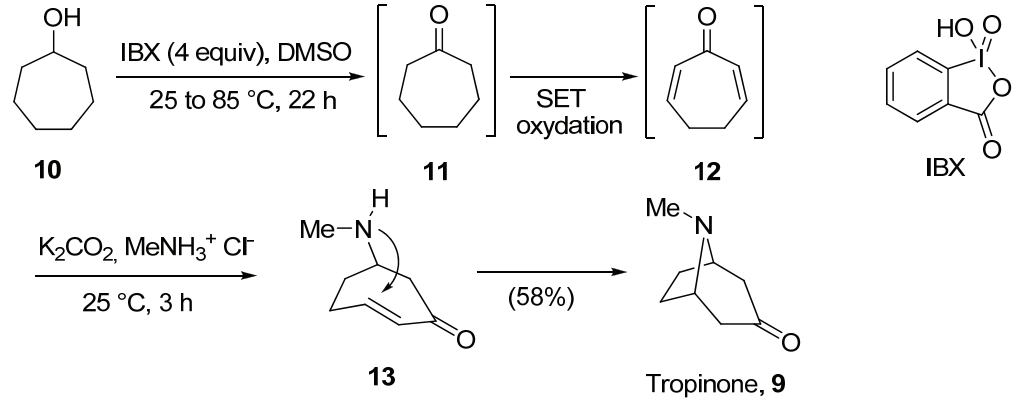
Biomimetic Mannich, Michael and aldol reactions

The history of biomimetic total synthesis began in 1917 with Robinson's famous three component synthesis of tropinone (**9**) from succinaldehyde (**1**), methylamine (**2**) and acetonedicarboxylic acid (**3**).[4] Condensation of methylamine with succindialdehyde formed a five-membered heterocycle which participated in sequential inter- and intramolecular Mannich reactions with calcium acetonedicarboxylate. Double decarboxylation of **8** provided tropinone (**9**) in 43 % yield by a remarkable one-pot reaction. Robinson's recognition of tropinone's symmetry led to a brilliant, direct synthesis from readily available starting materials.



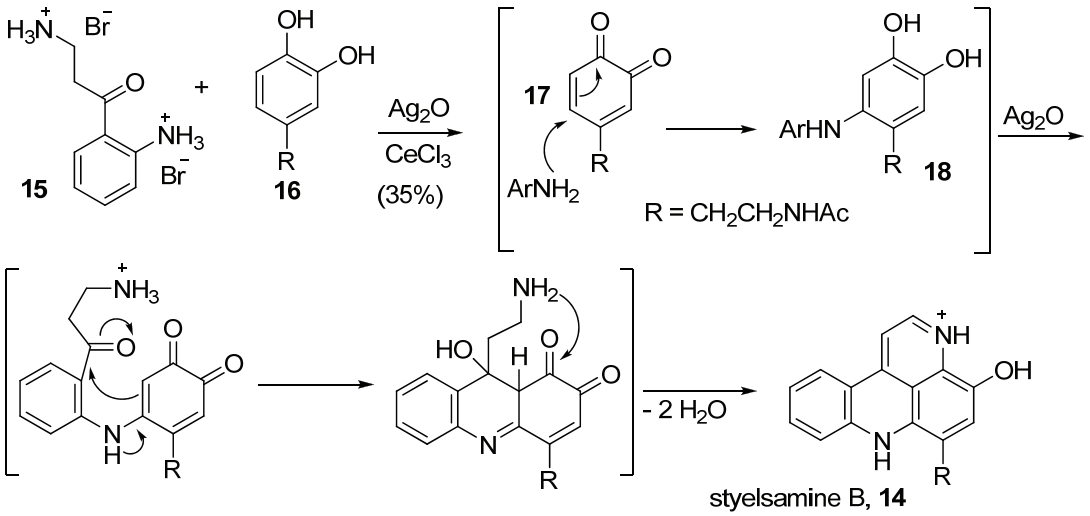
Scheme 1. Robinson's total synthesis of tropinone (**9**)

For comparing with the biomimetic Robinson's synthesis a modern one pot synthesis of tropinone (**9)** from cycloheptanol (**10**) using hypervalent iodine(V) oxidant IBX was recently achieved by K.C. Nicolaou and coworkers in 2002 (Scheme 2).[5] He developed a facile conversion of alcohols to α,β-unsaturated ketones with IBX (2-iodoxybenzoic acid) through a ketone intermediate, which is oxidized to an enone by single electron transfer (SET) mechanism. Double aza-Michael reaction of cyclohepta-2,6-diene-1-one (**12**) with methyl amine allowed to prepare tropinone from cycloheptanol (**10**) or cycloheptanone (**11**) in one pot and good yield (58 %).



Scheme 2. Nicolaou's total synthesis of tropinone (**9**)

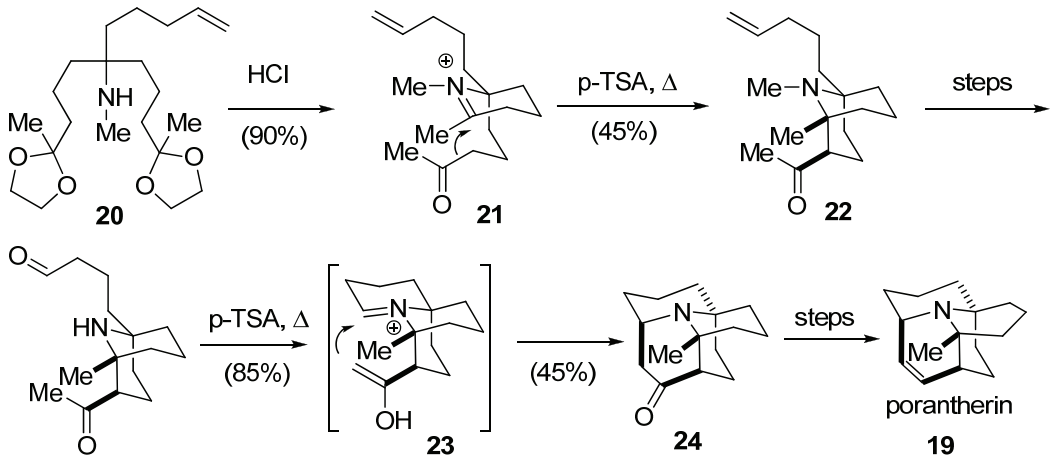
Another interesting biomimetic transformation is the one-step biomimetic synthesis of styelsamine B (**14**), containing a polyaromatic structure of zoochromes isolated from marine invertebrates, which was developed by Skyler and Heathcock.[3] This synthesis includes Michael addition of kynuramine (**15**) to *o*-quinone (**17**), which is obtained by oxidation of *N*-acetyl dopamine (**16**) with Ag_2O. Subsequent oxidation of the resulting catechol **18** initiated an aldol condensation/ cyclization/ aromatization cascade to give styelsamine B (**14**).



Scheme 3. Total synthesis of styelsamine B (**14**) by Skyler and Heathcock

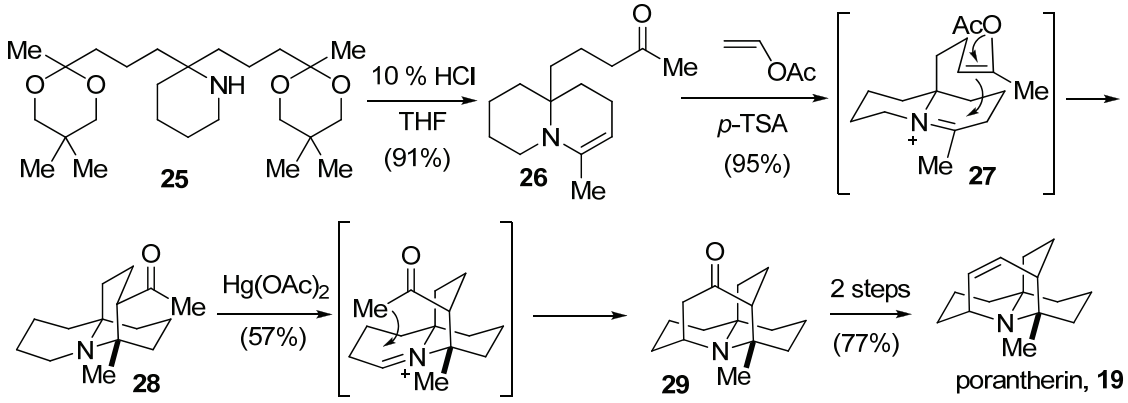
A stereoelectronically controlled Mannich cyclization is responsible for the diastereoselective construction of the tetracycle in Corey's synthesis of the porantherin alkaloid (**19**).[6] Starting from the symmetrical starting material **20**, a cyclic enamine **21** is

initially formed, with the help of acid. This enamine then yields the bicyclic compound **22** by means of a Mannich cyclization. The subsequent preparation of the iminium species **23** and cyclization to **24**, starting from the initially formed enamine, is achieved with catalytic quantities of acid. The complete reaction sequence from **20** to **24** (cleavage of the acetal protecting group, Mannich cyclization) is carried out sequentially, in order to guarantee water-free conditions for the Mannich reaction.



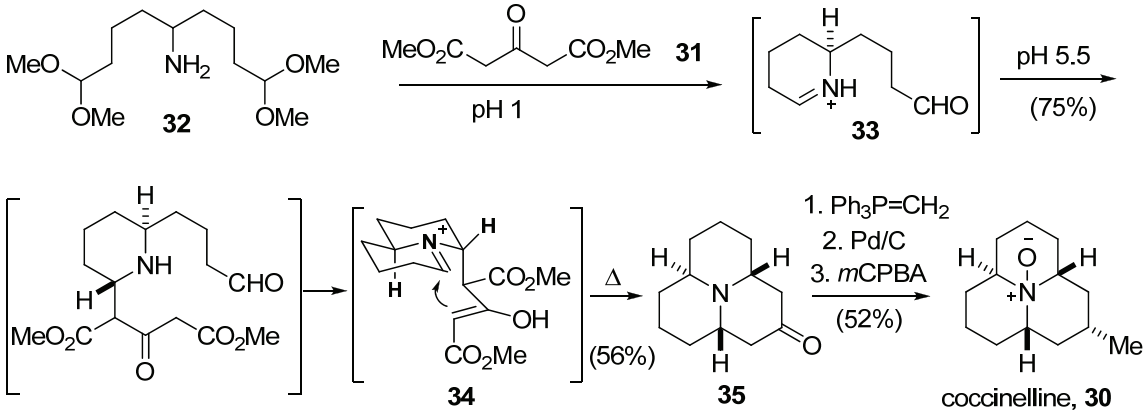
Scheme 4. Corey's synthesis of porantherin (**19**)

Another synthesis of porantherin was demonstrated by R. Stevens *et al.* in 1987.[7] Treatment of compound **25** with acid resulted in ketoenamine **26** after neutralization. By heating it in presence of vinyl acetate and *p*-toluenesulfonic acid ketone **26** was converted into enol acetate and the enamine isomerized into an imine. Intramolecular Mannich reaction of this intermediate **27** gave aminoketone **28** in good yield. Oxidation of amine **28** with mercuric acetate initiated a second Mannich reaction to obtain tetracyclic ketone **29**, which was converted to porantherin (**19**) in two steps by heating of **29** with phenylsulfonyl hydrazide and treatment of the hydrazone with *tert*-BuLi.



Scheme 5. Total synthesis of porantherin (**19**) by R. Stevens

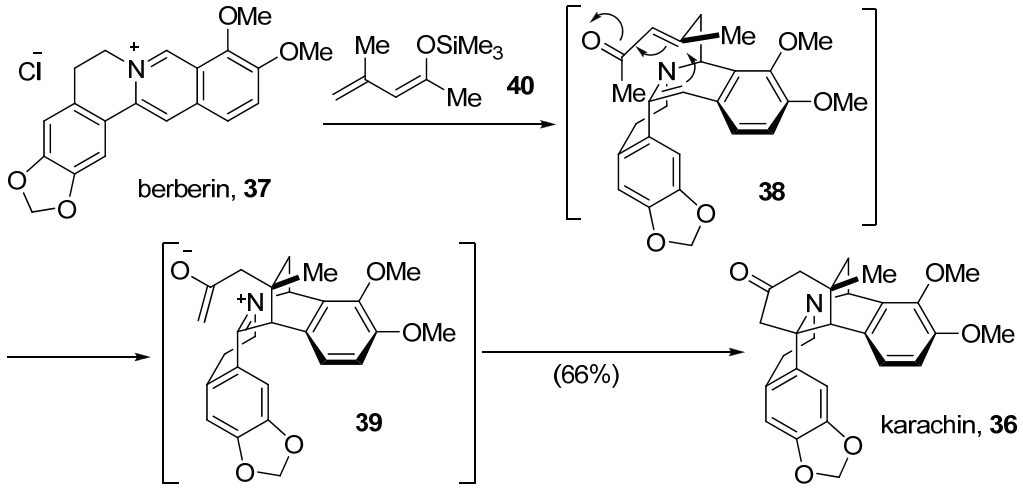
Similar to Robinson's synthesis of tropinone, total synthesis of coccinelline (**30**) by R. Stevens and Li published in 1979 is based on a Robinson-Schöpf condensation of an amine dialdehyde equivalent and acetone dicarboxylic ester **31**.[8] Treatment of diacetal **32** with acid gave iminium salt **33**, which was condensed with acetone dicarboxylic ester **31** after pH was adjusted to 5.5. The origin of stereoselectivity could be explained by transition state **34** at the **Scheme 6**. After decarboxylation, ketone **35** was obtained in 56 % yield.



Scheme 6. Total synthesis of coccinelline (**30**) by R. Stevens and Li

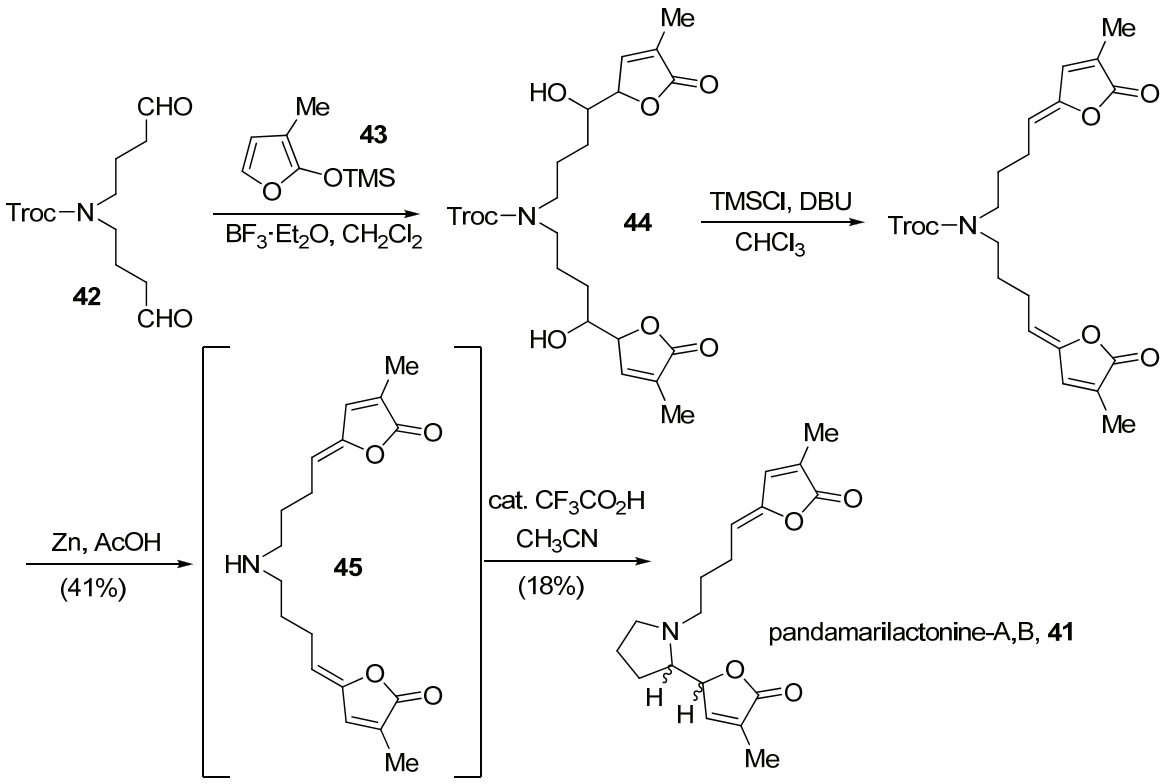
Such domino sequences can also be applied intramolecularly, as the synthesis of the alkaloid karachin (**36**) proves (**Scheme** 7). In this impressive example, a domino reaction takes place as follows: a vinylogous Mannich reaction (to **38**) is succeeded by a Michael reaction (to **39**) and then another Mannich reaction (to **36**). Three C−C bonds are formed sequentially by Domino Mannich + Michael + Mannich cyclization yielding karachin (**36**). When berberin **37**

was treated with 20 equivalents of the diene **40** for 18 h at 100 °C, the yield of **36** in this sequence was 66%.[9]



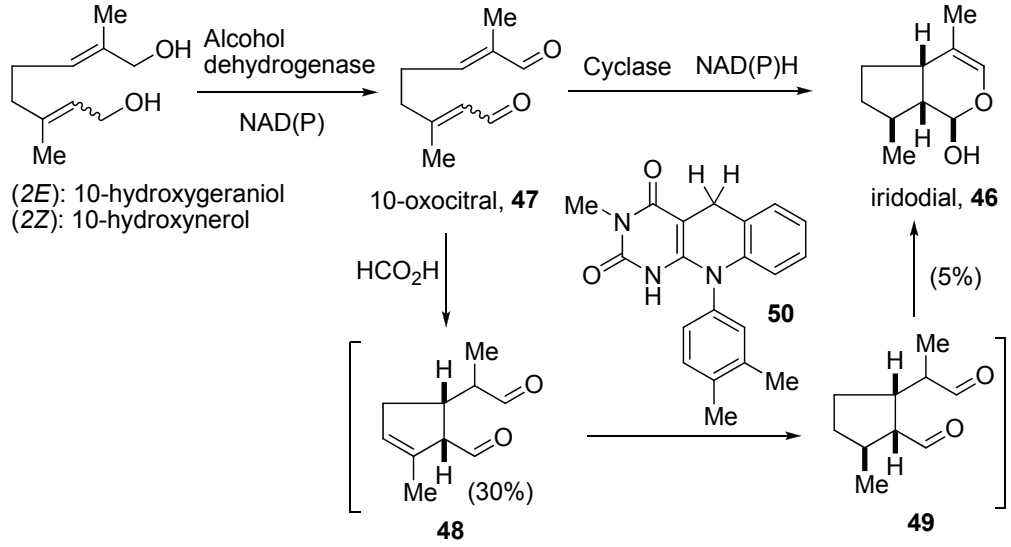
Scheme 7. Total synthesis of karachin (**36**) by R. Stevens

Another example of a biomimetic Michael reaction was published by H. Takayama and coworkers. This was a key reaction in the total synthesis of pandamarilactonine A and B (**41**) (**Scheme 8**).[10] These naturally occurring compounds were prepared in few steps using Mukaiyama aldol reaction of symmetrical aldehyde **42** with 2-trimethylsilyloxy-3-methyl furan (**43**) to give γ-lactone **44**. Dehydration and deprotection of **44** gave amine **45**, which underwent a vinylogous aza-Michael reaction to afford a mixture of stereoisomers of pandamarilactonine (**41**) in 18 % yield.



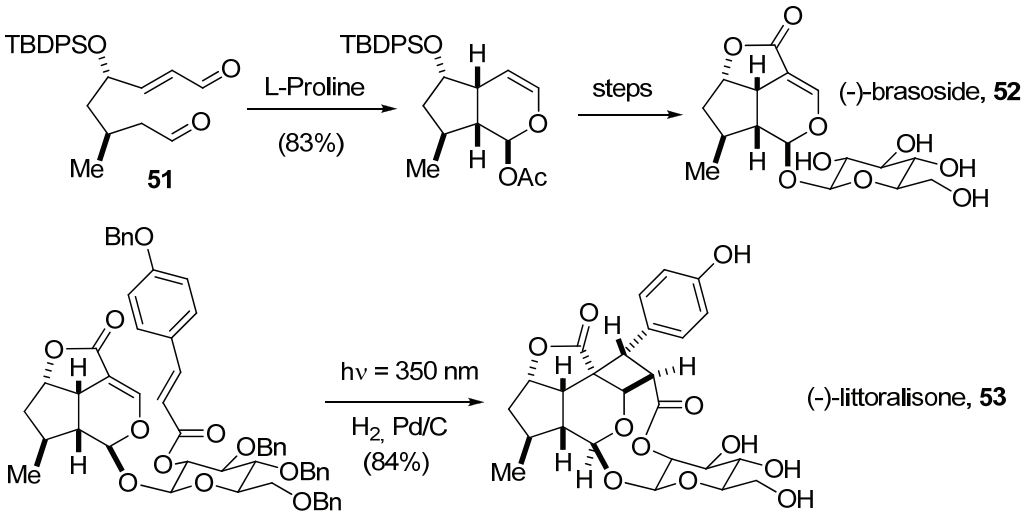
Scheme 8. Total synthesis of pandamarilactonine A and B (**41**)

Intramolecular cascade aldol reactions might be used for the synthesis of iridodial type natural products. For example, biosynthesis of iridodial (**46**) involves coenzyme reduction of unsaturated aldehyde **48**, which is formed by intramolecular aldol reaction of 10-oxocitral (**47**). A biomimetic synthesis of iridodial (**46**) was reported by Japanese authors in 1987.[11] Treatment of 10-oxocitral (**47**) with formic acid afforded dehydroiridodial (**49**) in 30 % yield. Addition of coenzyme model **50** resulted in hydrogenation, giving 5 % of iridodial (**Scheme 9**).



Scheme 9. Biosynthesis and total synthesis of iridodial (**46**)

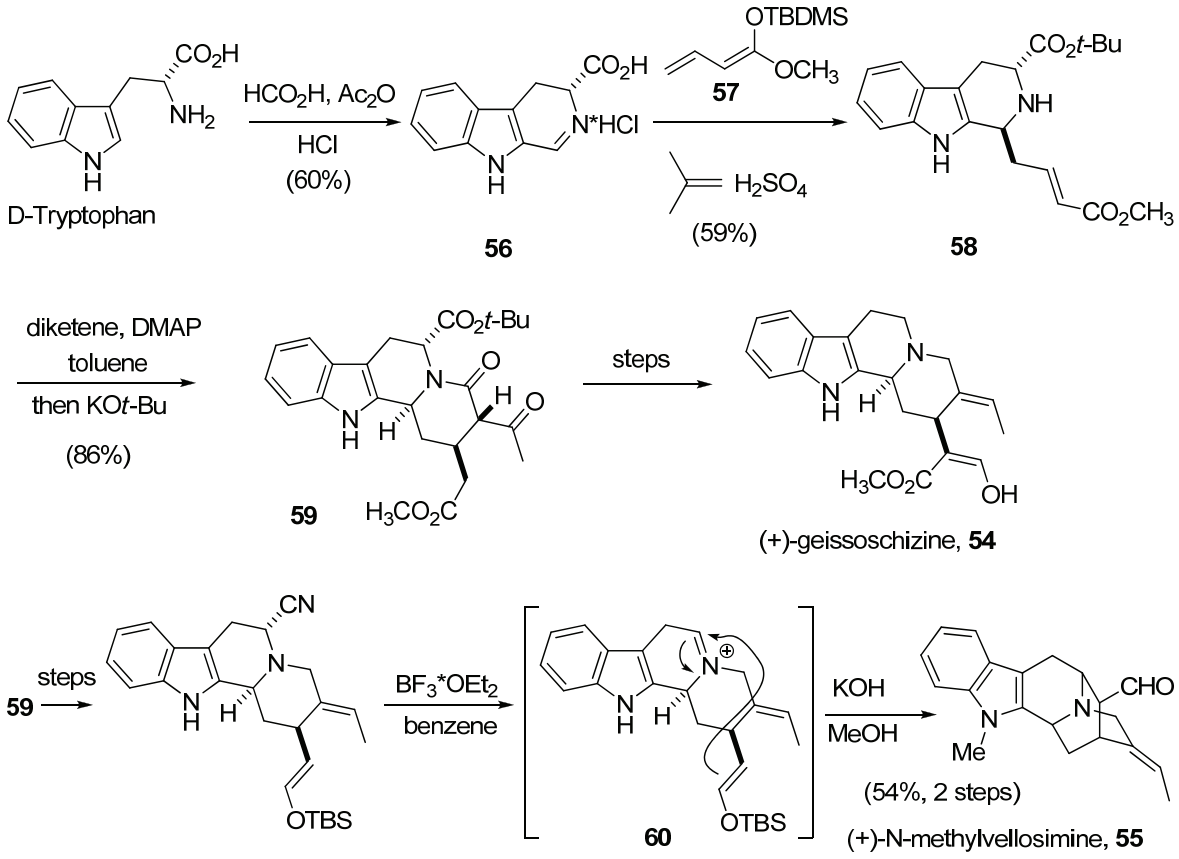
A modern synthesis of iridodial-type compounds was reported by D. MacMillan in 2005.[12] Intramolecular Michael reaction of dialdehyde **51** has been done under L-proline catalyzed conditions to give the iridodial core of (-)-brasoside (**52**) in good yield and diastereoselectivity. Another compound (-)-littoralisone (**53**), containing the same iridodial core structure, was synthesized by photochemical [2+2] cycloaddition (**Scheme 10**).



Scheme 10. Synthesis of (-)-brasoside (**52**) and (-)-littoralisone (**53**) by D. MacMillan

A great example of using biomimetic Mannich and Michael reactions in the total synthesis of monoterpenoid indole alkaloids (+)-geissoschizine **(54)** and (+)-N-

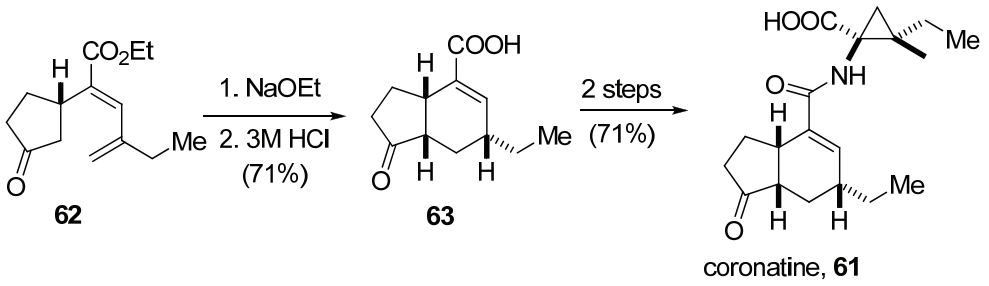
methylvellosimine (**55**) was shown by S.F. Martin and coworkers (**Scheme 11**).[13] The key steps of the synthesis of these compounds are a vinylogous Mannich reaction of dihydrocarboline **56** with silyl ketene acetal **57**, and an intramolecular Michael reaction of a dicarbonyl compound, generated by acylation of **58** with diketene, to provide compound **59**. Stereochemistry of these reactions is matched to that of authentic products. The alkaloid **55** was also prepared in a concise biomimetic manner by intramolecular Mukaiyama-Mannich reaction of intermediate **60**, to give a mixture of aldehydes **55.** Epimerization of isomers with NaOH gave the thermodynamically more stable compound **55**, which is the same as the naturally occurring product.



Scheme 11. Total syntheses of (+)-geissoschizine (**54**) and (+)-N-methylvellosimine (**55**) by S.F. Martin.

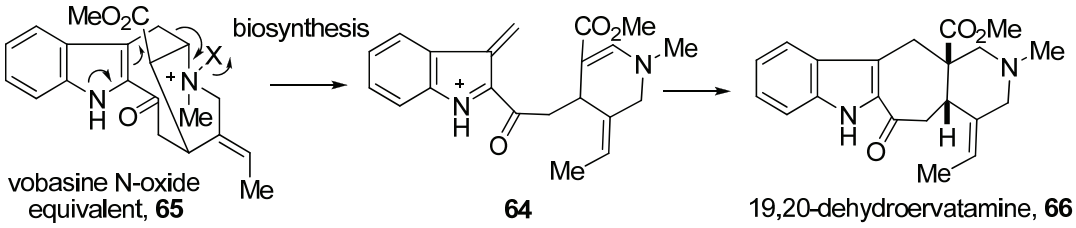
A total synthesis of coronatine (**61**), published by A. Ichihara, is based on an intramolecular vinylogous Michael reaction of cyclopentanone **62**.[14] Obtained bicyclic core

structure **63** of coronatine was formed in good yield and stereoselectivity to give only *cis*-bicyclononane core structure (**63**) of mentioned natural product.



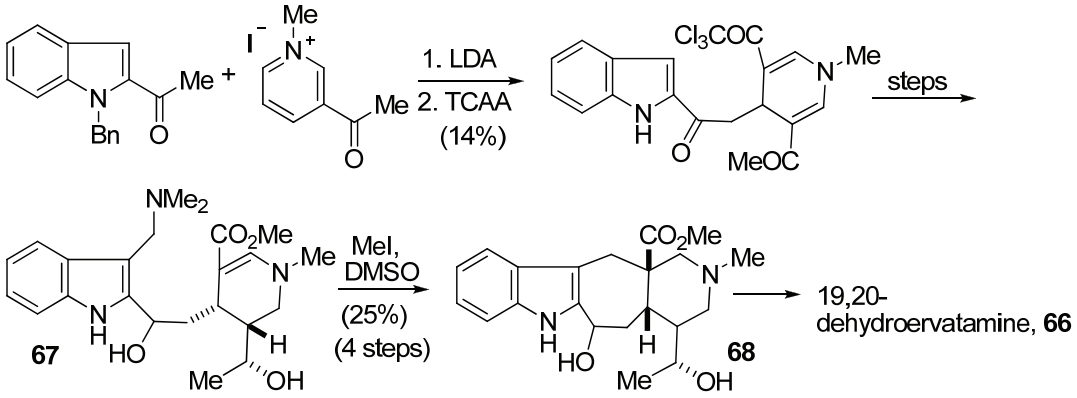
Scheme 12. Total synthesis of coronatine (**61**) by A. Ichihara

The biogenetic pathway toward the ervatamine alkaloids probably involves a cationic key intermediate **64**, formed from a vobasine *N*-oxide equivalent **65** as illustrated in **Scheme 13**, which would be transformed into 19,20-dehydroervatamine (**66**) by closure of the C ring via cyclization of the enamine moiety upon the 3-methyleneindoleninium cation **64**.[15]



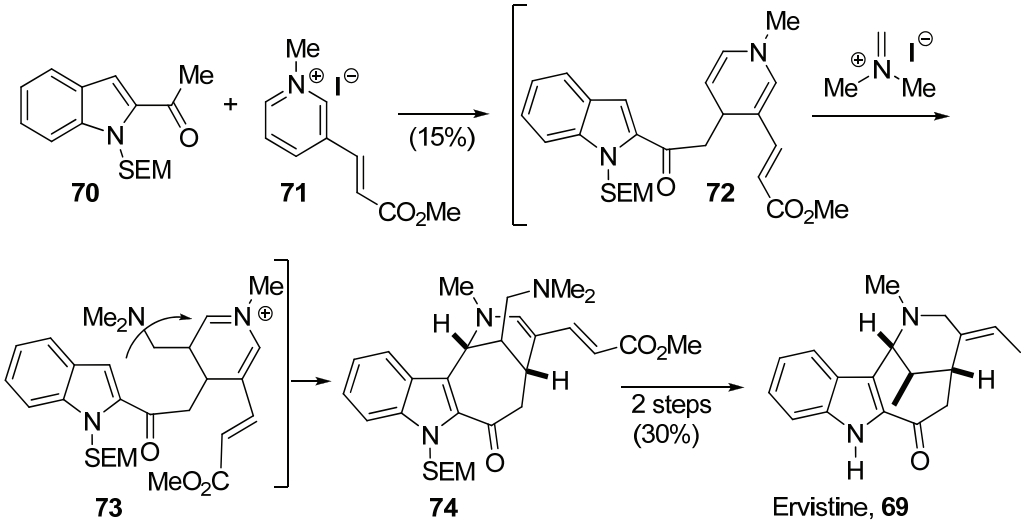
Scheme 13. Biogenetic pathway of ervatamine alkaloids

Total synthesis of ervatamine alkaloids, reported by M. Bennasar and J. Bosch, realized this biomimetic approach. Heating of compound **67** with MeI in DMSO afforded the tetracyclic skeleton of ervatamine alkaloids **68**.[16]



Scheme 14. Total synthesis of 19,20-dehydroervatamine (**66**) by M. Bennasar and J. Bosch

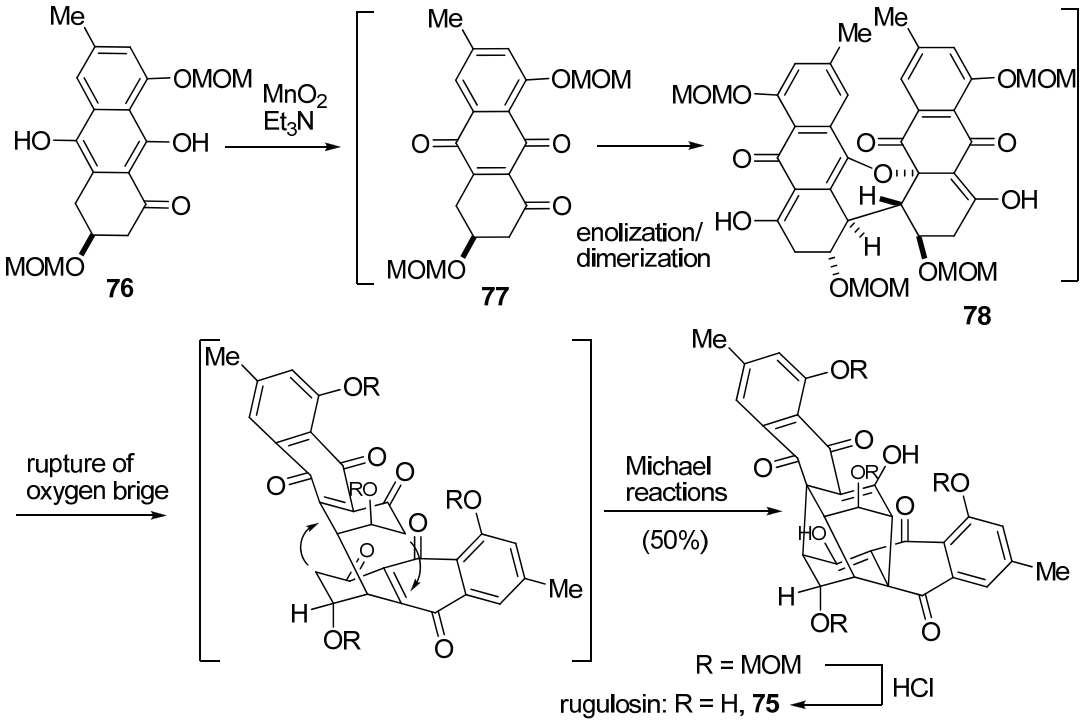
Total synthesis of indole alkaloid ervistine (**69**) was accomplished by M. Bennasar and coworkers in concise biomimetic manner.[17] Alkylation of indolacetone **70** with pyridinium salt **71** gave enamine **72**, which was dimethylaminomethylated to afford iminium salt **73**, which underwent cyclization resulting in tetracyclic compound **74**. This intermediate was converted to ervistine (**69**) in two steps.



Scheme 15. Total synthesis of ervistine (**69**) was accomplished by M. Bennasar

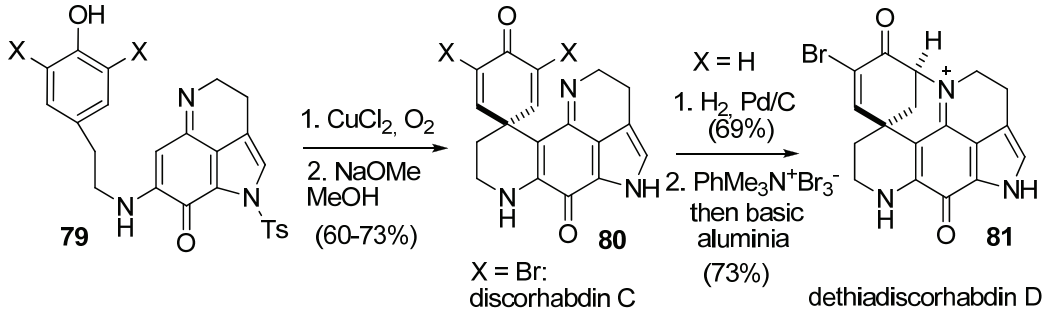
Recently, the Nicolaou group has published syntheses of rugulosin (**75**, **Scheme 16**) and several other family members, featuring an impressive biomimetic dimerization/cascade sequence.[18] Addition of MnO_2 and Et_3N to anthradihydroquinone **76** led to the formation of

cage structure (**78**), through a radical dimerization of quinone **77** followed by a series of intramolecular Michael reactions, in 50% overall yield.



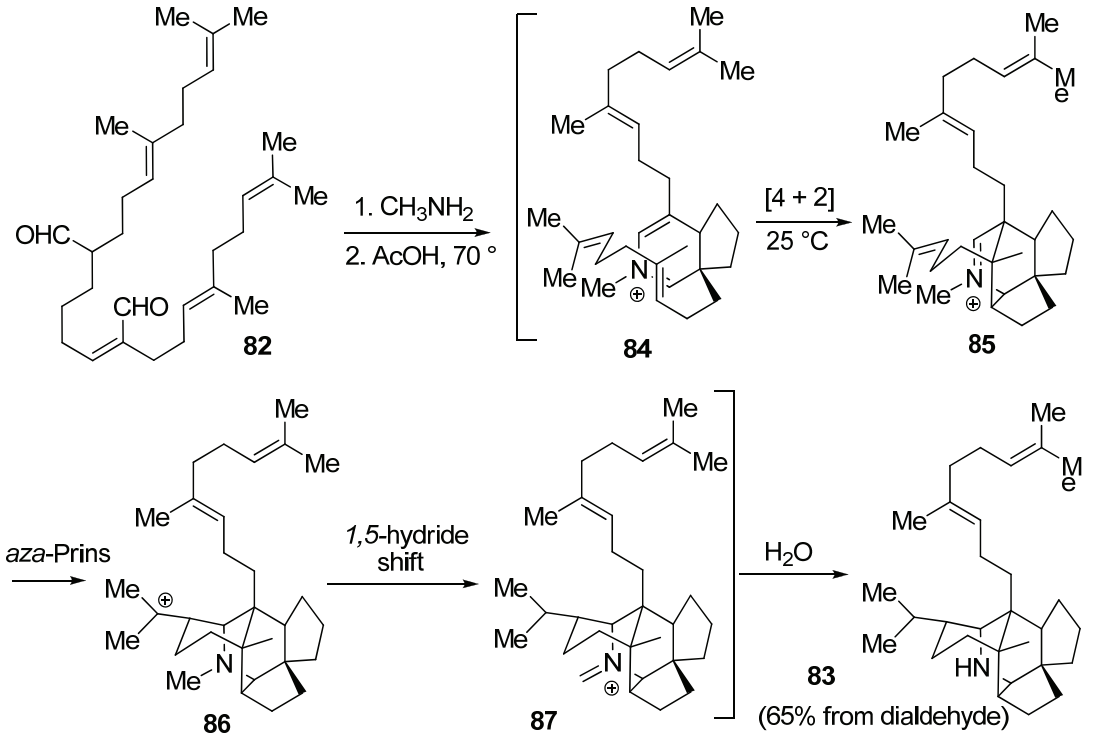
Scheme 16. Nicolaou's syntheses of rugulosin (**75**)

A biomimetic approach to the discorhabdin alkaloids, elaborated by C. Heathcock, involves intramolecular cyclization of tyramine-substituted indoloquinonimines under oxidative conditions to construct the characteristic spirodienone structure of the discorhabdin alkaloids.[19] Compound **79** was prepared from tryptamine and tyramine derivatives. Treatment of **79** with Cu(II) chloride under oxygen afforded discorhabdin C in good yield after deprotection. Hydrogenation of unbrominated spiroketone **80** and bromination of α-position gave bromoenones which underwent smooth conversion to dethiadiscorhabdin D (**81**) upon treatment with basic alumina.



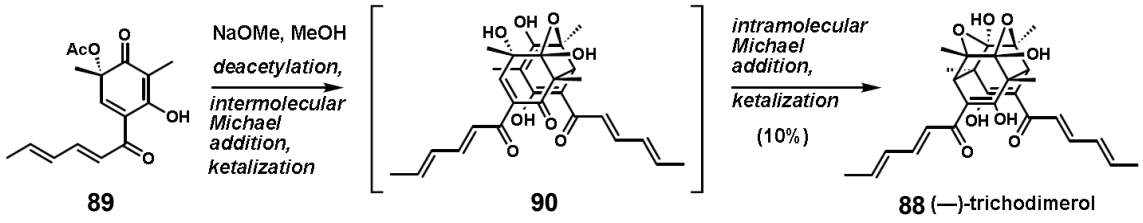
Scheme 17. Total synthesis of dethiadiscorhabdin D (**81**) by C. Heathcock

One of the most fascinating and educational accounts of a tandem biomimetic reaction sequence is Clayton Heathcock's 1996 paper on the *Daphniphyllum* alkaloids.[20] Following several years study of these molecules, it was found that squalene derivative **82** could be converted to pentacyclic amine **83** simply by sequential treatment with methylamine and warm acetic acid. A methylamine-induced Michael reaction and condensation gave rise to dihydropyridinium intermediate **84** which was poised for an intramolecular Diels-Alder reaction. The resultant tetracyclic iminium ion **85** was then attacked by a pendant alkene to give tertiary carbocation **86**. A 1,5-hydride shift followed by iminium ion hydrolysis provided compound **87**, a postulated biogenetic precursor of several *Daphniphyllum* alkaloids, in an amazing 65% yield from dialdehyde **82**. This remarkable sequence forms five rings and eight stereocenters with complete diastereo- and regiocontrol from the linear dialdehyde **82**. Heathcock's beautiful work on this and related compounds is a tribute to his genius and can be considered a chemical masterpiece.



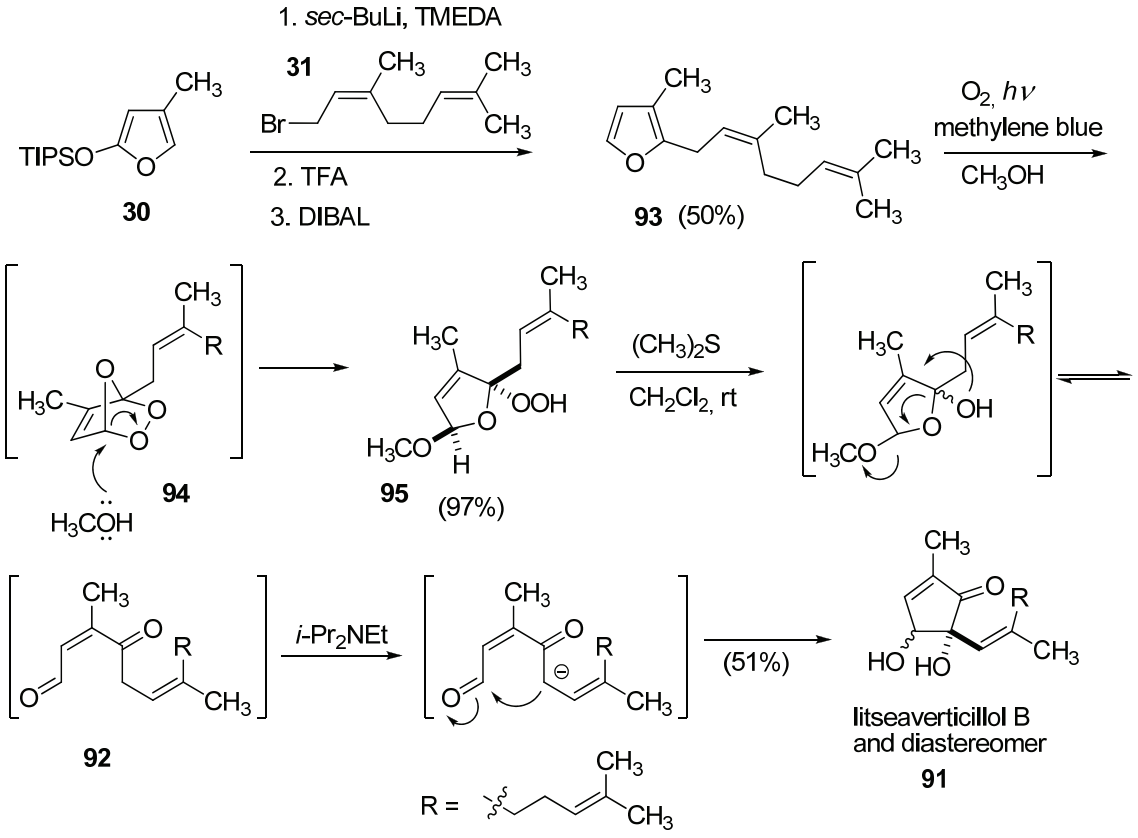
Scheme 18. Heathcock's biomimetic approach to *Daphniphyllum* alkaloids

A recent contribution to the area of tandem biomimetic reactions is the synthesis of trichodimerol (**88**) by the Corey[21] and Nicolaou[22] laboratories. Both groups took advantage of the C2-symmetry in **88** to design in situ dimerizations of acetate **89**. Deacetylation of **89** with sodium methoxide (Corey) or cesium hydroxide (Nicolaou) triggered the formation of trichodimerol **88** in a modest 10% (Corey) or 16% (Nicolaou) yield. Compound **90** may represent an actual intermediate in this remarkable pathway, or the formation of **88** may occur by way of another degenerate pathway (e.g., a different order of events or a photochemical [4+4] cycloaddition).



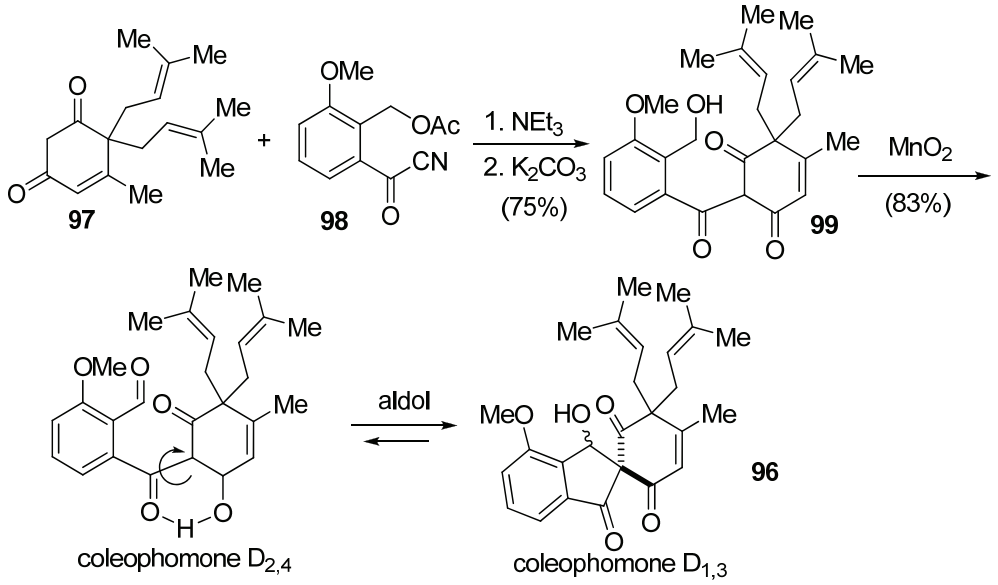
Scheme 19. Nicolaou's and Corey's total syntheses of (-)-trichodimerol (**88**)

A total synthesis of sesquiterpenes called litseaverticillols **91** using a biomimetic aldol condensation of ketoaldehyde **92** as a key reaction was accomplished by Greek authors in 2004.[23] Furan **93** underwent a Diels-Alder reaction with singlet oxygen, solvolysis of compound **94** gave hydroperoxide **95**. Reduction of hydroperoxide **95** with dimethyl sulfide gave ketoaldehyde **92**, which underwent aldol condensation *in situ* by treatment with Hünig's base in 51% yield. Prepared liseaverticillol B (**91**) was obtained along with it's diastereomeric product.



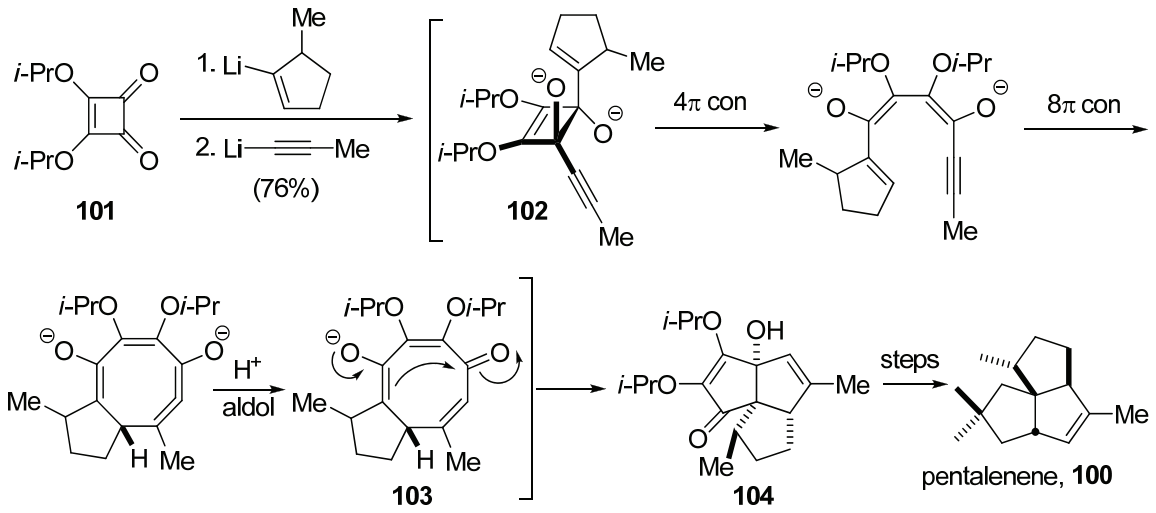
Scheme 20 Biomimetic total synthesis of litseaverticillol B (**91**)

Coleophomone D (**96**) exists in nature as a mixture of atropisomers $D_{2,4}$ and diastereomers $D_{1,3}$ due to very facile aldol/retroaldol equilibrium of these unusual metabolites (**Scheme 21**). In Nicolaou's[24] studies of the synthesis of different coleophomones the facile condensation of diketone **97** and cyanoketone **98** afforded benzyl alcohol **99.** Oxidation of **99** with MnO_2 gave all coleophomones D as a mixture of all the postulated isomers (D_1-D_4) in 83% yield.



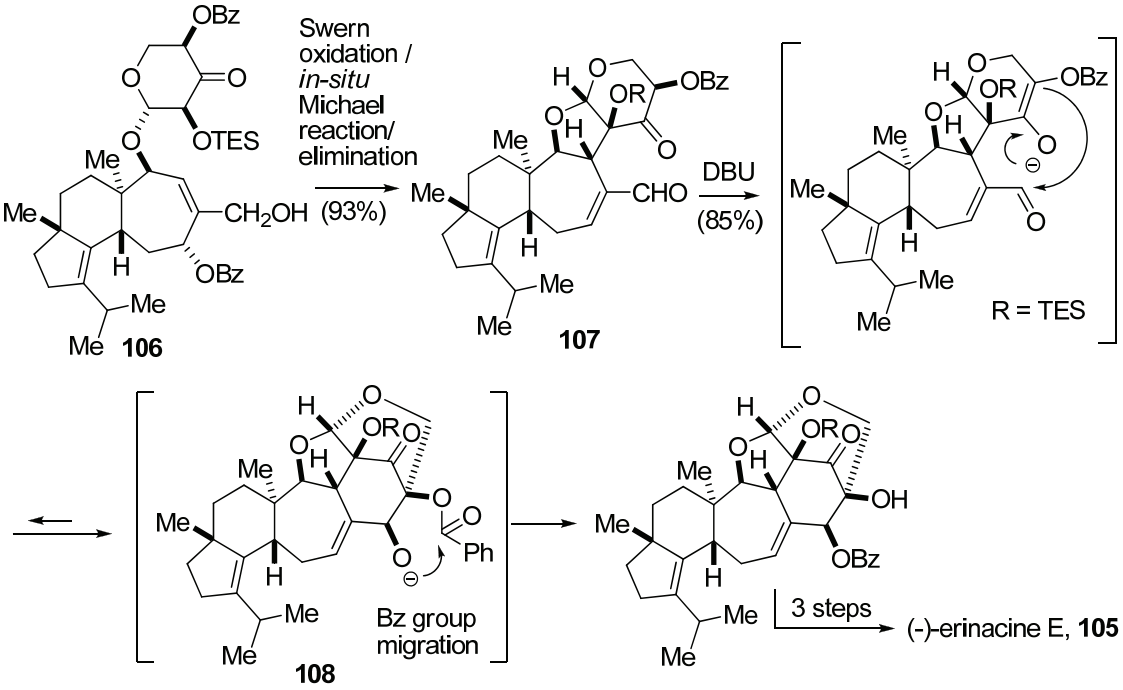
Scheme 21. Nicolaou's synthesis of coleophomones (**96**)

An original total synthesis of pentalenene (**100**) by means of the squarate ester cascade was recently reported by L. Paquette.[25] Starting from diisopropyl squarate (**101**), the tricyclic core of pentalenene (**100**) was furnished in one-pot and 76% yield. The mechanism of this cascade reaction includes 4π and 8π cyclizations of dialcoholate **102** prepared by double alkylation of diisopropyl squarate (**101**). On the last step of the domino sequence intermediate **102** undergoes transannular aldol reaction to form tricyclic pentalene architecture **104**.



Scheme 22. Total synthesis of pentalenene (**100**) by L. Paquette

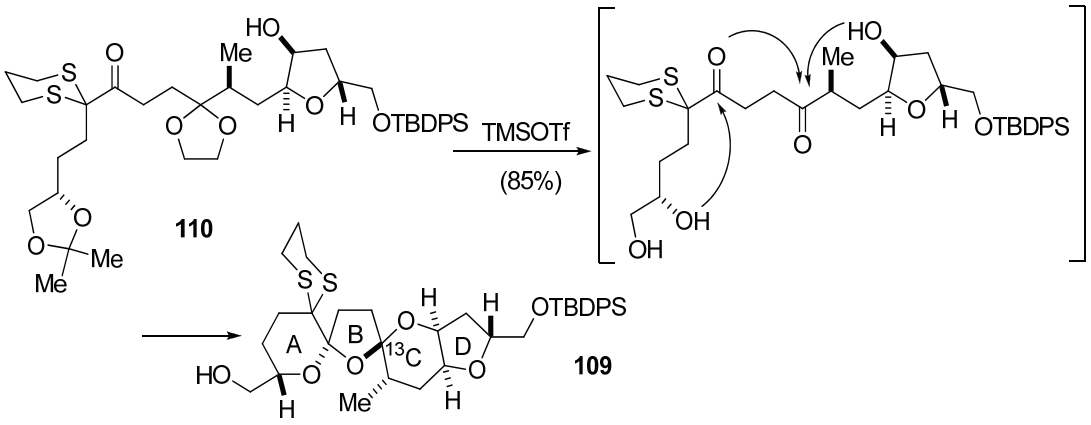
A biomimetic total synthesis of (-)-erinacine E (**105**) was reported by Japanese authors.[26] Swern oxidation of allylic alcohol **106** led to a subsequent intramolecular Michael cyclization of intermediate ketoaldehyde, and *in-situ* elimination, giving aldehyde **107** in 93% yield. Treatment of this ketoaldehyde with DBU provided the product of an intramolecular aldol reaction with concomitant migration of the benzoyl group **108** in good yield, which was converted to the natural product (-)-erinacine E (**105**) in 3 steps.



Scheme 23 Biomimetic total synthesis of (-)-erinacine E

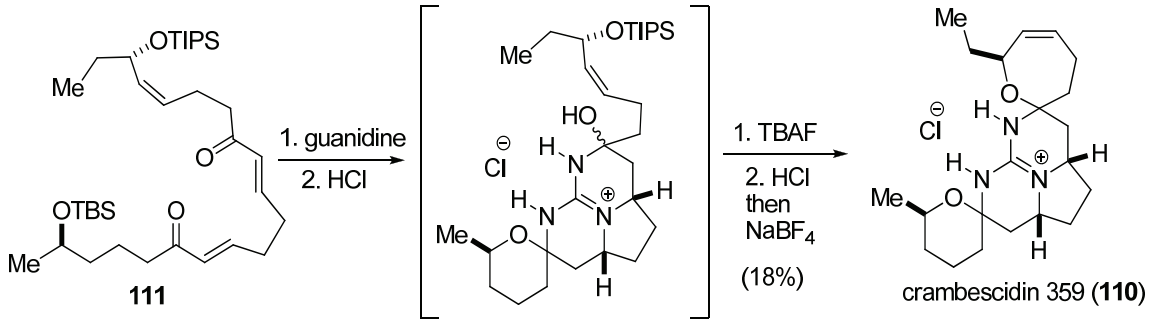
Biomimetic cyclization of polyketides

The polyketide pathway is one of the most common in the biosynthesis of natural compounds. In Nicolaou's synthesis of azaspiracid the ABCD rings of intermediate **109** were constructed by acidic treatment of protected ketone **110** which underwent thermodynamically controlled cyclization.[27] Although the produced isomer has wrong stereochemistry at C-13, it could be epimerized into the correct structure in the next steps.



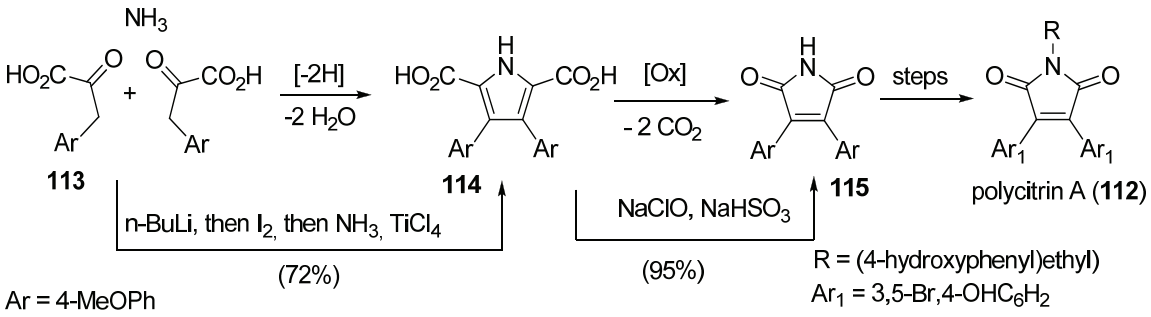
Scheme 24. Nicolaou's synthesis the ABCD ring system of azaspiracid

Recently a concise approach to the pentacyclic structure of ptilomycalin A and the total synthesis of crambescidin 359 (**110**) were reported.[28] The authors proposed that this polycyclic unit of requisite molecule might be synthesized by a biomimetic strategy from linear diketone **111**. Thus treatment of diketone **111** with guanidine, followed by cleavage of the silyl groups afforded the desired crambescidin 359 (**110**) in 18% overall yield.



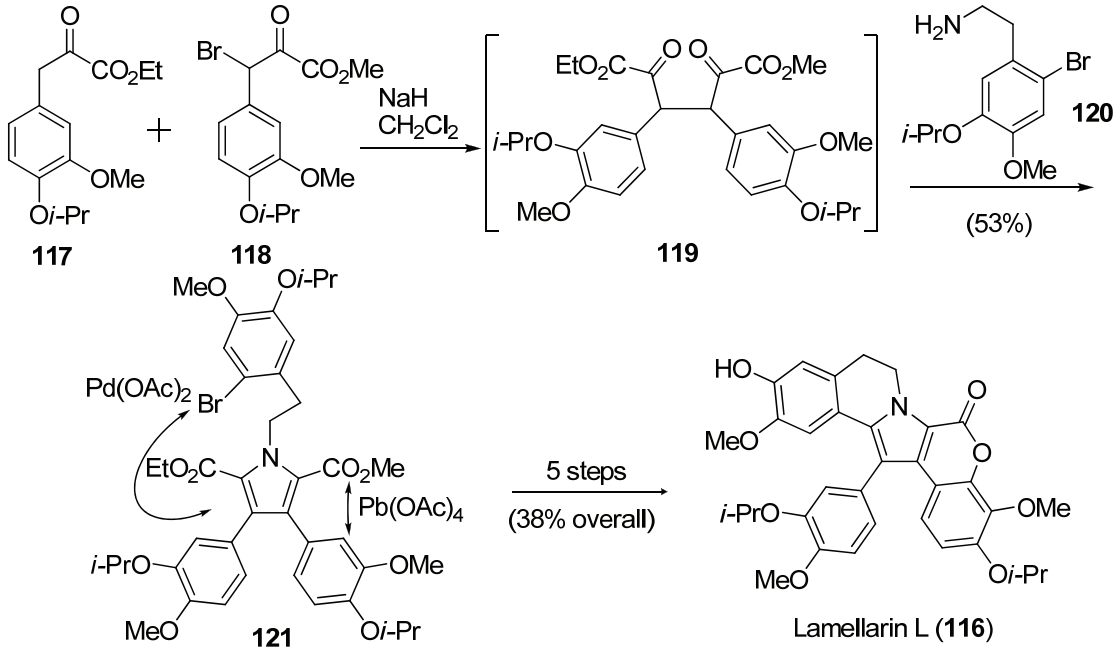
Scheme 25. Total synthesis of crambescidin 359 (**110**)

Many alkaloids contain a pyrrole moiety or another heterocyclic fragment. For example, polycitrin A (**112**) consist of a maleimide moiety, which biogenetically could be formed by oxidative dimerization of the two corresponding arylpyruvic acids and consecutive closure of the pyrrole ring with ammonia. In the total synthesis of polycitrin A (**112**) by W. Steglich *et al*. that biogenetic approach was successfully applied.[29] Treatment of the dianion derived from 3-(4-methoxyphenyl)pyruvic acid (**113**) and *n*BuLi with iodine followed by reaction of the resulting solution with ammonia and $TiCl_4$ at room temperature afforded 3,4-bis-(4-methoxyphenyl)pyrrole-2.5-dicarboxylic acid (**114**) in 72% yield. Oxidation with an aqueous sodium hypochlorite solution afforded 95% of maleimide **115**, which was converted to polycitrin A (**112**) in a few steps.



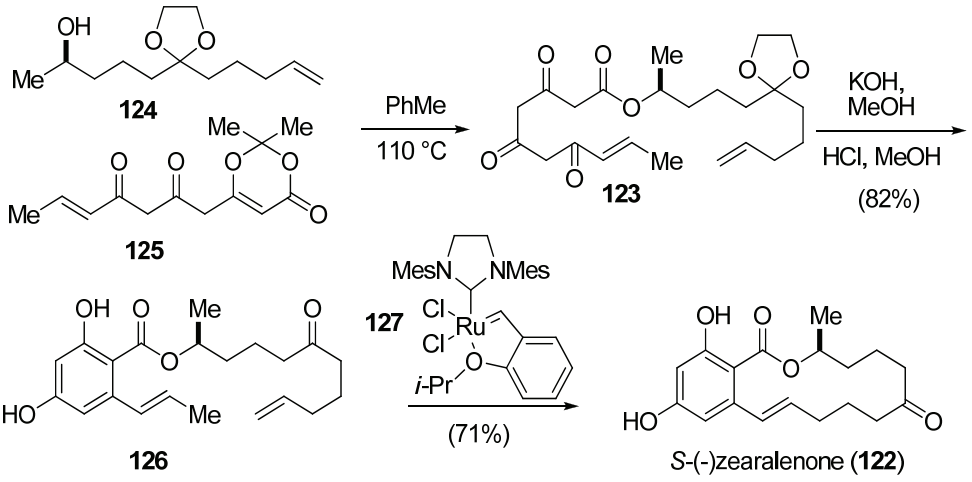
Scheme 26 Total synthesis of polycitrin A (**112**)

The total synthesis of lamellarin L (**116**), achieved by W. Steglich and coworkers, appears to be an elegant example for the biomimetic formation of pyrrole containing alkaloids.[30] Coupling of two different arylpyruvate units **117** and **118** gave diketone **119**, which was converted into pyrrole **121** by heating with amine **120**. Pyrrole **121** was converted to lamellarin L (**116**) in few steps with 38% overall yield.



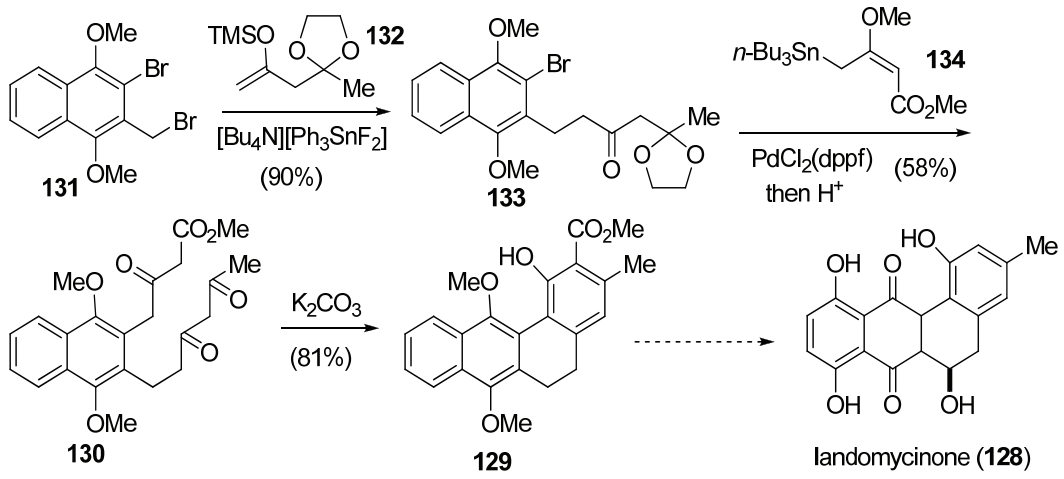
Scheme 27. Total synthesis of lamellarin L (**116**) by W. Steglich

Recently a concise synthesis of *S*-(-)-zearalenone (**122**) using an efficient late stage aromatization of polyketone **123** has been published.[31] Heating of alcohol **124** together with ester **125** afforded via a transesterification reaction formation of tetraketone **123**. Obtained ketone underwent aromatization under basic conditions to give resorcinol **126** in 82%. Finally, treatment with Hoveyda-Grubbs catalyst (**127**) completed the total synthesis of *S*-(-)-zearalenone (**122**) in a very efficient manner.



Scheme 28. Total synthesis of *S*-(-)-zearalenone (**122**)

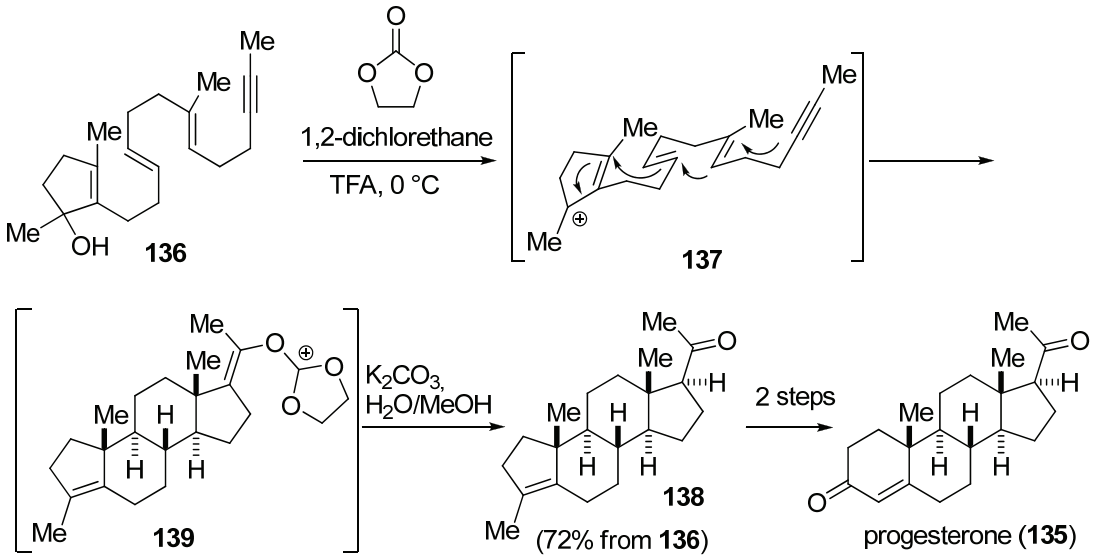
A possible precursor of the potent antibiotic landomycinone (**128**), tetracyclic compound **129** was synthesized following a biomimetic formation of the resorcylate ring by cylization of triketone **130**.[32] The dimethoxy naphthalene derivative **130** with two vicinal side chains was prepared by reaction of the dibromide **131** with silyl ether **132** ($[Bu_4N][Ph_3SnF_2]$-catalysis) followed by Stille reaction of **133** with stannane **134**. Acidic hydrolysis gave the triketo ester **130** that cyclized in a biomimetic-type reaction to the highly substituted dihydro benz[*a*]anthracene **129**.



Scheme 29. A biomimetic approach to landomycinone (**128**)

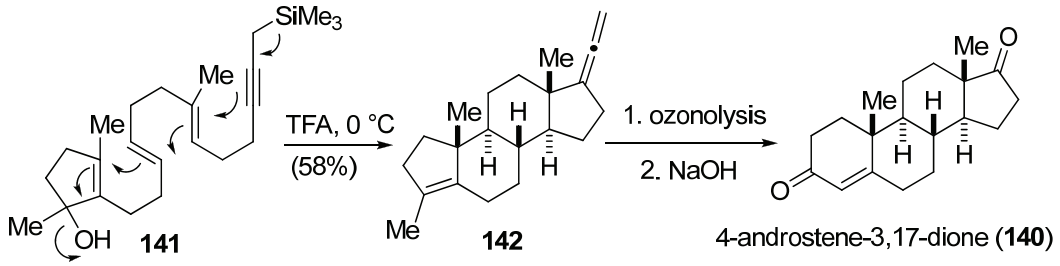
Cascade cation-π cyclizations

Fifty-three years ago, Gilbert Stork and Albert Eschenmoser independently proposed that the steroid ring system could be formed by tandem cation-π cyclizations of a polyene in an ordered transition state.[33] A non-enzymatic version of this reaction type was demonstrated in W. S. Johnson's classic synthesis of progesterone (**135**) in 1971 (**Scheme 30**).[34] Treatment of trienyne **136** with trifluoroacetic acid gave rise to cation **137** which cyclized cleanly to ketone **138** in excellent yield after hydrolysis of intermediate **139**. Unlike the enzymatic cation-π cyclizations used to form steroids in nature, Johnson's procedure produces progesterone as a racemate. Nevertheless, the striking cation-π cyclization strategy has proven to be very general for steroid synthesis and many other (racemic and enantioselective) variants have been developed by Johnson and others.



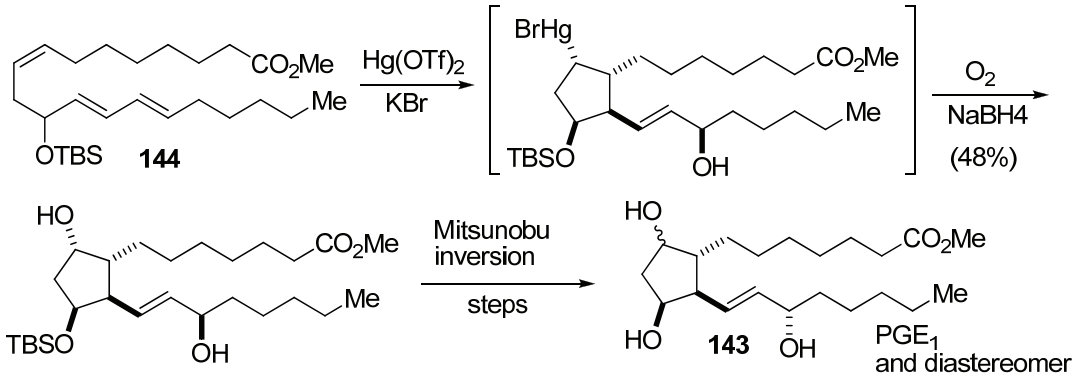
Scheme 30. Johnson's classic synthesis of progesterone (**135**)

For example, in the synthesis of 4-androstene-3,17-dione (**140**), published in 1980, Johnson *et al*. developed an improved cation-π-cyclization of propargyl silane functionalized polyene **141**.[35] The role of the propargyl silane function is to terminate the cation-π-cyclization by elimination of trimethylsilyl cation as shown in Scheme **31**. Ozonolysis of obtained allene **142** afforded the desired 4-androstene-3,17-dione (**140**).



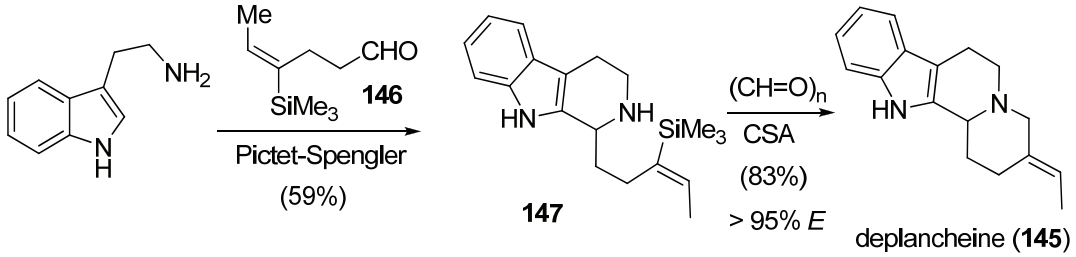
Scheme 31. Johnson's synthesis of 4-androstene-3,17-dione (**140**).

Cationic cyclization can be used for the synthesis of prostaglandins as well. The total synthesis of PGE_1 (**143**), published in 1982 by Japanese authors, involves a stereocontrolled bromomercuration cyclization of polyene **144**.[36] Although the wrong stereochemistry at C-11 was obtained, it was inverted under Mitsunobu conditions to reach the structure of PGE_1.



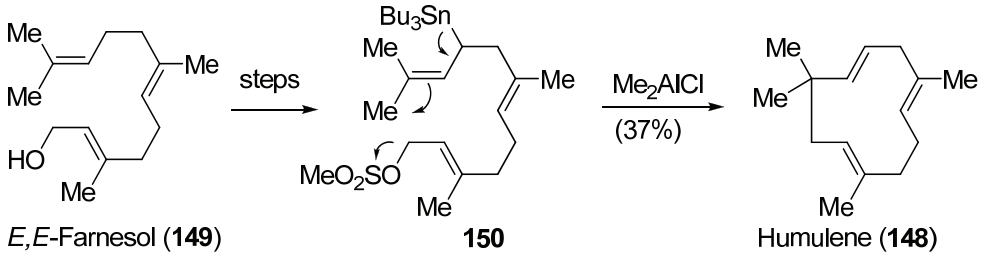
Scheme 32. Cationic cyclization applied to the synthesis of prostaglandins

A stereospecific iminium ion – vinylsilane cyclization was applied as a key reaction in Overman's synthesis of indoloquinolizidine alkaloid *dl*-deplancheine (**145**) in 1982.[37] Subjecting tryptamine hydrochloride in a Pictet-Spengler reaction with aldehyde **146** afforded vinylsilane **147**. Heating of **147** with paraformaldehyde and camphorsulphonic acid gave the indoloquinolizidine structure of alkaloid deplancheine **145** with complete retention of stereochemistry at the exocyclic double bond.



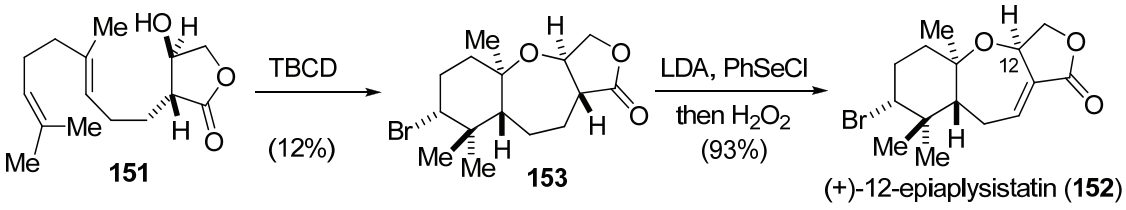
Scheme 33. Overman's synthesis of deplancheine (**145**)

The total synthesis of humulene (**148**) by Corey and coworkers is an interesting example for the formation of a macrocycle by cation olefin cyclization of mesylate **150** (Scheme 9).[38] Stannane **150**, prepared in few steps from *E,E*-farnesol (**149**), was treated with dimethylaluminium chloride to get humulene (**148**).



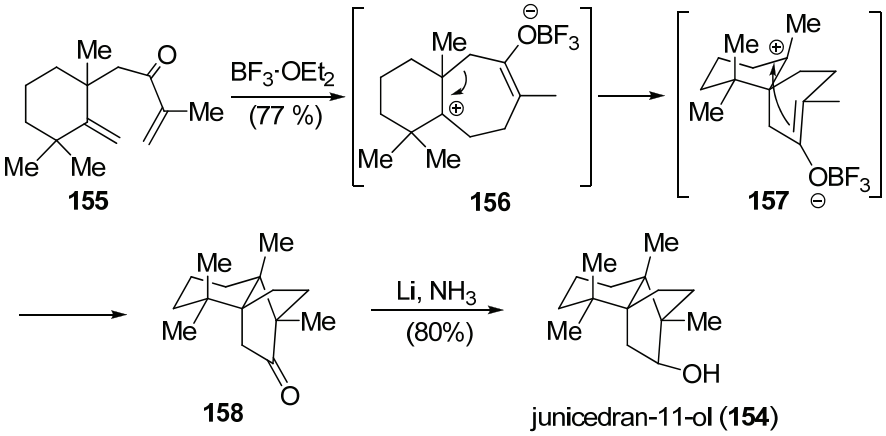
Scheme 34. Total synthesis of humulene (**148**) by Corey

A number of marine natural products could be prepared by bromonium ion-initiated cyclizations of sesquiterpenes. Biomimetic studies toward the synthesis of (-)-aplysistatin, published in 1982, showed that treatment of lactone **151** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCD) in dry nitromethane afforded cyclization to form, however, mostly the wrong diastereomer of dihydroaplysistatin **152**.[39] The ratio of products was 19:81 of 7,8-dihydroaplysistatin and the corresponding 12-epi isomer. An improved synthesis of (-)-aplysistatin was reported in 1984 by Japanese authors who performed a mercuric ion-induced brominative cyclization of **151** to obtain a 2:1 ratio of products.[40]



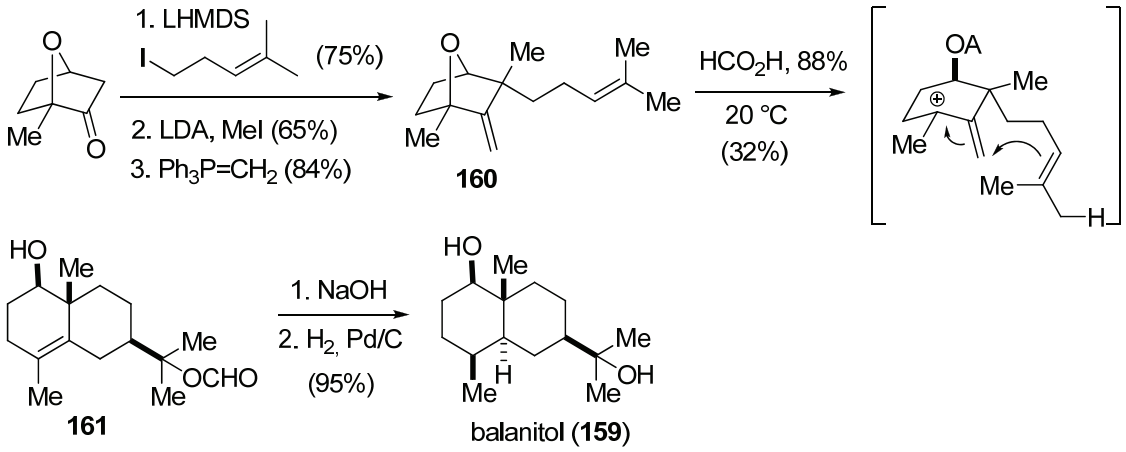
Scheme 35. Synthesis of (+)-12-epiaplysistatin (**152**) by bromonium ion-initiated cyclization

Another type of cascade cation-π cyclization for the synthesis of tricyclic sesquiterpene junicedran-11-ol (**154**) was published by Indian authors in 1997.[41] The synthesis involved a biogenetically patterned carbenium ion mediated cyclization of sesquiterpene **155** with subsequent rearrangement of carbocation **156** to spiro intermediate **157** which underwent final cationic cyclization to form ketone **158**, and then junicedran-11-ol (**154)** after reduction with lithium in liquid ammonia in a good yield.·



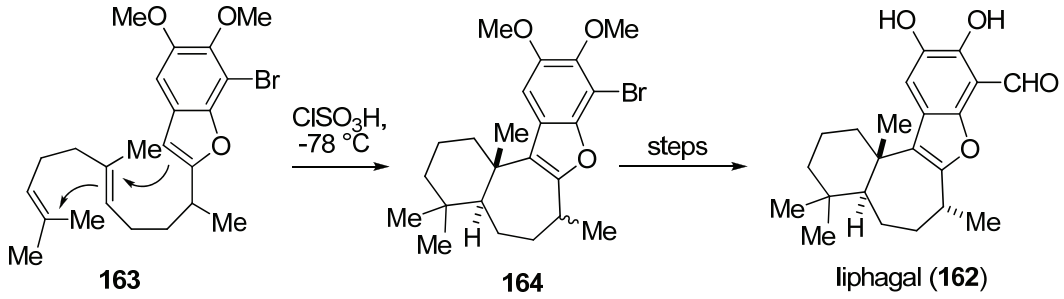
Scheme 36. Total synthesis of tricyclic sesquiterpene junicedran-11-ol (**154**)

The *trans*-decaline core can be found in many types of natural products. In the total synthesis of (±)-balanitol (**159**), published by Li *et al*., a characteristic eudesmane decalin ring system was constructed on the basis of an intramolecular electrophilic cation-olefin cyclization.[42] Formolysis of compound **160** in 88% fomic acid at 20 °C for 1.5 h afforded the corresponding decalin **161** in a stereoselective manner.



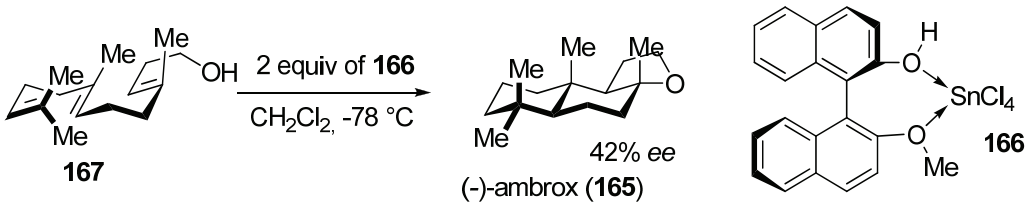
Scheme 37. Total synthesis of (±)-balanitol (**159**)

The autors of a very efficient synthesis of liphagal (**162**) proved the biogenetic pathway to this marine sponge metabolite by it's total synthesis applying a cascade cation-π cyclization for construction of the tetracyclic core of **162** (Scheme 8).[43] Treatment of benzofuran **163** with chlorosulfonic acid resulted in a region- and stereoselective cyclization to provide tetracyclic compound **164**, which is the direct precursor of liphagal (**162**).



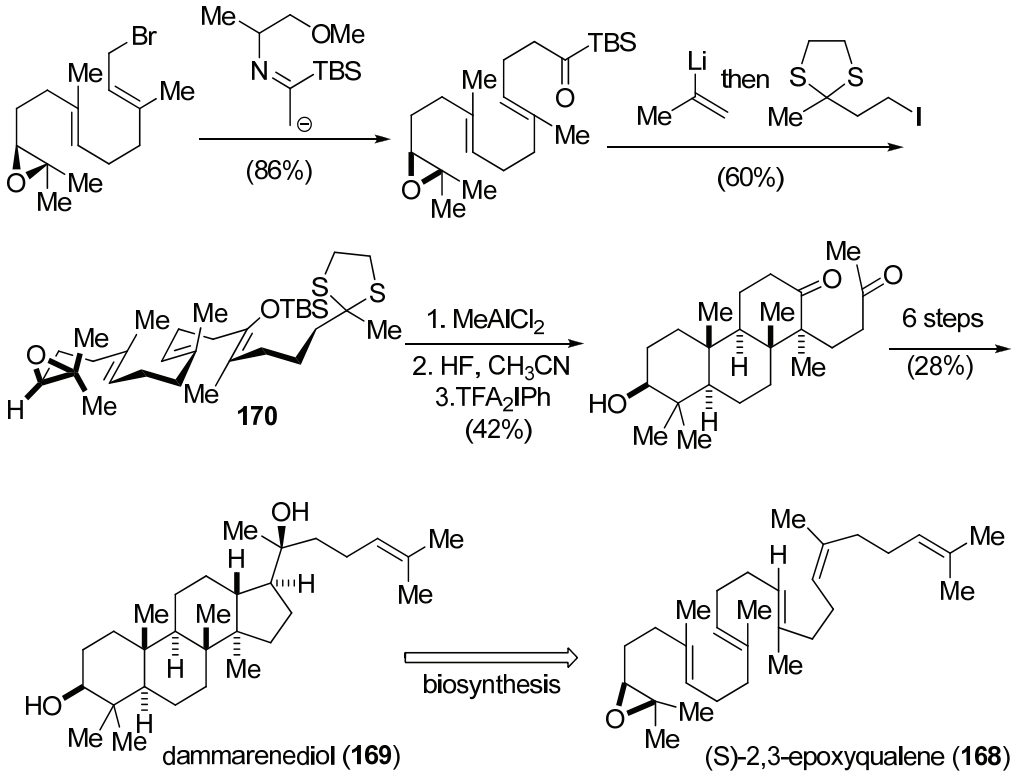
Scheme 38. Total synthesis of liphagal (**162**)

In 1999, Yamamoto developed the first enantioselective biomimetic cyclization of a polyprenoid using a Lewis acid-assisted chiral Brønsted acid (LBA) as an artificial cyclase and used it to synthesize (-)-ambrox (**165**).[44] In this synthesis binaphtol based LBA **166** was used for cyclization of trienol **167**, which proceeded with good diastereoselectivity but moderate *ee* value (**Scheme 39**).



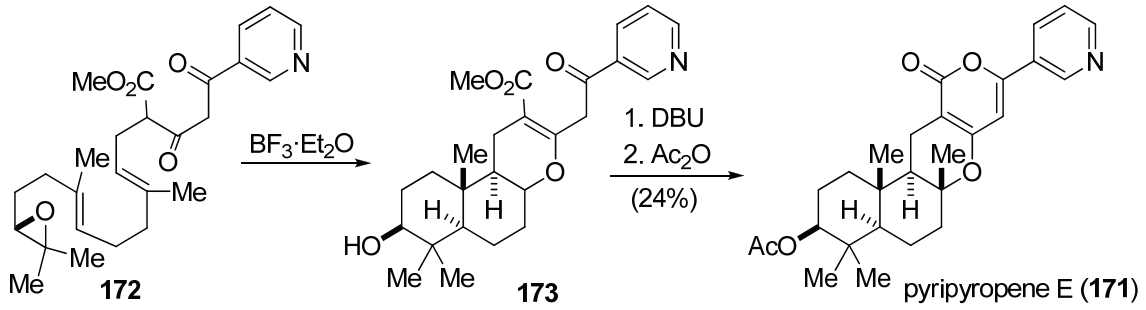
Scheme 39. Enantioselective total synthesis of (-)-ambrox (**165**).

(*S*)-2,3-Epoxysqualene (**168**) is cyclized in some plants primarily to dammarenediol (**169**). The first total synthesis of this tetracycle using a polyolefin cascade cyclization designed to mirror the biosynthetic transformation was reported by Corey in 1996.[45] In contrast to Johnson's use of fluorine to control the regioselectivity of C-ring formation (to cyclohexane instead of cyclopentane), a strategy later used in his own synthesis of dammarenediol,[46] Corey's strategy used an enolsilane **170** to direct C-ring formation during a biomimetic tricyclization (**Scheme 40**).



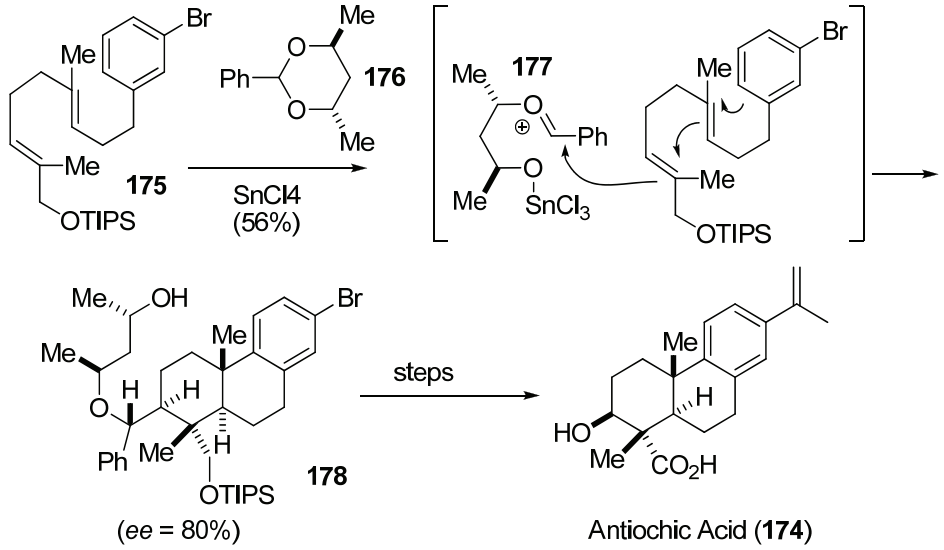
Scheme 40 Corey's synthesis of dammarenediol (**169**)

Biomimetic total synthesis of (+)-pyripyropene (**171**) was accomplished by A. Smith *et al.* [47] Epoxide **172** was treated with boron trifluoride diethyletherate to induce the formation of two C-C and one C-O bonds in a highly stereoselective manner. Base-catalyzed cyclization of **173** was achieved with DBU. A subsequent acylation gave pyripyropene E (**171**) in 24% overall yield.



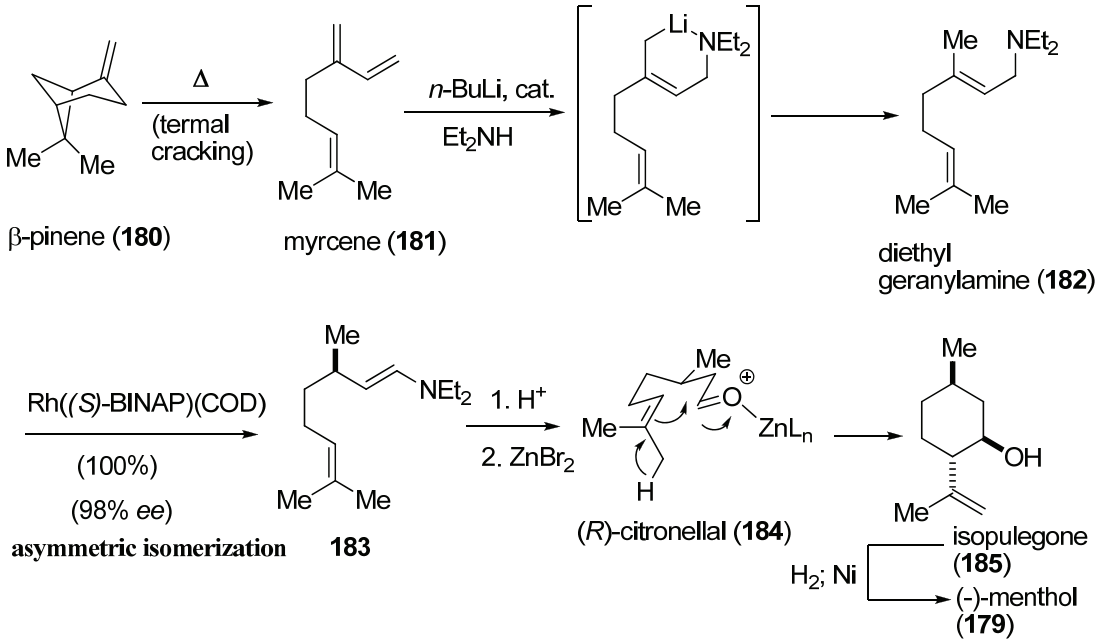
Scheme 41. Total synthesis of (+)-pyripyropene (**171**) by A. Smith

An asymmetric cascade cation-π cyclization in the total synthesis of antiochic acid (**174**) was recently published by Chinese authors.[48] The key reaction of polyene **175** with chiral acetal **176** under Lewis acid conditions proceeds with good diastereo- and enantioselectivity (**Scheme 42**). The origin of enantioselectivity could be explained by formation of a chiral carbonium cation as shown in the Scheme.



Scheme 42. Total synthesis of antiochic acid (**174**)

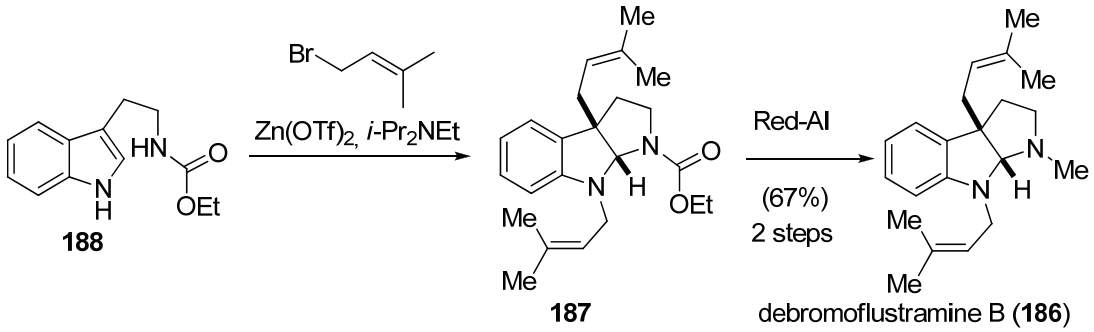
The Takasago corporation developed a highly practical and economically feasible commercial process for the production of (-)-menthol (**179**) based on a catalytic asymmetric biomimetic synthesis.[49] This synthesis begins with the termal cracking of β-pinene (**180**), which gives myrcene (**181**). Treatment of **181** with diethylamine and a catalytic amount of butyllithium afforded diethyl geranylamine (**182**). Amine **182** underwent a very efficient asymmetric isomerization with a rhodium binaphthyl catalyst to give enamine **183** with TON > 400,000, a quantitative yield and 98 % *ee*. Cleavage of enamine **183** was achieved with diluted sulfuric acid. The obtained citronellal (**184**) was treated with zinc bromide giving isopulegone (**185**). Hydrogenation of **185** in presence of a nickel catalyst afforded (-)-menthol (**179**).



Scheme 43. Commercial asymmetric synthesis of (-)-mentol (**179**)

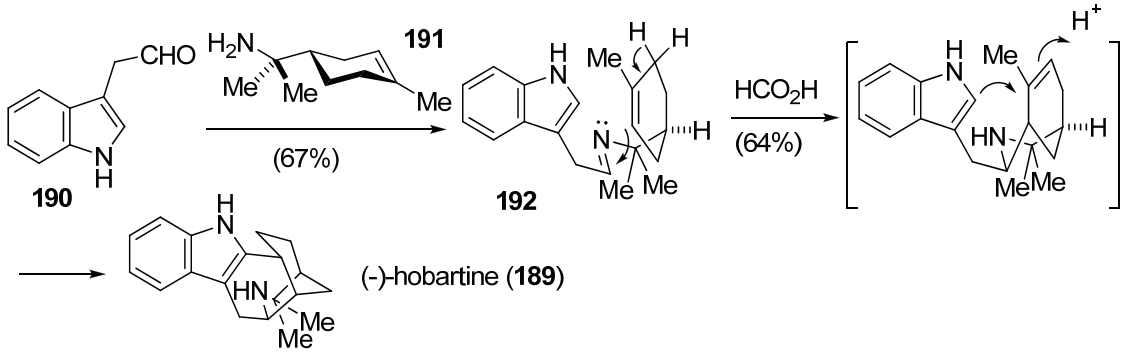
Many types of terpenoid indole alkaloids are formed by electrophilic cyclization. For example, debromoflustramine B (**186**) consists of a hexahydropyrrolo[2,3-*b*]indoline ring system, which is present in numerous alkaloid natural products. Biogenetically, it can be perceived to arise via electrophilic attack on a tryptophan or tryptamine unit at the indole C-3 position, followed by capture of the resulting C-2 iminium ion by the side-chain nitrogen. The authors of a short and efficient synthesis of debromoflustramine B (**186**) (three steps from

tryptamine, 57% overall), showed that the hexahydropyrrolo[2,3-*b*]indoline ring system (**187**) can be prepared by zinc triflate-mediated alkylation of tryptamine derivative **188**.[50]



Scheme 44. Total synthesis of debromoflustramine B (**186**)

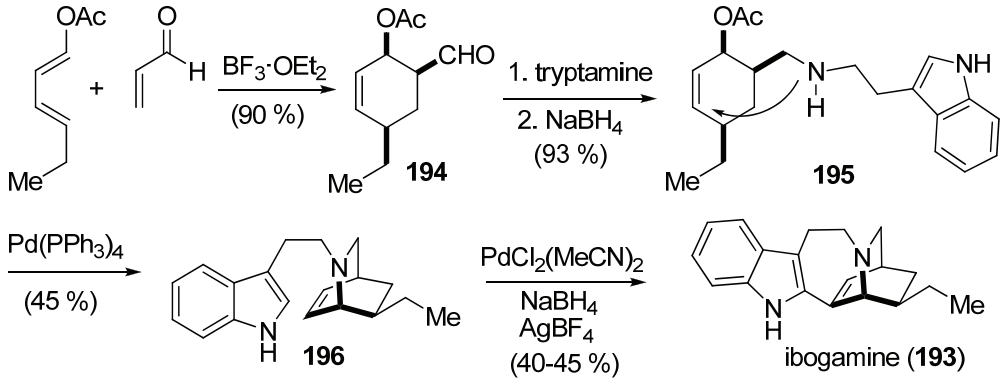
A total synthesis of indole monoterpene alkaloid (-)-hobartine (**189**) was published in 1984 by Borschberg and coworkers.[51] Condensation of indole-2-acetaldehyde (**190**) with chiral amine **191**, prepared from α-terpineol in few steps, gave imine **192**. Treatment of imine **192** with formic acid resulted in cationic cyclizations to give (-)-hobartine (**189**) as a single product in 64% yield.



Scheme 45. Total synthesis of indole monoterpene alkaloid (-)-hobartine (**189**)

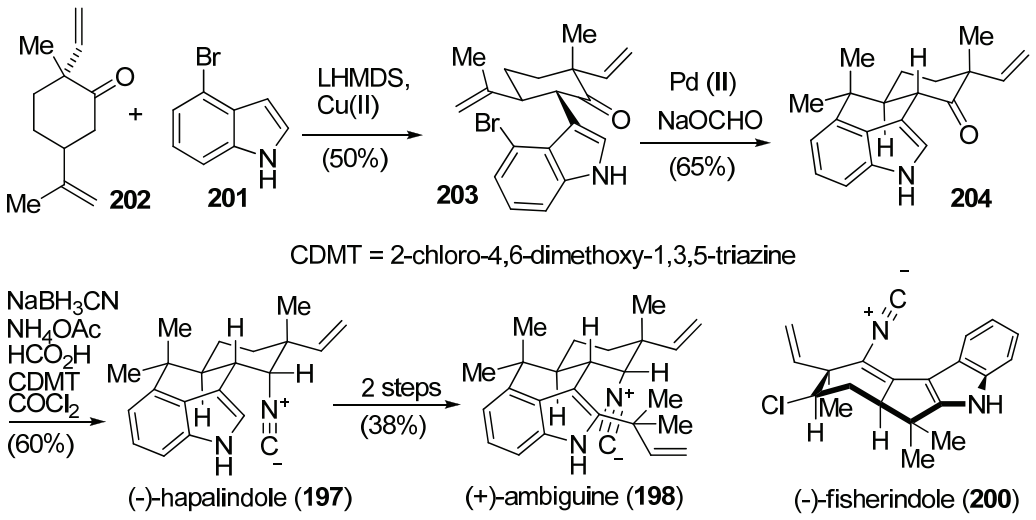
Metal-catalyzed reactions could mimic biogenetic cationic cyclization pathways. For example, B. Trost's synthesis of indole alkaloid ibogamine (**193**) is based on Pd-catalyzed reactions.[52] Condensation of aldehyde **194** with tryptamine and reduction of the obtained imine with $NaBH_4$ afforded amine **195**. A further metal catalyzed transformation of **195** with 3-6% of $Pd(PPh_3)_4$ gave quinuclidine **196** in 45% yield. Treatment of obtained compound with $PdCl_2(MeCN)_2$ and $AgBF_4$ followed by reduction of Pd-intermediates with $NaBH_4$ gave

racemic ibogamine (**193**) in 40-45 % yield. The asymmetric synthesis of this alkaloid is also reported in the same article.



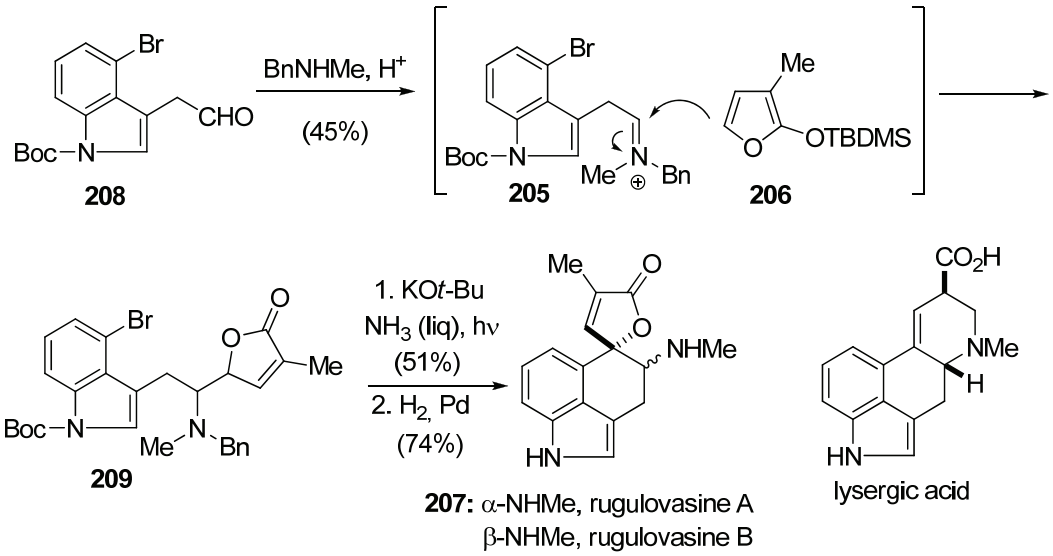
Scheme 46. B. Trost's synthesis of ibogamine (**193**)

The total synthesis of hapalindole U (**197**) and ambiguine H (**198**) was recently reported by P. Baran.[53] Welwitindolinone A (**199**), and fischerindole (**200**) were also synthesized using similar strategy. Oxidative coupling of 4-bromoindole (**201**) and ketone **202** gave compound **203**. Reductive intramolecular Heck reaction in a Pd/sodium formiate system afforded tetracyclic compound **204**, which was converted to isonitrile (-)-hapalindole **197** in one pot and 60 % yield.



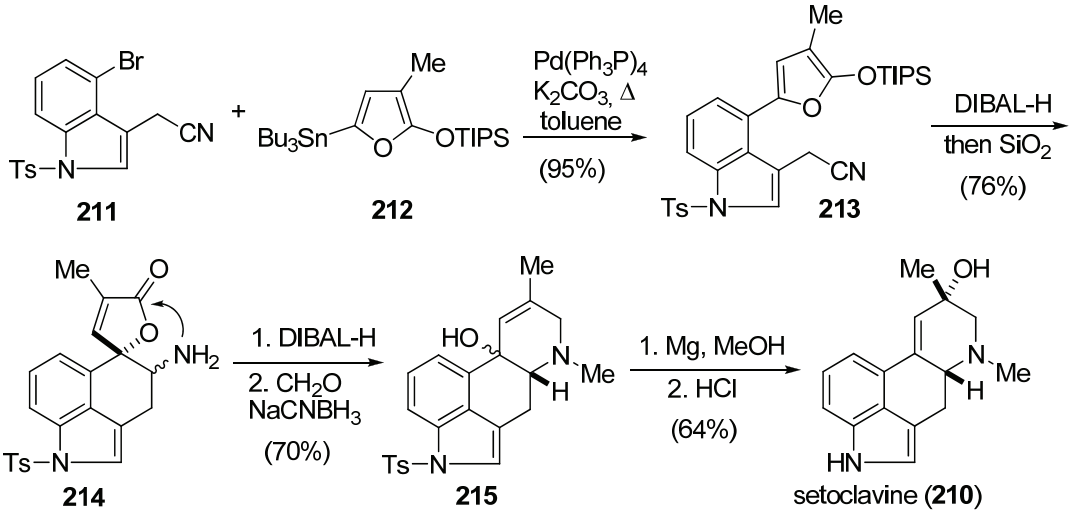
Scheme 47. Total synthesis of hapalindole U (**197**) and ambiguine H (**198**) by P. Baran

Ergot alkaloids represent a significant interest due to their unprecedented biological activity. A general strategy for the synthesis of some *Ergot* alkaloids could be a vinylogous Mannich reaction of tryptiminium salt **205** and substituted furan **206** (**Scheme 48**). Concise total synthesis of rugulovasines A and B (**207**) was performed in seven chemical operations from commercially available matherials.[54] Condensation of the indol-2-acetaldehyde **208** with N-benzyl-N-methylamine followed by reaction of the iminium salt **205,** produced *in situ*, with the furan **206** gave butenolide **209** as a mixture of diastereomers. Cyclization of **209** via an $S_{RN}1$-reaction then provided the tetracyclic core structure**,** which was further deprotected to give a mixture (1:2) of rugulovasines.



Scheme 48. S. F. Martin's total synthesis of rugulovasines A and B (**207**)

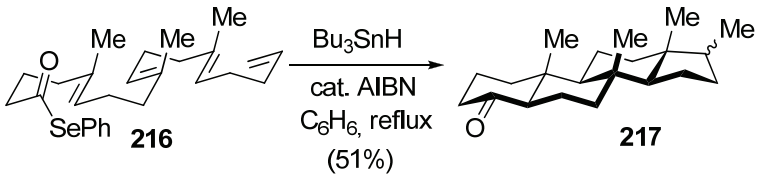
An improved approach to *Ergot* alkaloids is based on an intramolecular vinylogous Mannich reaction, which provides quick access to ruguvolasines A and B (**207**) and also setoclavine (**210**) (**Scheme 49**).[55] Stille coupling of bromoindol **211** and furan **212** gave adduct **213** which was reduced with diisobuthylaluminium hydride. Obtained iminium salt underwent spontaneous cyclization to afford spirocyclic butenolides **214**. Reduction of **214** with DIBAL-H provided an intermediate amino lactol which underwent facile isomerization and dehydration to generate a mixture of epimeric dihydropyridines **215**. This mixture of isomers was treated with acid to furnish 64% of racemic setoclavine (**210**) after deprotection.



Scheme 49. An improved approach to *Ergot* alkaloids by S. F. Martin

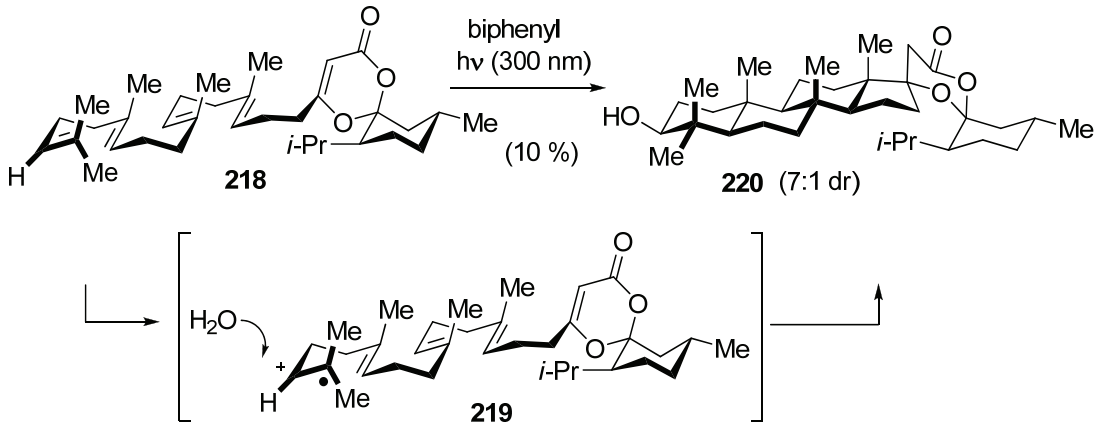
Radical mediated biomimetic coupling, cyclizations and rearrangements

Some biogenetic enzyme catalyzed processes transformation of molecules can be mimicked by radical mediated cyclizations or rearrangement reactions. For the synthesis of steroid structures radical-π cyclization cascade can be used, and it can provide a high level of diastereoselection. For example, the reaction of acyl selenide **216** and Bu_3SnH-AIBN effects a tetracyclization to give ketone **217**.[56]



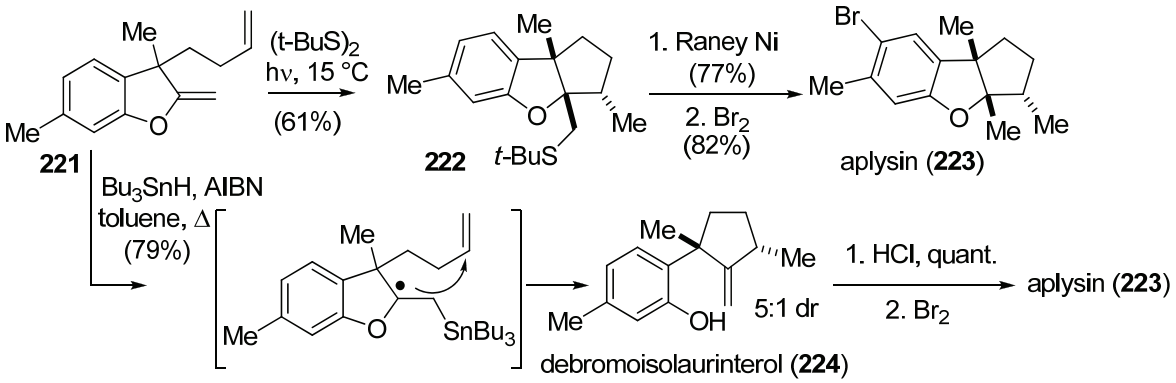
Scheme 50. An example of a radical-π cyclization cascade for synthesis of steroids

This strategy was more recently elaborated to a short biomimetic synthesis of a steroidal skeleton.[57] (-)-Menthone was used as a remote chiral auxiliary on a terminus of the polyalkene (**218**). Photoinduced electron transfer then initiated the polycyclization by formation of radical cation **219**. From the ensuing cascade, eight stereogenic centers were created to form only two of the greater than 200 possible isomers (**Scheme 51**). The resulting ketal **220** is formed in 10% yield as a 7:1 diastereomeric mixture and >99% ee, showcasing a remarkable example of remote asymmetric induction.



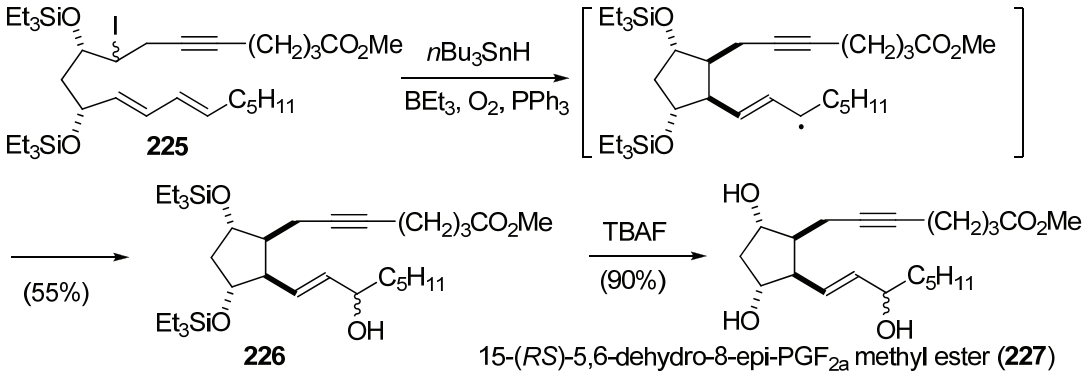
Scheme 51. Enantioselective steroid synthesis by radical-π cyclization cascade

A general approach to the aplysin group of natural products was developed by P. Howes *et al*.[58] Irradiation of a mixture of diene **221** and (*t*-BuS)$_2$ at 15 °C provided the product of a radical addition-cyclization **222** with 61% yield and 98% diastereoselectivity. Reductive desulfation with Raney nickel followed by bromination gave racemic aplysin (**223**). Exposure of diene **221** to standard conditions (AIBN, Bu_3SnH, heat) or just heating of compound **221** gave debromoisolaurinterol (**224**) as a 5:1 or 7:1 mixture of diastereomers, respectively. This compound underwent very facile cyclization under acid catalysis to give debromoaplysin in quantitative yield.



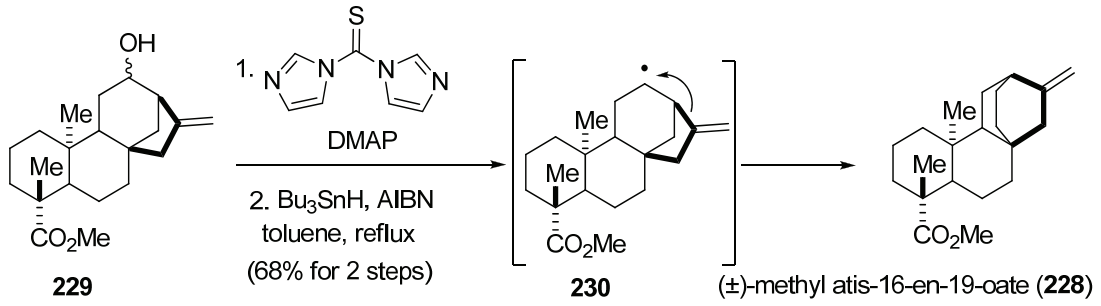
Scheme 52. Radical-π cyclization in the synthesis of aplysin (**223**)

Radical cyclization reactions have been used for construction of prostaglandin-type of products. For example, radical-mediated cyclization of linear polyene **225** resulted in the formation of *cis*-cyclopentadienyl structure of the isoprostane series. The key step includes the cyclization reaction of iodo-precursor **225** under radical conditions (Bu_3SnH, BEt_3) under a stream of dry argon followed by injection of dry air and, finally, addition of Ph_3P as reducing agent. Cleavage of silyl protecting groups of **226** gave 15-(*RS*)-5,6-dehydro-8-*epi*-PGF_{2a} methyl ester (**227**) in good yield.



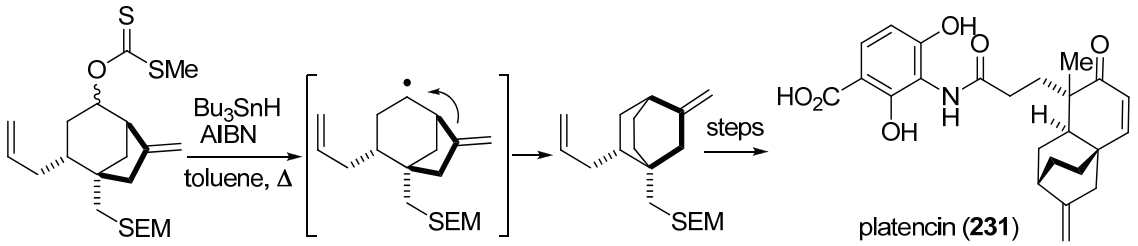
Scheme 53. Radical mediated synthesis of prostaglandin-type compounds

A biomimetic reaction, the rearrangement of [3.2.1]bicycle **229** into the corresponding [2.2.2]bicyclooctane structure has been accomplished by M. Toyota and coworkers in the last step of a synthesis of (±)-methyl atis-16-en-19-oate (**228**) (**Scheme 11**).[59] Preparation of imidazolyl thiocarbonates from a diastereomeric mixture of alcohols **229**, followed by radical hydrogenation resulted in deoxygenation and skeletal rearrangement of radical intermediate **230** with stereoselective formation of the more stable [2.2.2]bicyclooctane molecule **228**.



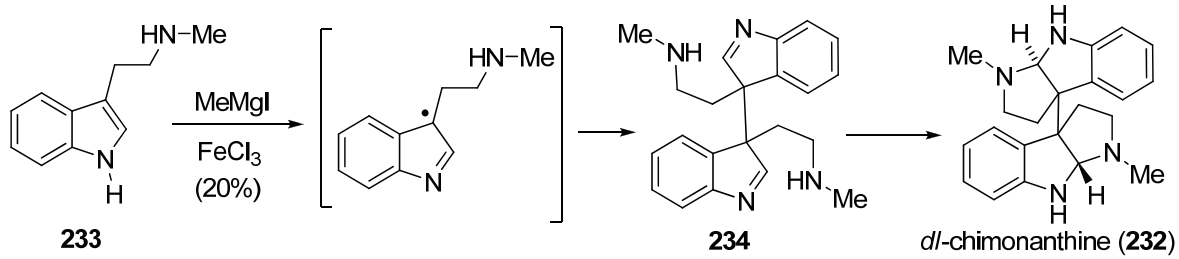
Scheme 54. Biomimetic total synthesis of (±)-methyl atis-16-en-19-oate (**228**)

The [2.2.2]bicyclooctane moiety of platencin might be biogenetically produced by enzyme catalyzed rearrangement of [3.2.1]bicyclooctane terpenes. This reaction could be mimicked by applying radical conditions. This strategy was successfully applied in Nicolaou's first synthesis of platencin (**231**).[60] This transformation and conditions are similar to that in the previous synthesis of methyl atis-16-en-19-oate (**228**) reported by M. Toyota.



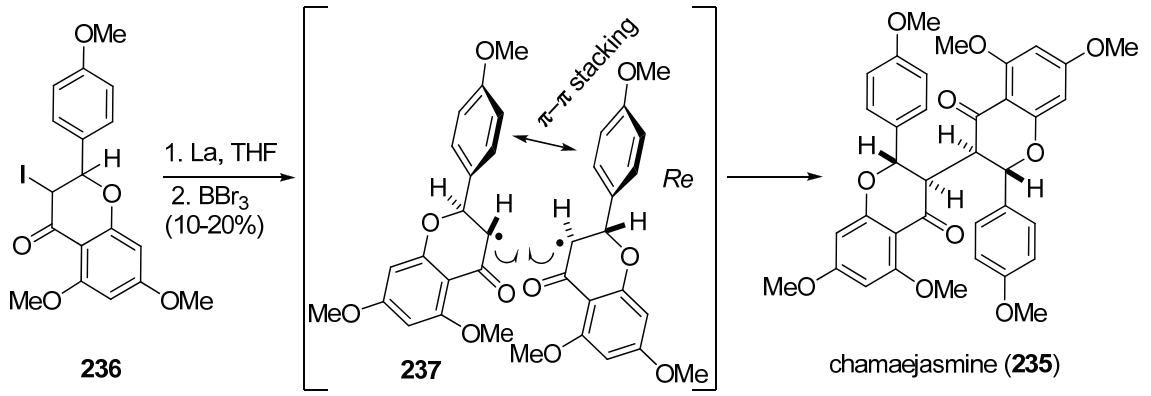
Scheme 55. Key step in Nicolaou's total synthesis of platencin (**231**)

Homolytic coupling is widely used for preparation of dimeric natural products. For example, a very efficient synthesis of *dl*-chimonanthine (**232**), was reported by A. Scott in 1964.[61] Treatment from N-methyltryptamine (**233**) with MeMgI followed by addition of ferric chloride induced formation of dimerized product **234** which was further cyclized to give *dl*-chimonanthine (**232**).



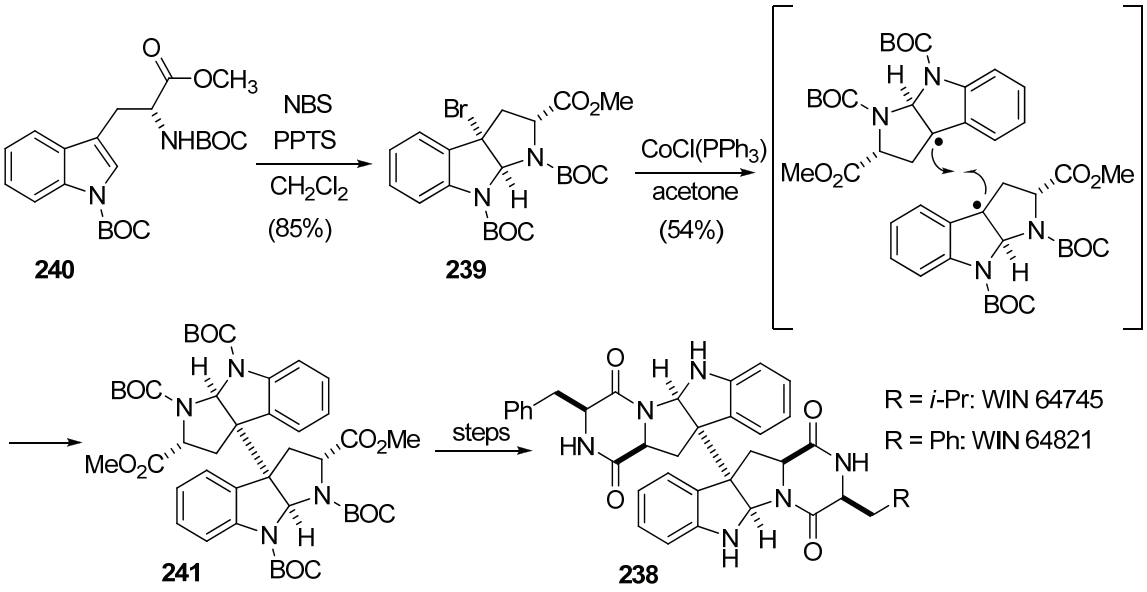
Scheme 56. Synthesis of *dl*-chimonanthine (**232**) by A. Scott

The traditional Chinesee herbal medicine, *Stellera chamaejasmae* L., has yielded an unusual biflavanone, chamaejasmine (**235**, **Scheme 57**). Li and coworkers found that metallic lanthanum in refluxing THF reductively homocoupled the requisite alkyl iodide (**236**) in a highly stereoselective radical mediated process, to form chamaejasmine (**235**) in 10–20% yield, after global deprotection.[62] The authors believe that π–π stacking interactions of radical intermediates **237** might be responsible for directing the predominate *Re–Re* facial selective dimerization of **236**.



Scheme 57. Radical dimerization in the synthesis of chamaejasmine (**235**)

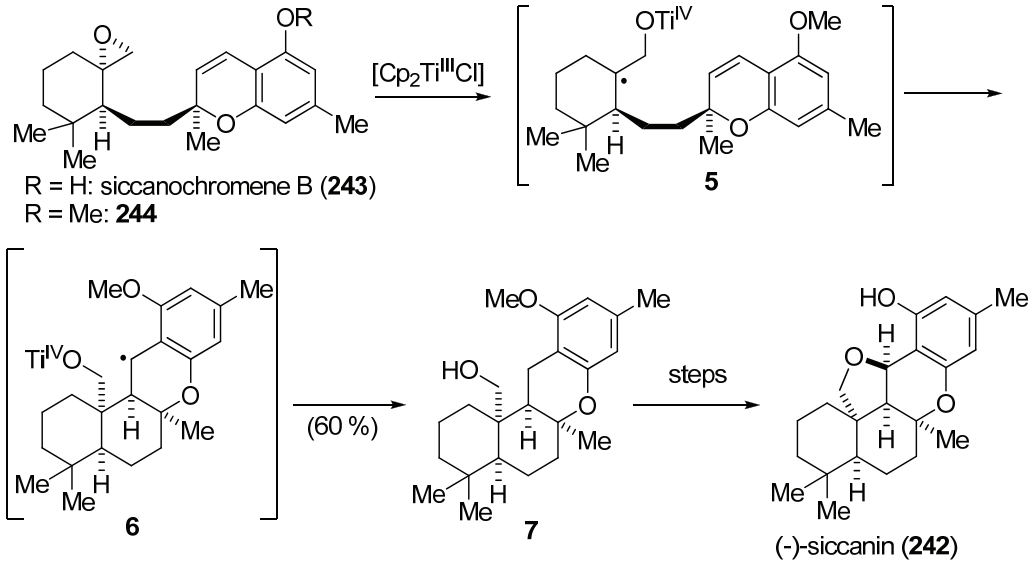
In 2008 bispyrrolidinoindoline diketopiperazine alkaloids WIN 64745 and 64821 (**238**) were synthesized by Co-catalyzed radical coupling of **239** which was prepared in few steps from commercially available amino acids.[63] Bromination of tryptophan derivative **240** resulted in cyclization providing bromoindoline **239**, which was smoothly converted to a bispyrrolidinoindoline **241**, using $CoCl(PPh_3)$ in acetone. This might be a general route to such type of indole alkaloids.



Scheme 58. Radical dimerization in the synthesis of WIN 64745 and 64821 (**238**)

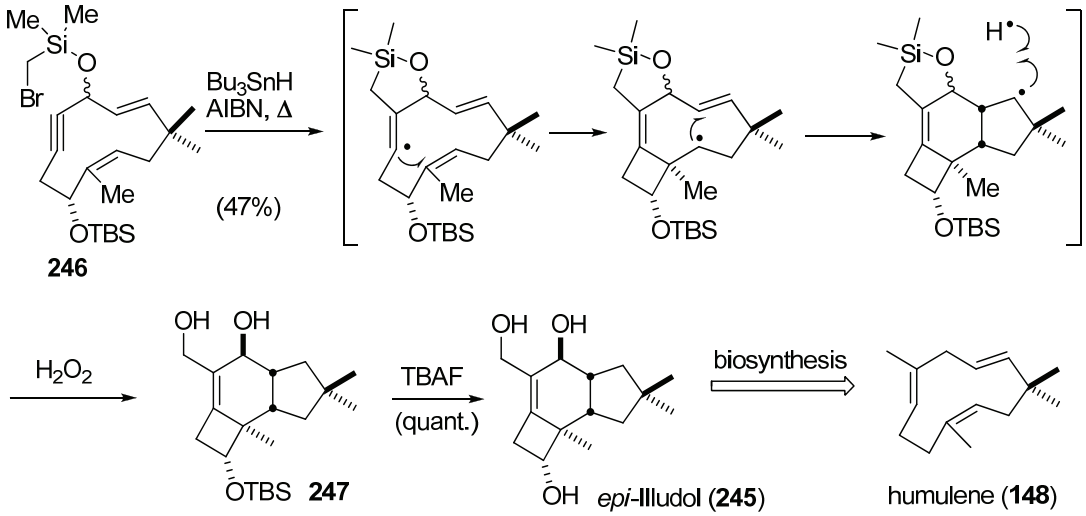
(-)-Siccanine (**242**), isolated in 1962, possesses an unusual *cis*,*syn*,*cis*-fused alicyclic ring system and also interesting biologic activity. The proposed biosynthesis of this substance

includes epoxyolefin cyclization of siccanochromene B (**243**). The biomimetic synthesis of (-)-siccanin (**242**) reported by B. Trost is based on a radical mediated cyclization of epoxide **244** which proceeded with good yield and stereoselectivity (**Scheme 59**).[64]



Scheme 59. B. Trost's synthesis of (-)-siccanin (**242**)

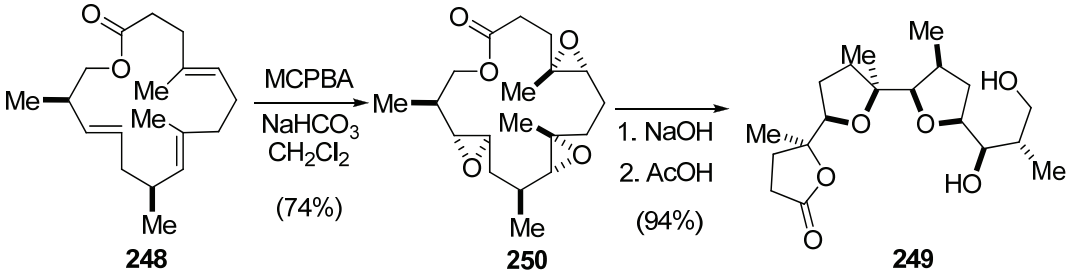
A biomimetic transannular radical cyclization for the total synthesis of *epi*-illudol (**245**) was successfully realized in 1997 by M. Malacria and coworkers.[65] In nature this tricyclic compound is produced from humulene (**148**) (**Scheme 60**). Heating of bromomethyl silane **246** with tributyltin hydride resulted in a radical cyclization cascade reaction to produce the core structure of illudol **247** in 47 % yield. Oxidation and deprotection of compound **247** afforded *epi*-illudol (**245**).



Scheme 60. Biomimetic transannular radical cyclization in the synthesis of *epi*-illudol (**148**)

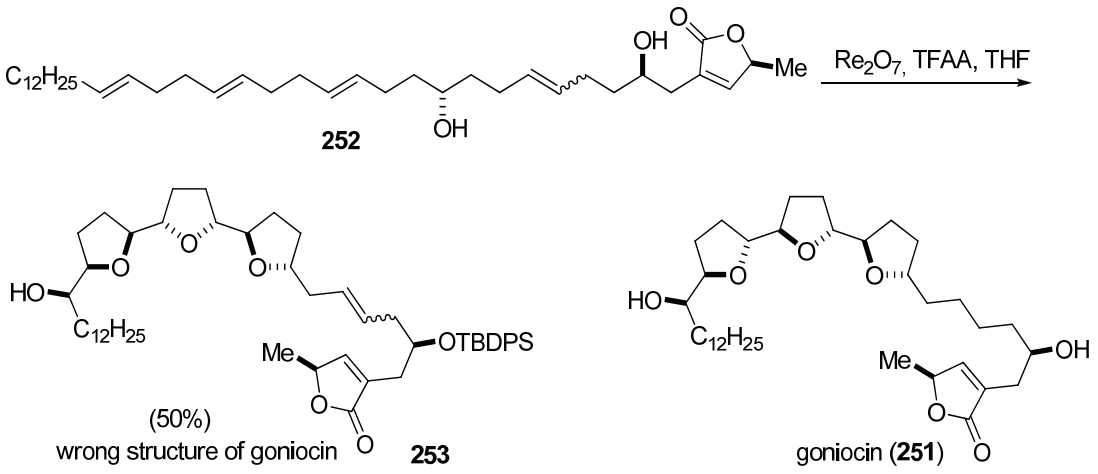
Biomimetic oxydative cyclization of polyenes (synthesis of polyethers)

In 1986 authors were able to prove the hypothesis of a two step biogenetic synthesis of polyethers through polyepoxyde intermediates, by producing polyether **249** in good yield and stereoselectivity.[66] Epoxydation of triene lactone **250** with *m*-CPBA, and basic hydrolysis of triepoxide **248** followed by acidic lactonization resulted in the diastereoselective formation of polyether **249** (**Scheme 61**).



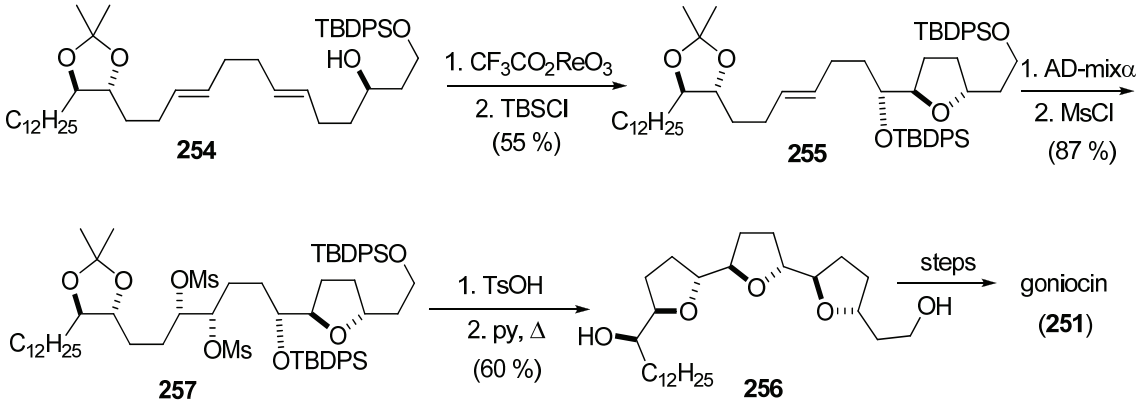
Scheme 61. Stereoselective synthesis of polyether **249** through polyepoxide cyclization

Another hypothesis involving metal-mediated hydroxylation of polyenes could not be proven in an attempt to synthesize goniocin (**251**) by rhenium mediated hydroxylation of **252**.[67] The obtained polyether **253** displayed wrong stereochemistry (*trans,threo,cis,threo,cis,threo*) instead of the desired (*trans,threo,trans,threo,trans,threo*) configuration (**Scheme 62**).



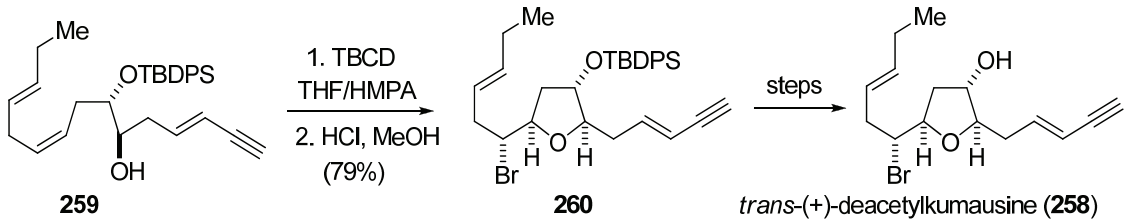
Scheme 62. Rhenium mediated hydroxylation of polyene **252**

The successful approach to goniocin (**251**) defined the correct stereochemistry on the first THF ring by treatment of diene **254** with $CF_3CO_2ReO_3$ in TFA to yield tetrahydrofuranyl compound **255** (**Scheme 63**).[68] Compound **255** was converted into tris-tetrahydrofuranyl **256** by asymmetric dihydroxylation of **255** and ring closure of bismesylate **257**.



Scheme 63. Total synthesis of goniocin (**251**)

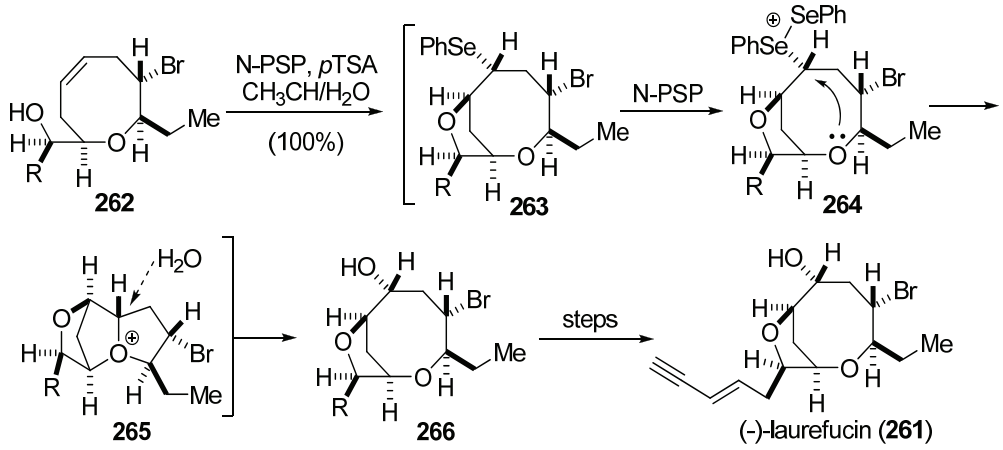
Some tetrahydrofuran-containing natural products can be synthesized by bromoetherification cyclization of unsaturated linear molecules. For example *trans*-(+)-deacetylkumausyne (**258**) was prepared by mild bromination of compound **259** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD) as source of Br^+.[69] After cleavage of the THP-group, the desired tetrahydrofuran **260** was obtained stereoselectively in good yield.



Scheme 64. Synthesis of *trans*-(+)-deacetylkumausyne (**258**) by bromoetherification

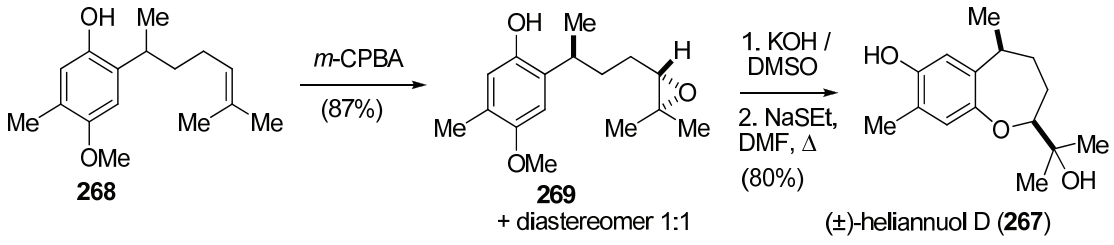
Biomimetic asymmetric total synthesis of (-)-laurefucin (**261**) via an organoselenium-mediated intramolecular hydroxyetherification was recently reported by Korean authors.[70] The treating of oxacycle **262** with *N*-phenylselenophthalimide (N-PSP) in the presence of *p*TSA generated an α-selenonium ion, which was converted via intramolecular cyclization to selenoether **263**. Subsequent activation of the phenylselenyl group of this compound by

exposure to an excess of N-PSP, followed by transannular cyclization of **264** through intramolecular attack by the oxocane oxygen atom produced the pivotal dioxatricyclic oxonium intermediate **265**, which led to hydroxyether **266** by reaction with water with an overall double inversion. This very efficient and stereospecific transformation goes with quantitative yield, allowing to produce the natural product (-)-laurefucin (**261**) in few steps.



Scheme 65. Total synthesis of (-)-laurefucin (**261**)

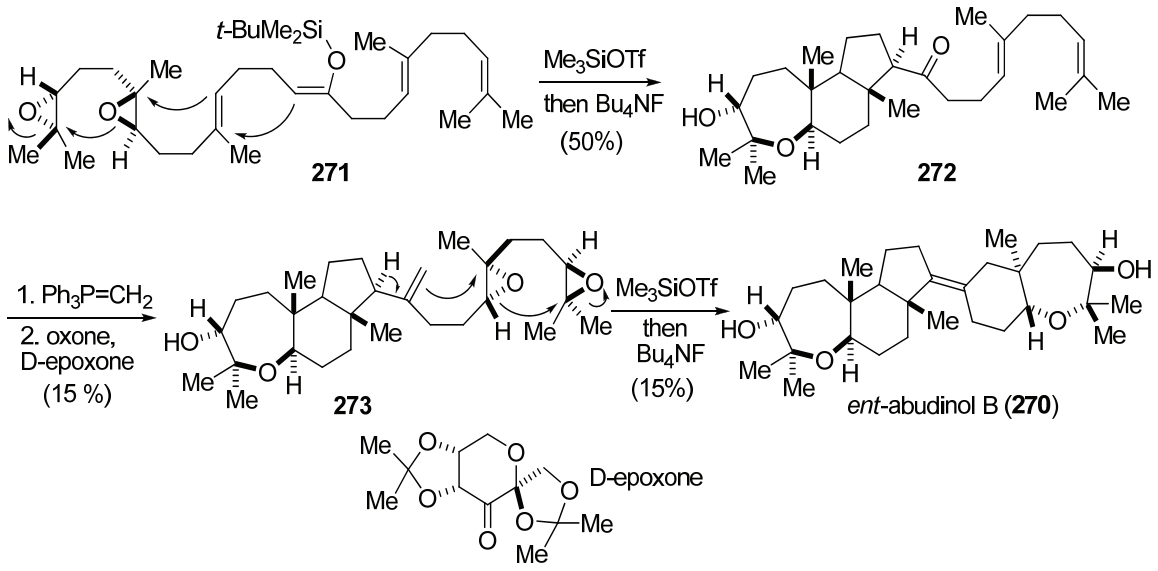
An epoxide opening cyclization strategy was applied toward the synthesis of (±)-heliannuol D (**267**) and its epimer.[71] The benzoxepane moiety of the title compound, a common structural feature of the heliannuol family of natural products, was prepared by intramolecular opening of epoxide **269** with phenol under basic conditions. Cleavage of aromatic methoxy function afforded corresponding natural product (±)-heliannuol D (**267**) in good yield.



Scheme 66. Synthesis of (±)-heliannuol D (**267**)

The total synthesis of triterpene natural product abudinol B (**270**) was recently published by F. McDonald *et al*.[72] This synthesis closely mimics the proposed biosynthetic pathway,

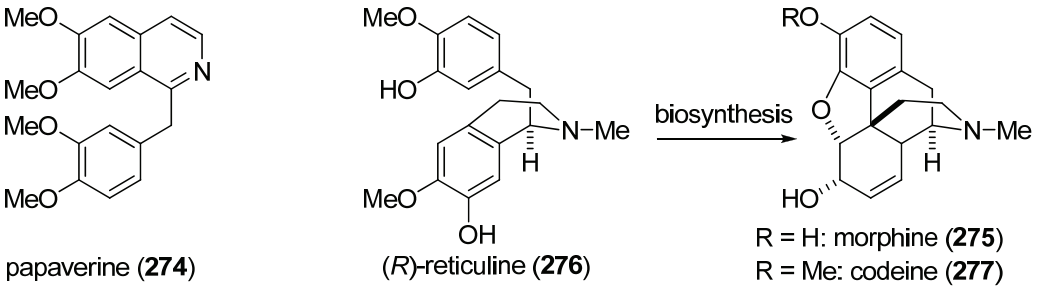
which involves cyclization of squalene-like linear precursor **271**. First, tricyclization of diepoxide **271** was achieved with trimethylsilyl triflate with 50 % yield. In this reaction two C-C bonds and one C-O bond were formed with high stereoselectivity to get 50 % yield of compound **272**. A second bicyclization of diepoxide **273** with formation of one C-C and one C-O bonds gave 15 % of *ent*-abudinol B (**270**) along with unreacted intermediates and isomers.



Scheme 67. Total synthesis of *ent*-abudinol B (**270**)

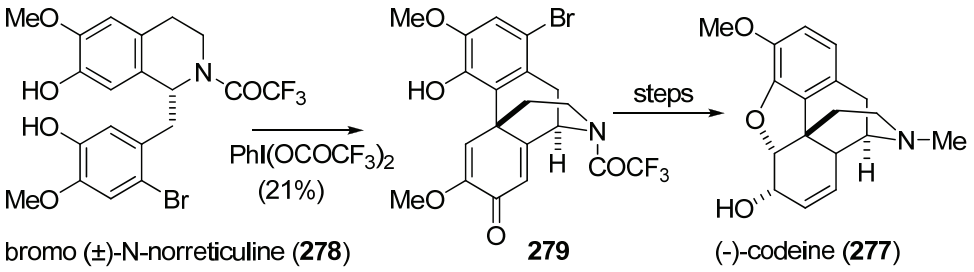
Oxidative aromatic coupling

As far as poppy produces papaverine (**274**) along with morphine and codeine, it was proposed that isoquinolines could be biosynthetic precursors for morphine related alkaloids. Later it was found that morphine (**275**) and related alkaloids are formed in *P. somniferum* through a series of benzylisoquinoline intermediates which culminate in (*R*)-reticuline (**276**).[73] Oxydative phenol coupling could be a good alternative to biosynthesis of opium alkaloids.



Scheme 68. Biogenetic precursors of morphine (**275**)

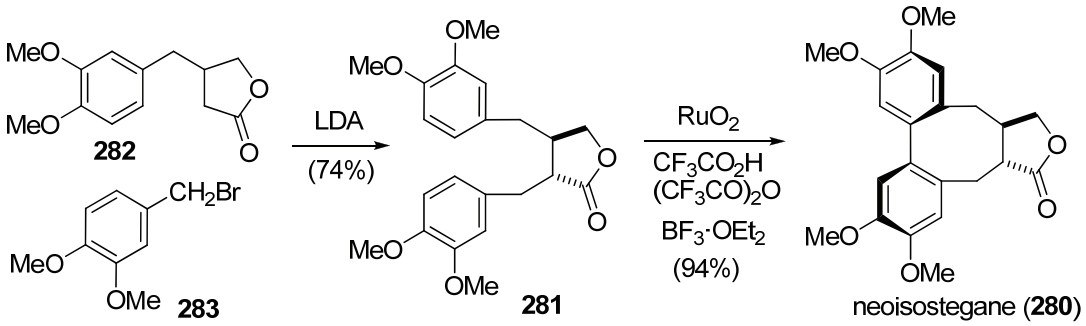
In 1983 the opium alkaloid (-)-codeine (**277**) was synthesized in eight steps from bromo (±)-N-norreticuline (**278**). The key step was oxidative phenol coupling mediated by bis(trifluoroacetoxyiodobenzene), which afforded tetracyclic compound **279**, which then was converted to codeine (**277**).[74]



Scheme 69. Biomimetic total synthesis of (-)-codein (**277**) in 1983

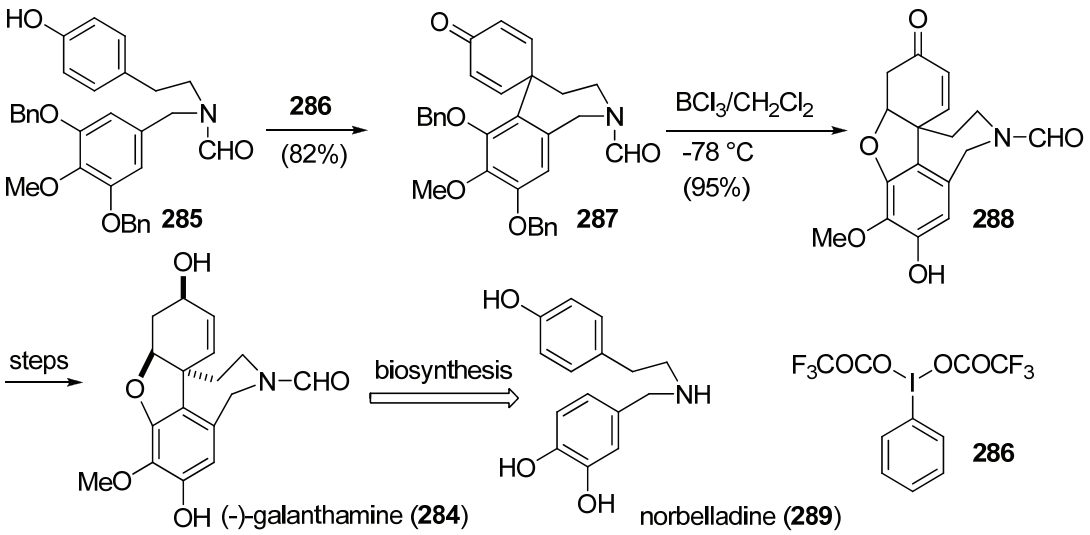
A biomimetic total synthesis of neoisostegane (**280**), published in 1986, is based on an intramolecular oxidative biaryl coupling of dibenzylbutanolide **281** with a ruthenium (IV) catalyst.[75] Compound **281** was prepared by alkylation of benzylbutanolide **282** with benzyl bromide **283** in 74% yield. Oxidative intramolecular coupling, achieved with ruthenium (IV)

tetrakis(trifluoroacetate), proceeded very efficiently in almost quantitative yield to give neoisostegane (**280**).



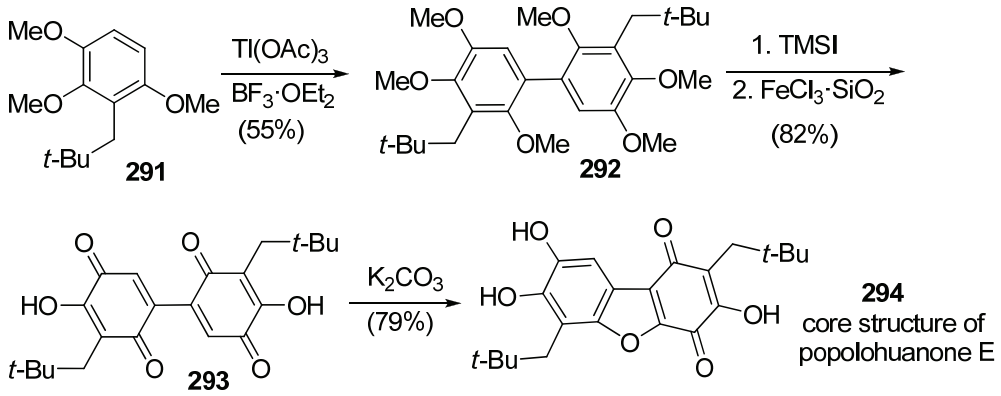
Scheme 70. Biomimetic total synthesis of neoisostegane (**280**).

A remarkable intramolecular phenol coupling in the total synthesis of (-)-galanthamine (**284**) has been published in 2001 (Scheme 10).[76] (-)-Galanthamine (**284**) is considered to be synthesized biologically by the phenolic oxidative coupling of norbelladine (**289**) (**Scheme 71**). The aromatic rings of norbelladine-like derivative **285** were coupled by using phenyliodine(III) bis(trifluoroacetate) (PIFA, **286**) to give the coupled product **287** in 82% yield, debenzylation of which provided the core structure of (-)-galanthamine **288**. The analogous coupling with hypervalent iodine (in this case, the reagent of choice was $PhI(OAc)_2$ was used to prepare a library of galanthamine-like molecules through biomimetic diversity-oriented synthesis.[77]



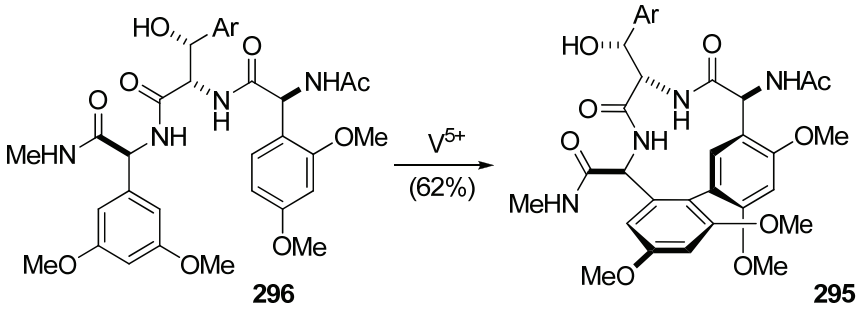
Scheme 71. Total synthesis of (-)-galanthamine (**284**)

Intermolecular oxidative coupling of aromatic compounds was used in total synthesis of the core structure of popolohuanone.[78] This tricyclic structure was synthesized by *non*-phenolic coupling of compound **291** with Tl(III) as an oxidant. After demethylation and oxidation quinone compound **293** underwent base-induced biquinone rearrangement reaction to form the tricyclic core structure of popolohuanone E (**294**) in good yield.·



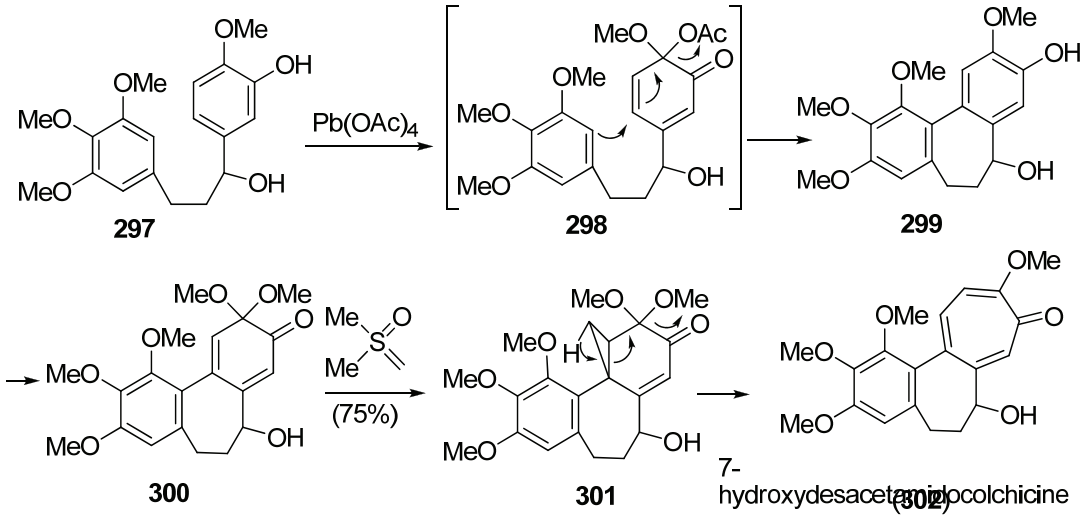
Scheme 72. Synthesis of core structure of popolohuanone (**294**)

Oxidative C-C coupling of the biaryl moiety was proposed as the last step in the biosynthesis of vancomycine aglycon, which was studied by Evans *et al.*[79] A fragment of vancomycine macrolactam **295** was prepared from **296** using vanadium (V) reagents in good yield.



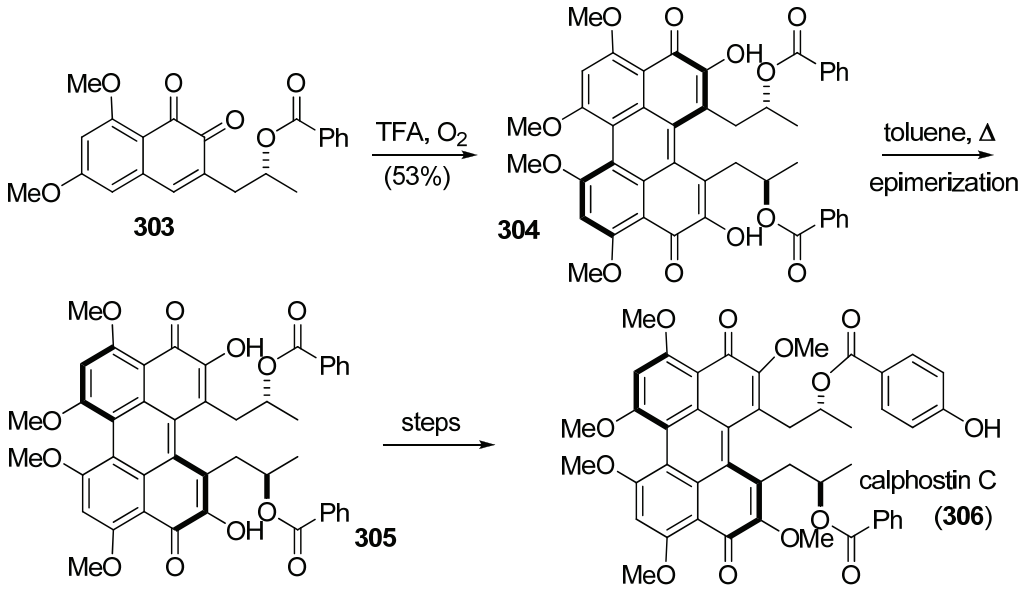
Scheme 73. Oxydative biaryl coupling in the synthesis of vancomycine

Another example relates to the remarkable observation that the formation of the very characteristic tropolone ring during the biosynthesis of colchicines employs a cyclopropane intermediate (**Scheme 74**).[80] Carrying a hydroxy group in the α-position this substructure can enter into a regioselective fragmentation and ring expansion process finally generating colchicines. Lead tetraacetate oxidation of the phenol ring of **297** gave rise to the semi-protected *o*-quinone **298** in a regioselective manner, which cleanly underwent the cyclization process to form the coupling product **299**. A second oxidation again provided an *o*-quinone derivative (**300**) which on subsequent treatment with dimethylsulfoxonium methylide ran through a highly regioselective and also diastereoselective nucleophilic cyclopropanation to generate a single tetracyclic alcohol (**301**) in respectable 75% yield. Mild acid treatment converted it directly to 7-hydroxydesacetamidocolchicine **302**.



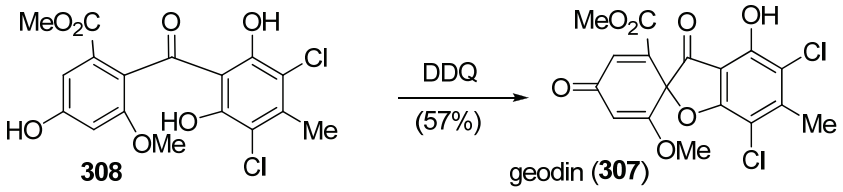
Scheme 74. A biomimetic approach to colchicines

The total syntheses of the potent protein kinase C inhibitor calphostin was reported by Craig A. Merlic *et al*.[81] Oxidative coupling of diketone **303**, accomplished in O_2/TFA-system probably proceeds by free radical mechanism. It should be noted, that in this reaction a wrong diastereomer **304** of calphostin structure was formed. Heating of **304**, however, affected epimerization to give the correct stereochemistry for the core structure **305** of calphostin C (**306**).



Scheme 75. Synthesis of of calphostin C (**306**) by oxidative aromatic coupling

Oxidative spirocyclization of a phenol was used for the total synthesis of (±)-geodin (**307**), the spirocoumaranone subunit of Sch 202596. The key step was oxidation of phenol **308** with DDQ, which afforded the desired product in 57% yield.



Scheme 76. Synthesis of (±)-geodin (**307**) by oxidative phenolic spirocyclization

Pericyclic reactions

Pericyclic reactions of polyenes represent a very attractive field of organic chemistry considering the biomimetic total synthesis of natural molecules. The most common are termal 6π-electron cyclizations. Photochemical 4π and termal 8π cyclizations are less common. In **Figure 1** the most common patterns of biomimetic electrocyclization reactions are shown.

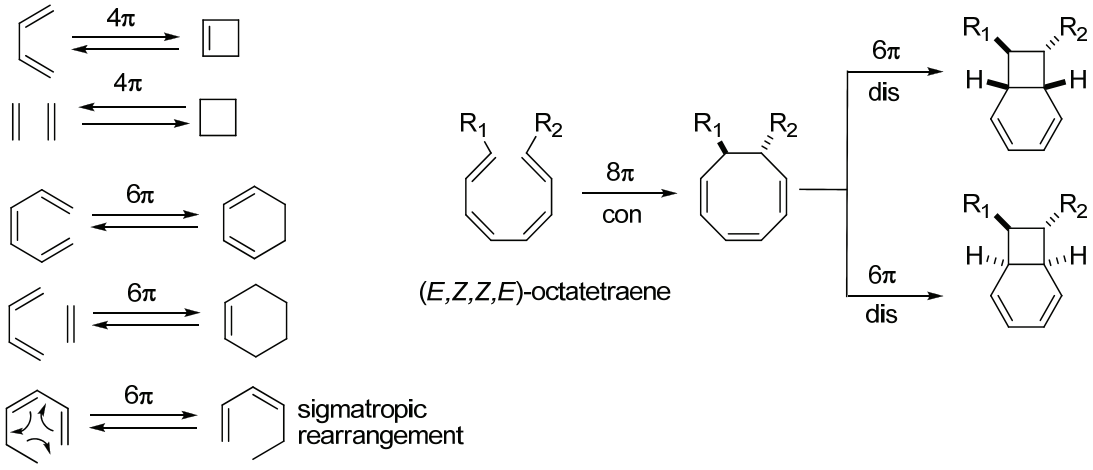
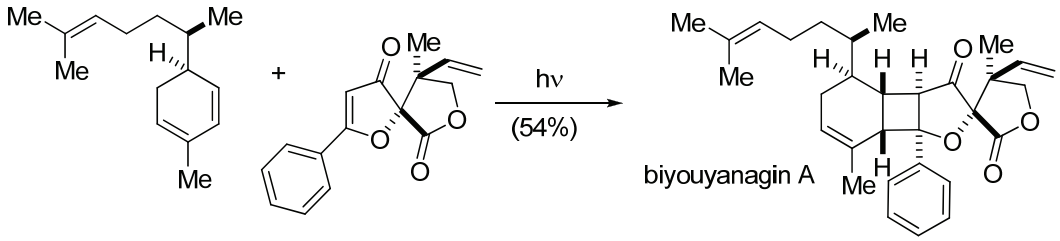


Figure 1. Common pericyclic reactions, related to the biosynthesis and chemical synthesis of natural products

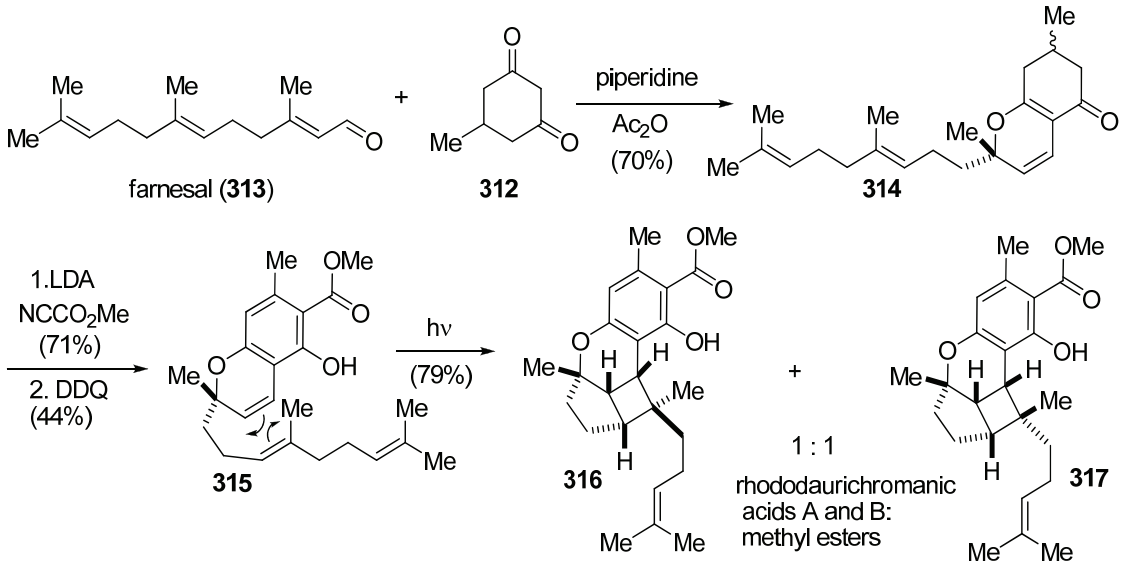
Biomimetic [2+2] cycloaddition reactions

[2+2] Cycloaddition is an obvious method for construction of cyclobutane rings. For example, an intermolecular photochemical [2+2]-cycloaddition of diene **309** and alkene **310** was successfully used for the synthesis of biyouyanagin A (**311**) and analogues.[82] Irradiation with UV-light afforded the [2+2] cycloaddition product in 54 % yield.



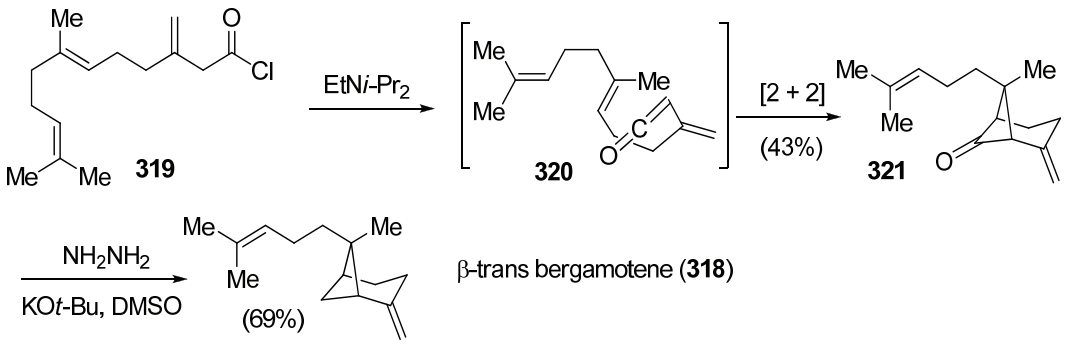
Scheme 77. Biomimetic synthesis of biyouyanagin A (**311**) by [2+2] cycloaddition

Hsung has achieved an expedient biomimetic synthesis of the rhododaurichromanic acids (**Scheme 78**).[83] Condensation of dione **312** with farnesal (**313**) and concomitant oxa-6π electrocyclization gave (*2H*)-pyran **314**. Acylation and oxidation of **314** provided **315**, the methyl ester of daurichromenic acid. Irradiation of this material provided rhododaurichromanic methyl esters **316** and **317** as a 1:1 mixture, whose saponification gave the natural products.



Scheme 78. [2+2]-Cycloaddition in the synthesis of rhododaurichromanic acids

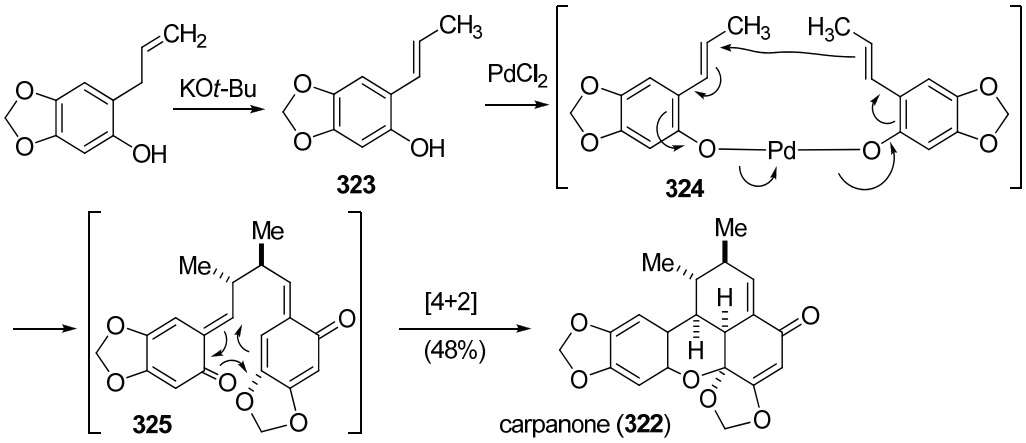
The ketene-olefin cycloaddition has been utilized in Corey's synthesis of β-*trans* bergamotene (**318**) in 1985.[84] The acid chloride **319** was synthesized from geranyl acetone in three steps. Slow addition of Hünig's base to acyl chloride **319** generated ketene **320**, which underwent [2+2]-cycloaddition to give bicyclo[3.1.1]heptane **321** isolated in 43% yield. Reduction of ketone **321** with hydrazine afforded the natural product β-*trans* bergamotene (**318**) in 69% yield (**Scheme 79**).



Scheme 79. Corey's synthesis of β-*trans* bergamotene (**318**)

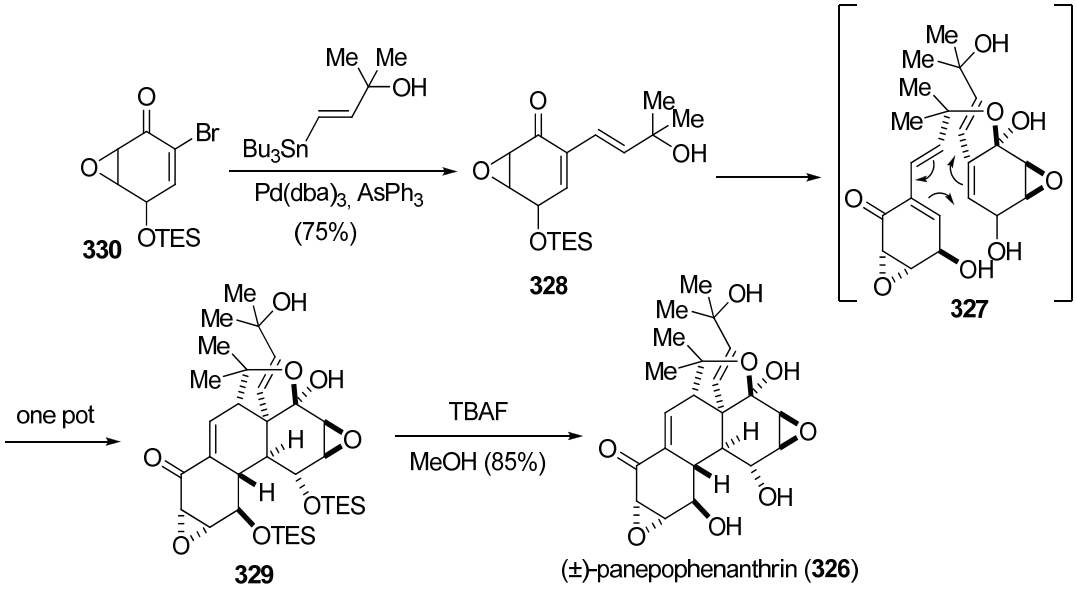
Biomimetic [4+2] cycloaddition reactions

Chapman's synthesis of carpanone (**322**) is a striking example illustrating the power of biomimetic strategies.[85] Palladium-catalyzed phenolic coupling of alcohol **323** generated the highly-reactive bis(*ortho*quinomethane) **324** which then readily participated in an intramolecular hetero Diels-Alder reaction to give carpanone directly from **323** in a single laboratory operation. Clearly, Chapman's synthesis was guided by an appreciation for the latent symmetry in carpanone (**322**) which is readily apparent in intermediate **325** and derives from oxidative dimerization of alcohol **323**. The fact that carpanone (**322**) and two minor stereoisomers are found as racemates in nature suggests a non-enzymatic dimerization in the biosynthesis of these compounds. Simple starting materials and a concise strategy distinguishes Chapman's synthesis of carpanone as truly practical.



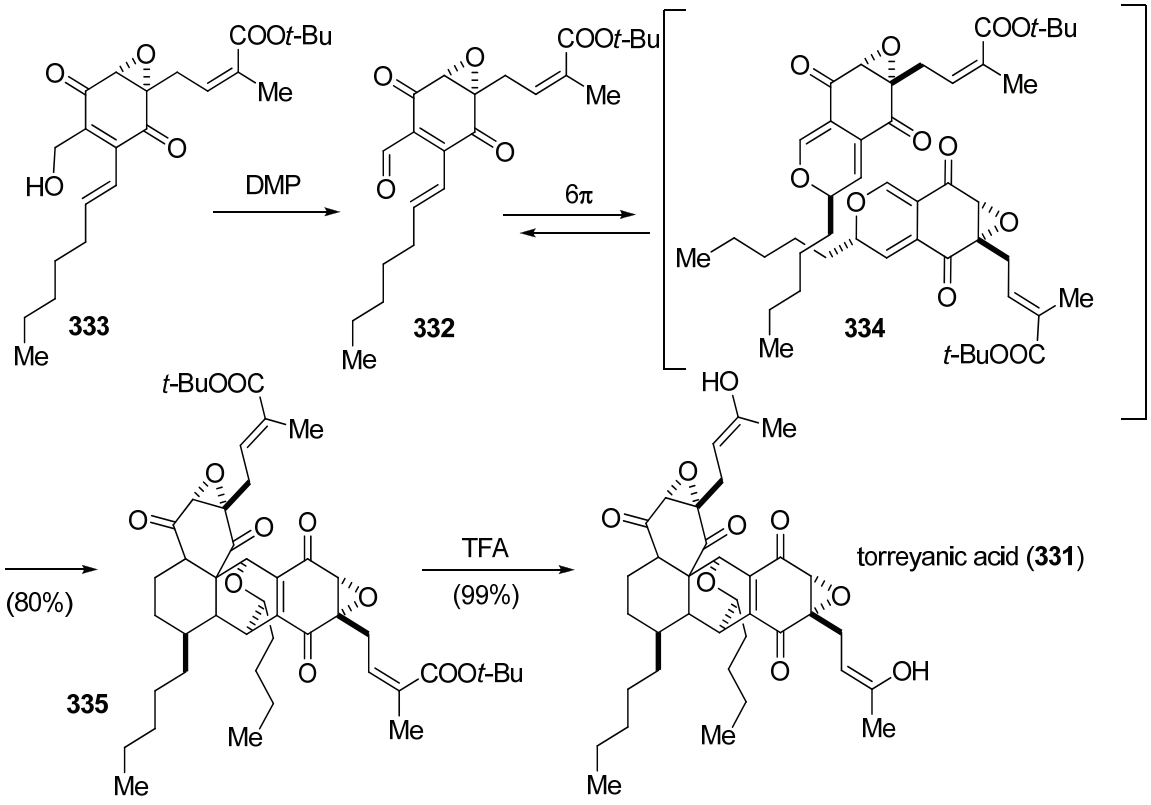
Scheme 80. Chapman's synthesis of carpanone (**322**)

A total synthesis of (±)-panepophenanthrin (**326**) by Diels-Alder reaction of hemiketal **327** was published by J. Baldwin.[86] Later an asymmetric synthesis of this natural product was published by J. Porco and coworkers.[87] The key step involves ketalization of ketone **328** by heating it with acid to form reactive intermediate **327**, which undergoes Diels-Alder cycloaddition. This cyclization is very efficient and proceeds with high stereoselectivity and provides 85% yield of the natural product **326** after deprotection.



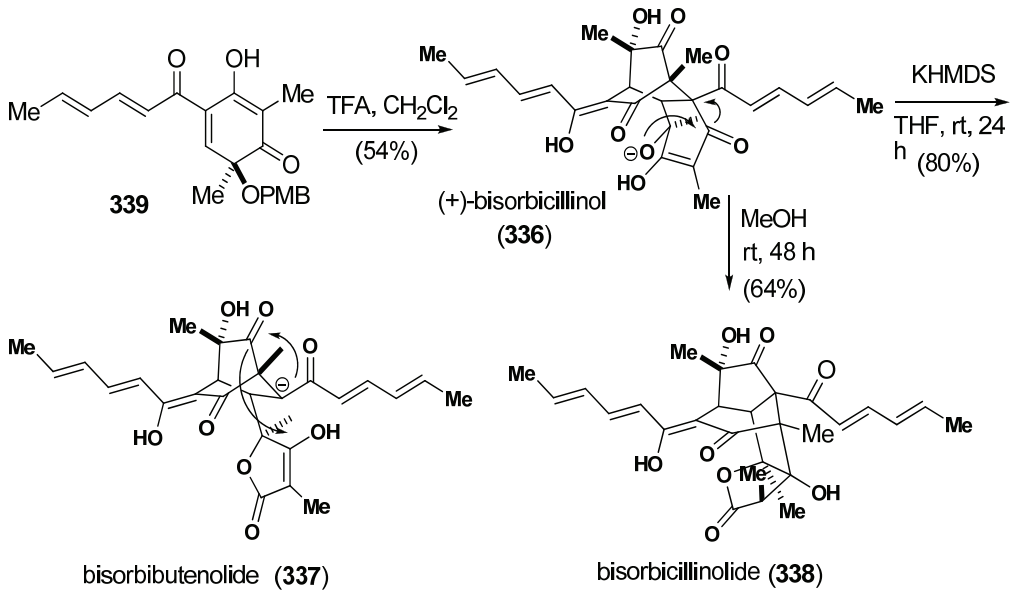
Scheme 81. Total synthesis of (±)-panepophenanthrin (**326**)

A remarkable example of a biomimetic Diels-Alder dimerization was shown by J. Porco *et al.* in the total synthesis of torreyanic acid (**331**).[88] The key intermediate **332** was synthesized by tartrate-mediated nucleophilic epoxidation involving hydroxyl group direction, which facilitated the asymmetric synthesis of a key chiral quinone monoepoxide intermediate. The cascade reaction sequence was initiated by oxidation of alcohol **333**, to give aldehyde intermediate **332**, which underwent a facile electrocyclization followed by a Diels-Alder dimerization resulting in **335**. Very efficient regio- and stereoselective Diels-Alder dimerization reaction gave torreyanic acid in 80% yield after deprotection.



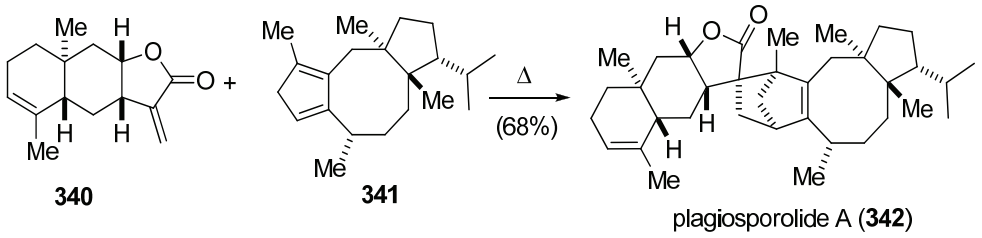
Scheme 82. J. Porco's total synthesis of torreyanic acid (**331**).

Firstly, bisorbicillinol (**336**) and bisorbibutenolide (**337**) were synthesized in Nicolaou and Corey groups.[89] The synthesis is based on biomimetic [4+2]-dimerization of the requisite quinol **339** which functioned as both diene and dienophile after deprotection. Later highly efficient enantioselective total syntheses of bisorbicillinolide (**338**), bisorbicillinol (**336**), and bisorbibutenolide (**337**) were accomplished in 2005 by Li Deng *et al*.[90] Treatment of PMB-protected sorbicillinol **339** with trifluoroacetic acid (TFA) accomplished the removal of the PMB group and the [4+2] dimerization of the resulting sorbicillinol in one pot to afford (+)-bisorbicillinol (**336**). This product could be converted into bisorbibutenolide (**337**) by anionic rearrangement with potassium *bis*-trimethylsilyl amide, or into bisorbicillinolide (**338**) by standing in methanol.



Scheme 83. Syntheses of bisorbicillinols (**336-338**)

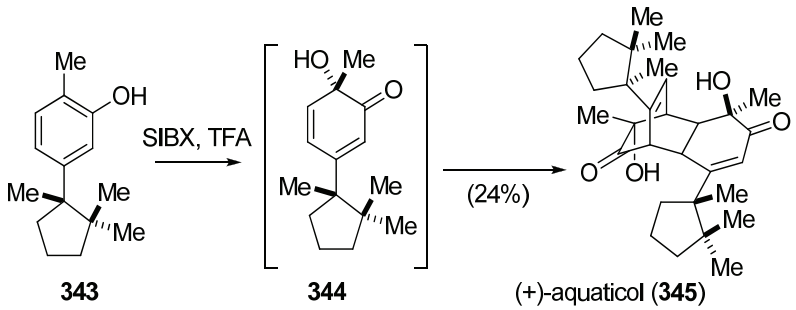
Plagiosporolides represent a wide class of biochemical Diels-Alder products, suggested to be biosynthesized from eudesmanolide sesquiterpenoids **340** and a fusicoccane diterpenic hydrocarbon **341** in a formal sense. This intermolecular Diels-Alder reaction was successfully accomplished by Japanese authors in the biomimetic synthesis of plagiosporolides A (**342**) and B.[91] This cycloaddition proceeds with high stereoselectivity and good yield.



Scheme 84. Biomimetic synthesis of plagiosporolides A (**342**)

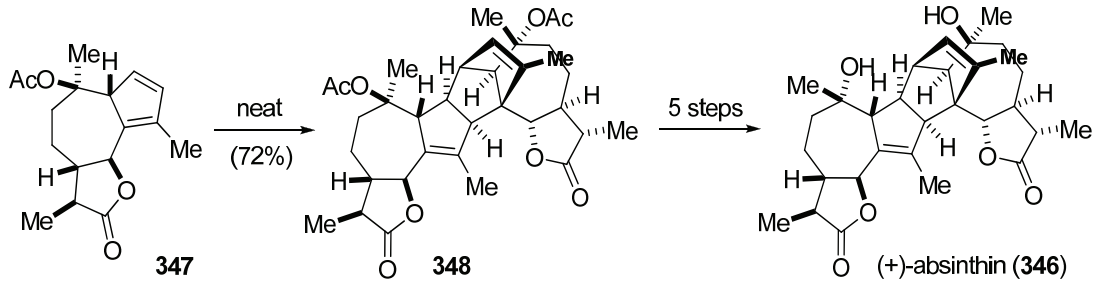
Quideau *et al.*, however, focused on an *in situ* dearomatization reaction to arise at the necessary quinol, and was able to subject hydroxycuparene (**343**), to their biomimetic dearomatizing *ortho*-selective hydroxylation conditions utilizing the hypervalent iodine oxidant SIBX (stabilized *o*-iodoxybenzoic acid), generating quinol **344**. This underwent the *endo*- and site selective [4+2] cycloaddition to form naturally occurring (+)-aquaticol (**345**), in 24% yield, along with (–)-aquaticol, and an overoxidized dihydroxycuparene.[92] Aquaticol is a

bissesquiterpene that has been isolated from a plant used in traditional Chinese medicine, *Veronica anagallis-aquatica*.[93]



Scheme 85. Synthesis of (+)-aquaticol (**345**)

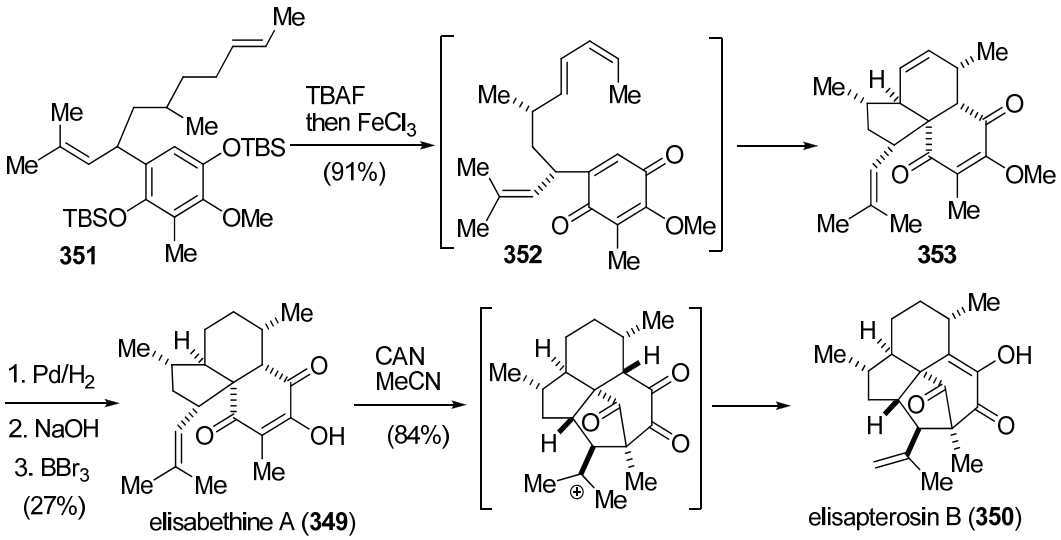
Synthesis of (+)-absinthin (**346**), a biologically active compound from the herb *Artemisia absinthium* L., used in traditional Chinese medicine, was published by Zhai *et al*.[94] Diene **347**, underwent biomimetic Diels-Alder dimerization with formation of **348**, in a regio and stereospecific manner, when stored neat under a nitrogen atmosphere at room temperature. The two identical Diels-Alder partners approached each other from their least hindered faces, adopting a head-to-head orientation with regard to the lactone carbonyl groups, thus minimizing steric interactions. A five step stereochemical inversion of the highly sterically congested teriary center provided (+)-absinthin (**346**) in 18.6% overall yield from readily available materials.



Scheme 86. Total synthesis of (+)-absinthin (**346**)

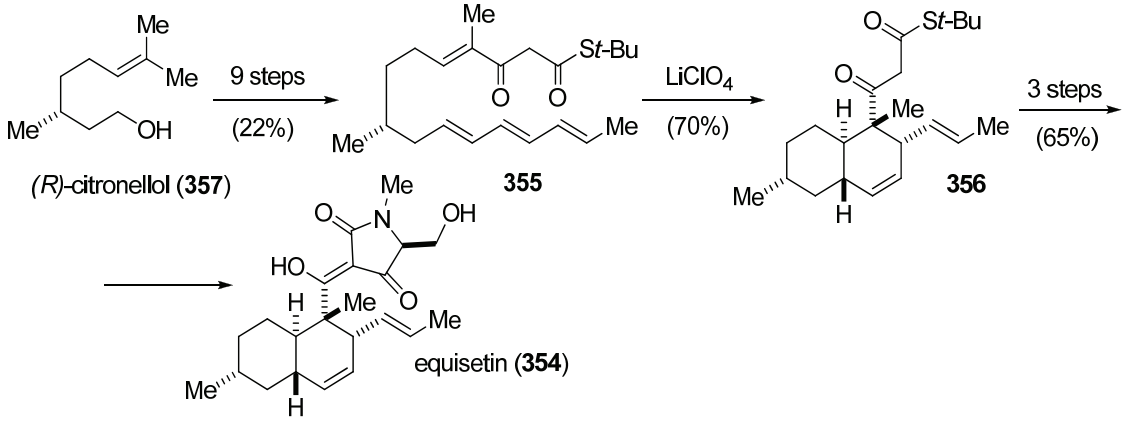
The total synthesis of elisabethine A (**349**) by intramolecular Diels-Alder reaction under biomimetic conditions was published by J. Mulzer (**Scheme 87**).[95] Independently V. Rawal and coworkers reported a similar synthesis of **349** and biomimetic synthesis of elisapterosin B (**350**) by oxidative cyclization of elisabethin analogs.[96] In Mulzer's synthesis of elisabethine A

(**349**), ether cleavage and oxidation of compound **351** gave quinone intermediate **352**, which underwent intramolecular Diels-Alder reaction to give the tricyclic skeleton of natural product **353**. Elisapterosine B (**350**) was obtained biomimetically by V. Rawal *et al*. using oxidation of elisabethine A (**349**) with cerium-ammonium nitrate in high yield.



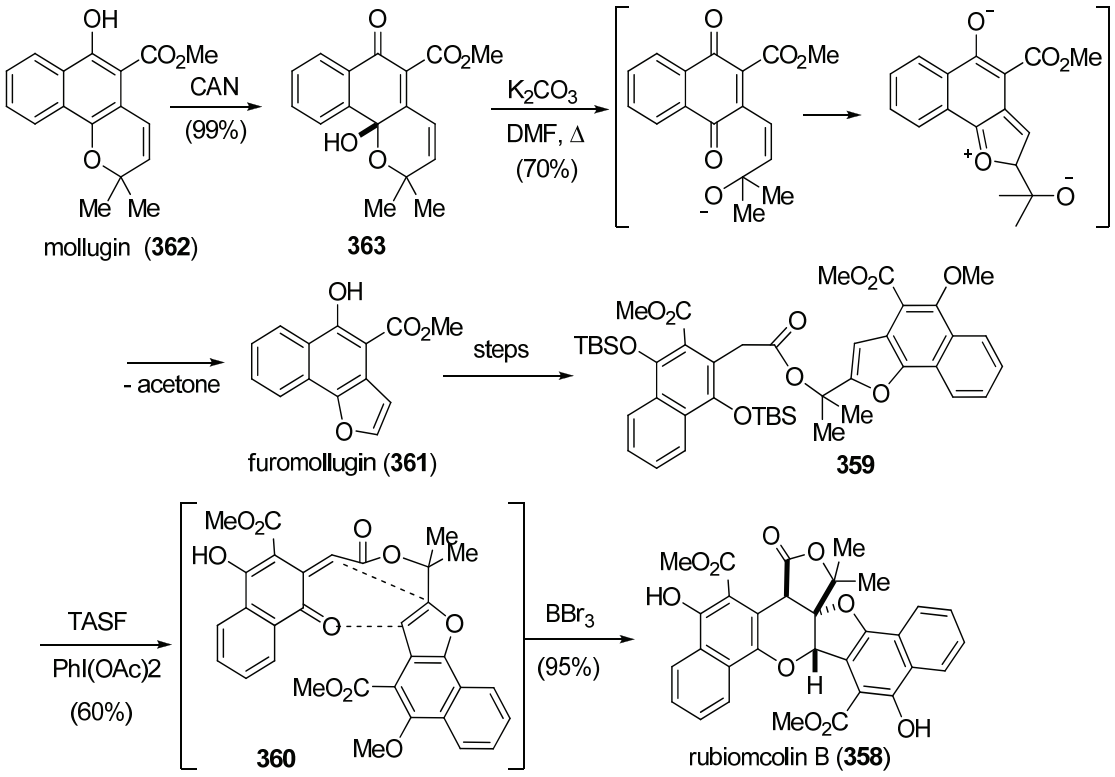
Scheme 87. Total synthesis of elisabethine A (**349**) and elisapterosine B (**350**)

An efficient stereoselective synthesis of the fusarium toxin equisetin (**354**), was reported by J. Dixon and S. Ley in 2000.[97] The key step is a stereoselective lithium perchlorate mediated intramolecular Diels-Alder reaction of a fully conjugated *E*,*E*,*E*-triene **355** with a trisubstituted γ,δ-unsaturated β-ketothioester. The Diels-Alder intermediate **356** was synthesized from commercially avaible *(R)*-citronellol (**357**) in 9 steps and 22 % yield and the cyclized product **356** was converted into the natural compound in three steps. That allowed to prepare *(-)*-equisetin only in 13 steps from citronellol.



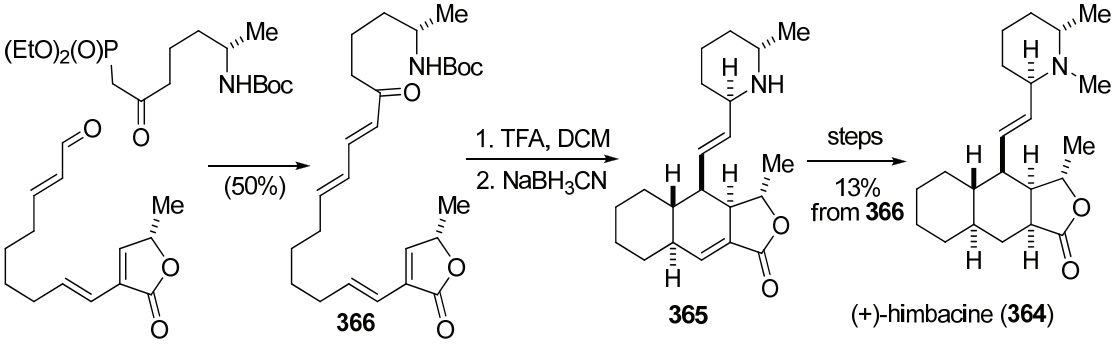
Scheme 88. Total synthesis of equisetin (**354**)

D. Trauner recently reported the total synthesis of rubiomcolin B (**358**).[98] The key reaction of this biomimetic synthesis is a tautomerization/Diels-Alder reaction of compound **359**. Ether cleavage of TBS protected phenol with TASF (tris[dimethylamino]sulfonium difluorotrimethyl silicate), and oxidation with $PhI(OAc)_2$ gave quinone intermediate **360**, which spontaneously underwent intramolecular Diels-Alder reaction in 60 % yield. The furan intermediate furomollugin (**361**) was obtained from the natural compound mollugin (**362**). Oxidation of mollugin (**362**) with CAN (cerium ammonium nitrate) gave *para*-quinone **363**, which which was converted to furomollugin (**361**) with loss of acetone under basic conditions.



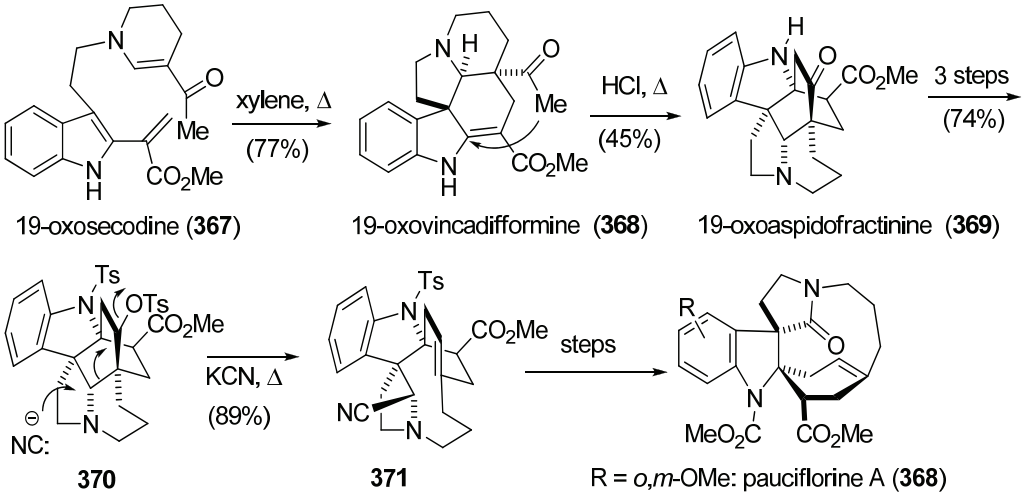
Scheme 89. Total synthesis of rubiomcolin B (**358**) by D. Trauner

(+)-Himbacine (**364**) was synthesized by J. E. Baldwin and coworkers by biomimetic intramolecular Diels-Alder cycloaddition of activated iminium ion derived from **366** (**Scheme 90**).[99] On treatment with trifluoroacetic acid butenolide **366** underwent N-Boc deprotection and condensation followed by an iminium ion activated intramolecular Diels-Alder cycloaddition to give the (+)-himbacine precursor **365** on reductive work up. Compound **365** was converted into (+)-himbacine in four synthetic steps.



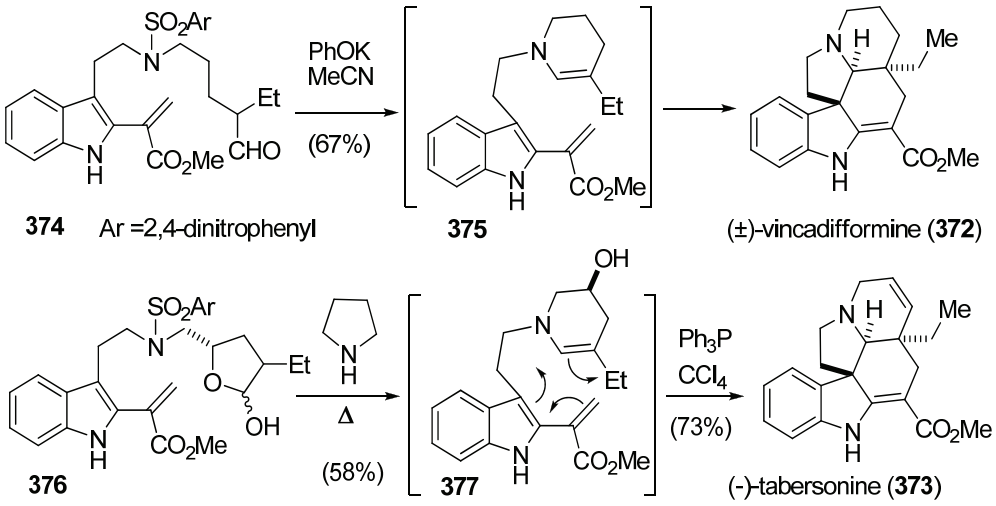
Scheme 90. Total synthesis of (+)-himbacine (**364**) by J. E. Baldwin

M. Kuehne in 1983 published the biomimetic Diels-Alder cyclization of 19-oxosecodine (**367**) into 19-oxovincadifformine (**368**), which proceeds with good yield in refluxing xylene.[100] N. Langlois showed that under acidic conditions **368** reacted to another alkaloid 19-oxoaspidofractinine (**369**) by intramolecular Michael reaction.[101] M. Kuehne and Y.-L. Li in 1999 achieved a formal total synthesis of alkaloid pauciflorine A (**368**).[102] In that synthesis 19-oxoaspidofractinine (**369**) was converted in three steps into tosylate **370**, which underwent nucleophile induced fragmentation to give nitrile **371**, a pauciflorine A precursor.



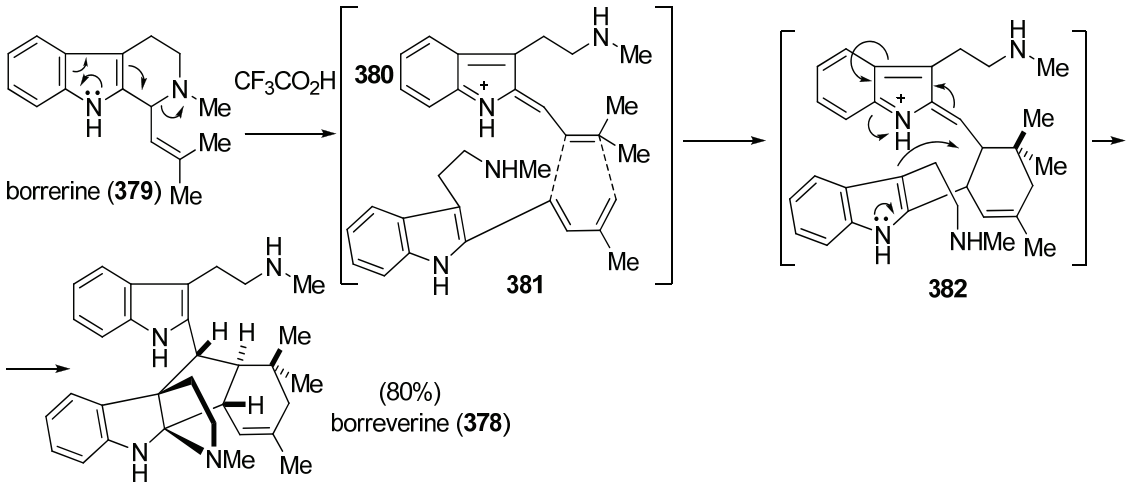
Scheme 91. Biomimetic synthesis of pauciflorine A (**368**)

Efficient total syntheses of (±)-vincadifformine (**372**) and (-)-tabersonine (**373**) were achieved by T. Fukuyama *et al.*[103] Deprotection of aminoaldehyde **374** gave enamine intermediate **375**, which underwent intramolecular Diels-Alder reaction to form (±)-vincadifformine (**372**) in 67 % yield. Similarly, heating of chiral hydroxyaldehyde **376** with Ph_3P/CCl_3 in 73% yield.



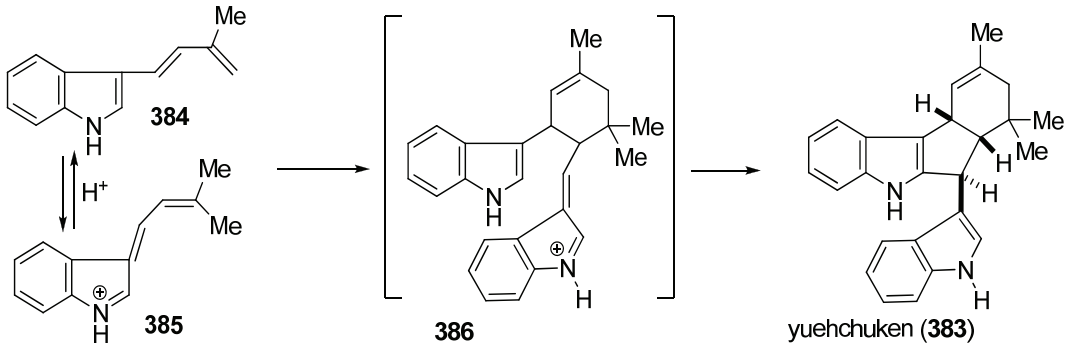
Scheme 92. Total syntheses of (±)-vincadifformine (**372**) and (-)-tabersonine (**373**)

The chemistry of indole alkaloids might sometimes appear weird and unexpected. The fact, however, that borreverine (**378**) co-occurred with its corresponding "monomer" borrerine (**379**) inspired M. Koch[104] and his collaborators to treat this simple alkaloid with acid, an operation that led to a mixture of borreverine (**378**) and isoborreverine in a yield of about 80%.[105] This biomimetic sequence passes through the ring opened material which as the iminium salt **380** offers an electron poor 2π-system which readily combines with the electron rich 4π-system of **381**. A subsequent Mannich cyclization (**Scheme 93**) finally generates the carbon framework of borreverine **382**, which picks up the methylamino group of the side-chain in a nucleophilic attack to the 3*H*-indole formed in the cyclization process.



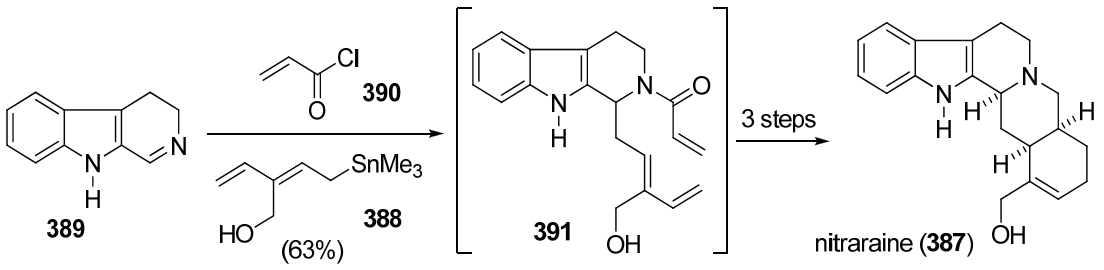
Scheme 93. Biomimetic synthesis of borreverine (**378**)

In that particular case (**Scheme 93**) biomimetic synthesis not only chemically links up two completely different looking molecules, but also makes a complex natural product like **378** look much less frightening to the synthetic chemist's eye. A very similar situation exists with yuehchuken (**383**) which again may be viewed as a Diels–Alder dimer, in this case resulting from the β-prenyl derivative **384** (electron rich) and the corresponding iminium salt **385**. β-Prenylation of indole to provide diene **384** was achieved by various groups[106] and dimerization as expected led to natural product yuehchuken (**383**) via Diels-Alder intermediate **386.**



Scheme 94. Total synthesis of yuehchuken (**383**)

A highly effective bicycloannulation methodology for the synthesis of berban and yohimban alkaloid systems was described by Japanese authors in 1993.[107] For example, in the total synthesis of nitraraine (**387**), a three-component coupling reaction of 2,4-pentadienyltin reagent **388** with the C=N bond of **389** and with α,β-unsaturated acyl chloride **390** furnished bicycloannulated products in a one-pot operation. The key cyclization of **391** took place in a highly stereoselective manner and allowed to prepare (±)-nitraraine (**387**) in 57% overall yield.



Scheme 95. Total synthesis (±)-nitraraine (**387**)

Studies using the *Corynanthe* alkaloid geissoschizine (**392**) showed that it is a biosynthetic precursor of strychnine[108] (**393**) and akuammicine (**394**) (**Figure 2**).[109]

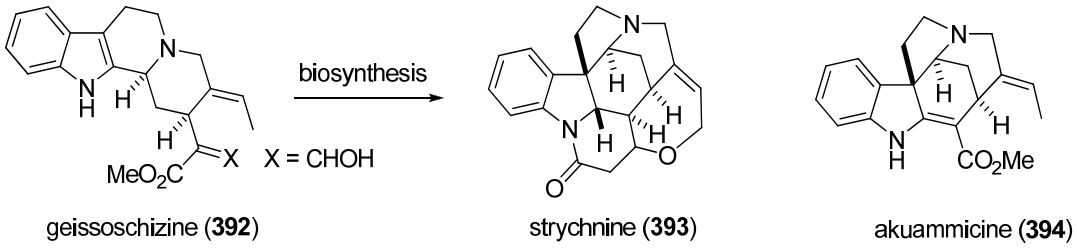
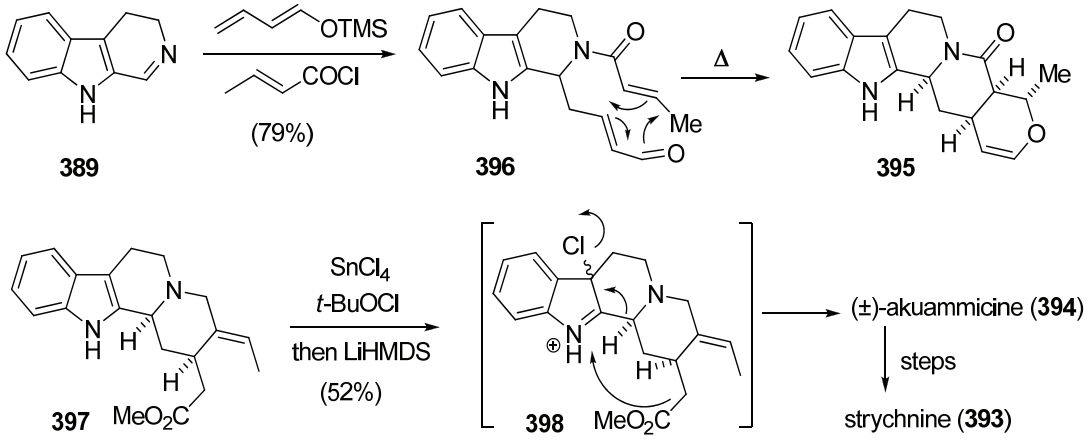


Figure 2. Structures of geissoschizine (**392**) strychnine (**393**) and akuammicine (**394**)

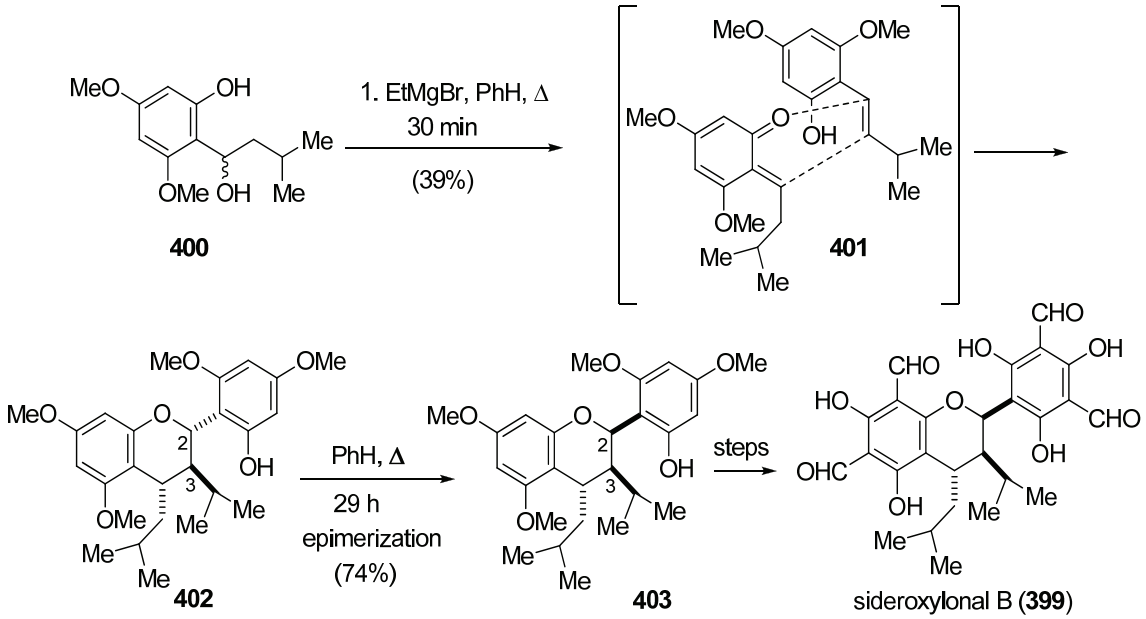
S. Martin and coworkers reported an efficient biomimetic total synthesis of (±)-akuammicine (**394**).[110] Biomimetic geissoschizine-type precursor **395** was quickly assembled by exploiting a vinylogous Mannich and intramolecular hetero Diels-Alder reaction of **396** as key steps. The subsequent elaboration of **397** into **394** was effected by a biomimetically patterned transformation that involved sequential oxidation and base-induced skeletal reorganization. Formal synthesis of strychnine was also reported by the same authors.



Scheme 96. Biomimetic total synthesis of (±)-akuammicine (**394**)

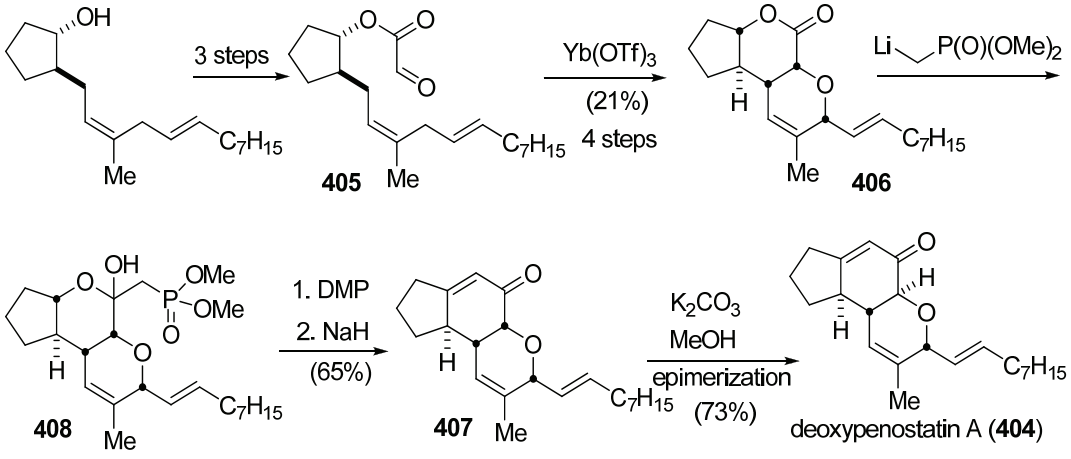
Sideroxylonal B (**399**) is a racemic flavonoid metabolite from extracts of *Eucalyptus sideroxylon,* which shows multiple biological activities. Biogenetically, this compound apparently is formed from isopentenyl phloroglucinol precursors by a hetero-Diels-Alder coupling process. Thus, treatment of alcohol **400** with EtMgBr afforded the *o*-quinone methide **401** and the isopentenyl derivative **402** *in situ*. Heating of this mixture for 30 min resulted in

hetero Diels-Alder cycloaddition to provide compound **403**, which possesses wrong stereochemistry at C-2. Additional heating for 29 h afforded complete thermodynamic epimerization of the 2,3-*trans* isomer **403** to the *2,3-cis* isomer **404** through a pyran ring-opening and -closing process.[111]



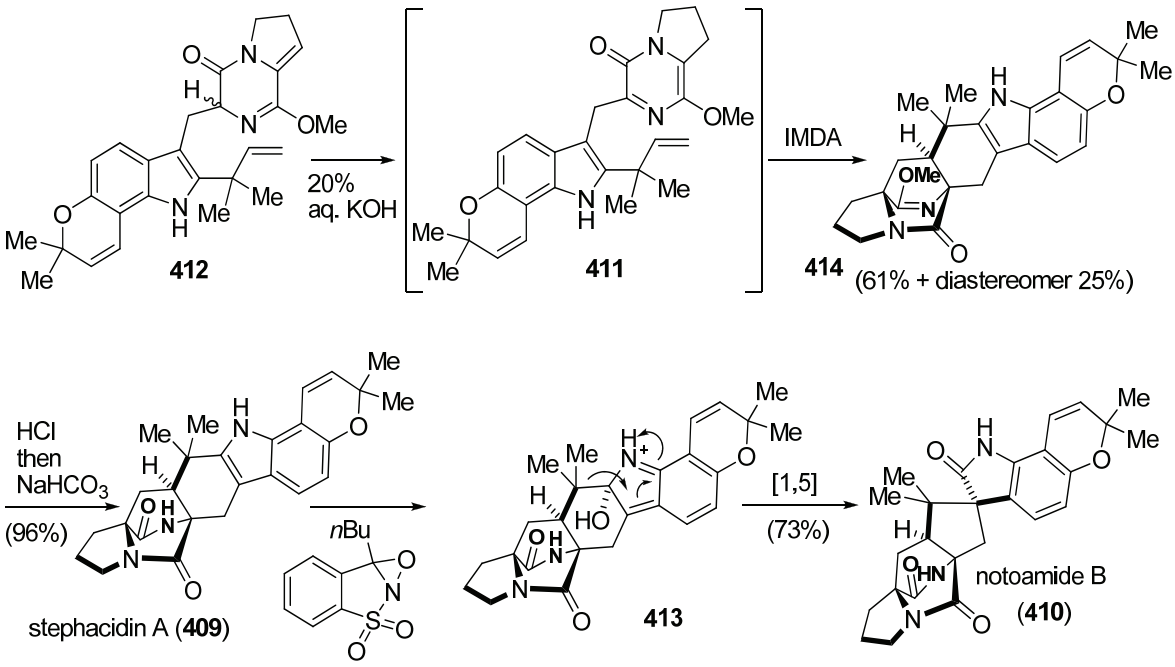
Scheme 97. Total synthesis of sideroxylonal B (**399**)

A total synthesis of deoxypenostatin A (**404**), reported by B. Snider,[112] is based on hetero Diels-Alder reaction of ketoaldehyde **405** under $Yb(OTf)_3$ catalysis. Then, lactone **406** was converted to unsaturated ketone **407** by intramolecular HWE (Horner-Wadsworth-Emmons) followed by oxidation of **408** and subsequent intramolecular aldolization reaction. Although, the obtained molecule possessed wrong stereochemistry at the α-ketone atom, it could be epimerized into correct deoxypenostatin A (**404**) with potassium carbonate in methanol (**Scheme 98**).

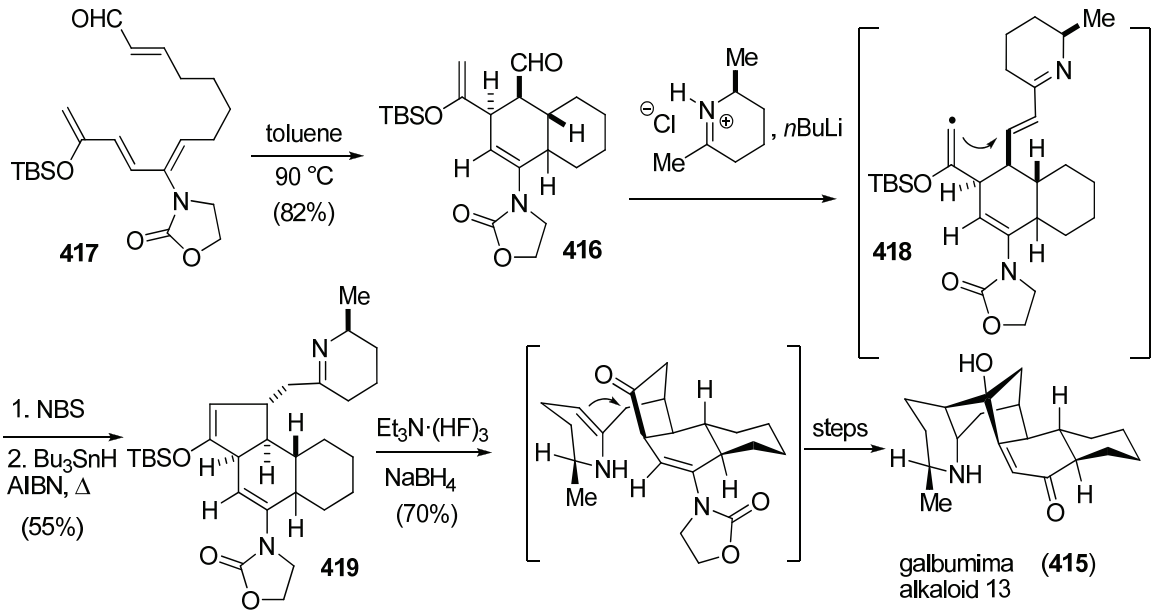


Scheme 98. Total synthesis of deoxypenostatin A (**404**) by B. Snider

Prenylated indole alkaloids like stephacidin A (**409**) and notoamide B (**410**) have potent cytotoxic properties and challenging polycyclic structures. Like stephacidins A and B, the notoamides possess a sensitive indolopyran ring system and a tryptophane/proline-derived bicyclo[2.2.2]diazaoctane embedded in their core. As a result of their inherent biological activity and structurally diverse ring systems, this family of prenylated indole alkaloids has become the subject of intense synthetic endeavors, including the first total synthesis of stephacidin B by Myers and Herzon,[113] and more recently stephacidin A (**409**) and stephacidin B by Baran and co-workers.[114] In the total synthesis of stephacidin A (**409**), reported by R. Williams, the [2.2.2]-fragment of the desired molecule **414** was constructed by intramolecular hetero Diels-Alder cycloaddition of enamide **411**, which was formed by tautomerization of compound **412**, which is biosynthetically formed from proline and tryptamine. [115] Notoamide B (**410**) was prepared from stephacidin A by oxidation of the sensitive indole moiety followed by rearrangement of **413**, which mimics its biogenetic pathway.

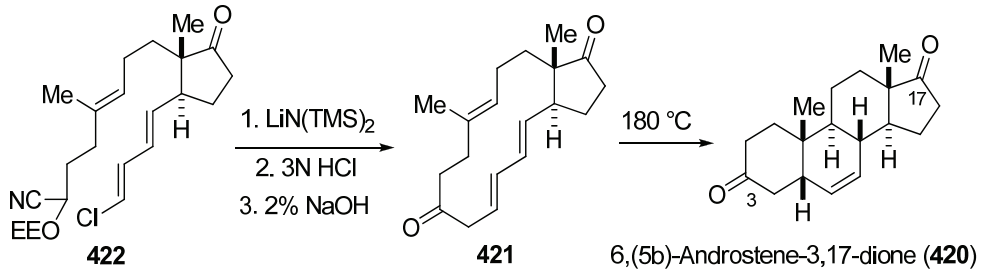


The galbulimima alkaloids, isolated from the bark of *Galbulimima belgra*V*eana*, have an interesting structure and biological activity. The biosynthetically inspired total synthesis of galbulimima alkaloid 13 (**415**) was based on a proposed polyketide biosynthetic pathway.[116] The decalene core **416** of this molecule was synthesized by Diels-Alder cycloaddition via heating of aldehyde **417** in toluene. Next ring was constructed by a Mukaiyama-Michael type vinyl radical cyclization. Subsequentally a tetracyclic structure was generated by aldol type condensation of enamine **419**. Remarkably, formation of the C8 stereocenter during the radical cyclization as well as the introduction of the three other stereocenters in the conversion of silyl enol ether **419** to pentacyclic amine **415** occured with a high level of diastereoselectivity.



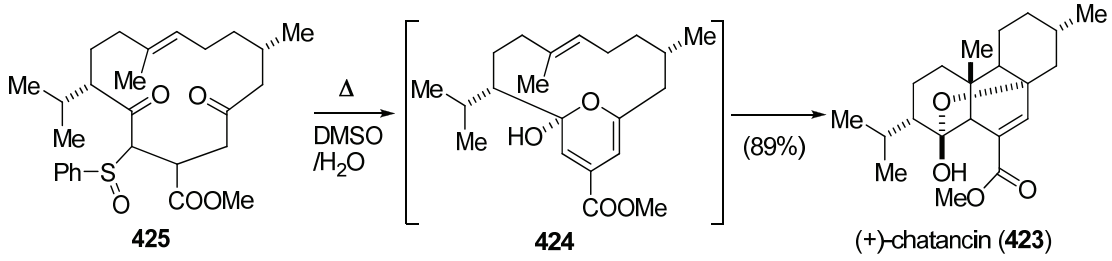
Scheme 99. Biomimetic total synthesis of galbulimima alkaloid 13 (**415**)

A transannular Diels-Alder reaction was successfully applied by T. Takahashi in 1988 for the synthesis of 6,(5b)-androstene-3,17-dione (**420**).[117] Macrocyclic ketone **421** was prepared by intramolecular alkylation of cyanhydrin **422** and subsequent hydrolysis. Heating of **421** cleanly afforded 6,(5b)-androstene-3,17-dione stereoselectively (**Scheme 100**).



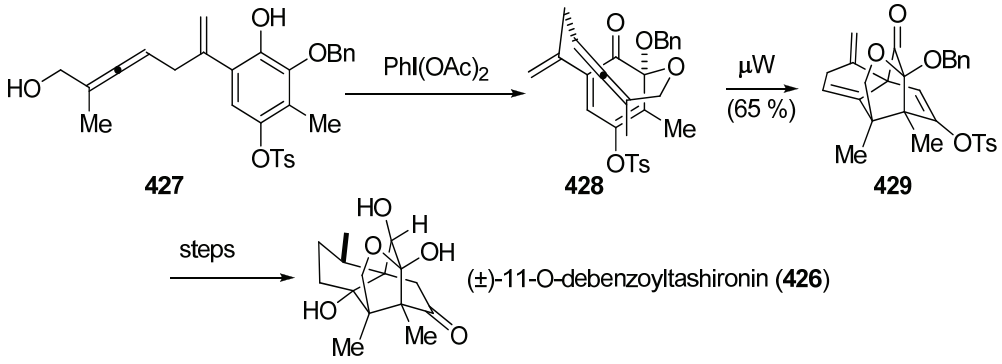
Scheme 100. Synthesis of 6,(5b)-androstene-3,17-dione (**420**) by transannular Diels-Alder reaction

A biomimetic asymmetric total synthesis of (+)-chatancin (**423**) has been reported by P. Deslongchamps and coworkers.[118] This synthesis is based on transannular Diels-Alder reaction (TADA) of pyranophane **424**, which was prepared by heating of sulfoxide **425**. The TADA reaction is high yielding and diastereoselective.



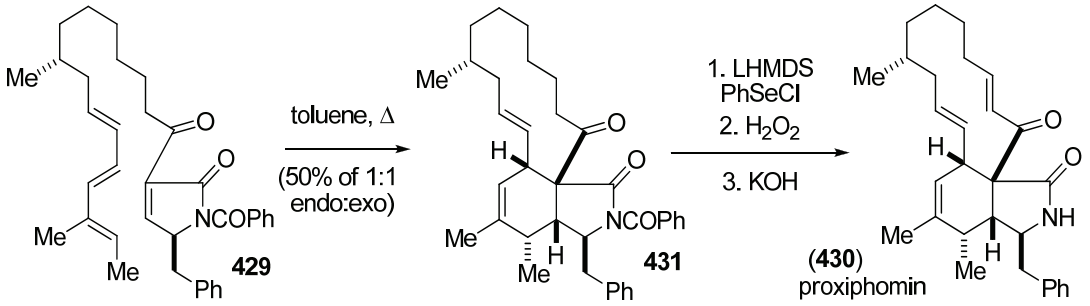
Scheme 101. A biomimetic total synthesis of (+)-chatancin (**423**)

Recently the total synthesis of (±)-11-*O*-debenzoyltashironin (**426**) by Danishefsky *et al.* was published.[119] The key transformation in this sequence involved a remarkable cascade of oxidative dearomatization of **427** and transannular Diels-Alder reaction of **428**, which allowed for the rapid assembly of the tetracyclic carbon skeleton **429** of the natural product.



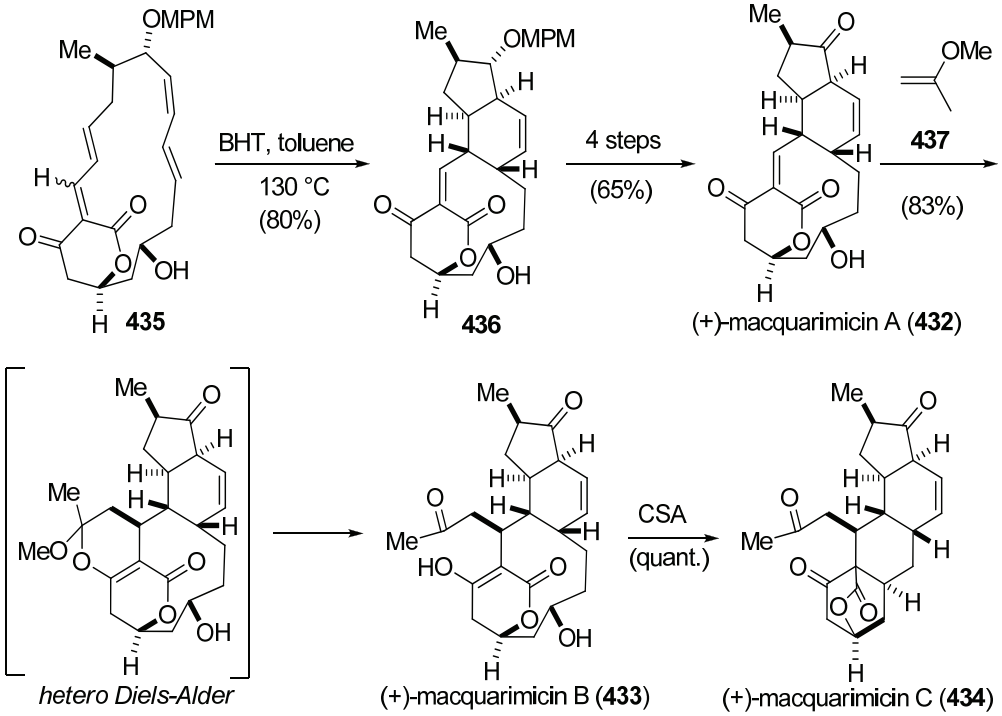
Scheme 102. Total synthesis of (±)-11-*O*-debenzoyltashironin (**426**) by Danishefsky

An interesting example of a biomimetic IMDA reaction was reported in 1989 by E. Thomas *et al.* (**Scheme 103**).[120] Cyclization of the long chain 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**429**) afforded the 13-membered ring system of proxiphomin (**430**). Although the stereoselectivity of cycloaddition was low, the desired *endo*-diastereomer of **431** could be separated from the *exo*-adduct with around 25% yield. Oxidation of the selenoketone and deprotection of the amide function gave natural product proxiphomin (**430**).



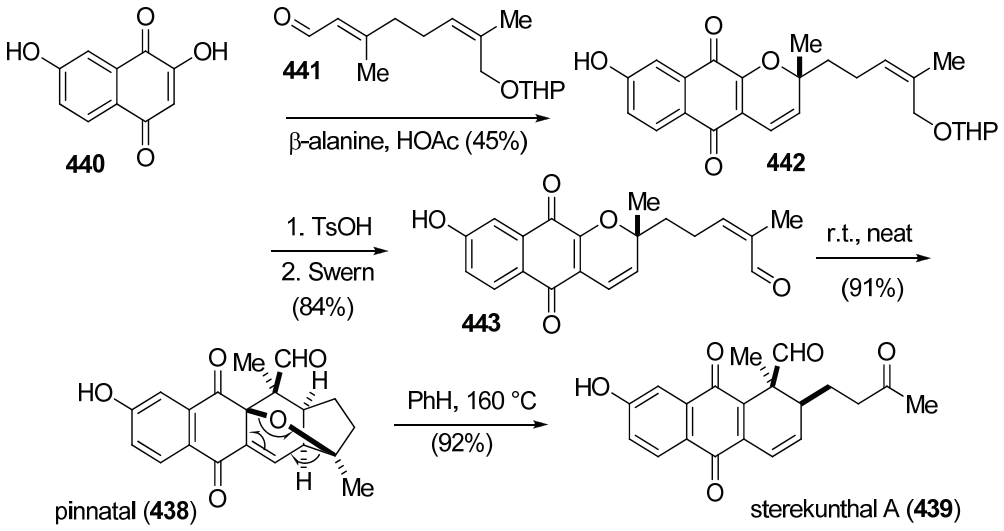
Scheme 103. Synthesis of proxiphomin (**430**) by biomimetic IMDA reaction

A transannular Diels-Alder reaction was used for the total synthesis of macquarimicins A (**432**), B (**433**) and C (**434**).[121] Heating of macrocycle **435** in toluene afforded Diels-Alder adduct **436** with 80% yield and as one diastereomer. This compound was converted to macquarimicin A (**432**) in four steps (**Scheme 104**). Accordingly, a biomimetic hetero Diels-Alder reaction of **432** with 2-methoxyprop-1-ene (**437**) led to macquarimicin B (**433**) in 83% yield. Treatment of **433** with acid promoted transannular alkylation to provide another metabolite, macquarimicin C (**434**) in quantitative yield.



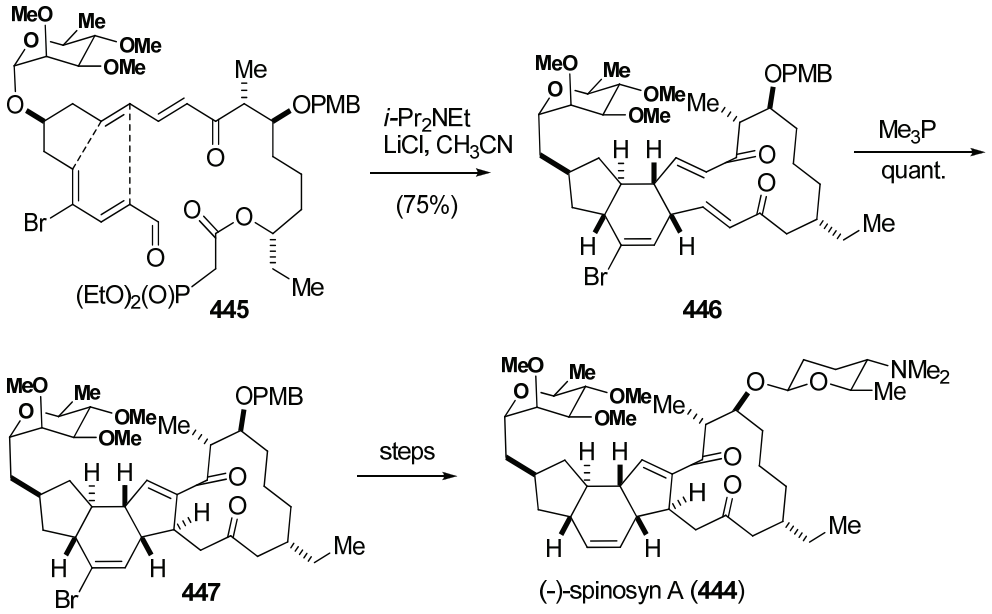
Scheme 104. Total syntheses of macquarimicins A (**432**), B (**433**) and C (**434**)

Malerich and Trauner achieved a biomimetic synthesis of pinnatal (**438**) and sterekunthal A (**439**).[122] Knoevenagel condensation of dihydroxy naphthoquinone **440** with unsaturated aldehyde **441** gave (*2H*)-pyran **442** (**Scheme 105**). Deprotection, followed by oxidation, then afforded the suspected biosynthetic intermediate **443**, which underwent intramolecular Diels-Alder reaction at room temperature to yield pinnatal (**438**). Heating of pinnatal in benzene solution effected retro-Diels-Alder reaction to give sterekunthal A (**439**).



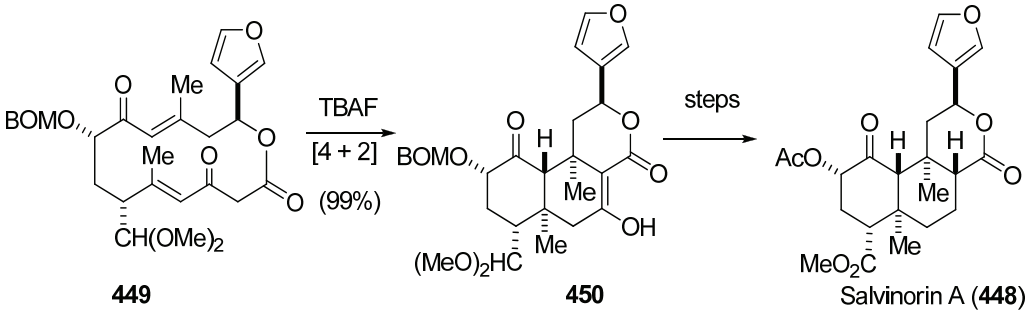
Scheme 105. Biomimetic synthesis of of pinnatal (**438**) and sterekunthal A (**439**)

Total synthesis of (-)-spinosyn A (**444**) was reported in 2004 by W. Roush.[123] Key features of the synthesis include a transannular Diels–Alder reaction of macrocyclic pentaene obtained from **445** and the transannular Morita–Baylis–Hillman cyclization of **446** that generates tetracycle **447**. The authors have found that intramolecular Horner-Wadswort-Emmons olefination of linear compound **445** led to a spontaneous transannular Diels-Alder cycloaddition, which proceeds stereoselectively to form the desired isomer. Treatment of dienone **446** with Me_3P resulted in transannular Morita–Baylis–Hillman reaction in quantitative yield (**Scheme 106**).



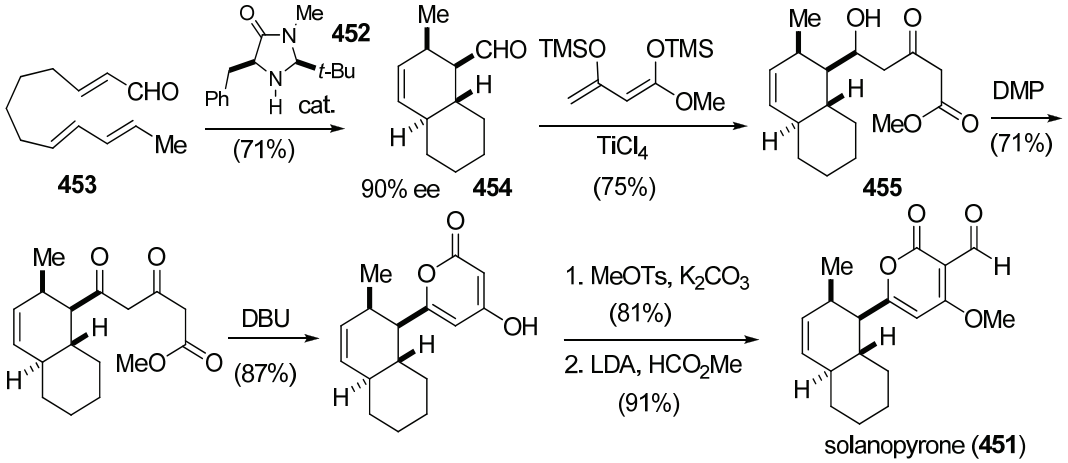
Scheme 106. Total synthesis of (-)-spinosyn A (**444**)

At the present moment salvinorin A (**448**) is the most potent hallucinogen found naturally occurring. The biosynthetic pathway of salvinorin A (**448**) was proposed to consist of a sequence of a transannular Michael reaction cascade of bisenone macrocycle **449**, which could be mimicked by a transannular Diels-Alder reaction. D. Evans *et al.*, recently reported an elegant asymmetric synthesis of salvinorin A (**448**) applying this biomimetic strategy.[124] Treatment of triketone **449** with a week base like TBAF generated a diene by enolization of the ketoester function, which underwent an *endo*-Diels-Alder reaction to provide the desired product **450** in quantitative yield.



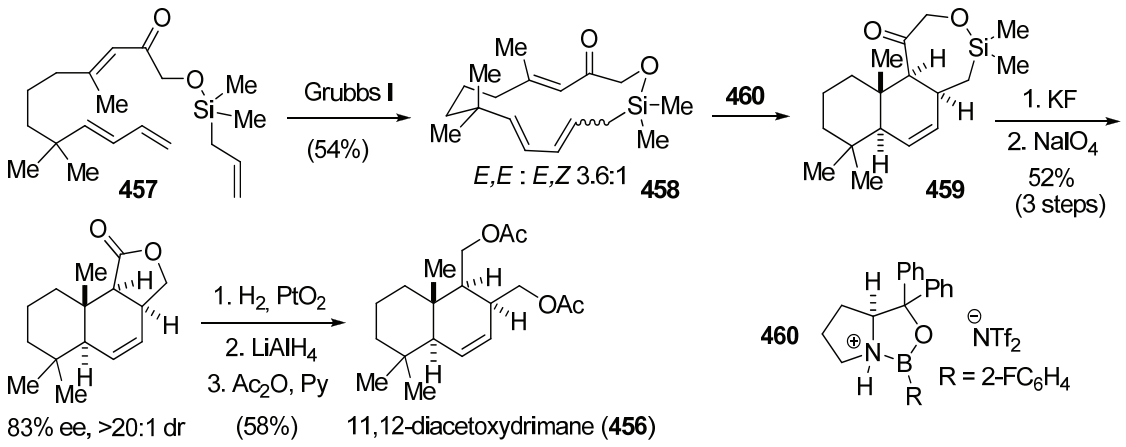
Scheme 107. Total synthesis of salvinorin A (**448**) by D. Evans

An organocatalytic biomimetic intramolecular Dies-Alder reaction for the synthesis of the decalene core of solanapyrone D (**451**) was recently reported by MacMillan *et al*.[125] Using 20 mol% of organic catalyst **452**, allowed for an enantioselective intramolecular cycloaddition of aldehyde **453** with good yield and 90 % ee. Obtained aldehyde **454** was elongated by Mukaiyama-aldol reaction, and the natural product solanapyrone D (**451**) was prepared in a few further steps.



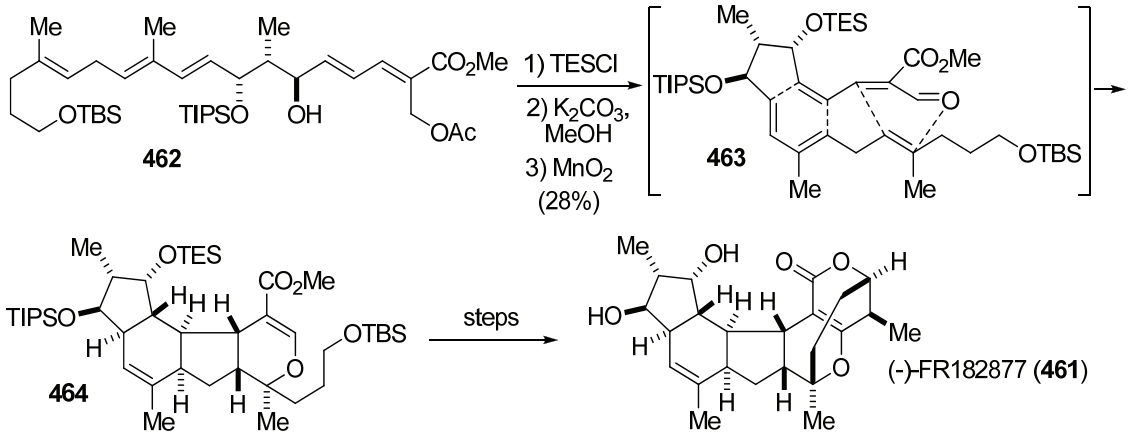
Scheme 108. Organocatalytic IMDA reaction in the synthesis of solanapyrone D (**451**)

A catalytic transannular asymmetric Diels-Alder (TADA) reaction was reported recently by E. Jacobsen.[126] He found, that silicon-containing macrocyclic ketones undergo catalytic TADA reaction in the presence of chiral Lewis acid catalyst (**460**) with good *endo*-selectivity and enantiomeric excess. This method could be applied for a number of terpenoid natural products, containing a *trans*-octalene core. He has shown the usability of this catalytic TADA reaction for the synthesis of sesquiterpene 11,12-diacetoxydrimane (**456**). Ring closing metathesis of linear compound **457** gave macrocycle **458**, which was subjected to the TADA reaction and after cleavage gave the desired product **459** with 83 % *ee* and a diastereomeric ratio of more than 20:1 (**Scheme 109**).



Scheme 109. Catalytic TADA reaction for the synthesis of 11,12-diacetoxydrimane (**456**)

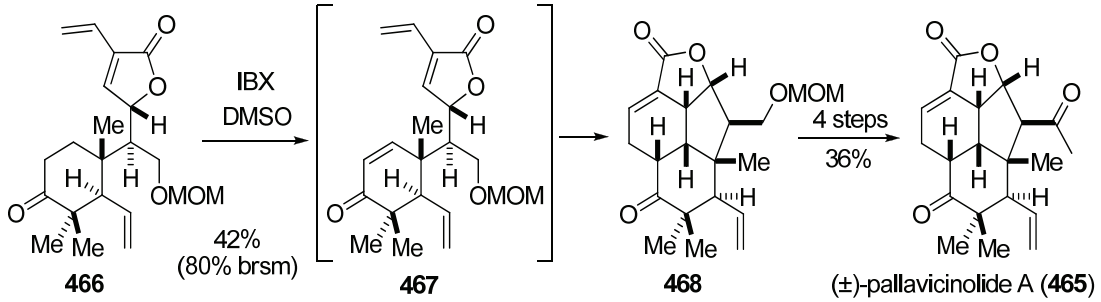
In a recent total synthesis of (-)-FR182877 (**462**) by Japanese authors a tandem biomimetic IMDA-IMHDA (intramolecular Diels-Alder - hetero Diels-Alder reaction) has been applied (**Scheme 110**).[127] Deprotection of the alcohol function of linear polyene **462**, and oxidation with MnO_2 resulted in the diastereoselective formation of tetracyclic compound **464**, which was further converted to (-)-FR182877 (**462**) in several steps. The first approaches to this molecule were reported by E. Sorensen in 2002[128] and D. Evans in 2003.[129]



Scheme 110. Total synthesis of (-)-FR182877 (**462**) by a tandem IMDA-IMHDA reaction

One more interesting example for a biomimetic Diels-Alder reaction is shown with the total synthesis of (±)-pallavicinolide A (**465**), reported by Chinese authors (**Scheme 111**).[130] Diketone **466** was treated with IBX (2-iodoxybenzoic acid) and the *in situ* formed unsaturated diketone **467** underwent intramolecular Diels-Alder cyclization with diastereoselective

formation of fused tetracycle **468**, which was converted to (±)-pallavicinolide A (**465**) via modification of the side chain in four steps.

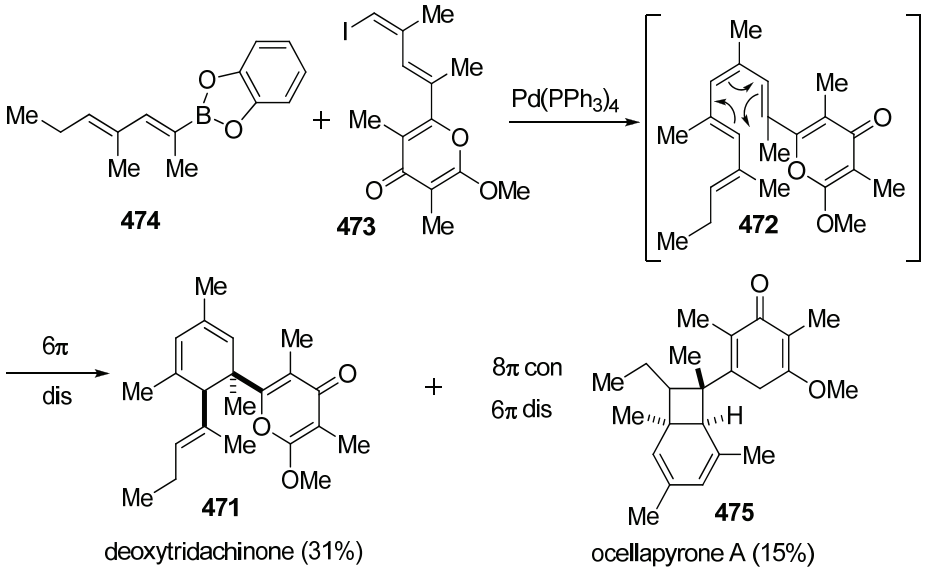


Scheme 111. Total synthesis of (±)-pallavicinolide A (**465**)

Since the Diels-Alder reaction is one of the most commonly used key transformation in the total synthesis of natural products, the number of its applications is too huge to show all of them in this modest review.

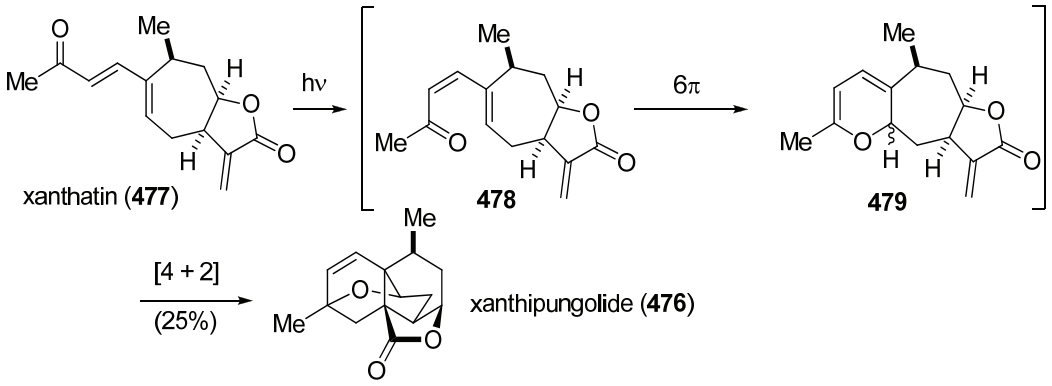
6π-Electrocyclization reactions

Baldwin[131] and Trauner[132] independently reported biomimetic syntheses of deoxytridachione (**471**). These syntheses follow the proposed biogenetic pathway, involving 6π-electrocyclization of tetraene **472**. In Trauner's synthesis tetraene **472** was prepared by Pd-catalyzed coupling of vinyl iodide **473** and boronate **474**. This intermediate spontaneously underwent 6π-cyclization to give 31 % of deoxytridachinone (**471**) and 15 % of ocellapyrone A (**475**), which was formed by an 8π-6π electrocyclization sequence.



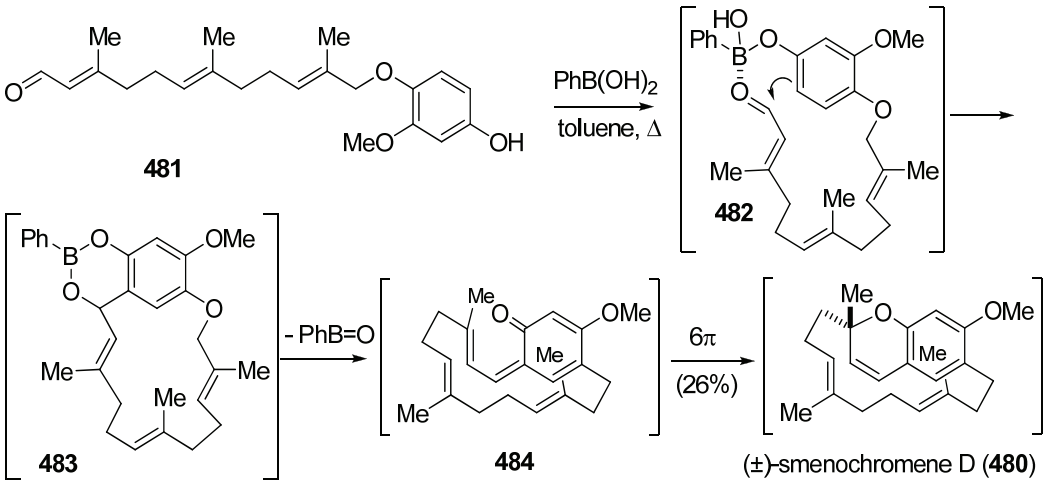
Scheme 112. Synthesis deoxytridachinone (**471**) by D. Trauner

Synthetic approaches toward sesquiterpene lactone xanthipungolide (**476**), isolated from the Egyptian weed *Xanthium pungens*, along with xanthatin (**477**) has been reported.[133] Xanthipungolide (**476**) was proposed to arise from xanthatin (**477**) via *Z*,*E*-isomerization (**478**) followed by oxa-6π electrocyclization to afford (*2H*)-pyran **479**, which then undergoes intramolecular Diels-Alder reaction (**Scheme 113**). Indeed, irradiation of **477** afforded **476** in 25% yield. Presumably, the oxa-6π electrocyclization step is not highly diastereoselective, yet it is reversible. As the two possible diastereomers rapidly interconvert, only one of the diastereomers of **479** can effectively undergo the intramolecular cycloaddition.



Scheme 113. Biomimetic synthesis of xanthipungolide (**476**)

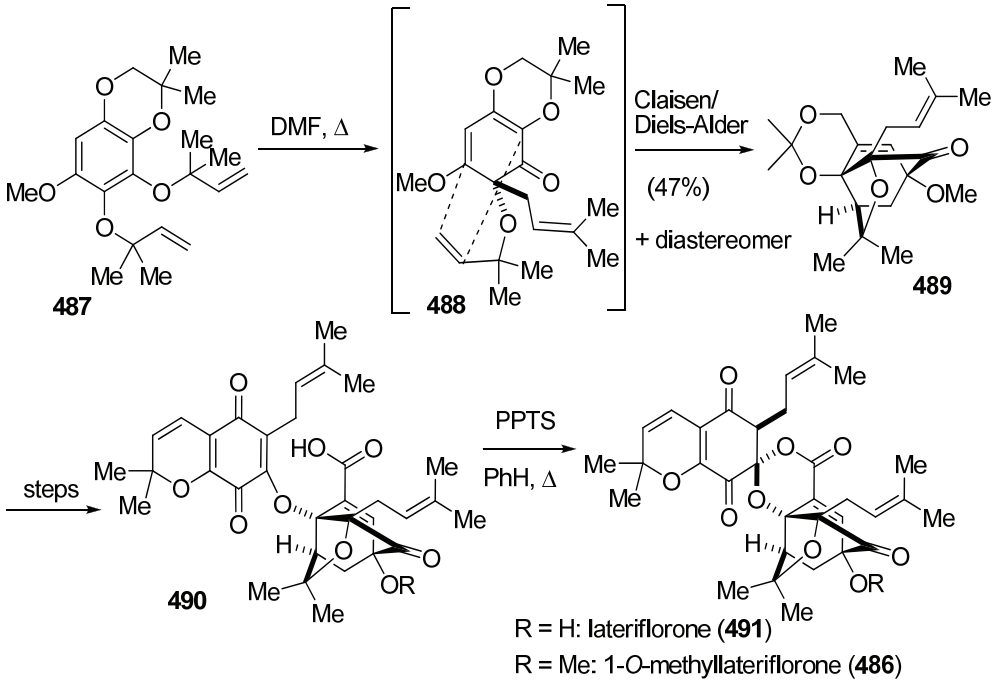
Biomimetic total synthesis of smenochromene D (**480**) was recently reported by D. Trauner (**Scheme 114**).[134] Heating of aldehyde **481** with phenylboronic acid affected macrocyclization (intramolecular Fridel-Crafts alkylation) to afford the natural product. This reaction presumably proceeds through the intermediacy of cyclic borate **483** and vinyl *ortho*-quinone methide **484**, whose oxa-6π electrocyclization installs the chromene system of **480**.



Scheme 114. Biomimetic synthesis of smenochromene D (**480**) by D. Trauner

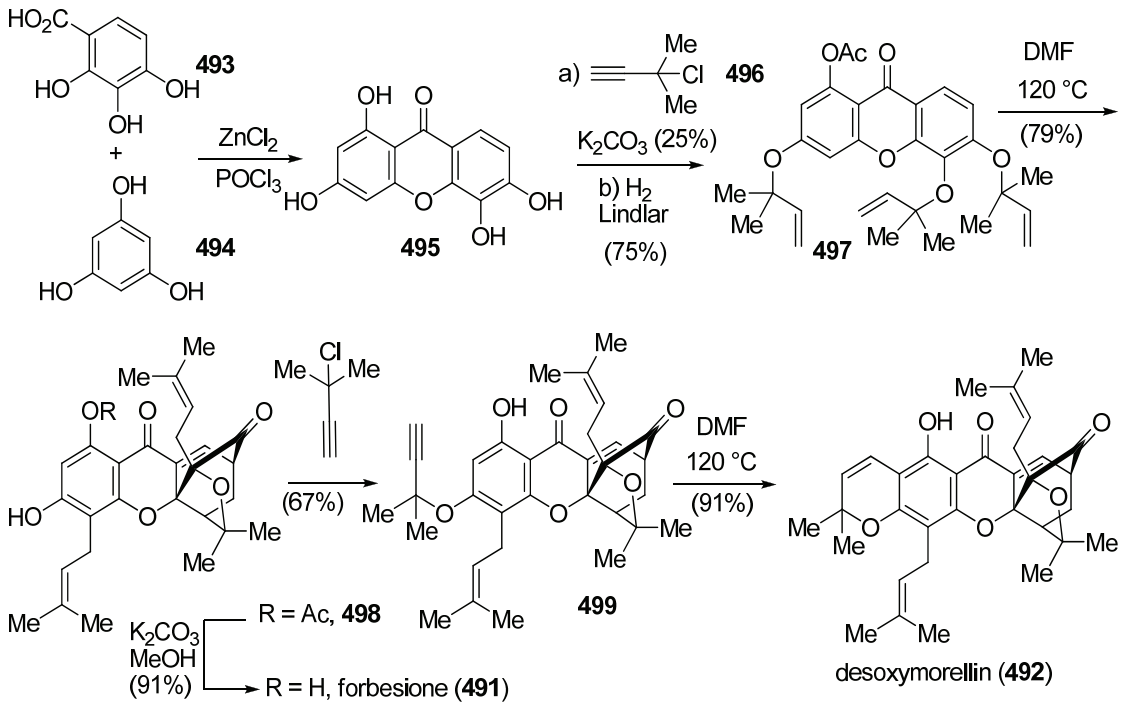
Biomimetic Cope rearrangement

The total synthesis of 1-*O*-methyllateriflorone (**486**) was described by K. C. Nicolaou (**Scheme 115**).[135] The construction of the cage-like domain of the molecule involved a biomimetic Claisen/Diels-Alder cascade of compound **487** to form Diels-Alder adduct **489** in 47 % yield. The spiroxalactone framework of lateriflorone (**491**) was generated by an intramolecular Michael reaction within precursor **490** involving the carboxylate residue as the nucleophile. This finding might bear on the biosynthetic pathway by which nature forms lateriflorone.



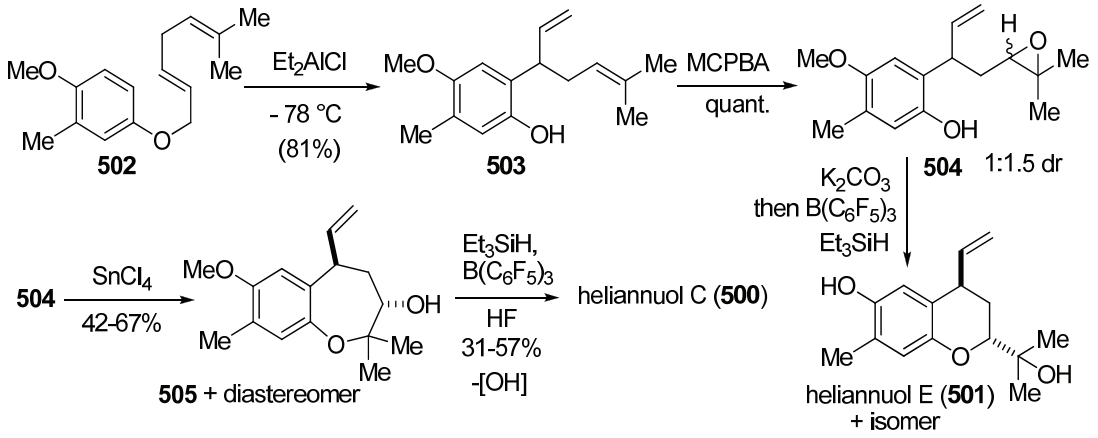
Scheme 115. Total synthesis of 1-*O*-methyllateriflorone (**486**) Nicolaou.

Synthesis of forbesione (**491**) and desoxymorellin (**492**) published by E. Theodorakis *et al.* is based on tandem Claisen/Diels-Alder/Claisen rearrangement (**Scheme 116**).[136] Heating of acid **493** and resorcinol **494** with $ZnCl_2$ and $POCl_3$ gave xanthone **495** in 46% yield. Alkylation with propionyl cloride **496** and hydrogenation gave compound **497**, which underwent a Claisen/Diels-Alder cascade to form regioselectively compound **498** which is converted to forbesione after solvolysis. Next, alkyne Claisen rearrangement afforded desoxymorellin (**492**) from **499** in 91 % yield. Nicolaou *et al.* has also published the total synthesis of methyl forbesione using a similar biomimetic strategy.[137]



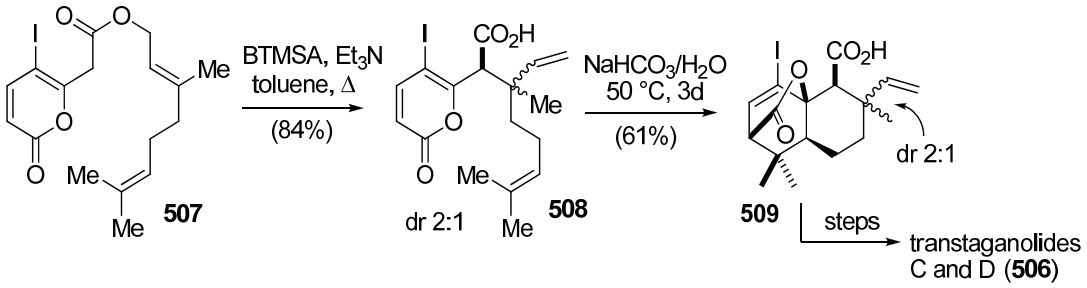
Scheme 116. Synthesis of forbesione (**491**) and desoxymorellin (**492**) by E. Theodorakis

Claisen rearrangement was also used in the synthesis of (±)-heliannuol C (**500**) and E (**501**).[138] Treatment of diene **502** with mild Lewis acid provided diene **503** by regioselective Claisen rearrangement in good yield. Epoxidation with *m*CPBA gave epoxide **504**, which could be converted to the benzoxepane ring of heliannuol C by acid-mediated cyclization, or to heliannuol E by base-mediated cyclization followed by deoxygenation.



Scheme 117. Claisen rearrangement in the synthesis of (±)-heliannuol C (**500**) and E (**501**)

A concise biomimetic approach toward transtaganolides C and D (**506**) involving an Ireland-Claisen rearrangement/intramolecular Diels-Alder reaction sequence suggesting the involvement of pericyclic reactions in the biosynthesis of these biologically active plant metabolites was recently reported (**Scheme 120**).[139] Heating of 2-pyranon allylic ester **507** in a microwave reactor with *N,O*-bistrimethylsilylacetamide (BTMSA) and triethylamine resulted in Ireland-Claisen reaction to give acid **508** in good yield as a 2:1 mixture of diastereomers. Mild heating of this product under basic conditions, to prevent decarboxylation, gave the tricyclic product of an intramolecular Diels-Alder reaction, polycycle **509**, which could lead to natural products transtaganolides C and D. The authors of this synthesis highlight the possibility of the existence of a rare Ireland-Claisen-type rearrangement in the biosynthesis of these compounds.

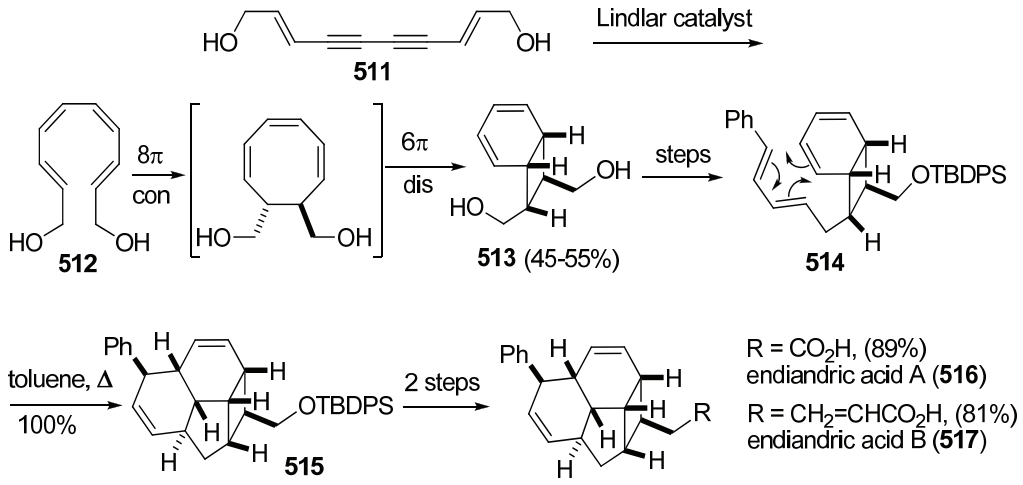


507 508 509

Scheme 118. A biomimetic approach toward transtaganolides C and D

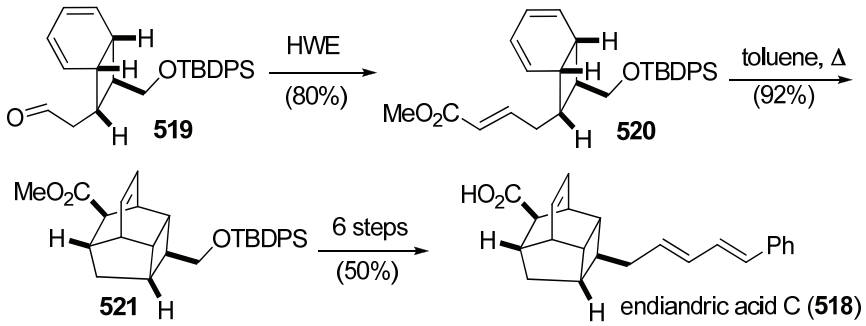
8π-Electrocyclization reactions

In 1980, Black proposed that the endiandric acids could arise biosynthetically from linear polyenes.[140] In 1982, K. C. Nicolaou gave chemical support to Black's hypothesis by chemically synthesizing endiandric acids A-G.[141] An example of the biomimetic approach to endiandric acids A-G is shown below (**Scheme 119, 120**).



Scheme 119. Synthesis of endiandric acids A and B

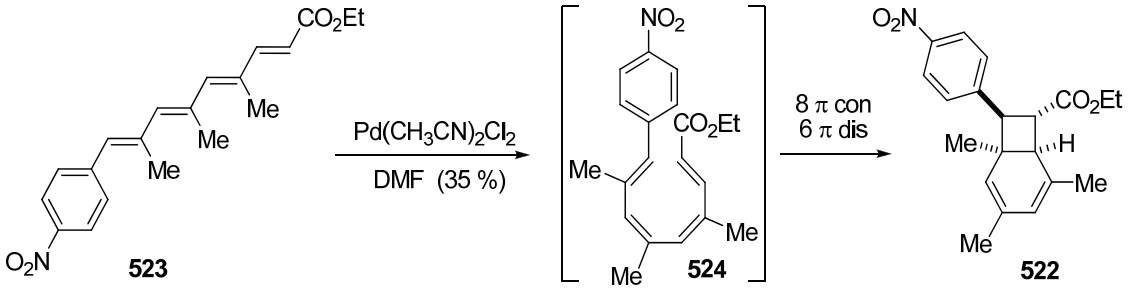
Hydrogenation of diendiyne **511** to tetraene **512** triggered a pair of spontaneous 8π conrotatory and 6π disrotatory electrocyclizations to give bicyclic compound **513** which corresponds to the core structure of endiandric acids D, E, F and G. After some functionalization, tetraene **514** was heated to undergo intramolecular Diels-Alder cycloaddition to provide after cleavage of the silyl protecting group and oxidation of the resulting alcohol tetracyclic endiandric acid A (**516**). Endiandric acid C (**518**) was prepared from aldehyde **519**. HWE reaction of this aldehyde gave methyl ester **520**, which was heated to undergo intramolecular Diels-Alder cycloaddition to get fused tetracyclic compound **521**, which was later converted to endiandric acid C (**518**) in 6 steps.



Scheme 120. Synthesis of endiandric acid C (**518**)

Baldwin and co-workers have also synthesized the SNF4435 core (**522**).[142] They chose to use a late stage introduction of the C4-C5 and C6-C7 *Z*-olefins using Pd(II) chemistry, which is known to promote olefin isomerization. It is notable that without the introduction of

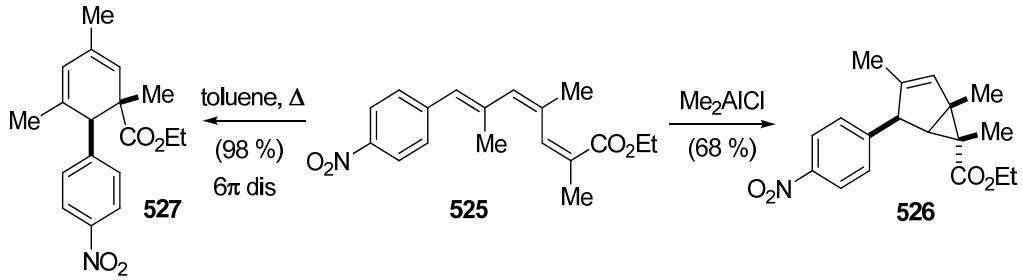
palladium to the reaction conditions, the all *E*-olefin isomer **523** does not undergo the requisite electrocyclizations to form bicyclo[4.2.0]octadiene **524**. It is also notable that the isomerization was specific for the C4-C5 and C6-C7 double bonds evident by the stereochemistry of the product **522**.



Scheme 121. Synthesis of SNF4435 core (**522**) by Baldwin

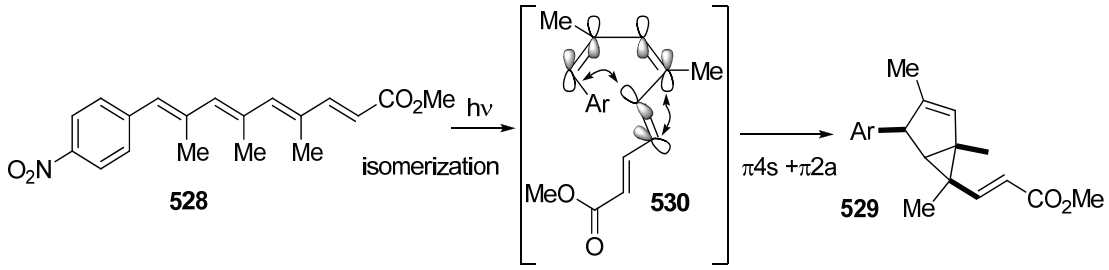
Unusual electrocyclization reactions.

Baldwin and Trauner have also, independently, used acyclic polyunsaturated compounds similar to **523** for their syntheses of the bicyclo[3.1.0]hexene core of the crispatene family of compounds. Trauner has shown that upon exposure to Lewis acids triene **525** undergoes an unusual stereospecific electrocyclization to provide bicyclo[3.1.0]hexene compound **526**.[143] Mechanism of this reaction could be identified as [π4s + π2a] Diels-Alder reaction, which is also shown in **Scheme 123**. In the absence of a Lewis acid, a 6π-disrotatory electrocyclization occurs to give compound **527**.



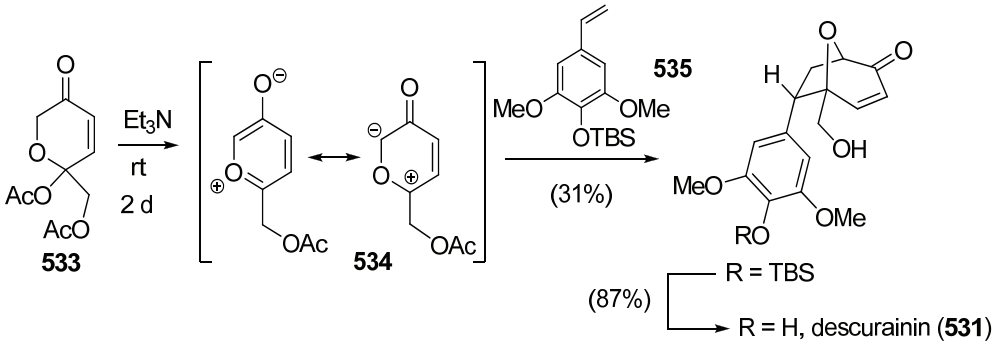
Scheme 122. Novel electrobicyclization reaction of triene **525**

Baldwin and co-workers used photochemical activation of a polyene for the synthesis of the core structure of crispatene type of compounds.[144] Irradiation of compound **528** resulted in the formation of the bicyclo[3.1.0]hexene arrangement **529**. Mechanistically, this is expected to occur via *E-Z* double bond isomerization of the C6-C7 and C8-C9 bonds of (*E,E,E,E*) tetraene **528** to (*Z,Z,E,E*) tetraene **530**, which undergoes an intramolecular photochemical [π4s +π2a] Diels-Alder reaction to form bicyclo[3.1.0]hexane **529** (**Scheme 123**).



Scheme 123. Photochemical activation of polyene **528** for synthesis of core of the crispatene type of compounds **529**

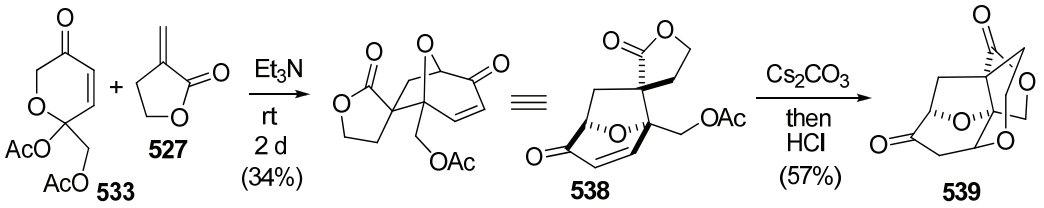
Biomimetic [5+2] cycloaddition could be a possible biosynthetic key step of descurainin (**531**) and cartorimine (**532**), which was shown by B. Snider by the total synthesis of these products.[145] Reaction of bisacetoxy pyranone **533** with Et_3N gave 3-oxidopyrylium ylide **534**, which underwent a stereo- and regiospecific [5+2] cycloaddition with styrene **535** in 31% yield to afford descurainin after hydrolysis (**Scheme 132**).



Scheme 124. Biomimetic [5+2] cycloaddition in the synthesis of descurainin (**531**)

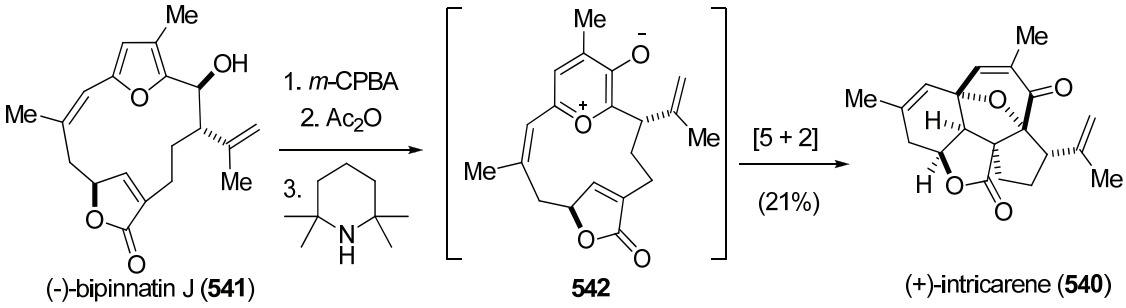
A biomimetic two-step synthesis of the core structure of (±)-polygalolides A, B using the same [5+2] cycloaddition was also reported by B. Snider *et al.* (**Scheme 125**).[146] Treatment

of bisacetoxy pyranone **533** with Et_3N and α-methylenebutyrolactone (**537**) afforded spirobicyclic product **538**. Treatment of **538** with cesium carbonate resulted in acetate hydrolysis, the translactonization and the conjugate addition of the hydroxyethyl group to the enone. Lactonization on acidification afforded the core structure of polygalolides A and B (**539**).



Scheme 125. Biomimetic synthesis of the core structure of (±)-polygalolides A, B

An asymmetric synthesis of (+)-intricarene (**540**), found in gorgonian corals, was described by G. Pattenden in 2006[147] and D. Trauner in 2007.[148] Treatment of (-)-bipinnatin J (**541)** with $VO(acac)_2$-^{t}BuOOH in Pattenden's synthesis or with *m*-CPBA in Trauner's synthesis, followed by acetylation, gave an acetoxypyranone, which underwent a transannular oxidopyrylium-alkene [5+2] cycloaddition of **542** by heating in the presence of 2,2,6,6-tetramethylpiperidine (TMP), producing the polycyclic diterpene (+)-intricarene (**540**). The total synthesis of intricarene **540** mimics most likely its biosynthesis via oxidation of bipinnatin J (**541**) in vivo.



Scheme 126. Biomimetic synthesis of the (+)-intricarene (**540**)

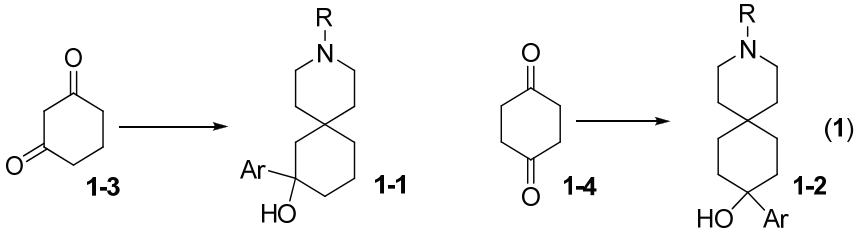
Conclusion and the goal of research

As the review shows, biomimetic strategies including domino sequences enable a rapid and efficient entry to polycyclic structures commonly found in natural products. Even though it is not in all cases clear whether all the reactions in fact do occur in nature and whether enzyme catalysis is involved. The goal of this thesis included the application of biomimetic transformations to the synthesis of various structures that are related to natural products. Thus, one project aimed at the synthesis of spirocyclic alkaloid structures via a rearrangement and reductive amination. Such polyfunctionalized structures should be of interest as scaffolds. Another project dealt with the synthesis of symbioimine and neosymbioimine, which contain a decalin core via an intramolecular Diels-Alder strategy. Finally, novel routes towards the polycyclic antibiotics platensimycin and platencin were investigated.

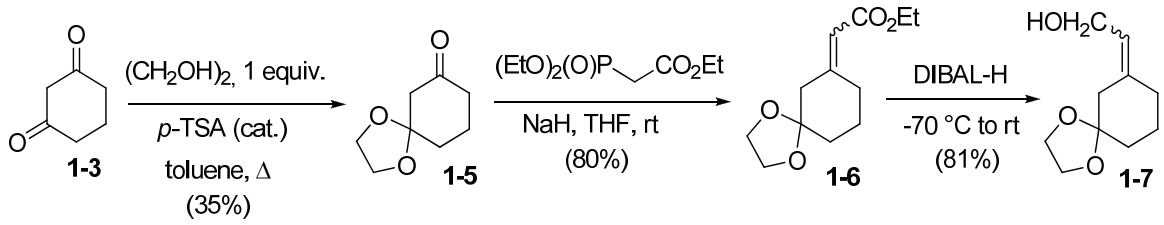
Results and Discussion

1. Synthesis of spirocyclic scaffolds

The goal of this project was a synthesis of *para*- and *meta*-substitued spirocyclic cyclohexanones **1-1** and **1-2**. To elaborate a convenient method for the synthesis of such compounds we took 1,3-cyclohexandione (**1-3**) and 1,4-cyclohexanedione (**1-4**) as starting materials (**eq. 1**).



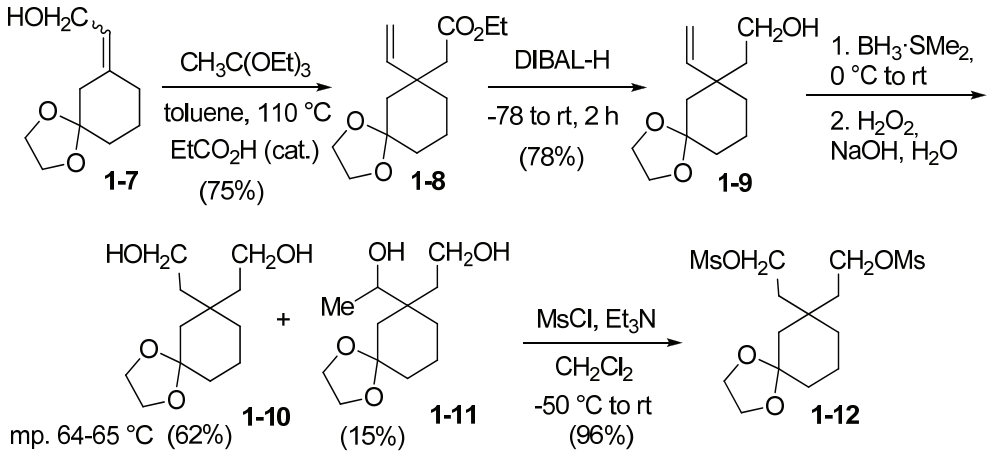
First of all we had to protect one carbonyl function, and functionalize the other one. Starting 1,3-cyclohexandione (**1-3**) could be protected by refluxing it with one equiv. of ethylene glycol and catalytic amounts of *p*-toluenesulphonic acid in toluene with a Dean-Stark apparatus for 2 h followed by work up and fractional distillation of the mono protected 1,3-cyclohexandione **1-5** (**Scheme 1**).[149] Horner Wadsworth Emmons reaction of **1-5** with triethyl phosphonoacetate gave ester **1-6** (1:1 mixture of diastereomers), which was reduced with DIBAL-H to give allylic alcohol **1-7** in good yield.



Scheme 1. Synthesis of allylic alcohol **1-7**

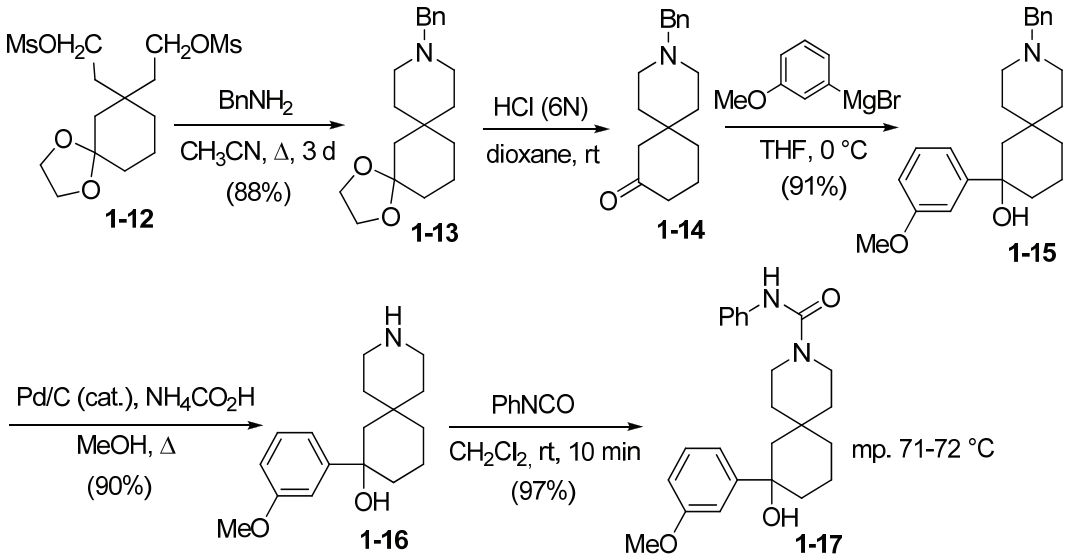
Attempts to create a quaternary spiro center by Michael addition to unsaturated ester **1-6** were unsuccessful. Thus, we decided to make it by Claisen rearrangement. However, the Ireland-Claisen rearrangement[150] of the corresponding acetate of **1-7** was unsuccessful. Then we found that heating of allylic alcohol **1-7** with triethyl orthoacetate in toluene with a catalytic amount of propionic acid (Johnson-Claisen rearrangement)[151] for 24 hours gave 51 % of the desired product of the rearrangement **1-8** (**Scheme 2**). This reaction is

reversible and starting material **1-7** could be recycled and introduced into the same reaction to give additional 16 % of ester **1-8**. The the yield of the product **1-7** could be increased to 75 %. The obtained ester **1-8** was reduced with DIBAL-H, and allylic alcohol **1-9** was hydroborated and oxidized under standard conditions to provide mixture of diols **1-10** and **1-11**. These diols could be separated by flash chromatography to obtain pure **1-10** in 62 % yield as colorless crystals. Mesylation of both alcohol functions of **1-10** gave bis-mesylate **1-12** in high yield.



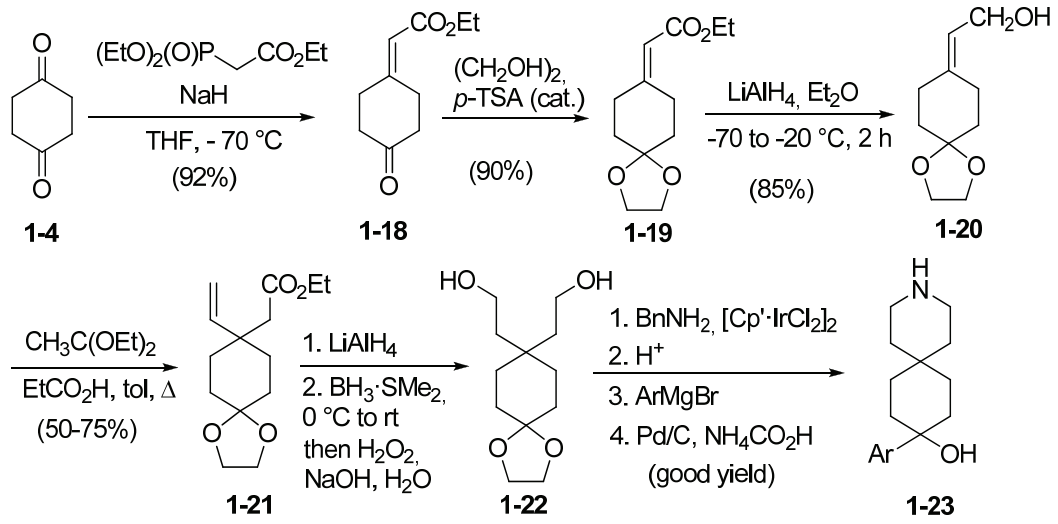
Scheme 2 Johnson-Claisen rearrangement of **7** and conversion to bis-mesilate **1-12**

Mesylate **1-12** could be cyclized to amine **1-13** by refluxing with excess of benzyl amine in acetonitrile for 3 days (**Scheme 3**). Deprotection of compound **1-13** under acidic conditions gave ketone **1-14**, which was converted to alcohol **1-15** by the reaction with *m*-methoxyphenylmagnesium bromide in good yield. The benzyl group was cleaved by Pd/C-catalyzed hydrogenation and the obtained secondary amine **1-16** was converted to carbamate **1-17** by the reaction with phenyl isocyanate. Thus, fully functionalized spirocyclic scaffold **1-17** was prepared in 12 steps from inexpensive starting material 1,3-cyclohexanedione.



Scheme 3. Synthesis of spirocyclic carbamide **1-17**

The corresponding *para*-substituted spirocyclic compounds were prepared by analogous way with minor change in the conditions (**Scheme 4**). 1,4-Cyclohexanedione (**1-4**) was selectively converted to ketoester **1-18** by the Horner-Wadsworth-Emmons reaction with triethylphosponoacetate with high yield. Obtained ketoester **1-18** was reduced to allylic alcohol **1-19**, which was converted to ester **1-20** by Johnson-Claisen rearrangement by heating of alcohol **1-19** with triethylorthoacetate as in the previous synthesis. Reduction of ester **1-21** with $LiAlH_4$ followed by hydroboration of the double bond gave diol **1-22**, which was cyclized with catalytic amounts (5 mol%) of *bis*-pentamethyl cyclopentadienyl iridium trichloride $[Cp'\cdot IrCl_2]_2$[152] with good yield. This efficient cyclization goes through the oxidation of alcohol to the aldehyde, formation of imine and reduction of the imine to the amine function with the iridium catalyst.[153] The obtained benzylamine was converted to aminoalcohol **1-23** by cleavage of ketal, addition of arylmagneium bromide to ketone and hydrogenative deprotection of benzylamine.



Scheme 4. Synthesis of *p*-substituted *spiro*-scaffolds

In conclusion, we have elaborated an efficient new synthesis of *meta*- and *para*-spiro scaffolds **1-17** and **1-23**. The Johnson-Claisen rearrangement was a key reaction for construction of the quaternary center in the described syntheses of the spirocyclic compounds.

2. A novel reaction for the synthesis of 7-aryltetralones

The palladium-catalyzed arylation of ketones and ester derivatives has greatly expanded the repertoire of useful methods in organic chemistry.[154] Key parameters for this transformation include the use of sterically hindered and electron-rich phosphine ligands and a suitable solvent. Important recent discoveries in this regard were made by the Buchwald[155] and Hartwig groups.[156] The arylation can be run with the carbonyl compound directly in the presence of a base. Alternatively, preformed enolates such as trialkylsilyl enol ethers can be arylated in the presence of ZnF_2 or $Zn(OtBu)_2$ as addititives.[156] Thus, the potential applications seem countless.

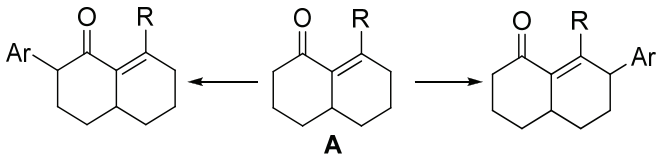
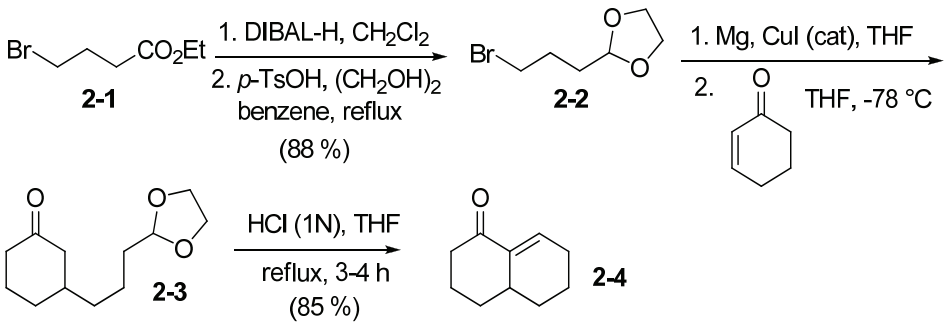


Figure 1. Issues of regio- and stereochemistry in the potential palladium-catalyzed arylation of 3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalenone derivatives **A**

In the context of the synthesis of functionalized decalin derivatives for the synthesis of the symbioimine molecule,[167] we became interested in the arylation of enone systems of type **A** (**Figure 1**).[1] Besides possible regioisomers, for each pathway stereoisomers (*cis*/*trans*) might form. The parent substrate, enone **2-4**, was prepared essentially according to the literature by the copper-catalyzed 1,4-addition of 2-(3-bromopropyl)-1,3-dioxolane[157] (**2-2**) followed by acid-induced deprotection-cyclization of the ketoacetal **2-3** (**Scheme 1**).[158]

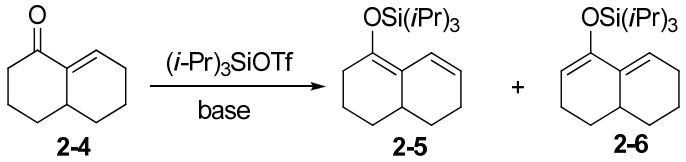


Scheme 1. Synthesis of enone **2-4**

[1] In each chapter, the numbering of Figures and Schemes start with 1.

Initially, we examined the regioselective formation of the two possible triisopropylsilyl dienol ethers. Although the selective formation of the unwanted isomer **2-6** is possible under various conditions, the best ratio in favor of the dienol derivative **2-5** was 68:32. The enone **2-4** was also subjected to modified Kharasch conditions [(a) MeMgBr, $FeCl_3$; (b) TMSCl, Et_3N, HMPA, 23 °C, 2 h] resulting in the exclusive formation of the trimethylsilyl dienol ether corresponding to **2-6**. These conditions are known to produce the thermodynamic dienol ether from a cyclic enone.[159] However, the trimethylsilyl derivative was not obtained very pure and proved to be somewhat unstable. Although the mixture of the two dienol ethers **2-5** and **2-6** could not be separated by chromatography, their structures could be assigned by comparison of the chemical shifts of the vinylic protons with corresponding signals of similar compounds.[160] Thus, the vinylic protons of **2-6** appear at δ = 4.92 and 5.96 ppm, whereas the two vinylic protons of **2-5** resonate at d = 5.53 and 6.50 ppm. The latter is a doublet (J = 9.8 Hz), which clearly supports the assignment.

Table 1 Regioselectivity in the formation of the silyl dienol ethers **5** and **6**



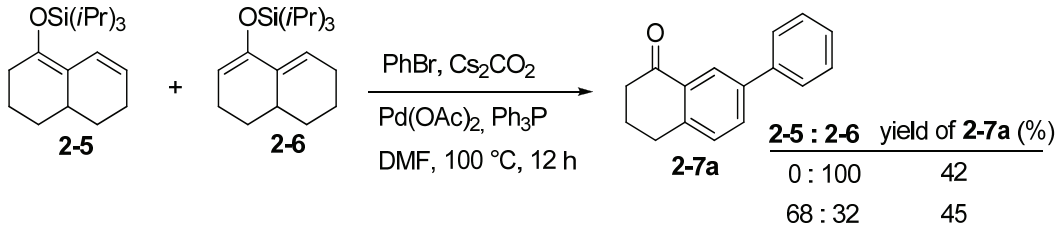
2-4 **2-5** **2-6**

entry	conditions	Ratio **2-5**: **2-6**[a]	Yield of **2-5** + **2-6** (%)
1	2,6-lutidine, CH_2Cl_2, -20 °C, 1 h	0:100	95
2	2,6-diisopropyl-*N,N*-dimethylaniline, CH_2Cl_2, -20 °C, 24 h	0:100	96
3	Cy_2NEt, CH_2Cl_2, -78 °C, 2 h	30:70	89
4	$KN(SiMe_3)_2$, THF/DMF (1:1), -78 °C, 24 h	50:50	82
5	*i*-Pr_2EtN, CH_2Cl_2, -20 °C, 24 h	58:42	95
6	*i*-Pr_2EtN, CH_2Cl_2, -78 °C, 24 h	68:32	98

[a] The ratio **2-5**/**2-6** was determined by ^1H NMR spectroscopy.

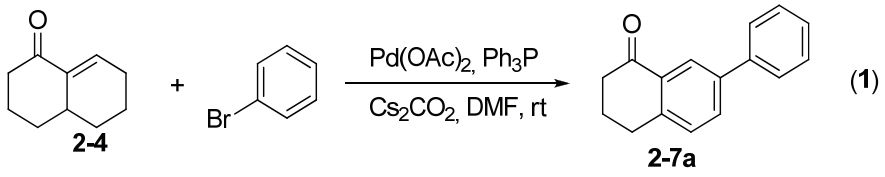
We then asked ourselves whether the regiochemistry of the dienol ethers would be transformed to the corresponding arylated derivatives in a Buchwald-Hartwig arylation. Thus, dienol **2-6** ether was subjected to a palladium-catalyzed arylation reaction with bromobenzene in the presence of $Pd(OAc)_2$, Ph_3P, and Cs_2CO_3 as additive (Scheme 2).

Suprisingly, the only product that we could isolate was the 7-phenyltetralone **2-7a**. There were no Heck-type products[161] and no α-arylated products detectable in the reaction mixture. If the reaction was run on a mixture of **2-5** and **2-6** (**2-5**:**2-6** = 68:32), the same compound **2-7a** was isolated as the only product.



Scheme 2 Arylation of silyl dienol ether **6** and a mixture of **5** and **6**

Since it was described earlier that α,β-unsaturated ketones could be directly arylated in the γ-position with bromoarenes and $Pd(OAc)_2/PPh_3$ in DMF/Cs_2CO_3 at 60-120 °C,[162] we applied these conditions directly to enone **2-4**. Treatment of enone **2-4** with bromobenzene under these conditions afforded as well the unexpected biaryl derivative **2-2-7a** in 32-45% yield (**eq 1**). The normal α-arylation product could not be detected by LC-MS after reaction workup.



Next, we tried to optimize this reaction by varying additives, solvent, and phosphine ligands. As described in the literature, certain tetraalkylammonium salts can positively affect palladium-catalyzed Heck-type reactions.[163] It was found that addition of 1 equiv.of tetrabutylammonium bromide (TBAB) to the reaction mixture dramatically increased the yield of the reaction, resulting in 71% yield of 7-phenyltetralone **2-7a** (**Table 2**, entry 3). In addition, heating of the mixture was not necessary. These optimization studies were followed by LC-MS using 10 mol % of biphenyl as an internal standard. Regarding the solvent, DMF gave the best yield (entry 3), followed by NMP (70%, entry 6). Among various ligands that were tried, triphenylphosphine was found to be the best one (entry 3). In the absence of a phosphine ligand the reaction does not take place at all. Electrondonating and hindered phosphines (*t*-Bu_3P, entry 8, $furyl_3P$, entry 10) seemingly

decrease the rate of the aromatization step. With these ligands, mixtures of bi- and triarylated products were detected by LC-MS.

Again, the reaction is highly γ-selective, and no α-arylated products were detected. Actually, the putative product of the normal γ-arylation was detected by LC-MS {[M]+(**2-7a**) +4} at the beginning of the reaction. Furthermore, in some cases intermediates with {[M]+(**2-7a**) + 2} were detected. The rate of the dehydrogenation-aromatization is very high, and only the aromatic product was detected at the end of the reaction. With 1 equiv.of bromobenzene, the reaction does give **2-7a** as well, but conversion and yield were lower.

Table 2. Effect of trialkylammonium salts, solvents, and phosphine ligands on the reaction of enone **2-4** with bromobenzene

entry	Key variables	Yield of **2-7a** (%)	entry	Key variables	Yield of **2-7a** (%)
1[a]	no PTC, 120 °C	45	6[b]	NMP	70
2[a]	Bu_4NBr, 60 °C	20	7[b]	dimethylacetamide	67
3[a]	Bu_4NBr, 23 °C	71	8[c]	tBu_3P	trace
4[a]	Bu_4NOAc, 23 °C	7	9[c]	(*o*-tolyl)$_3$P	27
5[a]	Bu_4NClO_4, 23 °C	48	10[c]	furyl$_3$P	0

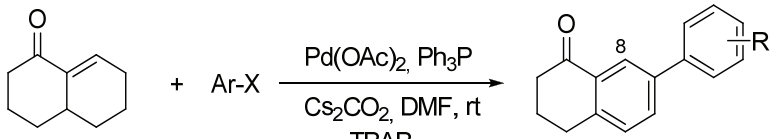
[a] Reaction conditions: DMF, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), additive (1 equiv). [b] Reaction conditions: solvent, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), TBAB (1 equiv), 3 d, 23 °C. [c] Reaction conditions: DMF, $Pd(OAc)_2$ (5 mol %), phosphine (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), TBAB (1 equiv), 3 d, 23 °C.

We assume that the reaction proceeds via γ-arylation of the dienolate anion, followed by a fast dehydrogenation/aromatization of the intermediate in a tandem process. Most likely the aromatization is initiated by insertion of a PdL_2 species into an activated C-H bond, followed by the elimination of PdL_2H_2. In essence, a reversal of classical hydrogenation steps must take place. Addition of some electron donors or hydrogen donors (HCO_2H, cyclohexadiene, CuBr) that could be sacrificed did not allow us to isolate nonaromatized intermediates. Addition of other reagents (styrene, methyl acrylate, benzoquinone) that might speed the aromatization step only decreased the yield of **2-7a**. In the absence of bromobenzene or in the presence of chlorobenzene only products of self-condensation of enone **2-4** were detected.

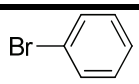
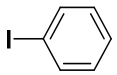
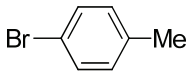
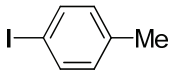
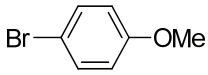
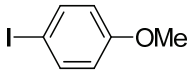
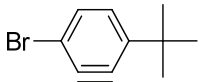
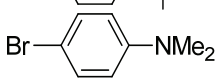
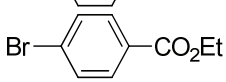
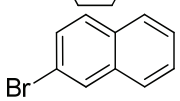
Using the optimized conditions we coupled a number of haloarenes with the enone **2-4**. As it turned out, the reaction has broad scope, at least for enone **2-4**, and both aryl bromides and iodides could be coupled in moderate to good yields (**Table 3**). The 7-aryltetralones show a characteristic peak in the ^{1}H NMR spectrum in the range between δ= 8.16- 8.33 ppm, which can be attributed to the isolated proton at C-8.

7-Aryltetralones have been used, for example, in the synthesis of CCR5 antagonists as anti-HIV-1 agents.[164] These aryltetralones were prepared in a multistep sequence consisting of an intramolecular Friedel-Crafts cyclization of the corresponding phenylbutyric acids followed by palladium-catalyzed Suzuki coupling with arylboronic acids. As a whole only a few examples of 7-aryltetralones **2-7** are described in the literature.[165]

Table 3. Synthesis of 7-aryltetralones **2-7a-g**

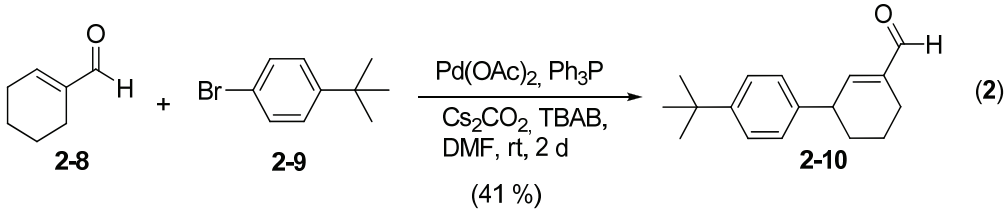


2-4 **2-7a-g**

entry	Ar-X	product	Isolated yield [%]
1		**2-7a**	71
2		**2-7a**	68
3		**2-7ba**	51
4		**2-7b**	54
5		**2-7c**	62
6		**2-7c**	55
7		**2-7d**	59
8		**2-7e**	47
9		**2-7f**	48
10		**2-7g**	50

[a] Reaction conditions: DMF, $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), PhBr (5 equiv), Cs_2CO_3 (2.5 equiv), TBAB (1 equiv), 23 °C.

In a control experiment we applied the optimized conditions to the coupling of 1-cyclohexene-1-carbaldehyde **2-8** and 1-bromo-4-*tert*-butylbenzene **2-9** (**eq 2**). Somewhat surprisingly, we isolated not the expected biphenyl-3-carbaldehyde but rather the normal γ-arylation product **2-10** (41% yield). Characteristic for this compound is a signal at δ = 6.79 ppm for the terminal enal H. The δ-H resonates at δ = 3.62 ppm. Related compounds are prepared by multistep sequences.[166]



2-8 **2-9** **2-10** (**2**)

In summary, we developed a new convenient synthesis of 7-aryltetralones by a novel room-temperature palladium-catalyzed arylation dehydroaromatization sequence. This strategy of applying the arylation/aromatization to a cyclic precursor containing one double bond and an electronwithdrawing group might be a valuable option for accessing certain biaryl compounds.

3. Total synthesis of (±)-symbioimine and analogs

Symbioimine (**3-1**) is a novel tricyclic iminium alkaloid which recently was isolated from the symbiotic marine dinoflagellate *Symbiodinium* sp.[167] This rather unusual compound occurs in nature as an inner salt of an imine and an aryl sulphuric acid (**Figure 1**). Such zitterionic compounds are very rare,[168] and the total synthesis of **3-1** certainly poses a challenging task. A related compound is the amphoteric neosymbioimine (**3-2**).[169] Besides the unique structural features, the biological activity of symbioimine (**3-1**) is noteworthy as well. Thus, it inhibits the differentiation of progenitor cells (RAW264) into mature osteoclasts with an EC_{50} = 44 μg mL^{-1}. Therefore, **3-1** has potential as a drug for the treatment of osteoporosis. In addition, symbioimine significantly reduces cyclooxygenase-2 (COX-2) activity at 10 μM.[169]

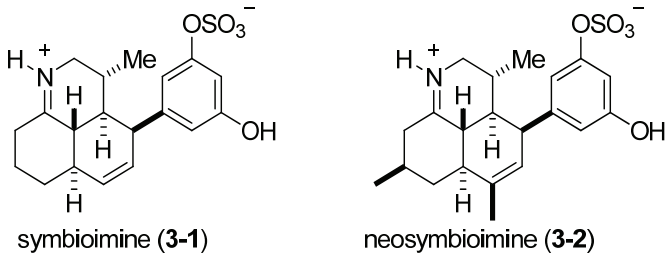
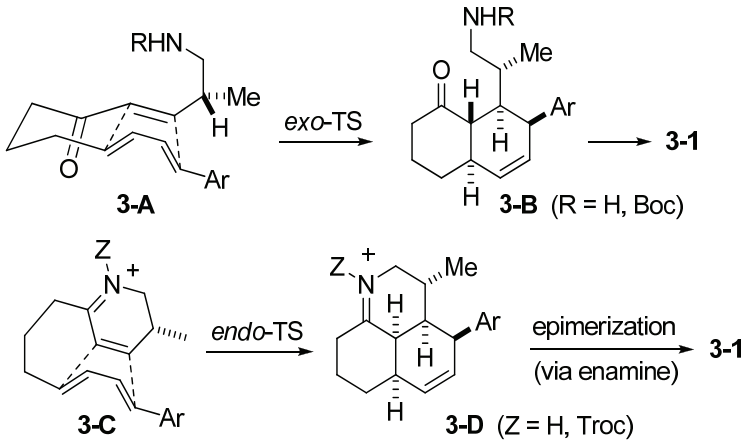


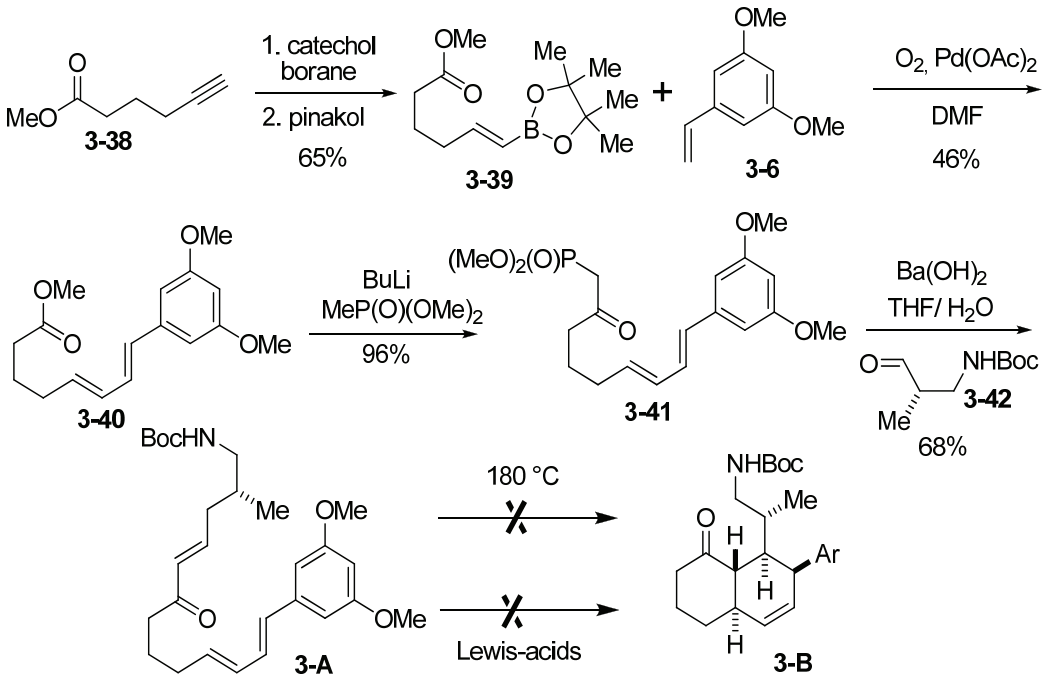
Figure 1. Alkaloids symbioimine (**3-1**) and neosymbioimine (**3-2**)

The biosynthesis of **3-1** might involve intramolecular Diels-Alder (IMDA) reactions, either of a trienone via an *exo* transition state of type **A** followed by cyclization to an imine (**Scheme 1**). Alternatively, an *endo*-IMDA of a dihydropyridinium cation (cf. transition state **C**) followed by epimerization of the cycloadduct via an enamine might be operative.[169] There is support for the latter mode from a model study of Snider et al.[170] who prepared deoxysymbioimine via an IMDA of a 2,3-dihydropyridinium cation **C** (Z = Troc, Ar = Ph).



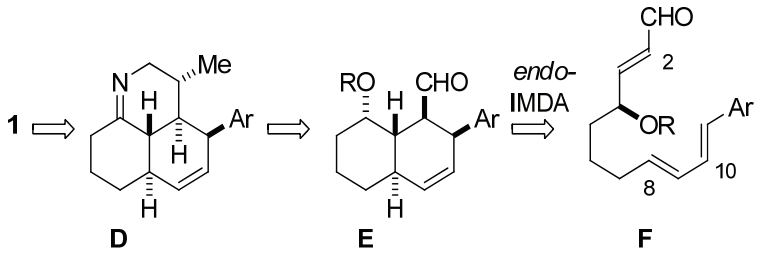
Scheme 1. Possible biosynthetic key steps for symbioimine (**3-1**)

In preliminary studies we found that trienone **3-A** (**Scheme 2**) did not undergo any Diels-Alder reaction, even after heating the substrate in a sealed tube (xylene, 180 °C) for 24 h. We considered that the orbital overlap is not ideal since large and small coefficients at the termini do not really match. This compound **3-A** was obtained by HWE reaction of ketophosphonate **4-41** and chiral aldehyde **3-42**, which was obtained according to the literature procedure.[171] Phosphonate **4-41** was obtained from ester **3-40**, and diene mojety was constructed by oxygen-promoted Heck-type reaction of boronate **3-39** and 3,5-dimethoxystyrene (**3-6**).[173]



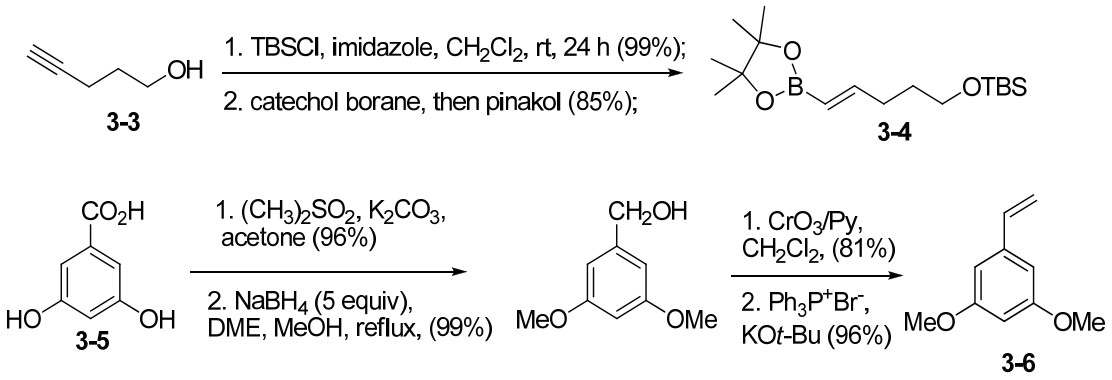
Scheme 2. An attempt of using exo-IMDA reaction of trienone **3-A** for synthesis of **3-1**

We reasoned that positioning an electron withdrawing group on the other side of the double bond should allow for a more facile IMDA (**Scheme 3**). Some literature precedence indicates that this approach should be feasible.[172] However, a solution for extension of the aldehyde function in the cycloadduct **E** combined with a diastereoselective introduction of the methyl group would have to be found.



Scheme 3. Retrosynthetic plan for the synthesis of symbioimine (**3-1**)

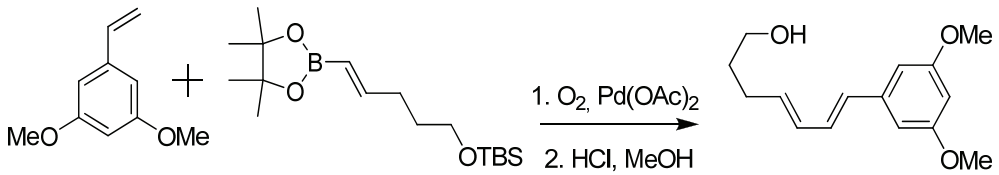
As an initial milestone we targeted an efficient and large scale synthesis of (*E,E,E*)-undeca-2,8,10-trienals **3-12** (structure **F**). A key step of this synthesis is the preparation of the 1-aryl-1,3-(*E,E*)-diene moiety which might be accessible via a palladium-catalyzed Stille or Suzuki coupling. For both methods *E*-vinyl halide building blocks are required. However, all attempts to prepare suitable Stille or Suzuki precursors were more or less unsuccessful. Therefore, we turned to the palladium-catalyzed oxygen-promoted Heck-type coupling of alkenes with vinyl boronates.[173] Accordingly, the vinyl boronate[174] **3-4** and the styrene[175] **3-6** were prepared by standard procedures (**Scheme 4**).



Scheme 4. Synthesis of starting matherials **3-4** and **3-6**

The Heck coupling of boronate **3-4** and styrene **3-6** under reported reaction conditions (5 mol% $Pd(OAc)_2$, DMA, 23 °C, slow addition of boronate **3-4**), led only to 30% of the coupling product (**Scheme 5**). We significantly improved the yield for this reaction by using 2 equiv. of styrene **3-6** and 10 mol% of $Pd(OAc)_2$ in DMF at 60 °C. The

unreacted styrene was easily recovered by flash chromatography after acidic cleavage of the TBS-group to provide the dienol **3-7** in 68% yield, based on the recovered styrene, and 59% based on **3-4**. This reaction is highly regio- and stereoselective, and only *E,E*-diene was found to be produced in more than 99% diastereomeric purity.



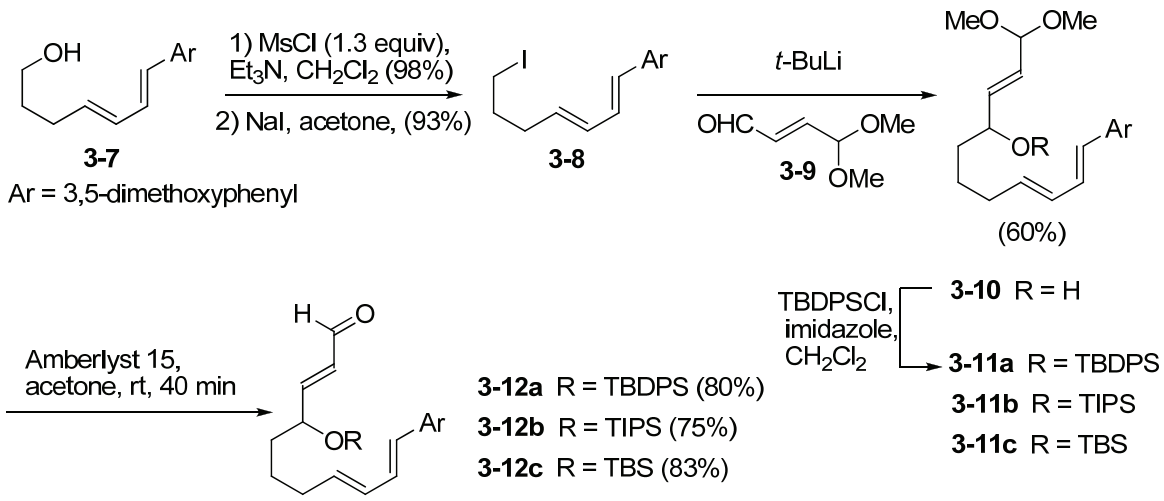
3-6 **3-4** **3-7**

T	solvent	styrene, equiv.	$Pd(OAc)_2$, %	Yield*
23 °C	DMA	3	2	**15%**
23 °C	DMA	3	5	**30-40%**
45 °C	DMF	3	10	**40-46%**
50 °C	DMF	1.8	5	**48%**
50 °C	DMF	3	10	**52%**
60 °C	DMF	2	10	**59%****

* Isolated yields based on the reacted boronate
** **68** % based on the recovered styrene

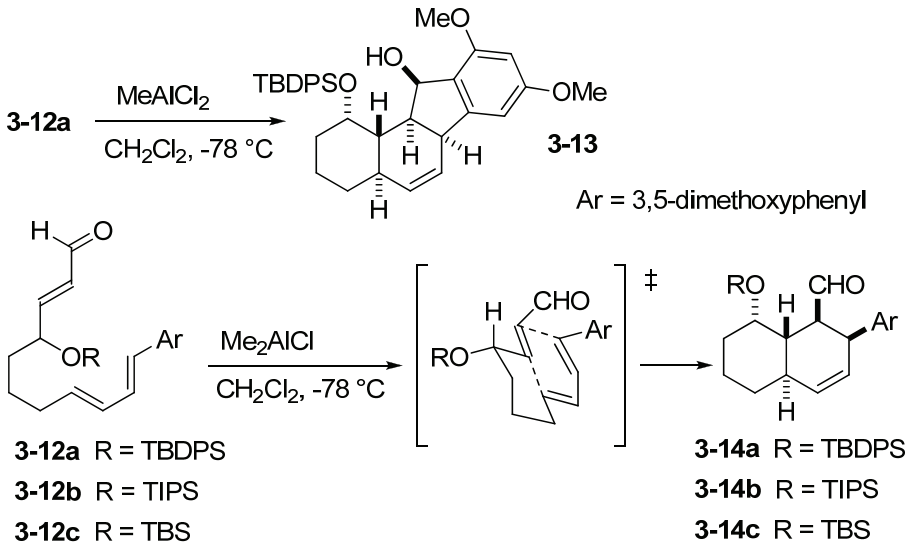
Scheme 5. Optimization of the Heck reaction of **3-4** and **3-6**

Continuing with the synthesis, alcohol **3-7** was converted to the iodide **3-8** in two steps by mesylation (98%) and S_N2-substitution using NaI in acetone (93%) (**Scheme 6**). Transmetalation of iodide **3-8** with *t*-BuLi at -80 °C followed by trapping of the organolithium intermediate with the known (2*E*)-4,4-dimethoxybut-2-enal[176] **3-9**, successfully afforded aldehydes **3-12** after protection of the hydroxyl group with a silicon protecting group followed by hydrolysis of the acetal **3-11**. Thus, syntheses of all-*E*-undeca-2,8,10-trienals **3-12** bearing TBDPS, TIPS and TBS protective groups were possible. The synthesis of **3-12c** was performed on a gram scale.



Scheme 6. Synthesis of the Diels-Alder substrates **3-12**

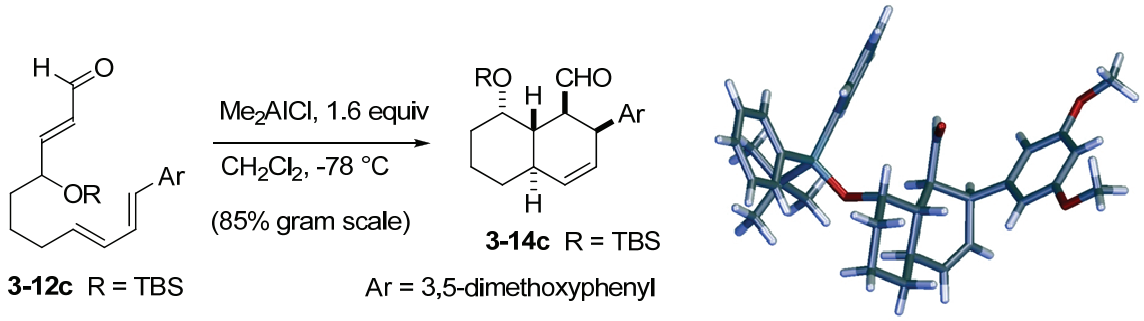
With substrates **3-12** in hand the Lewis acid catalyzed IMDA was investigated (**Scheme 7**).[177] Using $MeAlCl_2$ (1 equiv.) as Lewis acid in CH_2Cl_2 at –80 °C, a fast reaction of **3-12a** was observed. However, the reaction did not stop at the stage of the Diels-Alder product. Rather, a subsequent intramolecular Friedel-Crafts reaction of the aldehyde function with the electron rich aryl ring took place, leading to the tetracyclic compound **3-13** (50% yield). The reaction of **3-12a** with 1 equiv. of the weaker Lewis acid Me_2AlCl at -80 °C led to around 60% conversion of **3-12a** within 24 h to give 50% of isolated **3-14a** as a single diastereomer and no Friedel-Crafts adducts were observed.



Scheme 7. Lewis acid induced IMDA of trienals **3-12a-c**

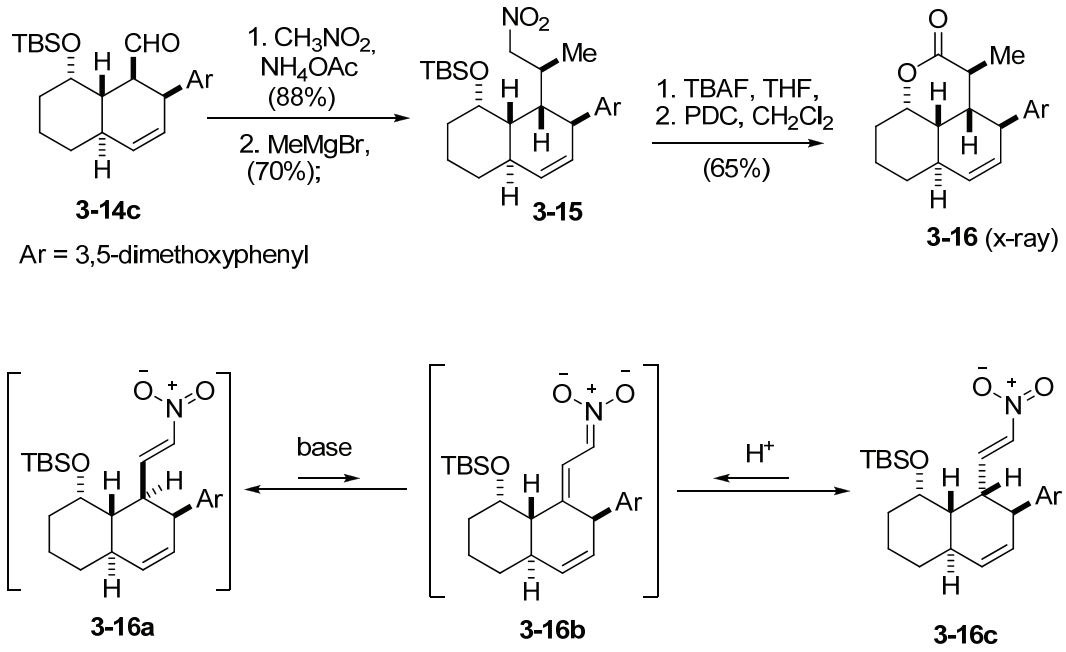
The configuration of **3-14a** could be secured by x-ray analysis (**Scheme 8**). It is interesting to note, that both bulky substituents (Ar and $OSiR_3$) are axially oriented relative

to the decalin ring. The silicon protecting groups do not affect significantly the outcome of the IMDA reaction. Also, the TIPS- and TBS-protected aldehydes **3-12b** and **3-12c** gave around 50% of the corresponding cycloadducts under these conditions. A higher yield could be realized by using 1.6 equiv. of Me_2AlCl yielding, for example, **3-14c** in 85% yield on a gram scale. The cycloadducts already contain four of the five required stereocenters with the correct relative configuration.



Scheme 8. IMDA reaction of **3-12c** and X-Ray structure of **3-14c**

For conversion of the aldehyde function to the aminopropyl appendage, several options were considered. In a first attempt **3-14c** was subjected to a Henry condensation[178] with nitromethane followed by a Michael addition of the resulting nitroalkene with MeMgBr at -80 °C. These transformations proceeded smoothly in good yields and were highly stereoselective producing the nitro compound **3-15** (**Scheme 9**). Attempts to cleave the silyl ether of **3-15** with TBAF surprisingly gave the corresponding lactol which was oxidized to lactone **3-16** with PDC in 65% isolated yield.



Scheme 9. Epimerization at γ-pozition of nitroalkene **3-16a**, synthesis of lactone **3-16**

The x-ray structure of lactone **3-16** (**Figure 2**) showed that two stereocenters were not correct. Most likely, the condition of the Henry reaction caused a base-catalyzed epimerization at the γ-atom of the nitroalkene **3-16a** to give the thermodynamically favored *trans*-1,2-substituted cyclohexane compound **3-16c**.

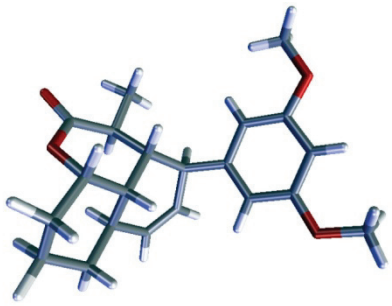
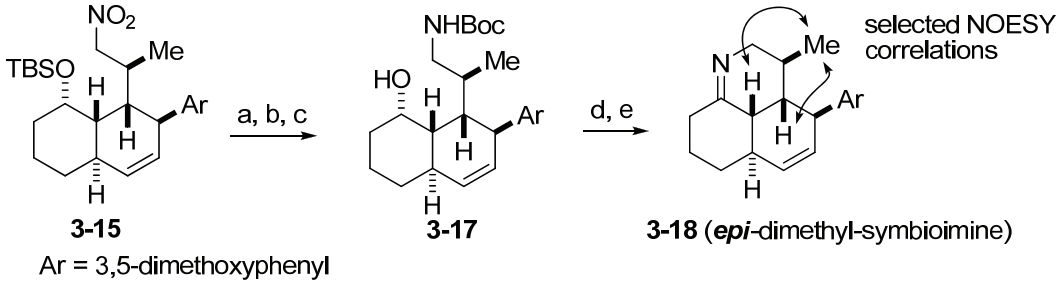


Figure 2. X-ray structure of lactone **3-16**

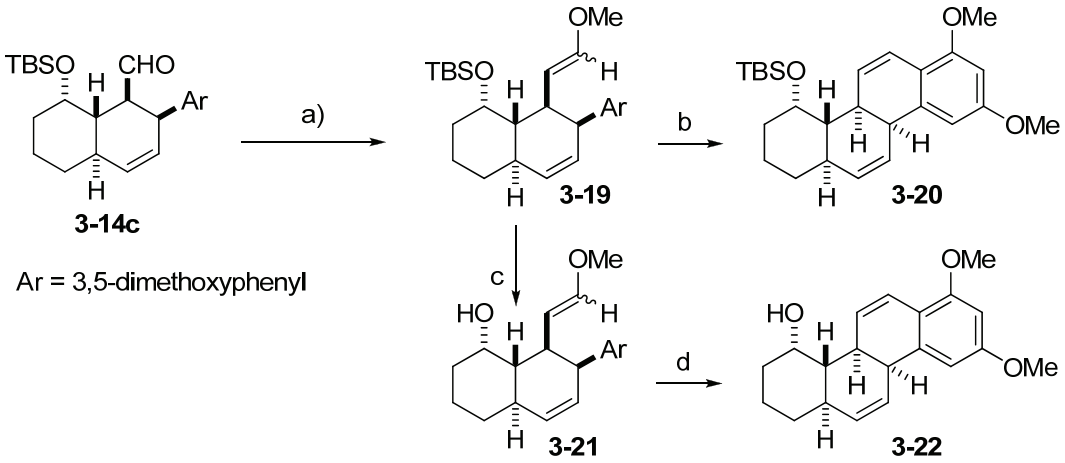
The stereochemistry of lactone **3-16** was also evident from NOESY data. In order to probe the formation of the tetrahydropyridine ring, the nitro group of **3-15** was reduced with $LiAlH_4$, the amino group protected with Boc anhydride, and the TBS-group cleaved with TBAF to give alcohol **3-17** (**Scheme 10**). Oxidation of **3-17** followed by acid-induced Boc cleavage gave indeed the imine **3-18** which might be called *epi*-dimethyl-symbioimine.



a) $LiAlH_4$, THF; b) Boc_2O, Et_3N, MeOH; c) TBAF, THF (55%, 3 steps);
d) PDC, CH_2Cl_2; e) AcCl, MeOH (80%, 2 steps).

Scheme 10. Synthesis of *epi*-dimethyl-symbioimine **3-18**

The next plan called for a C1 extension with methoxymethylphosphorane followed by alkylation of the enamine of the homologated aldehyde. As expected, the mixture of *cis/trans* enol ethers **3-19** was obtained in good yield (**Scheme 11**). However, the acid-induced cleavage of **3-19** afforded the tetracyclic compound **3-20**. Again, the Friedel-Crafts cyclization was so fast, that the desired homologated aldehyde could never be detected in the LC-MS of the reaction mixture. Even hydrolysis of the hydroxyl derivative **3-21**, which should have given a more stable cyclic hemiacetal led to the tetracyclic compound **3-22**.

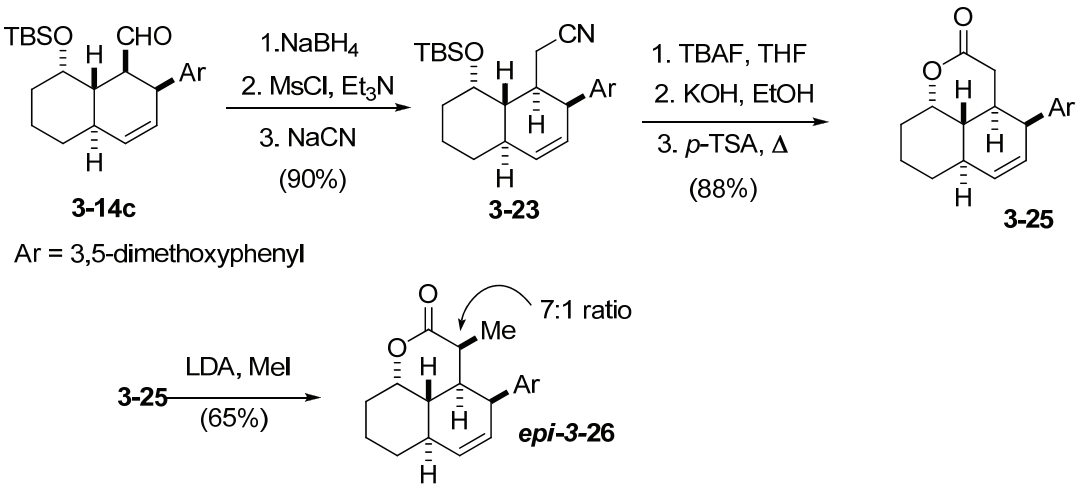


a) $MeOCH_2PPh_3^+Cl^-$, NaHMDS, (70%); b) Amberlyst 15, acetone, H_2O, **3-20** (52%) + **3-22** (31%); c) TBAF, THF, (85%); d) Amberlyst 15, acetone, H_2O (80%).

Scheme 11. Attempt to homologate aldehyde **3-14c** with methoxymethylphosphorane

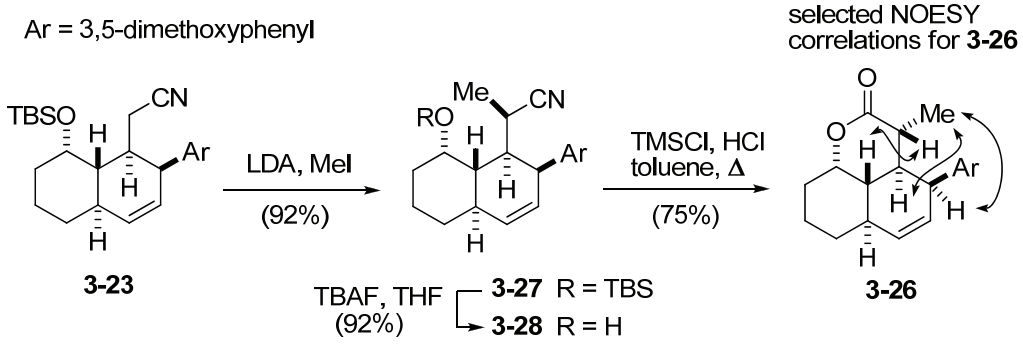
Finally, a practical solution was found starting with a three-step sequence involving $NaBH_4$ reduction of aldehyde **3-14c**, conversion of the alcohol to the corresponding mesylate and nucleophilic substitution of the mesylate with cyanide in DMSO leading to nitrile **3-23** in more than 90% yield from **3-14c** (**Scheme 12**). Removal of the TBS-group

with TBAF in THF followed by nitrile saponification allowed for the formation of lactone **3-25**. While monomethylation of lactone **3-25** was possible, careful NMR analysis of the major diastereomer showed that methylation had taken place from the wrong side of the enolate.



Scheme 12. Synthesis and methylation of lactone **3-25.**

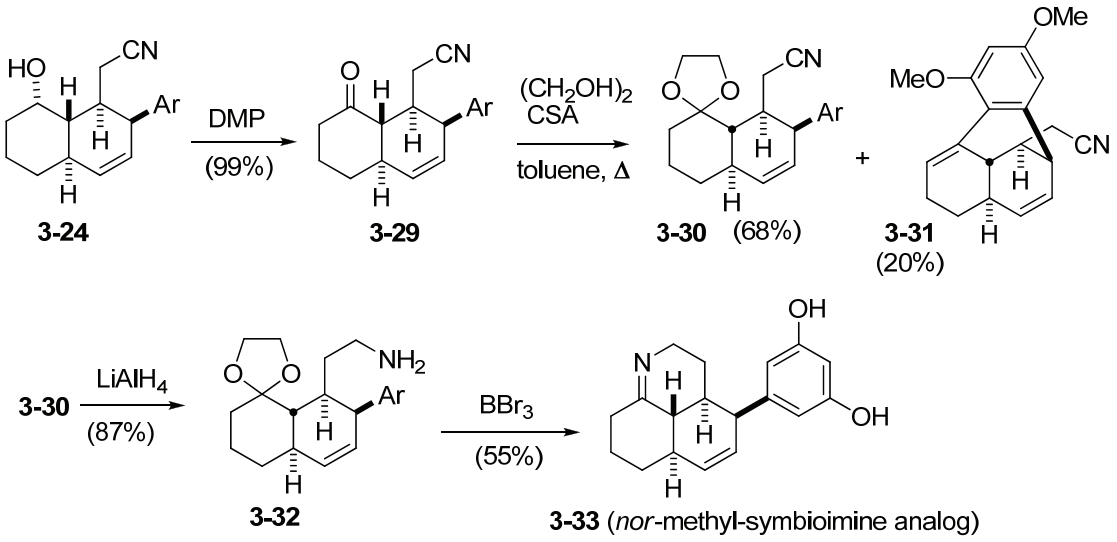
Next, methylation of the nitrile **3-23** was investigated. Deprotonation of **3-23** with LDA (2 equiv.), followed by addition of MeI gave a single isomer, tentatively assigned structure **3-27** in 92% isolated yield. Indeed, conversion of **3-27** to the corresponding lactone allowed for determination of the stereochemistry from the NOESY data (**Scheme 13**).



Scheme 13. Diastereoselective methylation of nitrile **3-23**

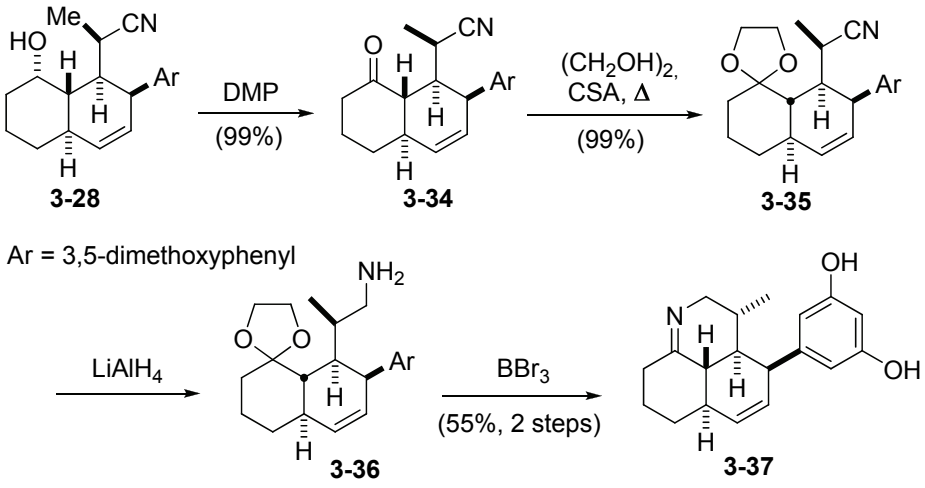
After having solved the diastereoselective introduction of the methyl group, a method was sought that would avoid protection of the amino group en route to the tetrahydropyridine. This was initially investigated using hydroxy nitrile **3-24** (**Scheme 14**). Dess-Martin oxidation of **3-24** afforded the ketone **3-29** quantitatively. Ketone **3-29** was

protected with ethylene glycol in toluene, to give 68% of the expected dioxolane **3-30** and 20% of the polycycle **3-31** resulting from attack of the aromatic ring to the keto function. The nitrile group of **3-30** was then reduced to the amine with $LiAlH_4$. Cleavage of the aryl methyl ethers, the 1,3-dioxolane, and cyclization to the imine could be achieved in one step using BBr_3 in CH_2Cl_2. The imine **3-33** is a close analog of symbioimine.



Scheme 14. Synthesis of *nor*-methyl symbioimine **3-33**

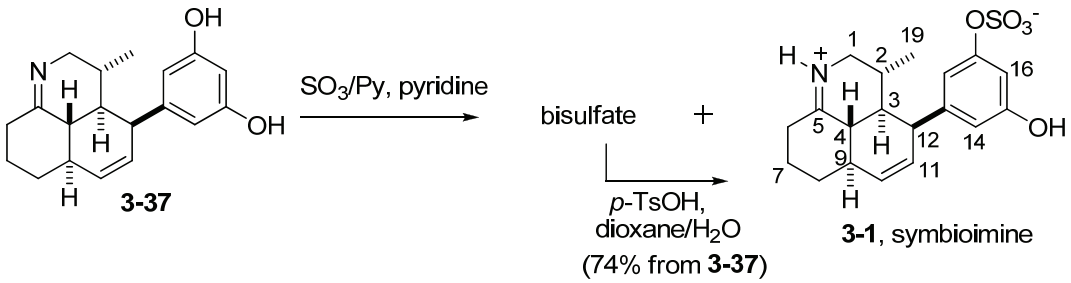
For the synthesis of symbioimine (**3-1**) hydroxy nitrile **3-28** served as starting material. As before, oxidation to the ketone **3-34** and protection of the keto function as 1,3-dioxolane led to nitrile **3-35** (**Scheme 15**). After reduction of the nitrile to the primary amine, treatment of **3-36** with BBr_3 generated imine **3-37**.



Scheme 15. Synthesis of imine **3-37**

The sulfatation of the resorcinol posed a real challenge since it was not known whether the imine or iminium function would be compatible with the reaction conditions. In addition, sulfonation of the aryl ring might take place with SO_3 or related agents. While sulfate monoesters are less common in nature as compared to phosphate monoesters, sulfated biomolecules do have a certain role in cellular events. Typical sulfated biomolecules are carbohydrates, proteins (tyrosines), and steroids.[179] The transfer of sulfate groups to OH functions is catalyzed by sulfotransferases which use 3'-phosphoadenosine 5'-phosphosulfate as sulfate source. In a laboratory setting, the attachment of the sulfate is preferentially done at the end of the synthesis, since the resulting products are very polar and the sulfate group is somewhat acid labile. Common methods for the preparation of aryl sulfates include the use of SO_3/amine complexes[180] (amine = pyridine, Et_3N) or tetrabutylammonium hydrogen sulfate (Bu_4N^+ HSO_4^-) in presence of DCC.[181]

In the case at hand, treatment of imine **3-37** with SO_3/Py complex (10 equiv) in pyridine for 6 h at 70 °C afforded about 20% of the symbioimine inner salt and 70% of a compound, which was characterized as a bisulfate derivative of **3-1** (**Scheme 16**). The bisulfate is a water soluble analog of symbioimine, which might also be biologically active. We found that the bisulfate could easily be converted to symbioimine (**3-1**) with *p*TsOH in a water-dioxane system at room temperature. Under these conditions one sulphate group is selectively hydrolyzed to give additional **3-1** (54%) and about 10% of **3-37** which could be recovered. The NMR spectra of **3-1** were found to be identical to the spectra from the isolated natural product.



Scheme 16. Completing of total synthesis of (±)-symbiomine (**3-1**).

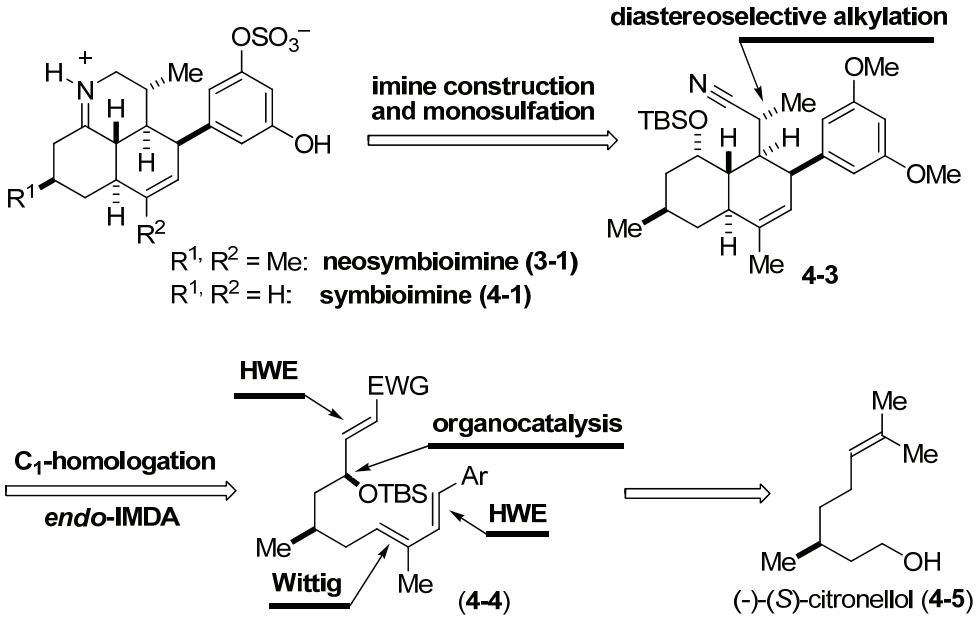
In summary, we developed an efficient synthesis of (±)-symbioimine (**3-1**), a novel tricyclic iminium alkaloid. The total synthesis of **3-1** was accomplished in 22 steps from 3,5-dihydroxy benzoic acid (**3-5**) in more than 5% total yield, which corresponds to an average yield of 88% per step. Our approach features a Lewis acid induced *endo*-IMDA reaction of 2,8,10-(*E,E,E*)-trienal **3-12** and a diastereoselective alkylation of nitrile **3-23** as

key steps. This route opens the way to other symbioimine-type compounds. This study also emphasizes the high reactivity of the electron rich aryl ring if it comes close to another electrophilic group yielding interesting polycyclic structures.

4. Total synthesis of (+)-neosymbioimine

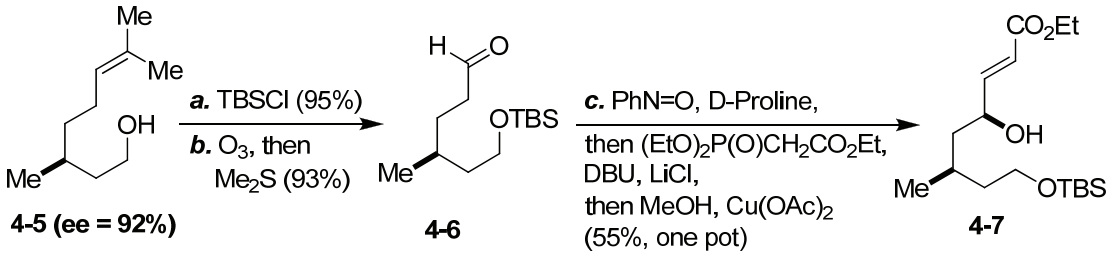
After our publication of the synthesis of (±)-symbioimine,[182] three other approaches to symbioimine appeared. Meanwhile, a synthesis of the octalene core of symbioimine, using a related *endo*-IMDA reaction of an (*E,E,E*)-undeca-2,8,10-trien-1-amide, was reported by D. Uemura.[183] Another approach to the synthesis of **4-1** was realized by Snider et al., who prepared (±)-symbioimine through an IMDA reaction of a 2,3-dihydropyridinium cation.[170,184] Later, the enantioselective synthesis of symbioimine was reported in 2007 by R. Thomson, which is based on a similar biomimetic *exo*-IMDA reaction.[185]

Neosymbioimine (**4-1**) is a minor amphoteric metabolite of the symbiotic marine dinoflagellate *Symbiodinium* sp.[167,169] Like symbioimine (**3-1**) this alkaloid is composed of a tricyclic iminium core with an attached resorcinol monosulfate unit, which causes these molecules to occur as inner salts (**Scheme 1**).[167,168,169] We proposed, that neosymbioimine (**4-1**) could be synthesized by the intramolecular Diels-Alder reaction of trienone **4-4**, and subsequent homologization and imine ring formation like in our previous synthesis of symbioimine. For the enantioselective synthesis of **4-1** we could use the chiral source (-)-*(S)*-citronellol (**4-5**), which is the main component of rose oil. Due to the trisubstituted diene unit and the nature of starting material we preferred Wittig reactions over cross-coupling reactions for construction of the triene **4-4**.

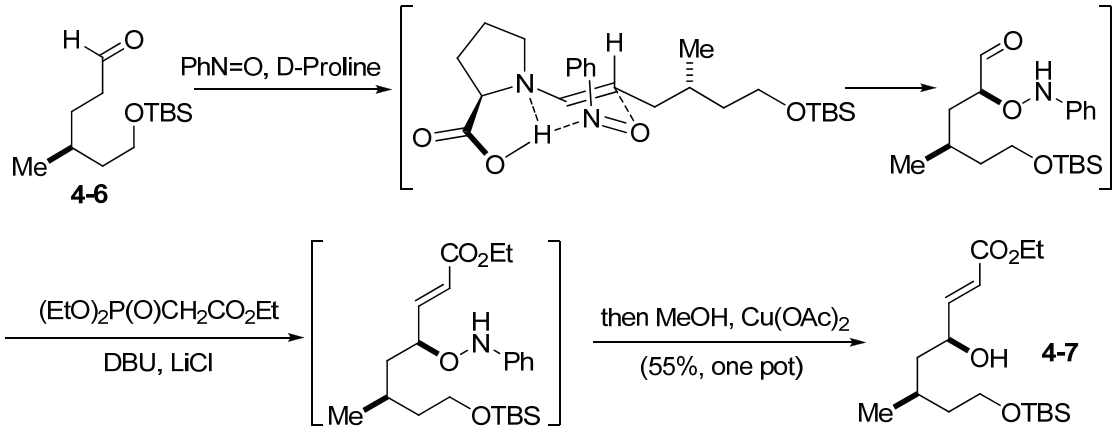


Scheme 1. Retrosynthetic analysis of neosymbioimine (**4-1**)

Initially, the alcohol function of (-)-(*S*)-citronellol (**4-5**) was protected as TBS ether and the double bond cleaved by ozonolysis to obtain aldehyde **4-6** (**Scheme 2**). Aldehyde **4-6** was converted to 4-hydroxy-8-silyloxy-enoate **4-7** by a one-pot MacMillan procedure, including α-hydroxylation followed by Horner-Wadsworth-Emmons (HWE) reaction and cleavage of the N-O bond in 55% yield (**Scheme 3**).[186]

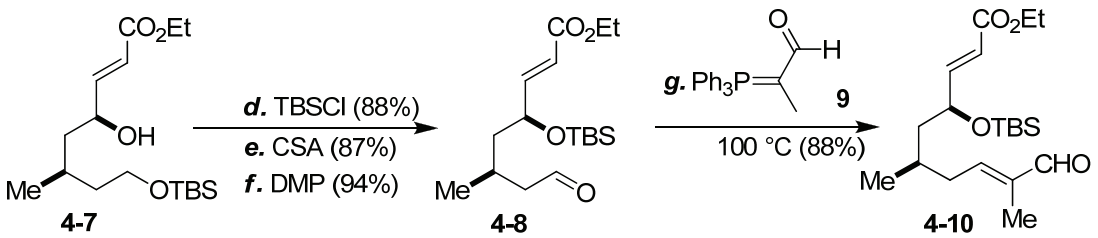


Scheme 2. Organocatalytic α-hydroxylation of aldehyde **4-6**



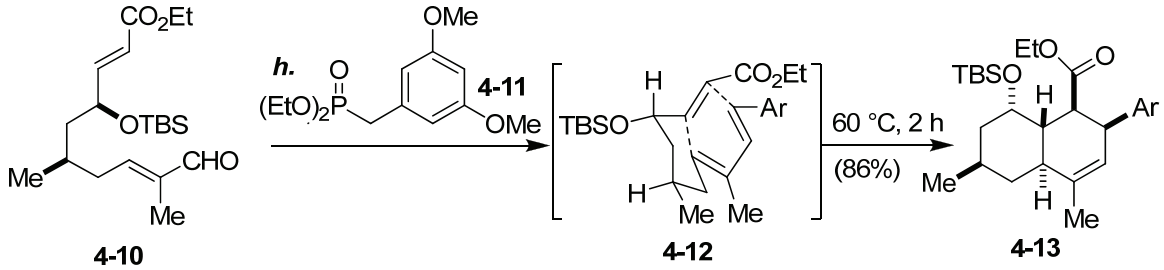
Scheme 3. Mechanism of proline catalyzed α-hydroxylation of aldehyde **4-6**

The secondary alcohol of enoate **4-7** was protected with a TBS-group, followed by selective liberation of the primary alcohol and its oxidation to provide aldehyde **4-8**. Wittig reaction of **4-8** with 2-(triphenylphosphoranylidene)propanal[187] (**4-9**) gave only the *E*-isomer of aldehyde **4-10** in 88% yield (**Scheme 4**).



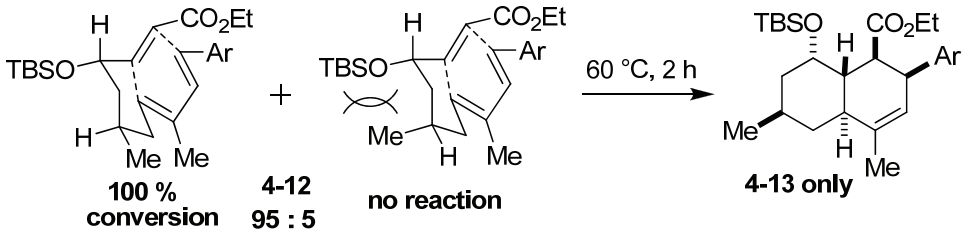
Scheme 4. Synthesis of aldehyde **4-10**

In the subsequent condensation of **4-10** with diethyl 3,5-dimethoxybenzylphosphonate[188] (**4-11**), we isolated approximately a 1:1 mixture of triene **4-12** and cyclized product **4-13** (**Scheme 5**). Heating of this mixture in chloroform for 2 h at 60 °C, induced conversion of trienoate **4-12** to **4-13** to about 95% (by NMR). The conversion did not increase even after 12 h. We assume that only the desired diastereomer of **4-12** cyclizes under these conditions. The diastereomeric impurity in substrate **4-12** most likely originates from the minor enantiomer contained in the commercial (-)-(*S*)-citronellol (92% ee).[189] In fact, around 5% of impurity can be seen in the ^{1}H NMR spectra of compounds **4-7** − **4-13**. The diastereomer of **4-12** does not cyclizes due to the steric hinderence in the transition state (**Scheme 6**).



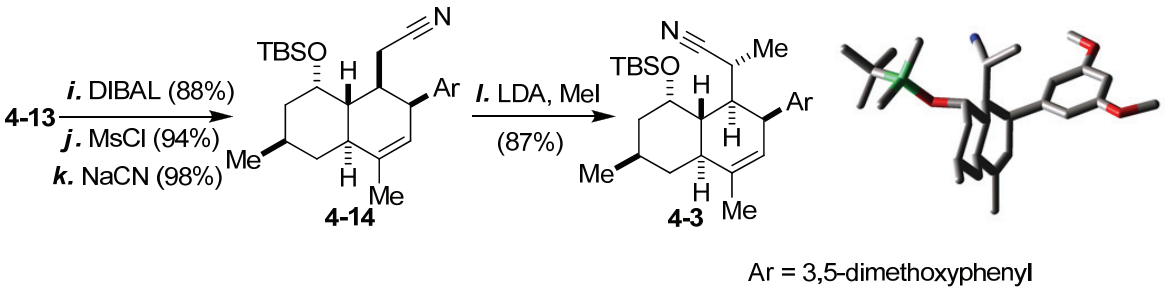
Scheme 5. Spontaneous IMDA reaction of **4-12**

After reduction of ester **4-13**, the target alcohol could be easily obtained in pure form. This crucial effect of the methyl group on the IMDA of **4-12**, allowed us to produce enantio- and diastereomerically pure products from enantio impure starting compound citronellol.



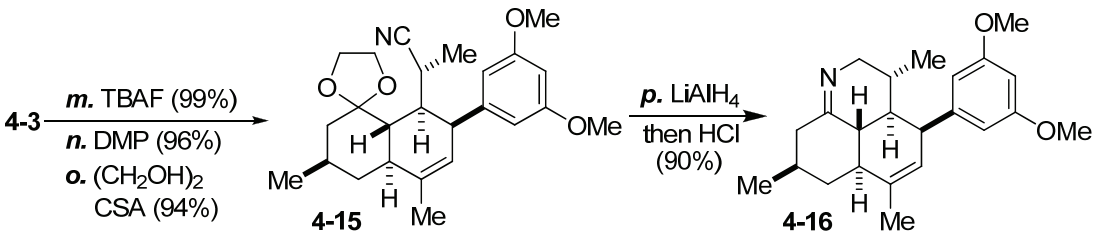
Scheme 6. Selectivity of IMDA reaction of **4-12**

Mesylation of the primary alcohol derived from cycloadduct **4-13** followed by S_N2 reaction with sodium cyanide gave nitrile **4-14** in exellent yield (**Scheme 7**). Methylation of acetonitrile derivative **4-14** proceeded very cleanly and efficiently, using 2 equiv.of LDA and 2 equiv.of MeI in THF at –80 °C. Despite the fact, that a small amount (10%) of the undesired diastereomer was also formed, pure **4-3** was isolated in 87% yield on a gram scale experiment. The stereochemistry of methylation is caused probably by the steric hindrance in the transition state of anion **4-14**. It attacks methyl iodide from the side, opposite to the aromatic ring.



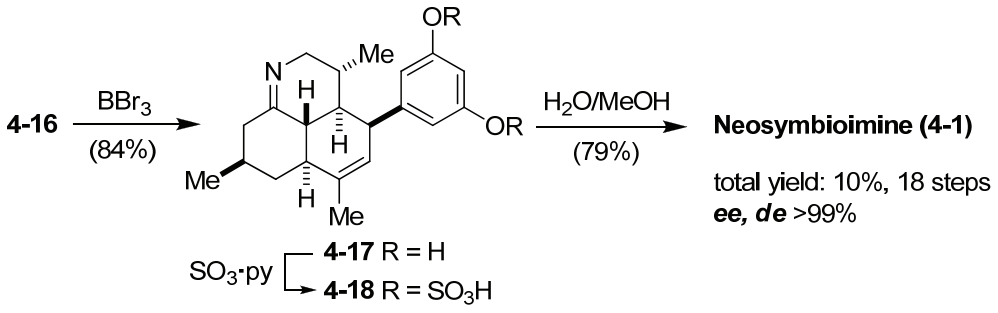
Scheme 7. Synthesis of nitrile **4-3**

The structure of nitrile **4-3**, featuring all stereocenters of the natural product, was confirmed by single crystal x-ray analysis (**Scheme 7**). In this molecule the methyl and propanenitrile groups occupy equatorial positions, whereas the bulky units (Ar, OTBS) are oriented axially. In the ^{1}H NMR spectra of nitrile **4-15** the signal of the α-methyl group is shifted towards high field (δ_H 0.6 ppm) due to the shielding by the aromatic ring current. Nitrile **4-3** was treated with TBAF to remove the TBS group. The obtained alcohol was oxidized to the corresponding ketone which was protected as 1,3-dioxolane **4-15** in exellent yield. Reduction of the nitrile to the amine with $LiAlH_4$ followed by acid-catalyzed imine formation gave imine **4-16** (**Scheme 8**).



Scheme 8. Synthesis of imine **4-16**

Finally, the aryl ether functions were cleaved with BBr_3 providing resorcinol **4-17** in 84% yield (**Scheme 9**). As a final challenge, efficient monosulfation of resorcinol remained. In our previous synthesis of (±)-symbioimine (**4-1)**, the monosulfatation of the resorcinol was achieved via the bis-sulfate, generated by reaction of the resorcinol with an excess of SO_3/pyridine complex followed by controlled hydrolysis of one of the sulfate groups. Another approach is based on sulfation with *i*-Bu-OSO_2Cl (isobutyl chlorosulfate) and *nP*-OSO_2Cl (neopentyl chlorosulfate), following by dealkylation with nucleophiles (NaI, NaN_3, NaSCN).[179] While the usability of this method for the preparation of sulfates of complex molecules, like steroids, carbohydrates, and proteins (tyrosines) could be shown, sulfation of polyfunctional substrates was not described. Initially, we tried to apply this method for the sulfation of resorcinol **4-17**. In our hands, the reaction of *neo*Pentyl-OSO_2Cl with **4-17** and NaHMDS (1 equiv) gave an unseparable mixture of chlorinated aromatic derivatives along with sulfated products in low conversion. In the case of resorcinols, we found that aromatic electrophilic substitution is predominant, and sulfochlorides seem too electrophilic. Therefore, optimisation of our earlier procedure was tried.



Scheme 9. Synthesis of (+)-neosymbioimine (**4-1**)

Excessive sulfation of **4-17** with SO_3·py (5 equiv) in pyridine gave bisulfate **4-18**. As expected, one sulfate group in **4-18** is more sensitive to hydrolysis (Scheme 9). Thus, keeping a solution of **4-18** in aqueous methanol at 35 °C for 18 h, led to complete

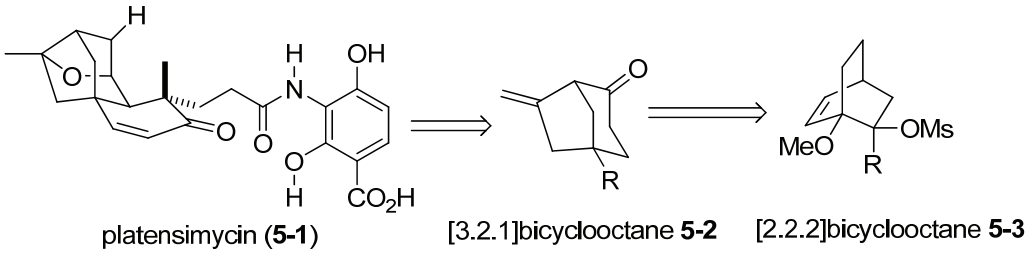
monohydrolysis of **4-18** (70% of **4-1** was isolated). At the same time, neosymbioimine (**4-1**) was not hydrolyzed significantly (10% of **4-17** was recovered). Thus, the formation of the inner salt contributes to the stability of the sulfate group. The product was purified by routine flash chromatography, on silica gel using MeOH/$CHCl_3$ as eluent. Synthetic neosymbioimine was identical by NMR to the natural compound. The optical rotation of synthetic neosymbioimine ($[\alpha]^{23}_D$ +172, *c* 0.1, MeOH) corrlelates well with the authentic one ($[\alpha]^{25}_D$ +149). Thus, the absolute stereochemistry of (+)-neosymbioimine was assigned.

In summary, we developed an efficient route to the natural alkaloid (+)-neosymbioimine, starting from readily available (-)-(*S*)-citronellol. The synthetic strategy is based on the extremely facile tandem HWE-IMDA reaction for construction of the neosymbioimine core, which allows for the preparation of significant amounts of (+)-neosymbioimine (**4-1**) in 10% total yield over 18 steps. So far this is the only total synthesis of neosymbioimine reported in the literature.

We also studied the inhibition of COX-2 (cyclooxygenase-2) activity of the synthetic neosymbioimine in the group of Prof. Dr. Laufer. Although for the related alkaloid symbioimine (**3-1**), the reported concentration, when the COX-2 activity is significantly reduced, is 10 μM, for neosymbioimine (**4-1**) we did not find any inhibition of COX-2 inside the range of concentrations of **4-1** from 0.1 to 10 μM, and very small (15%) inhibition at 0.01 μM. These results show that neosymbioimine (**4-1**) is rather inactive against COX-2.

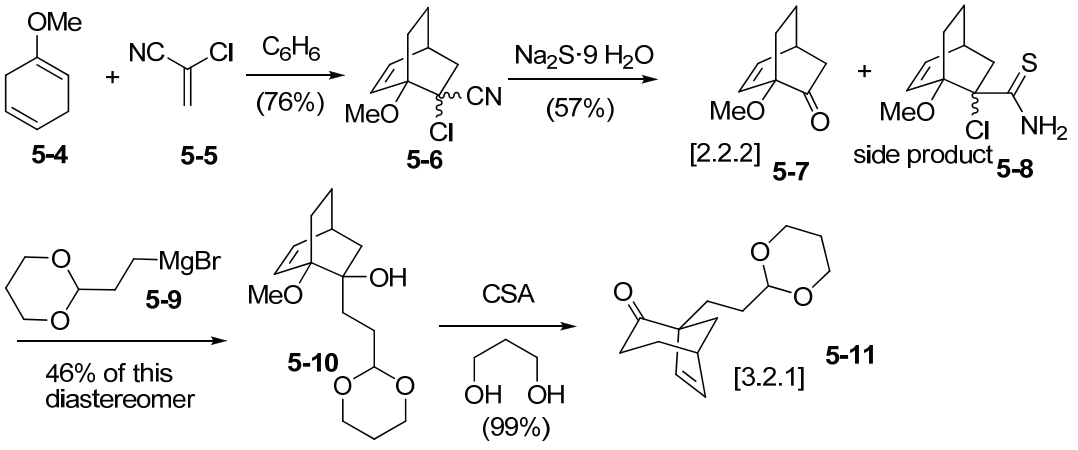
5. Attempts toward the synthesis of platensimycin

Platensimycin (**5-1**) is a novel antibiotic, which was recently isolated from several strains of *Streptomyces platensis.*[190] It imparts a potent Gram-positive antibacterial activity including that against drug-resistant organisms (e.g., MRSA, VRE) by uniquely inhibiting acyl enzyme intermediates of the condensing enzymes FabF and FabF/FabH, respectively, vital for fatty acid biosynthesis. This natural product is interesting not only due it's potent antibiotic activity, but also due to the novel structure, which could be a good challenge for total synthesis.



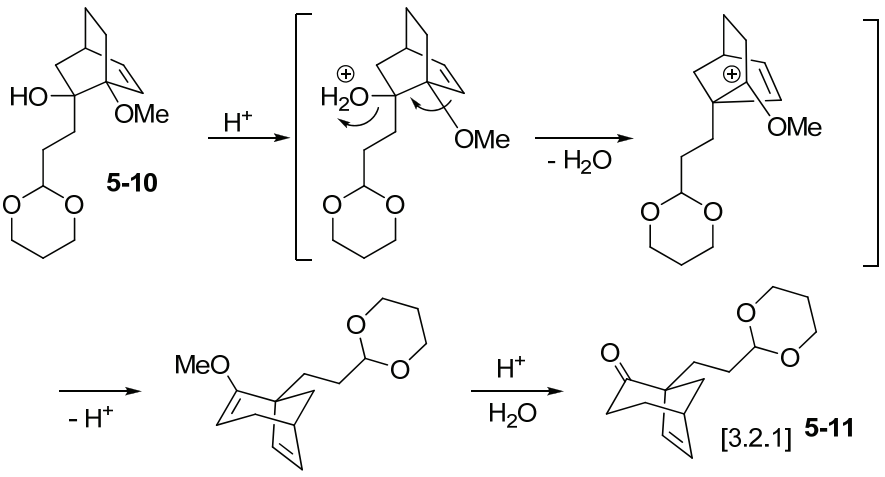
Scheme 1. Retrosynthetic strategy for synthesis of platensimycin **5-1**

Initial our strategy was to construct the [3.2.1]bicyclooctane carbon core fragment of platencimycin **5-2** by the rearrangement of [2.2.2]bicyclooctane mesylate **3**, which can be prepared according to a known literature method (**Scheme 1**).[191] Heating of commercially available 1-methoxycyclohexa-1,4-diene (**5-4**), the product of the Birch reduction of anisole,[192] with 2-chloroacrylonitrile (**5-5**) in benzene afforded the Diels-Alder adduct, which was distilled using a kugelrohr apparatus to yield 76 % of methoxybicyclooctene **5-6** as a mixture of diastereomers (**Scheme 2**).



Scheme 2. Synthesis of [3.2.1]bicyclooctane **11**

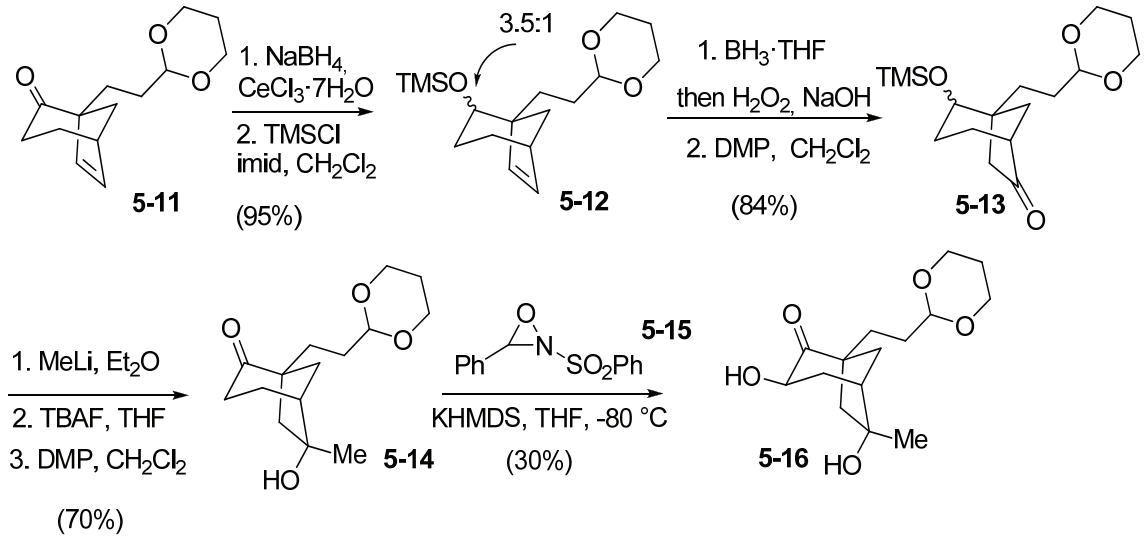
Hydrolysis of product **5-6** by heating it with sodium sulphide in a water/ethanol mixture afforded ketone **7** in 57 % yield.[191] The moderate yield of this reaction is caused by the side reaction involving the addition of sulfide ion to the nitrile function to produce thioamide **5-8** which could be isolated and characterized. Addition of Grignard reagent **5-9** to ketone **5-7** afforded a mixture of two diastereomeric alcohols **5-10** which could be separated by flash chromatography. For the subsequent rearrangement only one diastereomer of **5-10** could be used as it evident by looking at the mechanism of this reaction (**Scheme 3**). The desired alcohol **5-10** was isolated in pure form with 46 % yield. The cleavage with sodium iodide of the mesylate, obtained by mesylation of the corresponding alocohol, by the literature procedure[191] gave a poor yield of desired product **5-11**. However, we discovered that mild heating of alcohol **5-10** with 1.1 equiv. of camphorsulphonic acid in 1,3-propanediol surprisely gave a quantitative yield of the desired ketone **5-11**, which could be prepared in laboratory on a multigram scale.



Scheme 3. Mechanism of acid-induced rearrangement of **5-10**

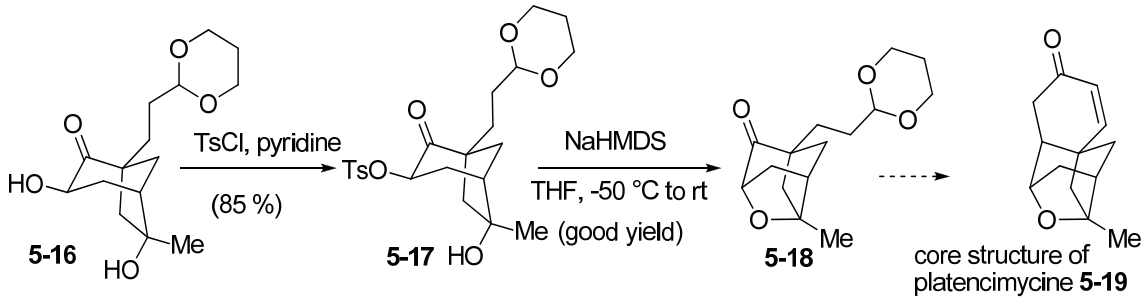
Reduction of ketone **5-11** with sodium borohydride, followed by protection with trimethyl chlorsilane afforded TMS-ether **5-12** in high yield as a 3.5/1 mixture of diastereomers (**Scheme 4**). We have found that the double bond of **5-12** could be selectively hydroborated, and after oxidation with Dess-Martin periodinane (DMP) we obtained ketone **5-13** in good yield. Methylation of that ketone could be done in a diastereoselective fashion with methyllithium in diethyl ether. Cleavage of the trimethylsilyl function with TBAF, followed by oxidation with DMP afforded ketone **5-14**. Several methods for installation of a hydroxyl group next to ketone **5-13** were tested, and we found that treatment of ketone **5-13** with potassium *bis*-trimethylsilylamide and Davis oxaziridine[193] **5-15** afforded 30 % of a single diastereomer of **5-16**. The low yield might be

explained by the negative influence of the free tertiary hydroxyl function. The yield might be improved by protection of that function before the anionic reaction with potassium *bis*-trimethylsilylamide.



Scheme 4. Conversion of bicyclic ketone **5-11** to hydroxyketone **5-16**

Treatment of diol **5-16** with tosyl chloride and pyridine allowed us to perform a selective tosylation of the secondary alcohol function in the presence of the tertiary alcohol providing a good yield of tosylate **5-17**. We found that treatment of **5-17** with sodium *bis*-trimethylsilylamide afforded smooth cyclization to furnish tricyclic product **5-18**, which represents a key fragment of the core structure of platencimycin **5-19** (**Scheme 5**).



Scheme 5. Cyclization of tosylate **5-17**

At this point we decided to cancel further research on the platensimycin synthesis progress, because several more efficient syntheses appeared in the literature. Instead we focused our efforts to synthesize another new natural product, platencin, which was discovered by the same scientists from the Merck company in 2007.[196]

6. Formal total synthesis of platencin

The increasing appearance of bacterial resistance stimulated a resumption of the search for novel antibiotics. In this regard not only various depsipeptides but also structurally novel polycyclic polyketide or terpene derivatives were discovered.[194,195] Thus, the two closely related antibiotics platencin[196] and platensimycin[197] were described by an industrial research group (**Figure 1**). The newest of these compounds, platencin (**6-1**) was isolated from a strain of *streptomyces platensis* MA 7339. Like platensimycin (**5-1**), platencin (**6-1**) shows potent antimicrobial activity against a broad spectrum of Gram-positive bacteria. In particular it inhibits key antibiotic resistant pathogens such as methicillin-resistant *staphylococus aureus*, vancomycin-resistant *enterococci* and *streptococcus pneumoniae*.

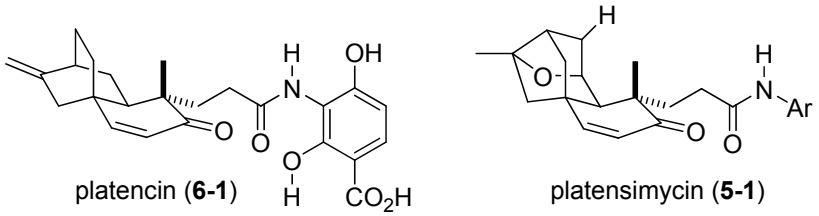


Figure 1. Structures of platencin (**6-1**) and platensimycin (**5-1**)

As the screening assay was targeted against the bacterial fatty acid biosynthesis both **6-1** and **5-1** inhibit this machinery.[198] In contrast to **5-1**, platencin (**6-1**) blocks two condensing enzymes namely keto acyl synthase (KAS) II and III. Both compounds contain a highly substituted 3-amino-2,4-dihydroxy benzoic acid and a rather hydrophobic polycyclic enone acid sector. Biosynthetic studies revealed that the terpene part originates from the non-mevalonate MEP pathway (**Figure 2**).[199,200] The two natural products might originate from copalyl pyrophosphate (***A***) and pass through the beyeran-16-yl cation ***C*** as a common intermediate (Figure 2).[201] A Wagner-Meerwein rearrangement and proton loss would lead to *ent*-kaurene (***E***), the likely precursor of platensimycin. The *ent*-atiserene (***I***) structure with the [2.2.2]bicyclooctane subunit can be reached by a 1,3-hydride shift to ***G*** prior to the final Wagner-Meerwein shift leading to carbenium ion ***H*** followed by deprotonation. Alternatively, a late stage interconversion of the two ring systems could be possible as shown with the carbenium ion structures ***K*** and ***L***.[196b]

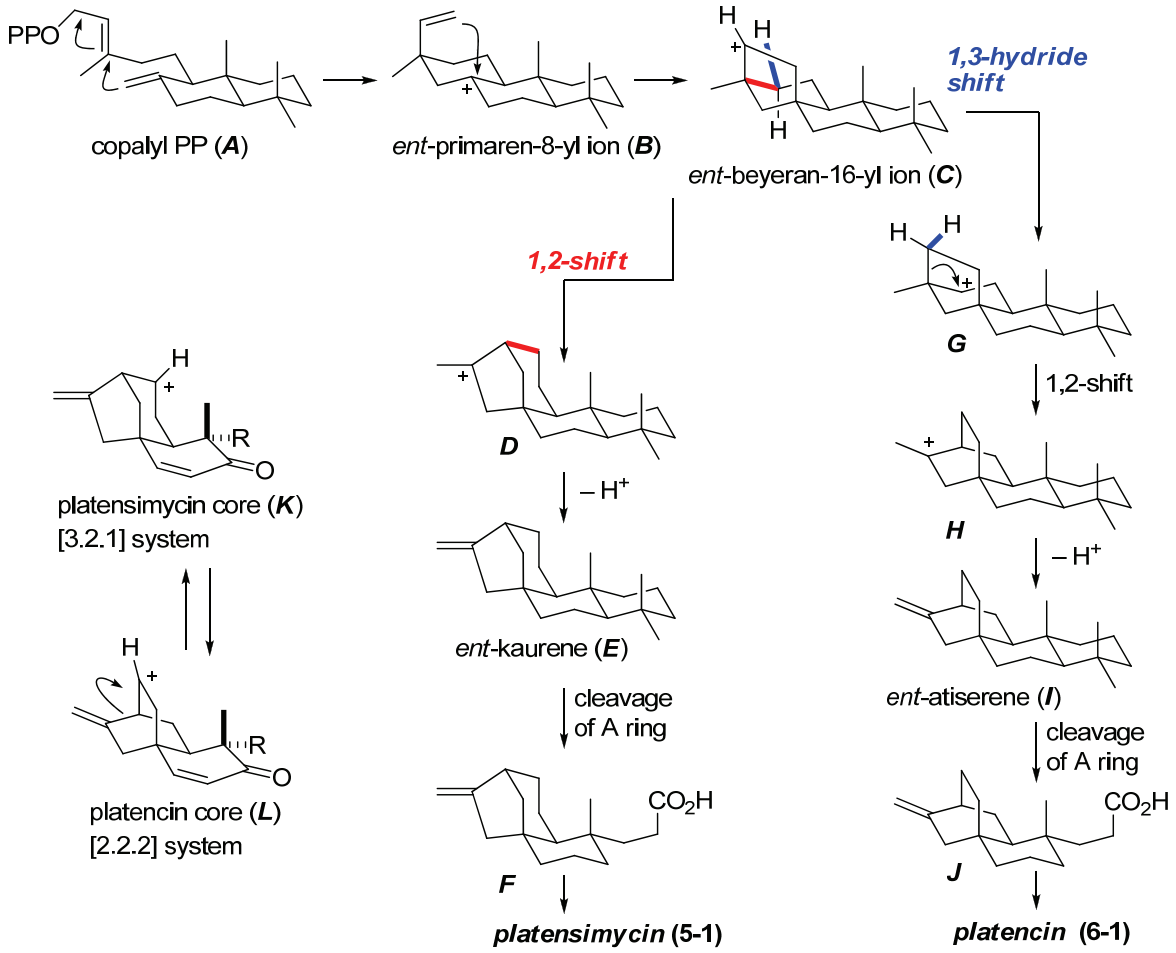


Figure 2. Possible key intermediates in the biosynthesis of platencin (**6-1**) and platensimycin (**5-1**)

The potent in vivo activities and the novel intriguing structures prompted a range of synthetic efforts. Thus, since the first disclosure of platensimycin in 2006 ten total or formal total synthesis were reported.[202,203] The year 2008 saw the publication of seven platencin synthesis.[204] We also became interested in the synthesis of platencin and conceived a unique route to the advanced intermediate **6-3** (**Figure 3**). Our design was inspired by the [3.2.1]- to [2.2.2]bicyclooctane interconversion that is evident from the two natural products. In the literature two prominent methods are known to achieve such transformations. Thus, Pinacol rearrangement of Diels-Alder derived bicyclo[2.2.2]octane systems offers an entry to [3.2.1] systems.[205,206] On the other hand, the homoallyl homoallyl radical rearrangement which might proceed through a cyclopropylcarbinyl radical was used by the group of Ihara to convert a [3.2.1] to a [2.2.2] system.[207,208] In fact, this skeleton interconversion strategy has also been used by Nicolaou and Lee in their syntheses of platencin. We also conceived independently a related strategy (**Figure 3**) but observed problems with the rearrangement of ***N*** to ***M***.[209] According to this plan, compound

O might be synthesized by the conjugate addition to bicyclic enone ***P***, which could be prepared, according to the work of Toyota[207,210] by palladium-catalyzed oxidative cyclization of allylcyclohexenone ***Q***. This substrate, in turn, could be made by alkylation and reduction of an 3-alkoxycyclohex-2-en-1-one like compound **6-4**.

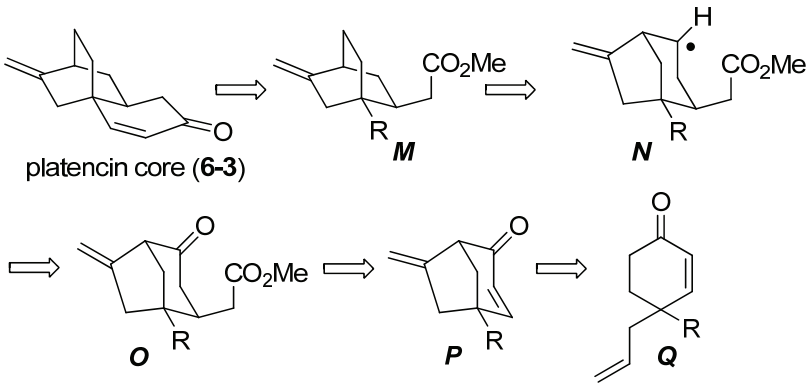
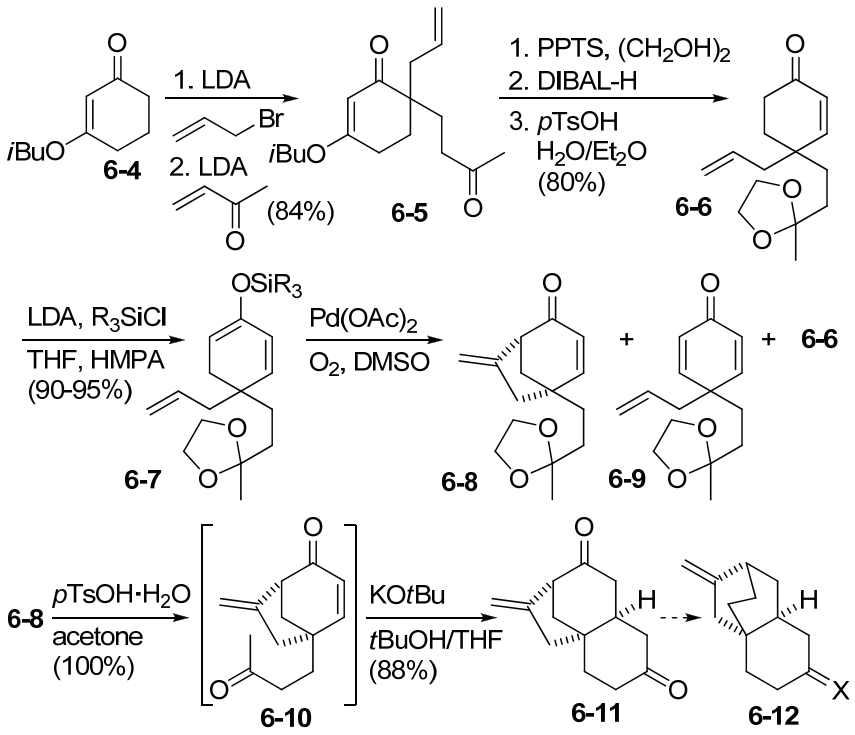


Figure 3. Synthetic plan for the platencin core structure **6-3**

Initially we performed some model studies on the Pd(II)-calalyzed cycloalkenylation reaction of silyl enol ether **6-7** (**Scheme 1**). The original plan was to convert the desired bicyclic product to decalin derivative **6-11** and then perform the key skeletal rearrangement on a tricyclic system derived **6-11**. However, with our model system **6-6**, which was derived via the Stork alkylation strategy[211] from 3-isobutoxy-cyclohex-2-en-1-one[212] (**6-4**), the conditions reported by Fukumoto et al.[210] resulted in the formation of a mixture of three products (**Scheme 1, Table 1**). 3-Isobutoxy-cyclohex-2-en-1-one (**6-4**) was alkylated under LDA conditions with allyl bromide the isolated product was deprotonated again with LDA and coupled with methyl vinyl ketone as a Michael acceptor. Obtained ketone **6-5** was protected with ethylene glycol under standard conditions (PPTS, Dean Stark, benzene, reflux) and the vinylogous carbonyl function was reduced with DIBAL-H. Acidic hydrolysis of the crude product afforded cyclohex-2-en-1-one **6-6**, whic was converted into silyl dienol ether and subjected to testing in the Pd(II)-catalyzed cycloalkenylation reaction (**Scheme 1**).



Scheme 1. Oxidative Pd-catalyzed conversion of silyl enol ether **6-7**; R_3Si = Me_3Si, $(iPr)_3Si$, or tBuMe$_2$Si. Ketoenone **6-10** was used crude.

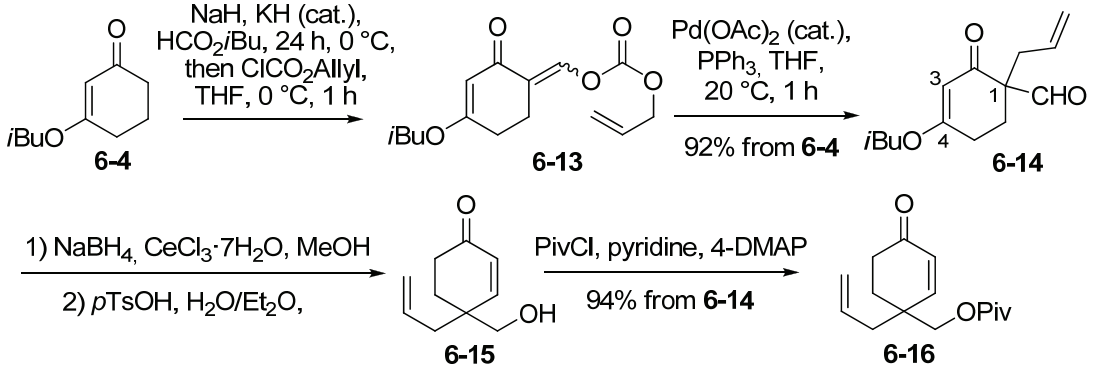
Varying the trialkylsilyl group at the silyl enol ether **6-7** from Me_3Si to tBuMe$_2$Si reduced the amount of the desilylated cyclohexenone **6-6** but did not diminish formation of cyclohexadienone **6-9**, resulting from oxidative desilylation.[213] Finally, a solution was found with the slow addition of the catalyst to the reaction mixture (**Table 1**, entry 6) Thus, addition of the catalyst solution over 4 h to a 0.05 m solution of silyl enol ether **6-7** (R= tBuMe$_2$Si) in DMSO resulted in a clean formation of the desired bicyclic product **6-8** in 85% yield. Enone **6-8** was then converted to tricyclic diketone **6-11** in two steps (**Scheme 1**). Unfortunately, the radical rearrangement on tricyclic derivatives derived from **6-11** did not give the desired products.[214]

Table 1. Optimization of the Pd-catalyzed alkene-silyl enol ether cyclization.

Entry[a]	R_3Si	T	Conc.	Pd [mol%]	Ratio **6-8**: **6-9**: **6-6**[b]
1	TMS	r.t.	0.05 M	10	40:50:trace
2	TMS	45 °C	0.2 M	10	33:17:50
3	TIPS	45 °C	0.3 M	1	38:trace:60
4	TBS	r.t.	0.1 M	10	80:20:trace
5	TBS	45 °C	0.1 M	10	80:20:3
6	**TBS**	**45 °C**	**0.05 M**	**5**[c]	**>95 %:trace:trace**

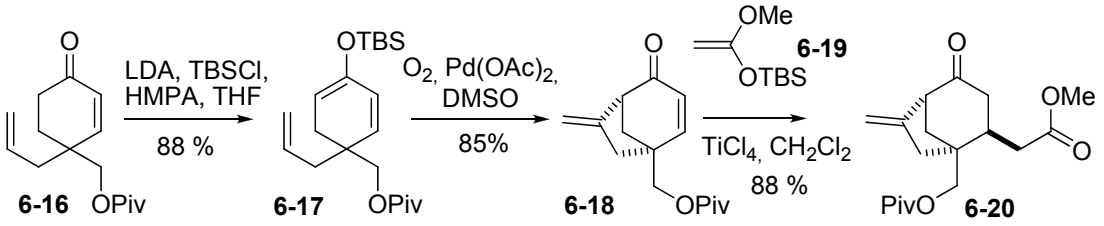
[a] All reactions were run at 0.5 mmol scale in DMSO under 1 atmosphere of oxygen for 24-48 h; [b] ratio determined by ^{1}H NMR; [c] slow (within 4 h) addition of catalyst.

After optimization of this cycloalkenylation reaction we focused on the synthesis of a functionalized 7-methylenebicyclo[3.2.1]octan-2-one such as **6-18** which would allow to form the cyclohexenone ring of platencin after the rearrangement of the biyclic substructure. The racemic synthesis began with vinylogous ester **6-4**[212] (**Scheme 2**). Thus, formylation of **6-4** with isobutyl formate followed by addition of allyl chloroformate gave an *E*/*Z* mixture of enol carbonates which upon flash chromatography isomerized to form mostly the *Z*-isomer **6-13**, assigned by NMR, in 89% yield. This enol carbonate underwent a rapid decarboxylative allylation[215,216] with formation of a quaternary center under $Pd(OAc)_2/PPh_3$ catalysis resulting in high yield of 2-oxocyclohex-3-ene carbaldehyde **6-14**. The next step using $NaBH_4$ and $CeCl_3$ in MeOH served to reduce the enone as well as the aldehyde function to give cyclohexenone **6-15**. Surprisingly, the vinylogous ester function was reduced as well under these conditions. This avoided the use of expensive reducing agents like DIBAL-H. The crude hydroxyketone **6-15** was then subjected to pivaloylation affording pivalate **6-16** in 94% yield from aldehyde **6-14**.



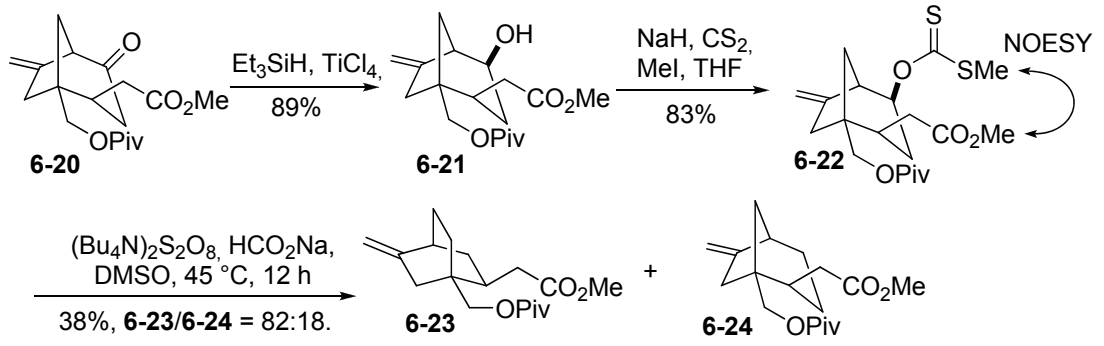
Scheme 2. Synthesis of cyclohexenone **6-16**

Enone **6-16** was converted to silyl enol ether **6-17** which could be cyclized using our optimized conditions to 7-methylenebicyclo[3.2.1]oct-3-en-2-one **6-18** (**Scheme 3**). A subsequent Mukaiyama-type Michael addition[217] of enone **6-18** with silyl ketene acetal[218] **6-19** promoted by $TiCl_4$ (1.2 equiv) gave only the desired diastereomer **6-20**. Thus, the nucleophile attacks the enone *syn* to the one carbon methylene bridge.



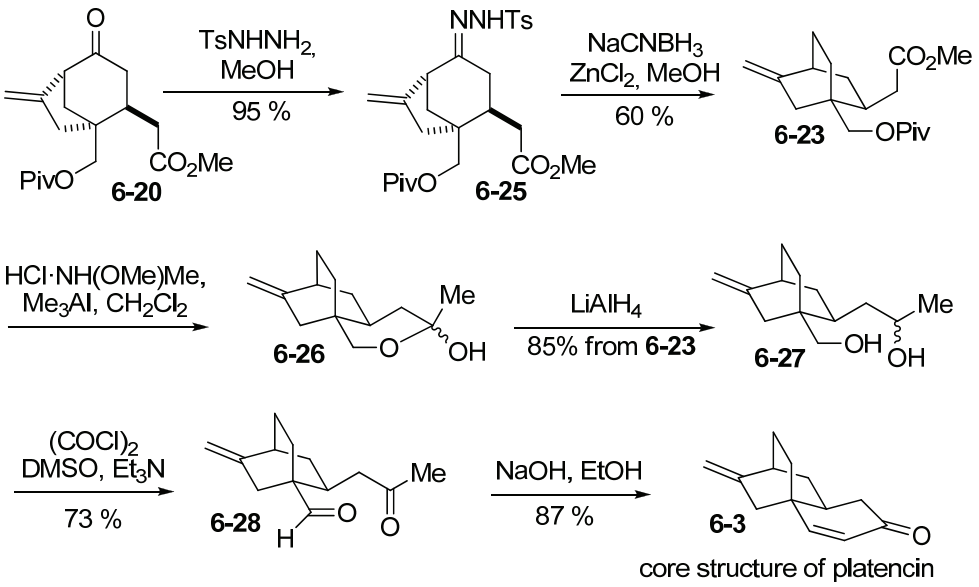
Scheme 3. Synthesis of bicyclic keto ester **6-20**

In preparation for the intended skeletal rearrangement, the keto function of **6-20** was reduced under various conditions (**Scheme 4**). However, using sodium borohydride, zinc borohydride or MVP conditions (aluminium isopropoxide/isopropanol) always gave a mixture of alcohols, at best in a 3:1 ratio. Finally, we discovered that reaction of **6-20** with Et_3SiH and $TiCl_4$ proceeds with the exclusive formation of only one diastereomeric alcohol **6-21**. The configuration of the OH bearing stereocenter could be determined from NOESY experiments. Alcohol **6-21** was then converted to xanthogenate **6-22**. However, radical rearrangement of xanthate ester **6-22** under the conditions reported in Nicolaou's first total synthesis[204a,219] of platencin (AIBN, Bu_3SnH, toluene, 100 °C) did not work for our substrate with no conversion of **6-22**. With methoxymethyl and acetyl protecting groups instead of the pivaloate this reaction gave a very poor yield of the desired rearrangement product together with large amounts of byproducts.[214] Better results were obtained using conditions reported by a Korean group, namely the combination of tetrabutyl ammonium peroxydisulfate and sodium formate.[220] This reaction, performed in DMSO gave a 38% yield of a mixture of the rearranged product **6-23** and the simple deoxygenation product **6-24** in a ratio of 82:18. In DMF, this reaction afforded the same product mixture in 25% yield.



Scheme 4. Rearrangement reactions on xanthogenate **6-22**

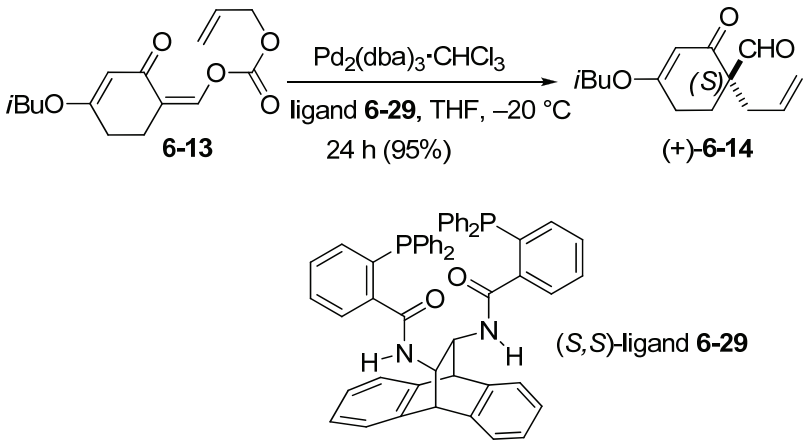
Looking for conditions that would provide a better yield and selectivity in the key radical rearrangement towards the[2.2.2]bicyclooctane core, we eventually found that heating a solution of hydrazone **6-25** in methanol in presence of $NaCNBH_3$ and $ZnCl_2$ resulted in the desired deoxygenative rearrangement to form the methylene-bicyclo[2.2.2]octane **6-23** in 60% yield (**Scheme 5**).[207b] While product **6-23** is still contaminated with 8 mol% of byproduct **6-24**, this impurity could be removed by flash chromatography of the derived diol **6-28** (vide infra). This diol was obtained in pure form via a very efficient three step sequence from **6-23**. Thus, conversion of ester **6-23** to Weinreb amide **6-26**, treatment of **6-26** with MeLi (6 equiv) and reduction of hemiketal **6-27** with $LiAlH_4$ furnished diol **6-28** in 85% yield from ester **6-23**. Oxidation of hemiketal **6-27** with TPAP/NMO by the literature procedure[204a] afforded a poor yield (< 25%) of the desired ketoaldehyde **6-29**. On the other hand, Swern oxidation of diol **6-28** led to ketoaldehyde **6-29** in good yield. A final aldol condensation on **6-29** with NaOH in EtOH gave the advanced intermediate **6-3** in 87% yield. The total yield of the platencin tricyclic core structure **6-3** from commercially available starting material **6-4** was 17.5% for 13 steps.



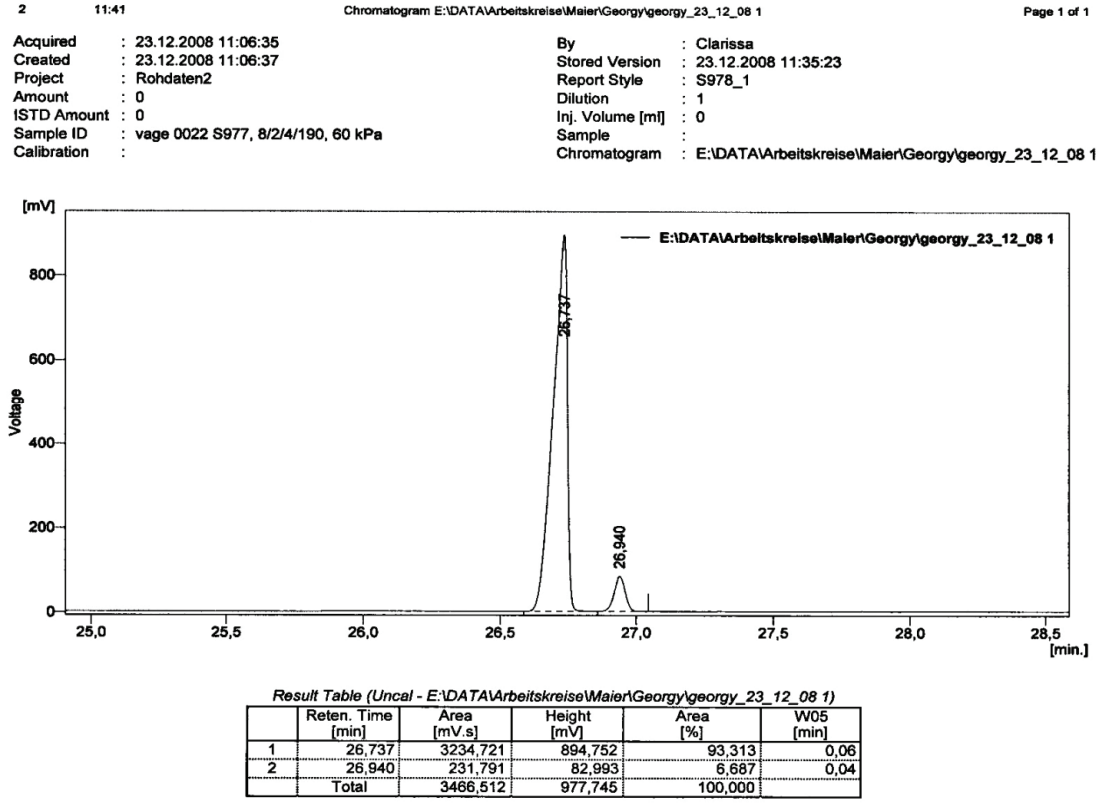
Scheme 4. Efficient conversion of keto ester **6-20** to the bicyclo[2.2.2]system **6-23** and its transformation to the core structure **6-3** of platencin

We also studied an enantioselective approach to **6-3** via the above sequence. This could involve an enantioselective Pd-catalyzed decarboxylative allylation[216] of allyl enol carbonate **6-13** with a chiral phosphine ligand (**Scheme 6**). According to the work of B. M. Trost the (*S*,*S*)-ligand **6-29** should result in (*S*)-**6-14**.[221,222] Indeed, this decarboxylative

allylation, performed in presence of ligand **6-29** at 0 °C in THF, resulted in an enantiomeric excess of 78% for (+)-**6-14**. Lowering the temperature to –20 °C gave an improved ee of 87% (**Figure 4**). Accordingly optically active **6-14** should lead to the optically enriched platencin core structure **6-3**.



Scheme 6. Asymmetric approach to platencin **(6-1)**



Result Table (Uncal - E:\DATA\Arbeitskreise\Maier\Georgy\georgy_23_12_08 1)

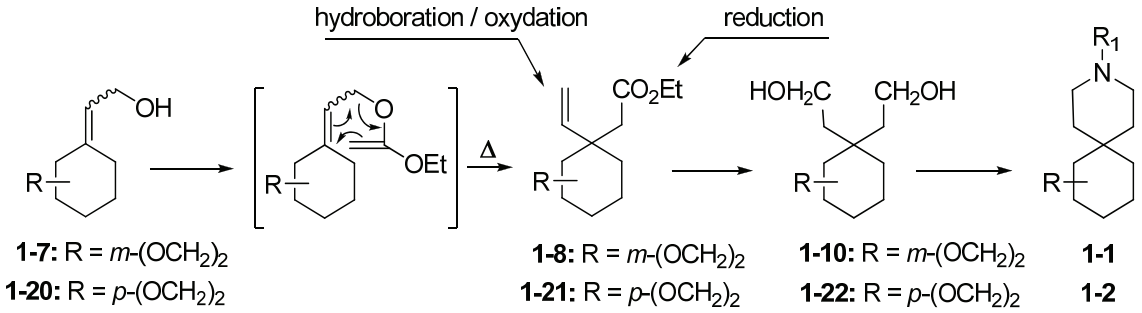
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	W05 [min]
1	26,737	3234,721	894,752	93,313	0,06
2	26,940	231,791	82,993	6,687	0,04
	Total	3466,512	977,745	100,000	

Figure 4. GS analysis of chiral aldehyde **6-14**

In summary, we have developed an efficient formal synthesis of platencin. The tricyclic advanced intermediate **6-3** was prepared in 13 steps and 17.5% overall yield from commercially available starting material **6-4**. Our approach is based on originally developed key reactions, namely the asymmetric decarboxylative allylation of allyl enol carbonate **6-13**, the optimized Pd-catalyzed cycloalkenylation of **6-7**, a highly diastereoselective Mukaiyama Michael addition of silyl ketene acetal **6-19** to bicyclic enone **6-18**, and a radical-mediated reductive rearrangement of tosyl hydrazone **6-25** for construction of the [2.2.2]bicyclooctane core of platencin.

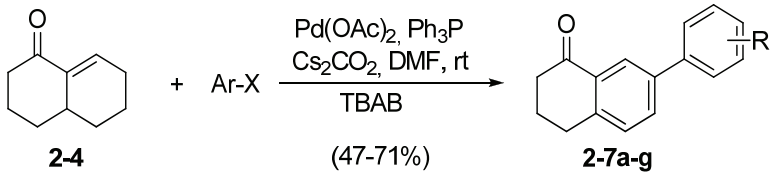
7. Conclusion

In summary, we have completed several research projects. Synthesis of the spirocyclic scaffold **1-1** and **1-2**, containing both *meta*- and *para*-functionalized ring systems, was accomplished via Johnson-Claisen rearrangement reaction of allylic alcohols **1-7** and **1-20** as a key step. Hydroboration of the terminal alkene bond, reduction of the carbethoxy function and cyclization of diols **1-10** and **1-22** into piperidines opened a convenient route to functionalized spirocyclic scaffolds **1-1** and **1-2**, where R and R_1 could be varied as follows from our synthesis (**Scheme 1**).



Scheme 1. Approach to spirocyclic scaffolds **1-1** and **1-2**

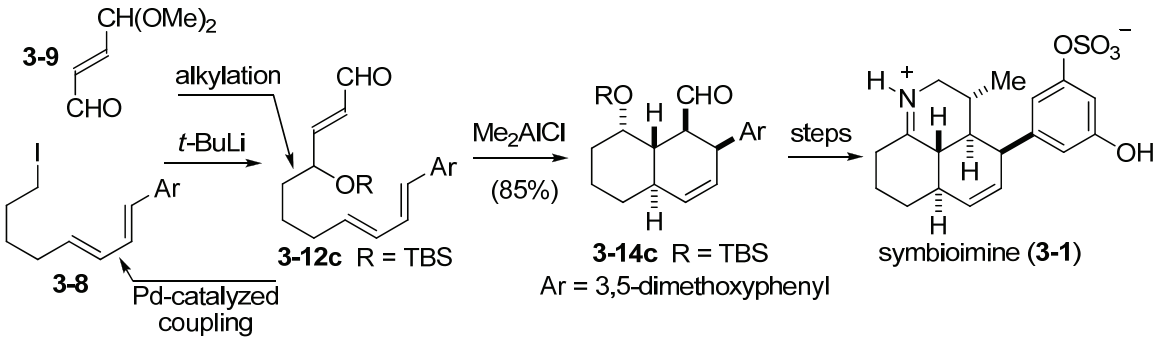
Another project was devoted to a new reaction of synthesis 7-aryl tetralones **2-7a-g** with palladium catalysis. This unusual reaction we discovered during the study of the Pd-catalyzed arylation of decalenone **2-4**. Initially, the yield of this reaction was low, but we found that addition of tetrabutylammonium bromide (TBAB) improved the yield of the palladium-catalyzed arylation dehydroaromatization reaction, which provides different 7-aryl tetralones **2-7a-g** which could not be synthesized by other methods in a such simple and straightforward manner (**Scheme 2**).



Scheme 2. Synthesis 7-aryl tetralones **2-7a-g**

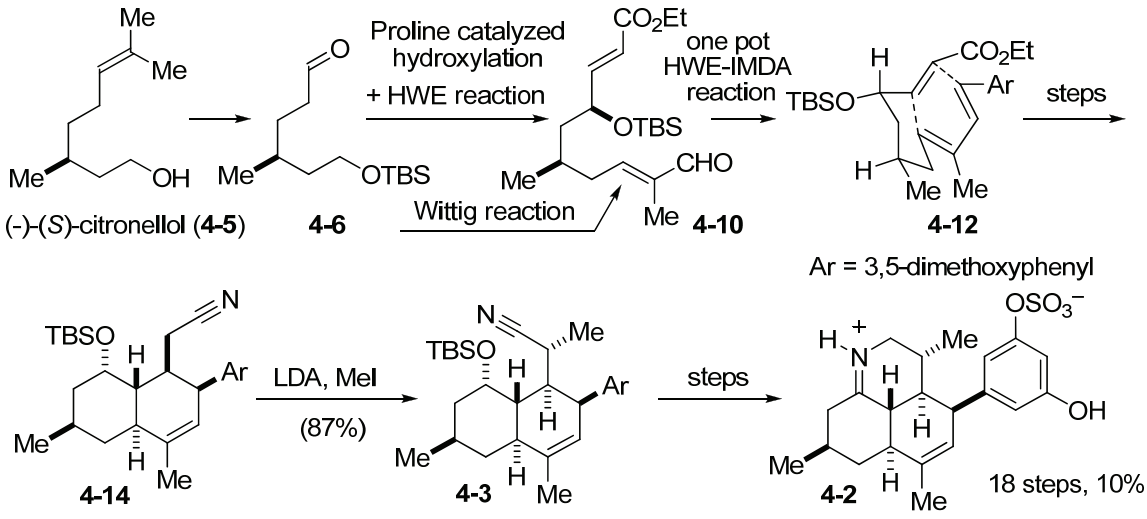
The total synthesis of (±)-symbioimine (**3-1**), a novel tricyclic iminium alkaloid, we accomplished, using a Lewis acid induced *endo*-IMDA reaction as a key step (**Scheme 3**). The Diels-Alder adduct **3-14** was synthesized from trienone **3-12** by treatment with the mild Lewis acid Me_2AlCl. The corresponding trienone was prepared by the alkylation of

aldehyde **3-9**, and 1,3-diene **3-8** was synthesized by the Pd-catalyzed oxygen-promoted coupling of 3,5-dimethoxystyrene **3-6** and the related vinyl boronate ester **3-4**. This synthesis was accomplished in 22 steps in >5% total yield, which corresponds to an average yield of 88% per step. Some analogs of this natural product were also synthesized using our original strategy.



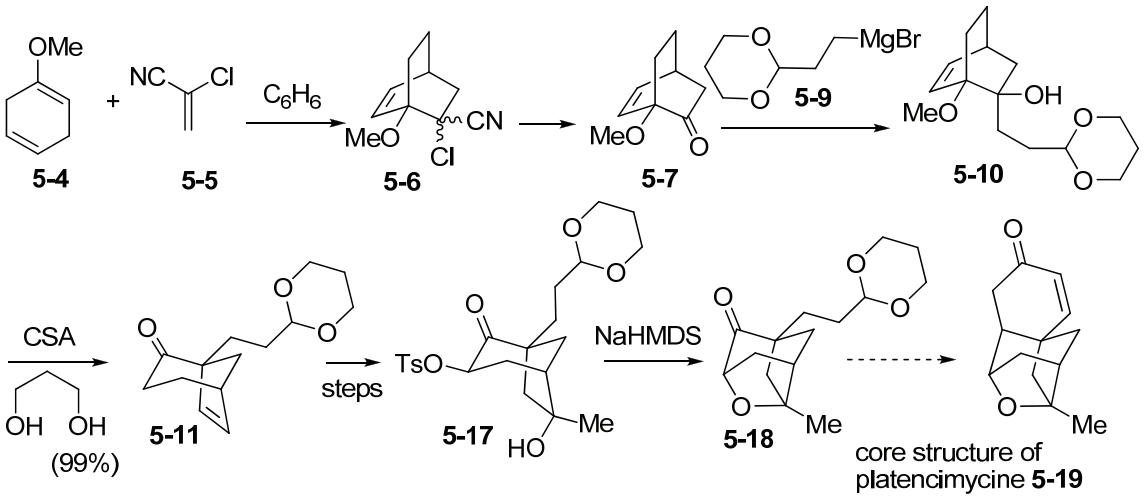
Scheme 3. Total synthesis of (±)-symbioimine (**3-1**)

Thereafter, a total synthesis of the related alkaloid neosymbioimine (**4-2**) was developed in enantioselective fashion from (-)-(*S*)-citronellol (**4-5**). Aldehyde **4-6**, prepared from (-)-(*S*)-citronellol in few steps, was further functionalized with organocatalytic α-hydroxylation and HWE reactions, prepared in one pot manner. Then, a HWE reaction of the aldehyde function of **4-10** with benzyl phosphonate **4-11** resulted in a spontaneous *endo*-IMDA reaction to produce the bicyclic decaline core of neosymbioimine (**4-2**). Elongation of the obtained aldehyde to the nitrile **4-14**, and alkylation with methyl iodide allowed us to introduce the methyl group with good diastereoselectivity. The aromatic sulfate function at the end of the synthesis was also prepared with a good yield and selectivity, which allowed us to produce significant amounts of (+)-neosymbioimine (**4-1**) in 10% total yield over 18 steps (**Scheme 4**).



Scheme 4. Total synthesis of (+)-neosymbioimine

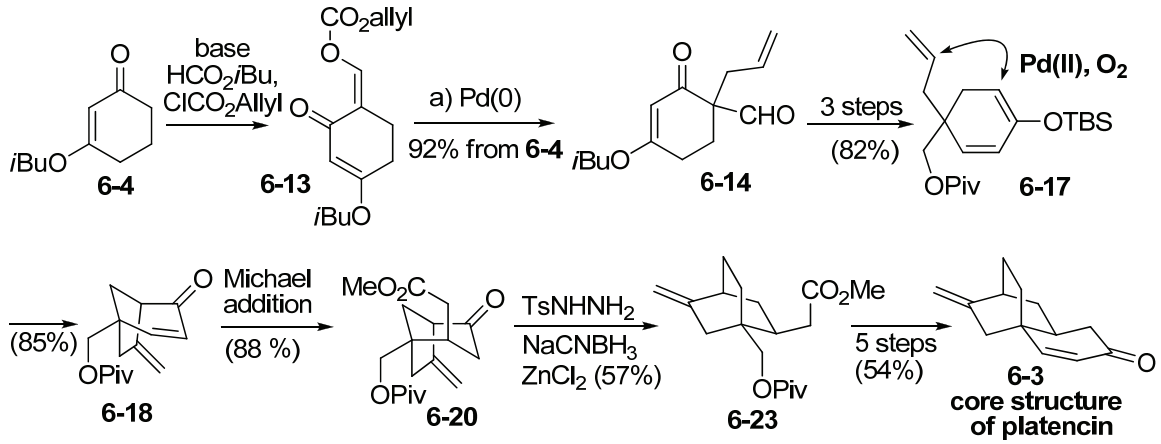
A possible original route to platensimycin (**5-1**) was also shown (**Scheme 5**). The key step of this strategy is the construction of the [3.2.1]bicyclooctane moiety of platensimycin by the rearrangement of the corresponding [2.2.2]bicyclooctane **5-10**, which was prepared by Grignard addition to the known ketone **5-7**. Ketone **5-11** was further functionalized by selective hydroboration of the double bond and α-hydroxylation of the carbon near the ketone function, providing after tosylation compound **5-17**. Tricyclic oxa-nonanone **5-18** was prepared by intramolecular S_N2 reaction with a strong base. This product **5-18** might serve as a plausible precursor for platensimycin (**5-1**).



Scheme 5. A route to platensimycin (**5-1**)

Finally, a concise formal total synthesis of platencin (**6-1**) was developed (**Scheme 6**). This approach is based on an efficient oxygen-mediated palladium-catalyzed cycloalkenylation reaction for the synthesis of [3.2.1]bicyclooctane **6-18** and a

deoxygenative radical-mediated biomimetic rearrangement reaction of derived tosyl hydrazone for construction of [2.2.2]bicyclooctane **6-23**. A catalytic asymmetric allylation reaction of enolcarbonate **6-13** for the construction of the quaternary carbon center of aldehyde **6-14** allowed for an enantioselective route to the natural product. The total yield of advanced intermediate **6-3** was 17.5% for 13 steps from commercially available compound **6-4**.



Scheme 6. Formal total synthesis of platencin (**6-1**)

Experimental Section

Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, Fluka, Lancaster, Avocado and Merck. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine and pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried by heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

NMR-spectroscopy

All the spectra were measured on a Bruker Advance 400 spectrometer, which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, respectively. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz): spectra were recorded at 295 K either in $CDCl_3$, CD_3OD or [D_6]DMSO; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH = 7.25 ppm, δC = 77.0 ppm), CD_3OD (δH 3.31, residual CD_2HOD; δC 49.0 ppm). [D_6]DMSO (δH = 2.49 ppm, δC = 39.5 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broadened, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet and so forth, *J* = coupling constant (Hz), integration, peak assignment in italic form).

Mass Spectrometry

Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol Spectrometer (TSQ-70) from Finnigan-Mat. High-resolution mass spectra were measured on a modified AMD Intectra MAT 711 A from the same company. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field desorption (FD). FT-ICR-mass spectrometry and HR-FT-ICR mass spectra were measured on an APEX 2 spectrometer from Bruker Daltonic with electrospray ionization method (ESI). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with

20/80/80/99/99% acetonitrile, flow: 0.6 mL min^{-1}. High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

Polarimetry

Optical rotations were measured on a JASCO Polarimeter P-1020 or a Perkin Elmer Polarimeter 341. They are reported as follows: $[\alpha]^{temperature}_{D}$ (concentration, solvent). The unit of *c* is g/100 mL. Anhydrous CH_2Cl_2, $CHCl_3$ or MeOH was used as a solvent. For the measurement the sodium D line = 589 nm was used.

Melting Points

Melting points were determined with a Büchi Melting point B-540 apparatus and were not corrected.

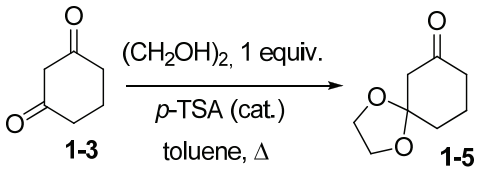
Chromatographic Methods

Flash column chromatography was performed using flash silica gel (40-63 μm, 230-400 mesh ASTM) from Macherey-Nagel.

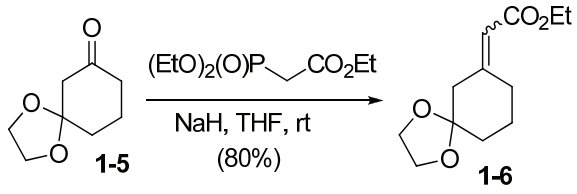
For GC-MS coupled chromatography, a GC-system series 6890 with an injector series 7683 and MS-detector series 5973 from Hewlett Packard was used, with EI method, and carrier gas He. Analytical HPLC was performed on a Hewlett Packard HP 1100 system.

Analytical thin layer chromatography (TLC) was performed on precoated with silica gel 60 F_{254} plates (Merck) or Polygram Sil G/UV_{254} (Macherey Nagel). The compounds were visualized by UV_{254} light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid (Hanessian's stain: 20 g ammonium molybdate $[(NH_4)_6Mo_7O_{24}\cdot 4H_2O]$ and 0.4 g $Ce(SO_4)_2\cdot 4H_2O$ were dissolved in 400 mL of 10% H_2SO_4, heating with the heat gun) or an aqueous solution of potassium permanganate (10% of $KMnO_4$ in 0.5% H_2SO_4, after expousing in permanganate plates were washed with water).

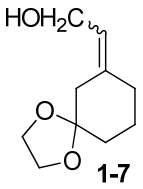
1. Synthesis of spirocyclic scaffolds



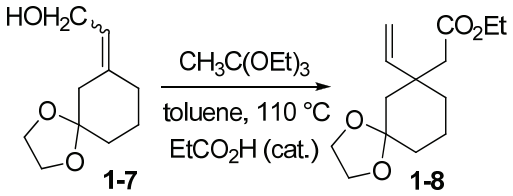
1,4-Dioxaspiro[4.5]decan-7-one (1-5): 1,3-Cyclohexanedione was disoolved in benzene or toluene. Ethylene glycol (1 equiv.) and p-TSA (5 mol%) were added, and the mixture was refluxed with azeotropic water removal until 1 equiv. of water was collected. Then the mixture (room temperature) was washed successively with water, $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, evaporated and distilled carefully in vacuum with a Vigreux column, providing 30-50 % of pure compound. Further distillation afforded a mixture of *mono*- and *di*-protected cyclohexanediones which also could be used in the next step.



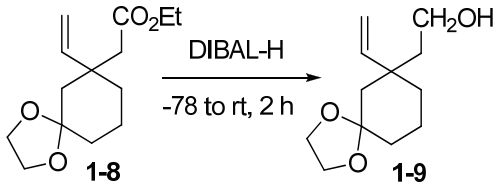
Ethyl (2*E*)-1,4-dioxaspiro[4.5]dec-7-ylideneacetate (1-6): To a suspension of NaH (60 % in mineral oil, 0.1 mol, 4.0 g) in dry DMF (100 mL) triethylphosphonoacetate (1 equiv., 20 mL) was added dropwise at 20 °C (external water bath). The mixture was stirred for 30 min at rt under inert atmosphere before 1,4-dioxaspiro[4.5]decan-7-one (**1-5**) (1 equiv) was added dropwise at 0-20 °C. The mixture was stirred for 1 h at rt and poured into 0.5 L of ice-cold water. The enoate was extracted with petroleum ether, dried, evaporated and chromatographed using 7.5:1 petroleum/EtOAc as an eluent ($\mathbf{R_f}$ = 0.25). Yield: 80 % as a colorless oil.



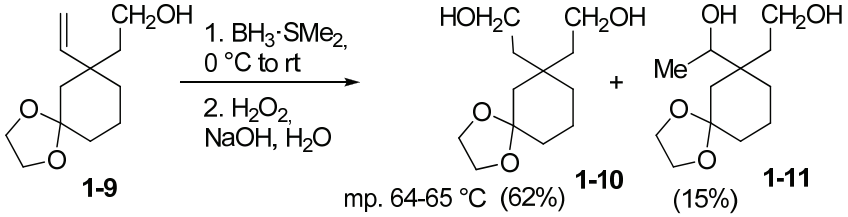
(2*E*)-2-(1,4-Dioxaspiro[4.5]dec-7-ylidene)ethanol (1-7): To a stirred solution of ethyl (2*E*)-1,4-dioxaspiro[4.5]dec-7-ylideneacetate (**1-6**) (6.55 g, 28.5 mmol) in CH_2Cl_2 (100 mL), DIBAL-H (2.5-3 equiv) has been added dropwise at -70 °C under N_2. Then the mixture was warmed to rt within 1 h, and stirred for 2 h at rt. Obtained mixture was transferred into a solution of 80 g of Rochelle salt (sodium-potassium tartrate) in 300 mL of water and stirred vigorously overnight. Then the organic layer was separated, water phase was extracted with Et_2O (2×100 mL). The combined organic extracts were washed with saturated NH_4Cl and NaCl solutions, dried, evaporated and chromatograhed in 1:2 petroleum/EtOAc ($\mathbf{R_f}$ = 0.5, EtOAc). Yield: 4.05g, 78 % as a colorless oil.



Ethyl (7-vinyl-1,4-dioxaspiro[4.5]dec-7-yl)acetate (1-8): (2*E*)-2-(1,4-Dioxaspiro[4.5]dec-7-ylidene)ethanol (**1-7**) (4.0 g, 21.7 mmol), $CH_3C(OEt)_3$ (36.5 g, 220 mmol, 10 equiv.) and $EtCO_2H$ (0.1 mL) were stirred at 110 °C in toluene for 24 h under N_2. Then toluene and triethyl ortoacetate were evaporated in vacuum and the residue was chromatographed eluating with petroleum ether:EtOAc 8:1 ($\mathbf{R_f}$ = 0.25) to get 2.78 g (51 %) of the target product. The more polar fractions were washed with pure EtOAc and evaporated to get 2.03 g of residue which contains starting material and intermediates. This residue was refluxed with the recovered toluene, triethyl ortoacetate and $EtCO_2H$ (0.05 mL) for 24 h under N_2. Evaporation and chromatography afforded additional 860 mg (16 %) of product. Repeated eluation with EtOAc and cooking with the recoverd recovered toluene and triethyl ortoacetate and $EtCO_2H$ (0.03 mL) afforded additional 425 mg (8 %) of product. Combined yield of compound **1-8** was 75 % as colorless oil.

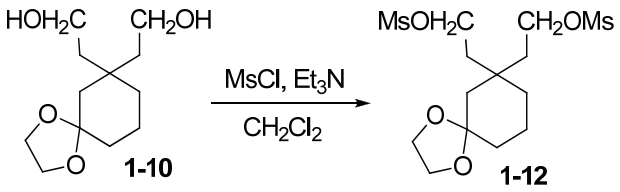


2-(7-Vinyl-1,4-dioxaspiro[4.5]dec-7-yl)ethanol (1-9): To a stirred solution of ethyl (7-vinyl-1,4-dioxaspiro[4.5]dec-7-yl)acetate (**1-8**) (3.64 g, 14.3 mmol) in CH_2Cl_2 (50 mL), DIBAL (min. 2 equiv) was added dropwise at -78 °C under N_2. Then the mixture was warmed to rt within 1 h, and stirred for 3 h at rt. Obtained mixture was transferred into a solution of 50 g of Rochelle salt (sodium-potassium tartrate) in 200 mL of water and stirred vigorously overnight. Then the organic layer was separated and the water phase was extracted with Et_2O (2*100 mL). Combined extracts were washed with saturated NH_4Cl and NaCl solutions, dried, evaporated and chromatograhed in 2:1 petroleum/EtOAc ($\mathbf{R_f}$ = 0.25). Yield of **1-9**: 2.38 g, 78 % as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.40-1.50 (m, 3H, CH_2), 1.57-1.75 (m, 6H, CH_2), 1.86-1.97 (m, 2H, CH_2), 3.61 (br s, 2H, CH_2OH), 3.87-3.98 (m, 4H, $(CH_2O)_2$), 4.95 (d, 1H, *J* = 17.7 Hz, CH=C*H*$_2$), 5.00 (d, 1H, *J* = 10.9 Hz, CH=C*H*$_2$), 5.77 (dd, *J* = 17.7, 10.9 Hz, C*H*=CH_2).

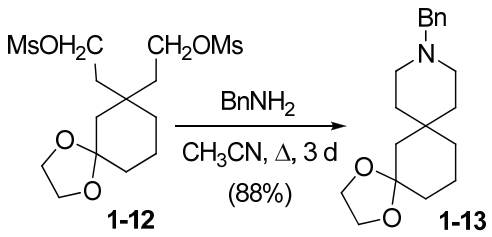


2-(1,4-Dioxaspiro[4.5]dec-7-yl)di-ethanol (1-10): $BH_3{\cdot}Me_2S$ (94 %, 1 equiv., 1.1 mL) was added dropwise to a stirred solution of 2-(7-vinyl-1,4-dioxaspiro[4.5]dec-7-yl)ethanol (**1-**

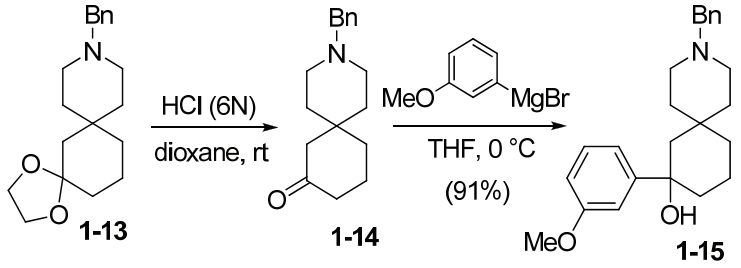
9) (2.3 g, 10.85 mmol) in dry THF (50 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, warmed gradually to rt and stirred at rt for 3 h. Then it was cooled to 0 °C and 3N solution of NaOH (7.2 mL) and 30% H_2O_2 (2.3 mL) were added dropwise. The mixture was warmed gradually to rt and stirred at rt for 1.5 h. Then the mixture was diluted with Et_2O (200 mL), washed with water and brine, dried over Na_2SO_4, evaporated and chromatographed, eluating with pure EtOAc. The fraction with $\mathbf{R_f}$ = 0.4 is the regioisomer **1-11**, 400 mg, 16 %, colorless oil. Fraction with $\mathbf{R_f}$ = 0.2 is the target product **1-10**, 1.55 g, 62 %, colorless crystals, **m.p.** 64-65 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.30-1.35 (m, 2H, CH_2), 1.50-1.66 (m, 8H, CH_2), 1.75-1.84 (m, 2H, CH_2), 2.56 (s, 2H, OH), 3.65-3.71 (m, 4H, CH_2), 3.87-3.91(m, 4H, CH_2).



2-(1,4-Dioxaspiro[4.5]dec-7-yl)di-(ethyl methanesulfonate) (1-12): To a solution of diol **1-10** from the previous reaction (230 mg, 1 mmol) and Et_3N (1.4 mL, 10 mmol) in CH_2Cl_2 (10 mL) under N_2 MsCl (0.31 mL, 4 mmol) was added dropwise at -50 °C. Then the mixture was gradually warmed to rt within 1 h and diluted with Et_2O (50 mL), washed with water, $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4 and evaporated. Product **1-12** was purified by flash chromatography with petrol ether:EtOAc 1:1 ($\mathbf{R_f}$ = 0.2). Yield: 370 mg, 96 %, $\mathbf{R_f}$ 0.7 (EtOAc), colorless oil.

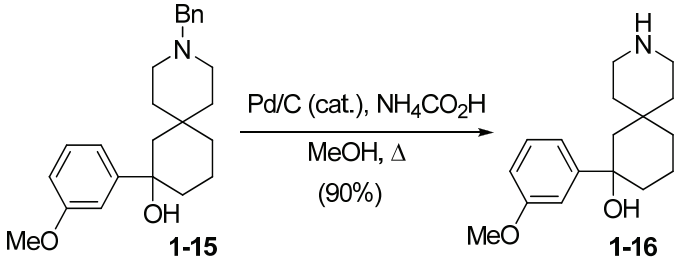


10-Benzyl-1,4-dioxa-10-azadispiro[4.1.5.3]pentadecane (1-13): To the corresponding dimesylate **1-12** from the previous reaction (320 mg, 0.83 mmol) in CH_3CN (10 mL) $BnNH_2$ (~4 equiv, 0.36 mL) and Et_3N (0.4 mL) were added. The mixture was refluxed under inert atmosphere for 3 days. After that, all volatiles were evaporated under vacuum, and Et_2O (15 mL) was added. A crystalline precipitate (probably $Et_3N{\cdot}MeSO_3H$) was filtered off and washed twice with 10 mL of Et_2O. Et_2O was removed under vacuum and the residue chromatographed on deactivated (with Et_3N) silica gel using petroleum ether:EtOAc 2:1 to 1:1 ($\mathbf{R_f}$ = 0.2-0.3). Isolated yield was 220 mg (88 %) of **1-13** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.32-1.39 (m, 2H, CH_2), 1.48-1.57 (m, 4H, CH_2), 1.58-1.67 (m, 6H, CH_2), 2.40 (br s, 4H, NCH_2), 3.51 (s, 2H, Ph$C\underline{H}_2$), 3.92 (br s, 4H, $(CH_2O)_2$), 7.23-734 (m, 5H, C_6H_5).

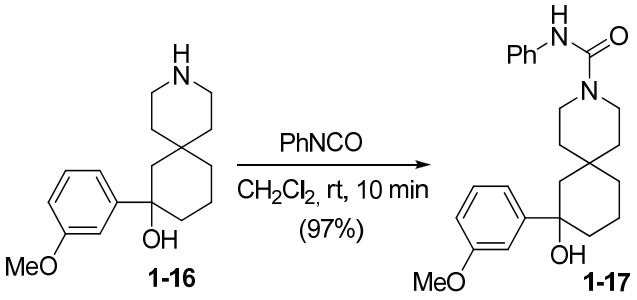


3-Benzyl-8-(3-methoxyphenyl)-3-azaspiro[5.5]undecan-8-ol (1-15): The product **1-13** from the previous step (200 mg, 0.66 mmol) was dissolved in dioxane (5 mL). HCl (6N, 5 mL) was added at rt (water bath) and the resulted mixture stirred at rt for 24 h to result in full deprotection (by LC/MS) of starting material. Then the mixture was diluted with Et_2O (50-80 mL) and washed with 2M NaOH, saturated $NaHCO_3$ and NaCl, dried over Na_2SO_4 and evaporated to dryness.

To a Grignard reagent, prepared from 3-bromoanisole (561 mg, 3 mmol) and Mg (80 mg, 3.3 mmol) in Et_2O (6 mL), crude ketone **1-14** in Et_2O (2 mL) was added dropwise at 0 °C. The mixture was allowed to warm to rt within 0.5 h and quenched (ice water bath) with half-saturated NH_4Cl solution (20 mL). The product was extracted with Et_2O, washed with $NaHCO_3$ and NaCl, dried over Na_2SO_4, evaporated and chromatographed on deactivated (with Et_3N) silica gel using petroleum ether/EtOAc 1:1 ($\mathbf{R_f}$ = 0.2-0.3). Yield: 220 mg, 91 % of a colorless oil.

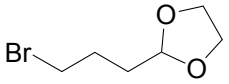


8-(3-Methoxyphenyl)-3-azaspiro[5.5]undecan-8-ol (1-16): The benzyl amine **1-15** from the previous step (180 mg, 0.49 mmol), Pd/C (20 % Pd, 50 mg, 0.094 mmol, ~ 0.2 equiv.) and ammonium formate (276 mg, 4.37 mmol, ~ 9 equiv.) were refluxed in dry MeOH (10 mL) for 1.5 h, then filtered, evaporated and chromatographed, using gradient elution with CH_2Cl_2:MeOH:AcOH 100:10:5 to 100:20:5. The fractions with $\mathbf{R_f}$ = 0.5 (CH_2Cl_2:MeOH:AcOH 100:20:5) were evaporated and shaken with Et_2O and 2N NaOH. The organic phase was separated, dried over Na_2SO_4 and evaporated to obtain the free base of the target product **1-16**. Yield: 121 mg (90%), colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.02-1.11 (m, 1H, CH_2), 1.14-1.28 (m, 2H, CH_2), 1.70-1.93 (m, 9H, CH_2), 2.68-2.80 (m, 4H, CH_2N), 3.78 (s, OCH_3), 6.72-6.77 (m, 1H, Ar), 7.01-7.08 (m, 2H, Ar), 7.23 (br t, 1H, *J* = 7.7 Hz, 5-Ph*H*).

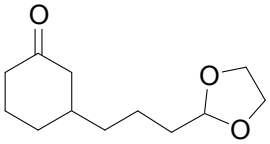


8-Hydroxy-8-(3-methoxyphenyl)-N-phenyl-3-azaspiro[5.5]undecane-3-carboxamide (1-17): Et_2O (5 mL) was added to 54 mg of the amine **1-16** from the previous step followed by addition of PhNCO (0.1 mL, ~ 5 equiv.). The mixture was stirred at rt for 10 min, during this time all solid was dissolved. The obtained clear solution was concentrated in vacuum and chromatographed, eluating with petroleum ether/EtOAc 1:1 ($\mathbf{R_f}$ = 0.4). Yield: 75 mg, (97 %) of the carbamate **1-17** as colorless crystals (**m.p.** 71-72 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.14-1.28 (m, 1H, CH_2), 1.31-1.41 (m, 2H, CH_2), 1.48-1.67 (m, 2H, CH_2), 1.70 (s, OH), 1.78-2.08 (m, 7H, CH_2), 3.35-3.55 (m, 4H, CH_2N), 3.83 (s, OCH_3), 6.48 (s, 2-Ph*H*), 6.82 (br d, 1H, *J* = 7.6 Hz, Ar), 6.98-7.12 (m, 3H, Ar), 7.24-7.38 (m, 5H, Ar).

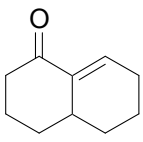
2. Synthesis of 7-aryltetralones



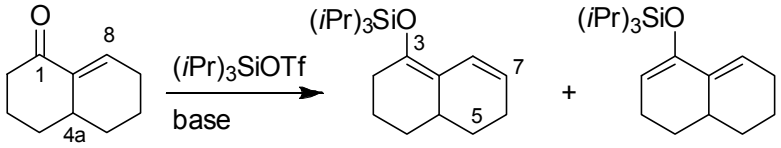
2-(3-Bromopropyl)-1,3-dioxolane (2-2):[223] DIBAL-H (100 mL of 1 M solution in hexane) was added dropwise to to a solution of ethyl 4-bromobutanoate (19.5 g, 0.1 mol) in CH_2Cl_2 (180 mL) under N_2 at -70 °C. After stirring for 1 h at –65 to –70 °C the reaction mixture was poured into an ice-cold 10 % HCl solution, and the mixture stirred at 0 °C for 1 h. After separation of the organic layer, the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with water, brine, dried with sodium sulphate, filtered, and concentrated in vacuo. The residue (16 g) was dissolved in benzene (350 mL), then ethylene glycol (46 g, 0.75 mol) and *p*-TsOH (0.68 g, 4 mmol) were added, followed by refluxing of the mixture with a Dean-Stark trap. After 3 h, the mixture was allowed to cool, and $NaHCO_3$ (3 g) were added. After stirring for 10 min, the contents were washed with saturated $NaHCO_3$ solution, dried with K_2CO_3, and filtered. The solvent was evaporated and the residue distilled resulting in 17.2 g (88%) of 2-(3-bromopropyl)-1,3-dioxolane (**2-2**), **b.p.** 87-88 °C (10 torr). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.72-1.81 (m, 2H, CH_2), 1.90-2.01 (m, 2H, CH_2), 3.39 (t, *J* = 6.7 Hz, 2H, CH_2Br), 3.79 (bt, *J* = 6.8 Hz, 2H, CH_2O), 3.90 (bt, *J* = 6.8 Hz, 2H, CH_2O), 4.83 (t, *J* = 4.6 Hz, 1H, CH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 27.6 (C_2), 32.7 (C_1), 34.0 (C_3), 65.3 (CH_2O), 104.1 (CH).



3-[3-(1,3-Dioxolan-2-yl)propyl]cyclohexanone (2-3):[224] This compound was prepared by CuI-catalyzed conjugate addition of the Grignard reagent derived from **2**.[225] To Mg turnings (0.62 g, 25.4 mmol) in 10 mL THF was added 2-(3-bromopropyl)-1,3-dioxolane (2.67 g, 12.6 mmol) at 22-24 °C over a period of 15 min. After being stirred for 1 h, the mixture was cooled to –30 °C and CuI (0.2 g, 1.05 mmol) was added at once. The mixtue was stirred for 15 min and cooled to –78 °C. Then, a solution of cyclohex-2-en-1-one (0.6 g, 6.24 mmol) in THF (5 mL) was added dropwise. The mixture was warmed to 0 °C within 1 h and quenched with saturated NH_4Cl solution (adj pH 8). After stirring for 30 min, the mixture was extracted with CH_2Cl_2, dried, filtered ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/EtOAc, 5:1) afforded 1.22 g (92%) of ketone **2-3** as a colorless oil. TLC (hexane/EtOAc, 5.1): $\mathbf{R_f}$ 0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.16-2.41 (m, 15H), 3.75-3.92 (m, 4H, CH_2O), 4.77 (t, *J* = 4.8 Hz, 1H, CH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 21.5 (CH_2), 25.7 (CH_2), 31.5 (CH_2), 34.3 (CH_2), 36.8 (CH_2), 39.4 (CH), 41.9 (α-CH_2), 48.5 (α-CH_2), 65.3 (CH_2O), 104.8 (CH-O), 212.4 (C=O).



3,4,4a,5,6,7-Hexahydronaphthalen-1(2*H*)-one (2-4):[224] 3-[3-(1,3-Dioxolan-2-yl)propyl]cyclohexanone (**2-3**) (1.2 g, 5.66 mmol) was slowly refluxed 3-4 h with 1 N HCl (15 mL) and THF (15 mL) (TLC monitoring). After cooling, the solution was neutralized with a saturated solution of $NaHCO_3$ solution, and extracted trice with CH_2Cl_2. The organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/EtOAc, 10:1) furnished the enone **2-4** (721 mg, 85%) as a colorless oil. TLC (hexane/EtOAc, 5:1): $\mathbf{R_f}$ 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.44-2.54 (m, 13H), 6.63-6.68 (m, 1H, CH). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 21.8 (CH_2), 23.0 (CH_2), 26.6 (CH_2), 30.7 (CH_2), 32.0 (CH_2), 38.2 (CH), 40.6 (CH_2), 136.2 (*C*H=C), 140.3 (CH=*C*), 201.5 (C=O).

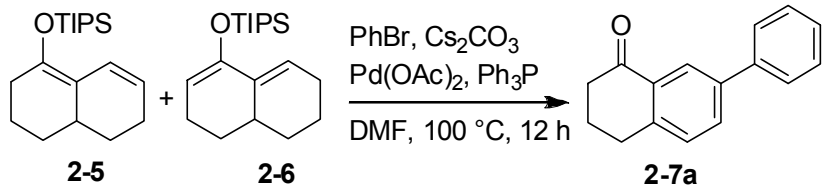


2-4 **2-5** **2-6**

General procedure for the synthesis of 2-5 and 2-6: To the solution of enone **2-4** (30 mg, 0.2 mmol) and amine (0.25 mmol) in dry CH_2Cl_2 (5 mL) TIPSOTf (69 mg, 0.21 mmol) was added dropwise, and the reaction stirred at N_2 under the conditions shown in Table 1. After completion of the reaction (by TLC), the mixture was diluted with 10% $NaHCO_3$ solution, extracted with hexane, dried with Na_2SO_4, filtered, concentrated. The residue was purified by filtration through a pad (length 2 cm) of silica gel (1% Et_3N in hexane). The yield of **2-5** + **2-6** was 80-95 %. However, the isomers could not be separated by column chromatography. The ratio of **2-5** and **2-6** was determined by ^{1}H NMR. The assigments of the isomers **2-5** and **2-6** was done by comparison of the ^{1}H NMR shifts of the vinylic hydrogens with that of similar compounds.[226]

***tri*-Isopropylsilyl 2,3,4,4a,5,6-hexahydro-1-naphthalenyl ether (2-5):** colorless oil. TLC (hexane): $\mathbf{R_f}$ 0.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.02 (d, *J* = 6.8 Hz, 18H, CH_3), 1.07-1.21 (m, 5H), 1.37-1.51 (m, 1H), 1.62-1.79 (m, 3H), 1.96-2.18 (m, 5 H), 5.50-5.56 (m, 1H, 7-H), 6.50 (d, *J* = 9.8 Hz, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 13.2 (*CH*-Si), 18.1 (d, *J* = 2.9 Hz, *CH*-Si), 22.6 (CH_2), 25.9 (CH_2), 30.6 (CH_2), 30.7 (CH_2), 30.9 (CH_2), 35.2 (C-4'), 106.2 (C-7), 123.1 (C-8), 135.0 (C'-8), 144.2 (C-1).

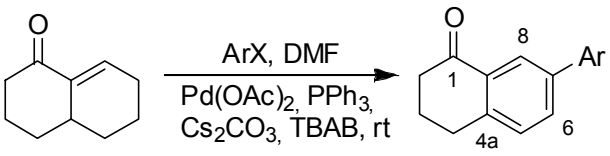
***tri*-Isopropylsilyl 3,4,4a,5,6,7-hexahydro-1-naphthalenyl ether (2-6):** colorless oil. TLC (hexane): $\mathbf{R_f}$ 0.7. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.02 (d, *J* = 6.8 Hz, 18H, CH_3), 1.07-1.21 (m, 5H), 1.37-1.51 (m, 1H), 1.62-1.79 (m, 3H), 1.96-2.18 (m, 5H), 4.92 (bd, *J* = 5.1 Hz, 1H, 2-H), 5.96 (bs, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 12.9 (*CH*-Si), 18.1 (CH_3), 18.2 (CH_3), 22.3 (CH_2), 24.1 (CH_2), 25.7 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 36.3 (C-4'), 105.8 (C-2), 120.1 (C-8), 135.0 (C'-8), 148.3 (C-1); **HRMS** (EI): $[M]^+$ calcd for $C_{19}H_{34}OSi$ 306.23789, found 306.23548.



2-5 **2-6** **2-7a**

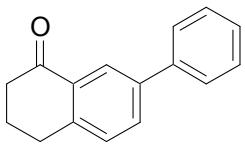
2-5 : 2-6	yield of **2-7a** [%]
0 : 100	42
68 : 32	45

Arylation of 2-5 and 2-6: A flask containing Cs_2CO_3 (165 mg, 0.5 mmol), and PPh_3 (5.3 mg, 0.02 mmol) was evacuated and flushed with nitrogen for 3 times. Then a solution of **2-5** + **2-6** (60 mg, 0.2 mmol), PhBr (150 mg, 1.0 mmol) and $Pd(OAc)_2$ (2.23 mg, 0.01 mmol) in absolute DMF (1.5 mL) was injected and the mixture stirred at 100 °C for 12 h. After completion of the reaction (disappearance of **2-5** + **2-6**, TLC-monitoring), the mixture was poured onto water, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography.

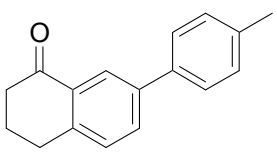


2-4 **2-7a-g**

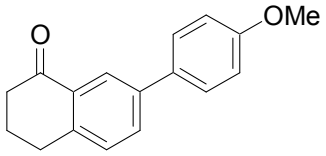
General procedure for palladium-catalyzed arylation of $\Delta^{8,9}$-octal-1-one (2-4): A flask containing Cs_2CO_3 (340 mg, 1.0 mmol), TBAB (128 mg, 0.4 mmol) and PPh_3 (10.5 mg, 0.04 mmol) was evacuated and flushed with nitrogen for 3 times. Then, a solution of enone **2-4** (60 mg, 0.4 mmol), aryl halide (2.0 mmol) and $Pd(OAc)_2$ (4.45 mg, 0.02 mmol) in degassed DMF (2.5 mL) was injected by syringe and the mixture stirred at rt for 3-5 days. After completion of the reaction (TLC-monitoring), the mixture was poured onto water and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography. During the optimization studies biphenyl (10 mol% based on **2-4**) was added as internal standard.



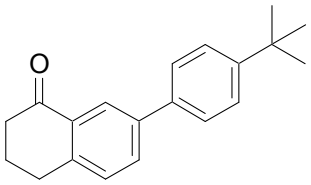
7-Phenyl-3,4-dihydronaphthalen-1(2*H*)-one (2-7a):[227] yield 63 mg (71%), colorless oil. TLC (hexane/EtOAc, 4:1): $\mathbf{R_f}$ 0.55; **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 2.06-2.16 (m, 2H, 3-H), 2.62 (t, *J* = 6.3 Hz, 2H, 4-H), 2.93 (t, *J* = 6.1 Hz, 2H, 2-H), 7.24-7.30 (m, 2H, 5-H and 4'-H), 7.37 (t, *J* = 7.6 Hz, 2H, 3'-H), 7.54 (d, *J* = 7.6 Hz, 2H, 2'-H), 7.64 (dd, *J* = 7.8, 1.8 Hz, 1H, 6-H), 8.22 (d, *J* = 1.8 Hz, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.2 (C-3), 29.4 (C-4), 39.2 (C-2), 125.5, 127.0, 127.5, 128.8, 129.4, 131.9, 132.9, 139.6, 140.0, 143.4, 198.4 (C-1).



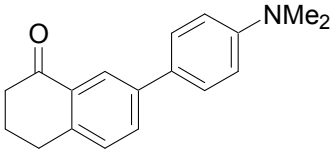
7-(4-Methylphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2-7b):[227] yield 48 mg (51%), colorless crystals, **m.p.** 76-77 °C. TLC (hexane/EtOAc, 4:1): $\mathbf{R_f}$ 0.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 2.09 (tt, 2H, *J* = 6.3 Hz, *J* = 6.1 Hz, 3-H), 2.32 (s, 3H, CH_3), 2.61 (t, 2H, *J* = 6.3 Hz, 4-H), 2.92 (t, 2H, *J* = 6.1 Hz, 2-H), 7.17 (d, 2H, *J* = 7.9 Hz, 3´-H), 7.24 (d, 1H, *J* = 7.8 Hz, 5-H), 7.45 (d, 2H, *J* = 7.9 Hz, 2´-H), 7.64 (dd, 1H, *J* = 7.8, *J* = 1.8 Hz, 6-H), 8.20 (d, 1H, *J* = 1.8 Hz, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 21.1 (CH_3), 23.3 (C-3), 29.4 (C-4), 39.2 (C-2), 125.2, 126.8, 129.3, 129.5, 131.7, 132.8, 137.1, 137.4, 139.5, 143.1, 198.4 (C-1).



7-(4-Methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2-7c):[228] yield 62 mg (62%), colorless crystals, **m.p.** 120-121 °C. TLC (hexane/EtOAc, 4:1): $\mathbf{R_f}$ 0.3. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 2.08 (tt, *J* = 6.3, 6.1 Hz, 2H, 3-H), 2.61 (t, *J* = 6.3 Hz, 2H, 4-H), 2.91 (t, *J* = 6.1 Hz, 2H, 2-H), 3.77 (s, 3H, OCH_3), 6.90 (d, *J* = 8.3 Hz, 2H, 3'-H), 7.23 (d, *J* = 7.8 Hz, 1H, 5-H), 7.48 (d, *J* = 8.3 Hz, 2H, 2'-H), 7.60 (dd, *J* = 7.8, 1.5 Hz, 1H, 6-H), 8.16 (d, *J* = 1.5 Hz, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.3 (C-3), 29.4 (C-4), 39.2 (C-2), 55.3 (OCH_3), 114.2, 124.9, 128.0, 129.3, 131.5, 132.5, 132.8, 139.2, 142.7, 159.3 (C-4'), 198.5 (C-1).

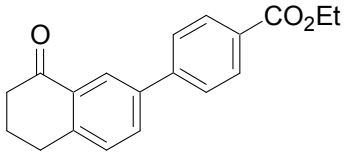


7-(4-*tert*-Butylphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (2-7d): yield 65 mg (59%), colorless oil. TLC (hexane/EtOAc, 4:1): $\mathbf{R_f}$ 0.7. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.28 (s, 9H, CH_3), 2.09 (tt, *J* = 6.3, 6.1 Hz, 2H, 3-H), 2.61 (t, *J* = 6.3 Hz, 2H, 4-H), 2.92 (t, *J* = 6.1 Hz, 2H, 2-H), 7.24 (d, *J* = 7.8 Hz, 1H, 5-H), 7.39 (d, *J* = 8.6 Hz, 2H, 3'-H), 7.50 (d, *J* = 8.6 Hz, 2H, 2'-H), 7.64 (dd, *J* = 7.8, 1.8 Hz, 1H, 6-H), 8.21 (d, *J* = 1.8 Hz, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.3 (C-3), 29.4 (C-4), 31.3 (CH_3), 34.5 (*C*Me_3), 39.2 (C-2), 125.2, 125.8, 126.6, 129.3, 131.8, 132.8, 137.0, 139.4, 143.1, 150.6, 198.4 (C-1); **HRMS** (EI): $[M]^+$ calcd for $C_{20}H_{22}O$ 278.16706, found 278.16580.

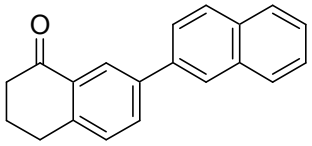


7-[4-(Dimethylamino)phenyl]-3,4-dihydronaphthalen-1(2*H*)-one (2-7e): yield 50 mg (47%), yellowish crystals, **m.p.** 110-111 °C. TLC (hexane/EtOAc, 4:1): $\mathbf{R_f}$ 0.35. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 2.07 (tt, *J* = 6.3, 6.1 Hz, 2H, 3-H), 2.59 (t, *J* = 6.3 Hz, 2H, 4-H),

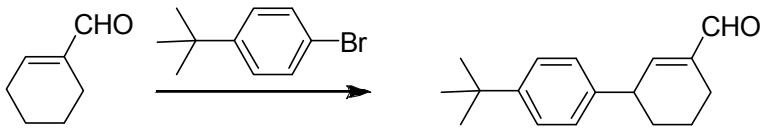
2.89 (t, *J* = 6.1 Hz, 2H, 2-H), 2.91 (s, 6H, CH_3), 6.71 (d, *J* = 8.3 Hz, 2H, 3'-H), 7.19 (d, *J* = 7.8 Hz, 1H, 5-H), 7.45 (d, *J* = 8.3 Hz, 2H, 2'-H), 7.60 (dd, *J* = 7.8, 2.2 Hz, 1H, 6-H), 8.17 (d, *J* = 2.2 Hz, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.3 (C-3), 29.3 (C-4), 39.2 (C-2), 40.5 (CH_3), 112.6, 124.2, 127.5, 127.8, 129.2, 131.1, 132.7, 139.6, 142.0, 150.1, 198.6 (C-1); **HRMS** (EI): $[M]^+$ calcd for $C_{18}H_{19}NO$ 265.14665, found 265.14554.



Ethyl 4-(8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzoate (2-7f): yield 56 mg (48%), colorless crystals, **m.p.** 79-80 °C. TLC (hexane/EtOAc, 4:1): **R_f** 0.35. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.34 (t, *J* = 7.1 Hz, 3H, CH_3), 2.10 (tt, *J* = 6.3, 6.1 Hz, 2H, 3-H), 2.63 (t, *J* = 6.3 Hz, 2H, 4-H), 2.94 (t, *J* = 6.1 Hz, 2H, 2-H), 4.31 (q, *J* = 6.1 Hz, 2H, OCH_2), 7.29 (d, *J* = 7.8 Hz, 1H, 5-H), 7.61 (d, *J* = 8.3 Hz, 2H, 2'-H), 7.67 (dd, *J* = 7.8, 1.8 Hz, 1H, 6-H), 8.04 (d, *J* = 8.3 Hz, 2H, 3´-H), 8.24 (d, *J* = 1.8 Hz, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 14.3 (CH_3), 23.1 (C-3), 29.4 (C-4), 39.1 (C-2), 61.0 (CH_2O), 125.7, 126.8, 129.5, 129.5, 130.1, 131.9, 132.9, 138.4, 144.3, 166.4 (CO_2Et), 198.2 (C-1); **HRMS** (EI): $[M]^+$ calcd for $C_{19}H_{18}O_3$ 294.12558, found 294.12690.



6,7-Dihydro-2,2'-binaphthalen-8(5*H*)-one (2-7g): yield 54 mg (50%), colorless crystals, **m.p.** 152 °C. TLC (hexane/EtOAc, 4:): **R_f** 0.6. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 2.08 (tt, *J* = 6.3, 6.1 Hz, 2H, 3-H), 2.61 (t, *J* = 6.3 Hz, 2H, 4-H), 2.91 (t, *J* = 6.1 Hz, 2H, 2-H), 7.26 (d, *J* = 7.8 Hz, 1H, 5-H), 7.35-7.45 (m, 2H), 7.67 (dd, *J* = 7.8, 1.5 Hz, 1H, 6-H), 7.73-7.85 (m, 4H), 7.98 (s, 1H), 8.33 (d, *J* = 1.5 Hz, 1H, 8-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.2 (C-3), 29.4 (C-4), 39.2 (C-2), 125.1, 125.6, 125.7, 126.1, 126.3, 127.6, 128.2, 129.4, 132.1, 133.7, 132.7, 132.9, 133.6, 137.2, 139.4, 143.5, 198.4 (C-1); **HRMS** (EI): $[M]^+$ calcd for $C_{20}H_{16}O$ 272.12011, found 272.1161.

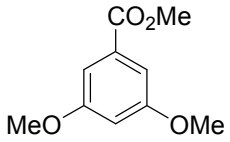


2-8 **2-9**

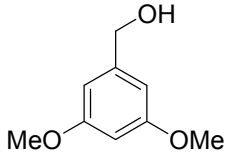
3-(4-*tert*-Butylphenyl)cyclohex-1-ene-1-carbaldehyde (2-9): This compound was prepared by the general procedure on a 1 mmol scale, yield 97 mg, 41%, pale yellow oil. TLC (hexane/EtOAc, 4:1): **R_f** 0.6. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.32 (s, 9H, $(CH_3)_3$), 1.59-1.69 (m, 2H, CH_2), 1.81-1.90 (m, 1H, CH_2), 2.05-2.43 (m, 3H, CH_2), 3.62 (br s, 1H, C-3), 6.79 (br s, 1H, 2-H), 7.11 (d, *J* = 8.2 Hz, 2H, Ar), 7.35 (d, *J* = 8.2 Hz, 2H, Ar), 9.48 (s, 1H,

CHO). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 20.5 (CH_2), 21.3 (CH_2), 31.3 (CH_3), 31.9 (CH_2), 34.4 ($C(CH_3)_3$), 42.7 (C-3), 125.6 (Ar), 127.4 (Ar), 140.8, 141.8, 149.7, 153.4 (C-2), 194.6 (CHO); **HRMS** (EI): $[M]^+$ calcd for $C_{17}H_{22}O$ 242.1728, found 242.1671.

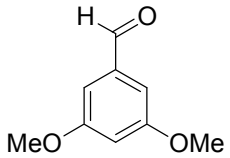
3. Total synthesis of (±)-symbioimine and analogs



Methyl 3,5-dimethoxybenzoate:[175] To a mechanically stirred suspension of 3,5-dihydroxybenzoic acid (100 g, 0.65 mol) and K_2CO_3 (360 g, 2.6 mol, 4 equiv) in acetone (1 L) was added dimethyl sulphate (217 mL, 2.3 mol, 3.5 equiv) at room temperature. The reaction mixture was vigorously stirred at reflux for 4 h, then cooled to room temperature and filtered. The filter solid was rinsed with acetone (2 × 100 mL) and most of the acetone was removed with a rotary evaporator. The residue was diluted with 5% NH_4OH solution (500 mL), stirred 5 min, and extracted with Et_2O (500 + 2 × 100 mL). The Et_2O solution was washed with 5% HCl, then with saturated $NaHCO_3$ solution, dried with Na_2SO_4, filtered and evaporated to dryness (10 mbar) at the rotary evaporator. The crude product was dissolved in hot MeOH (200 mL), and the solution allowed to cool to 23 °C, followed by slow dropwise addition of deionized water (100 mL) inducing crystallization. The crystals were filtered through a sintered frit, rinsed on the filter with a cooled (4 °C) mixture of deionized water/methanol (1/2), (2 × 100 mL), then dried under vacuum to remove all water; yield 122 g (0.624 mol, 96%) as a white powder, **m.p.** 42 °C.

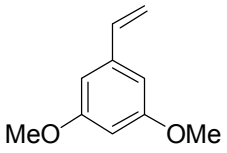


(3,5-Dimethoxyphenyl)methanol:[175] $NaBH_4$ (26.5 g, 0.70 mol, 5 equiv) was added to a solution of methyl 3,5-dimethoxybenzoate (27.46 g, 0.140 mol) in dimethoxyethane (250 mL). The mixture was heated to reflux and MeOH (125 mL) was slowly added within 2 h while keeping the inner temperature above 70 °C. The mixture was refluxed for an additional 1 h, and then most of the solvent was evaporated. The residue was diluted with Et_2O (200 mL) and quenched with water (100 mL). The layers were separated and the aqueous layer extracted with Et_2O. The combined organic layers were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to give pure (by NMR) (3,5-dimethoxyphenyl)methanol as a colorless oil, which crystallized when stored, yield 23.28 g (138.5 mmol, 99%), **m.p.** 47-47.5 °C.

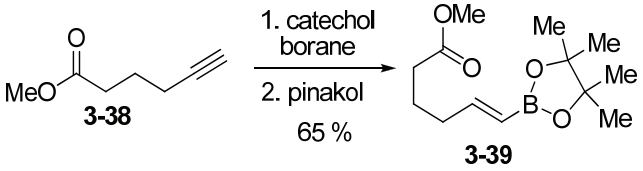


3,5-Dimethoxybenzaldehyde:[175] To a stirred suspension of pyridinium dichromate (45.1 g, 1.2 equiv) in CH_2Cl_2 (100 mL) was added a solution of (3,5-dimethoxyphenyl)methanol (16.8 g, 0.1 mol) in CH_2Cl_2 (50 mL) dropwise at room temperature. The mixture was stirred at room temperature for 24 h, and then filtered through a

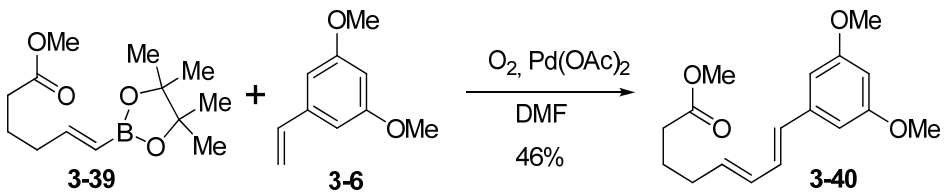
pad of celite. The filter pad was washed with CH_2Cl_2 (2 × 30 mL). Most of the CH_2Cl_2 was removed under reduced pressure, and the residue was diluted with Et_2O (100 mL). The ether solution was washed two times with 5% NaOH, then with 5% HCl, saturated $NaHCO_3$ solution, and finally with brine, followed by drying with Na_2SO_4 and concentration in vacuo. The crude product was dissolved in a minimum amount of hot MeOH, and recrystallized by slow addition of deionized water. The crystals were filtered, rinsed with a cold MeOH/H_2O (1:1) mixture, and then dried under vacuum to remove all water; yield 13.5 g (81 mmol, 81%) as colorless crystals, **m.p.** 46-47 °C.



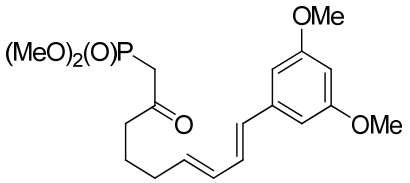
1,3-Dimethoxy-5-vinylbenzene (3-4):[175] This reaction was performed under an inert atmosphere. To a suspension of methyl triphenylphosphonium bromide (23.2 g, 65 mmol, 1.2 equiv) in dry THF (100 mL), KO*t*Bu (8.5 g, 76 mmol, 1.4 equiv.) was added in one portion. The mixture was stirred for 2 h at room temperature, then cooled to -70 to -80 °C followed by the dropwise addition of a solution of 3,5-dimethoxybenzaldehyde (9.0 g, 54.2 mmol) in dry THF (50 mL) at -70 to -65 °C. Then the cooling bath was removed, and the mixture allowed to warm to room temperature. Now, the reaction was quenched with dry MeOH (10 mL). The solvents were evaporated under reduced pressure and the residue passed through a short pad (4 cm) of silica gel using petroleum ether/ethyl acetate, 15:1 as eluent, to give 8.54 g (52.0 mmol, 96%) of 3,5-dimethoxystyrene **3-4** as a colorless oil. $\mathbf{R_f}$ = 0.45 (petroleum ether/ethyl acetate, 10:1).



Methyl (5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enoate (3-39): Catechol borane (13.09 g, 11.64 mL, 110 mmol) was slowly added via syringe to neat **3-38** (12.6 g, 100 mmol) under inert atmosphere at rt (water bath) with stirring, and stirred at 70 °C for 3 h (controlled by TLC, $\mathbf{R_f}$ of catechol boronate is 0.5, Hexane/EtOAc 1:1). The resulting mixture was cooled to rt, and pinacol (14.16 g, 120 mmol) was added, and the mixture was stirred for 3 h at rt. Obtained product was purified by passing through silica gel using Hexane/EtOAc 6:1 as eluant ($\mathbf{R_f}$ = 0.25). Yield 16.5 g (64.9 mmol, 65%).

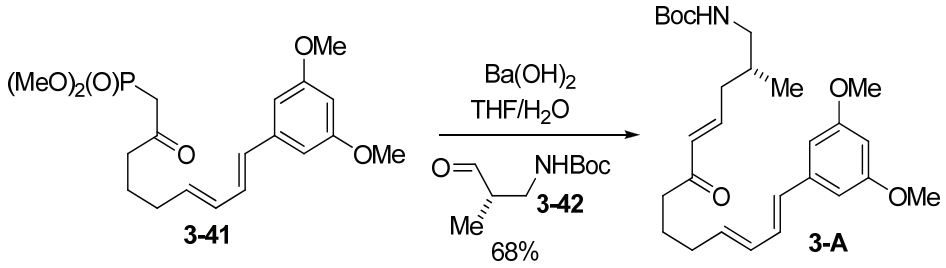


Methyl (5*E*,7*E*)-8-(3,5-dimethoxyphenyl)octa-5,7-dienoate (3-40): To a stirred mixture of styrene **3-6** (3.98 g, 24.2 mmol), $Pd(OAc)_2$ (150 mg, 8 mol%) and Na_2CO_3 (1.92 g, 17 mmol) in DMF (32 mL) at 45 °C a solution of boronate **3-39** (2.05 g, 8.12 mmol) in DMF (8 mL) was added via syringe pump during 24 h, and further stirred for 3 h at this temperature. Obtained mixture was cooled to 0 °C, and diluted with ethyl acetate (200 mL), washed with water (2×50 mL), dried with Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (**R_f** 0.3, Hexane/EtOAc, 5:1). Yield of diene **3-40** was 1.08 g (3.72 mmol, 46%) as colorless crystals (**mp.** 34-35 °C), or 61% based on recovered styrene **3-6**.

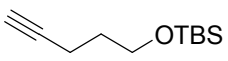


3-41

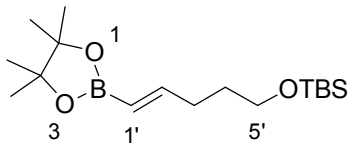
Dimethyl [(6*E*,8*E*)-9-(3,5-dimethoxyphenyl)-2-oxonona-6,8-dien-1-yl]phosphonate (3-41): To a solution of $MeP(O)(OMe)_2$ (0.816 mL, 7.6 mmol) in THF (7.5 mL) *n*BuLi in hexane (7.25 mmol, 3 mL of a 2.5M solution) was added dropwise at -78 °C. After the mixture was stirred at -78 °C for 1 h, a solution of ester **3-40** (550 mg, 1.896 mmol) in THF (2 mL) was added dropwise. After 15 min of stirring at -78 °C the reaction was quenched with NH_4Cl (30 mL of saturated solution) and allowed to warm to rt. The product was extracted with EtOAc (3×35 mL), washed with 30 mL of sat. NaCl, dried with Na_2SO_4 and evaporated. Product was purified by flash chromatography through a short column with EtOAc as an eluent (**R_f** 0.35) to provide 695 mg (96%) of ketophosphonate **3-41** as a yellowish oil.



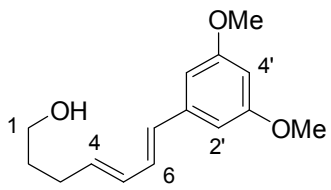
***tert*-Butyl [(2*R*,4*E*,10*E*,12*E*)-13-(3,5-dimethoxyphenyl)-2-methyl-6-oxotrideca-4,10,12-trien-1-yl]carbamate (3A):** A mixture of **3-41** (380 mg, 1 mmol) and $Ba(OH)_2 \cdot H_2O$ (150 mg, 0.8 mmol) in THF/ H_2O (10 mL/0.25 mL) was stirred at rt for 0.5 h. Aldehyde **3-42** (205 mg, 1.1 mmol) was added dropwise and the resulting mixture was stirred overnight, then treated with NH_4Cl (20 mL of saturated solution). The product was extracted with EtOAc (3×30 mL), washed with 30 mL of sat. NaCl, dried with Na_2SO_4 and evaporated. Product was purified by flash chromatography (R_f = 0.3, Hexane/EtOAc, 2:1) to provide 300 mg (68%) of enone **3-17** as a colorless oil.



***tert*-Butyl(dimethyl)(pent-4-ynyloxy)silane (3-5)**: A solution of TBSCl (59.0 g, 0.394 mol, 1.1 equiv) in dry DMF (200 mL) was added dropwise to a mixture of pentyn-5-ol (30.0 g, 0.357 mol) and imidazole (60.4 g, 0.89 mol, 2.5 equiv) at 0 °C. The mixture was stirred at room temperature for 12 h, then diluted with water (1 L) and extracted with petroleum ether (3 × 200 mL). The extracts were washed with water and brine, dried with Na_2SO_4, filtered, and evaporated in vacuo. The crude silyl ether was distilled at around 65 °C (10 mbar) to provide 64 g (90%) of product. Alternatively, it can be passed through a short pad of silica gel to yield 70 g (99%) of *tert*-butyl(dimethyl)(pent-4-ynyloxy)silane **3-5** as a colorless oil. $\mathbf{R_f}$ = 0.85 (petroleum ether/ethyl acetate, 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 6H, CH_3Si), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.71 (tt, J = 7.1, 6.1 Hz, 2H, CH_2CH_2O), 1.91 (t, J = 2.8 Hz, 1H, HC≡C), 2.26 (td, J = 7.1, 2.8 Hz, 2H, CH_2C≡), 3.68 (t, J = 6.1 Hz, 2H, CH_2O); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.4 (CH_3Si), 14.8 (CH_2C≡), 18.3 ($(CH_3)_3CSi$), 25.9 ($(CH_3)_3CSi$), 31.5 (CH_2CH_2O), 61.4 (CH_2O), 68.2 (HC≡C-), 84.2 (HC≡C-).

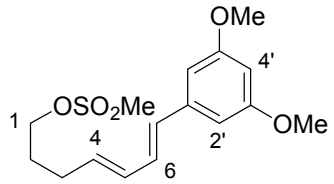


***tert*-Butyl(dimethyl){[(4E)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enyl]oxy}silane (3-6)**: To a stirred solution of *tert*-butyl(dimethyl)(pent-4-ynyloxy)silane (**3-5**) (30 g, 0.152 mol) was added dropwise at room temperature catecholborane (19.4 mL, 0.182 mol, 1.2 equiv) within 1 h under an inert atmosphere. After complete addition, the mixture was stirred at 70 °C for 12 h, then cooled to 23 °C, followed by the addition of pinacol (25.0 g, 0.212 mol, 1.4 equiv). The mixture was stirred for 3 h at room temperature before it was diluted with petroleum ether (400 mL) and stirred for 10 min. The precipitate was filtered off and the filtrate washed with 5% NaOH (5 × 100 mL) and once with brine. The organic layer was dried with Na_2SO_4, filtered, and evaporated in vacuo. The residue was distilled at 108-110 °C (0.4 mbar) to give 42 g (85%) of the vinyl boronate **3-6** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.02 (s, 6H, CH_3Si), 0.87 (s, 9H, $(CH_3)_3CSi$), 1.24 (s, 12H, $((CH_3)_2CO)_2B$-), 1.62 (tt, J = 7.1, 6.3 Hz, 2H, -CH_2CH_2O-), 2.19 (td, J = 7.1, 6.3 Hz, 2H, -CH_2CH=), 3.59 (t, J = 6.3 Hz, 2H, -CH_2O-), 5.43 (d, J = 17.9 Hz, 1H, -CH=CHB-), 6.63 (dt, J = 17.9, 6.3 Hz, 1H, -CH=CHBpin$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.3 (CH_3Si), 18.3 ($(CH_3)_3CSi$), 24.8 ($((CH_3)_2CO)_2B$-), 25.9 ($(CH_3)_3CSi$), 31.3 (CH_2), 32.1 (CH_2), 62.6 (-CH_2O-), 83.0 ($((CH_3)_2CO)_2B$-), 118.9 (-HC=CHB-), 154.2 (-HC=CHB-); **HRMS** (ESI): calcd for $C_{17}H_{35}BO_3Si$ $[M+H]^+$ 326.25576, found 326.25579.



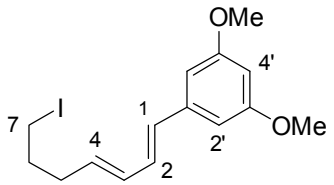
(4*E*,6*E*)-7-(3,5-Dimethoxyphenyl)hepta-4,6-dien-1-ol (3-7): Solid Na_2CO_3 (21.2 g, 0.2 mol) was added in one portion to a stirred solution of 3,5-dimethoxystyrene (**3-4**) (32.0 g, 0.195 mol) and $Pd(OAc)_2$ (2.24 g, 10 mmol) in dry DMF (300 mL). Then oxygen was

bubbled through the mixture for 10 min. The flask was connected to an oxygen filled rubber balloon and the mixture heated to 60 °C. Then, a solution of boronate **6** (32.6 g, 0.1 mol) in DMF (50 mL) was added via syringe pump over 12 h while keeping the temperature of the flask at 60 °C and the mixture under a positive oxygen pressure. After complete addition, the mixture was stirred for an additional 2 h at 60 °C before it was cooled to room temperature. The mixture was diluted with EtOAc (500 mL) and poured into ice-cold water (1.5 L). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude diene was filtered through a short pad of silica gel (5% of EtOAc in hexane, $R_f = 0.4$), giving a mixture of unreacted styrene **3-4** together with the TBS-protected dienol. The solvents were evaporated, and the residue dissolved in MeOH (300 mL). A solution of concentrated HCl (10 mL), dissolved in MeOH (50 mL) was added dropwise to this solution at room temperature. The mixture was stirred for 30 min, then MeOH was evaporated in vacuo at room temperature, and EtOAc (100 mL) and water (500 mL) were added to the residue. The layers were separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined EtOAc extracts were washed with 5% $NaHCO_3$ and with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. Flash chromatography of the residue (hexane/EtOAc, 2:1) afforded 17.75 g of styrene **3-4** (**R_f** = 0.7-0.8) and 14.6 g (68% based on the recovered styrene **3-4**, or 59% based on the reacted boronate **3-6**) of alcohol **3-7**. $R_f = 0.2$ (hexane/ethyl acetate, 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.69 (tt, *J* = 7.1, 6.5 Hz, 2H, 2-H), 2.23 (td, *J* = 7.3, 7.1 Hz, 2H, -C*H*$_2$CH=), 3.66 (t, *J* = 6.5 Hz, 2H, -CH_2O-), 3.78 (s, 6H, OCH_3), 5.82 (dt, *J* = 15.2, 7.3 Hz, 1H, 4-H), 6.20 (dd, *J* = 15.2, 10.6 Hz, 1H, 5-H), 6.33 (t, *J* = 2.3 Hz, 1H, 4'-H), 6.37 (d, *J* = 15.7 Hz, 1H, 7-H), 6.52 (d, *J* = 2.3 Hz, 2H, 2'-H), 6.72 (dd, *J* = 15.7, 10.6 Hz, 1H, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 29.1 (CH_2), 32.1 (CH_2), 55.2 (OCH_3), 62.2 (OCH_2), 99.5 (C-4'), 104.1 (C-2'), 129.6, 130.3, 130.8, 135.1, 139.5 (C-1'), 160.8 (C-3').

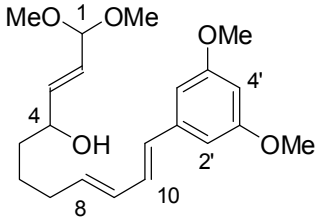


(4*E*,6*E*)-7-(3,5-Dimethoxyphenyl)hepta-4,6-dienyl methanesulfonate: MsCl (5.86 mL, 75 mmol, 1.3 equiv) was added dropwise at -30 °C to a stirred solution of alcohol **3-7** (14.4 g, 58 mmol) and NEt_3 (16.2 mL, 116 mmol, 2 equiv) in dry CH_2Cl_2 (300 mL) under inert atmosphere. The reaction was stirred 1 h at -30 °C, then allowed to warm to room temperature and quenched with water (300 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined CH_2Cl_2 extracts were washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was chromatographed through a short pad of silica gel (hexane/EtOAc, 2:1, **R_f** = 0.25), to provide 18.6 g (57 mmol, 98%) of the mesylate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.86 (tt, *J* = 7.3, 6.8 Hz, 2H, 2-H), 2.25 (td, *J* = 7.3, 7.1 Hz, 2H, -C*H*$_2$CH=), 2.98 (s, 3H, OSO_2CH_3), 3.78 (s, 6H, OCH_3), 4.22 (t, *J* = 6.5 Hz, 2H, 1-H), 5.76 (dt, *J* = 15.2, 7.3 Hz, 1H, 4-H), 6.22 (dd, *J* = 15.2, 10.3 Hz, 1H, 5-H), 6.33 (t, *J* = 2.3 Hz, 1H, 4'-H), 6.38 (d, *J* = 15.4 Hz, 1H, 7-H), 6.52 (d, *J* = 2.3 Hz, 2H, 2'-H), 6.70 (dd, *J* = 15.4, 10.3 Hz, 1H, 6-H). **^{13}C NMR**

(100 MHz, $CDCl_3$): δ[ppm] = 28.5 (CH_2), 28.5 (CH_2), 37.2 (OSO_2CH_3), 55.2 (OCH_3), 69.2 (OCH_2), 99.6 (C-4'), 104.1 (C-2'), 129.2, 130.9, 131.7, 133.1, 139.3 (C-1'), 160.8 (C-3'); **HRMS** (ESI): calcd for $C_{16}H_{22}O_5S$ $[M+H]^+$ 327.12606, found 327.12610.



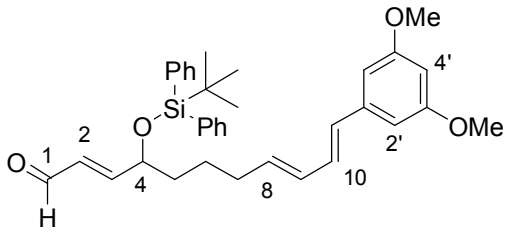
1-[(1*E*,3*E*)-7-Iodohepta-1,3-dienyl]-3,5-dimethoxybenzene (3-8): NaI (45 g, 0.3 mol, 5.2 equiv) was added in one portion to a stirred solution of the foregoing mesylate (18.6 g, 57 mmol) in dry acetone (200 mL) under inert atmosphere. The mixture was stirred in the dark for 24 h, then diluted with petroleum ether (100 mL) and water (200 mL). The layers were separated and the aqueous phase extracted with petroleum ether (100 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed through a short pad of silica gel (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.4), to yield 19.1 g (53.3 mmol, 93%) of the iodide **3-8** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.94 (tt, *J* = 7.1, 6.8 Hz, 2H, 6'-H), 2.26 (td, *J* = 7.1, 6.8 Hz, 2H, 5'-H), 3.20 (t, *J* = 6.8 Hz, 2H, 7'-H), 3.79 (s, 6H, OCH_3), 5.75 (dt, *J* = 15.2, 7.1 Hz, 1H, 4'-H), 6.25 (dd, *J* = 15.2, 10.4 Hz, 1H, 3'-H), 6.34 (t, *J* = 2.3 Hz, 1H, 4-H), 6.40 (d, *J* = 15.7, 1H, 1'-H), 6.53 (d, *J* = 2.3 Hz, 2H, 2,6-H), 6.71 (dd, *J* = 15.7, 10.4 Hz, 1H, 2'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 6.3 (C-7'), 32.7 (CH_2), 33.3 (CH_2), 55.3 (OCH_3), 99.6 (C-4), 104.2 (C-2,6), 129.4 (=CH-), 130.8 (=CH-), 131.7 (=CH-), 133.2 (=CH-), 139.4 (C-1), 160.8 (C-3); **HRMS** (ESI): calcd for $C_{15}H_{19}IO_2$ $[M+H]^+$ 359.05025, found 359.05007.



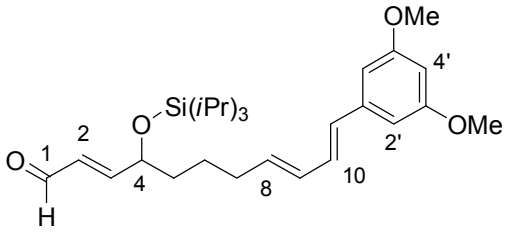
(2*E*,8*E*,10*E*)-11-(3,5-Dimethoxyphenyl)-1,1-dimethoxyundeca-2,8,10-trien-4-ol (3-10): To a solution of iodide **3-8** (1.5 g, 4.19 mmol) in dry Et_2O (20 mL), prepared under inert atmosphere, was added *t*-BuLi (1.5 M in hexane, 7 mL, 10.5 mmol, 2.5 equiv) in a dropwise fashion at -80 °C over 15 min. The mixture was stirred at -80 °C for 0.5 h, then fumaraldehyde monodimethyl acetal **3-9**[176] (0.65 g, 5.0 mmol, 1.2 equiv) in Et_2O (5 mL) was added dropwise. The mixture was stirred for 15 min at -80 °C, then quenched with half-saturated NH_4Cl solution, and allowed to warm to room temperature. After separation of the layers, the water phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed quickly through silica gel (hexane/EtOAc/NEt_3, 100:100:1, $\mathbf{R_f}$ = 0.35) to yield the acetal **3-10** (0.91 g, 3.3 mmol, 60%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.44-1.68 (m, 2H, H-5,6), 2.15 (q, *J* = 6.7 Hz, 1H, 7-H), 3.31 (s, 6H, acetal

OCH_3), 3.78 (s, 6H, OCH_3), 4.16 (br s, 1H, 4-H), 4.78 (d, *J* = 4.8 Hz, 1H, 1-H), 5.65 (ddd, *J* = 15.9, 4.8, 1.0 Hz, 1H, 2-H), 5.79 (dt, *J* = 15.2, 7.1 Hz, 1H, 8-H), 5.88 (dd, *J* = 15.2, 6.1 Hz, 1H, 3-H), 6.18 (dd, *J* = 15.2, 10.4 Hz, 1H, 9-H), 6.33 (t, *J* = 2.3 Hz, 1H, 4'-H), 6.36 (d, *J* = 15.7, 1H, 1'-H), 6.52 (d, *J* = 2.3 Hz, 2H, 2',6'-H), 6.70 (dd, *J* = 15.7, 10.4 Hz, 1H, 10-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 25.7 (C-6), 32.6 (C-7), 36.5 (C-5), 52.7 (acetal OCH_3), 52.7 (acetal OCH_3), 55.3 (OCH_3), 71.8 (C-4), 99.6 (C-4'), 102.4 (C-1), 104.2 (C-2',6'), 126.7 (C-2), 129.8 (C-10), 130.2 (C-11), 130.8 (C-9), 135.5 (C-8), 137.5 (C-3), 139.6 (C-1'), 160.8 (C-3',5').

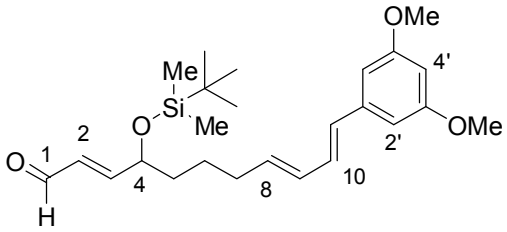
General procedure for silylation and acetal cleavage of 3-10: A solution of TBSCl (4.05 g, 27 mmol, 2 equiv) in anhydrous CH_2Cl_2 (10 mL) was added to a stirred solution of alcohol **3-10** (4.89 g, 13.5 mmol) and imidazole (4.66 g, 67.5 mmol, 5 equiv) in CH_2Cl_2 (40 mL) under an inert atmosphere within 15 min at 0 °C. The mixture was allowed to reach room temperature overnight, then diluted with petroleum ether (150 mL) and washed with 5% $NaHCO_3$ and with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in acetone (300 mL) and Amberlyst-15 (1.5 g) was added in one portion. The mixture was stirred at 23 °C for 40 min, then filtered through a pad of Na_2CO_3, and the filtrate was evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.25) to give 4.8 g (11.16 mmol, 83%) of **3-12c** as a colorless oil. The corresponding TBDPS and TIPS protected aldehydes **3-12a** and **3-12b** were prepared by the same procedure giving 80% of **3-12a** and 75% of **3-12b**.



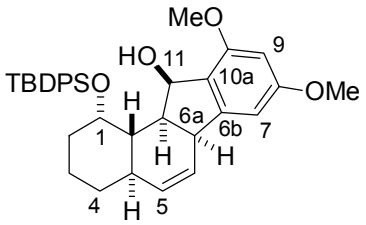
(2*E*,8*E*,10*E*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-11-(3,5-dimethoxyphenyl)undeca-2,8,10-trienal (3-12a): 0.45 mmol scale, yield 203 mg (80%). $\mathbf{R_f}$ = 0.2 (hexane/EtOAc, 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.08 (s, 9H, $(CH_3)_3CSi$), 1.24-1.60 (m, 6H, CH_2), 3.80 (s, 6H, OCH_3), 4.48 (q, *J* = 5.1 Hz, 1H, 4-H), 5.67 (dt, *J* = 15.2, 7.1 Hz, 1H, 8-H), 6.10 (dd, *J* = 15.2, 10.6 Hz, 1H, 9-H), 6.25 (ddd, 1H, *J* = 15.7, 8.1 Hz, *J* = 1.3 Hz, 1H, 2-H), 6.34 (t, 1H, *J* = 2.3 Hz, 1H, 4'-H), 6.35 (d, 1H, *J* = 15.7, 1H, 11-H), 6.53 (d, 2H, *J* = 2.3 Hz, 2H, 2',6'-H), 6.64-6.70 (m, 2H, 3,10-H), 7.32-7.47 (m, 6H, *m*,*p*-PhSi), 7.60 (br d, *J* = 6.8 Hz, 2H, *o*-PhSi), 7.60 (br d, 2H, *J* = 6.8 Hz, *o*-PhSi), 9.45 (d, 1H, *J* = 8.1 Hz, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 19.3 ($(CH_3)_3CSi$), 23.6 (CH_2), 27.0 ($(CH_3)_3CSi$), 32.5 (CH_2), 36.1 (CH_2), 55.3 (OCH_3), 72.3 (C-4), 99.6 (C-4'), 104.2 (C-2'), 127.7, 127.7, 129.7, 129.9, 130.3, 130.8, 131.0, 133.2, 133.5, 135.1, 135.8, 139.6 (C-1'), 159.0 (C-3), 160.9 (C-3'), 193.5 (C-1).



(2*E*,8*E*,10*E*)-11-(3,5-Dimethoxyphenyl)-4-[(triisopropylsilyl)oxy]undeca-2,8,10-trienal (3-12b): 0.105 mmol scale, yield 40 mg (75%). $\mathbf{R_f}$ = 0.25 (hexane/EtOAc, 20:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.05 (br s, 21H, *i*PrSi), 1.34-1.58 (m, 2H, CH_2), 1.65-1.72 (m, 2H, CH_2), 2.15 (q, *J* = 7.1 Hz, 2H, 7-H), 3.78 (s, 6H, OCH_3), 4.59 (q, *J* = 5.1 Hz, 1H, 4-H), 5.77 (dt, *J* = 14.9, 7.1 Hz, 1H, 8-H), 6.17 (dd, *J* = 14.9, 10.6 Hz, 1H, 9-H), 6.28 (dd, *J* = 15.6, 7.8 Hz, 1H, 2-H), 6.33 (t, *J* = 2.3 Hz, 1H, H-4'), 6.37 (d, *J* = 15.4 Hz, 1H, 11-H), 6.52 (d, *J* = 2.3 Hz, 2H, 2',6'-H), 6.70 (dd, *J* = 15.4, 10.6 Hz, 1H, 10-H), 6.79 (dd, *J* = 15.6, 5.1 Hz, 1H, 3-H), 9.58 (d, *J* = 7.8 Hz, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 12.3 ($(CH_3)_2CHSi$), 18.0 ($(CH_3)_2CHSi$), 23.6 (CH_2), 32.7 (CH_2), 36.8 (CH_2), 55.3 (OCH_3), 71.6 (C-4), 99.6 (C-4'), 104.2 (C-2'), 129.6, 130.3, 130.9, 131.0, 135.1, 139.5 (C-1'), 160.0 (C-3), 160.8 (C-3',5'), 193.6 (C-1); **HRMS** (ESI) calcd for $C_{28}H_{44}O_4Si$ $[M+H]^+$ 473.30816, found 473.30817.

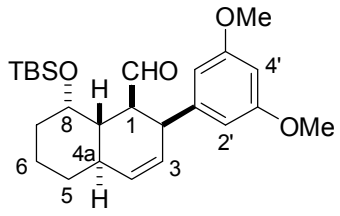


(2*E*,8*E*,10*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-11-(3,5-dimethoxyphenyl)undeca-2,8,10-trienal (3-12c): **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.02 (s, 3H, $(CH_3)_2Si$), 0.06 (s, 3H, $(CH_3)_2Si$), 0.91 (s, 9H, $(CH_3)_3CSi$), 1.43-1.53 (m, 1H, 6-H), 1.56-1.66 (m, 1H, 5-H), 2.15 (q, 1H, *J* = 7.1 Hz, 1H, 7-H), 3.78 (s, 6H, OCH_3), 4.42 (ddd, *J* = 5.8, 4.6, 1.5 Hz, 1H, 4-H), 5.78 (dt, *J* = 15.2, 7.1 Hz, 1H, 8-H), 6.17 (dd, *J* = 15.2, 10.6 Hz, 1H, 9-H), 6.25 (ddd, *J* = 15.6, 8.1, 1.5 Hz, 1H, 2-H), 6.33 (t, *J* = 2.3 Hz, 1H, 4'-H), 6.37 (d, *J* = 15.6, 1H, 11-H), 6.52 (d, *J* = 2.3 Hz, 2H, 2',6'-H), 6.71 (dd, *J* = 15.6, 10.6 Hz, 1H, 10-H), 6.78 (dd, *J* = 15.6, 4.6 Hz, 1H, 3-H), 9.56 (d, *J* = 8.1 Hz, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -4.9 ($(CH_3)_2Si$), -4.7 ($(CH_3)_2Si$), 18.1 ($(CH_3)_3CSi$), 24.4 (C-6), 25.7 ($(CH_3)_3CSi$), 32.6 (C-7), 36.5 (C-5), 55.3 (OCH_3). 71.4 (C-4), 99.6 (C-4'), 104.2 (C-2',6'), 129.6 (C-10), 130.3 (C-11), 130.7 (C-2), 130.9 (C-9), 135.2 (C-8), 139.5 (C-1'), 160.0 (C-3), 160.8 (C-3',5'), 193.6 (C-1).



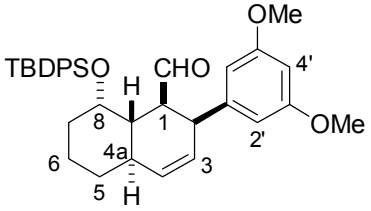
1-(2,2-Dimethyl-1,1-diphenylpropoxy)-8,10-dimethoxy-2,3,4,4a,6a,11,11a,11b-octahydro-1*H*-benzo[a]fluoren-11-ol (3-13): To a solution of trienal **3-12a** (50 mg, 0.09 mmol) in dry CH_2Cl_2 (5 mL) was added $MeAlCl_2$ (1 M in CH_2Cl_2, 0.1 mL, 1.1 equiv) dropwise at -80 °C under inert atmosphere. The mixture was stirred at -80 °C for 3 h, quenched with water (20 mL) and allowed to warm to room temperature. The resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were washed with saturated $NaHCO_3$ solution, dried over over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.35) to provide tetracycle **3-13** (25 mg, 50%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.66 (t, *J* = 11.2 Hz, 1H, CH), 0.88 (m, 1H, CH_2), 1.14 (s, 9H, $(CH_3)_3CSi$), 1.24-1.40 (m, 3H), 1.66-1.93 (m, 3H), 2.55 (br t, *J* = 11.2 Hz, 1H, 4a-H), 2.63 (dd, *J* = 12.1, 6.8 Hz, 1H, 11a-H), 3.75 (s, 1H, OCH_3), 3.77 (s, 1H, OCH_3), 3.96 (br s, 1H, 6a-H), 4.35 (s, 1H, 1-H), 4.78 (s, 1H, 11-H), 5.61 (br d, *J* = 9.9 Hz, 1H, 5-H), 6.02 (ddd, *J* = 9.9, 3.8, 3.0 Hz, 1H, 6-H), 6.21 (s, 1H, 9-H), 6.30 (s, 1H, 7-H), 7.35-7.50 (m, 6H, *m*-,*p*-PhSi), 7.75 (br d, *J* = 6.8 Hz, 2H, *o*-PhSi), 7.82 (br d, *J* = 6.8 Hz, 2H, *o*-PhSi); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 19.6 ($(CH_3)_3CSi$), 20.3 (CH_2), 27.3 ($(CH_3)_3CSi$), 33.0 (CH), 33.3 (CH_2), 33.5 (CH_2), 43.2 (CH), 44.0 (CH), 48.1 (CH), 55.2 (OCH_3), 55.4 (OCH_3), 68.4 (C-11), 73.6 (C-1), 96.7 (C-9), 99.6 (C-7), 124.7 (C-6), 127.5, 127.7, 129.7, 129.9, 133.8 (C-5), 136.2, 136.3, 150.0 (C-6b), 157.5 (C-10), 162.3 (C-8).

General procedure for the Me_2AlCl mediated IMDA reaction: To a stirred solution of trienal **3-12c** (650 mg, 1.5 mmol) in dry CH_2Cl_2 (30 mL) at -80 °C was added via syringe Me_2AlCl (1 M in CH_2Cl_2, 2.4 mL, 2.4 mmol, 1.6 equiv) within 0.5 h under an inert atmosphere. The mixture was stirred for 2.5 h at -80 °C, then treated with MeOH (5 mL) and 5% $NaHCO_3$ solution (10 mL) at this temperature, followed by warming to room temperature. The mixture was diluted with 5% $NaHCO_3$ solution (100 mL) and extracted with Et_2O (3 × 50 mL). The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.25) to yield 0.553 g (1.275 mmol, 85%) of cycloadduct **3-14c** as colorless crystals. The TIPS- and TBDPS-protected IMDA adducts were prepared in a similar fashion.

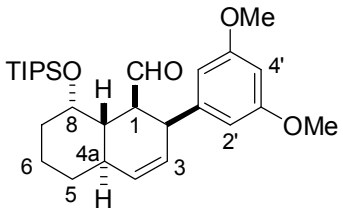


8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (3-14c): **m.p.** 65 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = -0.08 (s, 3H, $(CH_3)_2Si$), -0.02 (s, 3H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 1.20 (qd, *J* = 12.6, 3.8 Hz, 1H, CH_2), 1.43 (br t, *J* = 13.6 Hz, 1H, CH_2), 1.54 (br d, *J* = 13.6 Hz, 1H, CH_2), 1.70-1.90 (m, 3H, CH_2), 1.85 (dd, *J* = 11.6, 10.4 Hz, 1H, 8a-H), 2.43 (br t, *J* = 10.4 Hz, 1H, 4a-H), 2.79 (ddd, *J* = 11.6, 6.8, 4.3 Hz, 1H, 1-H), 3.74 (s, 6H, OCH_3), 3.75 (br s, 1H, 2-H), 3.95 (br s, 1H, 8-H), 5.54 (ddd, *J* = 9.9, 4.3, 2.8 Hz, 1H, 3-H), 5.74 (br d, *J* = 9.9 Hz, 1H, 4-H), 6.29 (d, *J* = 2.3 Hz, 2H, 2',6'-H), 6.31 (t, *J* = 2.3 Hz, 1H, 4'-H), 9.16 (d, *J* = 4.3 Hz, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.2 $(CH_3)_2Si$), -4.2 $(CH_3)_2Si$), 18.1

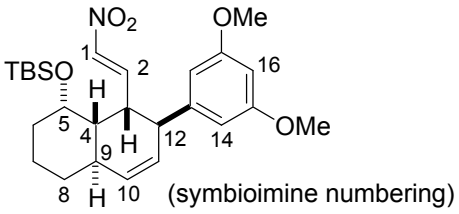
((CH_3)$_3$*C*Si), 20.5 (C-6), 25.9 ((CH_3)$_3$CSi), 33.1 (C-5), 33.2 (C-4a), 33.9 (C-7), 40.1 (C-8a), 43.2 (C-2), 51.4 (C-1), 55.2 (OCH_3), 67.1 (C-8), 98.7 (C-4'), 108.1 (C-2',6'), 125.9 (C-4), 133.9 (C-3), 141.7 (C-1'), 160.6 (C-3',5'), 205.9 (CHO); **HRMS** (ESI): calcd for $C_{25}H_{38}O_4Si$ $[M+Na]^+$ 453.24316, found 453.24298.



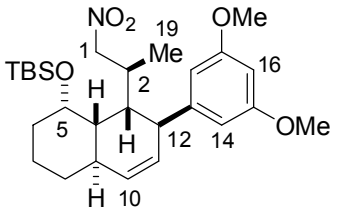
8-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (3-14a): **m.p.** 109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.06 (s, 9H, (CH_3)$_3$CSi), 1.14-1.30 (m, 2H, CH_2), 1.47 (br d, *J* = 13.1 Hz, 1H, CH_2), 1.64 (br d, *J* = 13.9 Hz, 1H, CH_2), 1.80 (t, *J* = 10.9 Hz, 1H, 8a-H), 1.83-1.94 (m, 2H, CH_2), 2.61 (br dd, *J* = 12.4, 10.9 Hz, 1H, 4a-H), 2.95 (ddd, *J* = 11.4, 6.6, 3.6 Hz, 1H, 1-H), 3.70 (s, 6H, OCH_3), 3.77 (br s, 1H, 2-H), 4.07 (br s, 1H, 8-H), 5.57 (ddd, *J* = 9.9, 4.3, 2.8 Hz, 1H, 3-H), 5.77 (br d, *J* = 9.9 Hz, 1H, 4-H), 6.22 (d, *J* = 2.3 Hz, 2H, 2',6'-H), 6.26 (t, *J* = 2.3 Hz, 1H, 4'-H), 7.30-7.42 (m, 6H, *m*-,*p*-PhSi), 7.57-7.64 (m, 4H, *o*-PhSi), 8.88 (d, *J* = 3.6 Hz, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 19.5 ((CH_3)$_3$*C*Si), 20.8 (CH_2), 27.2 ((CH_3)$_3$CSi), 33.2 (CH_2), 33.3 (CH_2), 33.4 (C-4a), 40.3 (C-8a), 43.2 (C-2), 51.1 (C-1), 55.2 (OCH_3), 68.6 (C-8), 98.6 (C-4'), 108.2 (C-2',6'), 126.1 (C-3), 127.3, 127.4, 129.5, 129.7, 133.3, 133.7 (C-4), 134.6, 136.0, 136.13, 141.6 (C-1'), 160.5 (C-3',5'), 204.7 (CHO).



2-(3,5-Dimethoxyphenyl)-8-[(triisopropylsilyl)oxy]-1,2,4a,5,6,7,8,8a-octahydro-naphthalene-1-carbaldehyde (3-14b): colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.02 (br s, 21H, *i*Pr_3Si), 1.22 (qd, *J* = 12.6, 3.8 Hz, 1H, CH_2), 1.43-1.59 (m, 2H, CH_2), 1.78-1.92 (m, 4H), 2.47 (br dd, *J* = 12.4, 10.6 Hz, 1H, 4a-H), 2.89 (ddd, *J* = 11.4, 6.6, 4.1 Hz, 1H, 1-H), 3.74 (s, 6H, OCH_3), 3.77 (m, 2-H), 4.16 (s, 1H, 8-H), 5.56 (ddd, *J* = 9.9, 4.6, 2.8 Hz, 1H, 3-H), 5.75 (br d, *J* = 9.9 Hz, 1H, 4-H), 6.29 (d, *J* = 2.3 Hz, 2H, 2',6'-H), 6.31 (t, *J* = 2.3 Hz, 1H, 4'-H), 9.25 (d, *J* = 4.1 Hz, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 12.9 ((CH_3)$_2$*C*HSi), 18.3 ((CH_3)$_2$CHSi), 20.9 (CH_2), 32.9 (C-4a), 33.2 (CH_2), 34.2 (CH_2), 40.6 (C-8a), 43.3 (C-2), 51.3 (C-1), 55.2 (OCH_3), 67.6 (C-8), 98.8 (C-4'), 108.2 (C-2',6'), 125.8 (C-3), 133.9 (C-4), 141.6 (C-1'), 160.6 (C-3',5'), 206.0 (CHO).

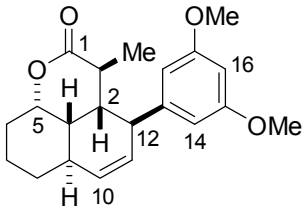


4*S*,4a*S*,5*R*,6*S*,8a*R*)-4-{[*Tert*-Butyl(dimethyl)silyl]oxy}-6-(3,5-dimethoxyphenyl)-5-[(*E*)-2-nitrovinyl]-1,2,3,4,4a,5,6,8a-octahydronaphthalene: A mixture of aldehyde **3-14c** (20 mg, 0.046 mmol) and NH_4OAc (20 mg) in $MeNO_2$ (1 mL) was stirred at 60 °C for 24 h under an inert atmosphere. Thereafter, excess $MeNO_2$ was evaporated under reduced pressure and the residue purified by flash chromatography (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.3) to provide 19 mg (0.04 mmol, 88%) of nitroalkene as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = -0.03 (s, 3H, $(CH_3)_2Si$), -0.03 (s, 3H, $(CH_3)_2Si$), 0.84 (s, 9H, $(CH_3)_3CSi$), 1.05-1.15 (m, 1H, CH_2), 1.24-1.61 (m, 3H, CH_2), 1.70 (br d, *J* = 12.9 Hz, 1H, CH_2), 1.77 (ddd, *J* = 13.1, 3.8, 3.5 Hz, 1H, 4-H), 1.93 (br d, *J* = 12.9 Hz, 1H, CH_2), 2.49 (dd, *J* = 13.1, 11.4 Hz, 1H, 9-H), 2.55 (br d, *J* = 9.9 Hz, 1H, 3-H), 3.28 (d, *J* = 3.8 Hz, 1H, 5-H), 3.79 (br s, 7H, H-12, OCH_3), 5.58 (ddd, *J* = 9.9, 4.6, 2.8 Hz, 1H, 11-H), 5.84 (br d, *J* = 9.9 Hz, 1H, 10-H), 6.36 (s, 3H, 16,14-H), 7.11 (d, *J* = 13.6 Hz, 1H, 1-H), 7.67 (dd, *J* = 13.6, 9.9 Hz, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] =-4.2 ($(CH_3)_2Si$), -4.1 ($(CH_3)_2Si$), 18.1 ($(CH_3)_3CSi$), 20.5 (CH_2), 25.9 ($(CH_3)_3CSi$), 31.0 (CH), 32.9 (CH_2), 34.1 (CH_2), 43.1 (CH), 45.6 (CH), 49.3 (CH), 55.4 (OCH_3), 71.1 (C-5), 98.4 (C-16), 107.1 (C-14), 124.1 (C-11), 135.0 (C-10), 139.0 (C-2), 145.3 (C-13), 146.9 (C-1), 160.8 (C-15).

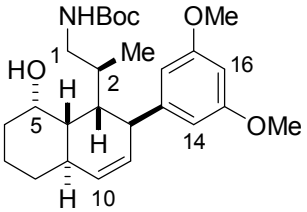


4-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-(3,5-dimethoxyphenyl)-5-[(1*S*)-1-methyl-2-nitroethyl]-1,2,3,4,4a,5,6,8a-octahydronaphthalene (3-15): A solution of the foregoing nitroalkene (180 mg, 0.38 mmol) in dry Et_2O (5 mL) was slowly added to a stirred solution of MeMgBr (3 M in Et_2O, 2 mL, 6 mmol) in Et_2O (12 mL) at -80 °C under inert atmosphere. The reaction was stirred at -80 °C for 3 h, then quenched with a 10% solution of glacial acetic acid in dry Et_2O (10 mL) and allowed to warm to 0 °C. Saturated $NaHCO_3$ solution (20 mL) was then added, the mixture stirred for 30 min at room temperature, and then extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.35) to give 0.148 g (0.30 mmol, 80%) of the nitro compound **3-15** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.08 (s, 3H, $(CH_3)_2Si$), 0.12 (s, 3H, $(CH_3)_2Si$), 0.92 (s, 9H, $(CH_3)_3CSi$), 1.00 (d, *J* = 7.1 Hz, 3H, CH_3), 1.01-1.07 (m, 1H, CH_2), 1.30 (br t, *J* = 11.4 Hz, 1H, CH_2), 1.48-1.57 (m, 2H, 3-H, CH_2), 1.65 (br d, *J* = 3.5 Hz, 1H, CH_2), 1.75 (br d, *J* = 15.6 Hz, 1H, CH_2), 1.83 (ddd, *J* = 13.1, 4.6, 3.5 Hz, 1H, 4-H), 1.90 (br d, *J* = 13.9 Hz, 1H, CH_2), 2.56 (br t, *J* = 11.4 Hz, 1H, 9-H), 3.17 (d, *J* = 4.6 Hz, 1H, 12-H), 3.52 (q, *J* = 7.1 Hz, 1H, 2-H), 3.78 (s, 6H, OCH_3), 3.90 (br s, 1H, 5-H), 4.36 (dd, *J* = 11.6, 7.1

Hz, 1H, 1-H), 4.55 (dd, *J* = 11.6, 8.9 Hz, 1H, 1-H), 5.60 (ddd, *J* = 9.9, 4.6, 2.1 Hz, 1H, 11-H), 5.78 (br d, *J* = 9.9 Hz, 1H, 10-H), 6.30 (t, *J* = 2.3 Hz, 1H, 16-H), 6.35 (d, *J* = 2.3 Hz, 2H, 14-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.0 (C-18), -3.2 (C-18), 14.6 (C-21), 18.3 (C-19), 20.3 (CH_2), 26.1 (C-20), 31.5 (CH), 32.9 (CH), 34.4 (CH_2), 35.0 (CH_2), 41.4 (CH), 43.0 (CH), 46.2 (CH), 55.3 (OCH_3), 72.0 (C-5), 81.8 (C-1), 98.1 (C-16), 106.6 (C-14), 126.2 (C-11), 134.8 (C-10), 147.4 (C-13), 160.6 (C-15).

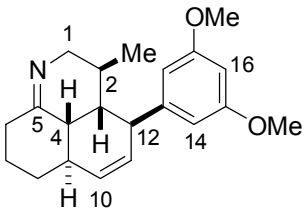


4-(3,5-Dimethoxyphenyl)-3-methyl-3a,4,6a,7,8,9,9a,9b-octahydrobenzo[de]chromen-2(3*H*)-one (3-16): To a solution of nitro compound **3-15** (48 mg, 0.098 mmol) in THF (1 mL) was added TBAF (1 M in THF, 1 mL), and the mixture was stirred for 24 h at room temperature. It was diluted with water (25 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was dissolved in dichloromethane (2 mL), PDC (200 mg) was added and the mixture stirred at room temperature for 24 h. Then, the mixture was diluted with Et_2O (30 mL), washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.3) to provide 21 mg (0.062 mmol, 65%) of lactone **3-16** as colorless crystals, **m.p.** 153-155 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.14 (qd, *J* = 12.1, 4.6 Hz, 1H, CH_2), 1.52 (d, *J* = 7.1 Hz, 3H, CH_3), 1.46-1.72 (m, 4H), 1.79 (dd, *J* = 11.4, 3.0 Hz, 1H, CH), 1.89 (dd, *J* = 12.6, 2.0 Hz, 1H, CH_2), 2.03 (br d, *J* = 14.7 Hz, 1H, CH_2), 2.13 (br t, *J* = 11.9 Hz, 1H, 9-H), 2.43 (qd, *J* = 7.1, 4.5 Hz, 1H, 2-H), 3.26 (br s, 1H, 12-H), 3.79 (s, 6H, OCH_3), 4.30-4.34 (br s, 1H, 5-H), 5.59 (dt, *J* = 9.9, 3.0 Hz, 1H, 11-H), 5.80 (br d, *J* = 9.9 Hz, 1H, 10-H), 6.34 (t, *J* = 2.3 Hz, 1H, 16-H), 6.37 (d, *J* = 2.3 Hz, 2H, 14-H); **^{13}C NMR** (100 MHz, CDCl3): δ[ppm] = 16.2 (C-19), 21.0 (CH_2), 30.0 (CH), 30.7 (CH_2), 31.3 (CH_2), 36.0 (CH), 37.1 (CH), 44.2 (CH), 46.3 (CH), 55.3 (OCH_3), 78.4 (C-5), 97.7 (C-16), 106.5 (C-14), 125.9 (C-10), 132.3 (C-11), 146.8 (C-16), 160.9 (C-15,17), 174.9 (C-1).



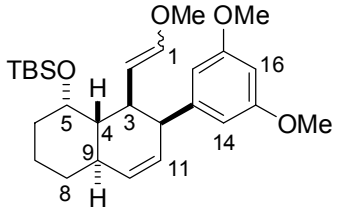
***tert*-Butyl-2-[2-(3,5-dimethoxyphenyl)-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]propylcarbamate (3-17)**: A solution of nitro compound **3-15** (100 mg, 0.204 mmol) in dry THF (5 mL) was added dropwise at -30 °C to a stirred mixture of $LiAlH_4$ (200 mg) in THF (2 mL) under an inert atmosphere within 20 min. Subsequently, the mixture was stirred at room temperature for 12 h and, finally refluxed for 1 h. Then the

mixture was cooled to 0 °C and treated with *i*-PrOH (3 mL). The resulting mixture was diluted with Et_2O and filtered through celite. The filtrate was concentrated and the crude amine dissolved in MeOH (10 mL). Then, NEt_3 (1 mL) and Boc_2O (0.7 g) were added sequentially at 0 °C and the mixture stirred at room temperature for 0.5 h. The MeOH was evaporated under reduced pressure and the residue diluted with Et_2O, washed with $KHSO_4$ (1 M) and with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 10:1, R_f = 0.35). The obtained carbamate was dissolved in THF (5mL) and TBAF (1 M in THF, 5 mL) was added dropwise. The mixture was heated to 60 °C for 48 h under an inert atmosphere, then diluted with water (50 mL), and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.15) to give 50 mg (0.112 mmol, 55% from **3-15**) of carbamate **3-17** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.95 (d, *J* = 7.1 Hz, 3H, CH_3), 1.04 (qd, *J* = 12.4, 3.5 Hz, 1H, CH_2), 1.41 (s, 9H, *t*-Bu), 1.46-1.91 (m, 6H), 2.44 (br dd, *J* = 11.6, 11.1 Hz, 1H, 9-H), 2.65 (qd, *J* = 7.1, 2.0 Hz, 1H, 2-H), 2.97-3.06 (m, 1H, 1-H), 3.20-3.30 (m, 2H, 1,3-H), 3.79 (s, 6H, OCH_3), 3.85 (br s, 1H, 12-H), 4.77 (s, 1H, 5-H), 5.60 (dt, *J* = 9.9, 3.0 Hz, 1H, 11-H), 5.75 (br d, *J* = 9.9 Hz, 1H, 10-H), 6.29 (t, *J* = 2.3 Hz, 1H, 16-H), 6.37 (d, *J* = 2.3 Hz, 2H, 14-H); **^{13}C NMR** (100 MHz, CDCl3): δ[ppm] = 15.6 (C-19), 20.2 (CH_2), 28.4 (CH_3)$_3$C), 30.9 (CH), 32.7 (CH), 33.9 (CH_2), 35.6 (CH_2), 42.0 (CH), 46.6 (CH), 47.7 (C-1), 55.3 (OCH_3), 71.1 (C-5), 79.2 (CH_3)$_3$*C*), 97.7 (C-16), 106.9 (C-14), 127.0 (C-11), 134.7 (C-10), 148.4 (C-13), 156.4 (C=O), 160.5 (C-15).

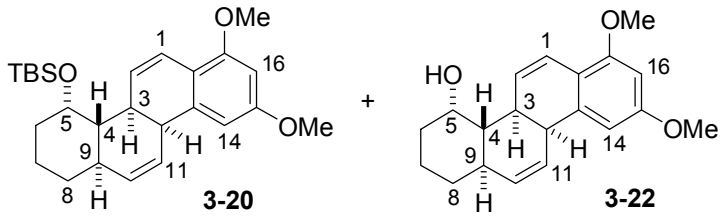


***Epi*-symbioimine analog, 4-(3,5-dimethoxyphenyl)-3-methyl-2,3a,4,6a,7,8,9,9b-octahydro-3H-benzo[de]quinoline (3-18)**: PDC (200 mg) was added to a solution of alcohol **3-17** (50 mg, 0.112 mmol) in CH_2Cl_2 (5 mL) and the mixture stirred for 24 h at room temperature. It was diluted with Et_2O and filtered through silica gel. The resulting solution was concentrated under reduced pressure and subjected to flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.25). The obtained ketone seems not to be all too stable, for example it quickly decomposes in $CDCl_3$. For the hydrolysis of the carbamate, AcCl (3 drops) was added to dry MeOH (5 mL) to generate an anhydrous solution of HCl. This solution was added to the previously obtained ketone, and the mixture refluxed for 0.5 h. Then, NEt_3 (0.2 mL) was added and the solution concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/NEt_3, 100:1, $\mathbf{R_f}$ = 0.5 in MeOH, 0.05 in EtOAc) to give 27 mg (0.086 mmol, 80%) of imine **3-18** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.08 (d, *J* = 6.3 Hz, 3H, CH_3), 1.38-1.52 (m, 1H, 8a-H), 1.59-1.69 (m, 1H, 7a-H), 1.65 (br d, *J* = 13.4 Hz, 1H, 3-H), 1.68-1.82 (m, 1H, 2-H), 1.95-2.13 (m, 4H, 4,7b,8b,9-H), 2.22 (tdd, *J* = 12.6, 5.3, 3.1 Hz, 1H, 6a-H), 2.35 (dd, *J* = 12.1, 3.8 Hz, 1H, 6b-H), 3.00 (ddd, *J* = 16.9, 10.6, 2.8 Hz, 1H, 1a-H), 3.47 (br s, 1H, 12-H), 3.72 (dd, *J* = 16.9, 4.5 Hz, 1H, 1b-H),

3.78 (s, 6H, OCH_3), 5.61 (br d, J = 10.2 Hz, 1H, 11-H), 5.73 (d, J = 10.2 Hz, 1H, 10-H), 6.31 (t, J = 2.3 Hz, 1H, 16-H), 6.36 (d, J = 2.3 Hz, 2H, 14,18-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 16.90 (CH_3), 27.6 (C-2), 28.1 (C-7), 33.2 (C-8), 39.0 (C-6), 39.6 (C-4), 40.5 (C-12), 41.7 (C-9), 44.0 (C-3), 55.3 (OCH_3), 58.3 (C-1), 97.4 (C-16), 106.3 (C-14), 127.4 (C-10), 130.6 (C-11), 148.9 (C-13), 160.8 (C-15), 175.3 (C-5).

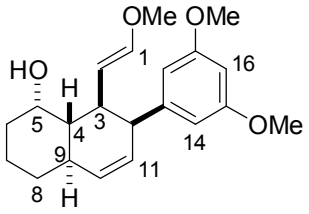


4-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-(3,5-dimethoxyphenyl)-5-[(*E*)-2-methoxyvinyl]-1,2,3,4,4a,5,6,8a-octahydronaphthalene (3-19): To a stirred slurry of methoxymethyl triphenylphosphonium chloride (600 mg, 1.75 mmol) in dry THF (5 mL), a solution of $NaN(SiMe_3)_2$ (275 mg, 1.5 mmol) in THF (3 mL) was added dropwise at 0 °C under an inert atmosphere. The deep red solution was stirred at 0 °C for 10 min then cooled to -50 °C. At this point, aldehyde **3-14c** (215 mg, 0.5 mmol) in THF (2 mL) was added -50 °C. Then the mixture was heated to 0 °C for 30 min, cooled and treated with saturated NH_4Cl solution (20 mL) and extracted with petroleum ether (3 × 25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.3) to give 159 mg (0.35 mmol, 70%) of enol ether **3-19** as a 30:70 mixture of *cis*/*trans* isomers as a colorless oil. **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.2, -4.0, -3.5, 18.2, 18.3, 20.6, 20.7, 25.9, 26.1, 33.5, 33.5, 34.2, 34.3, 34.4, 34.9, 38.9, 43.7, 43.9, 45.8, 49.2, 55.2, 55.2, 55.3, 59.2, 67.3, 67.4, 97.6, 98.1, 103.9, 107.5, 109.1, 109.2, 127.3, 127.4, 133.5, 133.8, 143.8, 144.6, 146.0, 159.6, 159.8; **HRMS** (ESI) calcd $C_{27}H_{42}O_4Si$ $[M+H]^+$ 459.29251, found 459.29309.

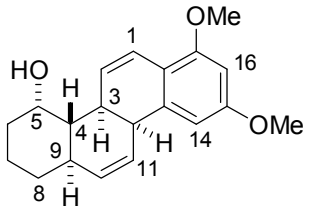


4-{[*tert*-Butyl(dimethyl)silyl]oxy}-7,9-dimethoxy-1,2,3,4,4a,4b,10b,12a-octahydrochrysene (3-20): To the enol ether **3-19** (142 mg, 0.31 mmol) in acetone (10 mL) was added Amberlyst-15 (400 mg), and the mixture stirred at room temperature for 24 h. The resulting solution was filtered through a pad of dry Na_2CO_3, and the filtrate concentrated under reduced pressure. The residue was subjected to flash chromatography (hexane/EtOAc, 10:1, R_f = 0.45) to furnish tetracycle **3-20** (69 mg, 0.16 mmol, 52%) as colorless crystals, **m.p.** 138-140 °C. Further elution with hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.3 gave the corresponding alcohol **3-22** (30 mg, 0.096 mmol, 31%) as colorless crystals, **m.p.** 153-155 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.07 (s, 3H, $(CH_3)_2Si$), 0.12 (s, 3H, $(CH_3)_2Si$), 0.93 (s, 9H, $(CH_3)_3CSi$), 0.83-0.98 (m, 1H, CH_2), 1.17-1.28 (m, 2H, CH, CH_2), 1.35-1.45 (m, 1H, CH_2), 1.64-1.72 (m, 2H, CH_2), 2.36-2.47 (m, 2H, CH), 3.53 (br t, J = 5.6 Hz, 1H, 12-H), 3.80 (s, 3H,

OCH_3), 3.81 (s, 3H, OCH_3), 4.08 (br s, 1H, 5-H), 5.68 (d, J = 9.9 Hz, 1H, 10-H), 5.96 (dd, J = 10.1, 6.1 Hz, 1H, 2-H), 6.13 (ddd, J = 9.9, 5.6, 2.5 Hz, 1H, 11-H), 6.28 (d, J = 2.0 Hz, 1H, 16-H), 6.45 (br s, 1H, 14-H), 6.78 (d, J = 10.1 Hz, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.1 $(CH_3)_2Si$), -3.6 $(CH_3)_2Si$), 18.2 $(CH_3)_3CSi$), 20.5 (CH_2), 25.9 $(CH_3)_3CSi$), 32.4 (CH_2), 33.7 (CH_2), 34.4 (CH), 35.3 (CH), 37.8 (C-12), 43.6 (CH), 55.2 (OCH_3), 55.5 (OCH_3), 67.1 (C-5), 95.4 (C-16), 104.5 (C-14), 115.0 (C-18), 120.6 (C-1), 125.1 (C-11), 127.1 (C-2), 134.5 (C-10), 141.2 (C-13), 155.4 (C-17), 159.7 (C-15); **HRMS** (ESI) calcd for $C_{26}H_{38}O_3Si$ $[M+H]^+$ 427.26630, found 427.26643.

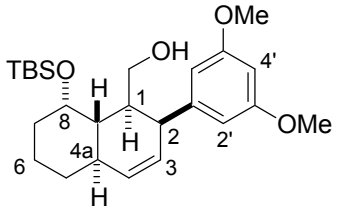


7-(3,5-Dimethoxyphenyl)-8-[(*E*)-2-methoxyvinyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (3-21): To a stirred solution of silyl ether **3-19** (70 mg, 0.15 mmol) in THF (1 mL), TBAF (1 M in THF, 2 mL) was added dropwise, and the mixture heated to 50 °C for 24 h under inert atmosphere. Then the mixture was diluted with water and extracted with Et_2O. The ether extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.2) to yield 44 mg (0.127 mmol, 85%) of alcohol **3-21** as a single *E*-isomer (enol ether double bond). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.06-1.17 (m, 1H, CH_2), 1.24-1.43 (m, 2H, 4-H, CH_2), 1.53-1.85 (m, 4H, CH_2), 2.35 (br dd, J = 12.4, 10.9 Hz, 1H, 9-H), 2.49 (ddd, J = 10.9, 6.4, 5.6 Hz, 1H, 3-H), 3.33 (br dd, J = 5.6, 4.6 Hz, 1H, 12-H), 3.38 (s, 3H, OCH_3), 3.76 (s, 6H, OCH_3), 3.85 (br s, 1H, 5-H), 4.02 (dd, J = 12.9, 10.9 Hz, 1H, 2-H), 5.58 (ddd, J = 9.9, 4.6, 2.8 Hz, 1H, 11-H), 5.73 (br d, J = 9.9 Hz, 1H, 10-H), 6.33 (s, 3H, 14,16-H), 6.43 (d, J = 12.9 Hz, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 20.6 (CH_2), 33.0 (CH_2), 33.2 (CH_2), 34.8 (C-9), 39.6 (C-3), 42.3 (C-4), 48.8 (C-12), 55.2 (OCH_3), 55.6 (OCH_3), 66.3 (C-5), 98.2 (C-16), 103.8 (C-2), 109.0 (C-14), 127.5 (C-11), 133.6 (C-10), 143.3 (C-13), 146.4 (C-1), 159.9 (C-15).

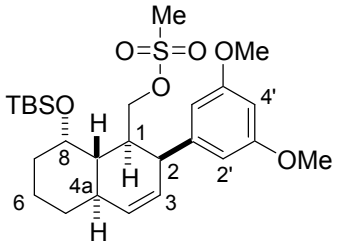


7,9-Dimethoxy-1,2,3,4,4a,4b,10b,12a-octahydrochrysen-4-ol (3-22): A mixture of the enol ether **3-21** (25 mg, 0.072 mmol) and Amberlyst-15 (100 mg) in acetone (2 mL) and water (0.07 mL) was stirred for 24 h at room temperature. The resulting mixture was worked up as described previously to give (18 mg, 0.058 mmol, 80%) of the tetracycle **3-22**. $\mathbf{R_f}$ = 0.3 (petroleum ether/ethyl acetate, 4:1), colorless crystals, **m.p.** 153-155 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.84-0.94 (m, 1H, CH_2), 1.23-1.31 (m, 2H, 4-H, CH_2), 1.38-1.47 (br d, 1H, CH_2), 1.53-1.68 (m, 3H, CH_2), 2.21 (br dd, J = 11.9, 11.6 Hz, 1H, 9-H), 2.40 (ddd, J = 10.9,

6.8, 5.8 Hz, 1H, 3-H), 3.50 (br dd, *J* = 5.8, 5.6 Hz, 1H, 12-H), 3.74 (s, 6H, OCH_3), 4.03 (d, *J* = 2.3 Hz, 1H, 5-H), 5.65 (d, *J* = 9.9 Hz, 1H, 10-H), 5.94 (dd, *J* = 10.1, 6.3 Hz, 1H, 2-H), 6.08 (ddd, *J* = 9.9, 5.6, 2.5 Hz, 1H, 11-H), 6.21 (d, *J* = 2.0 Hz, 1H, 16-H), 6.38 (br s, 1H, 14-H), 6.73 (d, *J* = 10.1 Hz, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 20.4 (CH_2), 32.2 (CH_2), 33.5 (CH_2), 34.6 (C-3), 35.4 (C-9), 37.8 (C-12), 42.5 (C-4), 55.3 (OCH_3), 55.5 (C-19), 66.3 (C-5), 95.5 (C-16), 104.5 (C-14), 114.8 (C-18), 120.8 (C-1), 125.5 (C-11), 126.4 (C-2), 133.9 (C-10), 140.7 (C-13), 155.5 (C-17), 159.8 (C-15); **HRMS** (ESI) calcd for $C_{20}H_{24}O_3$ $[M+H]^+$ 313.17982, found 313.17978.

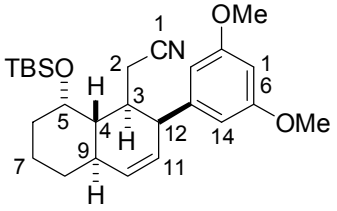


[8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methanol: $NaBH_4$ (74 mg, 2.0 mmol, 4 equiv) was added to a stirred solution of aldehyde **3-14c** (215 mg, 0.5 mmol) in EtOH (2 mL) at 0 °C. The mixture was stirred at room temperature until the starting material had disappeared (24 h). Thereafter, the mixture was diluted with water (10 mL) and petroleum ether (50 mL). Then saturated NH_4Cl (10 mL) was added dropwise to destroy the excess borohydride. The mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.2) to provide 214 mg (0.495 mmol, 99%) of the primary alcohol as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 3H, $(CH_3)_2Si$), 0.06 (s, 3H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3CSi$), 1.09-1.19 (m, 1H, CH_2), 1.37-1.53 (m, 3H, CH_2), 1.70-1.84 (m, 3H, 8a-H, CH_2), 2.06-2.15 (m, 1H, 1-H), 2.46 (br dd, *J* = 12.4, 10.4 Hz, 1H, 4a-H), 3.35-3.44 (m, 1H, C*H*$_2$OH), 3.77 (s, 6H, OCH_3), 3.79 (m, 1H, C*H*$_2$OH), 4.03 (br s, 1H, 8-H), 5.55 (ddd, *J* = 9.9, 4.8, 2.8 Hz, 1H, 3-H), 5.67 (br d, *J* = 9.9 Hz, 1H, 4-H), 6.35 (t, *J* = 2.3 Hz, 1H, 4'-H), 6.50 (d, *J* = 2.3 Hz, 2H, 2',6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.3 ($(CH_3)_2Si$), -3.5 ($(CH_3)_2Si$), 18.2 ($(CH_3)_3CSi$), 20.5 (CH_2), 25.9 ($(CH_3)_3CSi$), 33.4 (CH_2), 34.0 (CH_2), 34.8 (C-4a), 41.1 (C-8a), 41.3 (C-1), 44.5 (C-2), 55.2 (OCH_3), 61.7 (CH_2OH), 67.0 (C-8), 98.4 (C-4'), 108.2 (C-2',6'), 127.3 (C-3), 133.8 (C-4), 144.3 (C-1'), 160.6 (C-3',5'); **HRMS** (ESI) calcd for $C_{25}H_{40}O_4Si$ $[M+H]^+$ 433.27686, found 427.27694.

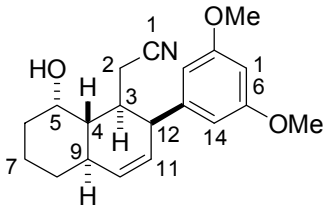


[8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methyl methanesulfonate: MsCl (0.115 mL, 1.5 mmol, 1.7

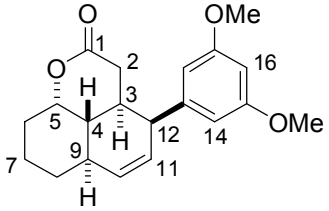
equiv) was added dropwise to a stirred solution of the foregoing primary alcohol (380 mg, 0.88 mmol) and NEt_3 (0.56 mL, 4 mmol, 4.5 equiv) in dry CH_2Cl_2 (10 mL) at -50 °C. The mixture was stirred for 1 h at -30 °C, then allowed to warm to room temperature within 1 h and treated with a saturated $NaHCO_3$ solution (30 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue (hexane/EtOAc, 10:1, $\mathbf{R_f}$ = 0.15-0.2) afforded 430 mg (0.84 mmol, 96%) of the mesylate as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.07 (s, 6H, $(CH_3)_2Si$), 0.91 (s, 9H, $(CH_3)_3CSi$), 1.20 (qd, *J* = 12.9, 3.6 Hz, 1H, CH_2), 1.30-1.43 (m, 2H), 1.52 (br d, 1H, *J* = 13.6 Hz, CH_2), 1.65-1.86 (m, 3H), 2.40 (dddd, *J* = 11.1, 10.8, 5.6, 3.6 Hz, 1H, 1-H), 2.49 (br dd, *J* = 12.4, 10.6 Hz, 1H, 4a-H), 2.83 (s, 3H, SO_2CH_3), 3.62 (dd, *J* = 10.8, 8.6 Hz, 2H, CH_2Oms, 2-H), 3.62 (br s, 1H, 2-H), 3.77 (s, 6H, OCH_3), 3.86 (br s, 1H, 8a-H), 4.32 (dd, *J* = 8.6, 3.6 Hz, 1H, CH_2OMs), 5.57 (ddd, *J* = 9.9, 4.8, 2.8 Hz, 1H, 3-H), 5.68 (br d, *J* = 9.9 Hz, 1H, 4-H), 6.34 (d, *J* = 2.3 Hz, 2H, 2',6'-H), 6.44 (t, *J* = 2.3 Hz, 1H, 4'-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.5 ($(CH_3)_2Si$), -3.5 ($(CH_3)_2Si$), 18.2 ($(CH_3)_3CSi$), 20.3 (CH_2), 25.8 ($(CH_3)_3CSi$), 33.1 (CH_2), 33.8 (CH_2), 34.8 (CH), 36.9 (CH), 38.3 (CH), 40.9 (CH), 43.1 (CH), 55.2 (OCH_3), 66.6 (C-8), 69.2 (CH_2OMs), 98.5 (C-4'), 108.8 (C-2',6'), 126.9 (C-3), 133.2 (C-4), 142.3 (C-1'), 160.3 (C-3',5'); **HRMS** (ESI) calcd for $C_{26}H_{42}NO_6SSi$ $[M+H]^+$ 511.25441, found 511.25345.



[8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]acetonitrile (3-23): A mixture of the foregoing mesylate (430 mg, 0.84 mmol) and NaCN (490 mg, 10 mmol) in DMSO (6 mL) was stirred at 50 °C for 48 h under an inert atmosphere. Afterwards, the mixture was poured into water (100 mL) and extracted with hexane (3 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 20:1, R_f = 0.25) to furnish 355 mg (0.805 mmol, 95%) of nitrile **3-23** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.04 (s, 3H, $(CH_3)_2Si$), 0.07 (s, 3H, $(CH_3)_2Si$), 0.91 (s, 9H, $(CH_3)_3CSi$), 1.14 (qd, *J* = 12.9, 3.8 Hz, 1H, CH_2), 1.25-1.40 (m, 2H, CH, CH_2), 1.52 (br d, *J* = 13.2 Hz, 1H, CH_2), 1.62 (dd, *J* = 16.2, 11.9 Hz, 1H, 2-H), 1.64-1.75 (m, 1H, CH_2), 1.82 (m, 2H, CH_2), 2.33 (dddd, *J* = 11.9, 9.1, 5.6, 2.8 Hz, 1H, 3-H), 2.43 (br dd, *J* = 12.4, 10.6 Hz, 1H, 9-H), 2.47 (dd, *J* = 16.2, 2.8 Hz, 1H, 2-H), 3.69 (br t, *J* = 5.6 Hz, 1H, 12-H), 3.78 (s, 6H, OCH_3), 3.82 (br s, 1H, 5-H), 5.60 (ddd, 1H, *J* = 9.9, 4.6, 2.8 Hz, 11-H), 5.69 (br d, *J* = 9.9 Hz, 1H, H-10), 6.37 (t, *J* = 2.3 Hz, 1H, 16-H), 6.50 (d, *J* = 2.3 Hz, 2H, H-14,18); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.4 ($(CH_3)_2Si$), -3.5 ($(CH_3)_2Si$), 17.6 (CH_2), 18.1 ($(CH_3)_3CSi$), 20.2 (CH_2), 25.8 ($(CH_3)_3CSi$), 32.9 (CH_2), 33.7 (CH_2), 35.0 (CH), 36.9 (CH), 42.3 (CH), 44.7 (CH), 55.3 (OCH_3), 66.5 (C-5), 99.0 (C-16), 108.5 (C-14), 119.6 (C-1), 126.7 (C-11), 133.3 (C-10), 141.8 (C-13), 160.5 (C-15); **HRMS** (ESI) calcd for $C_{26}H_{39}NO_3Si$ $[M+H]^+$ 442.27720, found 442.27717.

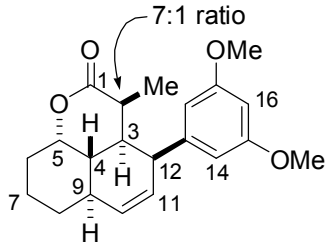


[2-(3,5-Dimethoxyphenyl)-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]acetonitrile (3-24): To a stirred solution of nitrile **3-23** (345 mg, 0.78 mmol) in THF (2 mL) was added dropwise TBAF (1 M in THF, 5 mL) at room temperature. The mixture was stirred at room temperature for 2 h then diluted with EtOAc (40 mL), washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue (hexane/EtOAc, 2:1, $\mathbf{R_f}$ = 0.25) afforded hydroxynitrile **3-24** (250 mg, 0.76 mmol, 98%) as colorless crystals, **m.p.** 142-143 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.14 (qd, *J* = 12.9, 3.8 Hz, 1H, CH_2), 1.34-1.88 (m, 7H), 1.78 (dd, *J* = 16.2, 11.1 Hz, 1H, 2-H), 2.30-2.44 (m, 2H, 3,9-H), 2.54 (dd, *J* = 16.2, 4.1 Hz, 1H, 2-H), 3.67 (br s, 1H, 12-H), 3.78 (s, 6H, OCH_3), 3.85 (br s, 1H, 5-H), 5.60 (ddd, *J* = 9.9, 4.6, 2.8 Hz, 1H, 11-H), 5.69 (br d, *J* = 9.9 Hz, 1H, 10-H), 6.37 (t, *J* = 2.3 Hz, 1H, 16-H), 6.48 (d, *J* = 2.3 Hz, 2H, 14,18-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 17.9 (CH_2), 20.1 (CH_2), 32.8 (CH_2), 34.0 (CH_2), 35.1 (CH), 36.9 (CH), 41.3 (CH), 45.0 (CH), 55.3 (OCH_3), 65.4 (C-5), 98.9 (C-16), 108.6 (C-14), 120.0 (C-1), 127.1 (C-11), 132.9 (C-10), 141.6 (C-13), 160.5 (C-15); **HRMS** (ESI) calcd for $C_{20}H_{25}NO_3$ $[M+H]^+$ 328.19072, found 328.19057.

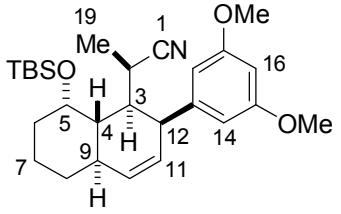


4-(3,5-Dimethoxyphenyl)-3a,4,6a,7,8,9,9a,9b-octahydrobenzo[de]chromen-2(3*H*)-one (3-25): The hydroxynitrile **3-24** (40 mg, 0.12 mmol) was dissolved in EtOH (4 mL). KOH (50% in water 0.4 mL) was added and the mixture stirred at 80 °C for 24 h under inert atmosphere. Then, the mixture was cooled to room temperature, diluted with water (30 mL) and acidified with 5% HCl to pH 1. The mixture was extracted with EtOAc (3 × 25 mL). The extracts were washed with water and dried over Na_2SO_4, filtered and concentrated in vacuo. The crude hydroxy acid, obtained as a white solid, was refluxed in toluene (10 mL) together with *p*TsOH·H_2O (50 mg, 0.26 mmol) for 1 h. After cooling, the toluene was evaporated under reduced pressure, and the residue subjected to flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.25) to give lactone **3-25** (36 mg, 0.110 mmol, 90%) as colorless crystals, **m.p.** 125-126 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.11-1.22 (m, 1H, CH_2), 1.42-1.52 (m, 1H, CH_2), 1.62-1.93 (m, 7H), 2.10-2.20 (m, 1H, 3-H), 2.29 (br dd, *J* = 14.9, 11.6 Hz, 1H, 9-H), 2.55 (dd, *J* = 15.2, 2.5 Hz, 1H, 2-H), 3.56 (br dd, *J* = 5.1, 4.6 Hz, 1H, 12-H), 3.77 (s, 6H, OCH_3), 4.24 (q, *J* = 7.5 Hz, 1H, 5-H), 5.65 (ddd, *J* = 9.6, 4.6, 2.8 Hz, 1H, 11-H), 5.83 (br d, *J* = 9.6 Hz, 1H, 10-H), 6.29 (d, *J* = 2.3 Hz, 2H, 14-H), 6.36 (t, *J* = 2.3 Hz, 1H, 16-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 18.2 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 35.0 (C-2), 35.6 (C-4), 36.1 (C-9), 38.3 (C-3), 45.8 (C-12), 55.3 (OCH_3), 74.6 (C-5), 98.3 (C-16), 108.2 (C-14),

127.9 (C-11), 134.1 (C-10), 141.3 (C-13), 160.5 (C-15), 174.5 (C-1). **HRMS** (ESI) calcd for $C_{20}H_{24}O_4$ $[M+H]^+$ 329.17474, found 329.17480.

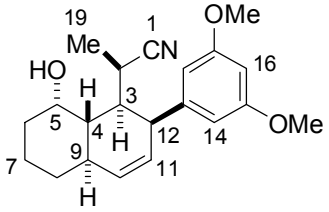


***epi*-4-(3,5-Dimethoxyphenyl)-3-methyl-3a,4,6a,7,8,9,9a,9b-octahydrobenzo[de]chromen-2(3*H*)-one, *epi*-3-26**: *n*BuLi (2.5 M in hexanes, 80 µL, 0.2 mmol, 2 equiv) was added dropwise to a stirred solution of *i*Pr_2NEt (28 µL, 0.2 mmol, 2 equiv) in anhydrous THF (1 mL) at 0 °C under inert atmosphere. The solution was stirred for 15 min at 0 °C then cooled to -80 °C. A solution of lactone **3-25** (33 mg, 0.10 mmol) in THF (0.5 mL) was added dropwise to the LDA solution. The mixture was stirred for 3 h at -80 °C followed by the addition of MeI (25 µL, 0.4 mmol, 4 equiv). Stirring was continued at -80 °C for 0.5 h then the mixture was allowed to reach room temperature. The reaction was quenched by addition of water and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.3) to give *epi*-**3-26** and **3-26** as a 7:1 mixture of diastereomers. It was not possible to separate the two diastereomers by flash chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.44 (d, *J* = 7.3 Hz, 3H, CH_3), 1.20-1.99 (m, 7H, 4-H, CH_2), 2.22 (ddd, *J* = 12.1, 6.3, 2.5 Hz, 1H, 3-H), 2.36 (br dd, *J* = 15.2, 11.9 Hz, 1H, 9-H), 2.83 (qd, *J* = 7.3, 2.5 Hz, 1H, 2-H), 3.54 (m, 1H, 12-H), 3.78 (s, 6H, OCH_3), 4.53 (dt, *J* = 8.9, 7.1 Hz, 1H, 5-H), 5.65 (ddd, *J* = 9.6, 3.6, 3.0 Hz, 1H, 11-H), 5.73 (br d, *J* = 9.6 Hz, 1H, 10-H), 6.38 (s, 3H, 14,16-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 9.5 (CH_3), 17.1 (CH_2), 26.1 (CH_2), 26.3 (CH_2), 32.0 (C-4), 34.3 (C-9), 39.6 (C-2), 40.5 (C-3), 45.9 (C-12), 55.3 (OCH_3), 75.4 (C-5), 98.4 (C-14), 108.9 (C-16), 128.3 (C-11), 133.2 (C-10), 143.3 (C-13), 160.8 (C-15), 176.1 (C-1).

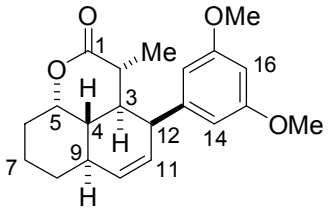


2-[8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]propanenitrile (3-27): *n*BuLi (2.5 M in hexanes, 0.8 mL, 2 mmol, 2 equiv) was added dropwise to a stirred solution of *i*Pr_2NEt (281 µL, 2 mmol, 2 equiv) in anhydrous THF (5 mL) at 0 °C under inert atmosphere. The solution was stirred for 15 min at 0 °C and cooled to -80 °C. A solution of nitrile **3-23** (420 mg, 0.95 mmol) in THF (5 mL) was added dropwise to this LDA solution. The mixture was stirred for 1 h at -80 °C followed by the addition of MeI (124 µL, 2 mmol, 2 equiv). Stirring was continued at -80 °C for 0.5 h then the mixture was allowed to reach room temperature. The reaction was quenched

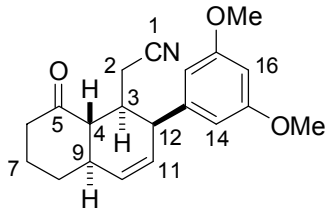
by the addition an excess of half-saturated NH_4Cl solution. The product was extracted with petroleum ether (3 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 20:1, $\mathbf{R_f}$ = 0.25) to provide 398 mg (0.874 mmol, 92%) of alkylated nitrile **3-27** as a colorless viscous oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.05 (s, 3H, $(CH_3)_2Si$), 0.08 (s, 3H, $(CH_3)_2Si$), 0.56 (d, 3H, *J* = 7.3 Hz, CH_3), 0.91 (s, 9H, $(CH_3)_3CSi$), 1.17-1.28 (m, 1H, CH_2), 1.37-1.60 (m, 3H, 4-H, CH_2), 1.67-1.90 (m, 3H, CH_2), 2.34 (ddd, *J* = 10.6, 6.0, 4.5 Hz, 1H, 3-H), 2.49 (br dd, *J* = 11.6, 10.8 Hz, 1H, 9-H), 2.96 (qd, *J* = 7.3, 4.5 Hz, 1H, 2-H), 3.75 (br s, 1H, 12-H), 3.79 (s, 6H, OCH_3), 3.89 (br s, 1H, 5-H), 5.58 (br d, *J* = 9.9 Hz, 1H, 11-H), 5.64 (br d, *J* = 9.9 Hz, 1H, 10-H), 6.36 (s, 1H, H-16), 6.57 (s, 2H, H-14); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = -5.5 $(CH_3)_2Si$), -3.4 $(CH_3)_2Si$), 12.7 (CH_3), 18.2 (($CH_3)_3$*C*Si), 20.4 (CH_2), 25.1 (C-2), 25.8 ((*C*$H_3)_3$CSi), 33.1 (CH_2), 33.9 (CH_2), 34.8 (C-9), 41.01 (C-3), 41.6 (C-4), 44.5 (C-12), 55.3 (OCH_3), 67.5 (C-5), 99.0 (C-16), 108.8 (C-14), 122.9 (C-1), 127.6 (C-11), 132.4 (C-10), 143.8 (C-13), 160.6 (C-15); **HRMS** (ESI) calcd for $C_{27}H_{41}NO_3Si$ $[M+H]^+$ 456.29285, found 456.29278.



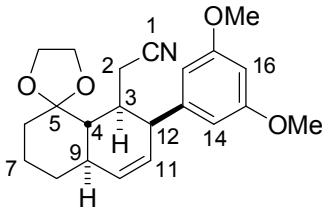
2-[2-(3,5-Dimethoxyphenyl)-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]propanenitrile (3-28): To a solution of silyl ether **3-27** (348 mg, 0.76 mmol) in THF (1.5 mL) was added TBAF (1 M in THF, 5 mL) dropwise at 0 °C under inert atmosphere followed by stirring of the mixture at room temperature for 24 h. After complete deprotection (checked by TLC), the mixture was diluted with EtOAc. The layers were separated, and the organic layer washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 2:1, $\mathbf{R_f}$ = 0.25) to give 240 mg (0.704 mmol, 92%) of hydroxynitrile **3-28** as colorless crystals, **m.p**. 159-160 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.86 (d, *J* = 7.3 Hz, 3H, CH_3), 1.17-1.30 (m, 1H, CH_2), 1.54-1.90 (m, 6H, 4-H, CH_2), 2.29-2.36 (m, 1H, 3-H), 2.40 (br dd, *J* = 11.6, 10.4 Hz, 1H, 9-H), 3.06 (qd, *J* = 7.3, 3.0 Hz, 1H, 2-H), 3.63 (br s, 1H, 12-H), 3.78 (s, 6H, OCH_3), 4.04 (br s, 1H, 5-H), 5.56 (br d, *J* = 9.9 Hz, 1H, 11-H), 5.63 (br d, *J* = 9.9 Hz, 1H, 10-H), 6.37 (br s, 1H, 16-H), 6.53 (br s, 2H, 14-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 14.9 (CH_3), 20.2 (CH_2), 26.0 (C-2), 33.2 (CH_2), 34.1 (CH_2), 34.9 (C-9), 40.7 (C-4), 40.8 (C-3), 45.6 (C-12), 55.3 (OCH_3), 66.0 (C-5), 98.9 (C-16), 109.1 (C-14), 122.5 (C-1), 127.7 (C-11), 131.9 (C-10), 142.9 (C-13), 160.6 (C-15); **HRMS** (ESI) calcd for $C_{21}H_{27}NO_3$ $[M+H]^+$ 342.20637, found 343.20625.



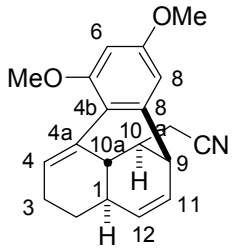
4-(3,5-Dimethoxyphenyl)-3-methyl-3a,4,6a,7,8,9,9a,9b-octahydrobenzo[de]chromen-2(3H)-one (3-26): TBAF (1 M in THF, 2 mL) was added to a solution of silyl ether **3-27** (20 mg, 44 μmol) at room temperature under inert atmosphere. The solution was stirred for 12 h, then diluted with EtOAc (40 mL) and washed with water (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude alcohol **3-28** ($\mathbf{R_f}$ = 0.6, hexane/EtOAc, 1:1) was dissolved in toluene (2 mL). To this solution TMSCl (0.5 mL) and concentrated HCl (0.05 mL) were added and the mixture was stirred at 110 °C for 24 h under inert atmosphere. After cooling, the toluene was removed in vacuo and the residue purified by flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.25) to furnish lactone **3-26** (11.2 mg, 33 μmol, 75%), **m.p.** 117-118 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.13 (m, 1H), 1.39 (d, *J* = 6.3 Hz, 3H, CH_3), 1.54-1.78 (m, 2H), 1.73-2.03 (m, 5H), 2.22 (br t, *J* = 11.6 Hz, 1H, 9-H), 2.26 (dq, *J* = 13.4, 6.8 Hz, 1H, 2-H), 3.65 (br s, 1H, 12-H), 3.79 (s, 6H, OCH_3), 4.27 (dd, *J* = 5.8, 5.6 Hz, 1H, 5-H), 5.65 (ddd, *J* = 9.6, 4.6, 2.8 Hz, 1H, 11-H), 5.78 (br d, *J* = 9.6 Hz, 1H, 10-H), 6.37 (t, *J* = 2.3 Hz, 1H, 16-H), 6.47 (d, *J* = 2.3 Hz, 2H, 14-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 13.0 (CH_3), 19.8 (CH_2), 27.7 (CH_2), 28.3 (CH_2), 36.5 (CH), 36.6 (CH), 39.2 (CH), 44.7 (CH), 45.7 (CH), 55.3 (OCH_3), 72.3 (C-5), 98.1 (C-16), 108.9 (C-14), 129.7 (C-11), 133.6 (C-10), 141.6 (C-13), 160.5 (C-15), 177.6 (C-1); **HRMS** (ESI) calcd for $C_{21}H_{26}O_4$ $[M+H]^+$ 343.19039, found 343.19018.



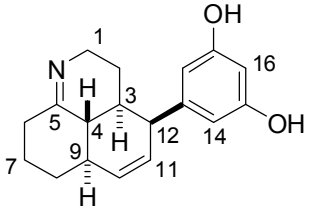
[2-(3,5-Dimethoxyphenyl)-8-oxo-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]acetonitrile (3-29): To a stirred solution of hydroxynitrile **3-24** (105 mg, 0.35 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise a solution of Dess-Martin periodinane (15% in CH_2Cl_2, 1.5 mL) at 0 °C. The mixture was stirred at room temperature for 3 h, before it was diluted with CH_2Cl_2 (20 mL) and washed with saturated Na_2CO_3 solution of (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.25) to give 103 mg (0.347 mmol, 99%) of ketone **3-29** as colorless crystals, **m.p.** 105 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.58-1.85 (m, 3H, CH_2), 2.02-2.49 (m, 7H), 3.11 (d, *J* = 16.2 Hz, 1H, CH_2), 3.68 (br s, 1H, 12-H), 3.79 (s, 6H, OCH_3), 5.72 (ddd, *J* = 10.1, 4.0, 2.0 Hz, 1H, 11-H), 5.76 (br d, *J* = 10.1 Hz, 1H, 10-H), 6.38 (t, *J* = 2.3 Hz, 1H, 16-H), 6.48 (d, *J* = 2.3 Hz, 2H, 14-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 18.0 (CH_2), 27.5 (CH_2), 35.3 (CH_2), 34.4 (CH), 42.8 (CH_2), 43.8 (C-12), 45.0 (CH), 50.4 (CH), 55.3 (OCH_3), 99.1 (C-16), 108.6 (C-14), 119.4 (C-1), 128.3 (C-11), 123.0 (C-10), 140.9 (C-13), 160.7 (C-15), 211.6 (C-5); **HRMS** (ESI) calcd for $C_{20}H_{23}NO_3$ $[M+Na]^+$ 348.15707, found 348.15690.



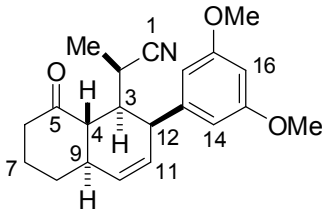
[7'-(3,5-Dimethoxyphenyl)-3',4',4a',7',8',8a'-hexahydro-2'H-spiro[1,3-dioxolane-2,1'-naphthalen]-8'-yl]acetonitrile (3-30): A solution of ethylene glycol (0.28 mL, 5 mmol), ketone **3-29** (145 mg, 0.48 mmol), and CSA (60 mg, 0.25 mmol) in toluene (20 mL) was refluxed for 12 h with azeotropic removal of water using a Dean-Stark apparatus. After cooling, the toluene was evaporated under reduced pressure and the residue subjected to flash chromatography (hexane/EtOAc, 4:1) yielding acetal **3-30** (111 mg, 0.326 mmol, 68%, $\mathbf{R_f}$ = 0.3) as colorless crystals, **m.p.** 146-147 °C, and polycycle **3-31** (29 mg, 0.096 mmol, 20%, $\mathbf{R_f}$ = 0.2) as colorless crystals, **m.p.** 128-130 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.15-1.30 (m, 2H, CH_2), 1.45-2.03 (m, 6H), 2.32 (br dd, *J* = 12.4, 10.4 Hz, 1H, 9-H), 2.38-2.47 (m, 1H, 3-H), 2.62 (dd, *J* = 16.9, 4.0 Hz, 1H, CH_2), 3.67 (br s, 1H, 12-H), 3.78 (s, 6H, OCH_3), 3.82-4.08 (m, 4H, acetal CH_2), 5.68 (s, 2H, 10,11-H), 6.36 (br s, 1H, 16-H), 6.50 (br s, 2H, 14-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 20.1 (CH_2), 22.9 (CH_2), 32.6 (CH_2), 34.0 (CH_2), 37.1 (C-3), 40.9 (C-9), 43.3 (C-4), 45.7 (C-12), 55.3 (OCH_3), 62.3 (acetal CH_2), 63.4 (acetal CH_2), 98.9 (C-16), 108.5 (C-14), 110.7 (C-5), 120.7 (C-1), 127.5 (C-11), 132.4 (C-10), 141.6 (C-13), 160.5 (C-15); **HRMS** (ESI) calcd for $C_{22}H_{27}NO_4$ $[M+Na]^+$ 392.18323, found 392.18339.



(5,7-Dimethoxy-1,2,3,9,10,10a-hexahydro-1,9-ethenophenanthren-10-yl)acetonitrile (3-31): **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.96-1.05 (m, 1H, CH_2), 1.96-2.42 (m, 8H), 2.78 (br s, 1H, CH_2), 3.31 (br s, 1H, 9-H), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.38 (br d, *J* = 9.6 Hz, 1H, 12-H), 5.55 (ddd, *J* = 9.6, 5.8, 2.5 Hz, 1H, 11-H), 6.36 (d, *J* = 2.3 Hz, 1H, 6-H), 6.41 (d, *J* = 2.3 Hz, 1H, 8-H), 6.80-6.85 (m, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 21.2 (CH_2), 23.5 (CH_2), 28.7 (CH_2), 36.5 (CH), 36.9 (CH), 37.9 (CH), 42.3 (CH), 55.3 (OCH_3), 55.3 (OCH_3), 97.7 (C-6), 104.8 (C-8), 115.9 (CN), 118.9 (C-4b), 125.1 (C-4), 129.9 (C-11), 132.0 (C-4a), 134.1 (C-12), 137.5 (C-8a), 157.7 (C-5), 159.1 (C-7).

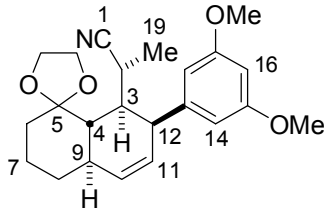


***Nor*-methyl-*de*-sulfo-symbioimine (freebase, 3-33)**: To a stirred solution of nitrile **3-30** (70 mg, 205 μmol) in dry Et_2O (2 mL) was added dropwise a solution of $LiAlH_4$ (1 M in Et_2O, 1 mL, 1 mmol) at 0 °C under inert atmosphere. The reaction was stirred at room temperature for 12 h then quenched by dropwise addition of *i*-PrOH (1 mL). The mixture was diluted with Et_2O and filtered through celite. Concentration of the filtrate under reduced pressure afforded 62 mg (179 μmol, 87%, colorless oil) of amine **3-32** which was used in the next step without further purification. To a stirred solution of the amine (50 mg, 144 μmol) in CH_2Cl_2 (2 mL) was added a solution of BBr_3 (1 M in CH_2Cl_2, 1 mL, 1 mmol) dropwise at -80 °C under inert atmosphere. The mixture was slowly warmed to room temperature and stirred for 10 h, then poured into a half-saturated solution of $NaHCO_3$ (20 mL), and extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography ($CHCl_3$/MeOH/NEt_3, 100:25:1, $\mathbf{R_f}$ = 0.3) to yield (22.5 mg , 80 μmol, 55%) of imine **3-33** as a white powder, **m.p.** 248-250 °C, decomp. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.52 (qd, 1H, *J* = 12.4, 4.6 Hz, CH_2), 1.22-1.37 (m, 1H, CH_2), 1.43-1.57 (m, 1H, CH_2), 1.73-2.11 (m, 5H), 2.08 (br dd, *J* = 12.9, 12.4 Hz, 1H, CH_2), 2.24 (br d, *J* = 12.9 Hz, 1H, CH_2), 2.85 (dd, *J* = 7.1, 6.6 Hz, 2H, 1-H), 3.24-3.31 (m, 1H, 12-H), 3.47 (br dd, *J* = 17.4, 15.9 Hz, 1H, 6-H), 5.57 (br d, *J* = 9.9 Hz, 1H, 11-H), 5.76 (d, *J* = 9.9 Hz, 1H, 10-H), 6.01 (s, 2H, 14-H), 6.07 (br s, 1H, 16-H), 9.13 (br s, 2H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 25.4 (CH_2), 25.8 (CH_2), 31.1 (CH_2), 36.7 (CH), 40.7 (CH), 41. 9 (CH), 45.0 (C-12), 45.5 (C-1), 48.3 (C-6), 100.8 (C-16), 107.9 (C-14), 129.0 (C-11), 132.2 (C-10), 142.0 (C-13), 157.7 (C-15), 170.8 (C-5); **HRMS** (ESI) calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.16451, found 284.16463.

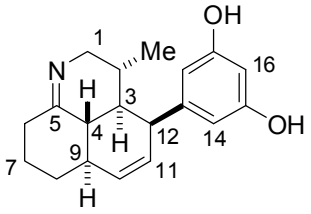


2-[2-(3,5-Dimethoxyphenyl)-8-oxo-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]propanenitrile (3-34): To a stirred solution of hydroxynitrile **3-28** (235 mg, 0.69 mmol) in dry CH_2Cl_2 (8 mL) was added a solution of Dess-Martin periodinane (15% in CH_2Cl_2, 4 mL) dropwise at 0 °C. The mixture was then stirred at room temperature for 8 h. The resulting mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated Na_2CO_3 solution (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was subjected to flash chromatography (hexane/EtOAc, 4:1, $\mathbf{R_f}$ = 0.25) providing 233 mg (0.69 mmol, 99%) of ketone **3-34** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.51 (d, *J* = 7.6 Hz, 3H, CH_3), 1.64-1.88 (m, 2H, CH_2), 2.08 (br d, 1H, CH_2), 2.16-2.31 (m, 2H, 3-H, CH_2), 2.37 (br d, *J* = 12.6 Hz, 1H, 6-H), 2.48 (td, *J* = 12.6, 6.6 Hz, 1H, 6-H), 2.60-2.67 (m, 2H, 4,9-H), 3.58-3.65 (m, 1H, 2-H), 3.72 (br s, 1H, 12-H), 3.79 (s, 1H, OCH_3), 5.73 (br d, *J* = 10.1 Hz, 1H, 10-H), 5.78 (br d, *J* = 10.1 Hz, 1H, 11-H), 6.37 (s, 1H, 16-H), 6.59 (s, 2H, 14-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 13.0 (C-20), 24.8 (C-2), 27.6 (CH_2), 32.6 (CH_2),

38.9 (C-9), 42.6 (C-6), 43.8 (C-12), 45.1 (C-3), 50.1 (C-4), 55.4 (OCH_3), 99.1 (C-16), 108.7 (C-14), 122.9 (C-1), 129.4 (C-11), 129.9 (C-10), 142.4 (C-13), 160.7 (C-15), 211.7 (C-5).

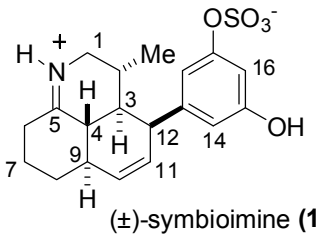


2-[7'-(3,5-Dimethoxyphenyl)-3',4',4a',7',8',8a'-hexahydro-2'H-spiro[1,3-dioxolane-2,1'-naphthalen]-8'-yl]propanenitrile (3-35): A solution of ethylene glycol (0.76 mL, 13.7 mmol), ketone **3-34** (233 mg, 0.69 mmol), and CSA (79 mg, 0.34 mmol) in benzene (20 mL) was refluxed for 6 h with azeotropic removal of water using a Dean-Stark apparatus. After cooling, the toluene was evaporated under reduced pressure and the residue purified by flash chromatography (hexane/EtOAc, 4:1) to give the acetal **3-35** (260 mg, 0.68 mmol, 99%) as a colorless oil. $\mathbf{R_f}$ = 0.3 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.93 (d, *J* = 7.1 Hz, 3H, CH_3), 1.33-1.43 (m, 2H, CH_2), 1.52-1.65 (m, 1H, CH_2), 1.71 (dd, *J* = 11.1, 5.8 Hz, 1H, 4-H), 1.70-1.79 (m, H, CH_2), 1.87-1.99 (m, 2H, CH_2), 2.21 (dd, *J* = 5.8, 2.8 Hz, 1H, 3-H), 2.36 (br dd, *J* = 11.6, 11.1 Hz, 1H, 9-H), 2.69 (qd, *J* = 7.1, 2.8 Hz, 1H, 2-H), 3.59 (br s, 1H, 12-H), 3.80 (s, 6H, OCH_3), 3.83-4.05 (m, 4H, acetal CH_2), 5.80 (br d, *J* = 9.1 Hz, 1H, 10-H), 6.06 (br d, *J* = 9.1 Hz, 1H, 11-H), 6.36 (s, 1H, 16-H), 6.53 (s, 2H, 14-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 16.4 (CH_3), 23.3 (CH_2), 27.0 (C-2), 31.7 (CH_2), 34.6 (CH_2), 39.2 (C-9), 43.1 (C-3), 45.2 (C-12), 46.9 (C-4), 55.3 (OCH_3), 63.8 (acetal CH_2), 64.0 (acetal CH_2), 98.3 (C-16), 107.4 (C-14), 110.7 (C-1), 123.6 (C-5), 128.7 (C-11), 133.5 (C-10), 144.0 (C-13), 160.9 (C-15); **HRMS** (ESI) calcd for $C_{23}H_{29}NO_4$ $[M+H]^+$ 384.21693, found 384.21699.



***De*-sulfo-symbioimine (3-37)**: To a stirred solution of nitrile **3-35** (170 mg, 0.44 mmol) in anhydrous Et_2O (5 mL) was added a solution of $LiAlH_4$ (1 M in Et_2O, 4 mL, 4 mmol) dropwise at 0 °C under inert atmosphere. The reaction was stirred at room temperature for 12 h then quenched by the dropwise addition of *iso*-propanol (10 mL). The mixture was diluted with Et_2O and filtered through celite. The filtrate was concentrated under reduced pressure to afford 151 mg (0.39 mmol, 89%, colorless oil) of amine **3-36** which was used in the next step without further purification. To a stirred solution of crude amine (151 mg, 0.39 mmol) in CH_2Cl_2 (10 mL) was added a solution of BBr_3 (1 M in CH_2Cl_2, 5 mL, 5 mmol) dropwise at -80 °C under inert atmosphere. The mixture was slowly warmed to room temperature while being stirred for 12 h, and finally poured into half-saturated $NaHCO_3$ solution (50 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography ($CHCl_3$/MeOH/NEt_3, 240:30:5, $\mathbf{R_f}$ = 0.3) to give (71 mg, 242 μmol,

55%) of imine **3-37** as a white powder (**m.p.** > 250 °C, decomp.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.92 (br s, 4H, H-2,19), 1.25-1.39 (m, 1H, CH_2), 1.42-1.57 (m, 2H), 1.84-2.14 (m, 5H), 2.23 (br d, *J* = 13.4 Hz, 1H, CH_2), 2.80-2.92 (m, 1H, 1-H), 3.38-3.50 (m, 2H, 1,12-H), 5.57 (br dd, *J* = 9.6, 4.3 Hz, 1H, 11-H), 5.70 (br d, *J* = 9.6 Hz, 1H, 10-H), 6.05 (s, 1H, 16-H), 6.15 (s, 2H, 14-H), 9.12 (br s, 2H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 16.6 (CH_3), 25.4 (C-7), 27.5 (C-2), 31.3 (C-8), 36.8 (C-6), 34.0 (C-9), 42.5 (C-12), 42.6 (C-4), 43.9 (C-3), 56.2 (C-1), 100.8 (C-16), 108.5 (C-14), 129.9 (C-11), 131.4 (C-10), 141.9 (C-13), 157.8 (C-15), 170.0 (C-5); **HRMS** (ESI) calcd for $C_{19}H_{23}NO_2$ $[M+H]^+$ 298.18016, found 298.18019.



(±)-symbioimine **(1)**

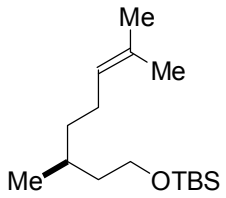
(±)-Symbioimine (3-1): To a solution of the free base **3-37** (15 mg, 50 μmol) in dry pyridine (2 mL) was added SO_3/Py complex (80 mg, 0.5 mmol) at room temperature. The mixture was stirred at 60-70 °C under inert atmosphere for 6 h, until the starting product had disappeared by TLC ($\mathbf{R_f}$ = 0.3-0.4 in $CHCl_3$/MeOH, 4:1). Then the pyridine was evaporated under reduced pressure and the residue purified by flash chromatography ($CHCl_3$/MeOH, 4:1, $\mathbf{R_f}$ = 0.25) affording the alkaloid **3-1** (3.8 mg, 10 μmol, 20%). Further elution with $CHCl_3$/MeOH/*i*PrOH/H_2O 2:2:1:0.5, $\mathbf{R_f}$ = 0.2) afforded 20 mg of the bisulfate derivative of symbioimine. To this bisulfate in dioxane (1 mL) and water (0.5 mL) was added *p*TsOH·H_2O (5 mg, 26 μmol) and the mixture stirred for 6 h at room temperature, before it was neutralized with 1 drop of pyridine. The solvents were evaporated under reduced pressure and the residue subjected to flash chromatography ($CHCl_3$/MeOH, 4:1, $\mathbf{R_f}$ = 0.25) to give further symbioimine (**3-1**) (10.3 mg, 27 μmol, 54%) as a white powder, **m.p**. 228-229 °C (decomp.). The combined yield of **3-1** from imine **3-37** was 74%. In addition, some amount of **3-37** (10%) was recovered from the hydrolysis experiment. **HRMS** (ESI) calcd for $C_{19}H_{23}NO_5S$ $[M+H]^+$ 378.13697, found 378.13664.

Table 1. Comparison of ^{13}C chemical shifts of synthetic symbioimine and with that of the natural compound

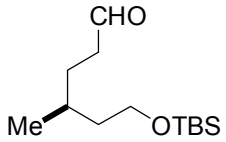
Atom No.	Synthetic, ppm	Natural, ppm	**Δ, ppm.**
1	50.0	50.0	**0.0**
2	26.2	26.2	**0.0**
3	40.8	41.1	**0.3**
4	40.3	40.1	**0.2**
5	187.4	188.0	**-0.6**
6	33.6	33.8	**-0.2**
7	24.4	24.4	**0.0**
8	29.8	29.8	**0.0**
9	41.5	41.4	**0.1**
10	130.5	130.4	**0.1**

11	129.6	129.5	**0.1**
12	41.7	41.7	**0.0**
13	139.9	139.8	**0.1**
14	112.8	112.8	**0.0**
15	154.1	154.1	**0.0**
16	106.0	105.8	**0.2**
17	157.3	157.2	**0.1**
18	111.8	111.7	**0.2**
19	15.6	15.6	**0.0**

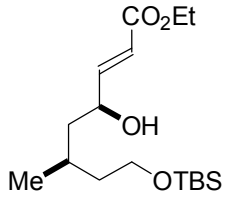
4. Total synthesis of (+)-neosymbioimine



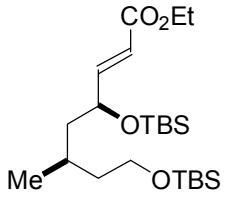
(6*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-2-octene (4-5a): To a solution of commercial (-)-(*S*)-citronellol **4-5** (5.0 g, 32 mmol) and imidazole (4.35 g, 64 mmol, 2 equiv) in dry DMF (35 mL) was added TBSCl (6.0 g, 40 mmol, 1.25 equiv) portionwise at 0 °C. The reaction mixture was allowed to warm to 20–25 °C and stirred for 12 h at this temperature. Then the mixture was poured into ice water (300 mL) and extracted with petroleum ether (3 × 100 mL). The combined organic layers were washed once with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether, $\mathbf{R_f}$ 0.3) using a short column, yield 8.2 g (95%) of **4-5a**, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiCH_3$), 0.87 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CH), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.09–1.19 (m, 1H), 1.28–1.37 (m, 2H), 1.50–1.58 (m, 2H), 1.59 (s, 3H, *Z*-CH=CC*H*$_3$), 1.67 (s, 3H, *E*-CH=CC*H*$_3$), 1.97 (ddd, *J* = 8.1, 6.8, 6.8 Hz, 2H, C*H*$_2$CH=C), 3.57–3.67 (m, 2H, CH_2OSi), 5.09 (dd, *J* = 6.8, 6.8 Hz, 1H, CH=C). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.3 ($SiCH_3$), 17.6 (*Z*-CH=C*C*H$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 19.6 (*C*H$_3$CH), 25.5 (*C*H$_2$CH=C), 25.7 (*E*-CH=C*C*H$_3$), 26.0 ($SiC(CH_3)_3$), 29.1 (CH_3CH), 37.2 (CH_3CHCH_2), 39.9 (CH_3CHCH_2), 61.4 (CH_2O), 124.9 (*C*H=CMe$_2$), 131.0 (CH=*C*Me$_2$). **$[\alpha]^D_{23}$** –4.5 (neat).



(4*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-methylhexanal (4-6): O_3 was bubbled through a solution of the foregoing TBS-protected citronellol (7.4 g, 27.4 mmol) in CH_2Cl_2 (25 mL) and MeOH (25 mL), containing pyridine (0.5 mL) at –78 °C until a blue color appeared (~3 h). Excess of ozone was purged out of the flask with nitrogen before Me_2S (2.34 mL, 32 mmol) was added dropwise at –78 °C. The reaction mixture was slowly warmed to 20 °C overnight. The mixture was concentrated under reduced pressure and the residue purified by flash chromatography (petroleum ether/EtOAc, 20:1), yield 6.2 g (93%), colorless oil. $\mathbf{R_f}$ 0.35 (petroleum ether/EtOAc, 20:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.88 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CH), 1.30–1.71 (m, 5H), 2.35–2.49 (m, 2H, C*H*$_2$CHO), 3.57–3.68 (m, 2H, CH_2OSi), 9.75 (s, 1H, CHO). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.4 ($SiCH_3$), 18.3 (Si*C*(CH$_3$)$_3$), 19.3 (CH_3CH), 25.9 ($SiC(CH_3)_3$), 28.9 (CH_3CHCH_2), 29.1 (CH_3CH), 39.5 (CH_3CHCH_2), 41.6 (*C*HCHO), 61.0 (CH_2O), 202.8. **HRMS** (ESI): calcd for $C_{13}H_{28}O_2Si$ $[M+Na]^+$ 267.1756, found 267.1753. **$[\alpha]^D_{23}$** –0.112 (neat).

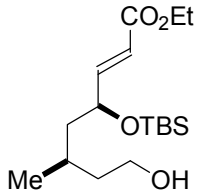


Ethyl (2*E*,4*S*,6*R*)-8-{[*tert*-butyl(dimethyl)silyl]oxy}-4-hydroxy-6-methyloct-2-enoate (4-7): To a solution of aldehyde **4-6** (5.0 g, 20 mmol) and nitroso benzene (2.14 g, 20 mmol, 1 equiv) in anhydrous DMSO (75 mL) was added D-proline (0.91 g, 8 mmol, 0.4 equiv) at 20 °C. The mixture was vigorously stirred for 25 min under nitrogen (the colour of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (10 mL, 50 mmol, 2.5 equiv), DBU (7.5 mL, 50 mmol, 2.5 equiv) and LiCl (2.1 g, 50 mmol, 2.5 equiv) in CH_3CN (75 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was stirred for 15 min at 0 to 10 °C and diluted with MeOH (380 mL). NH_4Cl (2.5 g, 53 mmol) and $Cu(OAc)_2$ (362 mg, 2 mmol) were added sequentially. The resulting mixture was stirred for 24 h at room temperature, then the MeOH was evaporated under vacum. Water (500 mL) was added and the mixture extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to give 3.62 g (55%) of the enoate **4-7** as a yellowish oil, which is sufficiently pure for the next step. $\mathbf{R_f}$ 0.5 (petroleum ether/EtOAc, 4:1), 0.2 (petroleum ether/EtOAc, 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.94 (d, *J* = 6.5 Hz, 3H, CH_3CH), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.31–1.60 (m, 4H), 1.78-1.88 (m, 1H), 2.26 (d, *J* = 4.6 Hz, 1H, CHO*H*), 3.60–3.70 (m, 2H, CH_2OSi), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.33–4.38 (m, 1H, C*H*OH), 6.02 (d, *J* = 15.7 Hz, 1H, CH=C*H*CO_2Et), 6.92 (dd, *J* = 15.7, 4.6 Hz, 1H, C*H*=$CHCO_2Et$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.4 ($SiCH_3$), 14.2 (OCH_2CH_3), 18.3 ($SiC(CH_3)_3$), 19.8 (CH_3CH), 25.9 ($SiC(CH_3)_3$), 26.6 (CH_3CH), 39.8 (CH_3CHCH_2), 43.7 (CH_3CHCH_2), 60.3 (CH_2O), 61.1 (CH_2O), 69.4 (*C*HOH), 119.7 (CH=*C*HCO_2Et), 150.8 (*C*H=$CHCO_2Et$), 166.6 (CO_2Et). **HRMS** (ESI): calcd for $C_{17}H_{34}O_4Si$ $[M+Na]^+$ 353.2119, found 353.2117. $\mathbf{[\alpha]^D_{23}}$ –5.16 (*c* 5.0, CH_2Cl_2).

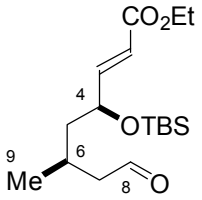


Ethyl (2*E*,4*S*,6*R*)-4,8-bis{[*tert*-butyl(dimethyl)silyl]oxy}-6-methyloct-2-enoate (4-7a): To a stirred solution of the 4-hydroxy enoate **7** (630 mg, 1.9 mmol) in CH_2Cl_2 (10 mL), imidazole (646 mg, 9.5 mmol, 5 equiv) and DMAP (23 mg, 0.19 mmol, 0.1 equiv) were added. Then, TBSCl (573 mg, 3.8 mmol, 2 equiv) was added in one portion at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The mixture was diluted with petroleum ether (50 mL), washed with water and with saturated NaCl solution. After drying the organic layer over Na_2SO_4, filtration, and concentration in vacuo, the residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1), yield 743 mg (88 %),

yellowish oil. $\mathbf{R_f}$ 0.3 (petroleum ether/EtOAc, 25:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = –0.02–0.07 (m, 12H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.21–1.36 (m, 2H), 1.49–1.58 (m, 2H), 1.72–1.82 (m, 1H), 3.58–3.65 (m, 2H, CH_2OTBS), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.30–4.37 (m, 1H, CHOTBS), 5.93 (d, *J* = 15.4 Hz, 1H, $CH{=}CHCO_2Et$), 6.90 (dd, *J* = 15.4, 5.3 Hz, 1H, $CH{=}CHCO_2Et$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.4 ($SiCH_3$), –5.3 ($SiCH_3$), –4.9 ($SiCH_3$), –4.3 ($SiCH_3$), 14.2 (OCH_2CH_3), 18.1 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 19.5 (CH_3CH), 25.6 (CH_3CH), 25.8 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 40.4 (C-7), 45.2 (C-5), 60.3 (CH_2O), 61.1 (CH_2O), 69.8 (CHOTBS), 119.6 ($CH{=}CHCO_2Et$), 151.4 ($CH{=}CHCO_2Et$), 166.7 (CO_2Et). **HRMS** (ESI): calcd for $C_{23}H_{48}O_4Si_2$ $[M+Na]^+$ 467.2983, found 467.2983. **$[\alpha]^D_{23}$** –8.67 (*c* 13.5, CH_2Cl_2).

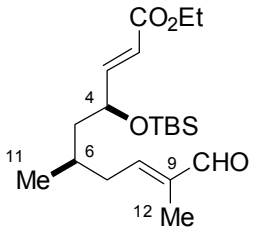


Ethyl (2*E*,4*S*,6*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-8-hydroxy-6-methyloct-2-enoate (4-7b): Camphor sulfonic acid (19 mg, 0.082 mmol, 0.05 equiv) was added to a solution of the foregoing disilyl ether **4-7a** (727 mg, 1.64 mmol) in MeOH (10 mL) at 20 °C. The mixture was stirred for 1 h at 20 °C (TLC monitoring). After the starting material had disappeared on TLC, the mixture was diluted with diethyl ether and washed with saturated $NaHCO_3$ solution and with saturated NaCl solution. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography to provide the primary alcohol **4-7b** (470 mg, 87%) as a colorless oil. $\mathbf{R_f}$ 0.25 (petroleum ether/EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.91 (d, *J* = 6.8 Hz, 3H, CH_3CH), 1.27 (t, *J* = 7.1 Hz, 3H, $HOCH_2CH_3$), 1.38–1.60 (m, 4H), 1.71–1.80 (m, 1H), 3.65 (dd, *J* = 6.8, 6.8 Hz, 2H, CH_2OH), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.30–4.37 (m, 1H, CHOTBS), 5.93 (d, *J* = 15.7 Hz, 1H, $CH{=}CHCO_2Et$), 6.89 (dd, *J* = 15.7, 5.3 Hz, 1H, $CH{=}CHCO_2Et$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.0 ($SiCH_3$), –4.4 ($SiCH_3$), 14.2 ($HOCH_2CH_3$), 18.1 ($SiC(CH_3)_3$), 19.8 (CH_3CH), 25.8 (CH_3CH), 25.8 ($SiC(CH_3)_3$), 40.2 (CH_3CHCH_2), 44.8 (CH_3CHCH_2), 60.3 (CH_2O), 60.8 (CH_2O), 69.8 (CHOH), 119.7 ($CH{=}CHCO_2Et$), 151.3 ($CH{=}CHCO_2Et$), 166.7 (CO_2Et). **HRMS** (ESI): calcd for $C_{17}H_{34}O_4Si$ $[M+Na]^+$ 353.2119, found 353.2119. **$[\alpha]^D_{23}$** –2.23 (*c* 10.0, CH_2Cl_2).

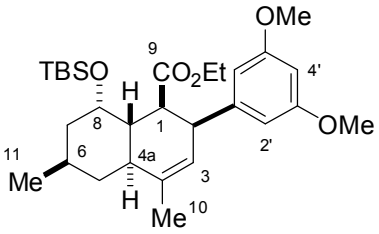


Ethyl (2*E*,4*S*,6*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-6-methyl-8-oxo-oct-2-enoate (4-8): To a stirred solution of the foregoing primary alcohol (417 mg, 1.26 mmol) in CH_2Cl_2 (6 mL) was added dropwise a solution of Dess-Martin periodinane (3 mL of a 15 ww% solution in CH_2Cl_2, 1.2 equiv) at 0 °C. After being stirred for 2 h at 20 °C, the mixture was diluted with diethyl ether (60 mL) and washed with half saturated $NaHCO_3$ solution (2 × 50 mL) and

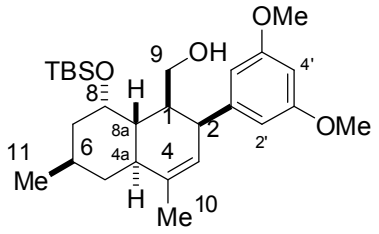
with saturated NaCl solution (20 mL). The water phase was extracted with diethyl ether, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue afforded 388 mg (1.18 mmol, 94%) of aldehyde **4-8** as a colorless oil. $\mathbf{R_f}$ 0.4 (petroleum ether/EtOAc, 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.97 (d, *J* = 6.1 Hz, 3H, H-9), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.35 (ddd, *J* = 12.6, 8.3, 4.1 Hz, 1H, H-5a), 1.55 (ddd, *J* = 12.6, 8.1, 4.1 Hz, 1H, H-5b), 2.20–2.30 (m, 2H, CH-6,7a), 2.37 (ddd, *J* = 10.1, 8.6, 1.8 Hz, 1H, H-7b), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 4.33 (dddd, *J* = 8.1, 5.3, 4.1, 1.3 Hz, 1H, H-4), 5.93 (dd, *J* = 15.6, 1.3 Hz, 1H, H-2), 6.87 (dd, *J* = 15.6, 5.3 Hz, 1H, H-3), 9.70 (dd, *J* = 2.0, 1.8 Hz, 1H, H-8). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.0 (SiCH$_3$), –4.3 (SiCH$_3$), 14.2 (OCH$_2$$CH_3$), 18.1 (Si$C$(CH$_3$)$_3$), 19.9 (C-9), 24.4 (C-6), 25.8 (SiC(CH$_3$)$_3$), 44.3 (C-5), 51.4 (C-7), 60.4 (CH$_2$O), 69.7 (C-4), 120.1 (C-2), 150.6 (C-3), 166.4 (C-1), 202.2 (C-8). **HRMS** (ESI) calcd for $C_{17}H_{32}O_4Si$ [M+CH$_3$OH+Na]$^+$ 383.2224, found 383.2221. **[α]$^D_{23}$** –31.1 (*c* 5.0, CH_2Cl_2).



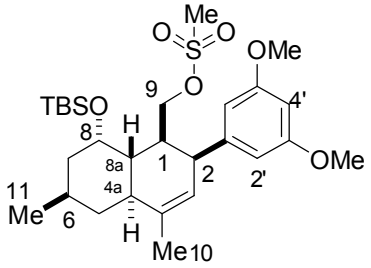
Ethyl (2*E*,4*S*,6*R*,8*Z*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-6,9-dimethyl-10-oxodeca-2,8-dienoate (4-10): Aldehyde **4-8** (1.84 g, 5.6 mmol) and 2-(triphenylphosphoranylidene)propanal (**4-9**)[187] (3.57 g, 11.2 mmol, 2 equiv) in toluene (50 mL) were heated to 100 °C for 30 h. Thereafter, the toluene was evaporated under reduced pressure and the residue diluted with Et_2O. The precipitate (Ph_3P=O) was filtered, washed with a small amount of Et_2O, and the filtrate was then concentrated. The resulting oil was purified by flash chromatography through a short column. $\mathbf{R_f}$ 0.4 (petroleum ether/EtOAc, 10:1), yield 1.82 g (4.95 mmol, 88%), colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.00 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.95 (d, *J* = 6.8 Hz, 3H,H-11), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.32 (ddd, *J* = 13.4, 9.1, 4.1 Hz, 1H, H-5a), 1.56 (ddd, *J* = 13.4, 8.3, 4.1 Hz, 1H, H-5b), 1.70 (s, 3H, H-12), 1.85–1.95 (m, 1H, H-6), 2.18–2.35 (m, 2H, H-7a,b), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 4.33 (dddd, *J* = 8.1, 5.3, 4.1, 1.3 Hz, 1H, H-4), 5.93 (dd, *J* = 15.6, 1.3 Hz, 1H, H-2), 6.45 (dd, *J* = 7.3, 7.3 Hz, 1H, H-8), 6.87 (dd, *J* = 15.6, 5.3 Hz, 1H, H-3), 9.39 (s, 1H, H-10). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –5.0 (SiCH$_3$), –4.3 (SiCH$_3$), 9.4 (C-12), 14.2 (OCH$_2$$CH_3$), 18.1 (Si$C$(CH$_3$)$_3$), 19.7 (C-11), 25.8 (SiC(CH$_3$)$_3$), 29.1 (C-6), 36.7 (C-7), 44.3 (C-5), 60.4 (CH$_2$O), 69.7 (C-4), 119.9 (C-2), 140.3 (C-9), 150.8 (C-2), 152.9 (C-8), 166.5 (C-1), 195.1 (C-10). **HRMS** (ESI): calcd for $C_{20}H_{36}O_4Si$ [M+Na]$^+$ 391.2275, found 391.2272. **[α]$^D_{23}$** -0.92 (*c* 10.0, CH_2Cl_2).



Ethyl (1*S*,2*S*,4a*S*,6*R*,8*S*,8a*S*)-8-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-4,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (4-13): To a solution of diethyl 3,5-dimethoxybenzylphosphonate (**4-11**) (5.53 g, 19.2 mmol, 4 equiv) in THF (40 mL), KO*t*Bu (1.34 g, 12.0 mmol, 2.5 equiv) was added at 20 °C in one portion (water bath used). The mixture was stirred for 1 h at ambient temperature under nitrogen. The resulting clear solution was cooled to –78 °C, before aldehyde **4-10** (1.80 g, 4.74 mmol) in THF (10 mL) was added dropwise between –70 and –80 °C. Then the reaction mixture was warmed to 0 °C for 30 min, and treated with half-saturated NH_4Cl solution (50 mL). The organic phase was extracted with petroleum ether (3 × 50 mL). The combined organic extracts were washed with water (25 mL) and saturated NaCl solution (25 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The intermediate triene **4-12** could not be obtained in pure form due to the rather facile Diels-Alder reaction, which already occurred at room temperature. For complete conversion, the obtained oil was dissolved in $CHCl_3$ (10 mL) and the solution heated to 60 °C for 2 h. Then the solvent was evaporated and the residue purified by flash chromatography ($\mathbf{R_f}$ 0.4, petroleum ether/EtOAc, 10:1) to afford 2.05 g (4.1 mmol, 86%) of 95% pure cycloadduct **4-13** as a colorless oil. The other 5% is the diastereomer of the uncyclized triene **4-12** (4% from (+)-(*R*)-citronellol, ~1% from proline). These compounds were separated in the next step after reduction of the ester group. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = –0.09 (s, 3H, SiCH_3), –0.02 (s, 3H, SiCH_3), 0.71 (ddd, 1H, *J* = 12.4, 12.4, 12.1 Hz, H-5a), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, H-11), 1.12 (m, 1H, H-7a), 1.13 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.61 (br d, *J* = 11.6 Hz, 1H, H-8a), 1.70 (d, *J* = 13.9 Hz, 1H, H-7b), 1.75 (s, 3H, H-10), 1.83–1.93 (m, 1H, H-6), 2.10 (d, *J* = 12.1 Hz, 1H, H-5b), 2.37 (dd, *J* = 11.1, 11.1 Hz, 1H, H-4a), 2.94 (dd, *J* = 11.9, 6.6 Hz, 1H, H-1), 3.69 (br s, 1H, H-2), 3.74 (s, 6H, OCH_3), 3.82–3.94 (m, 2H, OCH_2CH$_3$), 4.17 (br s, 1H, H-8), 5.83 (br s, 1H, H-3), 6.25 (d, *J* = 2.0 Hz, 2H, H-2', 6'), 6.30 (t, *J* = 2.0 Hz, 1H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.5 (SiCH$_3$), –4.2 (SiCH$_3$), 14.0 (OCH$_2$$CH_3$), 18.1 (Si$C$(CH$_3$)$_3$), 21.2 (C-10), 22.4 (C-11), 25.8 (SiC(CH$_3$)$_3$), 26.9 (C-6), 36.4 (C-4a), 38.6 (C-5), 40.2 (C-8a), 42.4 (C-7), 44.4 (C-2), 46.8 (C-1), 55.1 (OCH$_3$), 59.7 (OCH$_2$CH$_3$), 67.8 (C-8), 98.2 (C-4'), 108.0 (C-2', 6'), 122.0 (C-3), 138.0 (C-4), 143.7 (C-1'), 160.1 (C-3', 5'), 172.8 (C-9). **HRMS** (ESI): calcd for $C_{29}H_{46}O_5Si$ $[M+Na]^+$ 525.3008, found 525.3005. $\mathbf{[\alpha]^D_{23}}$ +180 (*c* 3.0, CH_2Cl_2).

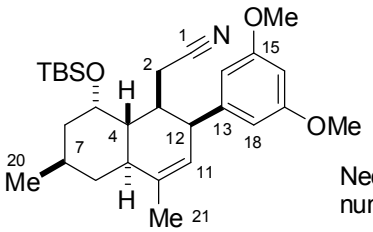


[(1*S*,2*S*,4a*S*,6*R*,8*S*,8a*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-4,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methanol (4-13a): To a stirred solution of ester **4-13** (2.0 g, 3.98 mmol) in CH_2Cl_2 (30 mL), a solution of DIBAL (17 mL of a 0.7–1.3 M solution in CH_2Cl_2, 12 mmol, 3 equiv) was added dropwise at –20 °C. The resulting mixture was allowed to warm to room temperature and stirred for 24 h, then diluted with Et_2O (100 mL) and poured into a cold solution of Rochelle's salt (40 g) in water (120 mL). The mixture was vigorously stirred for 24 h, then the organic phase was separated, and the water phase extracted with Et_2O (2 × 50 mL). The combined extracts were washed with water and with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography provide 1.610 g (88%, 3.50 mmol) of the primary alcohol **4-13a** as a colorless oil. $\mathbf{R_f}$ 0.25 (petroleum ether/EtOAc, 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3), 0.70 (ddd, *J* = 12.4, 12.4, 12.1 Hz, 1H, H-5a), 0.78 (dd, *J* = 8.6, 2.8 Hz, 1H, H-8a), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, H-11), 1.04 (dd, *J* = 13.6, 11.1 Hz, 1H, H-7a), 1.40 (dd, *J* = 11.1, 10.6 Hz, 1H, H-7b), 1.75 (s, 3H, H-10), 1.82–1.97 (m, 1H, H-6), 2.01–2.10 (m, 1H, H-1), 2.10 (d, *J* = 12.1 Hz, 1H, H-5b), 2.40 (dd, *J* = 12.4, 8.6 Hz, 1H, H-4a), 3.42 (dd, *J* = 19.2, 8.6 Hz, 1H, H-9a), 3.52 (br s, 1H, H-2), 3.77 (s, 6H, OCH_3), 3.78 (d, *J* = 19.2 Hz, 1H, H-9b), 4.03 (s, 1H, H-8), 5.34 (br s, 1H, H-3), 6.34 (t, *J* = 2.0 Hz, 1H, H-4'), 6.48 (d, *J* = 2.0 Hz, 2H, H-2', 6'). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.4 (Si*C*H$_3$), –3.6 (Si*C*H$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 21.2 (C-10), 22.3 (C-11), 25.9 (SiC(*C*H$_3$)$_3$), 26.8 (C-6), 37.7 (C-4a), 39.0 (C-5), 40.7 (C-8a), 41.1 (C-1), 42.5 (C-7), 44.3 (C-2), 55.2 (OCH_3), 62.0 (C-9), 67.6 (C-8), 98.1 (C-4'), 108.3 (C-2', 6'), 123.5 (C-3), 138.0 (C-4), 144.8 (C-1'), 160.5 (C-3', 5'). **HRMS** (ESI): calcd for $C_{27}H_{44}O_4Si$ $[M+Na]^+$ 483.2901, found 483.2896. **$[\alpha]^D_{23}$** +216 (*c* 2.7, CH_2Cl_2).

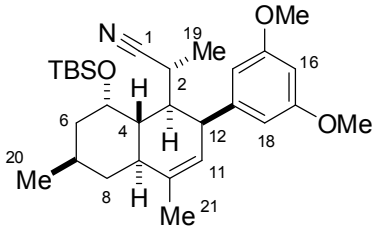


[(1*S*,2*S*,4a*S*,6*R*,8*S*,8a*S*)-8-{[*Tert*-butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-4,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methyl methanesulfonate (4-13b): To a stirred solution of the foregoing primary alcohol **4-13a** (1.45 g, 3.15 mmol) and Et_3N (4.3 mL, 31.5 mmol, 10 equiv) in CH_2Cl_2 (55 mL), MsCl (0.487 mL, 6.3 mmol, 2 equiv) was added dropwise at –50 °C. The reactiom mixture was warmed to 0 °C within 1 h and stirred for 1 h at this temperature. The mixture was then treated with half saturated $NaHCO_3$ solution. Extractive workup (3 × 40 mL of CH_2Cl_2) followed by flash chromatography afforded the mesylate (1.59 g, 2.96 mmol, 94%) as colorless crystals, **mp.** 129 °C). $\mathbf{R_f}$ 0.2 (petroleum ether/EtOAc, 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.07 (s, 6H, SiCH_3), 0.70 (ddd, *J* = 12.4, 12.1, 11.6 Hz, 1H, H-5a), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.91 (d, *J* = 6.8 Hz, 3H, H-11), 1.04 (dd, *J* = 14.2, 12.4 Hz, 1H, H-7a), 1.41 (dd, *J* = 11.4, 10.4 Hz, 1H, H-8a), 1.75 (s, 3H, H-10), 1.78 (br d, *J* = 12.4 Hz, 1H, H-7b), 1.81–1.94 (m, 1H, H-6), 2.10 (d, *J* = 12.1 Hz, 1H, H-5b), 2.35 (dddd, *J* = 12.4, 10.8, 5.3, 4.1 Hz, 1H, H-1), 2.40 (dd, *J* = 11.6, 10.8 Hz, 1H,

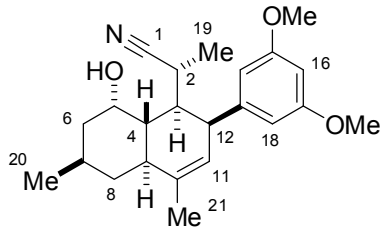
H-4a), 2.84 (s, 3H, H-12), 3.58 (br dd, *J* = 5.3, 4.3 Hz, 1H, H-2), 3.65 (dd, *J* = 10.8, 8.6 Hz, 1H, H-9a), 3.78 (s, 6H, OCH_3), 3.83 (br s, 1H, H-8), 4.32 (dd, *J* = 8.6, 4.1 Hz, 1H, H-9b), 5.37 (br d, *J* = 4.3 Hz, 1H, H-3), 6.33 (t, *J* = 2.0 Hz, 1H, H-4'), 6.42 (d, *J* = 2.0 Hz, 2H, H-2', 6'). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.5 (Si*C*H_3), –3.5 (Si*C*H_3), 18.2 (Si*C*$(CH_3)_3$), 21.1 (C-10), 22.2 (C-11), 25.8 (SiC(*C*$H_3)_3$), 26.7 (C-6), 37.1 (C-12), 37.8 (C-4a), 38.2 (C-1), 38.8 (C-5), 40.7 (C-8a), 42.3 (C-7), 42.8 (C-2), 55.3 (OCH_3), 67.1 (C-8), 69.5 (C-9), 98.3 (C-4'), 108.9 (C-2', 6'), 123.1 (C-3), 137.7 (C-4), 142.9 (C-1'), 160.3 (C-3', 5'). **HRMS** (ESI): calcd for $C_{28}H_{46}O_6SSi$ $[M+Na]^+$ 561.2677, found 561.2675. **$[\alpha]^D_{23}$** +192 (*c* 10.0, CH_2Cl_2).



[(1*S*,2*R*,4a*S*,6*R*,8*S*,8a*R*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-4,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]acetonitrile (4-14): A mixture of the foregoing mesylate (1.82 g, 3.38 mmol) and NaCN (1.65 g, 33.8 mmol, 10 equiv.) in dry DMSO (50 mL) was stirred for 3 d at 50 °C under inert atmosphere. The mixture was diluted with water (300 mL) and extracted with petroleum ether (3 × 75 mL). The combined organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4, filered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 1.55 g (3.31 mmol, 98%) of nitrile **4-14** as a colorless oil. **R_f** 0.2 (petroleum ether/EtOAc, 20:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3), 0.68 (ddd, *J* = 12.6, 12.1, 12.1 Hz, 1H, H-8a), 0.90 (s, 9H, SiC(C$H_3)_3$), 0.91 (d, *J* = 6.8 Hz, 3H, H-20), 1.02 (dd, *J* = 14.2, 12.4 Hz, 1H, H-6a), 1.30 (dd, *J* = 11.4, 10.4 Hz, 1H, H-4), 1.64 (dd, *J* = 16.2, 12.4 Hz, 1H, H-2a), 1.75(s, 3H, H-21), 1.76 (br d, *J* = 12.4 Hz, 1H, H-6b), 1.81–1.94 (m, 1H, H-7), 2.09 (br d, *J* = 12.1 Hz, 1H, H-8b), 2.30 (dddd, *J* = 12.4, 11.4, 5.3, 2.8 Hz, 1H, H-3), 2.37 (dd, *J* = 11.4, 10.4 Hz, 1H, H-9), 2.47 (dd, *J* = 16.2, 2.8 Hz, 1H, H-2b), 3.65 (br dd, *J* = 5.3, 4.3 Hz, 1H, H-12), 3.78 (s, 6H, OCH_3), 3.80 (br s, 1H, H-5), 5.41 (d, *J* = 4.3 Hz, 1H, H-11), 6.36 (t, *J* = 2.0 Hz, 1H, H-16), 6.48 (d, *J* = 2.0 Hz, 2H, H-14, 18). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.4 (Si*C*H_3), –3.5 (Si*C*H_3), 17.9 (C-2), 18.1 (Si*C*$(CH_3)_3$), 21.1 (C-21), 22.1 (C-20), 25.8 (SiC(*C*$H_3)_3$), 26.7 (C-7), 36.8 (C-3), 38.0 (C-9), 38.6 (C-8), 42.0 (C-4), 42.3 (C-6), 44.4 (C-12), 55.3 (OCH_3), 67.1 (C-5), 98.7 (C-15), 108.6 (C-14, 18), 119.7 (C-1), 122.9 (C-11), 137.8 (C-10), 142.4 (C-13), 160.4 (C-15, 17). **HRMS** (ESI): calcd for $C_{28}H_{43}NO_3Si$ $[M+Na]^+$ 492.2904, found 492.2905. **$[\alpha]^D_{23}$** +278 (*c* 10.0, CH_2Cl_2).

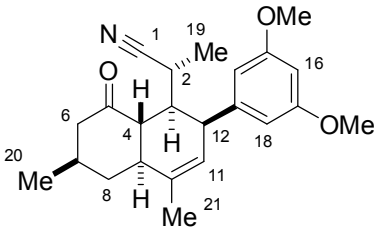


(2*R*)-2-[(1*R*,2*R*,4a*S*,6*R*,8*S*,8a*R*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3,5-dimethoxyphenyl)-4,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]propanenitrile (4-3): A solution of *n*BuLi (2.5 M in hexane, 1.92 mL, 4.8 mmol, 2 equiv) was added dropwise to a solution of *i*Pr_2NH (0.702 mL, 5 mmol, 2 equiv) in THF (10 mL) at 0 °C under N_2. The LDA solution was stirred for 0.5 h at this temperature, then cooled to –85 °C. Now, a solution of nitrile **4-14** (1.14 g, 2.4 mmol) in THF (15 mL) was added dropwise within 10 min. A yellowish color of the nitrile anion appeared within minutes. The mixture was stirred for 1 h at –80 °C before MeI (300 μL, 4.8 mmol, 2 equiv) was introduced at this temperature. The mixture was stirred for 30 min at –80 °C. The yellowish color completely disappeared at this time. Then the mixture was treated with half-saturated NH_4Cl solution (25 mL) and warmed to room temperature. The mixture was extracted with petroleum ether (3 × 30 mL). The combined organic extracts were washed with saturated solution of NaCl, dried over Na_2SO_4, and filtered. The petroleum ether was evaporated and the residue purified by flash chromatography ($\mathbf{R_f}$ 0.25, petroleum ether/EtOAc, 20:1) to afford diastereomerically pure nitrile **4-3** (1.005 g, 87%, de >99%) as colorless crystals (**m.p.** 124–125 °C). The other diastereomer ($\mathbf{R_f}$ 0.15) was formed in insignificant amounts (ca. 10%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.60 (d, *J* = 7.4 Hz, 1H, H-19), 0.80 (ddd, *J* = 12.4, 12.4, 12.1 Hz, 1H, H-8a), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.92 (d, *J* = 6.8 Hz, 3H, H-20), 1.10 (dd, *J* = 14.2, 12.4 Hz, 1H, H-6a), 1.50 (dd, *J* = 11.4, 10.4 Hz, 1H, H-4), 1.74 (s, 3H, H-21), 1.81 (br d, *J* = 14.2 Hz, 1H, H-6b), 1.85–1.95 (m, 1H, H-7), 2.11 (br d, *J* = 12.4 Hz, 1H, H-8b), 2.27 (ddd, *J* = 11.4, 5.3, 4.3 Hz, 1H, H-3), 2.46 (dd, *J* = 12.4, 11.4 Hz, 1H, H-9), 2.91 (qd, *J* = 7.1, 4.3 Hz, 1H, H-2), 3.69 (br s, 1H, H-12), 3.79 (s, 6H, OCH_3), 3.80 (s, 1H, H-5), 5.42 (br s, 1H, H-11), 6.35 (s, 1H, H-16), 6.54 (s, 2H, H-14, 18). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = –5.4 (Si*C*H_3), –3.4 (Si*C*H_3), 13.1 (C-19), 18.2 (Si*C*(CH_3)$_3$), 20.8 (C-21), 22.2 (C-20), 25.5 (C-2), 25.8 (SiC(*C*H_3)$_3$), 26.8 (C-7), 37.5 (C-9), 38.6 (C-8), 41.3 (C-3), 41.7 (C-4), 42.4 (C-6), 44.3 (C-12), 55.3 (OCH_3), 68.4 (C-5), 98.8 (C-16), 108.7 (C-14, 18), 122.9 (C-1), 123.7 (C-11), 137.0 (C-10), 144.5 (C-13), 160.6 (C-15, 17). **HRMS** (ESI): calcd for $C_{29}H_{45}NO_3Si$ $[M+Na]^+$ 506.3061, found 506.3060. **$[\alpha]^D_{20}$** +212 (*c* 10.0, CH_2Cl_2).

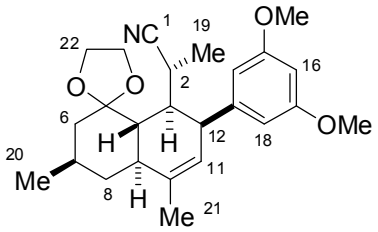


(2*R*)-2-[(1*R*,2*R*,4a*S*,6*R*,8*S*,8a*R*)-2-(3,5-Dimethoxyphenyl)-8-hydroxy-4,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]propanenitrile (4-3a): To a stirred solution of nitrile **4-3** (1.00 g, 2.07 mmol) in THF (2.5 mL), a 1M solution of TBAF in THF (12 mL, 12 mmol, 6 equiv) was added dropwise at 0 °C. The mixture was gradually warmed to 23 °C and stirred at this temperature until the starting compound had disappeared according to TLC (~24 h). The mixture was diluted with EtOAc (50 mL) and washed with water and saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated. Purification of the residue by flash chromatography afforded the hydroxy nitrile **4-3a** (757 mg, 2.05 mmol, 99%) as colorless crystals, **mp.** 127–128 °C. $\mathbf{R_f}$ 0.2 (petroleum ether/EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$):

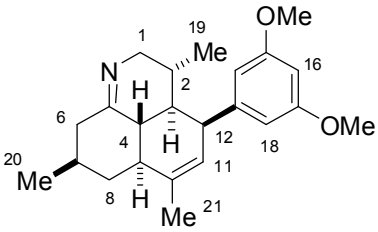
δ = 0.80 (ddd, *J* = 12.4, 12.4, 12.1 Hz, 1H, H-8a), 0.87 (d, *J* = 7.3 Hz, 3H, H-19), 0.95 (d, *J* = 6.3 Hz, 3H, H-20), 1.25 (dd, *J* = 14.4, 12.1 Hz, 1H, H-6a), 1.40 (d, *J* = 4.3 Hz, 1H, OH), 1.65 (dd, *J* = 11.6, 10.4 Hz, 1H, H-4), 1.73 (s, 3H, H-21), 1.82 (br d, *J* = 14.4 Hz, 1H, H-6b), 1.85–1.95 (m, 1H, H-7), 2.15 (br d, *J* = 12.4 Hz, 1H, H-8b), 2.27 (ddd, *J* = 11.6, 5.8, 3.6 Hz, 1H, H-3), 2.36 (dd, *J* = 12.4, 10.4 Hz, 1H, H-9), 3.04 (qd, *J* = 7.3, 3.6 Hz, 1H, H-2), 3.58 (br dd, *J* = 5.8, 4.3 Hz, 1H, H-12), 3.78 (s, 6H, OCH_3), 4.03 (s, 1H, H-5), 5.37 (d, *J* = 4.3 Hz, 1H, H-11), 6.36 (t, *J* = 2.0 Hz, 1H, H-16), 6.48 (d, *J* = 2.0 Hz, 2H, H-14, 18). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 15.0 (C-19), 20.9 (C-21), 22.2 (C-20), 26.2 (C-2), 26.9 (C-7), 37.7 (C-9), 38.8 (C-8), 40.5 (C-3), 40.8 (C-4), 42.6 (C-6), 45.4 (C-12), 55.3 (OCH_3), 66.7 (C-5), 98.6 (C-16), 109.1 (C-14,18), 122.5 (C-1), 123.8 (C-11), 136.2 (C-10), 143.4 (C-13), 160.5 (C-15, 17). **HRMS** (ESI): calcd for $C_{23}H_{31}NO_3$ $[M+Na]^+$ 392.2196, found 392.2197. **$[\alpha]^D_{20}$** +286 (*c* 5.0, CH_2Cl_2).



(2*R*)-2-[(1*R*,2*R*,4a*S*,6*R*,8a*R*)-2-(3,5-Dimethoxyphenyl)-4,6-dimethyl-8-oxo-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]propanenitrile (4-3b): A solution of Dess-Martin periodinane (15 wt.% in CH_2Cl_2, 6.4 mL, 3 mmol, 1.5 equiv) was added dropwise at 0 °C to a stirred solution of the foregoing secondary alcohol **4-3b** (738 mg, 2.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was gradually warmed to room temperature and stirred until the starting material had disappeared according to TLC (~ 12 h). The mixture was diluted with Et_2O (50 mL) and filtered. The undissolved solid was washed with Et_2O. The filtrate was washed with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded 705 mg (1.92 mmol, 96%) of the ketone **4-3b** as colorless crystals, **mp.** 49–51 °C. **R_f** 0.2 (petroleum ether/EtOAc, 8:1), 0.4 (petroleum ether/EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.52 (d, *J* = 7.3 Hz, 3H, H-19), 1.12 (d, *J* = 6.5 Hz, 3H, H-20), 1.34 (ddd, *J* = 12.6, 12.4, 12.1 Hz, 1H, H-8a), 1.79 (s, 3H, H-21), 1.92–2.06 (m, 1H, H-7), 2.17 (br dd, *J* = 12.6, 10.4 Hz, 1H, H-4), 2.21 (dd, *J* = 12.4, 12.1 Hz, 1H, H-6a), 2.32 (br d, *J* = 12.4 Hz, 1H, H-8b), 2.38 (dd, *J* = 12.4, 3.5 Hz, 1H, H-6b), 2.58 (dd, *J* = 10.4, 4.6 Hz, 1H, H-3), 2.63 (dd, *J* = 12.4, 10.4 Hz, 1H, H-9), 3.54 (qd, *J* = 7.1, 4.6 Hz, 1H, H-2), 3.67 (br s, 1H, H-12), 3.80 (s, 6H, OCH_3), 5.56 (d, *J* = 4.3 Hz, 1H, H-11), 6.37 (t, *J* = 2.0 Hz, 1H, H-16), 6.56 (d, *J* = 2.0 Hz, 2H, H-14, 18). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.2 (C-19), 20.8 (C-21), 22.4 (C-20), 24.9 (C-2), 35.6 (C-7), 38.5 (C-8), 38.8 (C-3), 43.6 (C-12), 46.4 (C-4), 49.9 (C-9), 50.7 (C-6), 55.4 (OCH_3), 98.2 (C-16), 108.7 (C-14, 18), 123.0 (C-1), 125.3 (C-11), 135.1 (C-10), 143.0 (C-13), 160.7 (C-15, 17), 211.4 (C-5). **HRMS** (ESI): calcd for $C_{23}H_{29}NO_3$ $[M+Na]^+$ 390.2040, found 390.2042. **$[\alpha]^D_{20}$** +323 (*c* 3.55, $CHCl_3$).

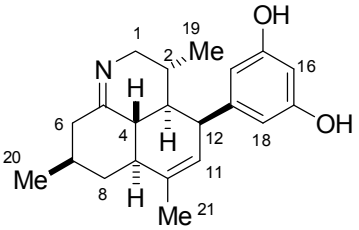


(2*R*)-2-[(3'*R*,4a'*S*,7'*R*,8'*R*,8a'*R*)-7'-(3,5-Dimethoxyphenyl)-3',5'-dimethyl-3',4',4a',7',8',8a'-hexahydro-2'*H*-spiro[1,3-dioxolane-2,1'-naphthalen]-8'-yl]propanenitrile (4-15): A mixture of the foregoing ketone (700 mg, 1.9 mmol), $(CH_2OH)_2$ (2.0 mL, 20 equiv) and CSA (200 mg, 0.9 mmol, 0.5 equiv) was refluxed in benzene (20 mL) with azeotropic removal of water for 10 h. After cooling, the mixture was washed with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to provide 734 mg (1.78 mmol, 94%) of acetal **4-15** as colorless crystals, **mp.** 56 °C. $\mathbf{R_f}$ 0.25 (petroleum ether/EtOAc, 8:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.3 Hz, 3H, H-20), 1.04 (d, *J* = 7.1 Hz, 3H, H-19), 1.06–1.14 (m, 2H, H-6a, 8a), 1.57 (dd, *J* = 10.8, 3.8 Hz, 1H, H-4), 1.70–1.80 (m, 1H, H-7), 1.82 (s, 3H, H-21), 1.90 (dd, *J* = 13.4, 2.8 Hz, 1H, H-6b), 2.01–2.10 (m, 2H, H-3, 8b), 2.44 (dd, *J* = 12.4, 10.8 Hz, 1H, H-9), 2.56 (br q, *J* = 7.1 Hz, 1H, H-2), 3.47 (br s, 1H, H-12), 3.80 (s, 6H, OCH_3), 3.85–3.94 (m, 1H, H-22), 3.98–4.05 (m, 3H, H-22), 5.91 (s, 1H, H-11), 6.35 (s, 1H, H-16), 6.49 (s, 2H, H-14, 18). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.5 (C-19), 19.1 (C-21), 22.0 (C-20), 26.8 (C-2), 30.0 (C-7), 36.9 (C-8), 40.7 (C-9), 43.1 (C-6), 44.4 (C-3), 44.9 (C-12), 48.2 (C-4), 55.3 (OCH_3), 64.3 (C-22), 64.5 (C-22), 98.0 (C-16), 106.9 (C-14, 18), 110.9 (C-5), 123.3 (C-1), 123.4 (C-11), 139.7 (C-10), 144.5 (C-13), 160.9 (C-15, 17). **HRMS** (ESI): calcd for $C_{25}H_{33}NO_4$ $[M+Na]^+$ 434.2302, found 434.2303. **$[\alpha]^D_{23}$** –28.3 (*c* 10.0, $CHCl_3$).



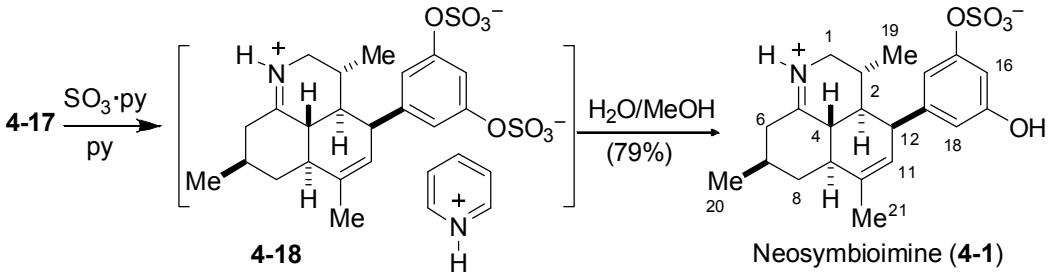
(3*R*,3a*R*,4*R*,6a*S*,8*R*,9b*R*)-4-(3,5-Dimethoxyphenyl)-3,6,8-trimethyl-2,3a,4,6a,7,8,9,9b-octahydro-3*H*-benzo[*de*]quinoline (4-16): $LiAlH_4$ (290 mg, 7.65 mmol, 5 equiv) was dissolved in dry Et_2O (60 mL) at room temperature, then the solution was concentrated under reduced pressure to around 6 mL. To this solution nitrile **4-15** (630 mg, 1.53 mmol) in Et_2O (6 mL) was added dropwise at 0 °C. After the mixture was stirred for 24 h at 23 °C, it was diluted with Et_2O (50 mL) and quenched by dropwise addition of Rochelle's salt solution (20 g in 60 mL of deionized water), then vigorously stirred for 24 h. After this time the organic phase was separated and the water phase extracted with Et_2O (3 × 20 mL). The combined organic layes were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated to yield 625 mg (98%) of the corresponding primary amine as a colorless semi-solid, which was used in the next step as such. To a solution of this amine in THF (15 mL) was added dropwise at 20 °C aqueous HCl (3M, 10 mL). The mixture was

heated to 50 °C for 2 h, then cooled to 20 °C and neutralized with saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc. The organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography using deactivated silica gel (to the slurry of SiO_2 and solvent, about 1% of Et_3N based on the volume of SiO_2 was added; the eluent itself did not contain Et_3N). **R_f** 0.25 (5% MeOH in $CHCl_3$). To remove Et_3N salts from the compound, the collected fractions were evaporated and dissolved in EtOAc (40 mL). This solution was washed with saturated solution of $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo, yield of **4-16** is 490 mg (1.386 mmol, 90%) from nitrile **4-15**, yellowish viscous oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.92 (ddd, *J* = 12.4, 12.1, 11.8 Hz, 1H, H-8a), 0.95 (d, *J* = 6.3 Hz, 3H, H-20), 0.97 (d, *J* = 5.8 Hz, 3H, H-19), 1.01–1.12 (m, 1H, H-2), 1.54 (ddd, *J* = 10.8, 10.1, 5.1 Hz, 1H, H-3), 1.62–1.72 (m, 1H, H-7), 1.70 (s, 3H, H-21), 1.75 (br dd, *J* = 13.1, 11.9 Hz, 1H, H-6a), 1.92 (dd, *J* = 12.4, 11.8 Hz, 1H, H-9), 1.98 (dd, *J* = 12.4, 10.8 Hz, 1H, H-4), 2.08 (br d, *J* = 12.1 Hz, 1H, H-8b), 2.29 (br d, *J* = 11.9 Hz, 1H, H-6b), 2.90 (br dd, *J* = 16.9, 10.6 Hz, 1H, H-1a), 3.52 (dd, *J* = 16.9, 4.3 Hz, 1H, H-1b), 3.54 (br s, 1H, H-12), 3.71 (s, 6H, OCH_3), 5.88 (d, *J* = 4.6 Hz, 1H, H-11), 6.27 (t, *J* = 2.0 Hz, 1H, H-16), 6.37 (d, *J* = 2.0 Hz, 2H, H-14, 18). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.9 (C-19), 21.0 (C-21), 22.4 (C-20), 27.6 (C-2), 32.9 (C-7), 37.8 (C-8), 39.7 (C-4), 43.0 (C-12), 44.6 (C-3), 45.4 (C-9), 45.9 (C-6), 55.2 (OCH_3), 57.1 (C-1), 97.6 (C-16), 109.0 (C-14, 18), 125.3 (C-11), 137.2 (C-10), 143.0 (C-13), 160.1 (C-15,17), 171.9 (C-5). **HRMS** (ESI): calcd for $C_{23}H_{31}NO_2$ $[M+H]^+$ 354.2428, found 354.2425. **$[\alpha]^D_{23}$** +258 (*c* 7, $CHCl_3$).



5-[(3*R*,3a*R*,4*R*,6a*S*,8*R*,9b*R*)-3,6,8-Trimethyl-2,3a,4,6a,7,8,9,9b-octahydro-3*H*-benzo[*de*]quinolin-4-yl]benzene-1,3-diol (4-17): To a stirred solution of imine **4-16** (176 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise a solution of BBr_3 (1M in CH_2Cl_2, 2.5 mL, 2.5 mmol, 5 equiv) at –80 °C under nitrogen. The mixture was warmed to 0 °C within 1 h, and stirred at this temperature for 1.5 h and finally treated with excess of saturated $NaHCO_3$ solution. This mixture was diluted with deionized water and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with saturated solutions of $NaHCO_3$ and NaCl, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was chromatographed on flash silica gel, deactivated with Et_3N using 10% MeOH in $CHCl_3$ as an eluent (**R_f** 0.25). To remove Et_3N salts from the isolated compound, the collected fractions obtained after evaporation were diluted with EtOAc and washed with saturated $NaHCO_3$ solutions and NaCl, dried over Na_2SO_4, filtered and evaporated to dryness, to give 137 mg (0.42 mmol, 84%) of the free base **4-17** as a yellowish powder, **mp.** 280 °C, decomp. **^{1}H NMR** (400 MHz, DMSO): δ = 0.90–1.00 (m, 2H, H-2, 8a), 0.92 (s, 3H, H-19), 0.98 (d, *J* = 6.1 Hz, 3H, H-20), 1.45 (ddd, *J* = 10.3, 9.3, 4.8 Hz, 1H, H-3), 1.60-1.75 (m, 2H, H-7, 6a), 1.71 (s, 3H, H-21), 1.85-2.01 (m, 2H, H-9, 4), 2.10 (br d, *J* = 12.1 Hz, 1H, H-8b), 2.21 (br d, *J* = 12.1 Hz, 1H, H-

6b), 2.80-2.90 (m, 1H, H-1a), 3.25-3.48 (m, 2H, H-12,1b), 5.35 (d, *J* = 4.3 Hz, 1H, H-11), 6.04 (s, 1H, H-16), 6.11 (s, 2H, H-14, 18), 9.13 (br s, 2H, OH). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.6 (C-19), 20.8 (C-21), 22.4 (C-20), 27.6 (C-2), 32.4 (C-7), 37.3 (C-8), 39.2 (C-4), 42.4 (C-12), 44.1 (C-3), 44.7 (C-9), 45.4 (C-6), 56.4 (C-1), 100.7 (C-16), 108.5 (C-14, 18), 125.6 (C-11), 136.1 (C-10), 142.3 (C-13), 157.7 (C-15, 17), 167.8 (C-5). **HRMS** (ESI) calcd for $C_{21}H_{27}NO_2$ $[M+H]^+$ 326.21146, found 326.21145. **$[\alpha]_D^{23}$** +282 (*c* 1.0, MeOH).



Neosymbioimine (4-1): The cyclic imine **4-17** (202 mg, 0.62 mmol) was dissolved in pyridine (10 mL). SO_3·Py (500 mg, 3 mmol, 5 equiv) was added under nitrogen. The mixture was stirred at 60 °C under nitrogen for 24 h and then treated with MeOH (10 mL). Volatiles were evaporated at room temperature under vacuum to dryness, and the residue was filtered through a flash silica gel pad (6 × 3 cm) using a mixture of $CHCl_3$/*n*PrOH/MeOH/H_2O, 5:5:2:1 as eluent in order to remove the excess of SO_3·Py. The filtered fractions mostly contain bis-sulfate **4-18** (**R_f** 0.3) along with neosymbioimine **4-1** (**R_f** 0.7). Bis-sulfat **4-18** is unstable and hydrolyses in solution itself. The filtrate fractions were evaporated and dissolved in MeOH (4 mL) and water (2 mL). This solution was kept at 36 °C for 18 h to achieve complete mono hydrolysis of the bis-sulfate. Then pyridine (0.1 mL) was added, and volatiles were evaporated in vacuo to dryness at room temperature. The residue was chromatographed on flash silica gel (10 × 3 cm) column using $CHCl_3$/MeOH, 6:1 as eluent. This way, some starting imine **4-17** (32 mg, 0.064 mmol, 10%) (pyridinium sulfate salt) was recovered as a yellowish solid (**R_f** 0.35), followed by neosymbioimine **4-1** (177 mg, 0.44 mmol, 70%) as a white powder (**R_f** 0.25, mp. 245 °C, decomp.). Based on the recovered starting material, the yield of neosymbioimine is 79% from **4-17**. **HRMS** (ESI): calcd for $C_{21}H_{27}NO_5S$ $[M-H]^-$ 404.15372, found 404.15365, Δ 0.16 ppm. **$[\alpha]^D_{23}$** +172 (*c* 0.1, MeOH).

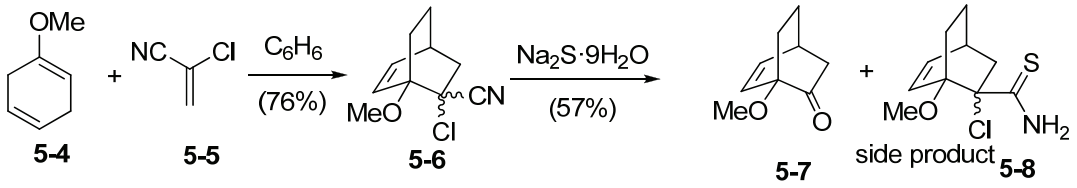
^{1}H and ^{13}C NMR data of natural and synthetic neosymbioimine in CD_3OD.[a]

Atom	^{1}H		$\Delta\delta^1$H, ppm	^{13}C		$\Delta\delta^{13}$C, ppm
	Natural, 800 MHz	Synthetic, 400 MHz		Natural, 150 MHz	Synthetic, 100 MHz	
1a	3.14 br dd (11.2, 15.8)	3.20 ddd (15.7, 11.4, 3.0)	**-0.06**	52.6	51.8	**0.8**
1b	3.55 dd (3.9, 15.8)	3.56 dd (15.7, 4.6)	**0.01**			
2	1.33 m	1.34 dqd (11.4, 5.9, 4.6)	**-0.01**	27.9	27.8	**0.1**
3	1.77 dt (4.8, 11.1)	1.80 ddd (11.4, 11.2, 5.0)	**-0.03**	43.6	43.2	**0.4**
4	2.62 br dd (11.1, 12.4)	2.65 br dd (12.4, 11.2)	**-0.03**	41.6	41.8	**0.2**

5				189.3	190.1	**-0.8**
6a	2.25 m	2.25 m	**-0.01**	42.8	42.3	**0.5**
6b	2.56 m	2.52 m	**0.04**			
7	1.91 m	1.94 m	**-0.03**	34.0	34.0	**0.0**
8a	1.28 q (12.4)	1.28 ddd (12.6, 12.4, 12.1)	**0.00**	37.5	37.4	**0.1**
8b	2.25 td (3.4, 12.4)	2.26 br d (12.6)	**-0.01**			
9	2.32 dt (3.4, 12.4)	2.39 br d (12.4, 11.9)	**-0.07**	46.1	45.9	**0.2**
10				137.6	137.6	**0.0**
11	5.52 br d (4.8)	5.52 br d (4.8)	**0.00**	126.4	126.4	**0.0**
12	3.70 t (4.8)	3.71 br dd (5.0, 4.8)	**-0.01**	43.3	43.2	**0.0**
13				142.3	142.3	**0.0**
14	6.58 t (1.9)	6.60 br s	**-0.02**	114.9	114.9	**0.0**
15				158.8	158.9	**-0.1**
16	6.60 t (1.9)	6.60 br s	**0.00**	108.5	108.5	**0.0**
17				154.4	154.4	**0.0**
18	6.79 t (1.9)	6.78 br s	**0.01**	115.7	115.6	**0.1**
19	1.15 d (5.9) 3H	1.16 d (6.2) 3H	**-0.01**	16.3	16.2	**0.1**
20	1.12 d (6.5) 3H	1.13 d (6.5) 3H	**-0.01**	22.1	22.1	**0.0**
21	1.83 br s 3H	1.84 br s 3H	**-0.01**	21.1	21.1	**0.0**

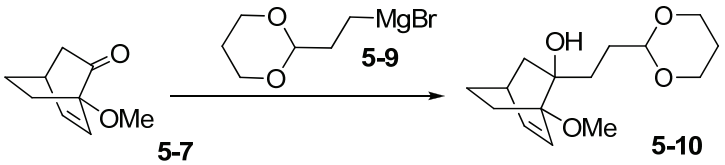
(a) Kita, M.; Ohishi, N.; Washida, K.; Kondo, M.; Koyama, T.; Yamada, K.; Uemura, D. *Bioorg. Med. Chem.* **2005**, *13*, 5253-5258.

5. The attempts toward the synthesis of platensimycin

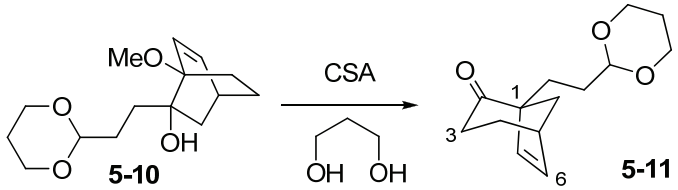


1-Methoxybicyclo[2.2.2]oct-5-en-2-one (5-7): A solution of 2,5-dihydroanisole (**5-4**) (25 g, 22.7 mmol) and 2-chloroacrylonitrile (**5-5**) (30 g, 34 mmol) was refluxed in benzene (200 mL) under inert atmosphere for 20 h. After that time the solvent was evaporated and the residue was distilled using a Kugelrohr apparatus (T = 180 °C, at 9 mbar).[191] Yield of bicyclic compound **5-6** is 34 g (0.172 mol, 76%).

A solution of 33.0 g (0.165 mol) of 6-chloro-6-cyano-1-methoxybicyclo[2.2.2]oct-2-ene **5-6** and 79.0 g (0.33 mol) of $Na_2S·9H_2O$ in 250 mL of ethanol was heated under reflux for 14 h. The solution was poured into H_2O (500 mL) and extracted three times with ether (150 mL). The combined extracts were washed with saturated aqueous NH_4C1 solution, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated, and distilled under reduced pressure to give 12.54 g (50% yield) of **5-7**, **bp.** 80 °C/1 mm.

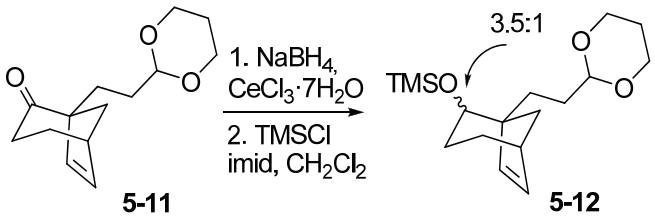


2-[2-(1,3-Dioxan-2-yl)ethyl]-1-methoxybicyclo[2.2.2]oct-5-en-2-ol (5-10): 2-(2-Bromoethyl)-1,3-dioxane (**5-9**) (21.8 mL, 31.2 g, 160 mmol) was added dropwise to a solution of activated (with 2 drops of dibromoethane) Mg (4.37 g, 180 mmol) in THF (120 mL) at 20-25 °C during 1 h, and further stirred at this temperature for 20 min. Then THF (60 mL) was added and the mixture was cooled to -20 °C. Neat ketone **5-7** (12.2 g, 80 mmol) was added at -20 °C for 30 min, and the mixture was stirred at -15…-20 °C for 30 min (TLC-monitoring). After completing of the reaction the mixture was treated with NH_4Cl (100 mL of satd. solution) and worked up by extraction with diethyl ether. The mixture of diastereomeric alcohols **5-10** was separated by flash chromatography ($\mathbf{R_f}$ 0.3, petroleum ether/EtOAc, 2:1) to yield 9.86 g (46 %) of *exo*-alcohol **5-10** as a colorless oil.

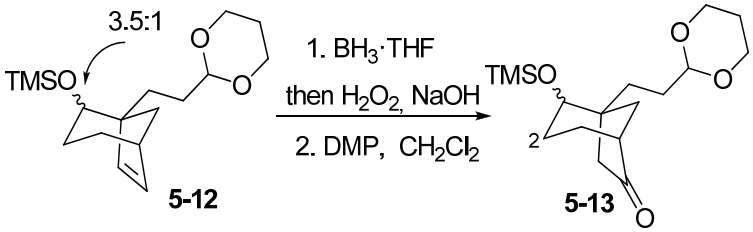


1-[2-(1,3-Dioxan-2-yl)ethyl]bicyclo[3.2.1]oct-6-en-2-one (5-11): A mixture of alcohol **5-10** (5.95 g, 22.2 mmol) and camphorsulphonic acid (5.7 g, 24.4 mmol, 1.1 equiv) in 1,3-propanediol (40 mL) was stirred at 75 °C for 4 h under inert atmosphere. After completing of the reaction (by TLC) the mixture was cooled to rt and diluted with water (200 mL). The

product was extracted with diethyl ether (3×150 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography ($\mathbf{R_f}$ 0.25, petroleum ether/EtOAc, 4:1) to yield 5.21 g (0.22 mol, 99 %) of ketone **5-11**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.26-1.32 (m, 1H, CH_2), 1.43-1.59 (m, 2H, CH_2), 1.43-1.59 (m, 4H, CH_2), 1.85-1.93 (m, 1H, CH_2), 1.97-2.09 (m, 1H, CH_2), 2.15-2.20 (m, 1H, CH_2), 2.21-2.28 (m, 1H, H-3), 2.58-2.67 (m, 1H, H-3), 2.82-2.88 (m, 1H, H-5), 3.67-3.76 (m, 2H, CH_2O), 4.02-4.08 (m, 2H, CH_2O), 4.50 (t, J = 5.1 Hz, 1H, CHO_2), 5.66 (d, J = 5.6 Hz, 1H, H-7), 6.10 (dd, J = 5.6, 2.8 Hz, 1H, H-6).

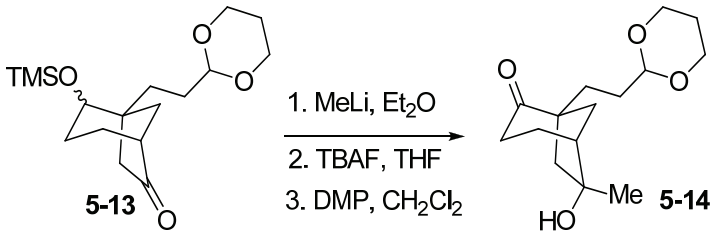


({1-[2-(1,3-Dioxan-2-yl)ethyl]bicyclo[3.2.1]oct-6-en-2-yl}oxy)(trimethyl)silane (5-12): To a solution of ketone **5-11** (1.27 g, 5.4 mmol) and $CeCl_3·7H_2O$ (2.012 g, 5.4 mmol) in MeOH (15 mL) $NaBH_4$ (205 mg, 5.4 mmol) was added at 0 °C. The mixture was stirred for 10 min (ice bath) and diluted with NH_4Cl (50 mL of satd. solution) and EtOAc (50 mL). After shaking, layers were separated and the water phase was extracted with EtOAc (2×30 mL). Combined extracts were dried with Na_2SO_4, filtered and concentrated. To a crude mixture of the alcohols in CH_2Cl_2 (20 mL), imidazole (1.36 g, 20 mmol) and TMSCl (1.26 mL, 10 mmol) were added sequentially at 0 °C. The resulting mixture was allowed to warm to rt and stirred for 15 min, then quenched with $NaHCO_3$ (30 mL) and extracted with petroleum ether (3×50 mL). The combined extracts were dried with Na_2SO_4, concentrated, and the residue was chromatographed ($\mathbf{R_f}$ 0.35, petroleum ether/EtOAc 15:1) to yield 1.6 g (5.16 mmol, 95%) of a 3.5:1 diastereomeric mixture of silyl ethers **5-12** as a colorless oil.

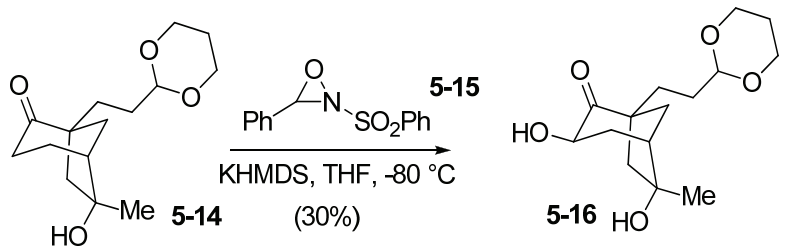


1-[2-(1,3-Dioxan-2-yl)ethyl]-2-[(trimethylsilyl)oxy]bicyclo[3.2.1]octan-6-one (5-13): To a stirred solution of a mixture of silyl ethers **5-12** (1.57 g, 5.06 mmol) in THF (15 mL) $BH_3·THF$ (10 mL of 1M THF solution, 10 mmol) was added at -80 °C. The resulting mixture was slowly allowed to warm to 0 °C within 2 h and stirred at 0 °C for 1 h. Then a solution of NaOH (3N, 7.5 mL) was added dropwise at 0 °C followed by dropwise addition of 30 % H_2O_2 (2.5 mL). The mixture was warmed to rt for 1 h and worked up by extraction with diethyl ether, drying and concentration. Crude alcohol (1.81 g) was dissolved in dichloromethane (25 mL) and DMP (16 mL of 15 % CH_2Cl_2 solution) was added at 0 °C. The resulting mixture was stirred at rt overnight and diluted with with $NaHCO_3$ (100 mL of satd. solution). Extractive workup with dichloromethane (3×50 mL), drying with Na_2SO_4 and concentration afforded after chromatography 1.38 g (0.42 mmol, 84%) of ketone **5-13** as a

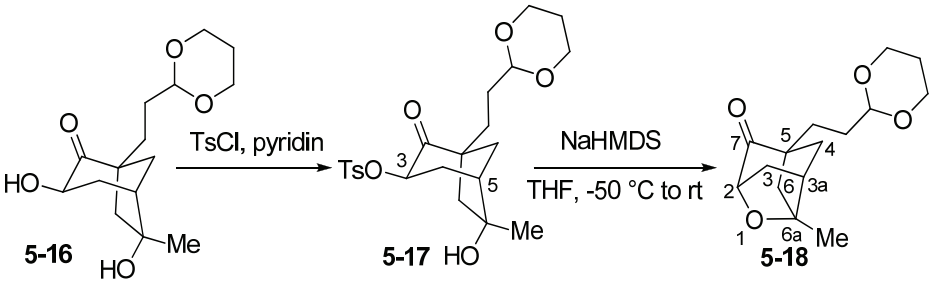
colorless oil (**R_f** 0.3, petroleum ether/EtOAc, 15:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.05-0.10 (m, 9H, $(CH_3)_3Si$), 1.20-2.40 (m, 15 H), 3.54-3.70 (m, 1H, H-2), 3.55-3.75 (m, 2H, CH_2O), 4.00-4.10 (m, 2H, CH_2O), 4.43-4.47 (m, 1H, CHO_2).



1-[2-(1,3-Dioxan-2-yl)ethyl]-6-hydroxy-6-methylbicyclo[3.2.1]octan-2-one (5-14): To a stirred solution of ketone **5-13** (1.35 g, 4.1 mmol) in diethyl ether (15 mL) MeLi (10 mL, 16 mmol of 1.6M diethyl ether solution) was added at -85 °C. The mixture was slowly warmed to rt. The reaction was worked up by quenching with NH_4Cl, extracting with diethyl ether, drying and concentrating. Crude ketone was dissolved in THF (10 mL) and treated with TBAF (10 mL of 1 M THF solution) at rt for 1 h. The resulting mixture was treated with water (40 mL) and extracted with diethyl ether (3×30 mL). The combined extracts were washed with saturated NaCl solution (20 mL), dried with Na_2SO_4 and concentrated. Crude diol was dissolved in dichloromethane and treated with DMP (15 mL of 15 % CH_2Cl_2 solution) at rt overnight. The reaction was worked up as in the previous synthesis of **5-13**, and the product was isolated by chromatography (**R_f** 0.2-0.3, petroleum ether/EtOAc 1:1) to yield 769 mg (2.87 mmol, 70%) of hydroxyketone **5-14**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.27-1.34 (m, 1H, CH_2), 1.43 (s, 3H, CH_3), 1.46-1.64 (m, 6H, CH_2), 1.72-2.10 (m, 6H, CH_2), 2.17-2.24 (m, 1H, H-5), 2.22-2.28 (m, 1H, H-3), 2.76-2.86 (m, 1H, H-3), 3.68-3.78 (m, 2H, CH_2O), 4.03-4.09 (m, 2H, CH_2O), 4.48 (t, J = 4.8 Hz, 1H, CHO_2).



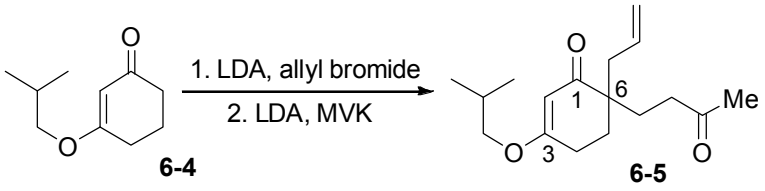
1-[2-(1,3-Dioxan-2-yl)ethyl]-3,6-dihydroxy-6-methylbicyclo[3.2.1]octan-2-one (5-16): To a stirred solution of ketoalcohol **5-14** (310 mg, 1.15 mmol) in THF (12 mL) NaHMDS (2.9 mmol, 2.5 equiv, 1 M THF solution) was added dropwise at -80 °C. The mixture was stirred at -80 °C for 3 h followed by dropwise addition of oxaziridine **5-15** (825 mg, 3 mmol) in THF (3 mL). The resulted mixture was stirred for 2 h at this temperature and quenched with NH_4Cl (20 mL of saturated solution) and extracted with Et_2O (3×30 mL). The combined extracts were washed with satd. NaCl solution (20 mL), dried with Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (**R_f** 0.15, petroleum ether/EtOAc 1:1) to yield 98 mg (0.345 mmol, 30%) of ketodiol **5-16** as a colorless oil.



5-[2-(1,3-Dioxan-2-yl)ethyl]-6a-methylhexahydro-2*H*-2,5-methanocyclopenta[*b*]furan-7-one (5-18): To a stirred solution of compound **5-16** (70 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) and pyridine (0.24 mL, 3 mmol) *p*-toluenesulphonyl chloride (190 mg, 1 mmol) was added. The mixture was stirred at rt overnight (TLC-monitoring). The obtained mixture was concentrated and the crude product was chromatographed ($\mathbf{R_f}$ 0.25, petroleum ether/EtOAc 1:1) to afford 89 mg (0.204, 85%) of tosylate **5-17**. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.17-1.21 (m, 1H, CH_2), 1.27-1.45 (m, 3H, CH_2), 1.44 (s, 3H, CH_3), 1.59-2.12 (m, 9H, CH_2), 2.41 (s, 1H, $ArCH_3$), 2.59-2.70 (m, 1H, H-5), 3.44-3.49 (m, 2H, CH_2O), 3.67-3.76 (m, 2H, CH_2O), 4.46 (t, *J* = 5.0 Hz, 1H, CHO_2), 5.52 (dd, *J* = 10.6, 8.6 Hz, H-3), 7.30 (d, J = 8.2 Hz, 2H, Ar), 7.84 (d, J = 8.2 Hz, 2H, Ar).

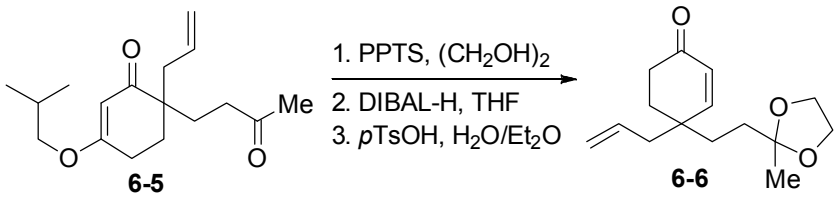
The obtained tosylate **5-17** (35 mg, 0.08 mmol) was dissolved in THF (1 mL), and NaHMDS (0.25 mmol, 0.25 mL of 1M THF solution) was added at -50 °C. The mixture was warmed to rt for 1 h, quenched with NH_4Cl (5 mL) and worked up by extraction with Et_2O drying with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography ($\mathbf{R_f}$ 0.25, petroleum ether/EtOAc 3:1) to afford 15 mg (0.56 mmol, 70 %) of tricyclic product **5-18** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.27-1.32 (m, 1H, CH_2), 1.50 (s, 3H, CH_3), 1.51-1.70 (m, 5H, CH_2), 1.75-1.83 (m, 2H, CH_2), 1.88-1.94 (m, 1H, CH_2), 1.99-2.24 (m, 3H, CH_2), 2.49-2.54 (dd, *J* = 6.1, 6.1 Hz, 1H, H-3a), 3.70-3.77 (m, 2H, CH_2O), 4.04-4.10 (m, 2H, CH_2O), 4.22 (d, *J* = 4.6 Hz, 1H, H-2), 4.51 (t, *J* = 4.8 Hz, 1H, CHO_2).

6. Formal total synthesis of platencin



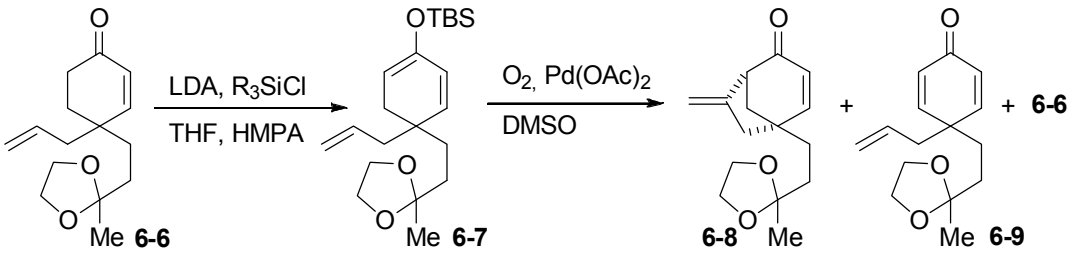
6-Allyl-3-isobutoxy-6-(3-oxobutyl)cyclohex-2-en-1-one (6-5). To a solution of *i*Pr_2NH (3.92 mL, 28.0 mmol) in anhydrous THF (30 mL) was added dropwise *n*BuLi (10 mL, 2.5 M solution in hexanes, 25 mmol, 1.1 equiv) at –20 °C. The mixture was stirred for 15 min and then cooled to –80 °C. At this point, a solution of 3-isobutoxycyclohex-2-en-1-one[229] **6-4** (3.78 g, 22.5 mmol) in THF (10 mL) was added dropwise and the mixture stirred for 1 h at this temperature before allyl bromide (2.57 mL, 30.0 mmol, 1.33 equiv) was injected. The resulting mixture was allowed to warm to room temperature overnight, and then treated with a half saturated solution of NH_4Cl (30 mL) and Et_2O (50 mL). After shaking in a separatory funnel and separation of the layers, the water phase was extracted with Et_2O (2 × 35 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:1 ($\mathbf{R_f}$ ~ 0.35) to provide 4.2 g (0.20 mmol, 90%) of 6-allyl-3-isobutoxycyclohex-2-en-1-one as colorless crystals (**m.p.** 36 °C).

The allylated compound, dissolved in THF (20 mL) was added to a solution of LDA [22 mmol, 1.1 equiv, prepared from *n*BuLi (8.8 mL, 2.5 M, 22.0 mmol) and *i*Pr_2NH (3.37 mL, 24 mmol) at –20 °C for 20 min] in THF (100 mL) at –80 °C with stirring. The mixture was stirred for 1 h, before methyl vinyl ketone (1.68 mL, 20.0 mmol, 1 equiv) was added dropwise. The resulting mixture was stirred for 0.5 h at –80 °C and then treated with water (50 mL). Extractive work-up like in the previous step followed by flash chromatography of the crude product ($\mathbf{R_f}$ ~ 0.3, petroleum ether/EtOAc, 4:1) afforded 4.68 g (16.8 mmol, 84%) of 6-allyl-3-isobutoxy-6-(3-oxobutyl)cyclohex-2-en-1-one (**6-5**) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.95 (d, *J* = 6.8 Hz, 6H, (CH_3)$_2$CH), 1.68–1.91 (m, 4H), 2.00 (qt, *J* = 6.8, 6.5 Hz, 1H, (CH_3)$_2$C*H*), 2.10 (s, 3H, $COCH_3$), 2.15–2.22 (m, 1H), 2.30–2.52 (m, 5H), 3.55 (d, *J* = 6.3 Hz, 2H, *i*PrCH_2O), 5.02–5.08 (m, 2H, CH_2CH=CH_2), 5.21 (s, 1H, 2-H), 5.63–5.74 (m, 1H, CH_2CH=CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 19.0 ((CH_3)$_2$CH), 25.6 (CH_2), 27.7((CH_3)$_2$CH), 28.0 (CH_2), 29.9 (CH_2), 30.0 ($COCH_3$), 38.3 (CH_2), 39.3 (CH_2), 45.5 (C-6), 74.8 (*i*PrCH_2O), 101.7 (C-2), 118.3 (CH_2CH=CH_2), 133.8 (CH_2CH=CH_2), 176.2 (C-3), 202.1 (C-1), 208.7 ($COCH_3$). **HRMS** (ESI): calcd for $C_{17}H_{26}O_3$ $[M+Na]^+$ 301.17742, found 301.17733.



4-Allyl-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclohex-2-en-1-one (6-6). Vinylogous ester **6-5** (2.5 g, 9.0 mmol), ethylene glycol (10.17 mL, 180.0 mmol, 20 equiv) and PPTS (900 mg, 3.6 mmol, 0.4 equiv) in benzene (90 mL) were refluxed with a Dean-Stark trap for 2-12 h (TLC-monitoring, $\mathbf{R_f}$ 0.25, petroleum ether/EtOAc, 4:1). The mixture was cooled and treated with saturated $NaHCO_3$ solution (60 mL). After separation of the layers, the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with saturated NaCl solution (40 mL), dried with anhydrous Na_2SO_4, filtered, and evaporated to dryness to obtain 6-allyl-3-isobutoxy-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclohex-2-en-1-one (quant.), which was sufficiently pure for the next step.

The obtained dioxolane was dissolved in anhydrous THF (80 mL), and DIBAL-H (13.5 mL, 1 M in hexane, 1.5 equiv) was added dropwise at –80 °C. The mixture was warmed to –60 °C and kept at this temperature for 1 h before it was poured into a vigorously stirred, ice-cold solution of Rochelle's salt (60 g) in water (150 mL). The mixture was stirred for 2 h, then Et_2O (50 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 35 mL) and the combined organic extracts were washed with saturated NaCl solution (40 mL), dried with anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in Et_2O (100 mL), water (0.9 mL) and *p*TsOH·H_2O (72 mg, 0.375 mmol, ~ 0.04 equiv) were added with stirring at 20 °C. The mixture was stirred for 20–30 minutes (TLC-monitoring), then saturated $NaHCO_3$ solution (30 mL) was added. After shaking in a separatory funnel and separation of the layers, the aqueous phase was reextracted with ether (50 mL). The combined organic extracts were washed with saturated NaCl solution (40 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography ($\mathbf{R_f}$ 0.3, petroleum ether/EtOAc, 3:1) of the residue afforded 1.80 g (7.2 mmol, 80% from **6-5**) of 4-allyl-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclohex-2-en-1-one (**6-6**) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.28 (s, 3H, CH_3), 1.50–1.58 (m, 4H, CH_2), 1.82–1.87 (m, 2H, CH_2), 2.20 (br d, *J* = 7.6 Hz, 2H, CH_2), 2.40–2.45 (m, 2H, CH_2), 3.86–3.96 (m, 4H, $(CH_2O)_2$), 5.05–5.13 (m, 2H, CH=CH_2), 5.70–5.80 (m, 1H, C*H*=CH_2), 5.91 (d, *J* = 10.4 Hz, 2H, 2-H), 6.65 (d, *J* = 10.4 Hz, 2H, 3-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.8 (CH_3), 30.9 (CH_2), 31.5 (CH_2), 33.4 (CH_2), 33.8 (CH_2), 38.0 (C-4), 42.4 (CH_2), 64.7 ((*C*$H_2O)_2$C), 109.7 ($(CH_2O)_2$*C*), 118.7 (CH=*C*H_2), 128.3 (C-2), 133.3 (*C*H=CH_2), 157.6 (C-3), 199.4 (C-1). **HRMS** (ESI): calcd for $C_{15}H_{22}O_3$ $[M+Na]^+$ 273.14612, found 273.14614.



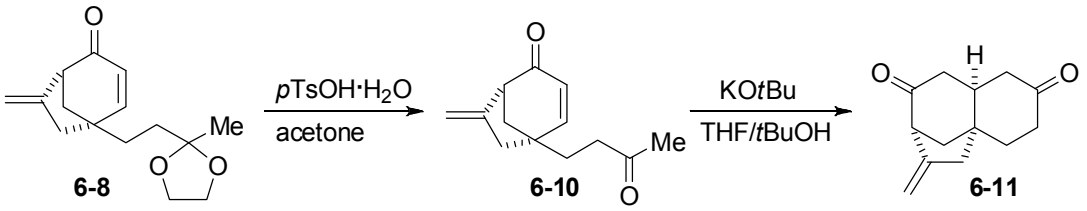
Conversion of enone xx into bicyclic ketone 5-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-7-methylenebicyclo[3.2.1]oct-3-en-2-one (6-8). a) Silyl dienol ether **7**. To a stirred solution of LDA [1.5 mmol, 1.5 equiv, prepared from *n*BuLi (0.6 mL, 2.5 M, 1.5 mmol) and *i*Pr_2NH (0.22 mL, 1.56 mmol) at –20 °C for 20 min] in THF (5 mL), a solution of enone **6-6**

(250 mg, 1.0 mmol) in THF (5 mL) was added dropwise at –80 °C. The mixture was stirred for 1 h at this temperature, then a solution of TBSCl (300 mg, 2.0 mmol, 2 equiv) or TMSCl (0.251 mL, 2.0 mmol) or TIPSCl (0.449 mL, 2.0 mmol) in THF (1.5 mL) was added dropwise followed by HMPA (1.5 mmol, 0.27 mL). The mixture was allowed to warm to room temperature within 1 h, and stirred for an additional 0.5 h at 20 °C. Then the mixture was diluted with water (20 mL) and petroleum ether (30 mL). After shaking in a separatory funnel, and separation of the layers, the aqueous layer was extracted with petroleum ether (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was passed through a short column of silica gel [petroleum ether/EtOAc, 20:1 ($\mathbf{R_f}$ ~ 0.25 – 0.35)] to provide the silyl dienol ethers **6-7** in about 90% yield as colorless oils.

The obtained silyl enol ether **6-7** (0.5 mmol) was dissolved in DMSO (see Table in the Results and Discussion) to give the indicated concentration, $Pd(OAc)_2$ was added, and the resulting solution was stirred under oxygen atmosphere (ballon with O_2) until TLC showed complete consumption of silyl enol ether **6-7** (24–48 h). The mixture was diluted with Et_2O (30 mL) and water (30 mL). After separation of the layers, the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was analyzed by ^{1}H NMR. The product **6-8** was also purified by flash chromatography ($\mathbf{R_f}$ ~ 0.25, petroleum ether/EtOAc, 4:1) to provide 85% yield, a colorless oil.

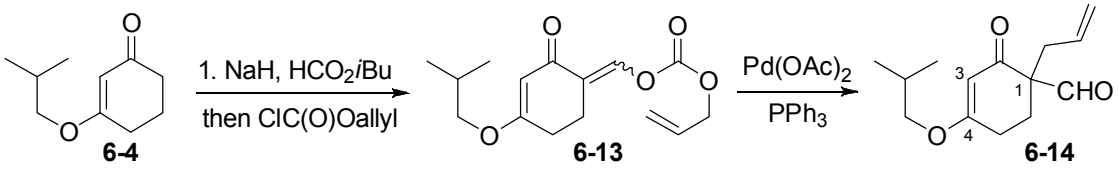
Compound **6-8**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.28 (s, 3H, CH_3), 1.51–1.78 (m, 5H), 2.03 (d, *J* = 10.4 Hz, 1H, CH_2), 2.25–2.37 (m, 2H), 3.39 (d, *J* = 4.8 Hz, 1H, 1-H), 3.86–3.95 (m, 4H, $(CH_2O)_2$), 4.98 (s, 1H, 7'a-H), 4.95 (s, 1H, 7'b-H), 5.76 (dd, *J* = 9.6, 1.5 Hz, 1H, 3-H), 6.95 (dd, *J* = 9.6, 2.0 Hz, 1H, 4-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.8 (CH_3), 31.4 (CH_2), 35.1 (CH_2), 42.6 (CH_2), 44.6 (CH_2), 46.2 (C-5), 58.6 (C-1), 64.6 (($CH_2O)_2C$), 109.5 (($CH_2O)_2C$), 112.0 (C-7'), 126.6 (C-3), 145.4 (C-7), 158.1 (C-4), 198.6 (C-2). **HRMS** (ESI): calcd for $C_{15}H_{20}O_3$ $[M+Na]^+$ 271.13047, found 271.13072.

Compound **6-9**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.22 (s, 3H, CH_3), 1.39–1.45 (m, 2H, CH_2), 1.71–1.79 (m, 2H, CH_2), 2.34 (d, *J* = 7.3 Hz, 2H, CH_2), 3.83–3.92 (m, 4H, $(CH_2O)_2$), 4.97–5.03 (m, 2H, CH=CH_2), 5.49-5.61 (m, 1H, C*H*=CH_2), 6.30 (d, *J* = 10.4 Hz, 2H, 2,6-H), 6.68 (d, *J* = 10.4 Hz, 2H, 3,5-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 23.9 (CH_3), 32.6 (CH_2), 33.8 (CH_2), 44.1 (CH_2), 45.3 (C-4), 64.4 (($CH_2O)_2C$), 109.4 (($CH_2O)_2C$), 118.8 (CH=CH_2), 130.4 (C-2,6), 132.1 (*C*H=CH_2), 154.1 (C-3,5), 186.4 (C-1). **HRMS** (ESI): calcd for $C_{15}H_{20}O_3$ $[M+Na]^+$ 271.13047, found 271.13036.



6-Methylenehexahydro-4a,7-methanobenzo[7]annulene-2,8(1*H*,5*H*)-dione (6-11). To a stirred solution of enone **6-8** (574 mg, 2.3 mmol) in acetone (27 mL) was added *p*TsOH·H_2O (0.44 g, 2.3 mmol, 1 equiv) at 20 °C, and the solution was stirred for 40 min (TLC-monitoring, $\mathbf{R_f}$ ~ 0.3, petroleum ether/EtOAc, 2:1) until complete conversion. The resulting solution was diluted with water (20 mL), saturated $NaHCO_3$ solution (20 mL) and Et_2O (50 mL). After shaking in a separatory funnel and separation of the layers, the aqueous layer was re-extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give pure ketonenone **6-10** in quantitative yield (470 mg), colorless oil.

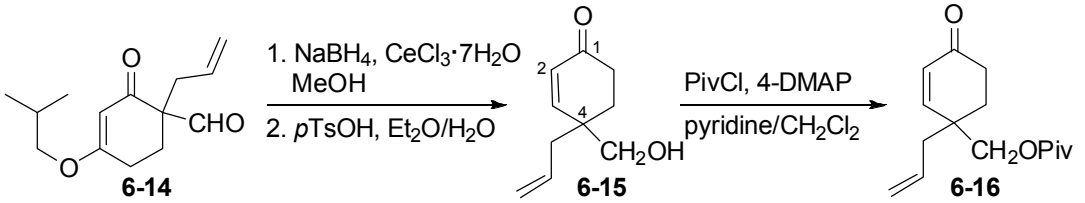
The obtained ketoenone **6-10** (2.3 mmol) was dissolved in THF (10 mL) and *t*BuOH (5 mL). A solution of KO*t*Bu (570 mg, ~ 5 mmol, ~ 2.2 equiv) in THF (3 mL) was added dropwise at –80 °C. The mixture was stirred for 2.5 h at –80 °C, then treated with half saturated NH_4Cl solution (20 mL), and diluted with Et_2O (40 mL). After shaking in a separatory funnel and separation of the layers, the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 3:1, $\mathbf{R_f}$ ~ 0.3) provided tricyclic diketone **6-11** (412 mg, 2.0 mmol, 88%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.76–1.89 (m, 3H), 1.94–2.02 (m, 1H), 2.21–2.41 (m, 6H), 2.52 (s, 1H, CH_2), 2.77–2,85 (m, 1H, CH_2), 3.30 (d, 1H, *J* = 5.1 Hz, 7-H), 4.95 (br s, 1H, 6'a-H), 4.95 (dd, *J* = 2.5, 2.0 Hz, 1H, 6'b-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 35.2 (CH_2), 36.4 (CH_2), 39.0 (CH_2), 41.1 (CH_2), 42.9 (C-4'), 43.4 (C-1'), 43.9 (CH_2), 45.0 (CH_2), 59.8 (C-7), 109.3 (C-6'), 147.0 (C-6), 208.0 (C=O), 209.3 (C=O). **HRMS** (ESI): calcd for $C_{13}H_{16}O_2$ $[M+Na]^+$ 227.10425, found 227.10407.



1-Allyl-4-isobutoxy-2-oxocyclohex-3-ene-1-carbaldehyde (6-14). NaH (2.25 g, 56.25 mmol, 1.5 equiv) and KH (100 mg) were washed with dry THF (40 mL) under inert atmosphere. Then dry THF (260 mL) was added followed by isobutyl formate (8.64 mL, 2 equiv) at 0 °C. This was followed by the dropwise addition of 3-isobutoxycyclohex-2-en-1-one[229] **6-4** [6.3 g, 37.5 mmol ($\mathbf{R_f}$ 0.25, petroleum ether/ethyl acetate, 4:1)] in THF (10–20 mL) was added with stirring. The mixture was stirred at 0 °C (bath temperature) for 24 h. When the reaction started, gas evolution was observed. If the reaction does not start (checked by TLC) a small amount of KH should be added. When the formylation reaction was finished (TLC, $\mathbf{R_f}$ 0.75, petroleum ether/ethyl acetate, 4:1), allylchloroformate (6.8 g, 1.5 equiv) was added, and the mixture stirred at 0 °C for 1 h. The reaction was quenched by addition of water (200 mL) and saturated NH_4Cl solution (50 mL), and the mixture extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, saturated NaCl solution, dried with Na_2SO_4, filtered. All volatiles of the filtrate were evaporated very well. The crude residue, which represents *E*/*Z* mixture of allyl enol

carbonates **6-13** ($\mathbf{R_f}$ 0.25 and 0.4, petroleum ether/ethyl acetate, 4:1), was dissolved in absolute THF (260 mL) under inert atmosphere. Ph_3P (262 mg, 1 mmol, 2.67 %) and $Pd(OAc)_2$ (112 mg, 0.5 mmol, 1.33 %) were added at 20 °C, followed by stirring of the mixture for 1 h. After TLC showed complete reaction, Me_2S (0.1 mL) was added (to deactivate the palladium catalyst) and the solvent was evaporated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1, $\mathbf{R_f}$ 0.3) to provide aldehyde **6-14** as a colorless oil (8.15 g, 34.5 mmol, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.95 (d, *J* = 6.8 Hz, 6H, CH_3), 1.89 (dddd, 1H, *J* = 14.4, 8.1, 5.6, 1.3 Hz, 1H, 6a-H), 2.00 (qt, *J* = 6.8, 6.5 Hz, 1H, C*H*$(CH_3)_2$), 2.26 (ddd, *J* = 13.9, 5.8, 5.5 Hz, 1H, 5a-H), 2.37 (ddd, *J* = 18.2, 5.8, 5.5 Hz, 1H, 5b-H), 2.59 (d, *J* = 7.3 Hz, 2H, CH_2CH=CH_2), 3.57 (dd, *J* = 6.5, 1.3 Hz, 2H, *i*PrCH_2O), 5.06–5.14 (m, 2H, CH_2CH=CH_2), 5.34 (s, 1H, 3-H), 5.53–5.65 (m, 1H, CH_2C*H*=CH_2), 9.55 (d, 1H, *J* = 1.3 Hz, CH=O). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 19.0 (CH_3), 24.3, 25.8, 27.7, 36.2 (*C*H_2CH=CH_2), 60.2 (C-1), 75.1 (($CH_3)_2$*C*H), 102.4 (C-3), 119.4 (CH_2CH=*C*H_2), 132.0 (CH_2*C*H=CH_2), 178.1 (C-4), 195.8 (C-2), 200.7 (CH=O). **HRMS** (ESI): calcd for $C_{14}H_{20}O_3$ $[M+Na]^+$ 259.13047, found 259.13054.

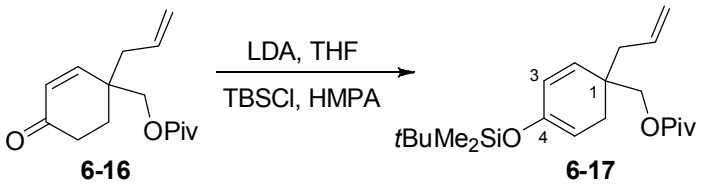
The enol carbonate **6-13** could be purified by flash chromatography (petroleum ether/EtOAc, 4:1, $\mathbf{R_f}$ 0.4). On the silica gel column, enol carbonate **6-13** isomerized to give mostly the *Z*-isomer in 89% yield as yellow crystals, **m.p.** 45–46 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 0.96 (d, *J* = 6.6 Hz, 6H, CH_3), 2.02 (m, 1H, C*H*$(CH_3)_2$), 2.45 (t, *J* = 6.8 Hz, 2H, 5-H), 2.75 (td, *J* = 6.8, 1.8 Hz, 2H, 6-H), 3.61 (d, *J* = 6.6 Hz, 2H, *i*PrCH_2O), 4.71 (d, *J* = 7.1 Hz, 2H, OCH_2CH=CH_2), 5.31 (br d, *J* = 10.4 Hz, 1H, CH_2CH=CH_2), 5.39 (br d, *J* = 17.2 Hz, 1H, CH_2CH=CH_2), 5.46 (s, 1H, 3-H), 5.88–5.99 (m, 1H, CH_2C*H*=CH_2), 7.94 (t, *J* = 1.8 Hz, 1H, 1'-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 19.0 (CH_3), 21.0 (C-5), 27.7 (*C*H$(CH_3)_2$), 27.8 (C-6), 69.5 (O***C***H_2CH=CH_2), 75.0 (*i*Pr*C*H_2O), 103.3 (C-3), 118.7 (C-1), 120.0 (CH_2CH=*C*H_2), 130.6 (CH_2*C*H=CH_2), 141.5 (O*C*(O)O), 151.9 (C-1'), 177.4 (C-4), 188.1 (C-2). **HRMS** (ESI): calcd for $C_{15}H_{20}O_5$ $[M+Na]^+$ 303.12029, found 303.12007.



(1-Allyl-4-oxocyclohex-2-en-1-yl)methyl pivalate (6-16). To a stirred solution of aldehyde **6-14** (8.14 g, 34.5 mmol) and $CeCl_3 \cdot 7H_2O$ (0.2 equiv, 2.6 g) in MeOH (135 mL), was added $NaBH_4$ (2.67 g, 70 mmol, 2 equiv) portionwise, keeping the inner temperature between 0–10° C, using an ice/NaCl bath for cooling. The addition time is around 30 min. After complete addition of $NaBH_4$, the mixture was stirred for 0.5 h and treated with saturated NH_4Cl solution (50 mL). It was then diluted with water and extracted with Et_2O (2 × 200 mL + 100 mL). To this ether solution water (4 mL) and *p*TsOH·H_2O (0.4 g) were added and the mixture was stirred for 0.5 h at room temperature. After complete hydrolysis, (checked by TLC), the reaction was quenched with saturated $NaHCO_3$ solution (20 mL). After separation of the layers, the organic phase was washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo very well. The obtained

hydroxyketone **6-15** ($\mathbf{R_f}$ 0.25, petroleum ether/ethyl acetate, 1:1) was pure enough for the next transformation**.** **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.83–2.00 (m, 2H, 5-H), 2.04 (t, *J* = 5.6 Hz, 1H, OH), 2.28(d, *J* = 7.6 Hz, 2H, C*H*$_2$CH=CH$_2$), 2.40–2.54 (m, 2H, 6-H), 3.51–3.63 (m, 2H, C*H*$_2$OH), 5.10–5.19 (m, 2H, CH$_2$CH=C*H*$_2$), 5.72–5.85 (m, 1H, CH$_2$C*H*=CH$_2$), 6.01 (d, *J* = 10.4 Hz, 1H, 2-H), 6.76 (d, *J* = 10.4 Hz, 1H, 3-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 28.4 (C-5), 33.8 (*C*H$_2$CH=CH$_2$), 39.9 (C-6), 41.0 (C-4), 67.3 (CH$_2$OH), 119.0 (CH$_2$CH=*C*H$_2$), 129.8 (C-2), 133.2 (CH$_2$*C*H=CH$_2$), 154.6 (C-3), 199.5 (C-1). **HRMS** (ESI): calcd for $C_{10}H_{14}O_2$ $[M+Na]^+$ 189.08860, found 189.08872.

Thus, the crude compound **6-15** was dissolved in dry CH_2Cl_2 (70 mL). Then pyridine (11.2 mL, 140 mmol, 4 equiv) and 4-dimethylaminopyridine (210 mg, 1.725 mmol, 0.05 equiv) were added followed by the addition of pivaloyl chloride (8.55 mL, 70.0 mmol, 2 equiv) at 0 °C. The mixture was stirred for 48 h at room temperature, then treated with water (50 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 layers were washed with saturated $NaHCO_3$ solution (25 mL), saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was flash chromatographed (petroleum ether/ethyl acetate, 8:1, $\mathbf{R_f}$ 0.3) to provide pure (1-allyl-4-oxocyclohex-2-en-1-yl)methyl pivalate **6-16** (8.1 g, 32.4 mmol, 94%) as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.18 (s, 9H, C(CH$_3$)$_3$), 1.89 (br t, *J* = 6.8 Hz, 2H, 5-H), 2.25 (d, *J* = 7.5 Hz, 2H, C*H*$_2$CH=CH$_2$), 2.44 (br t, *J* = 6.8 Hz, 2H, 6-H), 3.87 (d, *J* = 11.1 Hz, 1H, C*H*$_2$OPiv), 4.05 (d, *J* = 11.1 Hz, 1H, C*H*$_2$OPiv), 5.04–5.13 (m, 2H, CH$_2$CH=C*H*$_2$), 5.63–5.75 (m, 1H, CH$_2$C*H*=CH$_2$), 5.97 (d, *J* = 10.4 Hz, 1H, 2-H), 6.64 (d, *J* = 10.4 Hz, 1H, 3-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 27.2 (C(*C*H$_3$)$_3$), 29.0 (C-5), 33.7 (C-6), 39.0 (*C*(CH$_3$)$_3$), 39.5 (C-4), 40.2 (*C*H$_2$CH=CH$_2$), 67.7 (*C*H$_2$OPiv), 119.6 (CH$_2$CH=*C*H$_2$), 130.0 (C-2), 132.3 (CH$_2$*C*H=CH$_2$), 153.0 (C-3), 178.1 (*C*-C(CH$_3$)$_3$), 198.7 (C-1). **HRMS** (ESI): calcd for $C_{15}H_{22}O_3$ $[M+Na]^+$ 273.14614, found 273.14612.

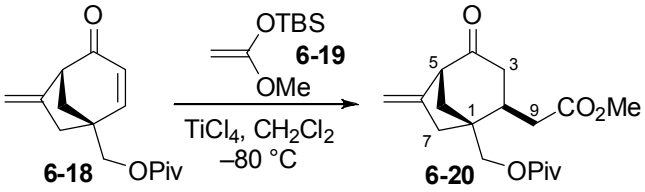


6-16 **6-17**

(1-Allyl-4-{[*tert*-butyl(dimethyl)silyl]oxy}cyclohexa-2,4-dien-1-yl)methyl pivalate (6-17). To a stirred solution of *i*Pr$_2$NH (6.79 mL, 48 mmol) in anhydrous THF (80 mL), *n*BuLi (18 mL, 2.5 M in hexane, 45 mmol) was added dropwise at –20 °C. After stirring for 20 min at this temperature, the LDA solution was cooled to a temperature between –85 and –90 °C, before (1-allyl-4-oxocyclohex-2-en-1-yl)methyl pivalate (**6-16**) (7.25 g, 29 mmol) in THF (35 mL) was added during 0.5 h at a temperature between –80 and –90 °C. The mixture was stirred at –80 °C for 1 h, then TBSCl (8.7 g, 58 mmol, 2 equiv) in THF (20 mL) was added dropwise followed by HMPA (5.25 mL, 30 mmol, 1.03 equiv). The mixture was allowed to warm to room temperature overnight, then diluted with water and NH_4Cl solution, and finally extracted with petroleum ether (3 × 150 mL). The organic extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was flash chromatographed (petroleum ether/ethyl acetate, 75:1 to 60:1, $\mathbf{R_f}$ 0.3 at 60:1) to furnish silyl dienol ether **6-17** in 88% yield (9.3 g, 25.52 mmol) as a colorless oil. **^{1}H**

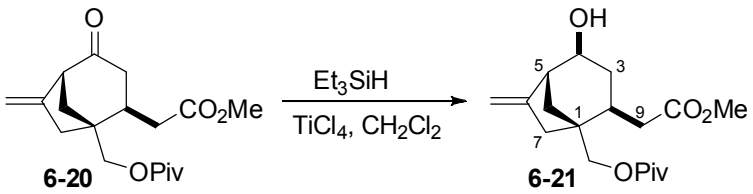
NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.12 (s, 6H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.20 (s, 9H, $O{=}CC(CH_3)_3$), 2.12–2.25 (m, 4H, 6-H, $CH_2CH{=}CH_2$), 3.85 (d, *J* = 10.9 Hz, 1H, CH_2OPiv), 3.93 (d, *J* = 10.9 Hz, 1H, CH_2OPiv), 4.77 (ddd, *J* = 6.3, 4.6, 2.0 Hz, 1H, 5-H), 4.99–5.08 (m, 2H, $CH_2CH{=}CH_2$), 5.54 (d, *J* = 10.1 Hz, 1H, 2-H), 5.69–5.80 (m, 1H, $CH_2CH{=}CH_2$), 5.72 (dd, *J* = 10.1, 2.0 Hz, 1H, 3-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = –4.5 ($SiCH_3$), 18.0 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 27.2 ($C(CH_3)_3$), 29.7 (C-6), 38.0 (C-1), 39.0 ($CC(CH_3)_3$), 39.7 ($CH_2CH{=}CH_2$), 67.5 (CH_2OPiv), 100.9 (C-5), 118.1 ($CH_2CH{=}CH_2$), 126.9 (C-3), 132.6 (C-2), 134.0 ($CH_2CH{=}CH_2$), 147.4 (C-4), 178.3 ($CC(CH_3)_3$). **HRMS** (ESI): calcd for $C_{21}H_{36}O_3Si$ $[M+Na]^+$ 387.23259, found 387.23283.

(6-Methylene-4-oxobicyclo[3.2.1]oct-2-en-1-yl)methyl pivalate (6-18). The silyl dienol ether **6-17** was dissolved in DMSO (550 mL). Oxygen was bubbled through the solution for 5 min, then the flask was connected to a balloon with O_2 and heated to 45 °C. To this mixture a stirred solution of $Pd(OAc)_2$ (336 mg, 1.5 mmol, 0.058 equiv) in DMSO (10 mL) was slowly injected within 4 h via syringe pump. Then, the resulting mixture was stirred under an oxygen atmosphere at 45 – 50 °C for 24–30 h until complete conversion was observed by TLC. The mixture was cooled, diluted with Et_2O (350 mL) and poured onto ice (1 L). The ether layer was separated using a 2 L separating funnel. The aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was flash chromatographed (petroleum ether/ethyl acetate, 8:1, $\mathbf{R_f}$ 0.3) to yield cyclohexenone **6-18** as a colorless oil. Yield: 85% (5.4 g, 21.7 mmol) or 75% for two steps. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.20 (s, 9H, $O{=}CC(CH_3)_3$), 1.85 (ddd, *J* = 11.4, 5.1, 2.0 Hz, 1H, 8a-H), 2.13 (ddd, *J* = 11.4, 2.1 Hz, 1H, 8b-H), 2.37 (br d, *J* = 15.9 Hz, 1H, 7a-H), 2.49 (dt, *J* = 15.9, 2.5 Hz, 1H, 7b-H), 3.49 (br d, *J* = 5.1 Hz, 1H, 5-H), 4.15 (d, *J* = 11.1 Hz, 1H, CH_2OPiv), 4.26 (d, *J* = 11.1 Hz, 1H, CH_2OPiv), 5.08 (br s, 1H, $C{=}CH_2$), 5.29 (br s, 1H, $C{=}CH_2$), 5.86 (dd, *J* = 9.7, 1.5 Hz, 1H, 3-H), 7.04 (dd, *J* = 9.7, 2.0 Hz, 1H, 2-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 27.2 ($C(CH_3)_3$), 39.0 ($CC(CH_3)_3$), 39.4 (C-7), 42.7 (C-8), 47.0 (C-1), 58.2 (C-5), 67.2 (CH_2OPiv), 113.0 ($C{=}CH_2$), 127.2 (C-3), 144.1 (C-6), 154.6 (C-2), 178.2 (C=O ester), 198.0 (C-4). **HRMS** (ESI): calcd for $C_{15}H_{20}O_3$ $[M+Na]^+$ 271.13047, found 271.13044.

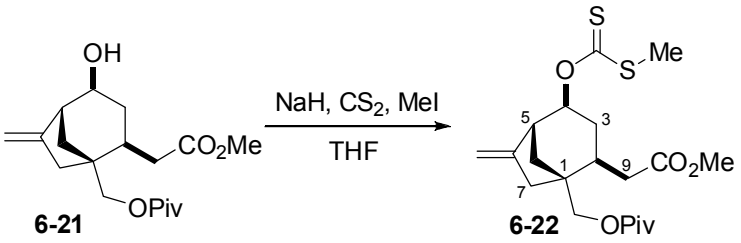


[2-(2-Methoxy-2-oxoethyl)-6-methylene-4-oxobicyclo[3.2.1]oct-1-yl]methyl pivalate (6-20). To a stirred solution of (6-methylene-4-oxobicyclo[3.2.1]oct-2-en-1-yl)methyl pivalate **6-6-18** (4.46 g, 18 mmol) and silyl ketene acetal[230] **6-19** (5.9 mL, 27 mmol, 1.5 equiv,

Aldrich) in anhydrous CH_2Cl_2 (180 mL) was added $TiCl_4$ (2.37 mL, 21.6 mmol, 1.2 equiv) dropwise at a temperature between –85 and –90 °C. The mixture was stirred at –80 °C overnight, then treated with water (150 mL) and adjusted with citric acid to pH ~ 3–4. Then, the CH_2Cl_2 layer was separated and the water phase extracted with CH_2Cl_2 (100 mL). The combined CH_2Cl_2 extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was flash chromatographed (petroleum ether/ethyl acetate, 6:1 to 4:1, $\mathbf{R_f}$ 0.4 at 4:1) to deliver 5.1 g (15.84 mmol, 88%) of ketoester **6-20** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.21 (s, 9H, O=CC(CH_3)$_3$), 1.75 (ddd, *J* = 12.4, 4.8, 1.8 Hz, 1H, 8a-H), 1.81 (br d, *J* = 12.4 Hz, 1H, 8b-H), 2.05 (d, *J* = 15.9 Hz, 1H, 9a-H), 2.18 (dd, *J* = 15.9, 10.6 Hz, 1H, 7a-H), 2.47 (dd, *J* = 15.9, 2.2 Hz, 1H, 7b-H), 2.59–2.67 (m, 2H, 3-H), 2.67–2.72 (m, 1H, 2-H), 2.77 (dd, *J* = 15.9, 7.8 Hz, 1H, 9b-H), 3.24 (d, *J* = 4.8 Hz, 1H, 5-H), 3.65 (s, 3H, CO_2CH_3), 3.95 (d, *J* = 11.4 Hz, 1H, CH_2OPiv), 4.21 (d, *J* = 11.4 Hz, 1H, CH_2OPiv), 4.98 (s, 1H, C=CH_2), 5.05 (s, 1H, C=CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 27.2 (C(CH_3)$_3$), 35.2 (C-7), 35.3 (C-8), 38.2 (C-2), 39.0 (CC(CH_3)$_3$), 40.3 (C-9), 42.0 (C-3), 45.7 (C-1), 51.9 (CO_2CH_3), 59.4 (C-5), 67.7 (CH$_2$OPiv), 109.3 (C=CH$_2$), 147.0 (C-6), 172.4 (CO_2CH_3), 178.1(*t*BuCO_2CH$_2$), 208.4 (C-4). **HRMS** (ESI): calcd for $C_{18}H_{26}O_5$ $[M+Na]^+$ 345.16725, found 345.16729.

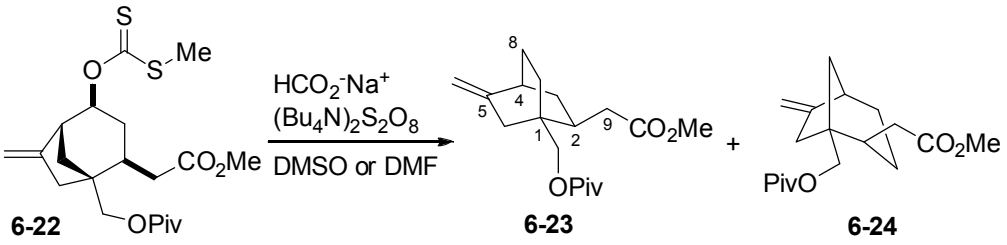


{2-(2-Methoxy-2-oxoethyl)-6-methylene-4-(hydroxy)bicyclo[3.2.1]oct-1-yl}methyl pivalate (6-21). To a stirred solution of ketoester **6-20** (425 mg, 1.32 mmol) and triethylsilane (0.84 mL, 5.28 mmol, 4 equiv) in anhydrous CH_2Cl_2 (20 mL) was added $TiCl_4$ (1.2 equiv, 1.58 mmol, 0.175 mL) at –40 °C. After 15 min of stirring at this temperature, TLC showed complete reaction. Now, the reaction mixture was treated with $NaHCO_3$ solution before the CH_2Cl_2 layer was separated. The aqueous layer was reextracted with CH_2Cl_2 and the combined CH_2Cl_2 extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was flash chromatographed (petroleum ether/ethyl acetate, 2:1, $\mathbf{R_f}$ 0.35) to provide 380 mg (1.17 mmol, 89%) of hydroxy ester **6-21** as a single isomer and a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.12–1.18 (m, 1H, 3a-H), 1.18 (s, 9H, C(CH_3)$_3$), 1.45 (br d, *J* = 15.7 Hz, 1H, 8a-H), 1.81–1.89 (m, 3b-H), 1.97 (s, OH), 2.15–2.22 (m, 1H, 8b-H), 2.03 (dd, *J* = 11.9, 1.8 Hz, 1H, 3b-H), 2.15–2.23 (m, 1H, 2-H), 2.28–2.44 (m, 2H, 9-H), 2.48 (dd, 1H, *J* = 14.7, 3.5 Hz, 7a-H), 2.71 (br dd, 1H, *J* = 4.8, 4.6 Hz, 5-H), 2.78 (dd, 1H, *J* =14.7, 11.1 Hz, 7b-H), 3.64 (s, 3H, CO_2CH_3), 3.81 (d, *J* = 11.4 Hz, 1H, 1'a-H), 3.75–3.85 (m, 1H, 4-H), 4.14 (d, *J* = 11.4 Hz, 1H, 1'b-H), 4.82 (s, 1H, 6'a-H), 4.88 (s, 1H, 6'b-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 27.2 (C(CH_3)$_3$), 28.5 (C-3), 30.3 (C-8), 35.8 (C-2), 35.9 (C-9), 38.9 (C(CH_3)$_3$), 41.9 (C-7), 45.8 (C-1), 49.6 (C-5), 51.6 (CO_2CH_3), 69.0 (C-1'), 71.8 (C-4), 106.2 (C-6'), 151.0 (C-6), 174.3 (C-10), 178.4 ((*t*BuCO_2CH$_2$). **HRMS** (ESI): calcd for $C_{18}H_{28}O_5$ $[M+Na]^+$ 347.18290, found 347.18286.



6-21 **6-22**

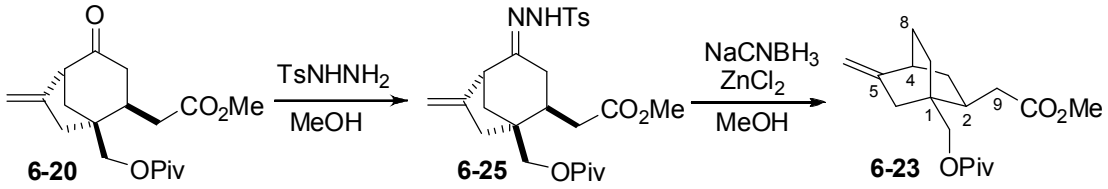
(2-(2-Methoxy-2-oxoethyl)-6-methylene-4-{[(methylthio)carbonothioyl]oxy}-bicyclo[3.2.1]oct-1-yl)methyl pivalate (6-22). To a stirred solution of alcohol **6-21** (210 mg, 0.65 mmol) in anhydrous THF (5 mL) was added NaH (80 mg, 60% in mineral oil, 2 mmol, 3 equiv) at 0 °C. After 10 min, CS_2 (0.125 mL, 2.0 mmol, 3 equiv) was added. The mixture was stirred for 30 min before MeI (0.126 mL, 2.0 mmol, 3 equiv) was added. The stirred mixture was allowed to warm to room temperature within 1 h (TLC monitoring) and treated with half-saturated NH_4Cl solution (15 mL). The mixture was extracted with petroleum ether (2 × 35 mL). The combined organic extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was flash chromatographed (petroleum ether/ethyl acetate, 20:1, $\mathbf{R_f}$ 0.3) to give 225 mg (0.54 mmol, 83%) of xanthogenate **6-22** as a yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.20 (s, 9H, $C(CH_3)_3$), 1.28 (dd, *J* = 12.1, 4.8 Hz, 1H, 3a-H), 1.76 (br d, *J* = 16.2 Hz, 1H, 8a-H), 1.87 (br d, *J* = 12.1 Hz, 1H, 8b-H), 2.00–2.09 (m, 3b-H), 2.30–2.39 (m, 1H, 2-H), 2.40–2.50 (m, 2H, 9-H), 2.52–2.57 (m, 2H, 7-H), 2.54 (s, 3H, SCH_3), 3.11 (br dd, 1H, *J* = 4.8, 4.6 Hz, 5-H), 3.63 (s, 3H, $CO_2C\mathit{H}_3$), 3.87 (d, *J* = 11.4 Hz, 1H, 1'a-H), 4.15 (d, *J* = 11.4 Hz, 1H, 1'b-H), 4.93 (s, 1H, 6'a-H), 5.03 (s, 1H, 6'b-H), 5.55 (br s, 1H, 4-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 18.9 (SCH_3), 27.2 ($C(\mathit{C}H_3)_3$), 27.7 (C-8), 29.7 (C-3), 35.5 (C-2), 35.5 (C-9), 39.0 ($\mathit{C}(CH_3)_3$), 41.8 (C-7), 45.5 (C-1), 45.9 (C-5), 51.6 ($CO_2\mathit{C}H_3$), 68.6 (C-1'), 82.8 (C-4), 108.2 (C-6'), 149.0 (C-6), 173.4 (C-10), 178.3 (*t*Bu$\mathit{C}O_2CH_2$), 214.7 (C=S). **HRMS** (ESI): calcd for $C_{20}H_{30}O_5S_2$ $[M+Na]^+$ 437.14269, found 437.14288.



6-22 **6-23** **6-24**

[2-(2-Methoxy-2-oxoethyl)-5-methylenebicyclo[2.2.2]oct-1-yl]methyl pivalate (23) and [4-hydroxy-2-(2-methoxy-2-oxoethyl)-6-methylenebicyclo[3.2.1]oct-1-yl]methyl pivalate (6-24). To a stirred mixture of xanthogenate **6-22** (320 mg, 0.77 mmol), sodium formate (0.42 g, 6.16 mmol, 8 equiv) and sodium carbonate (408 mg, 3.81 mmol, 5 equiv) in DMSO (11 mL) a first batch (1.3 mL) of $(Bu_4N)_2S_2O_8$ (771 mg, 2.3 mmol, 3 equiv), dissolved in DMSO (4 mL) was injected at 45 °C. The remaining amount (2.7 mL) of the $(Bu_4N)_2S_2O_8$ solution was injected slowly (during 6 h) to the stirred mixture under inert atmosphere at 45 °C. The resulting mixture was stirred at 45 °C overnight, then cooled and diluted with ether and water. Usual extractive workup followed by flash chromatography (petroleum ether/ethyl acetate, 15:1, R_f 0.3) afforded 90 mg (0.29 mmol, 38%) of the desired product from the

deoxygenative rearrangement, namely [2-(2-methoxy-2-oxoethyl)-5-methylenebicyclo[2.2.2]oct-1-yl]methyl pivalate (**6-23**), which is 82% pure by NMR. It is contaminated with the [3.2.1] skeletal isomer **6-24**, which could not be separated. In addition, the product of hydrolysis of the xanthate ester, [4-hydroxy-2-(2-methoxy-2-oxoethyl)-6-methylenebicyclo[3.2.1]oct-1-yl]methyl pivalate (40 mg, 0.12 mmol) was recovered. Thus, the yield based on recovered starting material (brsm) was adjusted to be 47%. Running this reaction in DMF, as described in the original paper,[220] afforded only 26% of product **6-23**. Attempts to generate this product under standard conditions, as described in the Nicolaou paper,[204a] (AIBN, Bu_3SnH) were unsuccessful with no conversion of starting xanthate ester.



[2-(2-Methoxy-2-oxoethyl)-5-methylenebicyclo[2.2.2]oct-1-yl]methyl pivalate (6-23).

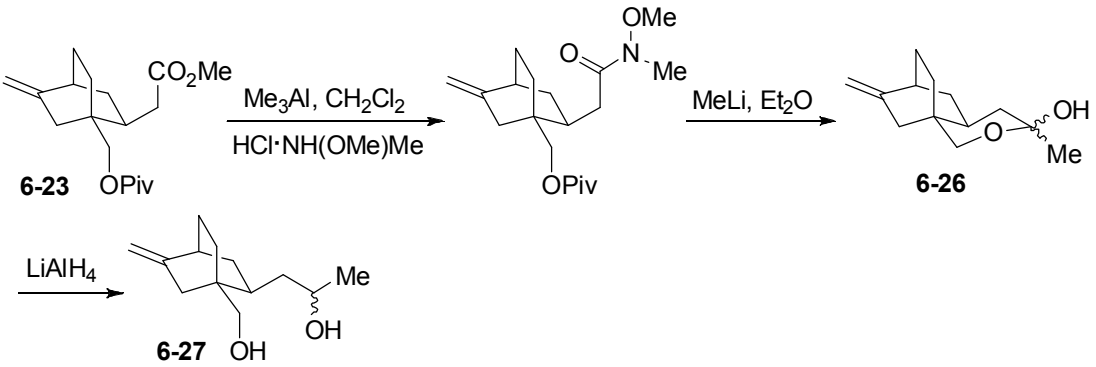
Two-step procedure. A solution of ketoester **6-20** (240 mg, 0.745 mmol) and tosyl hydrazone (186 mg, 1.0 mmol, 1.34 equiv) in MeOH (10 mL) was refluxed under inert atmosphere for 5 h. Then the solvent was evaporated and the residue subjected to flash chromatography (petroleum ether/ethyl acetate, 2:1, $\mathbf{R_f}$ 0.25) to afford 359 mg (0.73 mmol, 98 %) of hydrazone **6-25**. **HRMS** (ESI): calcd for $C_{25}H_{34}N_2O_6S$ $[M+Na]^+$ 513.20298, found 513.20284.

Obtained hydrazone **6-25** (300 mg, 0.61 mmol), $ZnCl_2$ (136 mg, 1.0 mmol, 1.64 equiv) and $NaCNBH_3$ (100 mg, 1.56 mmol, 2.56 equiv) in MeOH (10 mL) were heated to 60 °C under inert atmosphere for 3 h. The reaction vessel was cooled to room temperature and treated with 0.5 M NaOH solution (10 mL) and saturated NaCl solution (10 mL). The mixture was extracted with petroleum ether (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was flash chromatographed (petroleum ether/ethyl acetate, 15:1, $\mathbf{R_f}$ 0.3) to provide 110 mg (0.37 mmol, 60%) of [2-(2-methoxy-2-oxoethyl)-5-methylenebicyclo[2.2.2]oct-1-yl]methyl pivalate (**6-23**), which is 92% pure according to ^{1}H NMR.

One-pot procedure. Ketone **6-20** (0.84 g, 2.6 mmol) and $TsNHNH_2$ (0.632 g, 3.4 mmol, 1.3 equiv) in MeOH (40 mL) were heated to 60 °C for 5 h. After being cooled to room temperature to the mixture were added $ZnCl_2$ (0.565 g, 4.16 mmol, 1.6 equiv) and $NaCNBH_3$ (400 mg, 6.24 mmol, 2.4 equiv). The mixture was heated to 60 °C for 3 h under inert atmosphere. Isolation of the product was done as descibed before to furnish 430 mg (1.4 mmol, 54%) of the desired rearranged and deoxygenated product **6-23**.

^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.18–125 (m, 1H, 8a-H), 1.19 (s, 9H, $C(CH_3)_3$), 1.20–1.27 (m, 1H, 3a-H), 1.43–1.52 (m, 1H, 3b-H), 1.58–1.65 (m, 2H, 7ab-H), 1.88–1.96 (m, 1H, 8b-H), 2.13–2.24 (m, 4H, 2,4,6a,9a-H), 2.26–2.35 (m, 1H, 9a-H), 2.36–2.46 (m, 1H, 6b-H), 3.54 (s, 3H, CO_2CH_3), 3.68 (d, J = 11.4 Hz, 1H, 1'a-H), 3.81 (d, J = 11.4 Hz, 1H, 1'b-H),

4.62 (dd, *J* = 1.8, 2.0 Hz, 1H, 5'a-H), 4.75 (dd, *J* = 2.0, 2.0 Hz, 1H, 5'b-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 22.7 (C-3), 25.9 (C-7), 27.2 (C($\underline{C}H_3)_3$), 33.7 (C-2), 33.9 (C-8), 35.7 (C-4), 36.1 (C-1), 36.8 (C-6), 39.0(*C*($CH_3)_3$), 39.2 (C-9), 51.5 (CO_2CH_3), 68.7 (C-1'), 105.8 (C-5'), 149.9 (C-5), 173.4 (C-10), 178.3 (*t*Bu*C*O_2CH_2). **HRMS** (ESI): calcd for $C_{18}H_{28}O_4$ $[M+Na]^+$ 331.18798, found 331.18777.

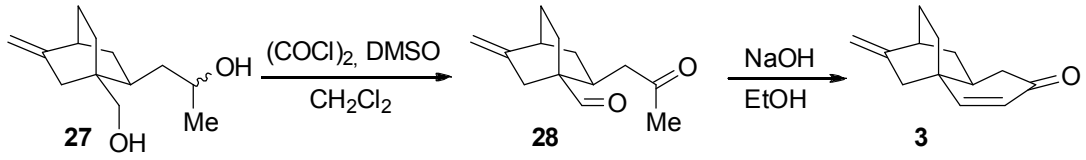


1-[1-(Hydroxymethyl)-5-methylenebicyclo[2.2.2]oct-2-yl]propan-2-ol (6-27). To a stirred mixture of diester **6-23** (616 mg, 2.0 mmol) and HCl·NH(OMe)Me (1.2 g, 12 mmol, 6 equiv) in CH_2Cl_2 (15 mL) a toluene solution of Me_3Al (5 mL, 2 M, 10 mmol, 5 equiv) was injected within 1 h (via syringe pump) at –10 °C. The resulting solution was stirred at 0 °C overnight. The reaction was quenched by slow injection of water (1 mL), and the mixture was poured into a solution of Rochelle's salt (50 g in 120 mL of water). This mixture was vigorously stirred for 2 h and then extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and evaporated to dryness to give the crude Weinreb amide.

To a solution of the Weinreb amide ($\mathbf{R_f}$ 0.3, petroleum ether/ethyl acetate, 4:1) in Et_2O (12 mL) was added slowly MeLi (7.5 mL, 1.6 M solution in Et_2O, 12 mmol, 6 equiv) at –80 °C. Then the mixture was warmed to –30 °C overnight, and carefully treated with water (5 mL). The mixture was diluted with half-saturated NH_4Cl solution (25 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1, $\mathbf{R_f}$ 0.3) to afford 397 mg (1.92 mmol, 96%) of hemiketal **6-26** as colorless crystals (**m.p.** 115 °C, lit.[204a] 115-117 °C). **HRMS** (ESI): calcd for $C_{14}H_{22}O_2Na$ $[M+Na+MeOH-H_2O]^+$ 245.15120, found 245.15122.

The obtained hemiketal **6-26** (397 mg, 1.92 mmol) was dissolved in anhydrous Et_2O (30 mL) and $LiAlH_4$ (73 mg, 1.92 mmol, 1 equiv) was added at –80 °C. The resulting mixture was stirred at 0 °C for 2–3 h and the reaction quenched with a few drops of water. The mixture was poured into a solution of Rochelle's salt (30 g) in water (100 mL) and vigorously stirred for 2 h before being extracted with Et_2O (3 × 50 mL). The ether layers were washed with saturated NaCl solution, dried with Na_2SO_4, filtered, and evaporated. Crude diol **6-27** was purified by flash chromatography ($\mathbf{R_f}$ 0.2, petroleum ether/EtOAc, 1:1) to separate the undesired [3.2.1]-isomer, which is less polar ($\mathbf{R_f}$ 0.25, petroleum ether/EtOAc, 1:1) to provide pure **6-27** (354 mg, 1.7 mmol, 85% yield, for 3 steps) as colorless crystals (**m.p.** 85–94 °C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.02–1.15 (m, 1H), 1.17, 1.19 (d, *J* = 6.3 Hz, 3H,

Me), 1.22–1.26 (m, 1H), 1.32–1.49 (m, 2H), 1.52–1.75 (m, 4H), 2.03–2.13 (m, 1H), 2.17–2.22 (m, 1H), 2.33 (br s, 2H, OH), 2.38–2.50 (m, 1H), 3.11, 3.20 (d, 1H, J = 11.4 Hz, 1'a-H), 3.48, 3.52 (d, 1H, J = 11.4 Hz, 1'b-H), 3.81–3.98 (m, 1H, 10-H), 4.62 (br s, 5'a-H), 4.75 (br s, 1H, 5'b-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 22.8 (CH_2), 22.9 (CH_3), 23.0 (CH_2), 25.1 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 31.6 (CH), 31.8 (CH), 34.9 (CH_2), 35.8(CH_2), 36.3 (CH), 36.4 (CH), 37.5 (C-1), 37.7 (C-1), 39.2 (CH_2), 39.1 (CH_2), 41.4 (CH_2), 41.5 (CH_2), 65.9 (C-10), 66.7 (C-10), 67.6 (C-1'), 68.2(C-1'), 105.0 (C-5'), 105.1 (C-5'), 151.4 (C-5), 151.6 (C-5). **HRMS** (ESI): calcd for $C_{13}H_{22}O_2$ $[M+Na]^+$ 233.15120, found 245.15110.

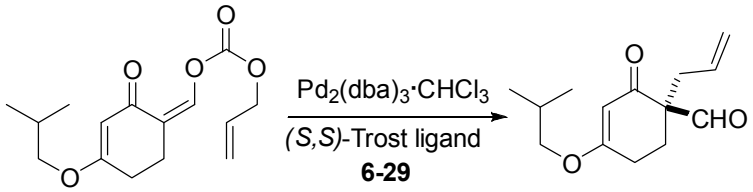


3-Methylene-1,2,3,4,8,8a-hexahydro-7*H*-2,4a-ethanonaphthalen-7-one (6-3).

a) Ketoaldehyde **6-28**. To a stirred solution of oxalyl chloride (0.5 mL, 5.8 mmol, 5.8 equiv) in CH_2Cl_2 (7 mL) DMSO (0.64 mL, 9.0 mmol, 9 equiv) was added dropwise at –80 °C. After 0.5 h a solution of diol **6-27** (210 mg, 1.0 mmol) in CH_2Cl_2 (7 mL) was injected during 20 min. The resulting mixture was stirred for 3 h at –80 °C before Et_3N (1.6 mL) was added at this temperature. After 2 h the reaction was quenched with a half-saturated NH_4Cl solution, then water was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and evaporated. Flash chromatography of the residue (petroleum ether/ ethyl acetate 6:1, $\mathbf{R_f}$ 0.3) provided ketoaldehyde **6-28** in 65% yield (135 mg, 0.65 mmol). Another product, which is the more polar mixture of unreacted hemiketal, was recovered by reduction with $LiAlH_4$ (20 mg) in Et_2O (5 mL) to furnish 24 mg (0.11 mmol) of diol **6-27**. Thus, the yield of ketoaldehyde **6-28** brsm amounts to 73%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.12 (ddd, J = 13.3, 5.3, 2.7 Hz, 1H, CH_2), 1.50–1.65 (m, 3H, CH_2), 1.75–1.83 (m, 2H, CH_2), 2.02–2.10 (m, 1H, CH_2), 2.10 (s, 3 H), 2.22–2.29 (m, 2H), 2.35 (dd, J = 17.9, 10.4 Hz, 1H), 2.44–2.53 (m, 3H), 4.71 (dd, J = 2.0, 1.5 Hz, 1H, 5'a-H), 4.83 (dd, J = 2.3, 1.5 Hz, 1H, 5'b-H), 9.40 (s, 1H, CH=O). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 20.2 (CH_2), 25.5 (CH_2), 30.3 (CH_3), 31.2 (CH), 34.4 (CH_2), 36.0 (CH), 36.4 (CH_2), 47.4 (C-9), 48.4 (C-1), 107.1 (C-5'), 147.5 (C-5), 205.3 (C-1'), 207.4 (C-10). **HRMS** (ESI): calcd for $C_{13}H_{18}O_2$ $[M+Na]^+$ 229.11990, found 229.12005.

b) Tricyclic enone **6-3**. The obtained ketoaldehyde **6-28** (135 mg, 0.65 mmol) was dissolved in EtOH (27 mL) and solid NaOH (170 mg, 4.25 mmol, 6.5 equiv) was added at 20 °C. The mixture was stirred at this temperature for 20 h, then concentrated. The residue was dissolved in ether (60 mL) and washed with 1 N aqueous HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ solution (25 mL), and brine (25 mL). The combined water washes were reextracted with Et_2O and the combined organic extracts were then dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification of the residue by flash column chromatography (petroleum ether/ ethyl acetate 10:1, $\mathbf{R_f}$ 0.3) afforded enone **6-3** (108 mg, 0.57 mmol, 87 % yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ[ppm] = 1.18 (ddd, J = 12.6, 7.6, 1.5 Hz, 1H, CH_2), 1.45–1.53 (m, 1H, CH_2), 1.66–1.80 (m, 3H), 1.94–2.02 (m, 1H), 2.05–2.17 (m,

2H), 2.28–2.32 (m, 1H), 2.30 (dd, *J* = 16.7, 13.4 Hz, 1H), 2.38–2.47 (m, 2H), 4.67 (dd, *J* = 2.3, 1.8 Hz, 1H, 3'a-H), 4.81 (dd, *J* = 2.5, 1.8 Hz, 1H, 3'b-H), 5.85 (dd, *J* = 10.1, 0.8 Hz, 1H, 6-H), 6.54 (d, *J* = 10.1 Hz, 1H, 5-H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ[ppm] = 24.5 (CH_2), 26.4 (CH_2), 34.9 (CH_2), 35.4 (CH), 35.5 (C-4a), 36.0 (CH), 40.8 (CH_2), 41.6 (CH_2), 106.9 (C-3'), 127.7 (C-6), 148.9 (C-3), 156.7 (C-5), 200.1 (C-7). **HRMS** (ESI): calcd for $C_{13}H_{16}O$ $[M+Na]^+$ 211.10934, found 211.10936.

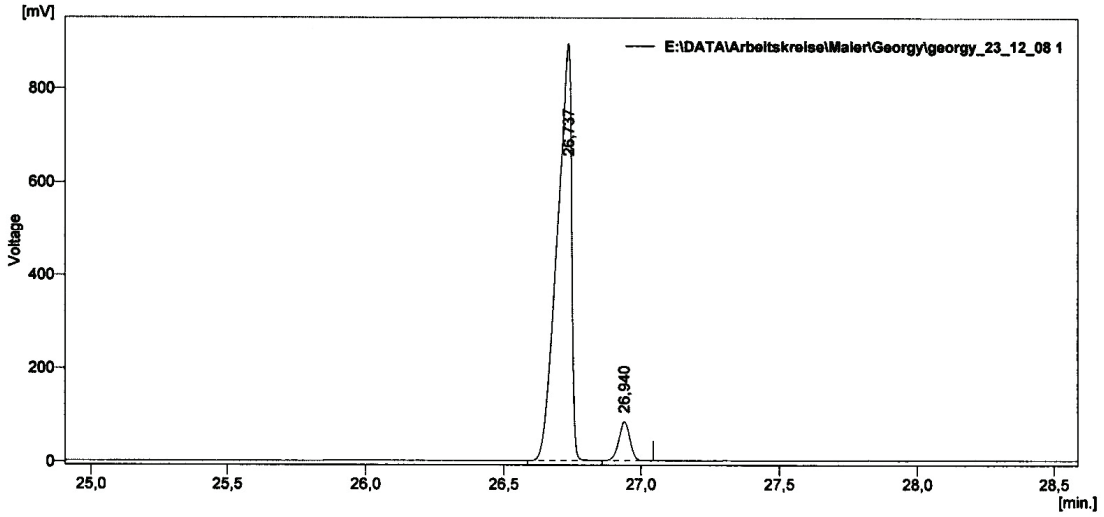


(*Z*)-**6-13** (+)-**6-14**

Asymmetric allylic alkylation, synthesis of (+)-6-14. $Pd_2(dba)_3 \cdot CHCl_3$ (13 mg, 0.0125 mmol, 2.5 mol% of Pd) and (*S,S*)-Trost ligand **6-29** (25.1 mg, 0.03 mmol, 3 mol%) were stirred in dry degassed THF (5 mL) at 20 °C under nitrogen for 0.5 h to form an orange solution. This solution was cooled to –20 °C and added dropwise to a cold (–20 °C) solution of (*Z*)-**6-13** (280 mg, 1.0 mmol) in THF (5 mL) and stirred at this temperature for 48 h. When the reaction was finished (TLC-monitoring) one drop of Me_2S was added to poison the palladium catalyst, and then the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1, $\mathbf{R_f}$ 0.3) to give **(+)-6-14** as a colorless oil (225 mg, 95%), $\mathbf{[\alpha]_D}$ = +83.7 (*c* = 2.0, CH_2Cl_2). The ee of **(+)-6-14** was determined by chiral GC (column 977, 28 m × 0.25 mm, 30% 6-TBDMS-2,3-diacetyl β-cyclodextrin in PS 086. Temperature program: 80 °C, 2 min isothermal, then 4 ° min^{-1} up to 190 °C, P_i 60 kPa H_2. A typical chromatogram is shown below.

2 11:41 Chromatogram E:\DATA\Arbeitskreise\Maier\Georgy\georgy_23_12_08 1 Page 1 of 1

Acquired	: 23.12.2008 11:06:35	By	: Clarissa
Created	: 23.12.2008 11:06:37	Stored Version	: 23.12.2008 11:35:23
Project	: Rohdaten2	Report Style	: S978_1
Amount	: 0	Dilution	: 1
ISTD Amount	: 0	Inj. Volume [ml]	: 0
Sample ID	: vage 0022 S977, 8/2/4/190, 60 kPa	Sample	:
Calibration	:	Chromatogram	: E:\DATA\Arbeitskreise\Maier\Georgy\georgy_23_12_08 1

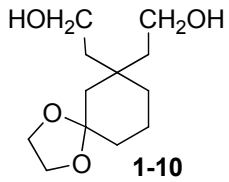


Result Table (Uncal - E:\DATA\Arbeitskreise\Maier\Georgy\georgy_23_12_08 1)

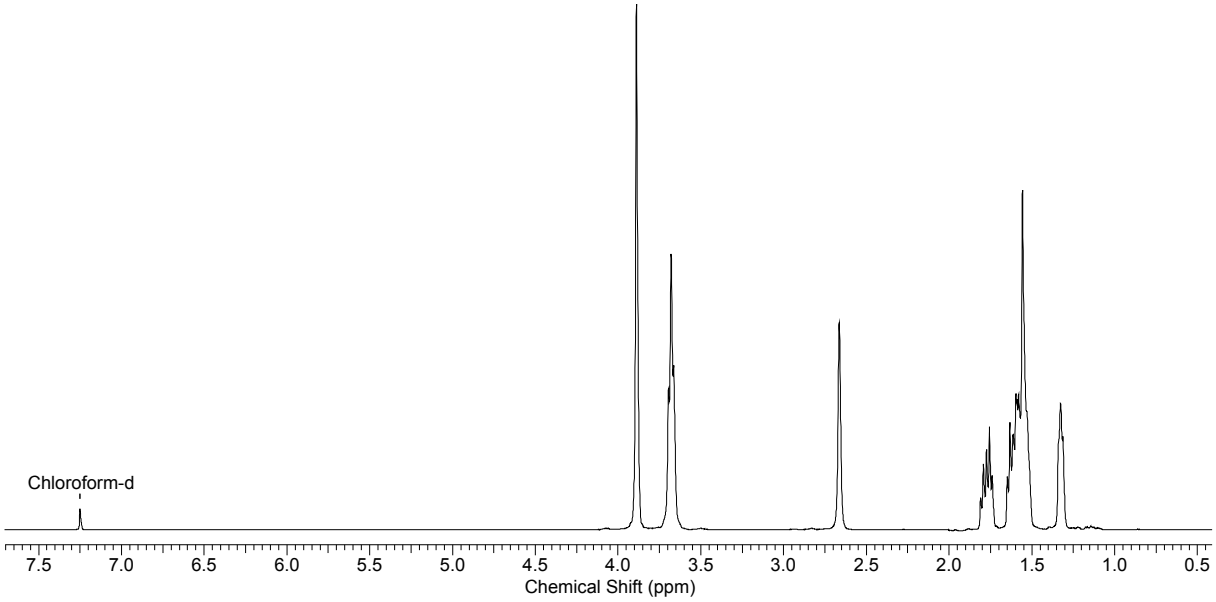
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	W05 [min]
1	26,737	3234,721	894,752	93,313	0,06
2	26,940	231,791	82,993	6,687	0,04
	Total	3466,512	977,745	100,000	

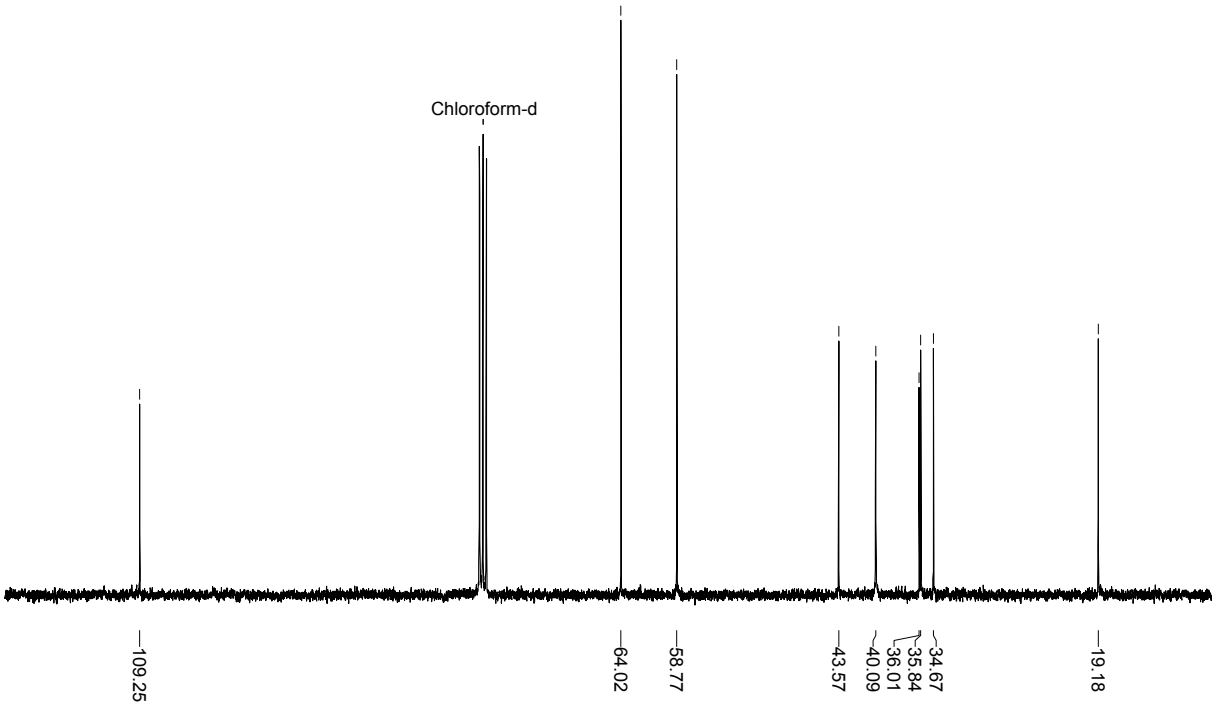
7. Selected NMR spectra for important compounds.

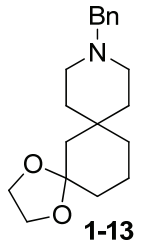
Additional spectra are included in the supporting information of the published papers from this work and are available via internet at http://pubs.acs.org and http://www.angewandte.org.


HOH2C
CH2OH
O
O

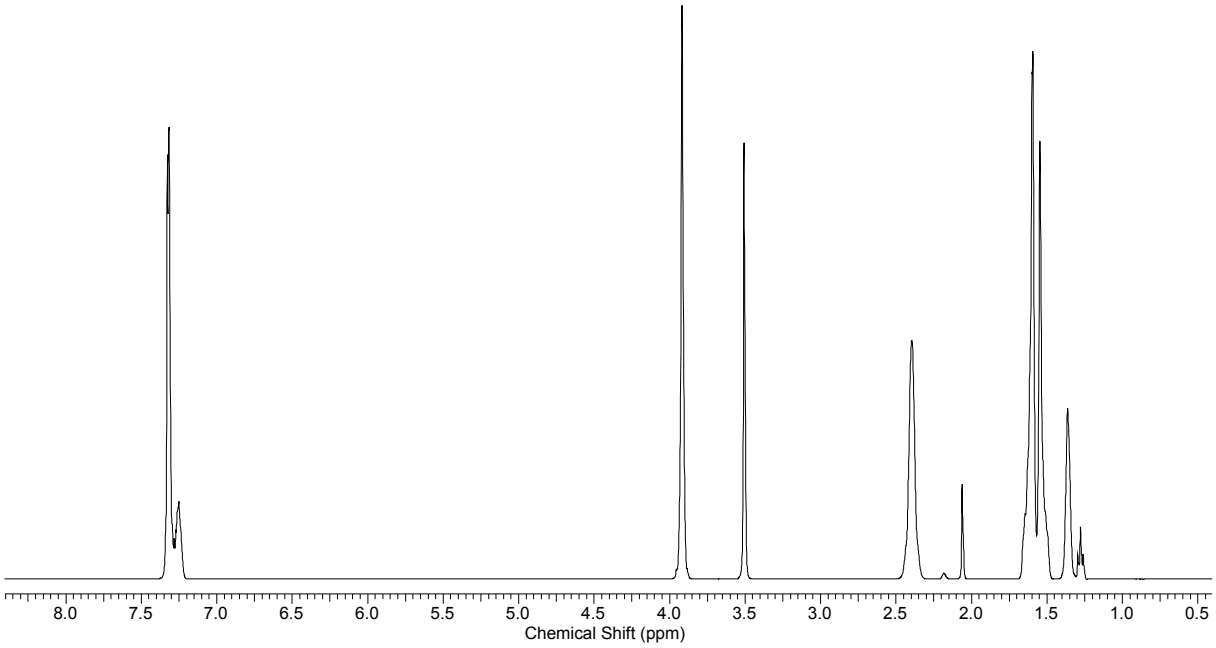
1-10

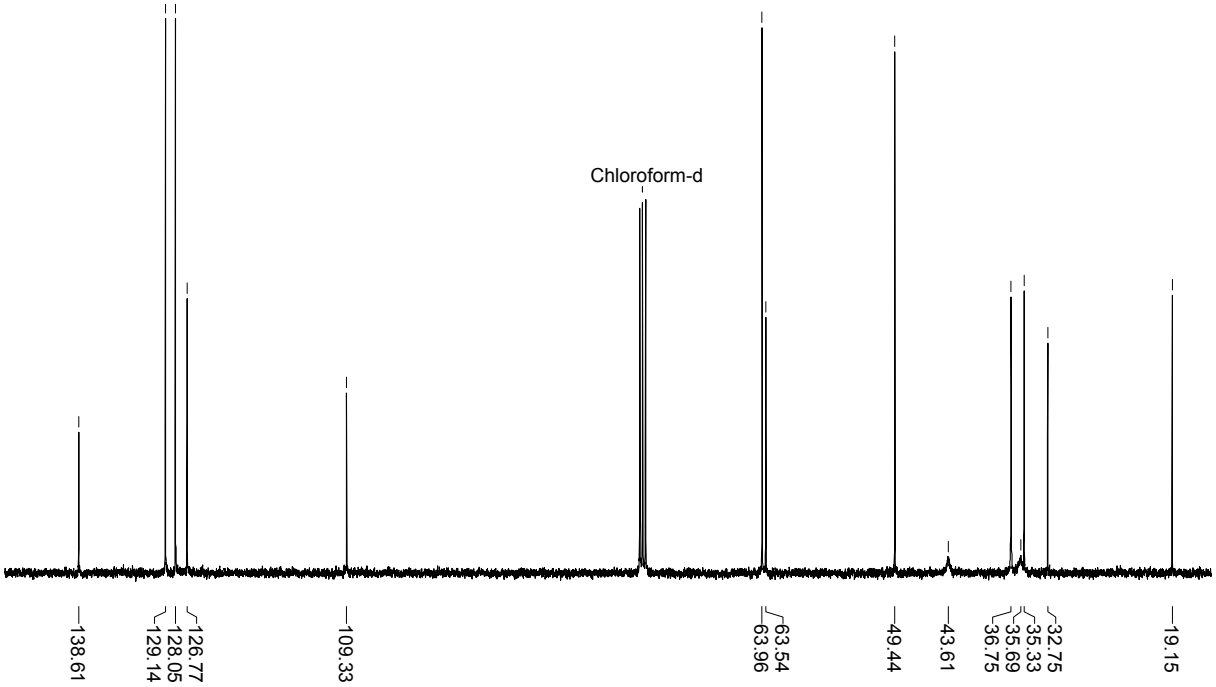

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

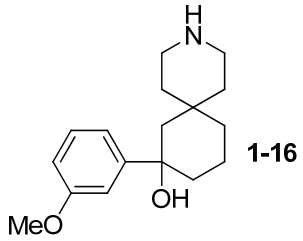

Chloroform-d
109.25
64.02
58.77
43.57
40.09
36.01
35.84
34.67
19.18


Bn
N
O
O

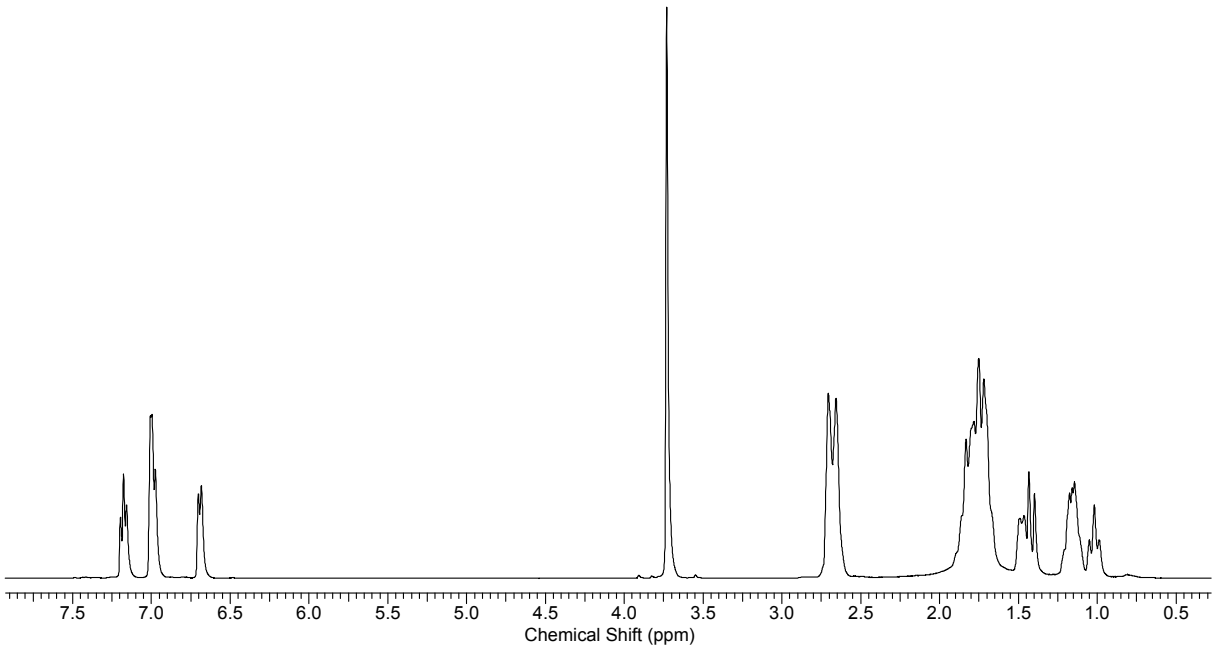
1-13

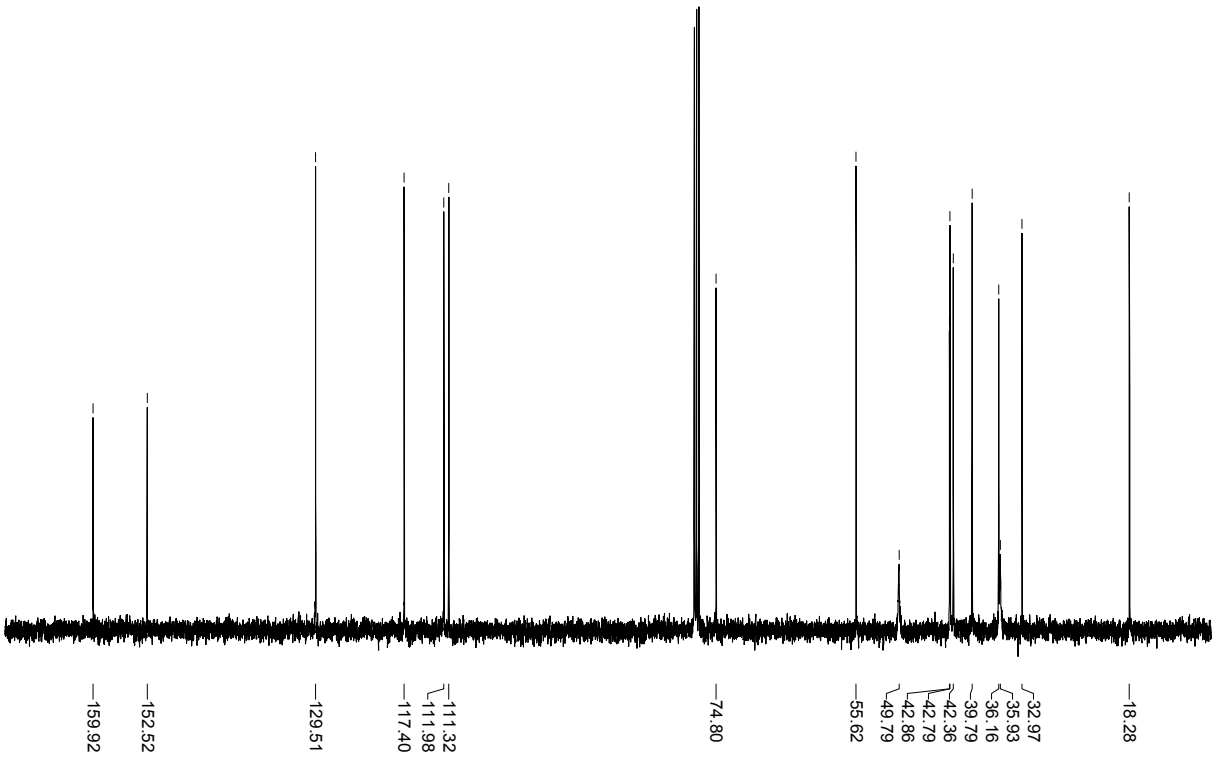

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

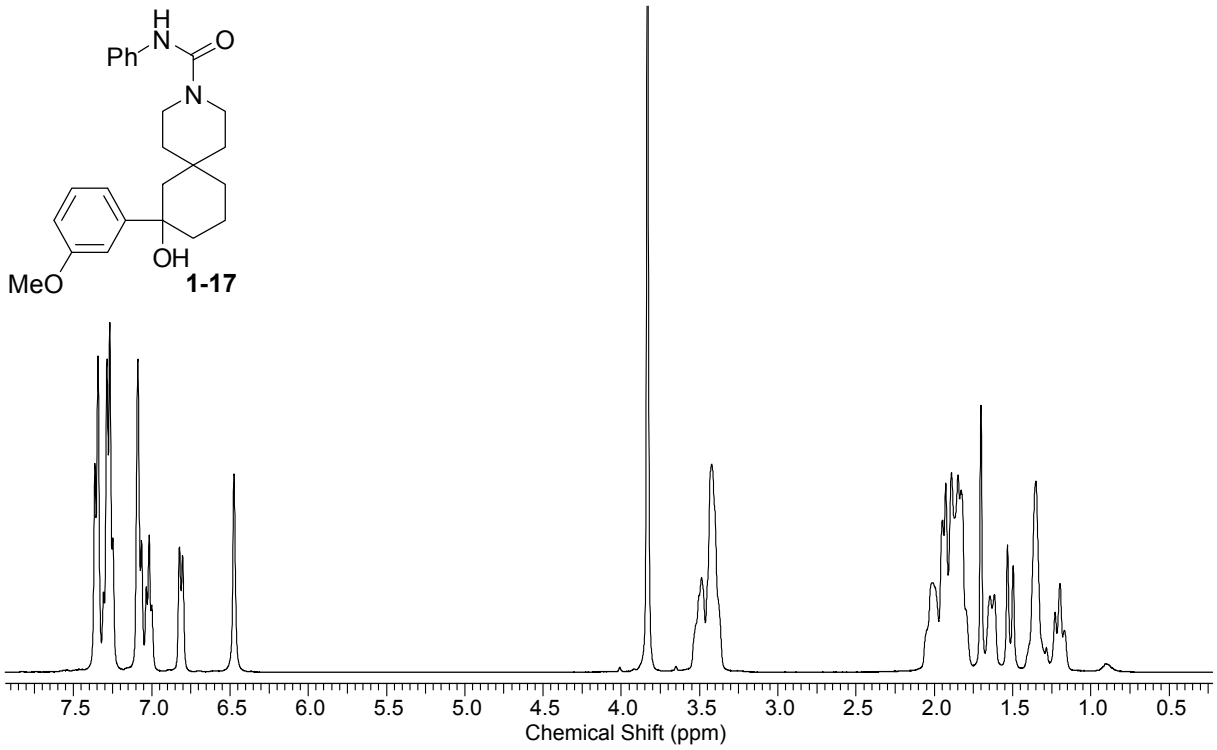

Chloroform-d
138.61
129.14
128.05
126.77
109.33
63.96
63.54
49.44
43.61
36.75
35.69
35.33
32.75
19.15

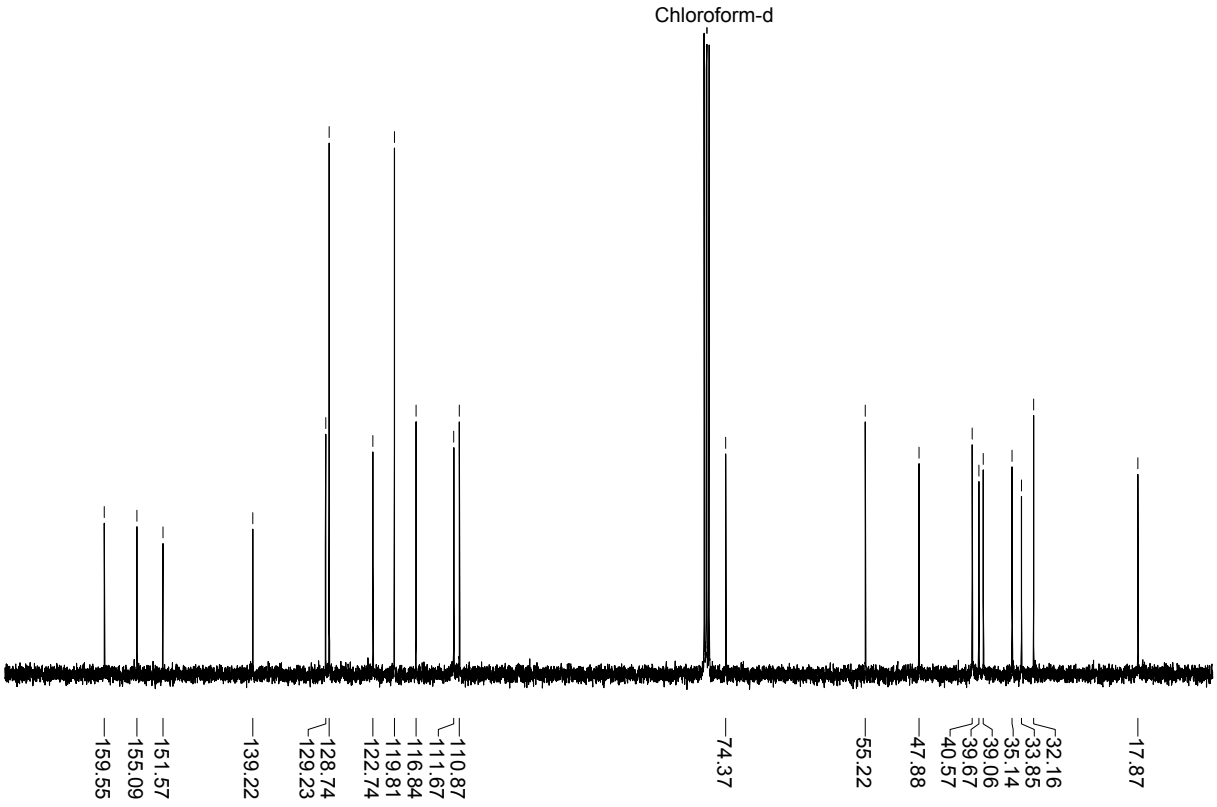

H
N
OH
MeO

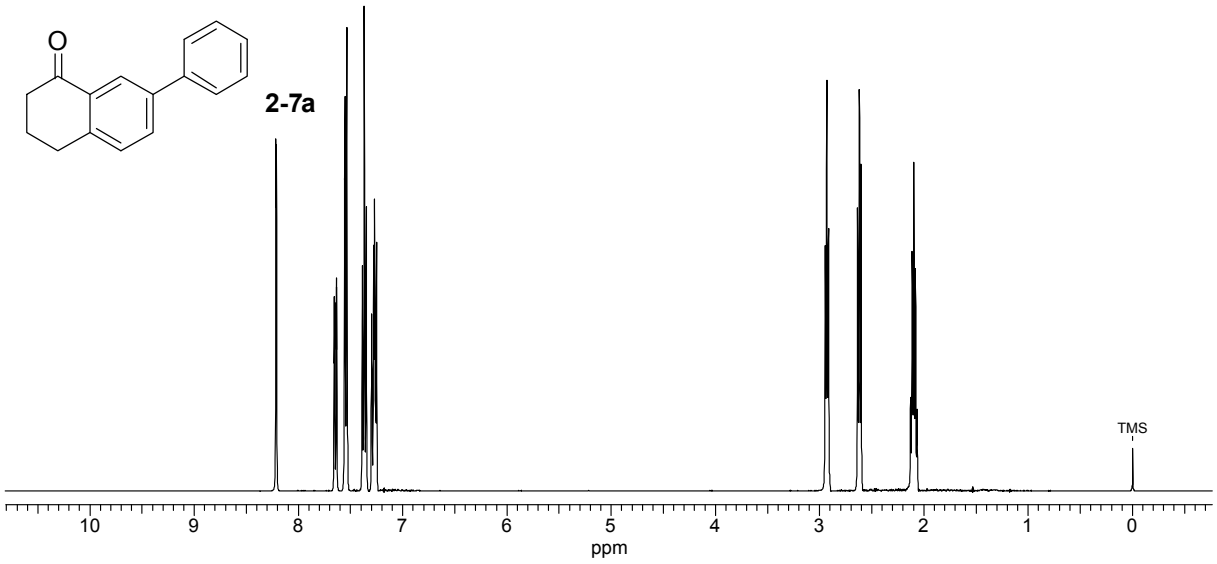
1-16

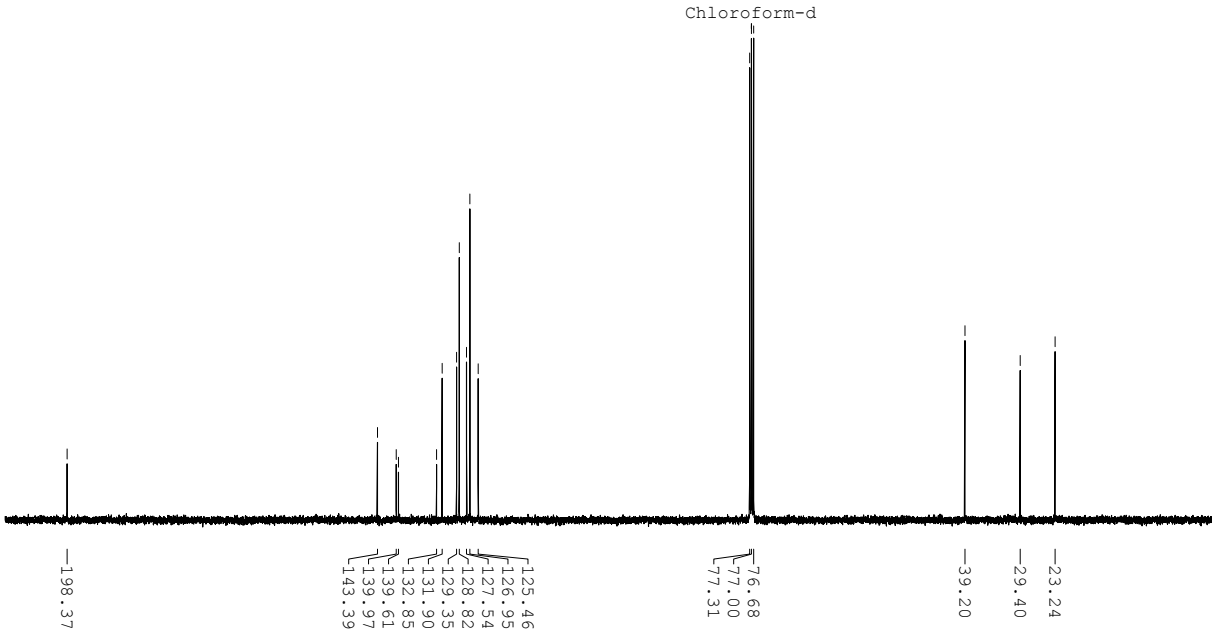

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

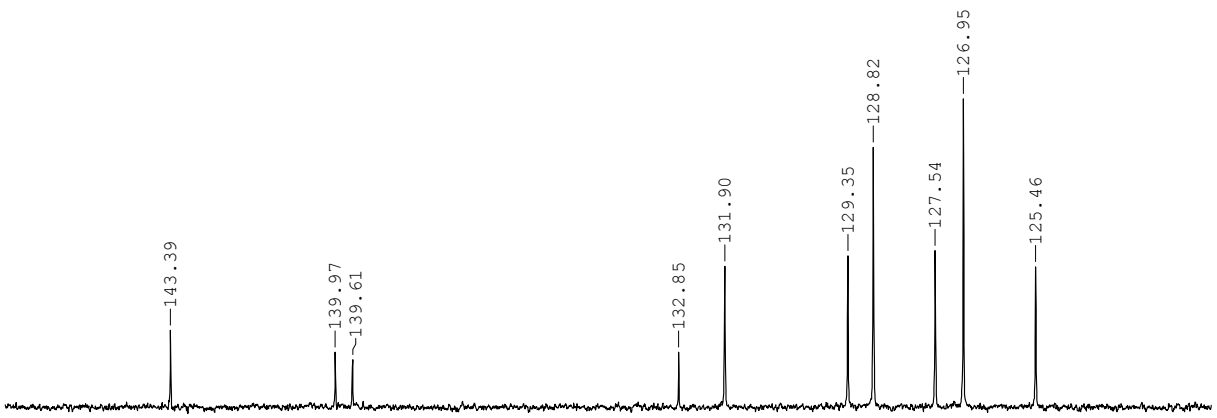

159.92
152.52
129.51
117.40
111.32
111.98
74.80
55.62
49.79
42.86
42.79
42.36
39.79
36.16
35.93
32.97
18.28

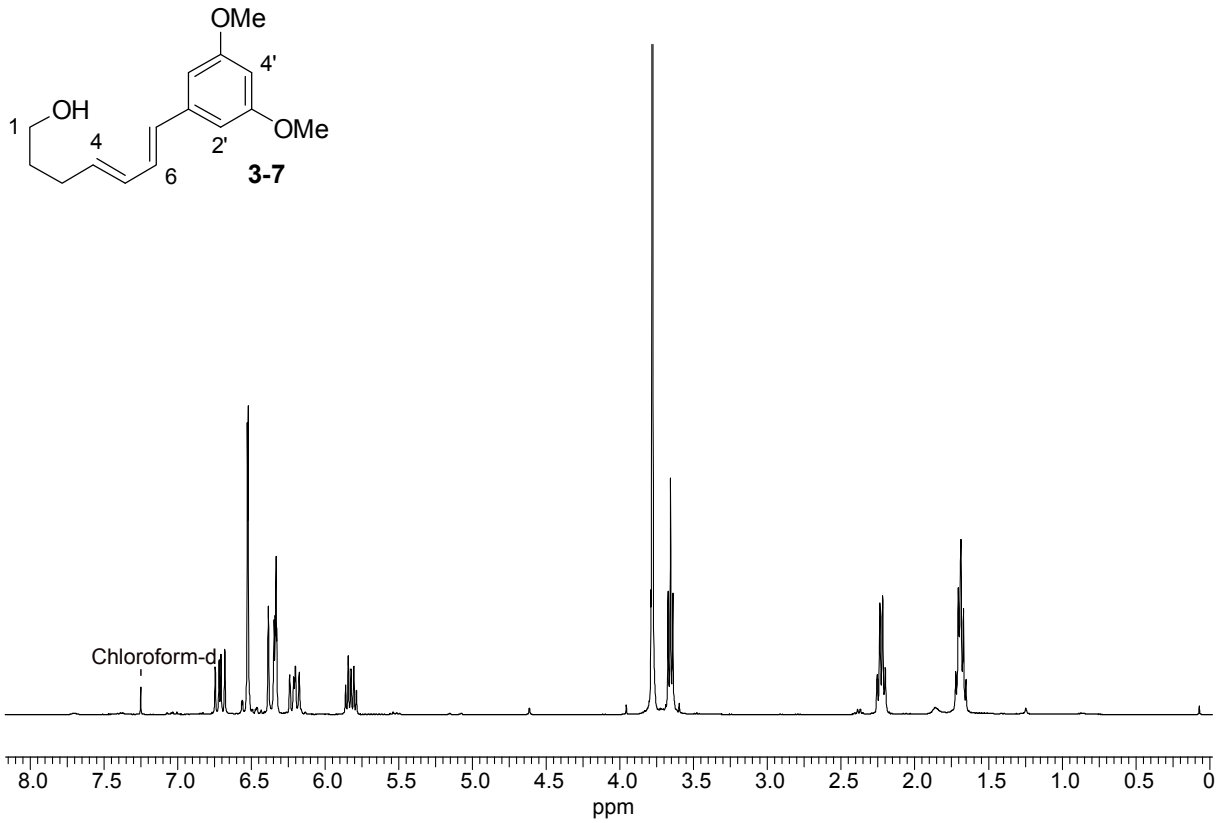

H
N
O
Ph
N
OH
MeO
1-17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

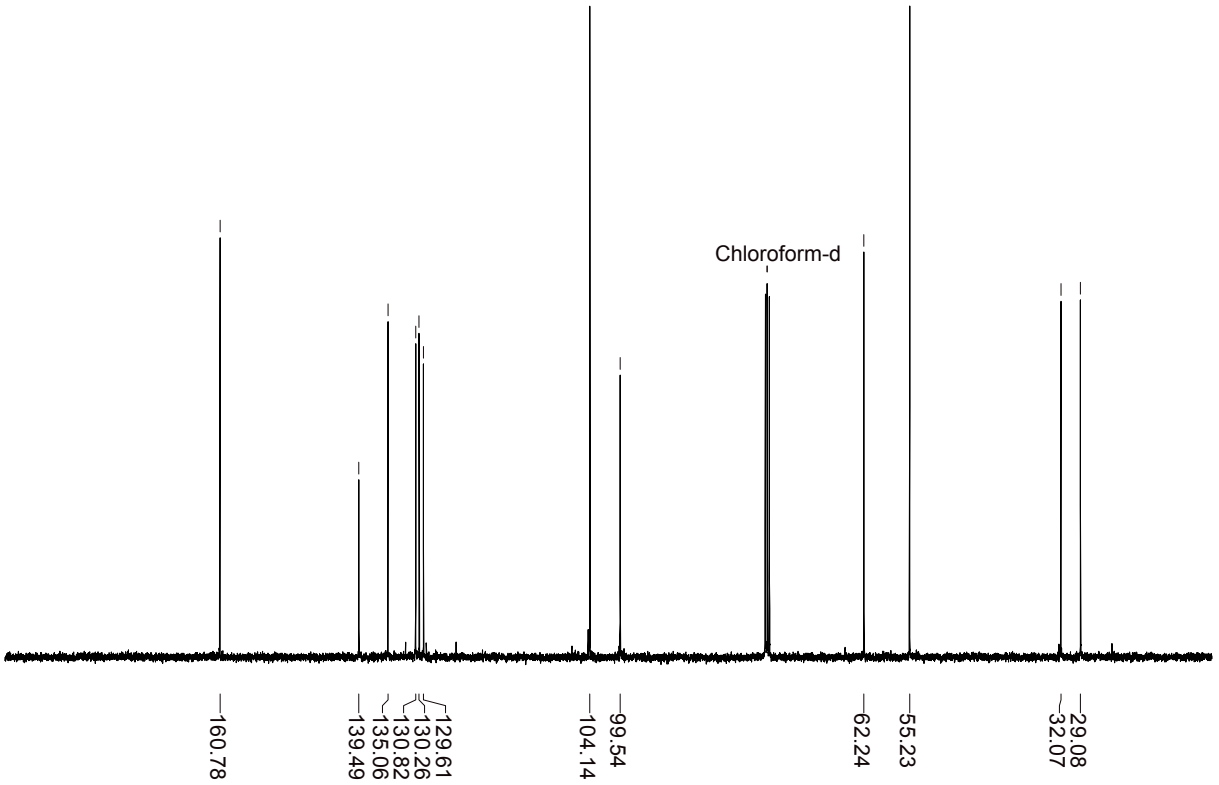

Chloroform-d
159.55
155.09
151.57
139.22
128.74
129.23
122.74
119.81
116.84
111.67
110.87
74.37
55.22
47.88
40.57
39.67
39.06
35.14
33.85
32.16
17.87

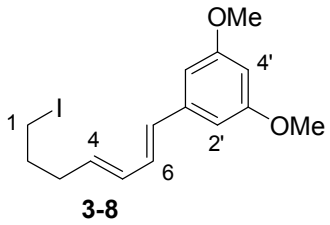

O
2-7a
TMS
10
9
8
7
6
5
4
3
2
1
0
ppm


Chloroform-d
198.37
143.39
139.97
139.61
132.85
131.90
129.35
128.82
127.54
126.95
125.46
77.31
77.00
76.68
39.20
29.40
23.24


143.39
139.97
139.61
132.85
131.90
129.35
128.82
127.54
126.95
125.46

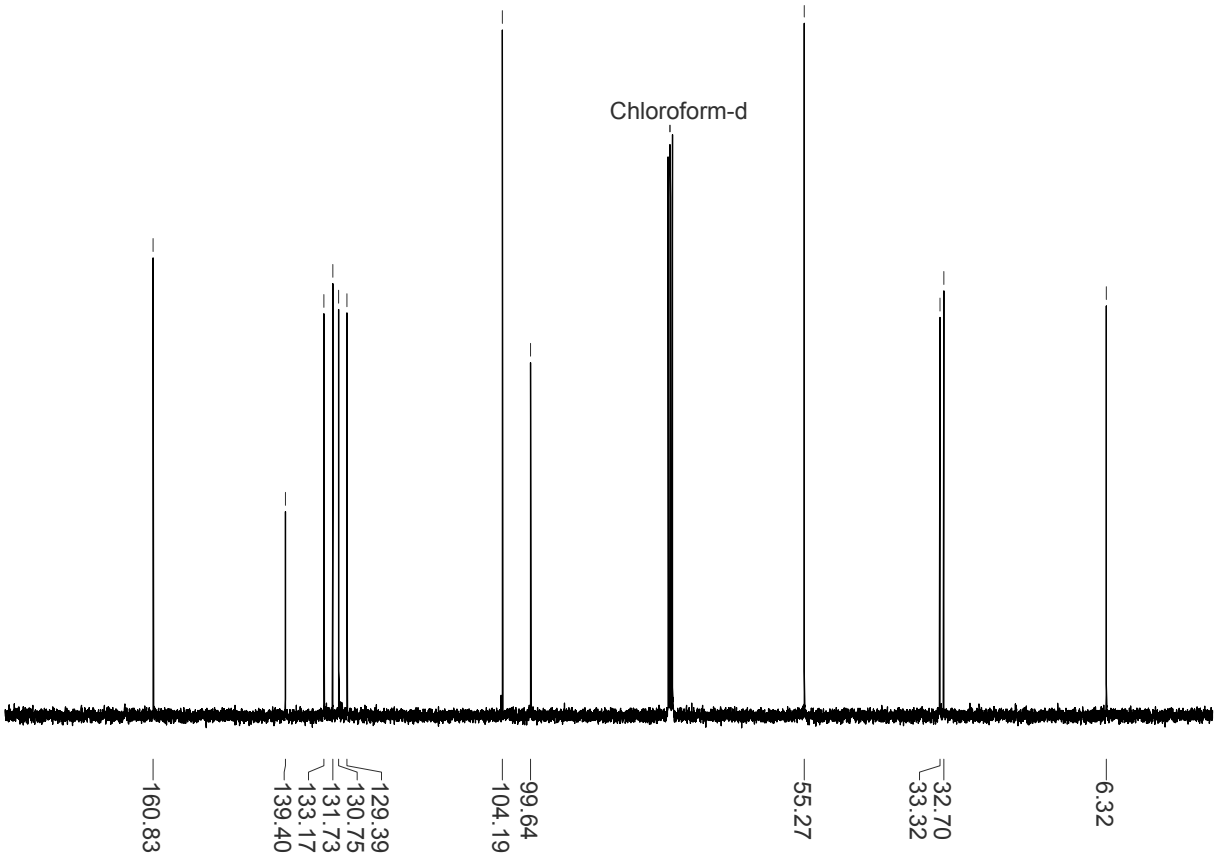

OMe
4'
OH
1
4
2'
OMe
6
3-7
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
ppm

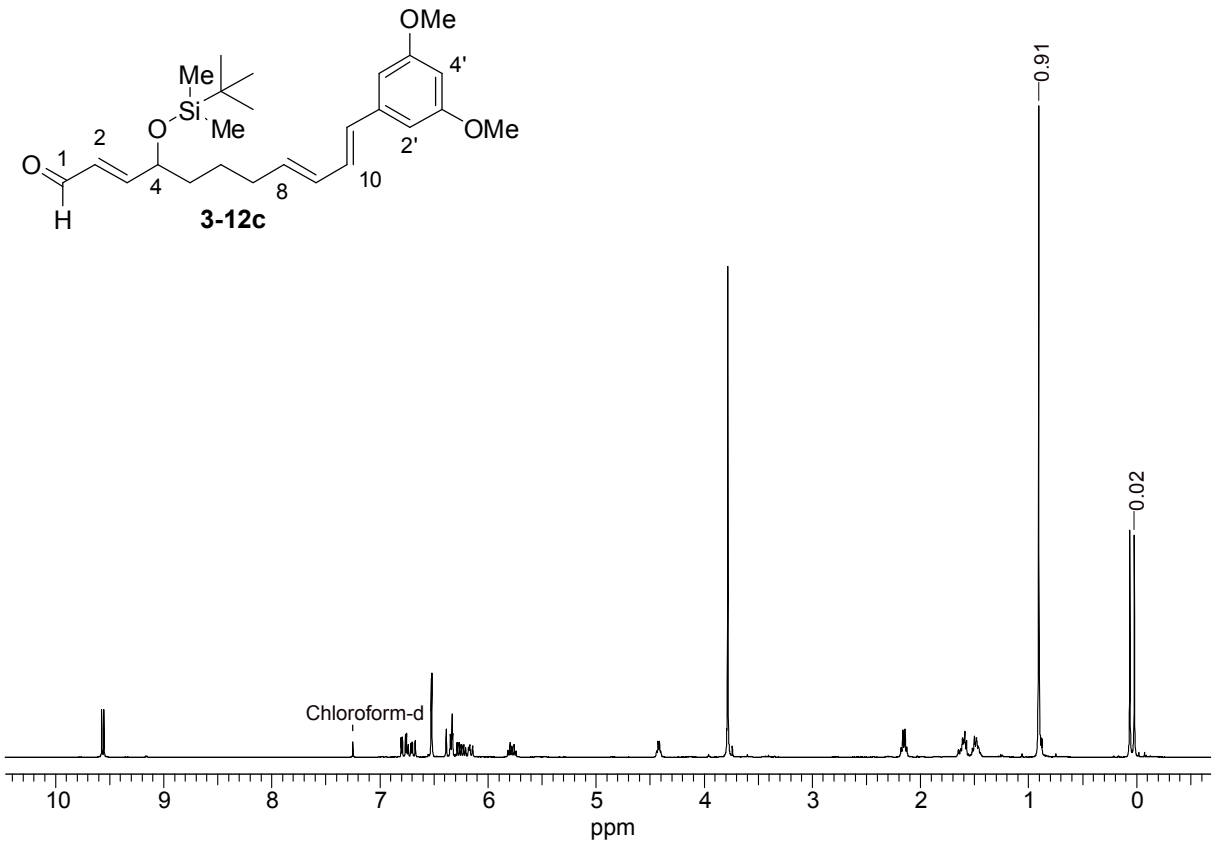

Chloroform-d
160.78
139.49
135.06
130.82
130.26
129.61
104.14
99.54
62.24
55.23
32.07
29.08

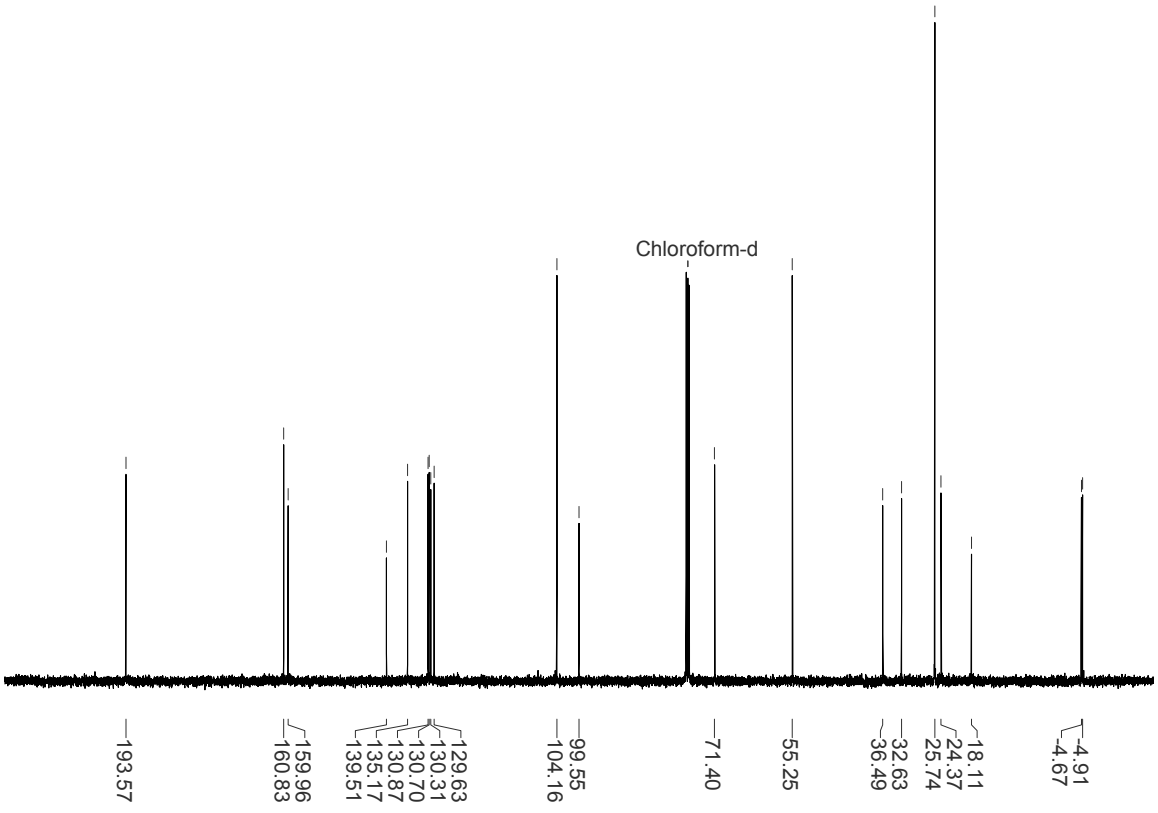

OMe
4'
1
I
4
2'
OMe
6

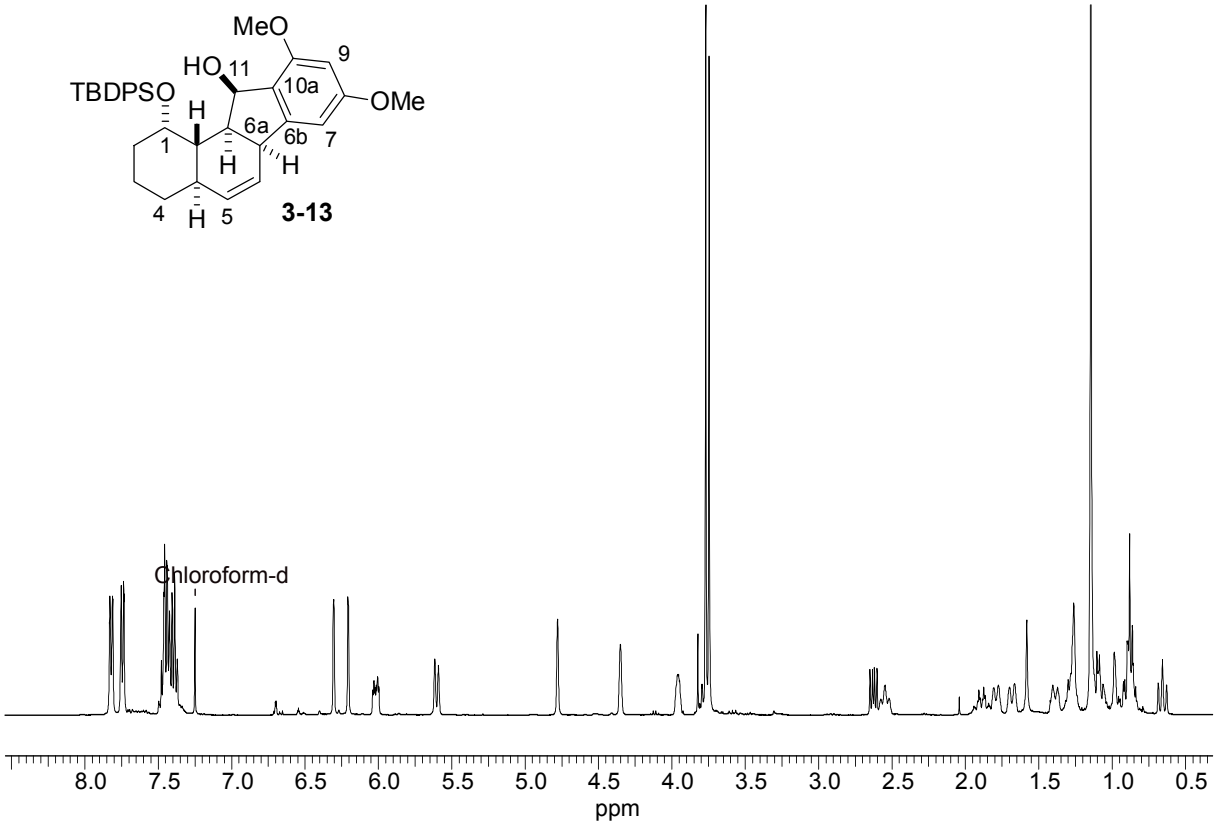
3-8

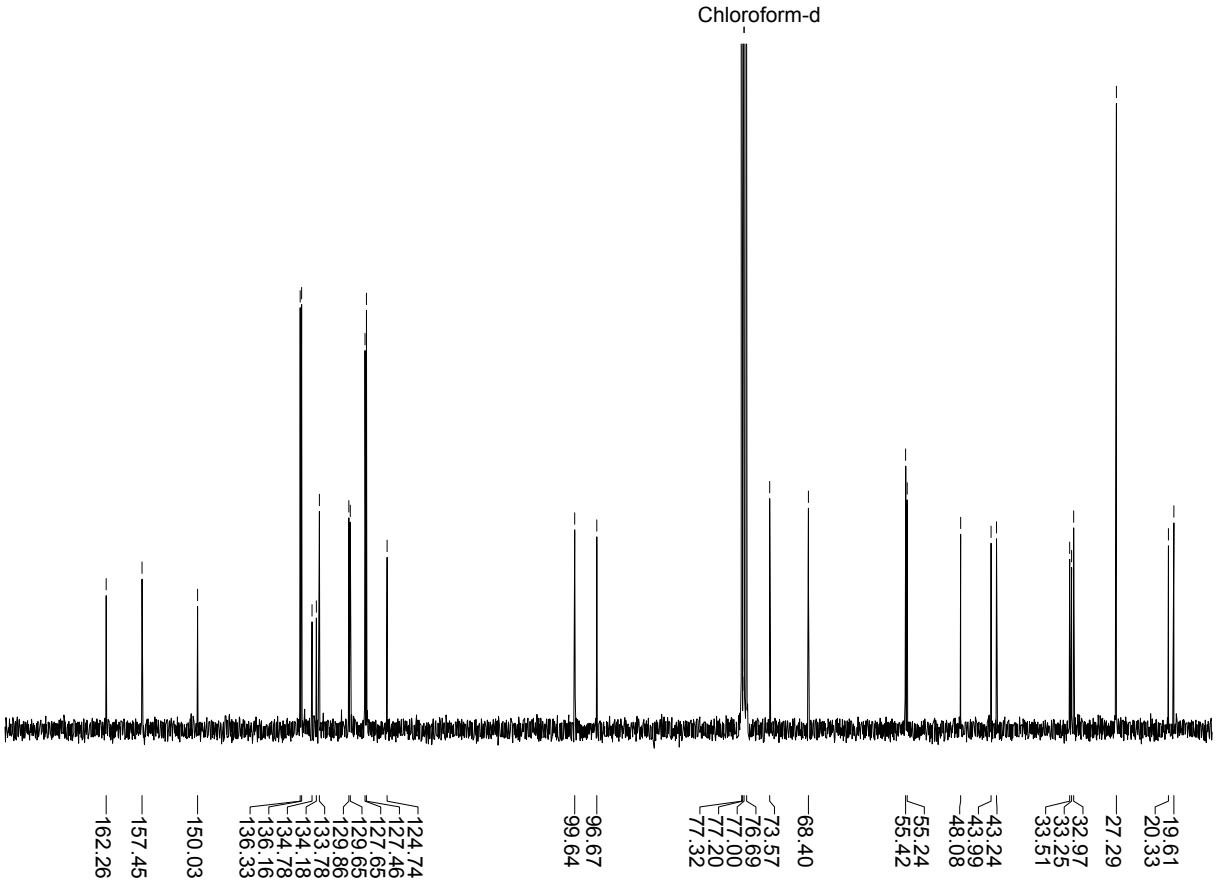
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

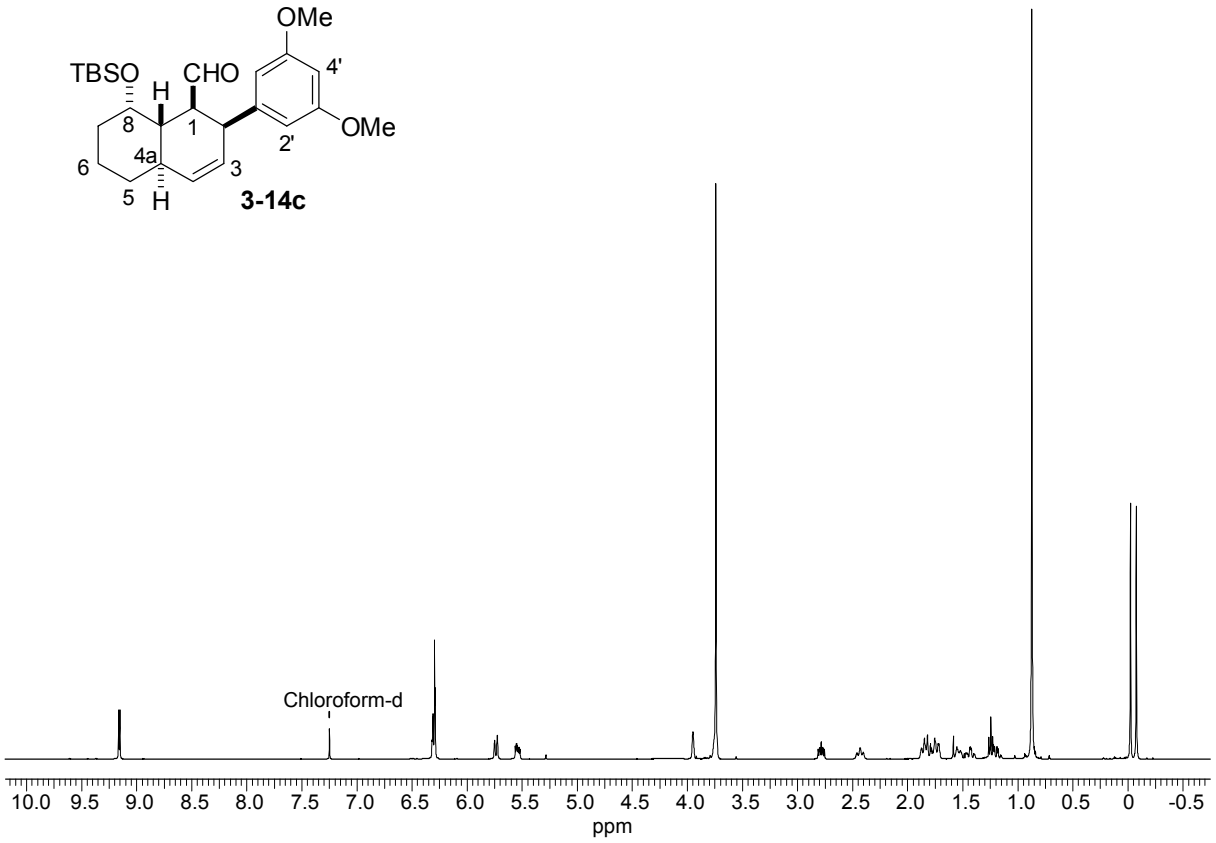

Chloroform-d
160.83
139.40
133.17
131.73
130.75
129.39
104.19
99.64
55.27
33.32
32.70
6.32

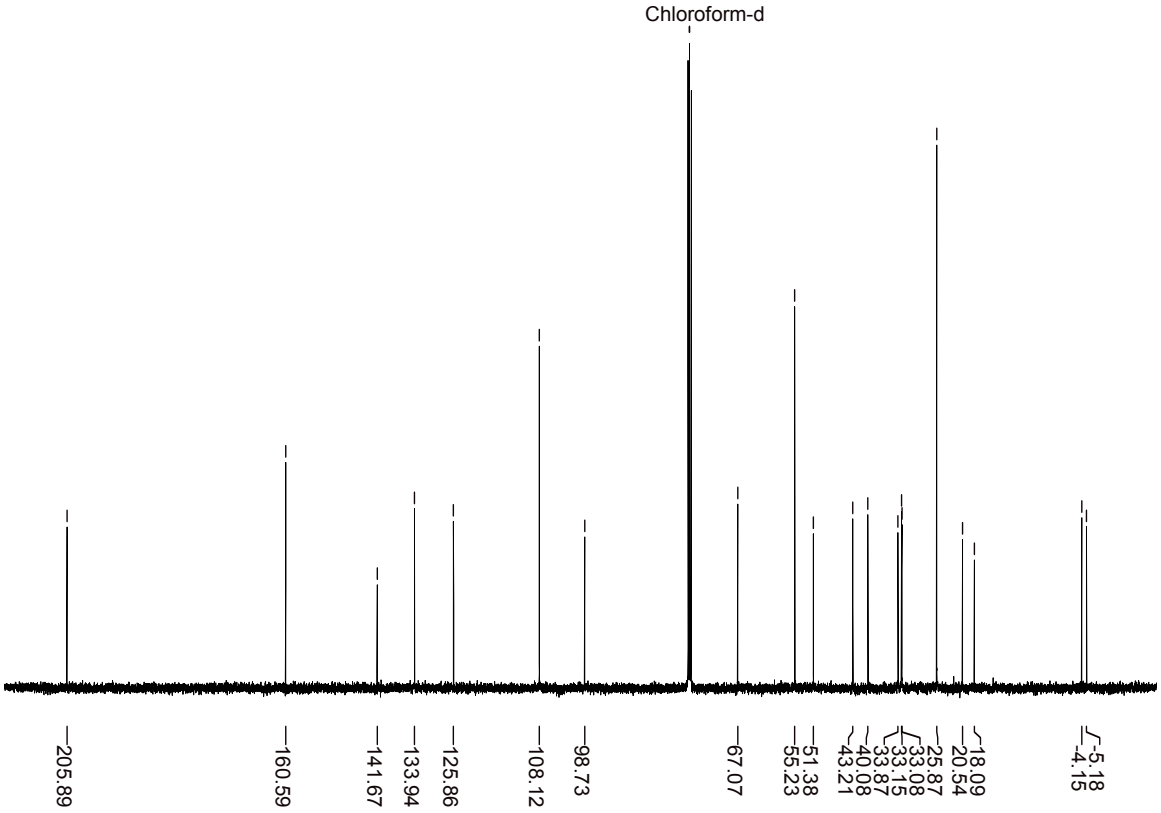

OMe
4'
Me
Si
Me
O
2
1
O
H
4
8
10
2'
OMe
3-12c
1.00
0.02
Chloroform-d
10
9
8
7
6
5
4
3
2
1
0
ppm

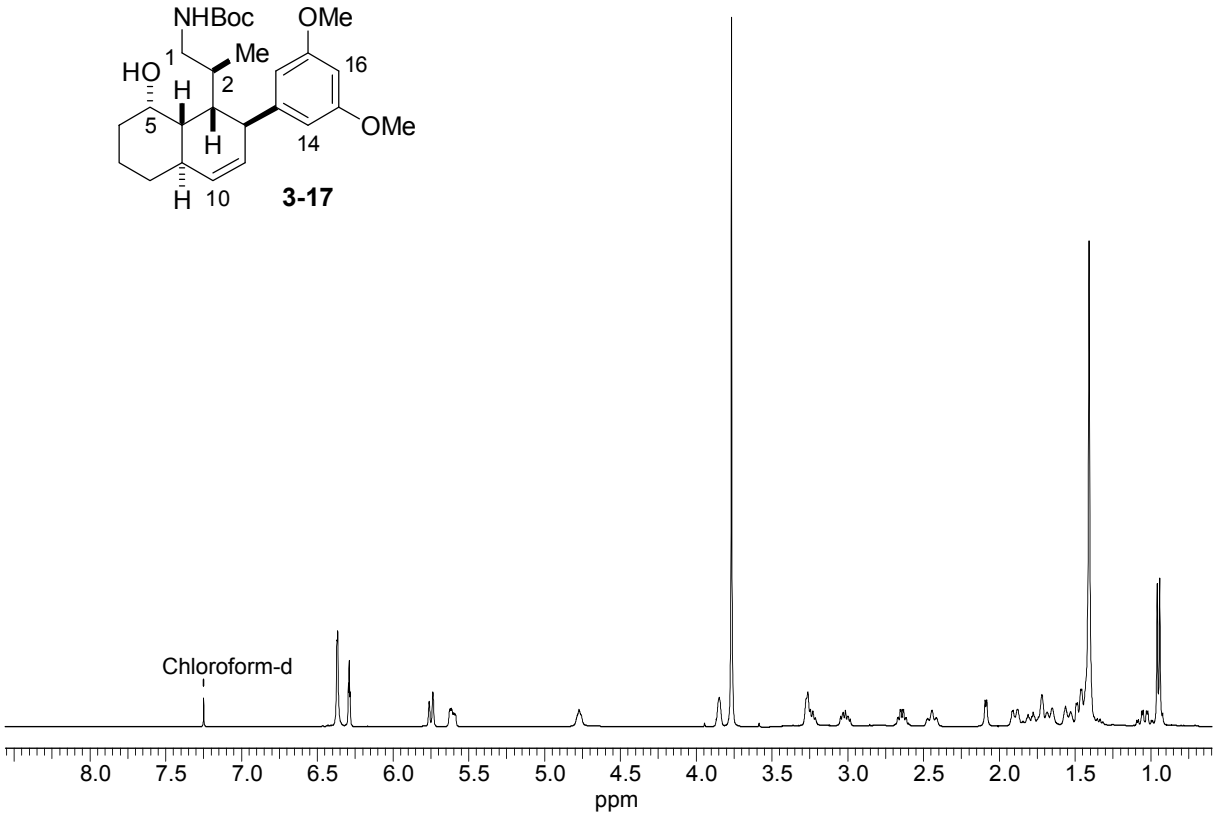

Chloroform-d
193.57
159.96
160.83
135.17
139.51
130.87
130.70
130.31
129.63
99.55
104.16
71.40
55.25
36.49
32.63
25.74
24.37
18.11
4.91
4.67

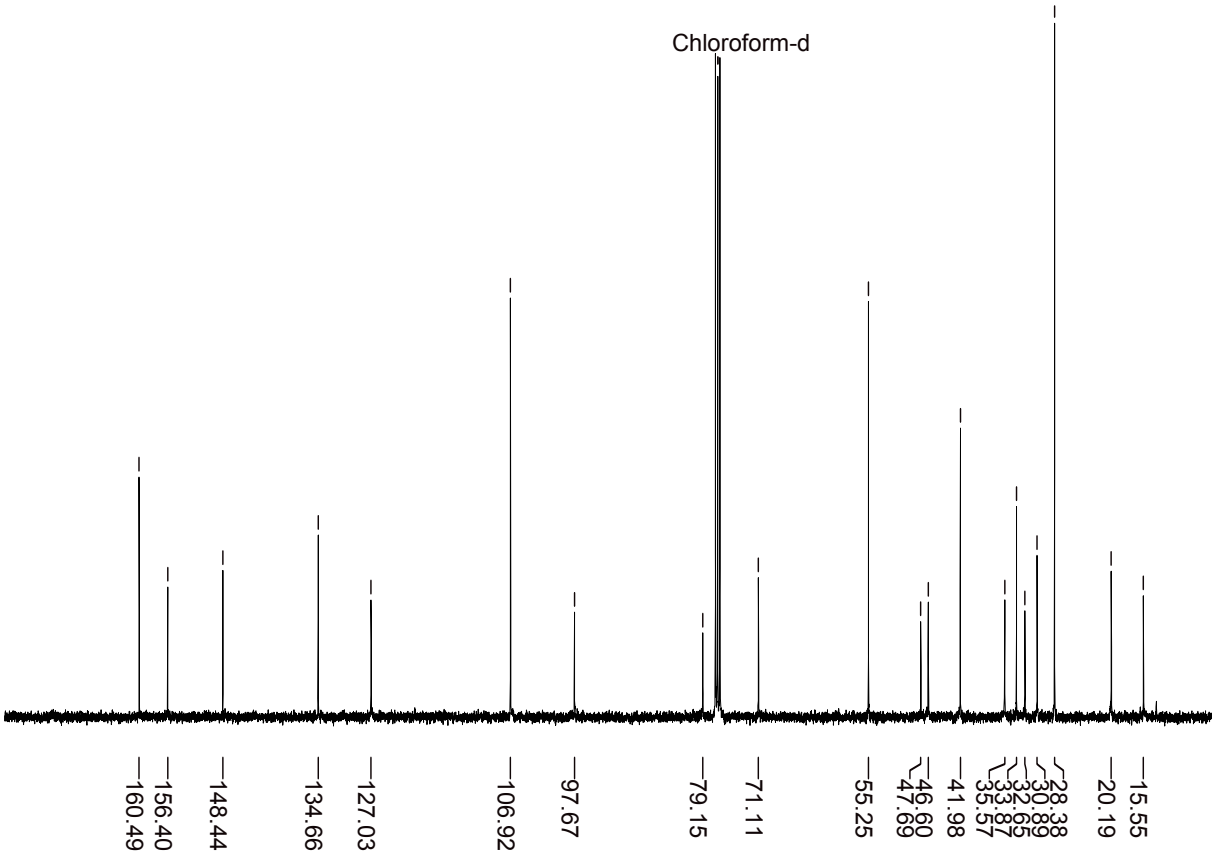

MeO
HO
11
9
10a
TBDPSO
H
OMe
6a
1
6b
7
H
H
4
H
5
3-13
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

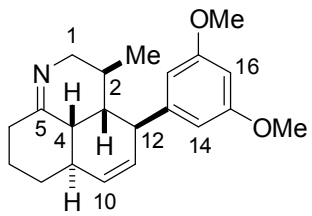

Chloroform-d
162.26
157.45
150.03
136.33
136.16
134.78
134.18
133.78
129.86
129.65
127.46
124.74
99.64
96.67
77.32
77.00
76.69
73.57
68.40
55.42
55.24
48.08
43.99
43.24
33.51
33.25
32.97
27.29
20.33
19.61


OMe
TBSO
CHO
H
4'
8
1
2'
OMe
6
4a
3
5
H
3-14c
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
ppm

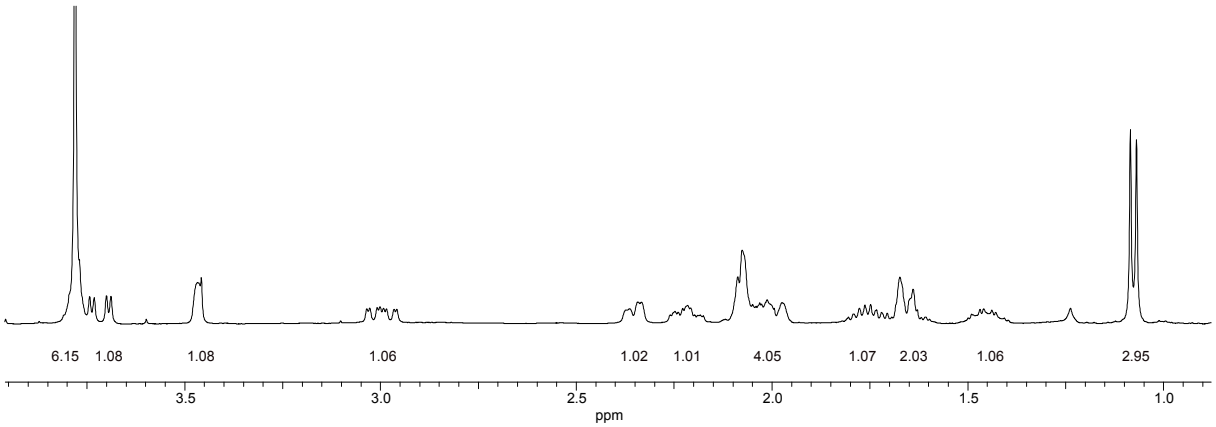

Chloroform-d
205.89
160.59
141.67
133.94
125.86
108.12
98.73
67.07
55.23
51.38
43.21
40.08
33.87
33.15
33.08
25.87
20.54
18.09
-4.15
-5.18

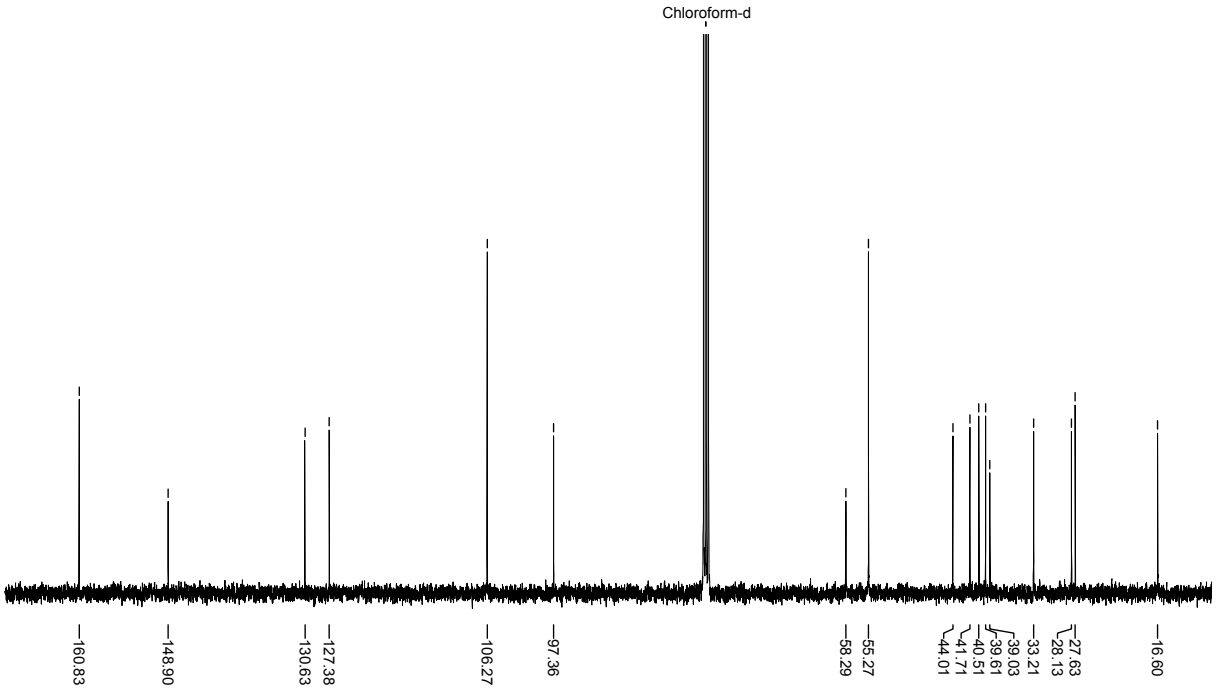

NHBoc
OMe
1
Me
16
HO
H
2
5
OMe
H
14
H
10
3-17
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

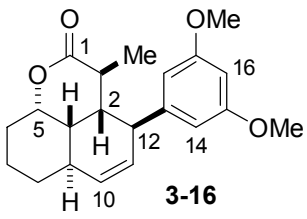

Chloroform-d
160.49
156.40
148.44
134.66
127.03
106.92
97.67
79.15
71.11
55.25
47.69
46.60
41.98
35.57
33.87
32.65
30.89
28.38
20.19
15.55



3-18 (***epi***-dimethyl-symbioimine)

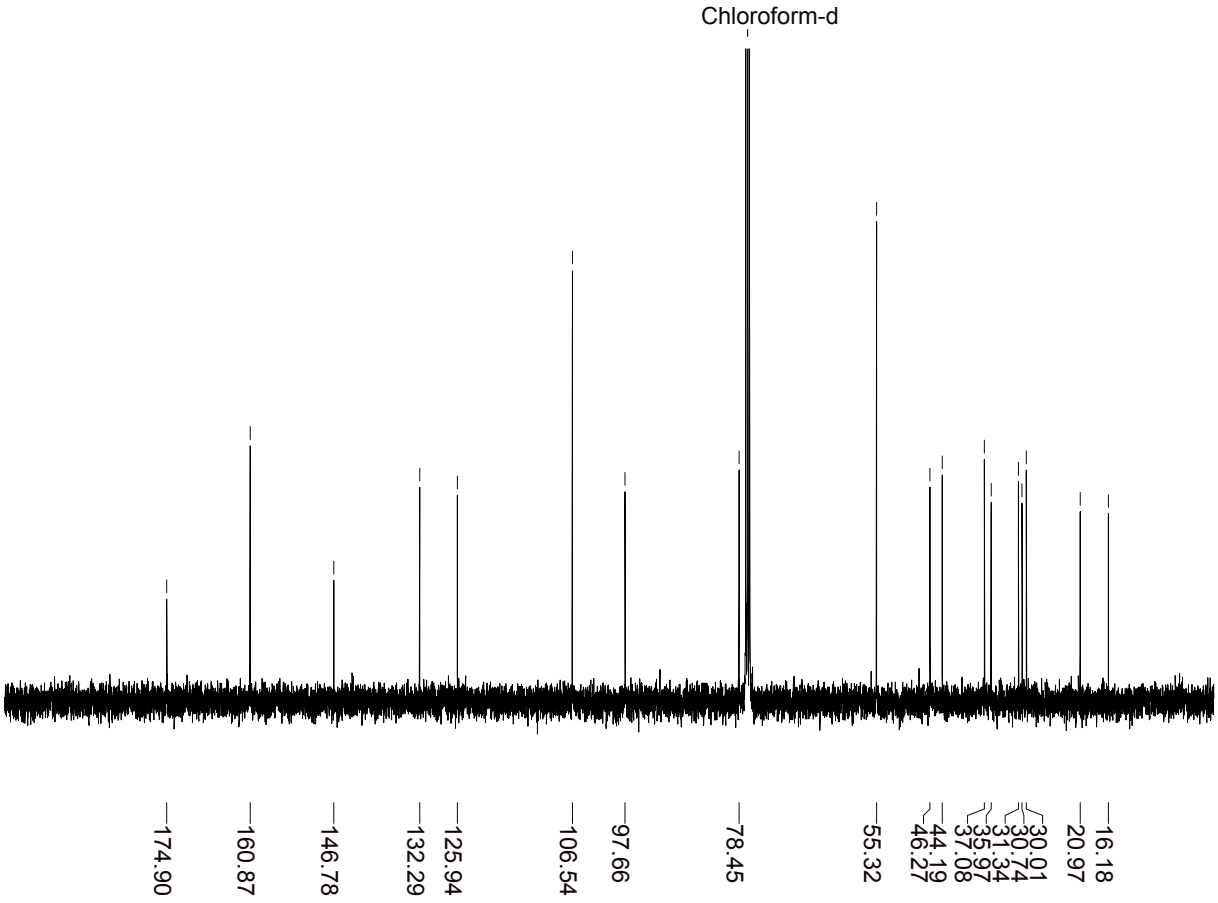





O
1
Me
OMe
16
O
H
2
5
H
12
14
OMe
H
10

3-16

Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
174.90
160.87
146.78
132.29
125.94
106.54
97.66
78.45
55.32
46.27
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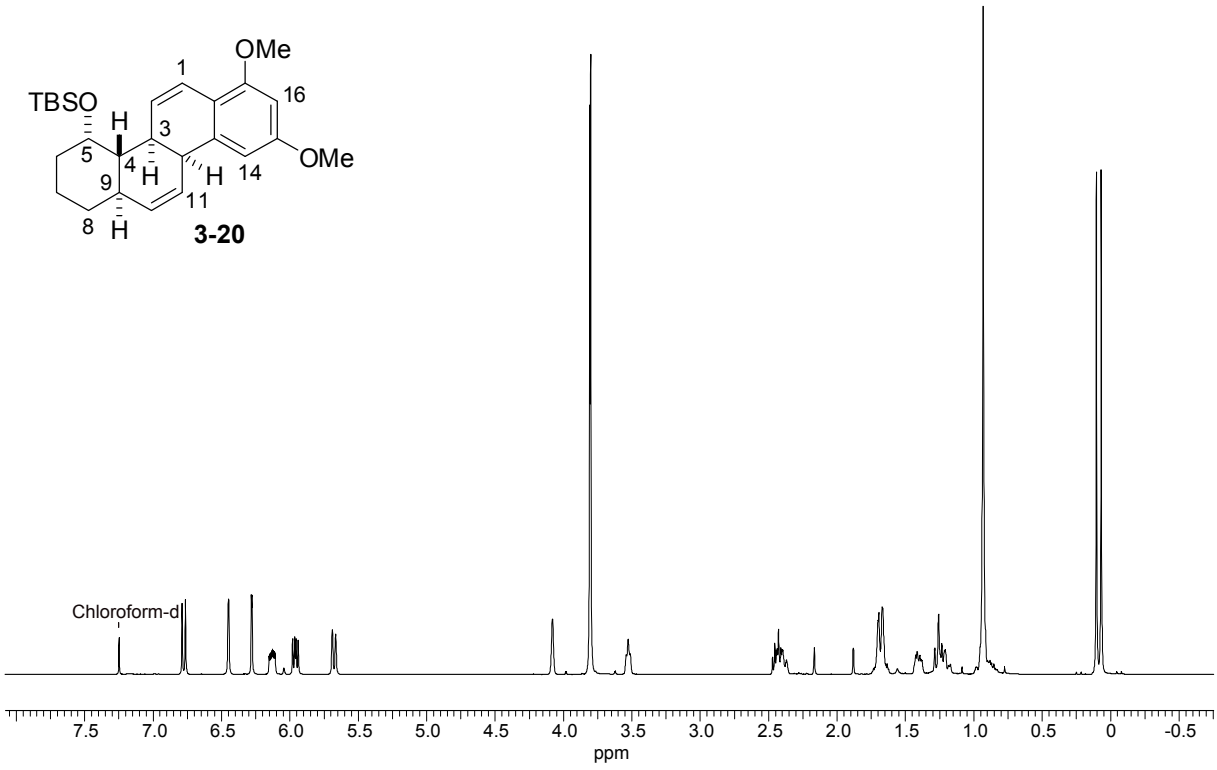
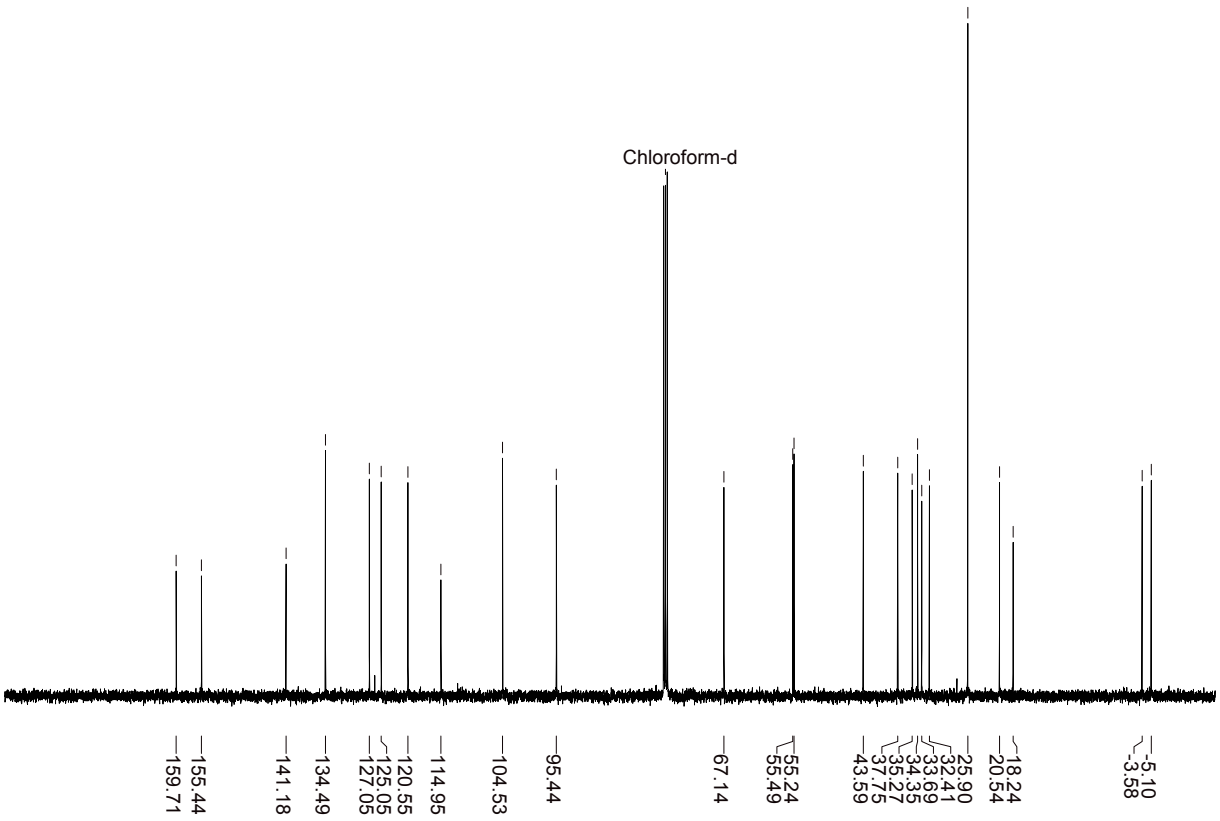
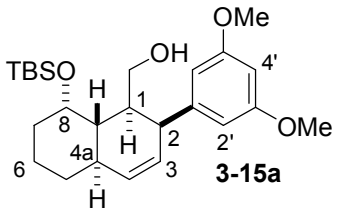
37.08
35.97
31.34
30.74
30.01
20.97
16.18

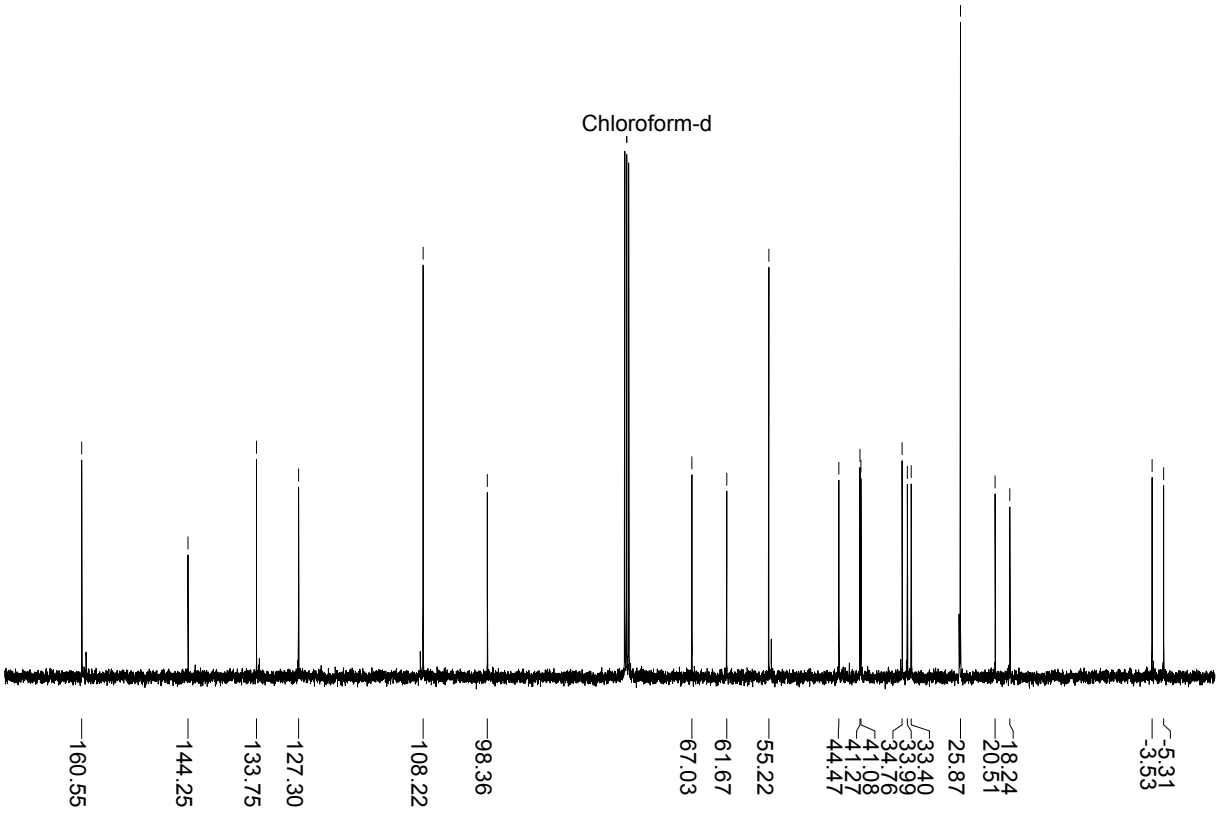

OMe
1
16
TBSO
H
3
5
4
H
H
14
OMe
9
11
8
H
3-20
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
ppm

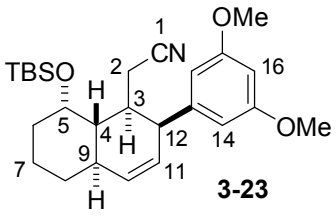

Chloroform-d
159.71
155.44
141.18
134.49
127.05
125.05
120.55
114.95
104.53
95.44
67.14
55.49
55.24
43.59
37.75
35.27
34.35
33.69
32.41
25.90
20.54
18.24
-3.58
-5.10


OMe
OH
TBSO
H
4'
1
8
2
2'
OMe
H
4a
3
6
H

3-15a

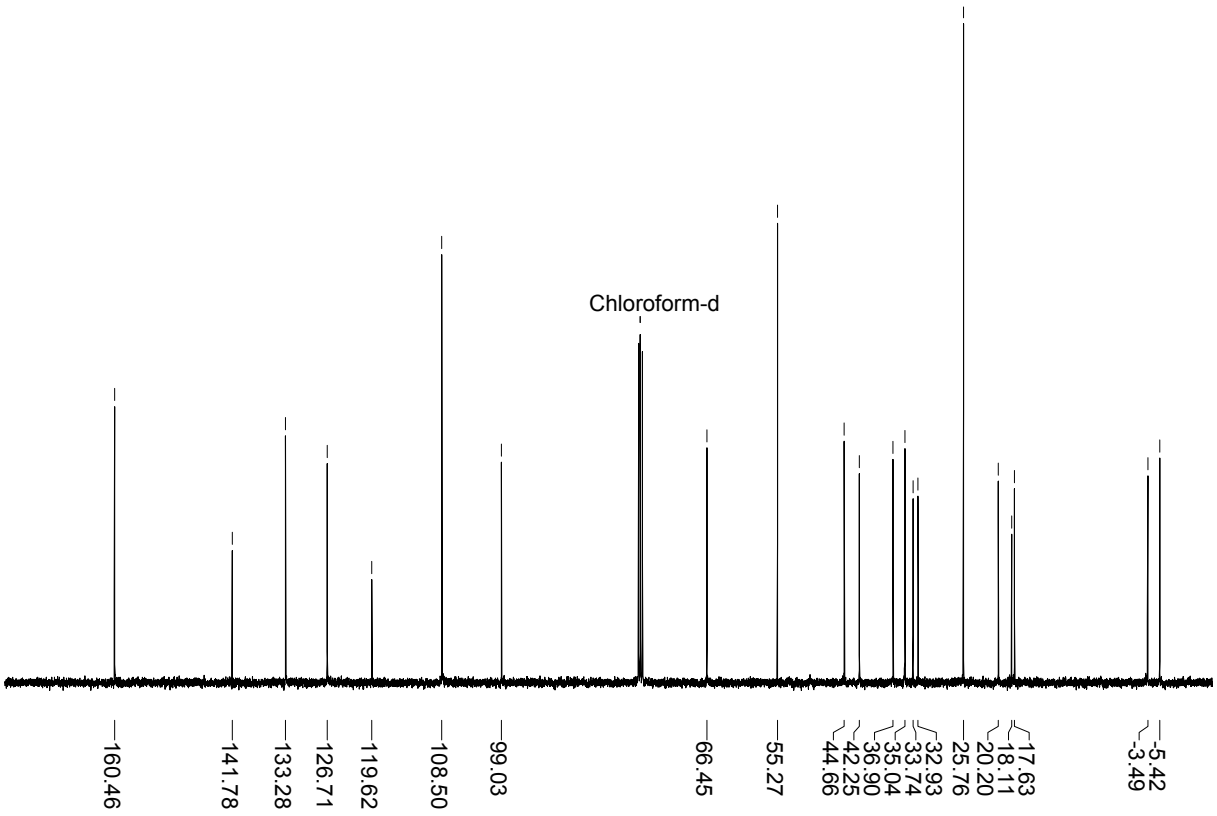
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
ppm

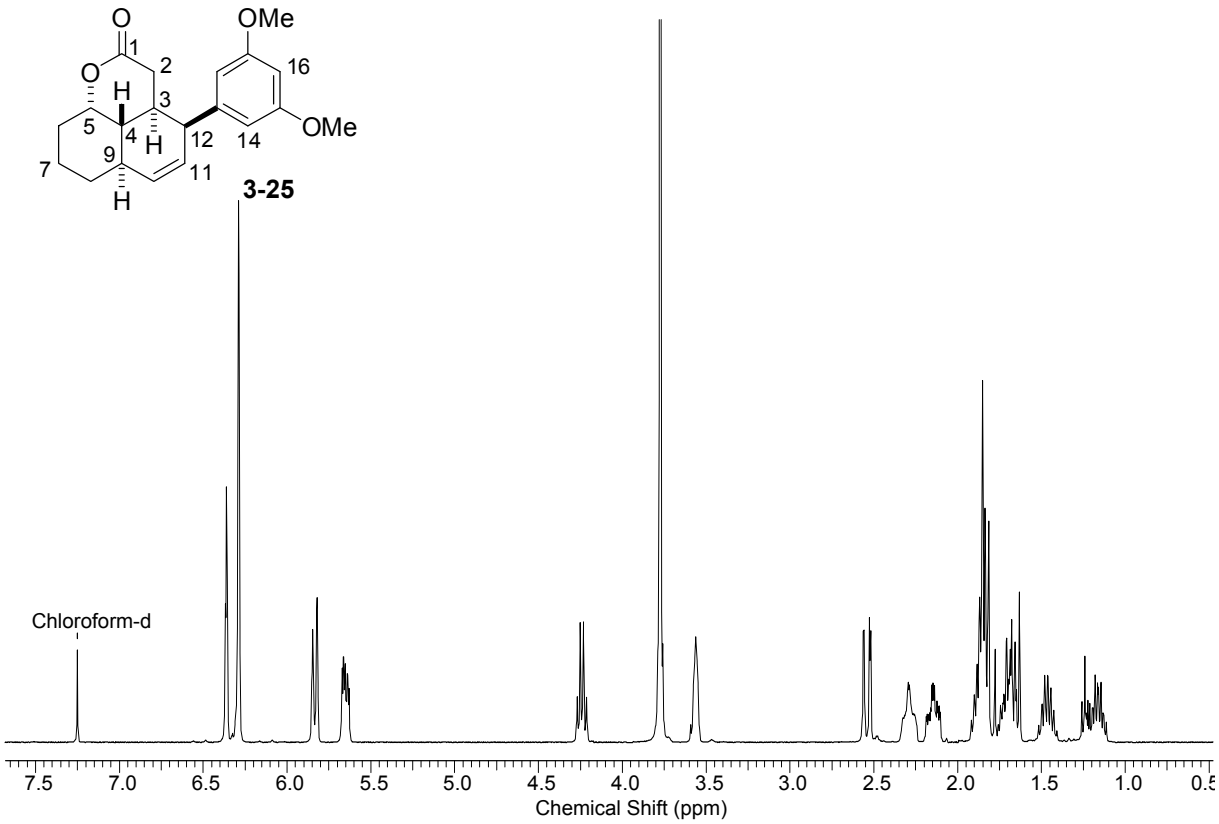

Chloroform-d
160.55
144.25
133.75
127.30
108.22
98.36
67.03
61.67
55.22
44.47
41.27
41.08
34.76
33.99
33.40
25.87
20.51
18.24
-3.53
-5.31

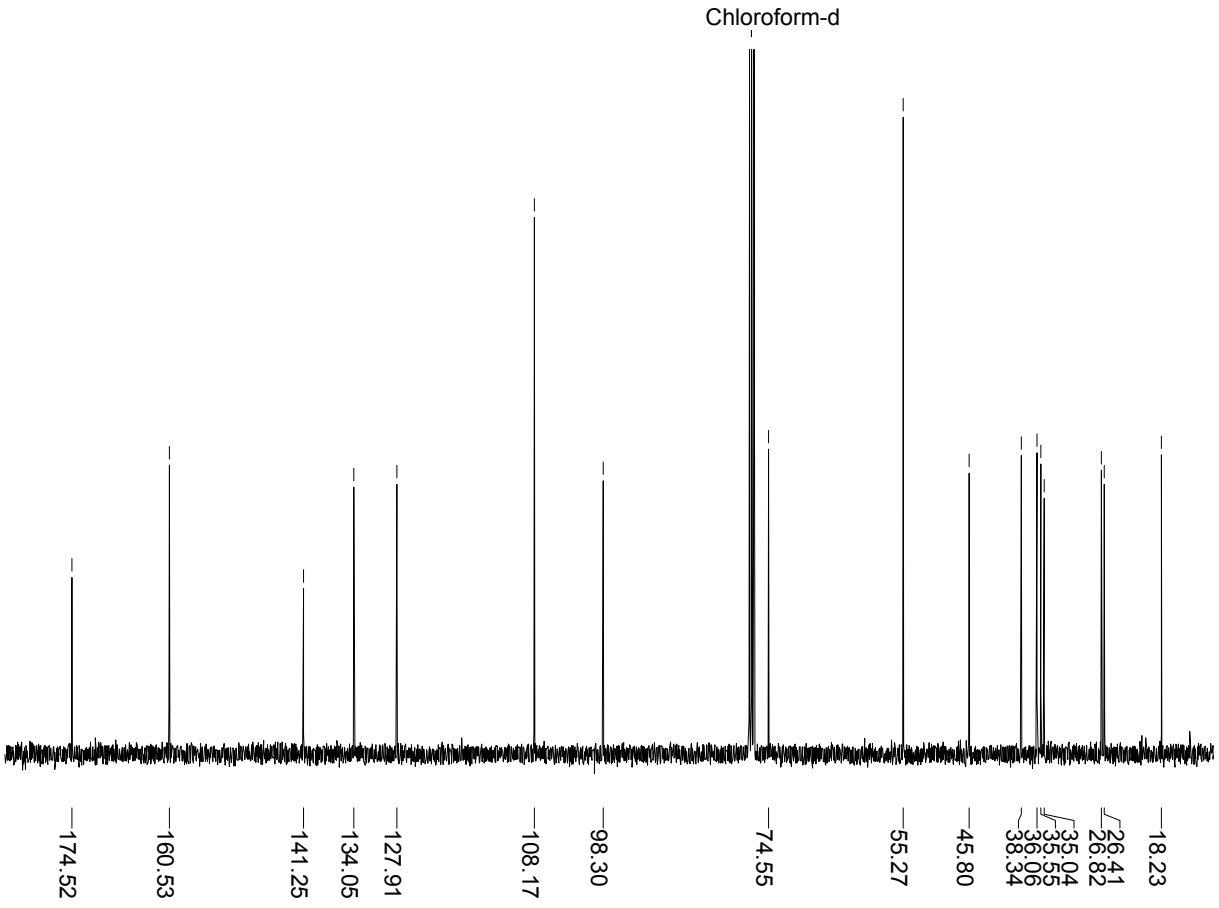

1
OMe
CN
2
16
TBSO
H
3
5
4
H
12
14
OMe
9
7
11
H

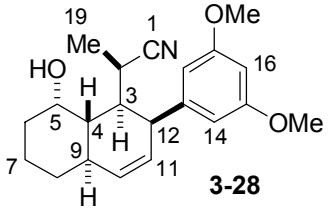
3-23

Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
ppm


Chloroform-d
160.46
141.78
133.28
126.71
119.62
108.50
99.03
66.45
55.27
44.66
42.25
36.90
35.04
33.74
32.93
25.76
20.20
18.11
17.63
-3.49
-5.42

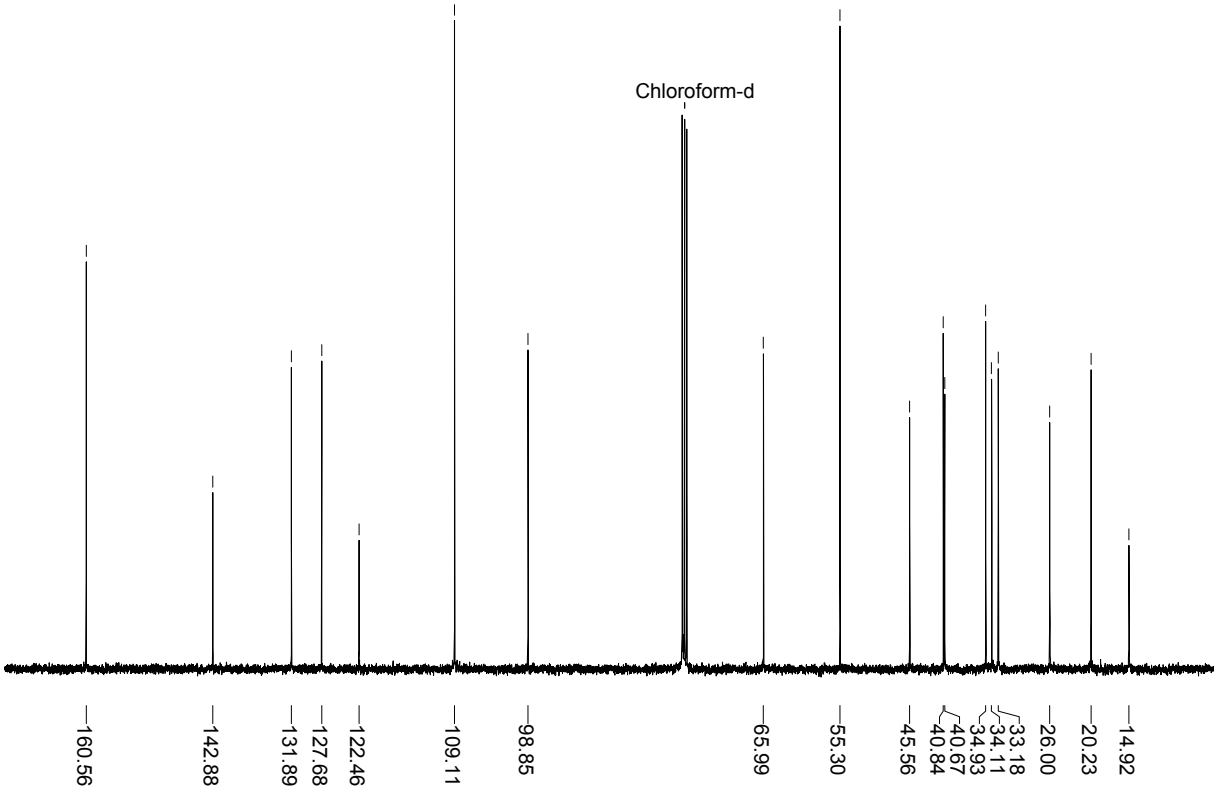

O
OMe
1
2
16
O
H
3
5
4
H
12
14
OMe
9
7
11
H
3-25
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

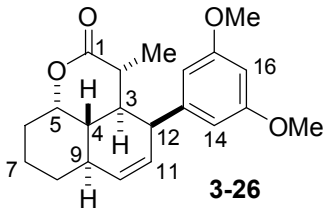

Chloroform-d
174.52
160.53
141.25
134.05
127.91
108.17
98.30
74.55
55.27
45.80
38.34
36.06
35.55
35.04
26.82
26.41
18.23


19
Me
1
CN
OMe
HO
H
3
16
5
4
H
12
14
OMe
9
7
11
H

3-28

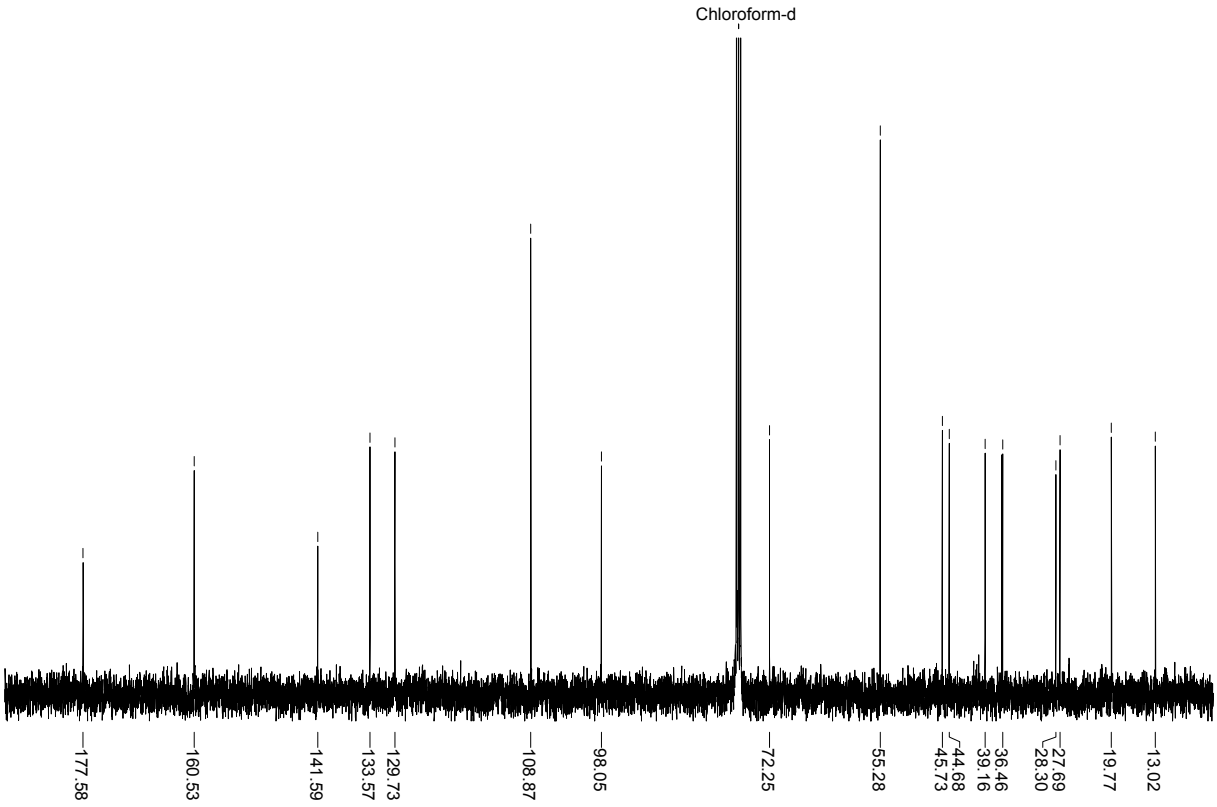
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
ppm

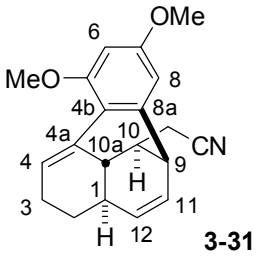

Chloroform-d
160.56
142.88
131.89
127.68
122.46
109.11
98.85
65.99
55.30
45.56
40.84
40.67
34.93
34.11
33.18
26.00
20.23
14.92


O
OMe
1
Me
16
O
H
3
5
4
H
12
14
OMe
9
7
11
H

3-26

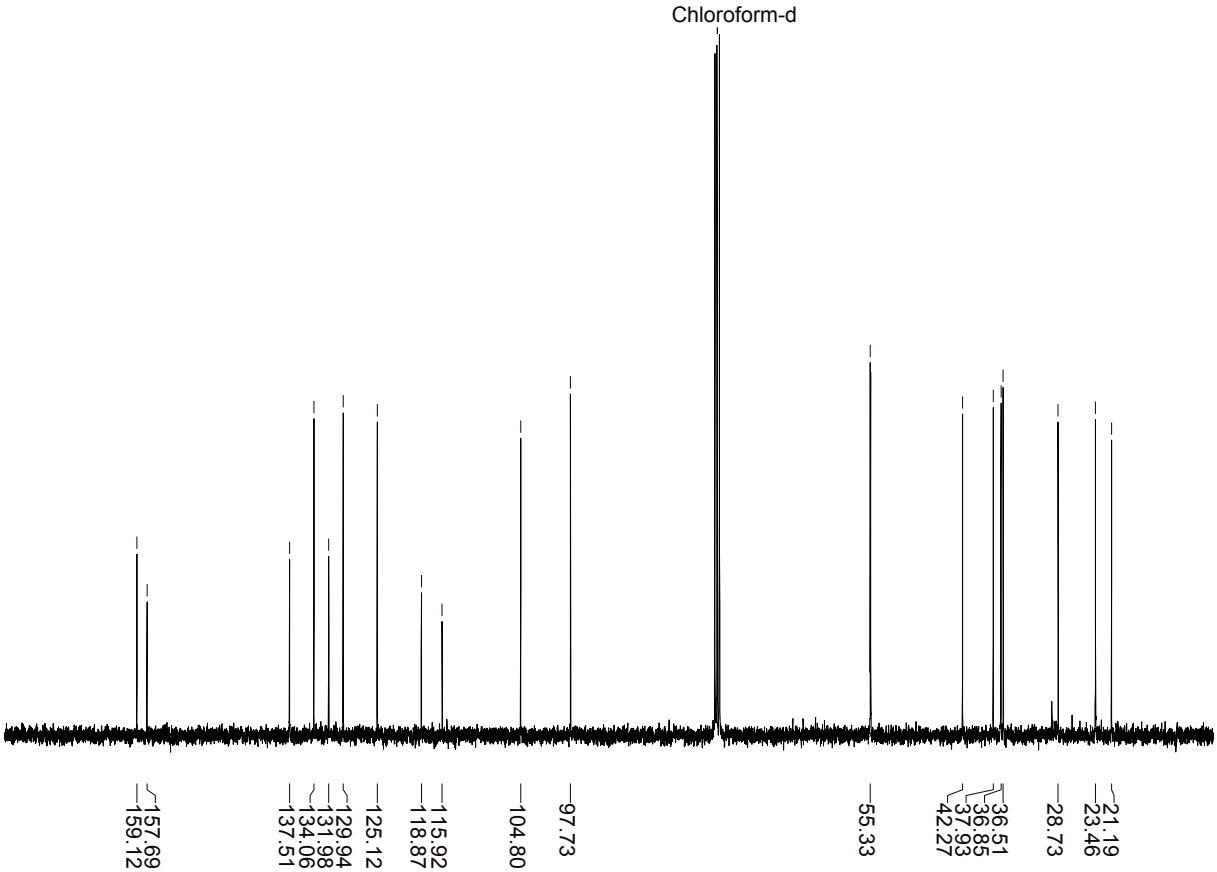
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
ppm

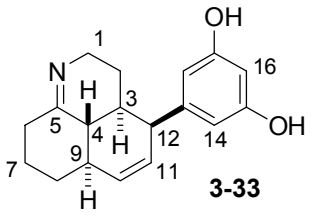

Chloroform-d
177.58
160.53
141.59
133.57
129.73
108.87
98.05
72.25
55.28
45.73
44.68
39.16
36.46
28.30
27.69
19.77
13.02


OMe
6
MeO
8
4b
8a
4a
10
10a
CN
4
9
1
H
3
11
H
12

3-31

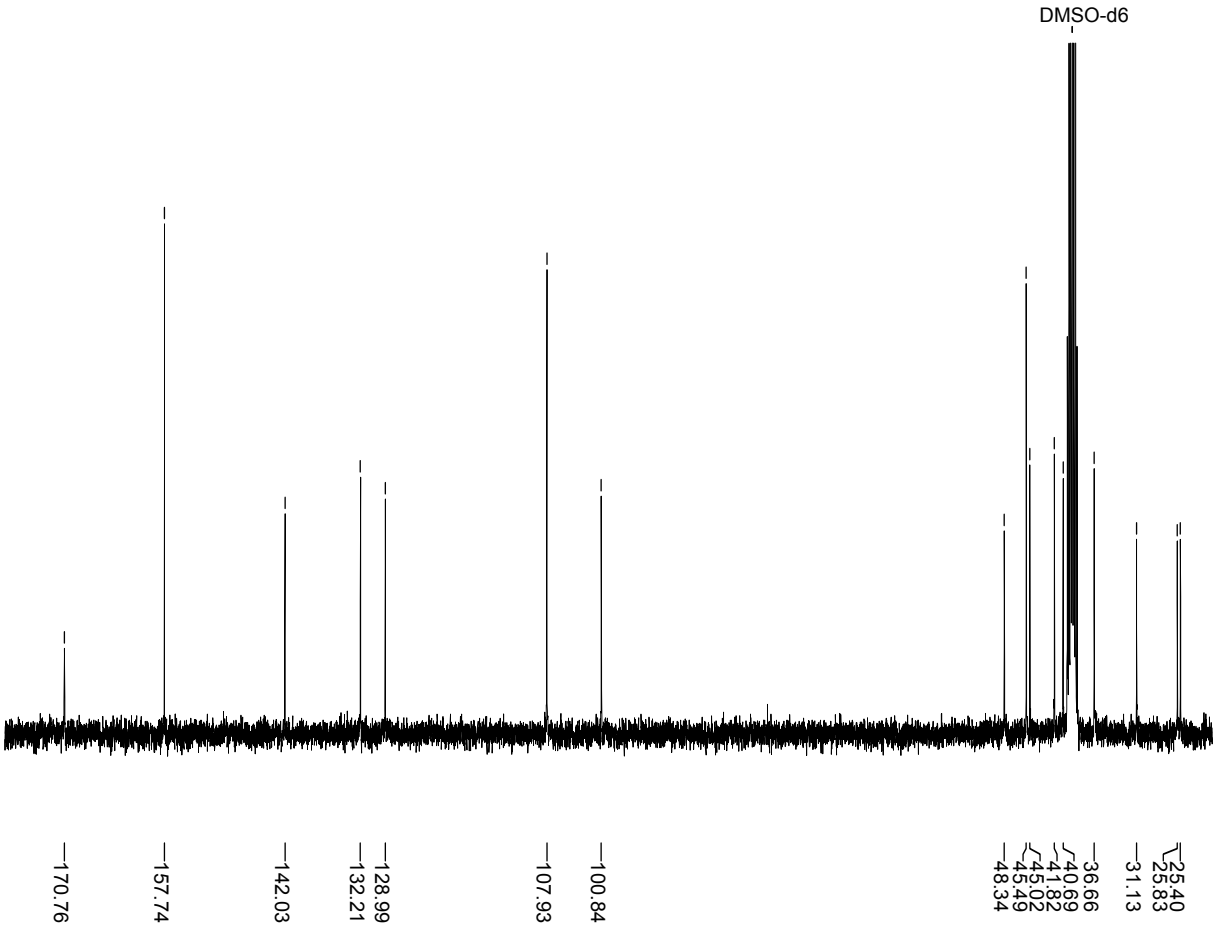
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

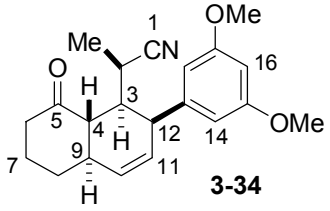

Chloroform-d
157.69
159.12
137.51
134.06
131.98
129.94
125.12
118.87
115.92
104.80
97.73
55.33
42.27
37.93
36.85
36.51
28.73
23.46
21.19


OH
1
N
H
16
3
5
4
H
12
14
OH
9
7
11
H

3-33

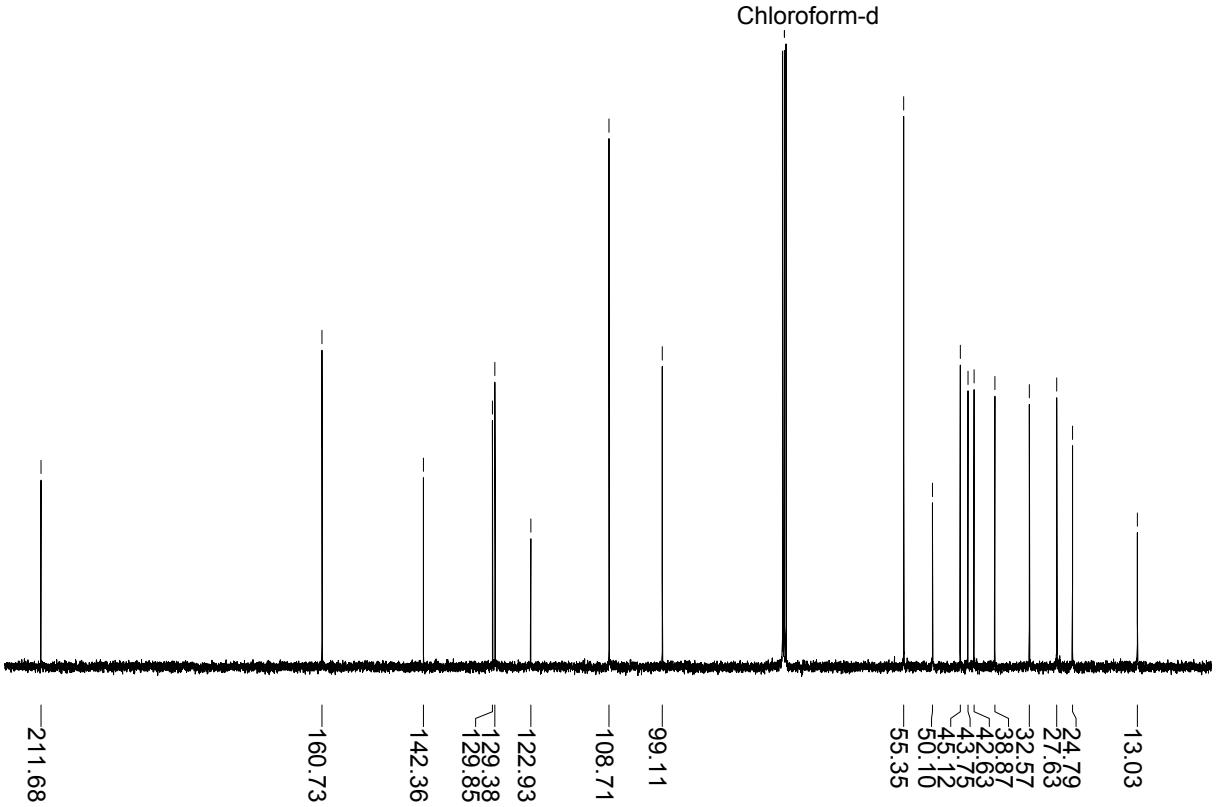
DMSO-d6
water
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm

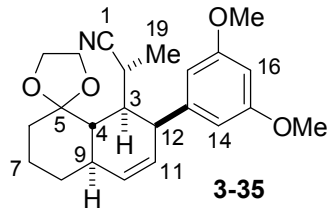

DMSO-d6
170.76
157.74
142.03
132.21
128.99
107.93
100.84
48.34
45.49
45.02
41.82
40.69
36.66
31.13
25.83
25.40


1
OMe
Me
CN
16
O
H
3
5
4
H
12
14
OMe
9
7
11
H

3-34

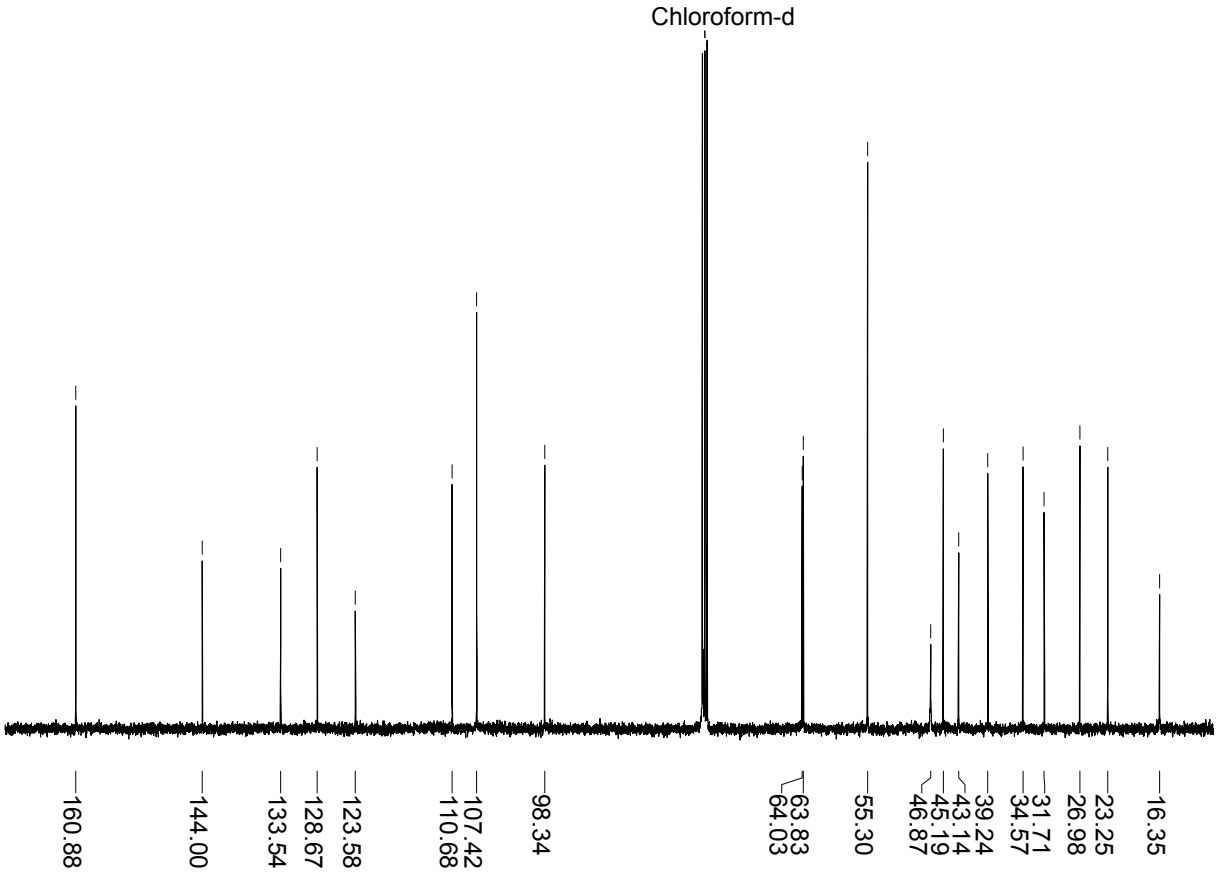
Chloroform-d
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
ppm

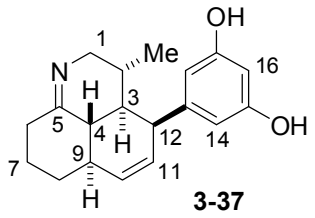

Chloroform-d
211.68
160.73
142.36
129.38
129.85
122.93
108.71
99.11
55.35
50.10
45.12
43.75
42.63
38.87
32.57
27.63
24.79
13.03


1
NC
19
Me
OMe
16
O
O
3
5
4
H
12
14
OMe
9
7
11
H

3-35

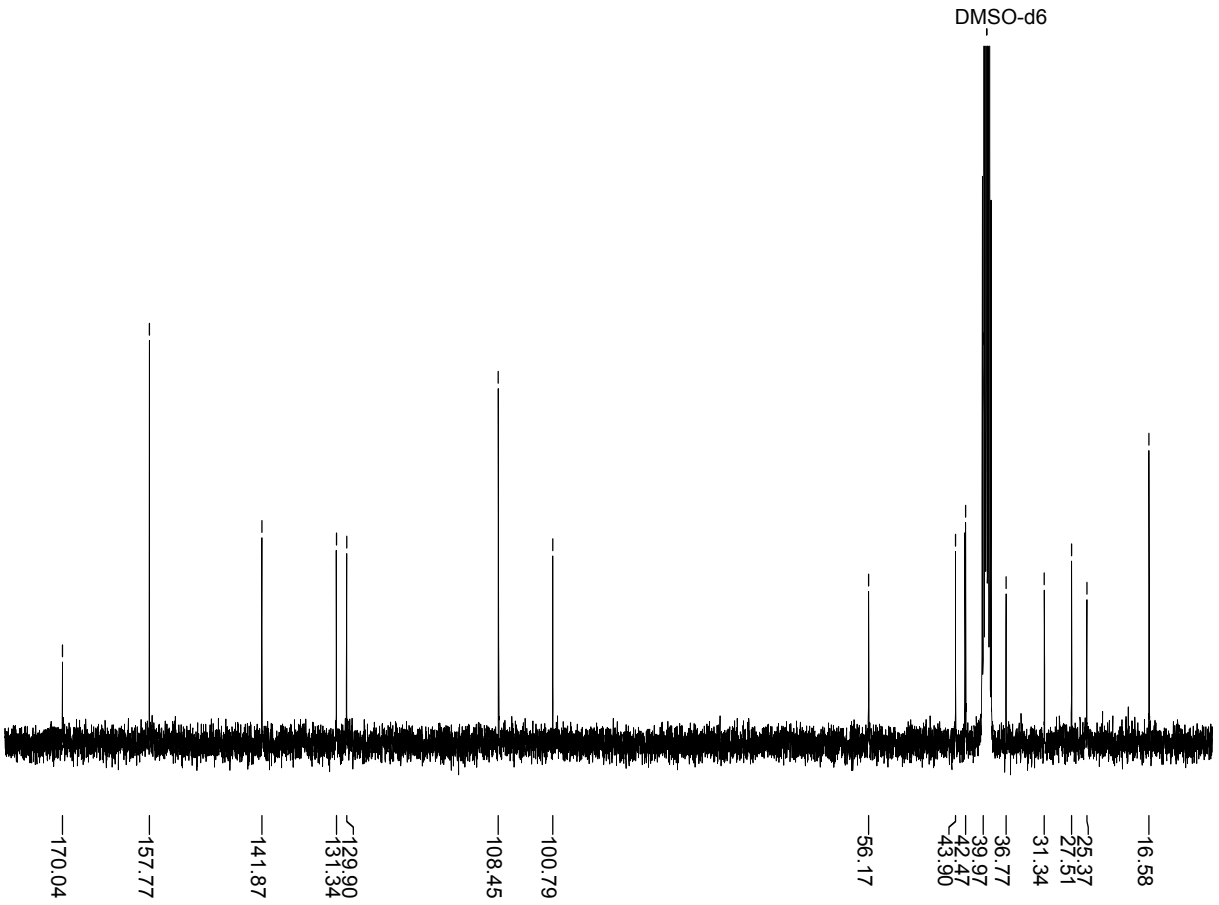
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

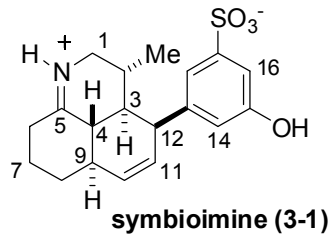

Chloroform-d
160.88
144.00
133.54
128.67
123.58
110.68
107.42
98.34
64.03
63.83
55.30
46.87
45.19
43.14
39.24
34.57
31.71
26.98
23.25
16.35


OH
1
Me
16
N
H
3
5
4
H
12
14
OH
9
7
11
H

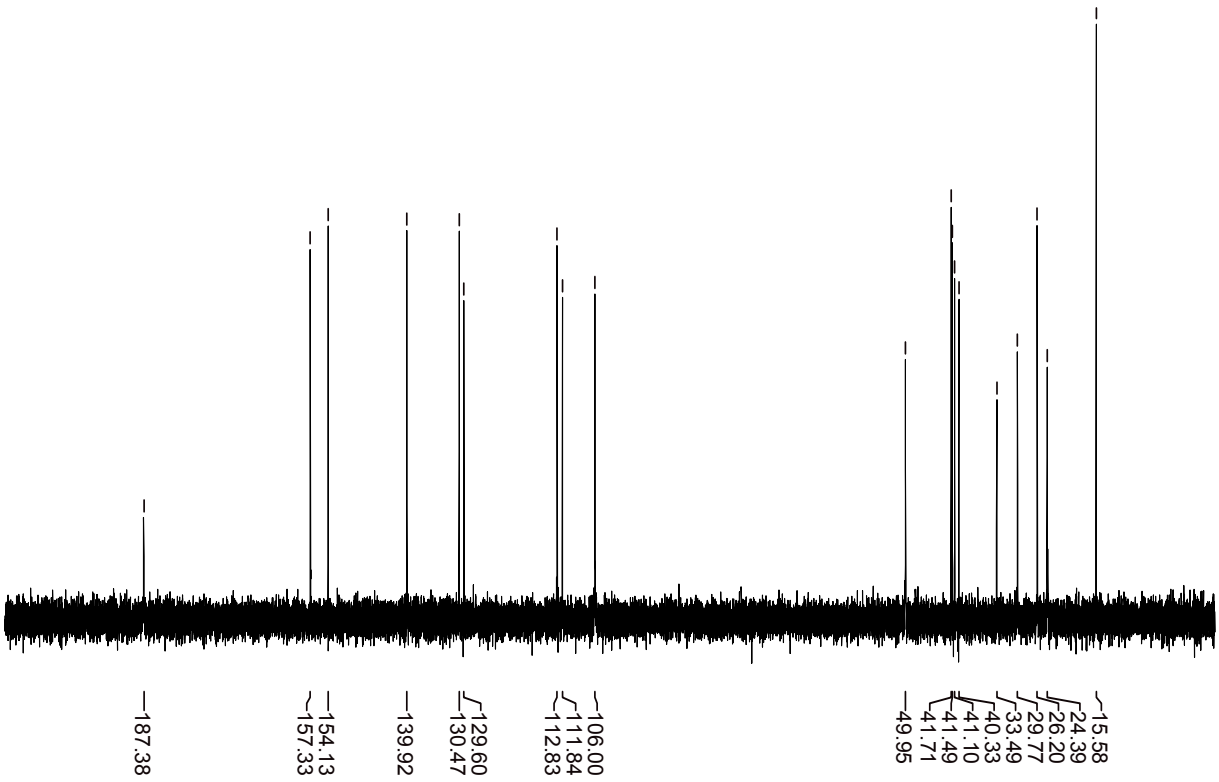
3-37

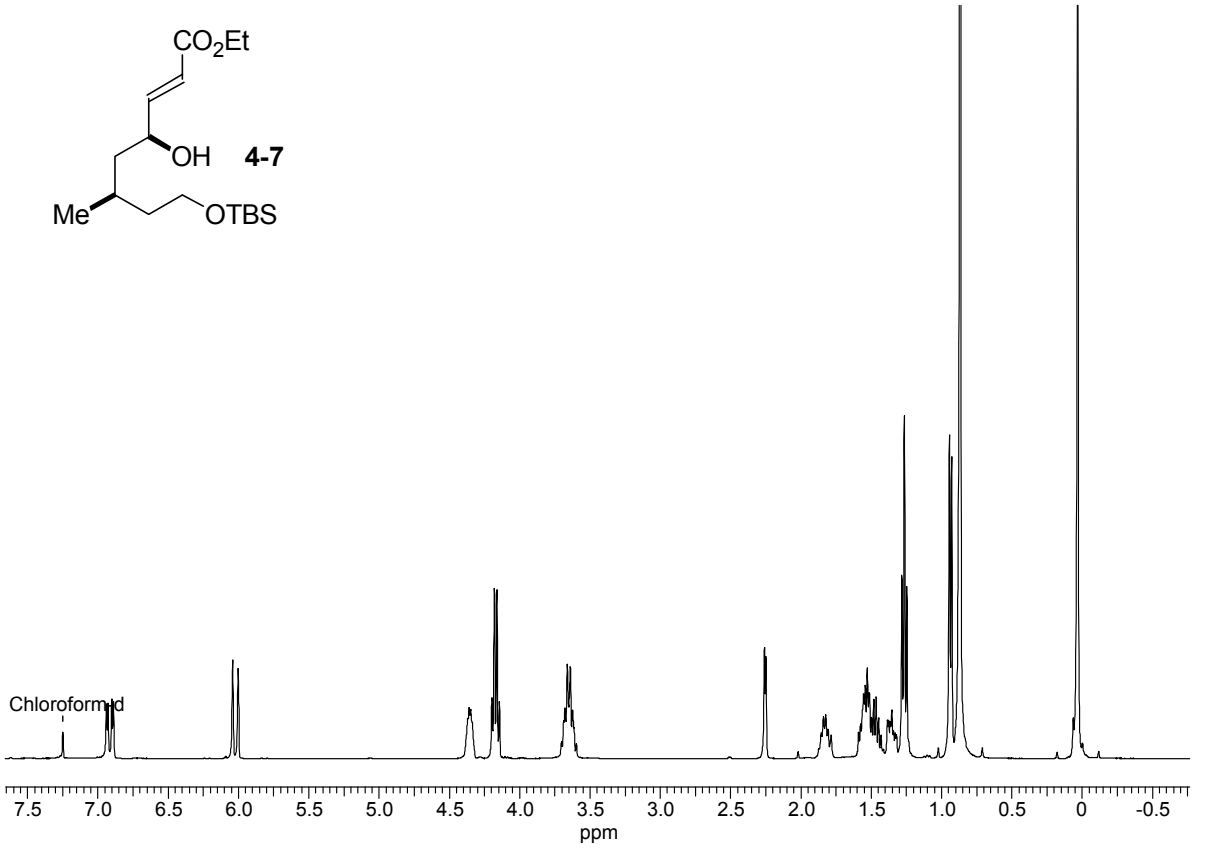
DMSO-d6
water
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

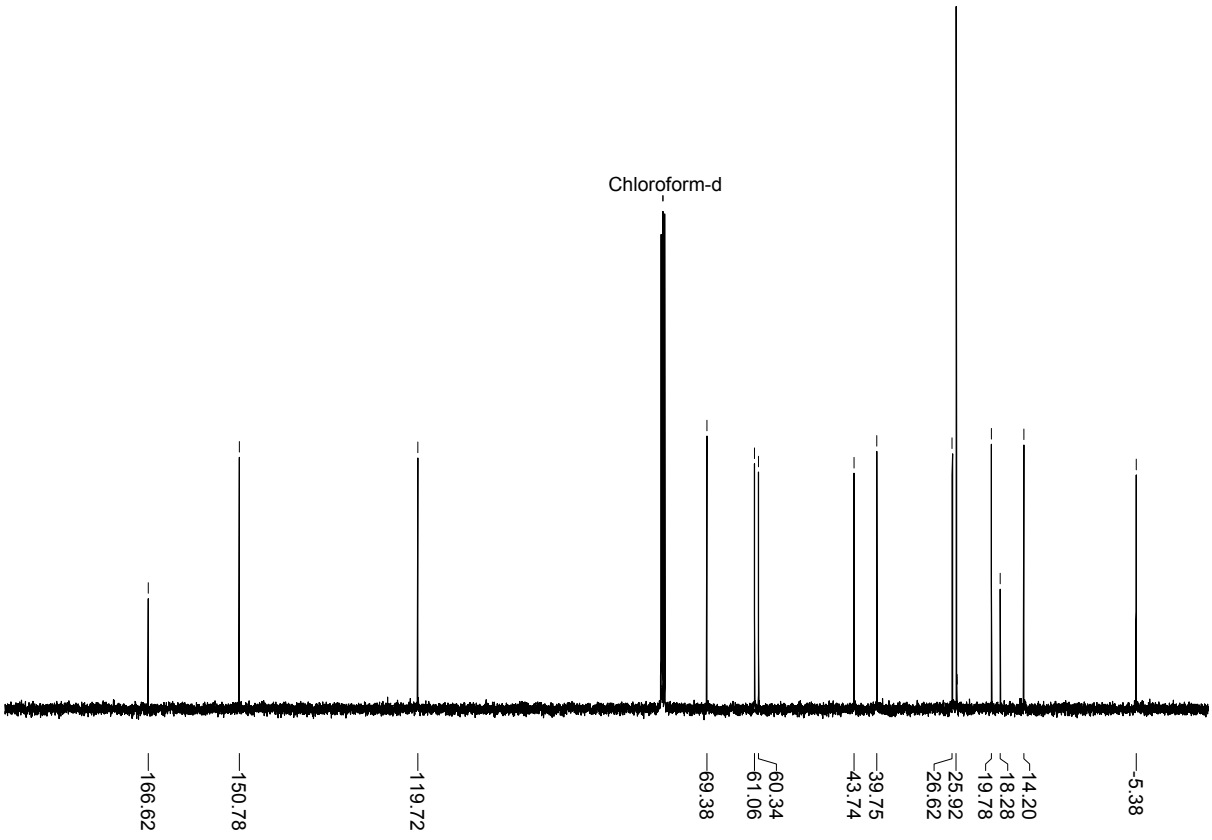

DMSO-d6
170.04
157.77
141.87
129.90
131.34
108.45
100.79
56.17
42.47
43.90
39.97
36.77
31.34
25.37
27.51
16.58

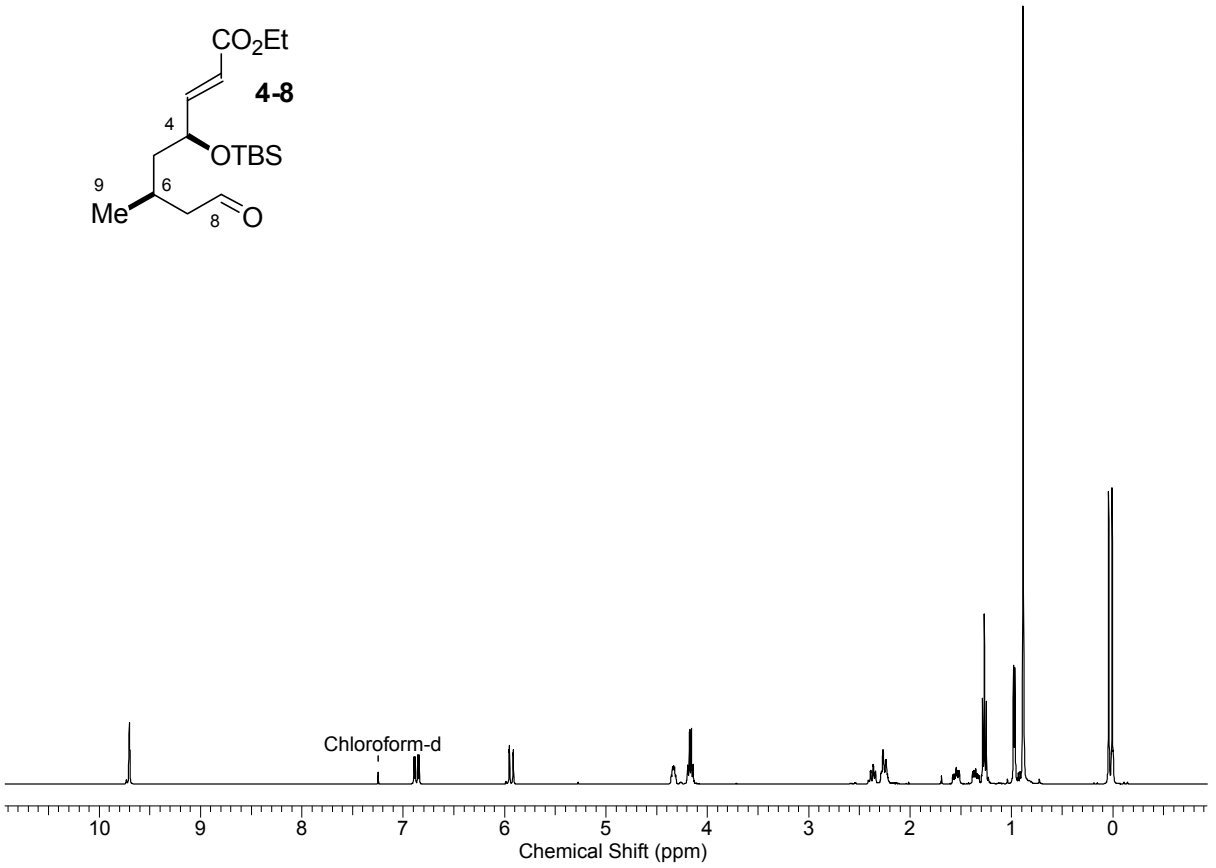


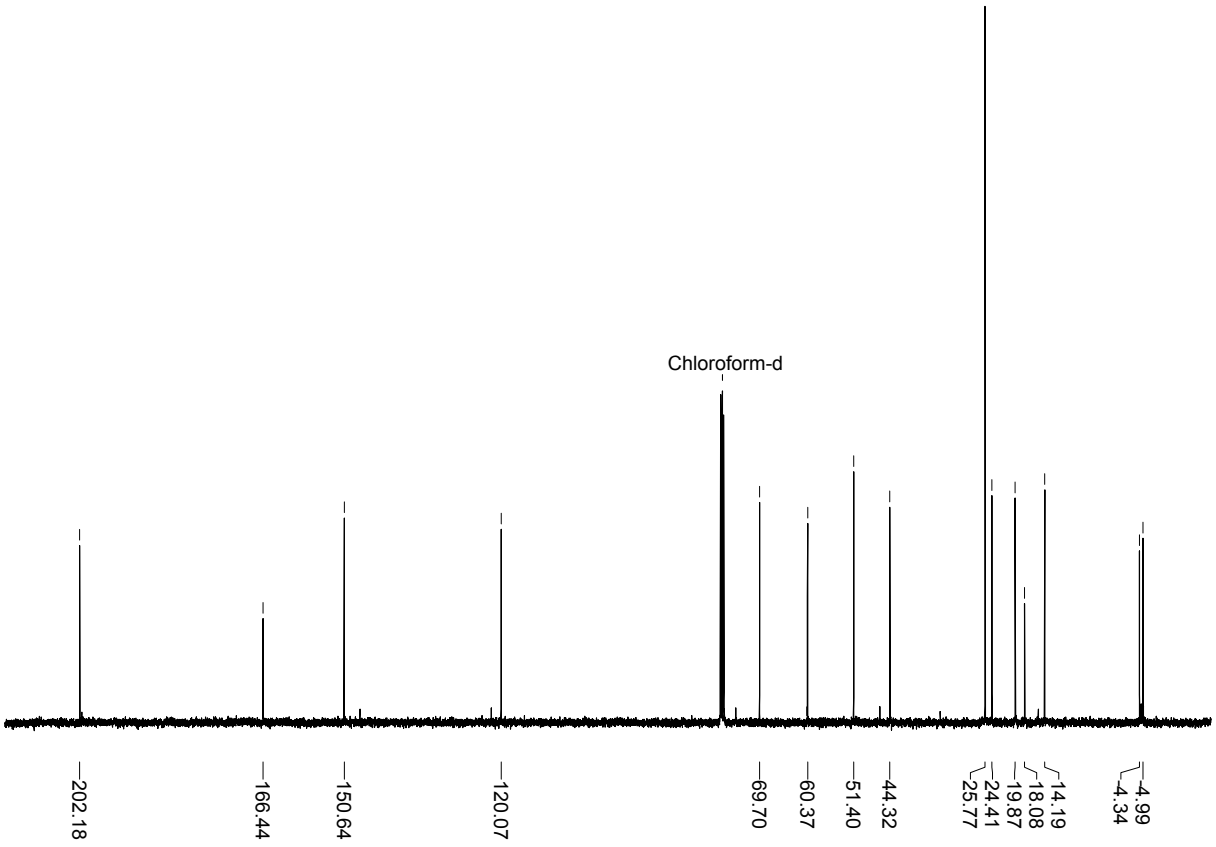
symbioimine (3-1)

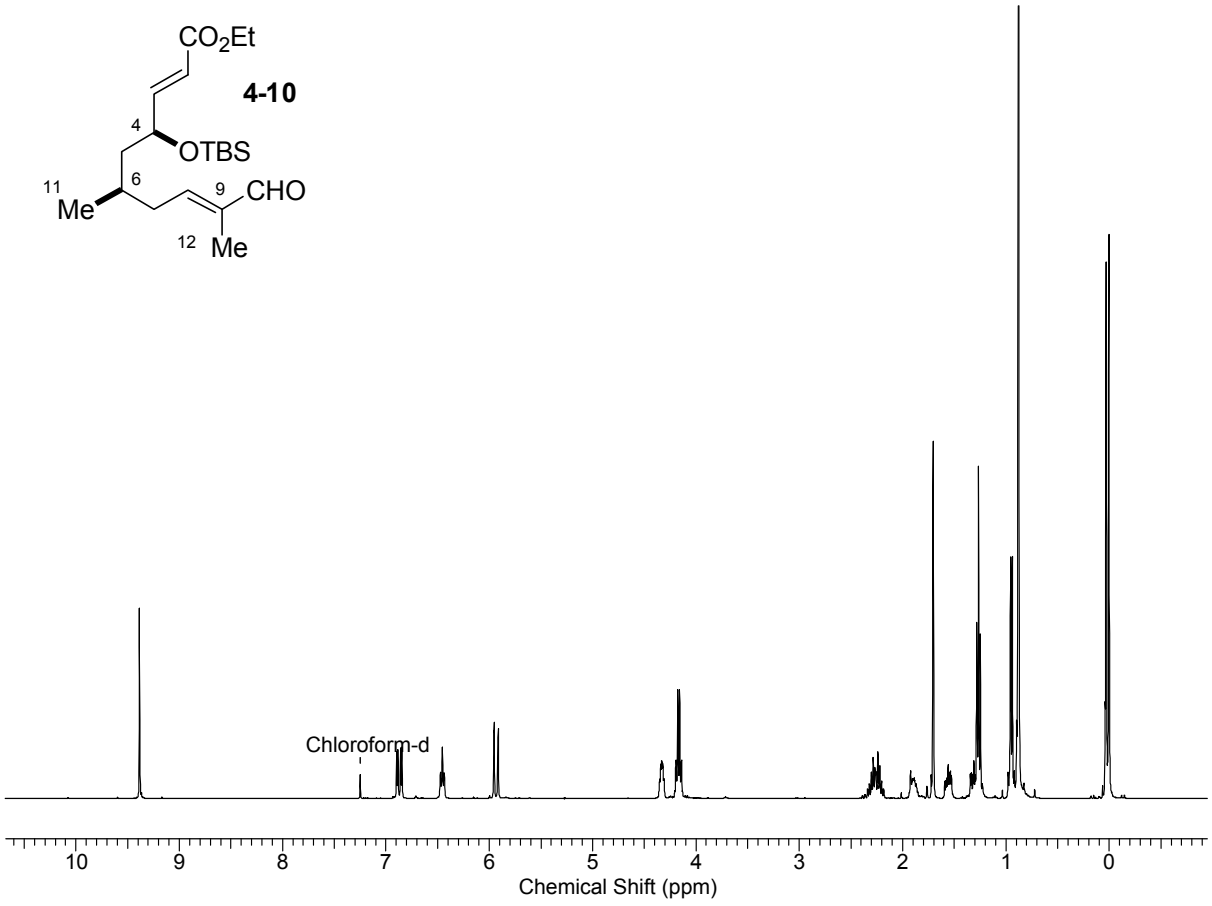


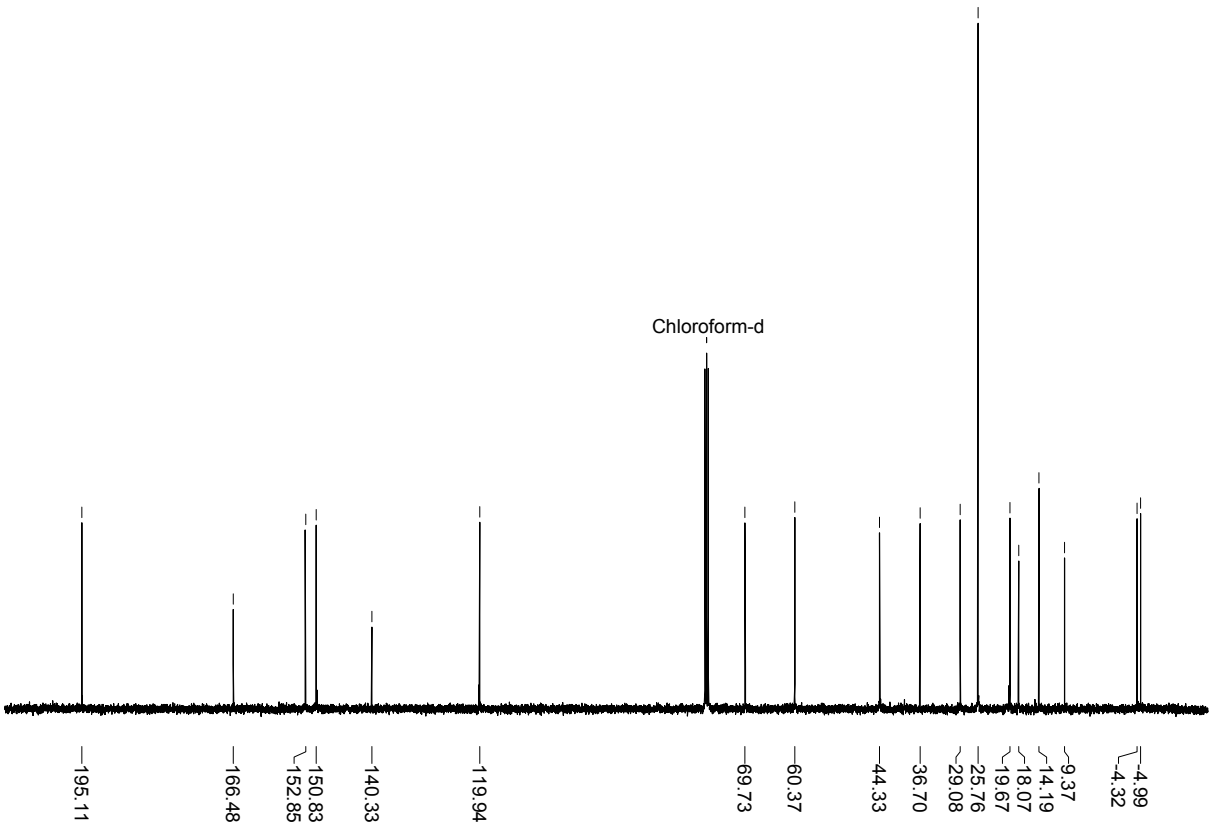

CO2Et
OH
4-7
Me
OTBS
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
ppm

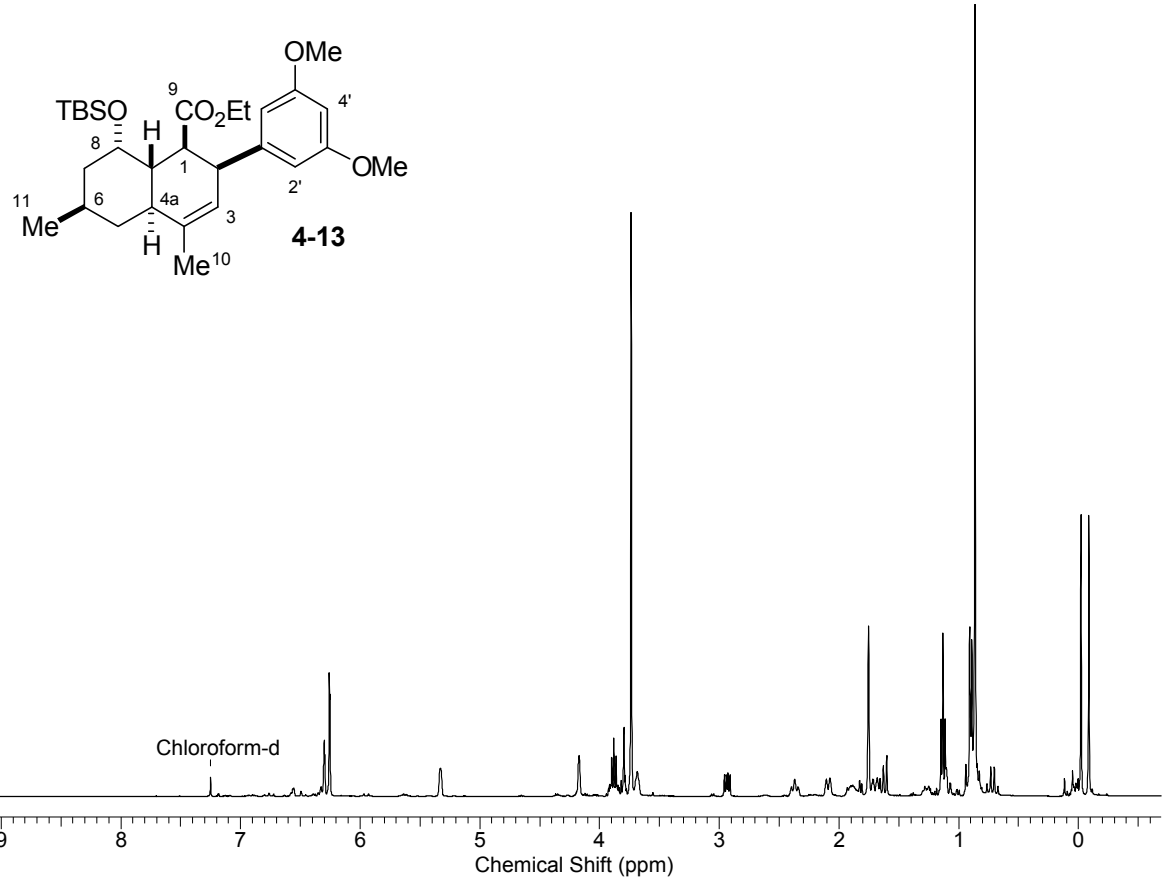

Chloroform-d
166.62
150.78
119.72
69.38
60.34
61.06
43.74
39.75
26.62
25.92
19.78
18.28
14.20
-5.38

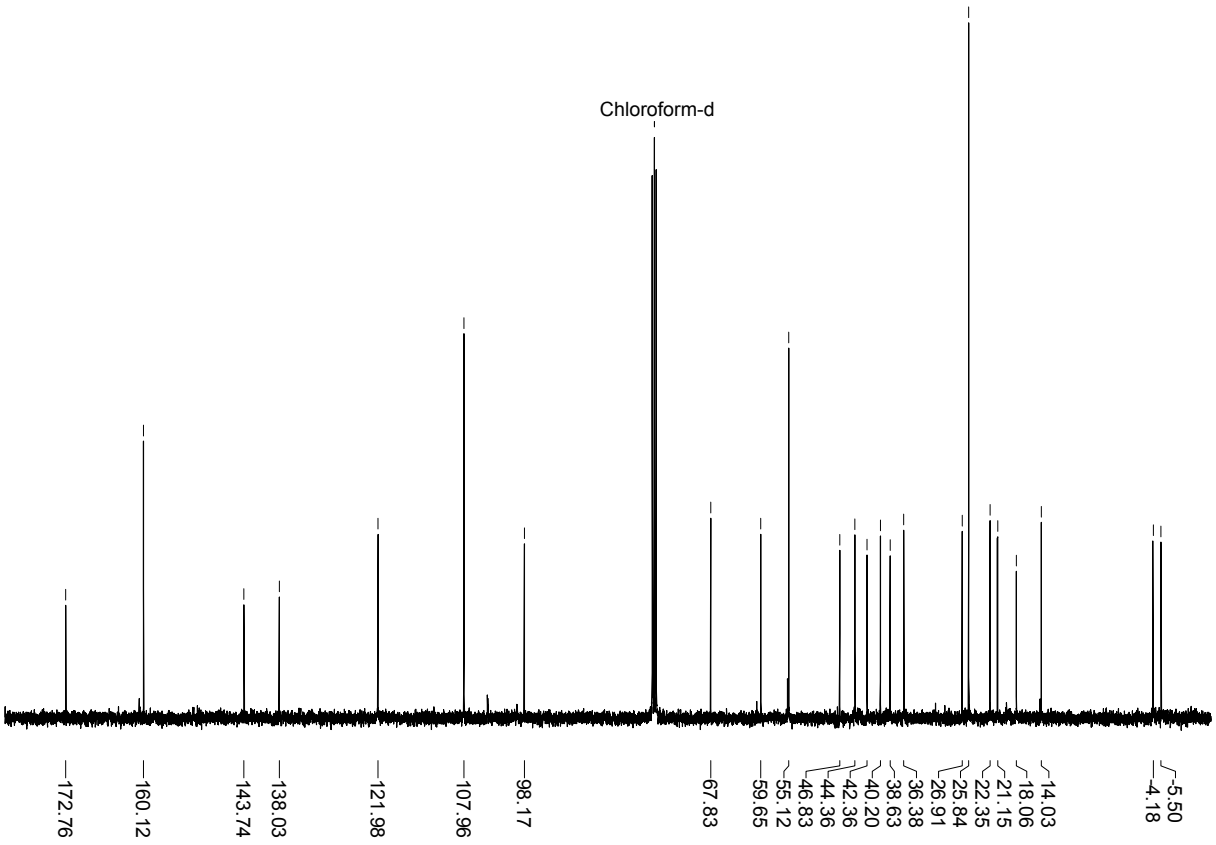

CO2Et
4-8
4
OTBS
9
6
Me
8
O
Chloroform-d
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

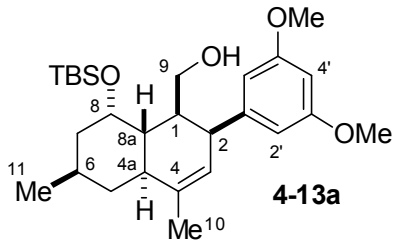

Chloroform-d
202.18
166.44
150.64
120.07
69.70
60.37
51.40
44.32
25.77
24.41
19.87
18.08
14.19
4.99
4.34


CO2Et
4-10
4
OTBS
6
11
Me
9
CHO
12
Me
Chloroform-d
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Chloroform-d
195.11
166.48
152.85
150.83
140.33
119.94
69.73
60.37
44.33
36.70
29.08
25.76
19.67
18.07
14.19
9.37
4.32
4.99

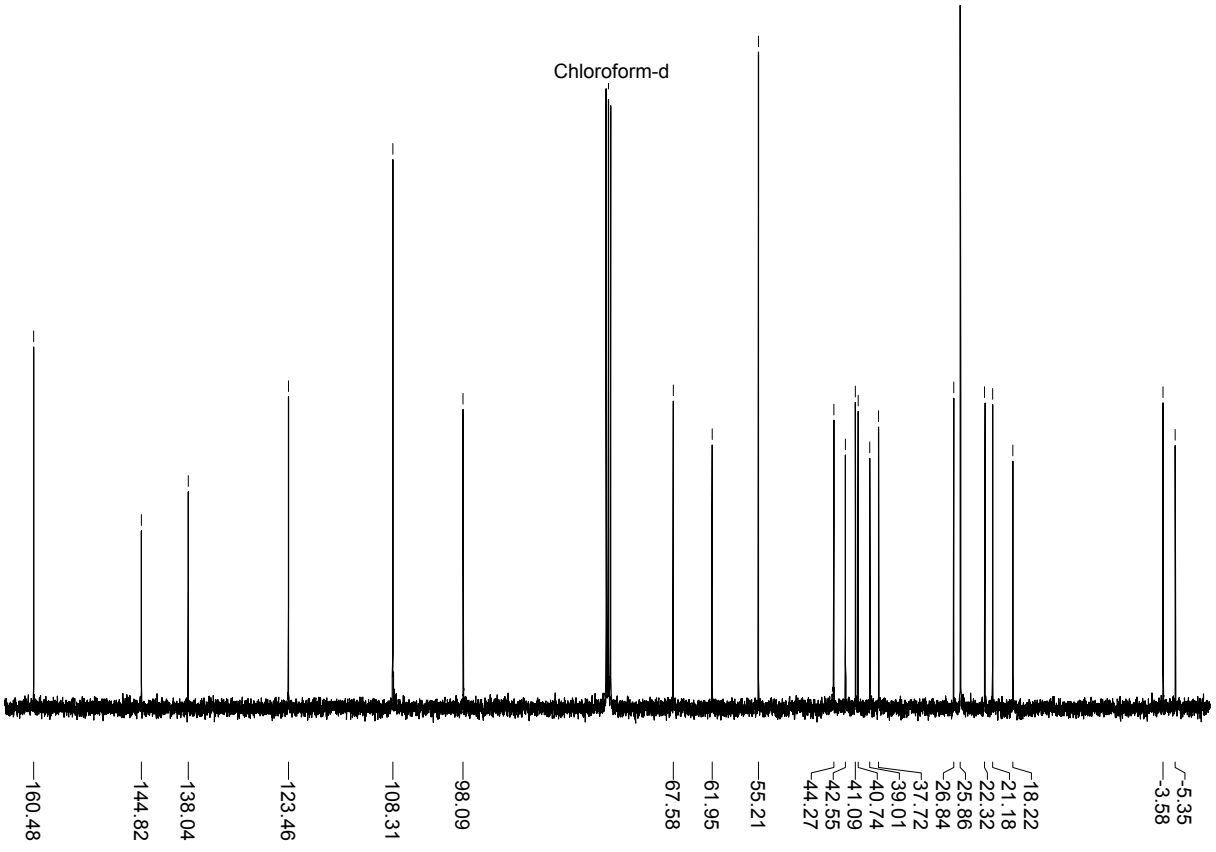

OMe
9
TBSO
CO2Et
4'
H
8
1
OMe
2'
11
6
4a
3
Me
H
Me10
4-13
Chloroform-d
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

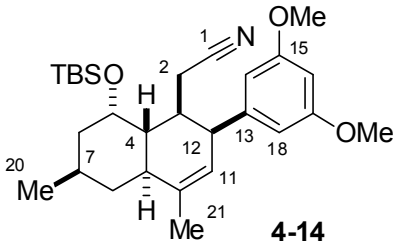

Chloroform-d
172.76
160.12
143.74
138.03
121.98
107.96
98.17
67.83
59.65
55.12
46.83
44.36
42.36
40.20
38.63
36.38
26.91
25.84
22.35
21.15
18.06
14.03
-4.18
-5.50


OMe
TBSO
9
OH
4'
8
H
1
2
OMe
8a
2'
11
6
4a
4
Me
H
Me10

4-13a

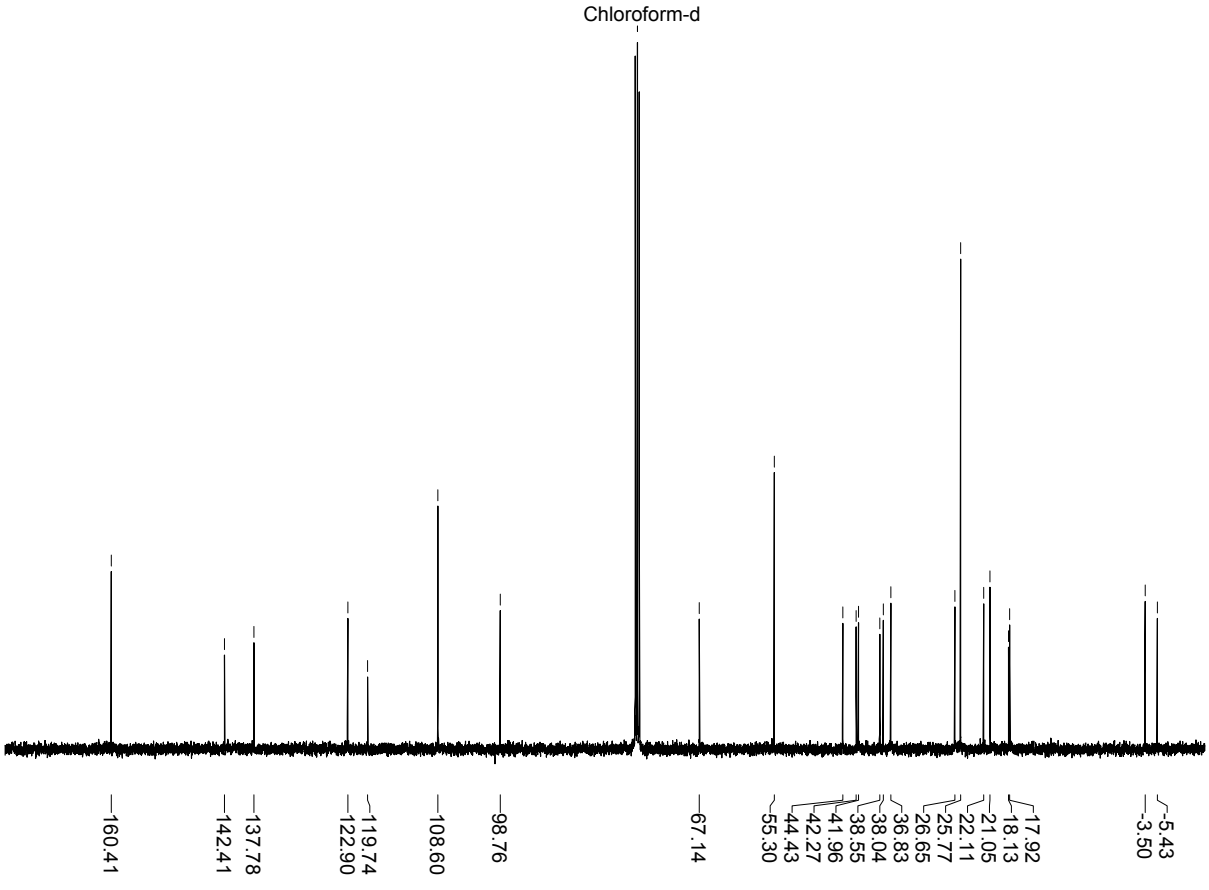
Chloroform-d
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

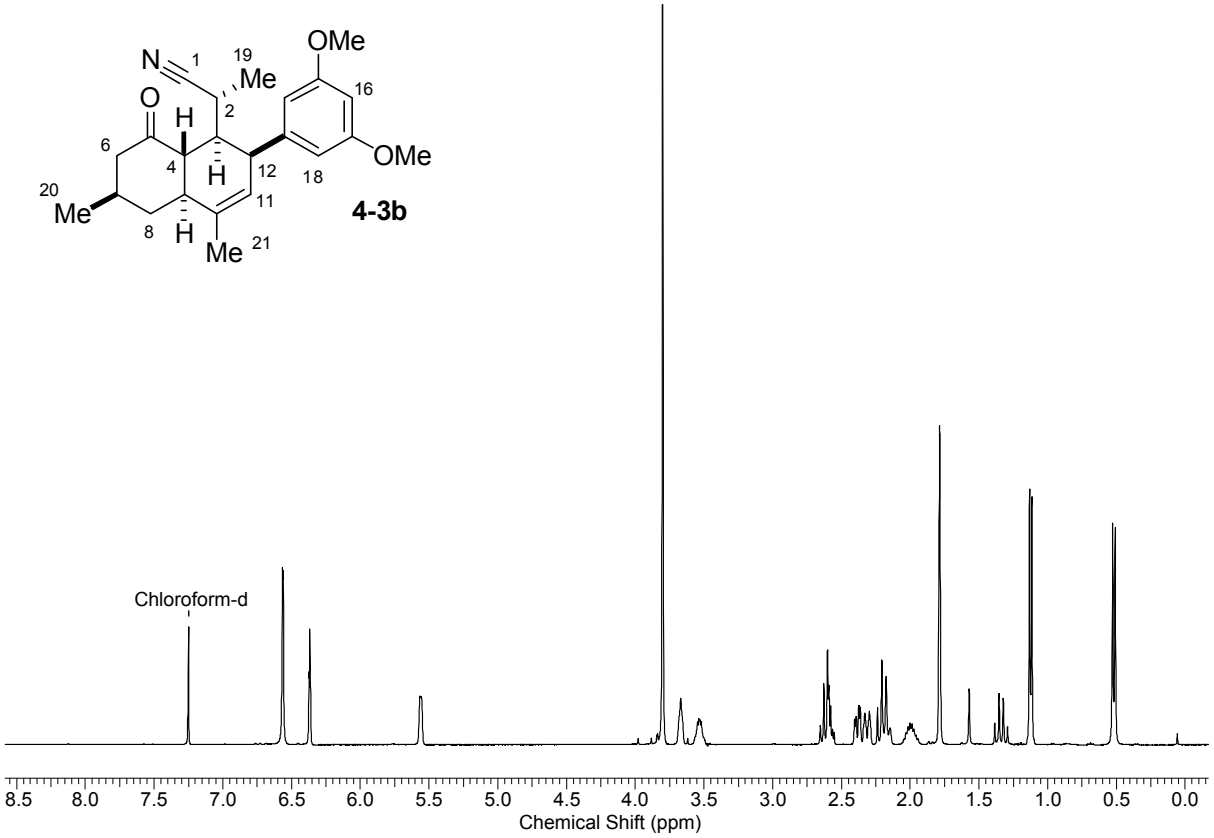

Chloroform-d
160.48
144.82
138.04
123.46
108.31
98.09
67.58
61.95
55.21
44.27
42.55
41.09
40.74
39.01
37.72
26.84
25.86
22.32
21.18
18.22
-3.58
-5.35

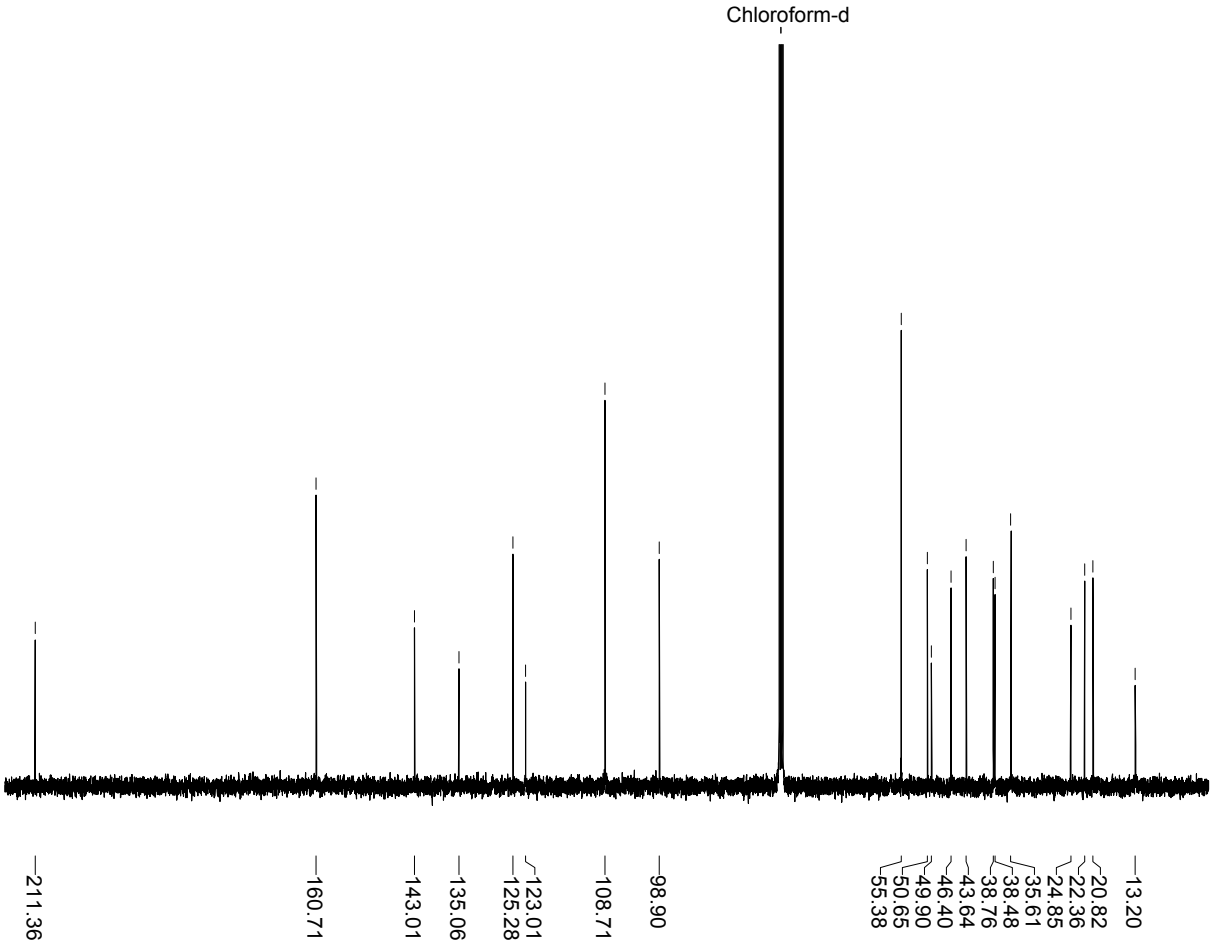

OMe
1
N
15
TBSO
2
H
4
12
13
18
OMe
20
7
11
Me
H
Me
21

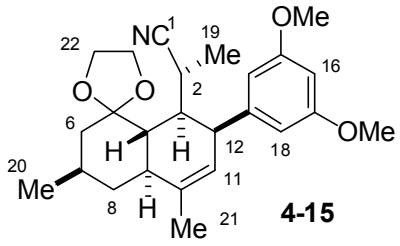
4-14

Chloroform-d
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Chloroform-d
160.41
142.41
137.78
122.90
119.74
108.60
98.76
67.14
55.30
44.43
42.27
41.96
38.55
38.04
36.83
26.65
25.77
22.11
21.05
18.13
17.92
-3.50
-5.43

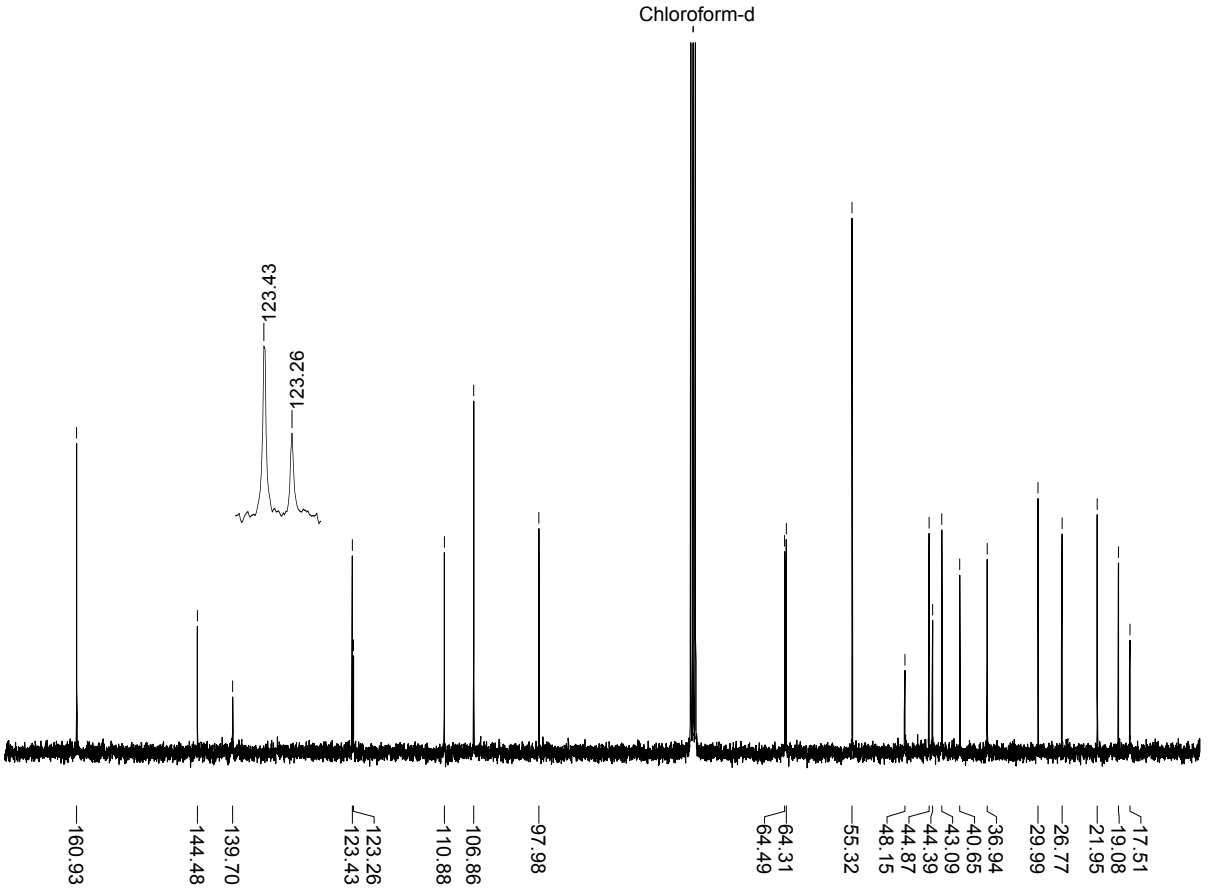

OMe
N
1
19
Me
16
O
H
2
6
4
12
18
OMe
H
20
Me
11
8
H
Me
21
4-3b
Chloroform-d
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)

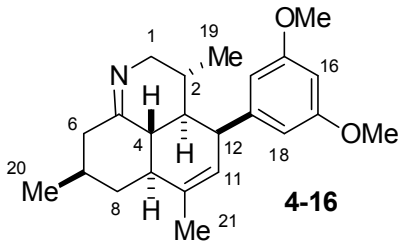

Chloroform-d
211.36
160.71
143.01
135.06
125.28
123.01
108.71
98.90
55.38
50.65
49.90
46.40
43.64
38.76
38.48
35.61
24.85
22.36
20.82
13.20


NC
1
19
Me
OMe
22
16
O
O
2
6
OMe
H
H
12
18
20
Me
11
8
H
Me
21

4-15

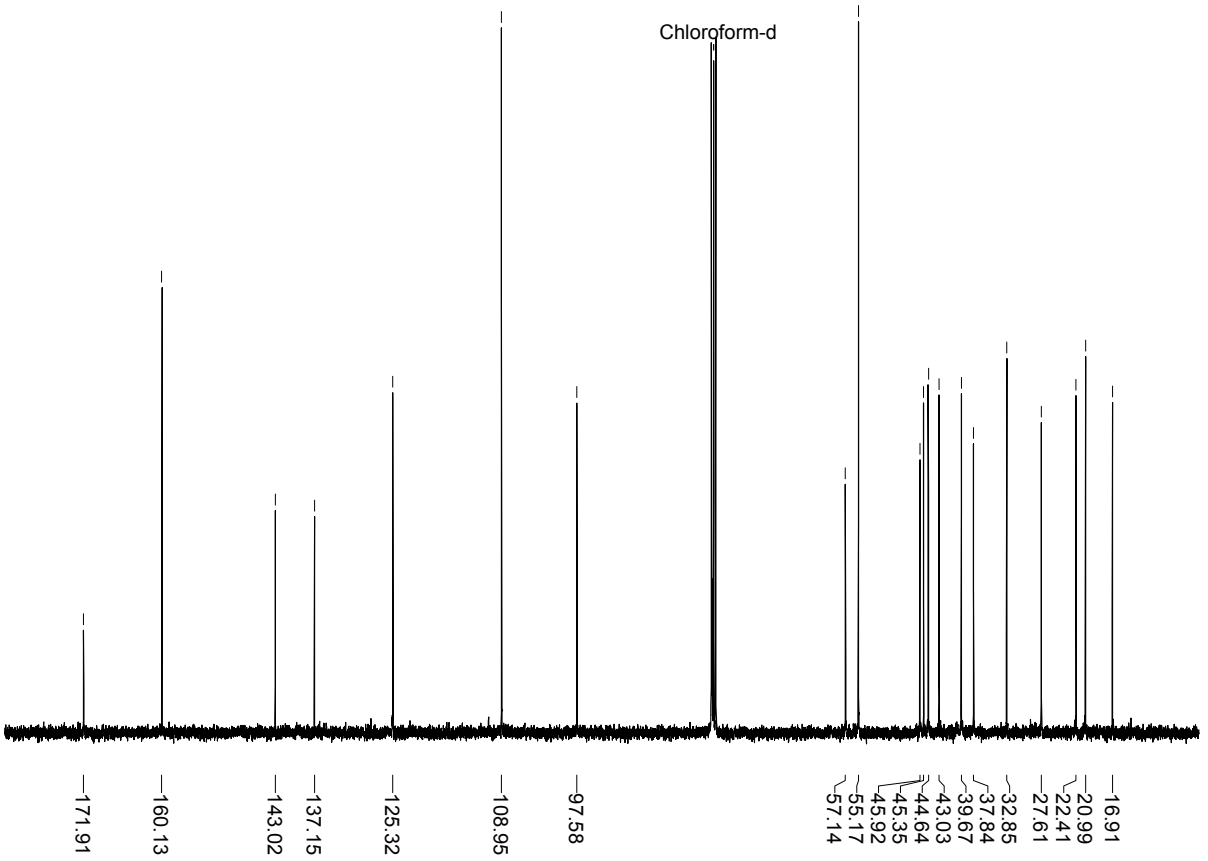
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

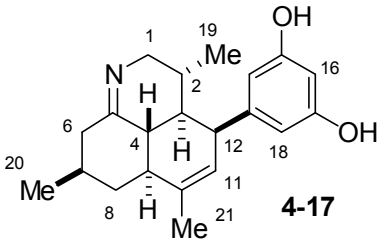

Chloroform-d
123.43
123.26
160.93
144.48
139.70
123.43
123.26
110.88
106.86
97.98
64.49
64.31
55.32
48.15
44.87
44.39
43.09
40.65
36.94
29.99
26.77
21.95
19.08
17.51


OMe
1
19
Me
16
N
H
2
6
4
H
12
18
OMe
20
Me
11
8
H
Me 21

4-16

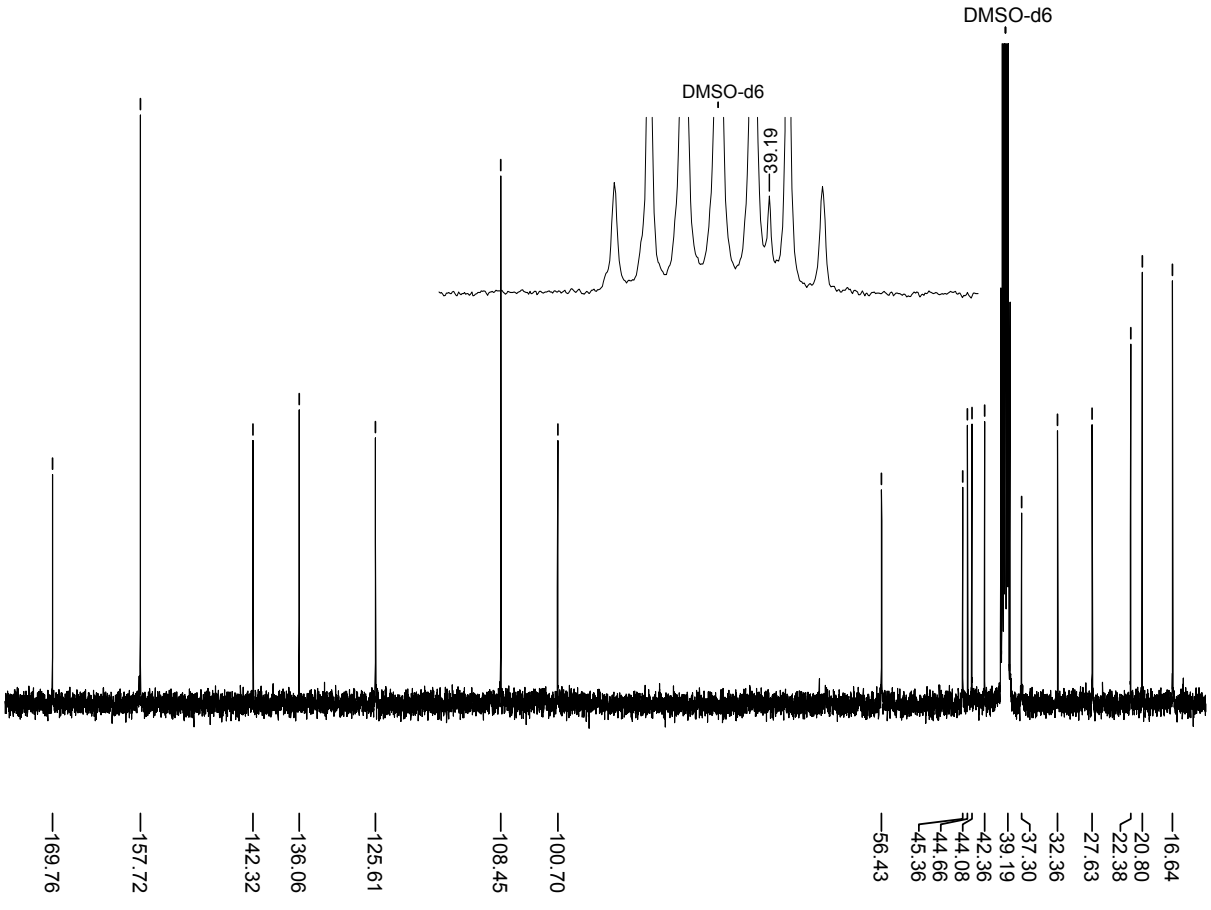
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

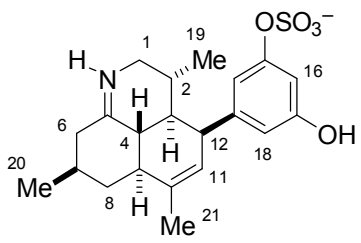

Chloroform-d
171.91
160.13
143.02
137.15
125.32
108.95
97.58
57.14
55.17
45.92
45.35
44.64
43.03
39.67
37.84
32.85
27.61
22.41
20.99
16.91


OH
19
Me
1
N
H
2
16
6
4
H
12
18
OH
20
Me
11
8
H
21
Me

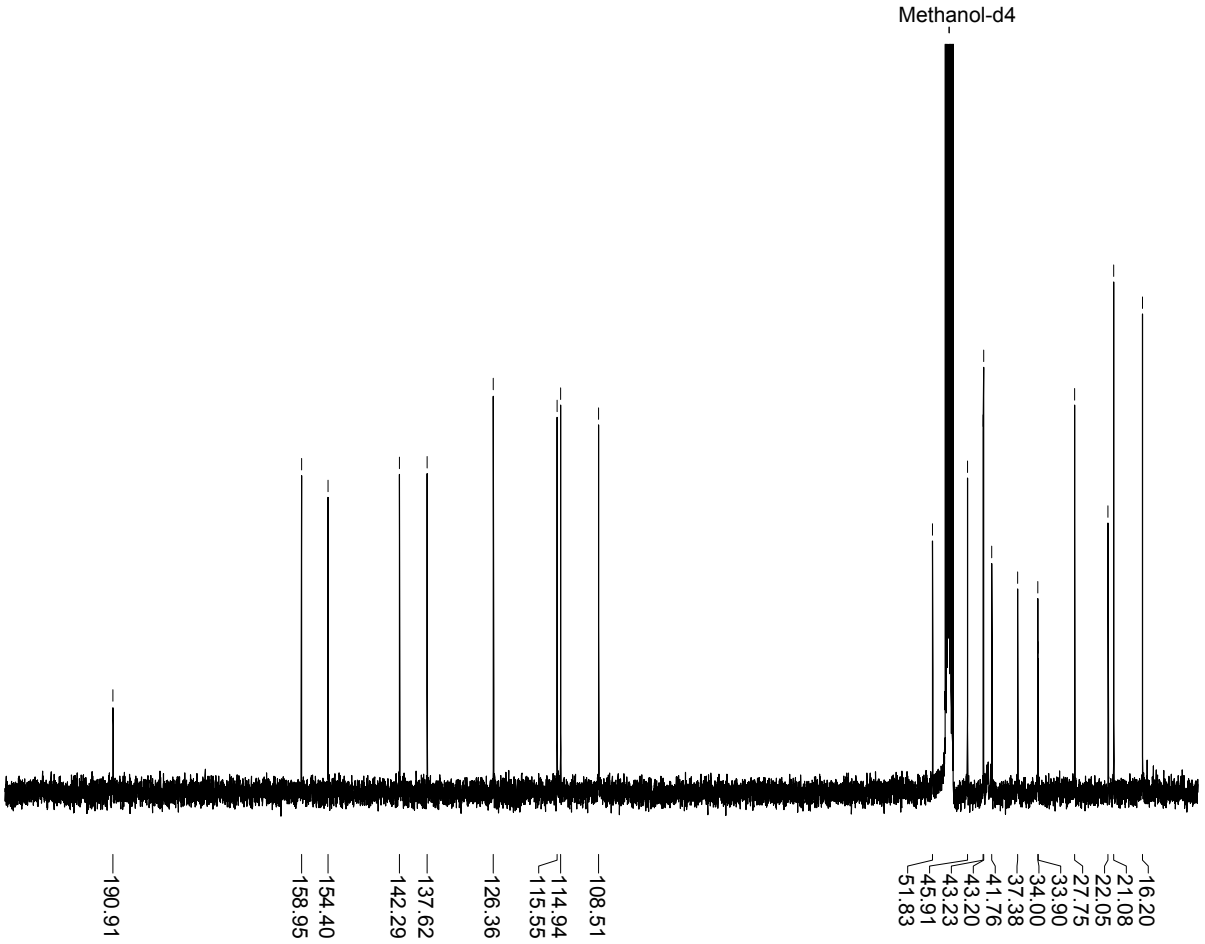
4-17

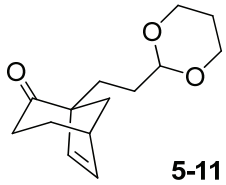
DMSO-d6
10
9
8
7
6
5
4
3
2
1
0
ppm


DMSO-d6
DMSO-d6
39.19
169.76
157.72
142.32
136.06
125.61
108.45
100.70
56.43
45.36
44.66
44.08
42.36
39.19
37.30
32.36
27.63
22.38
20.80
16.64

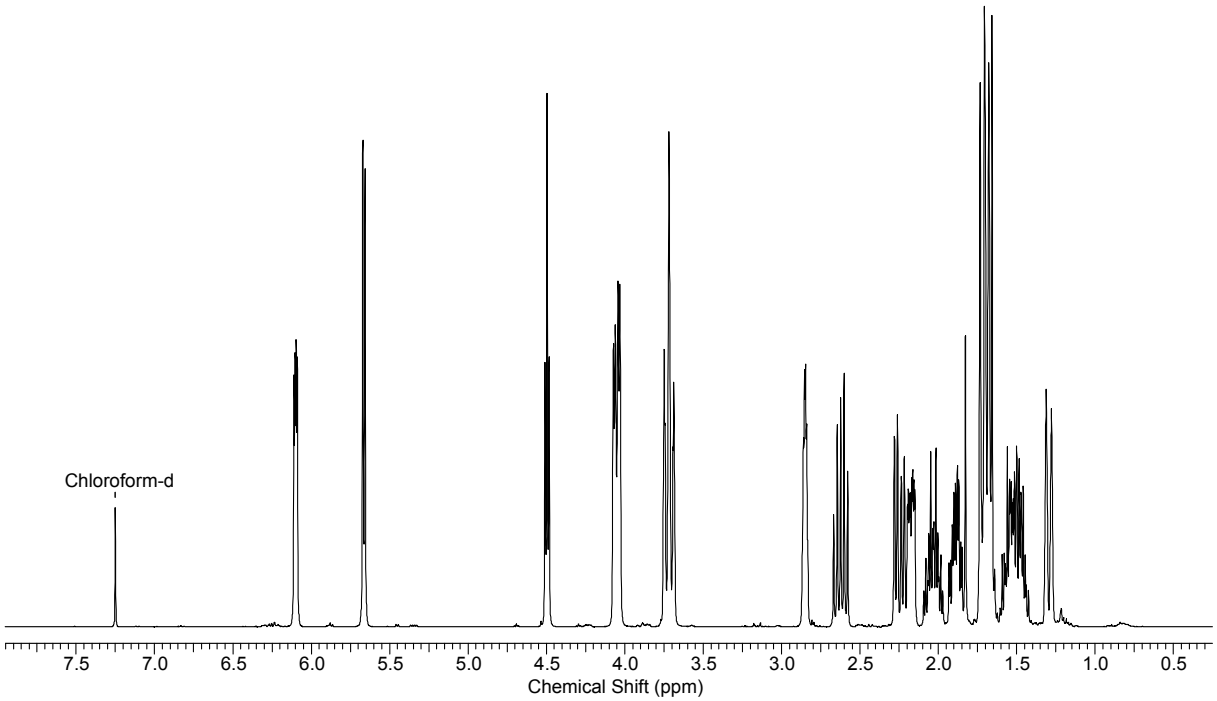


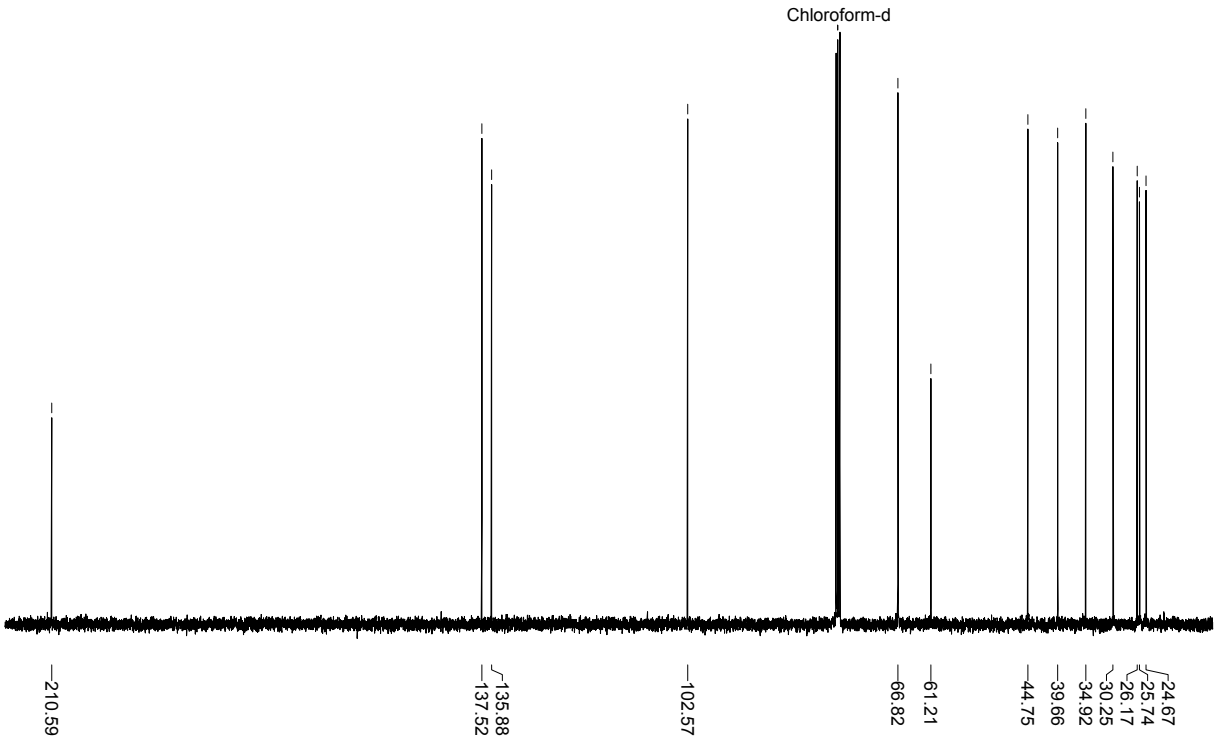
Neosymbioimine (4-1)

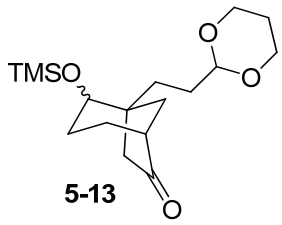




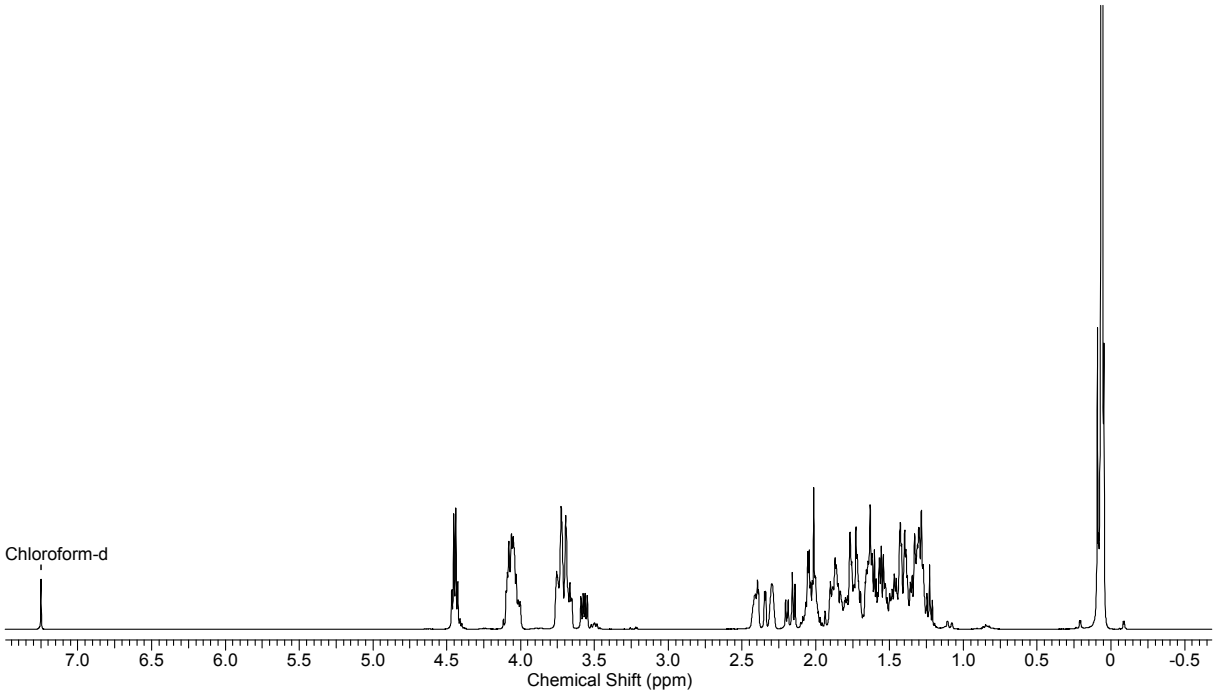
5-11

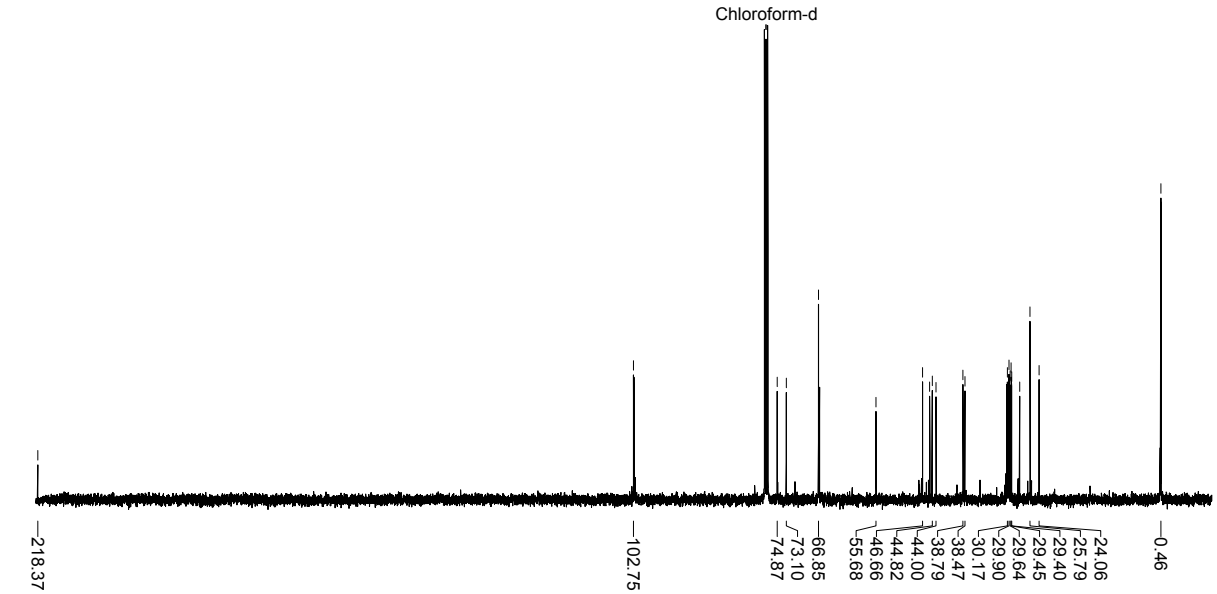

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

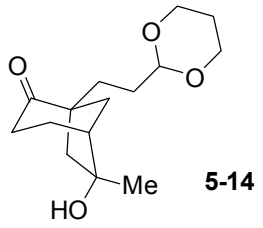

Chloroform-d
210.59
137.52
135.88
102.57
66.82
61.21
44.75
39.66
34.92
30.25
26.17
25.74
24.67


TMSO
O
O
O

5-13

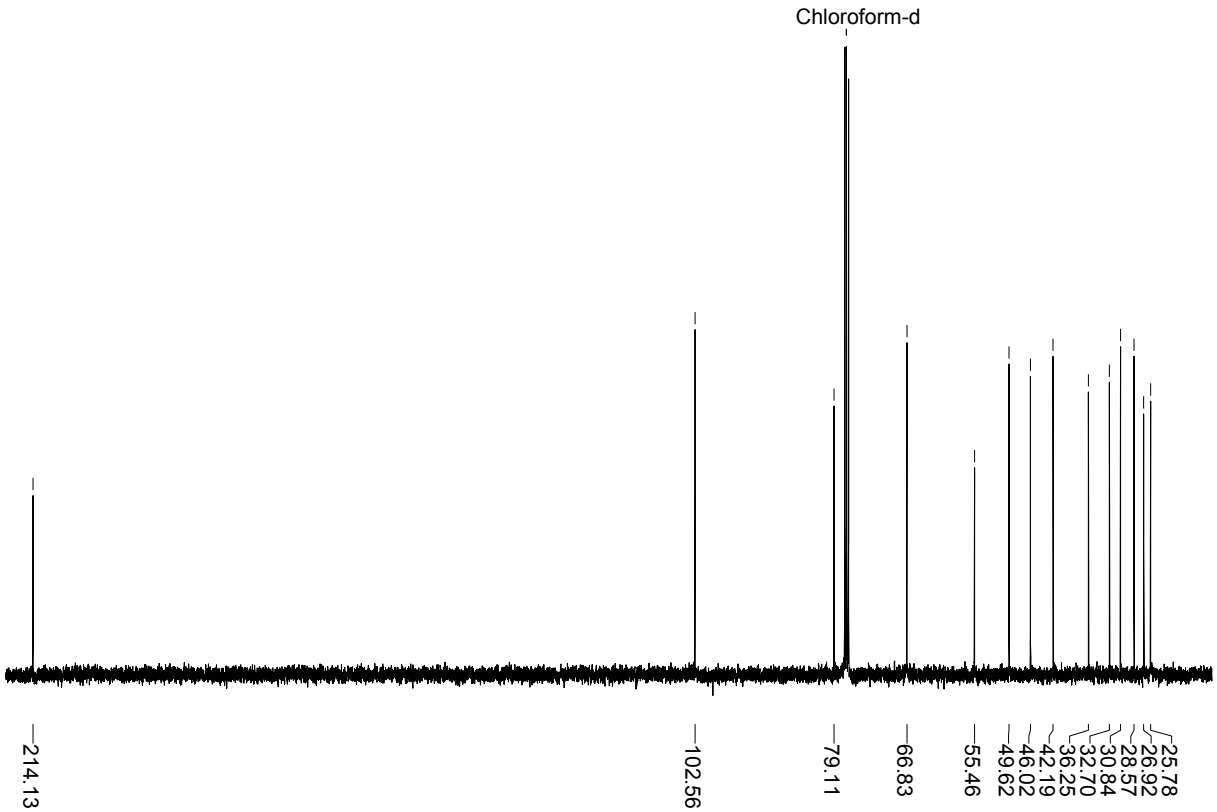

Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

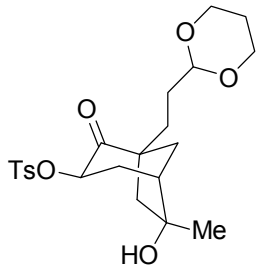

Chloroform-d
218.37
102.75
74.87
73.10
66.85
55.68
46.66
44.82
44.00
38.79
38.47
30.17
29.90
29.64
29.45
29.40
25.79
24.06
0.46


O
O
O
Me
HO

5-14

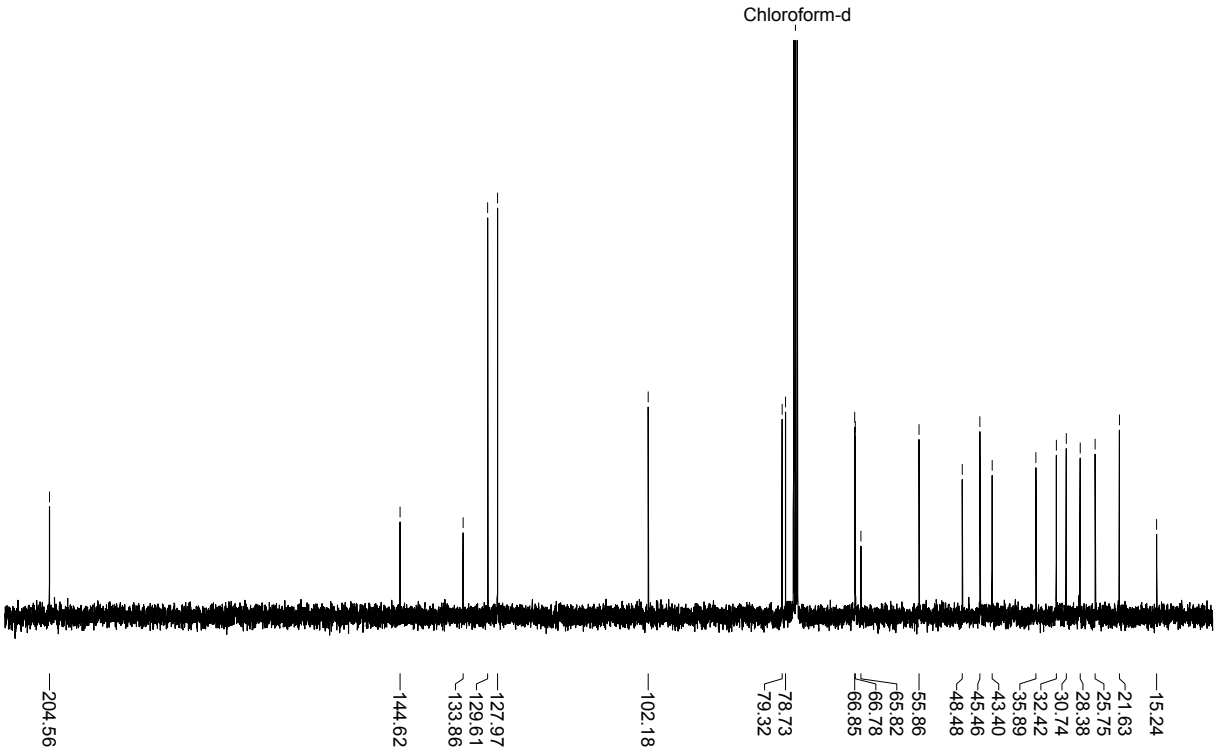
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

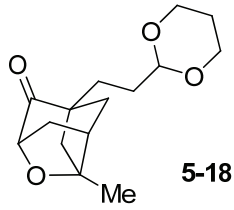

Chloroform-d
214.13
102.56
79.11
66.83
55.46
49.62
46.02
42.19
36.25
32.70
30.84
28.57
26.92
25.78


O
O
O
TsO
Me
HO

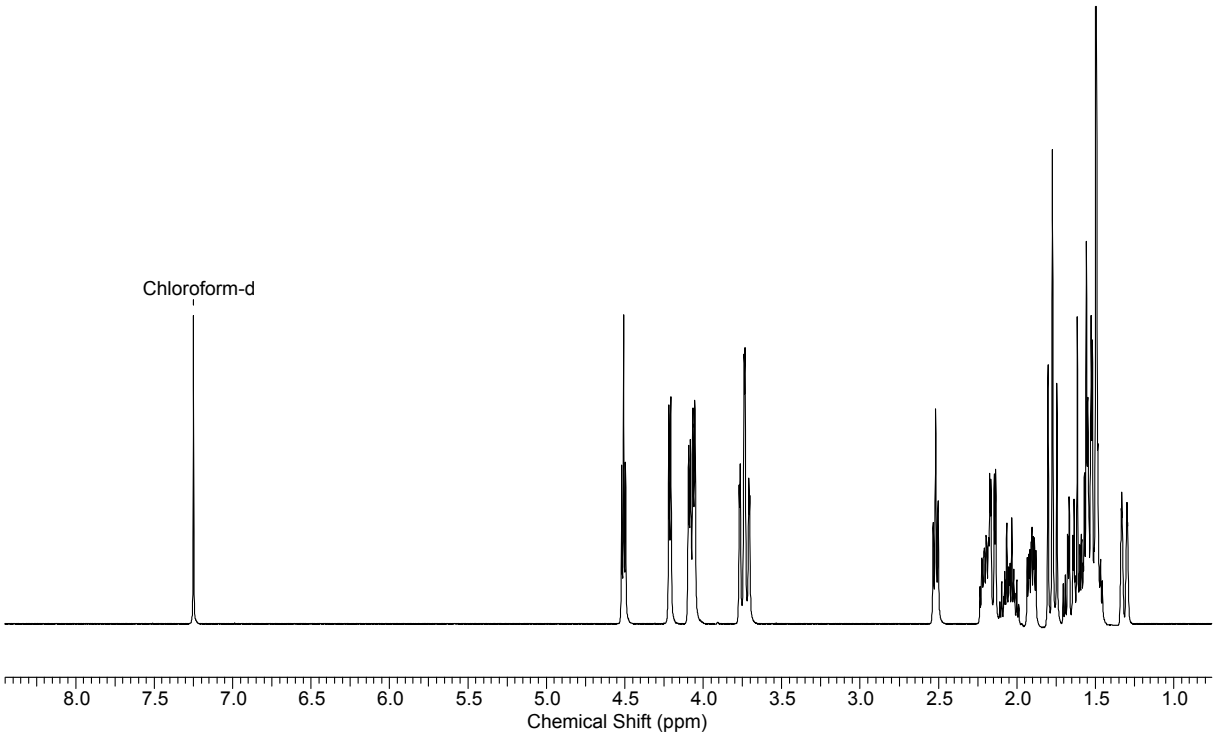
5-17

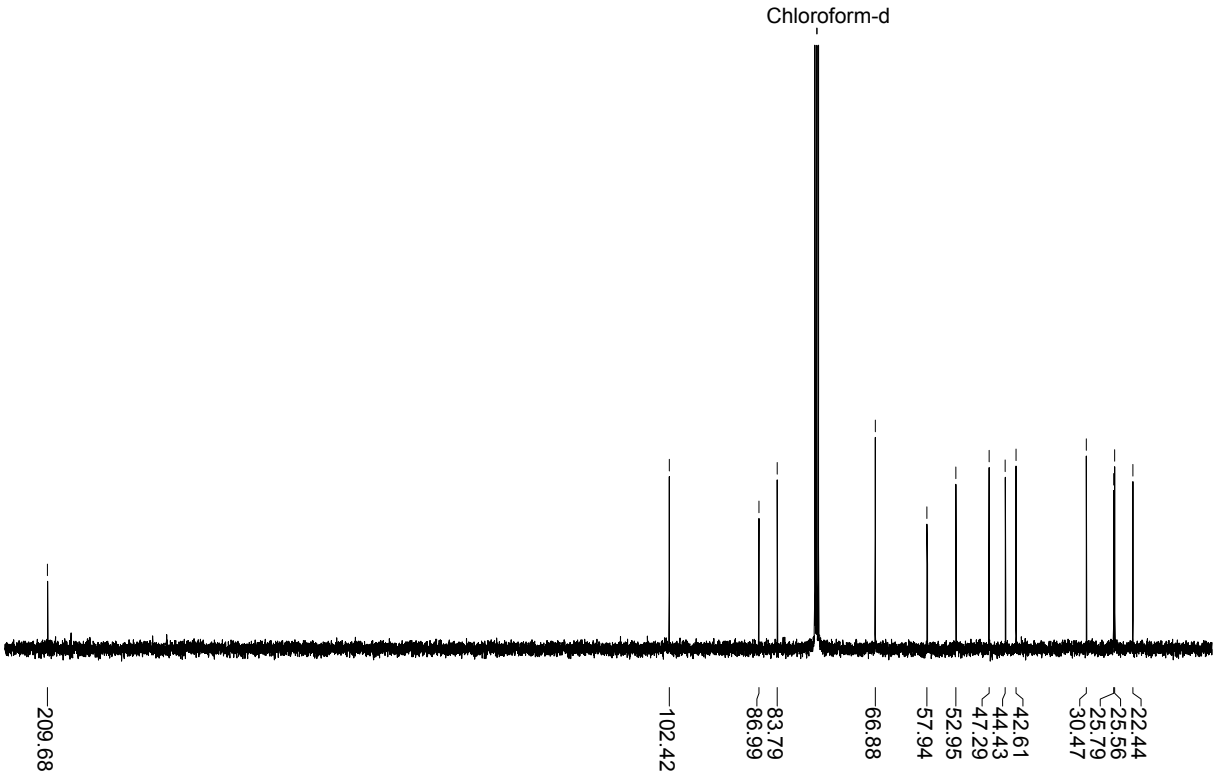
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

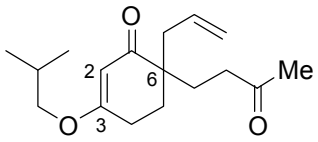

Chloroform-d
204.56
144.62
133.86
129.61
127.97
102.18
79.32
78.73
66.85
66.78
65.82
55.86
48.48
45.46
43.40
35.89
32.42
30.74
28.38
25.75
21.63
15.24


O
O
O
O
Me

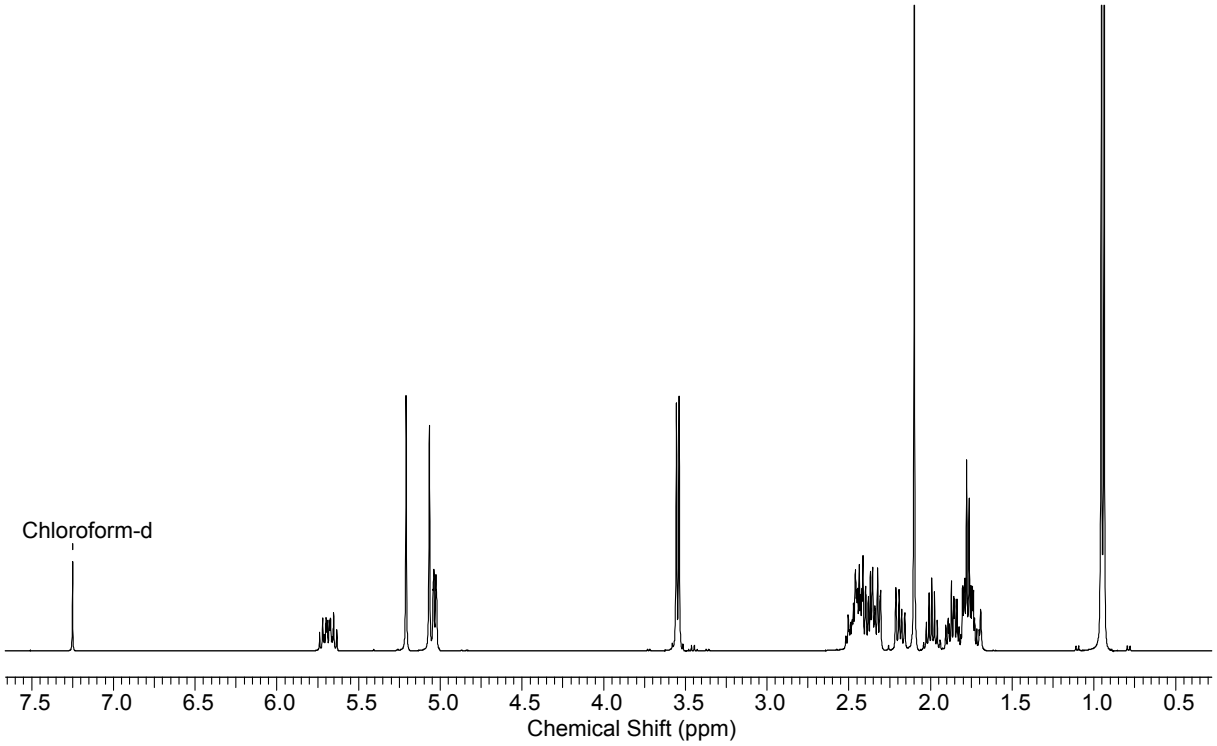
5-18

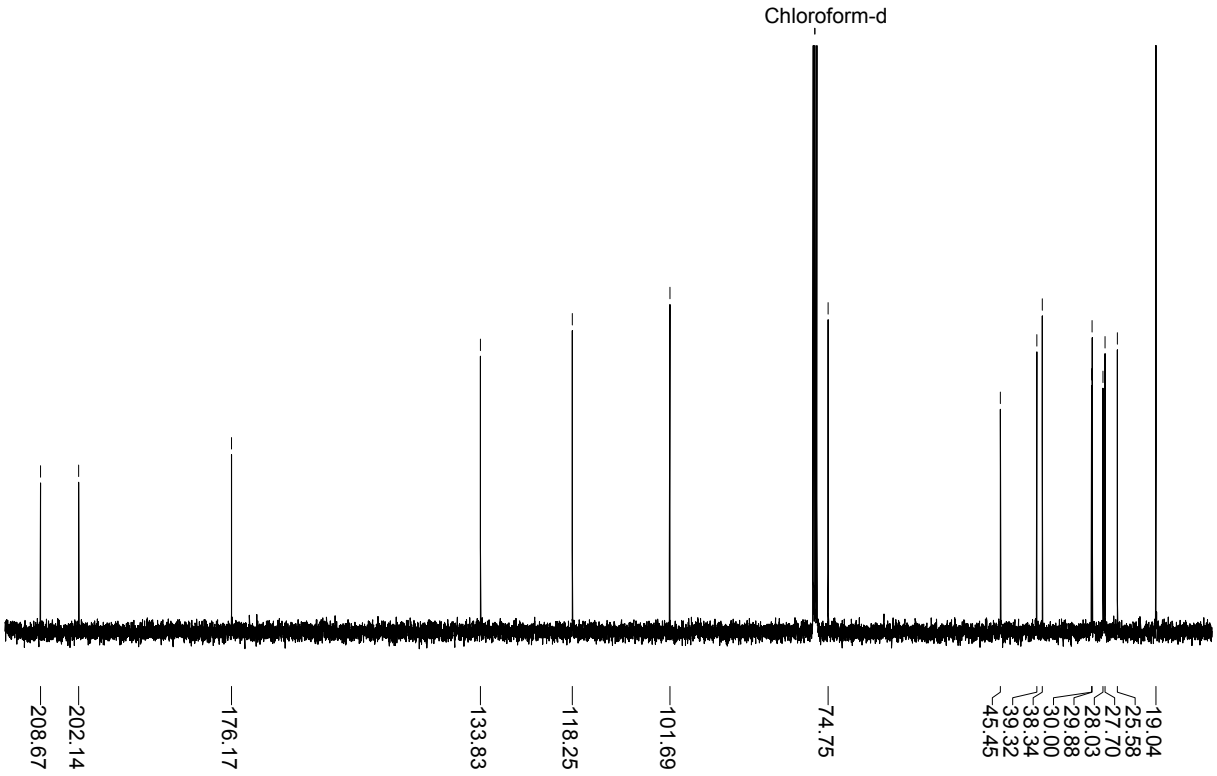

Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

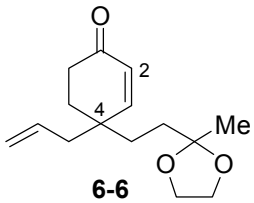

Chloroform-d
209.68
102.42
86.99
83.79
66.88
57.94
52.95
47.29
44.43
42.61
30.47
25.79
25.56
22.44


O
2
6
Me
O
3
O

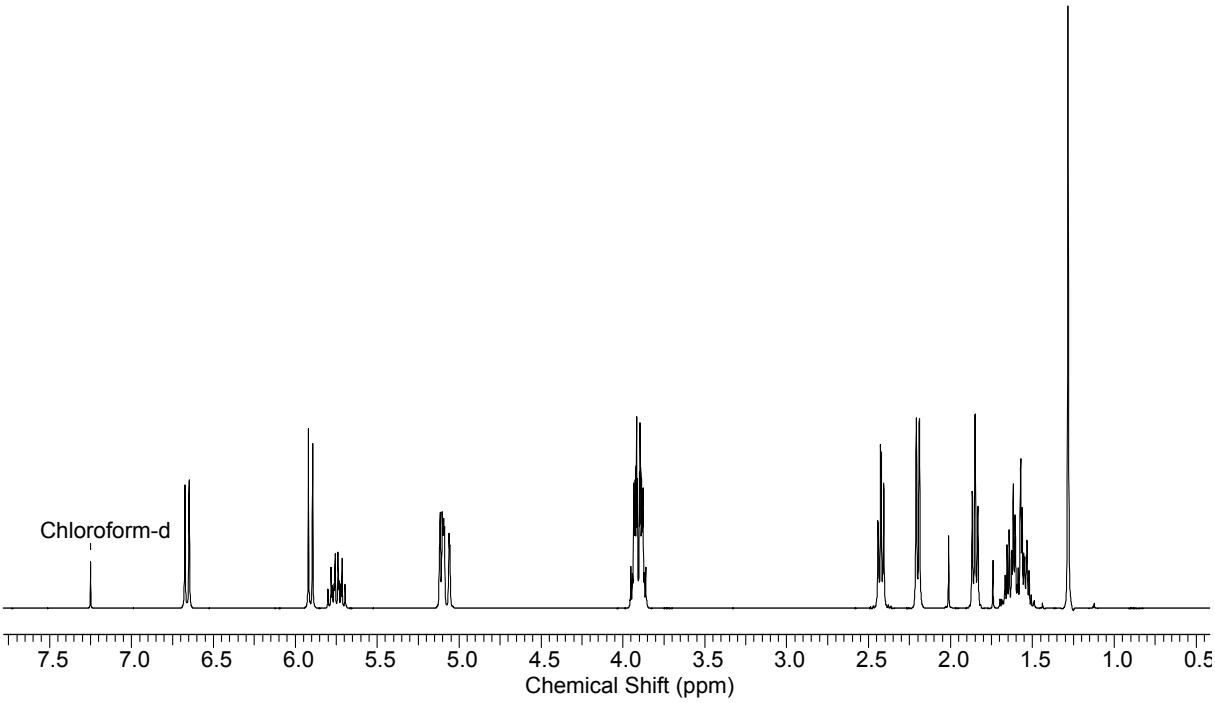
6-5

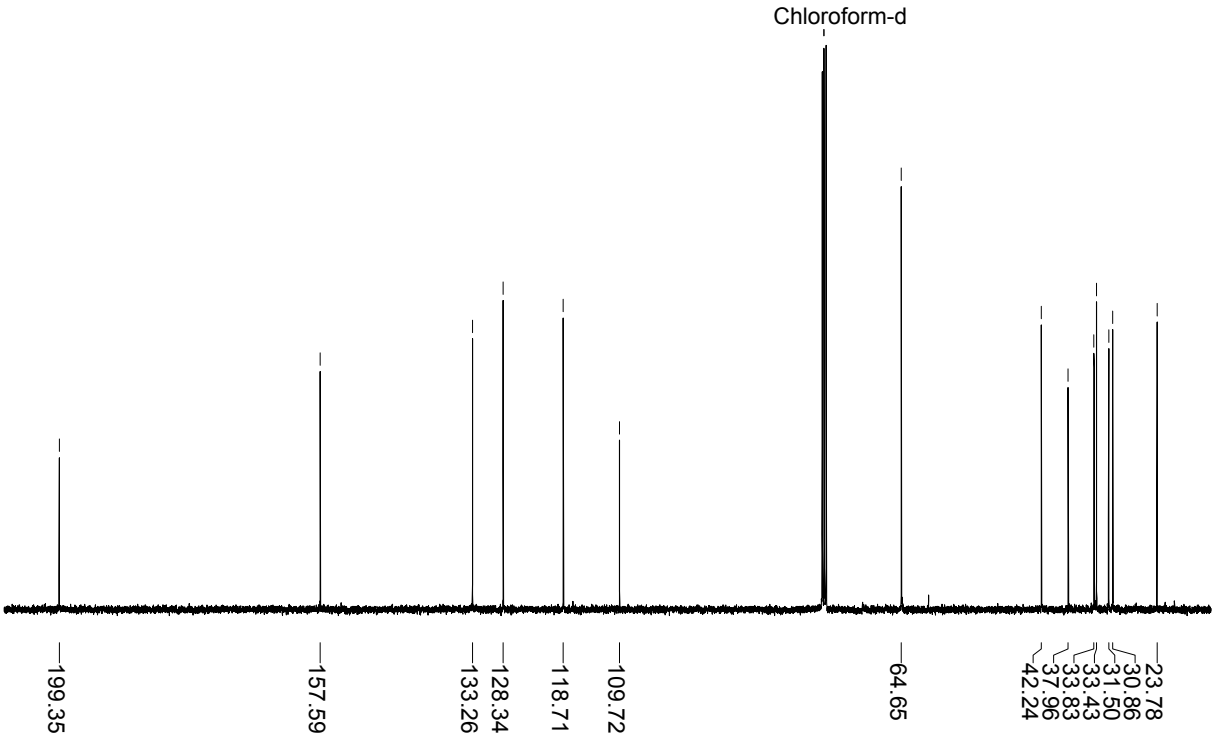

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

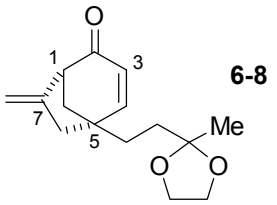

Chloroform-d
208.67
202.14
176.17
133.83
118.25
101.69
74.75
45.45
39.32
38.34
30.00
29.88
28.03
27.70
25.58
19.04


O
2
4
Me
O
O

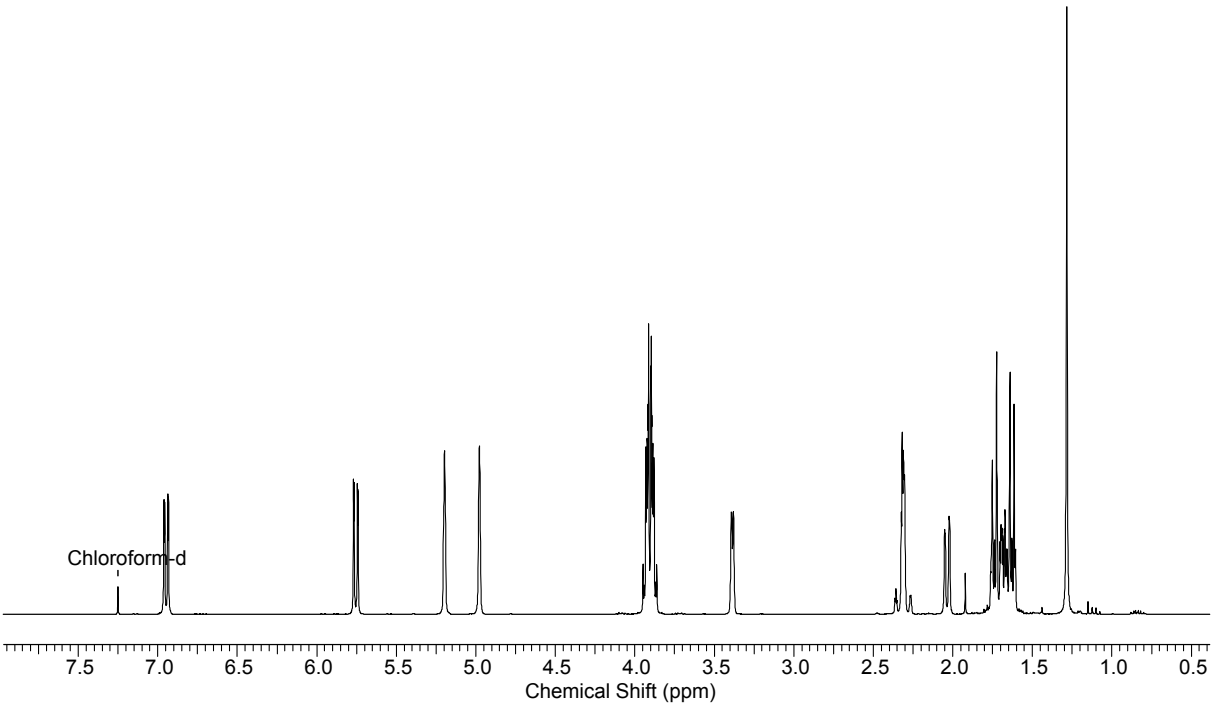
6-6

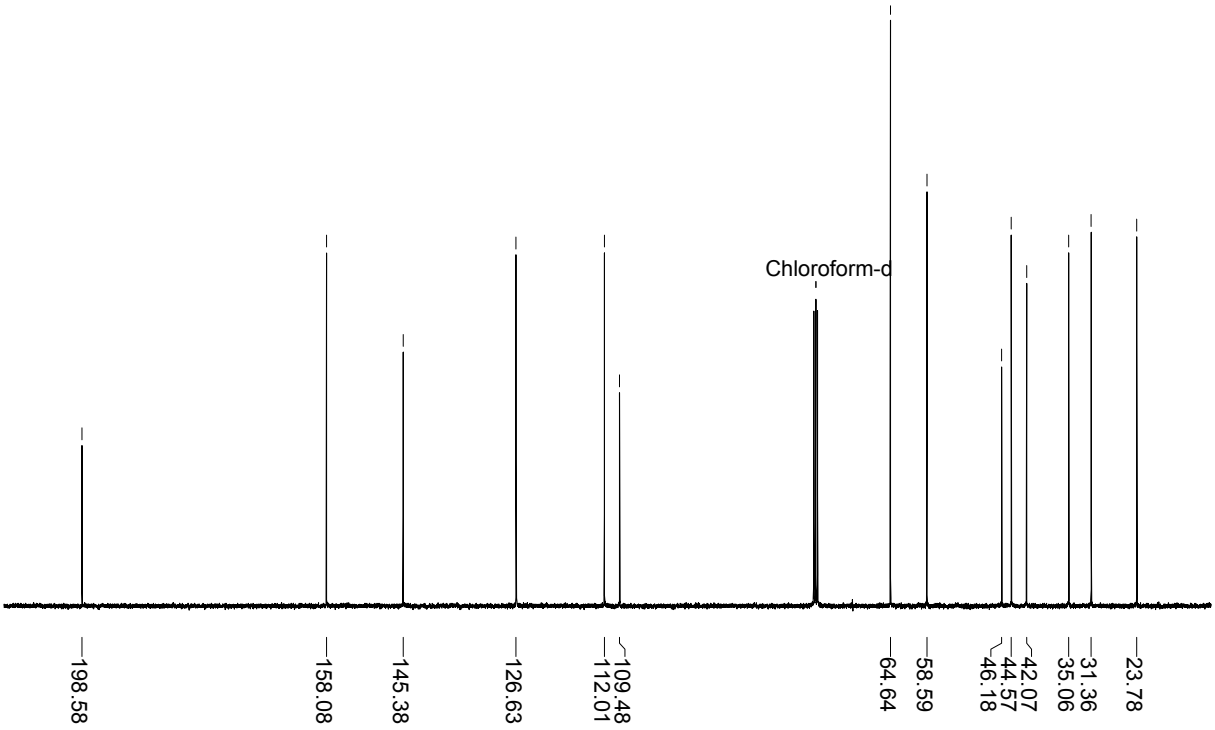

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

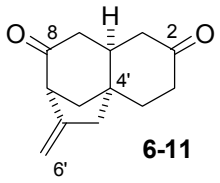

Chloroform-d
199.35
157.59
133.26
128.34
118.71
109.72
64.65
42.24
37.96
33.83
33.43
31.50
30.86
23.78


O
1
3
7
5
Me
O
O

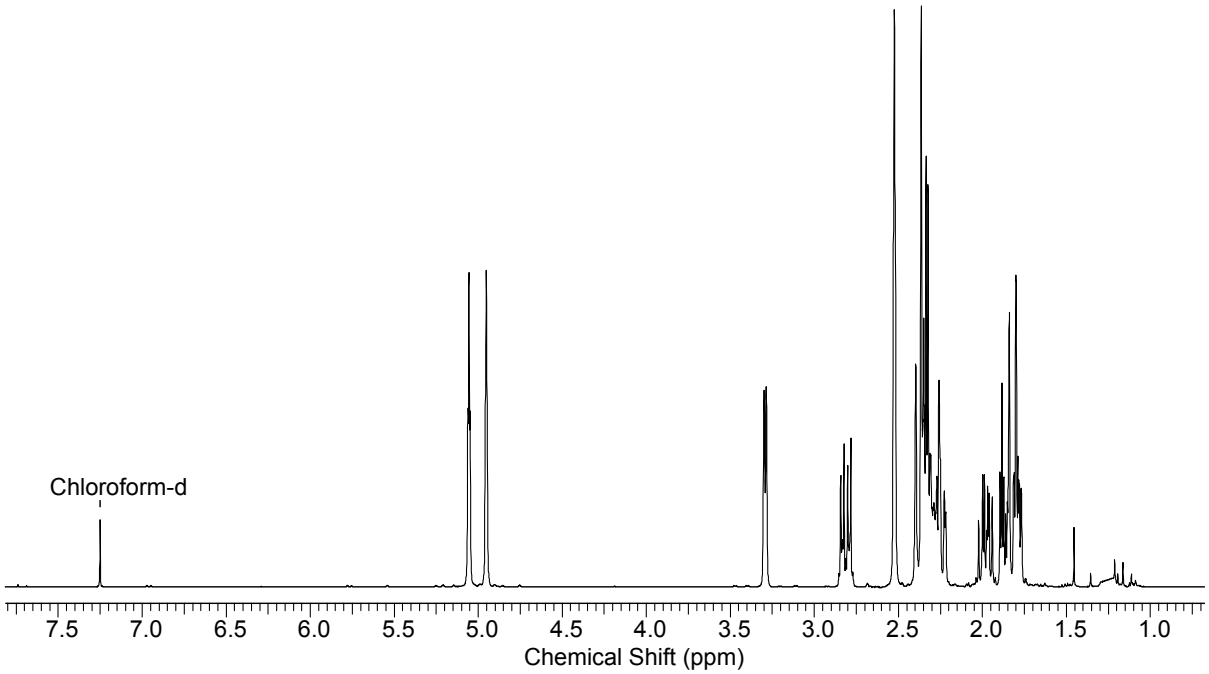
6-8

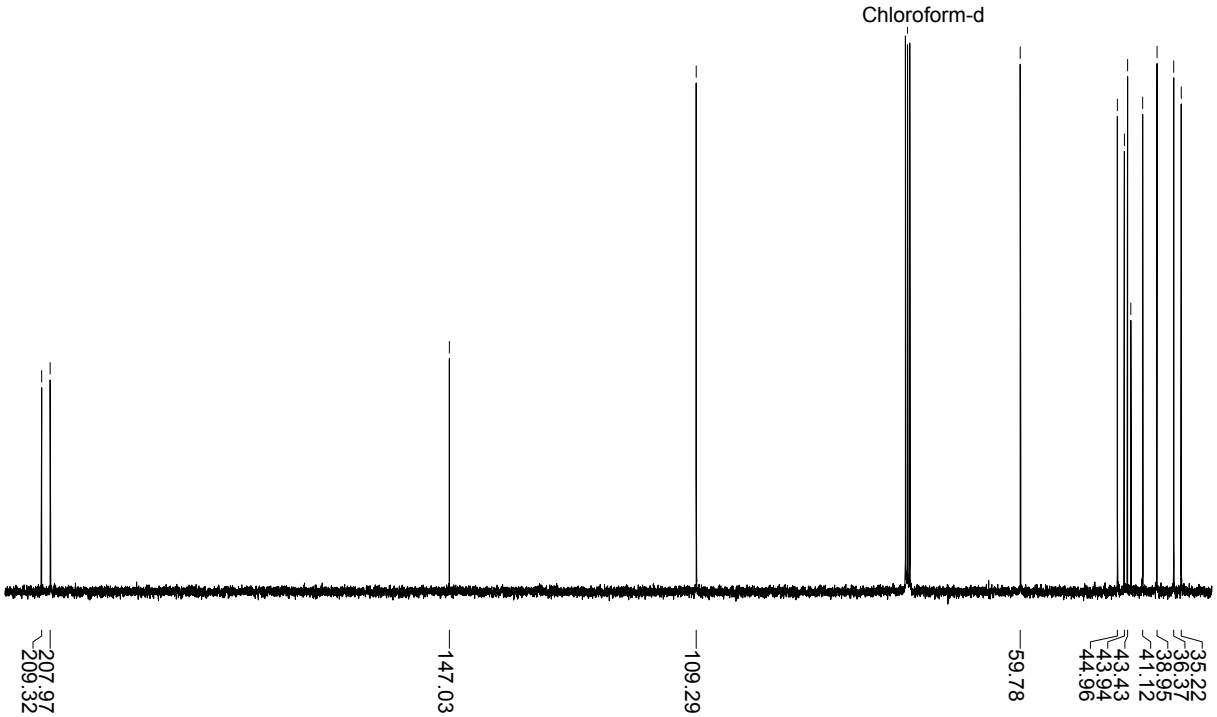

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

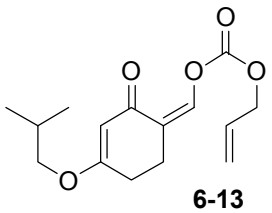

Chloroform-d
198.58
158.08
145.38
126.63
112.01
109.48
64.64
58.59
46.18
44.57
42.07
35.06
31.36
23.78


H
O
8
2
O
4'
6'

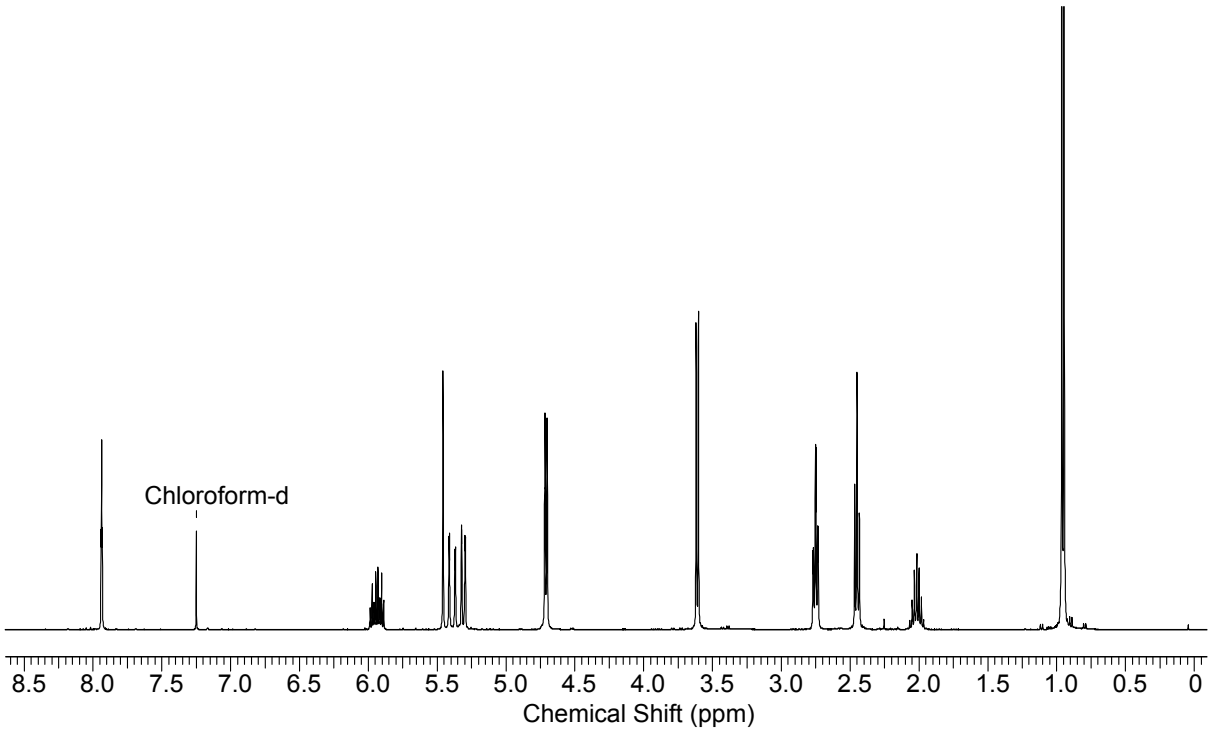
6-11

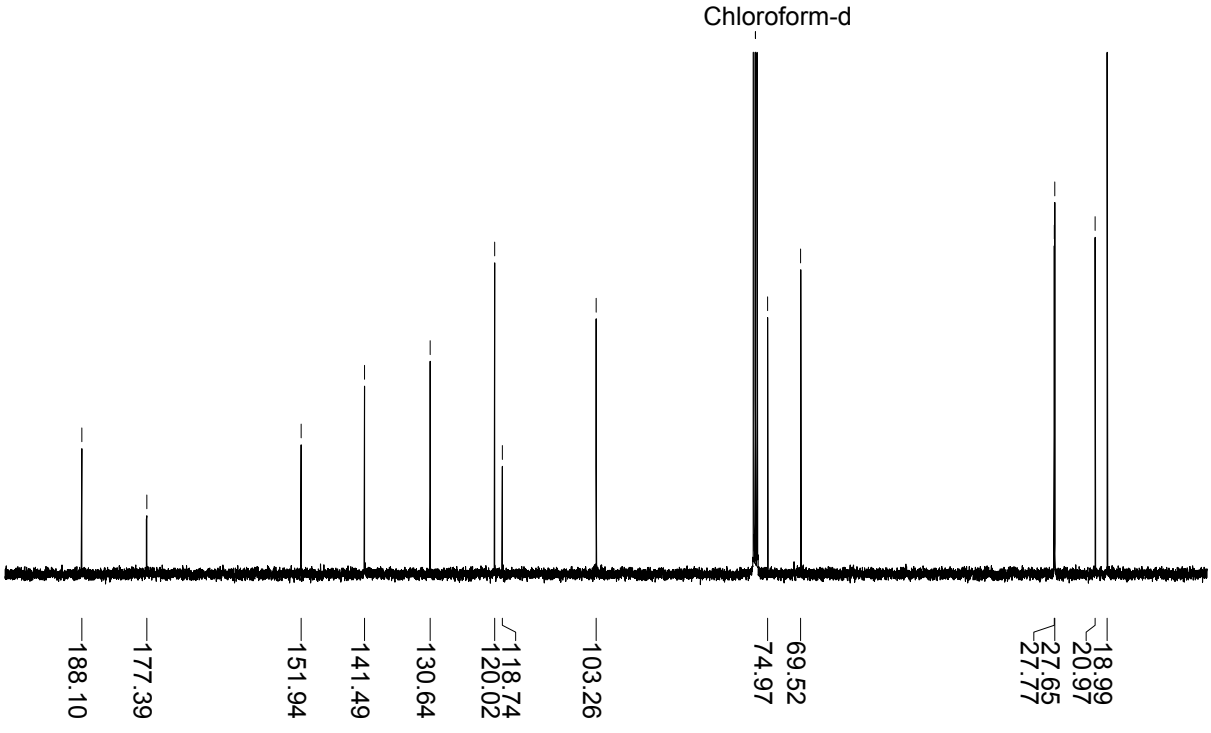

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

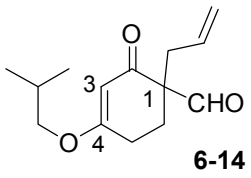

Chloroform-d
207.97
209.32
147.03
109.29
59.78
43.43
43.94
44.96
41.12
38.95
36.37
35.22



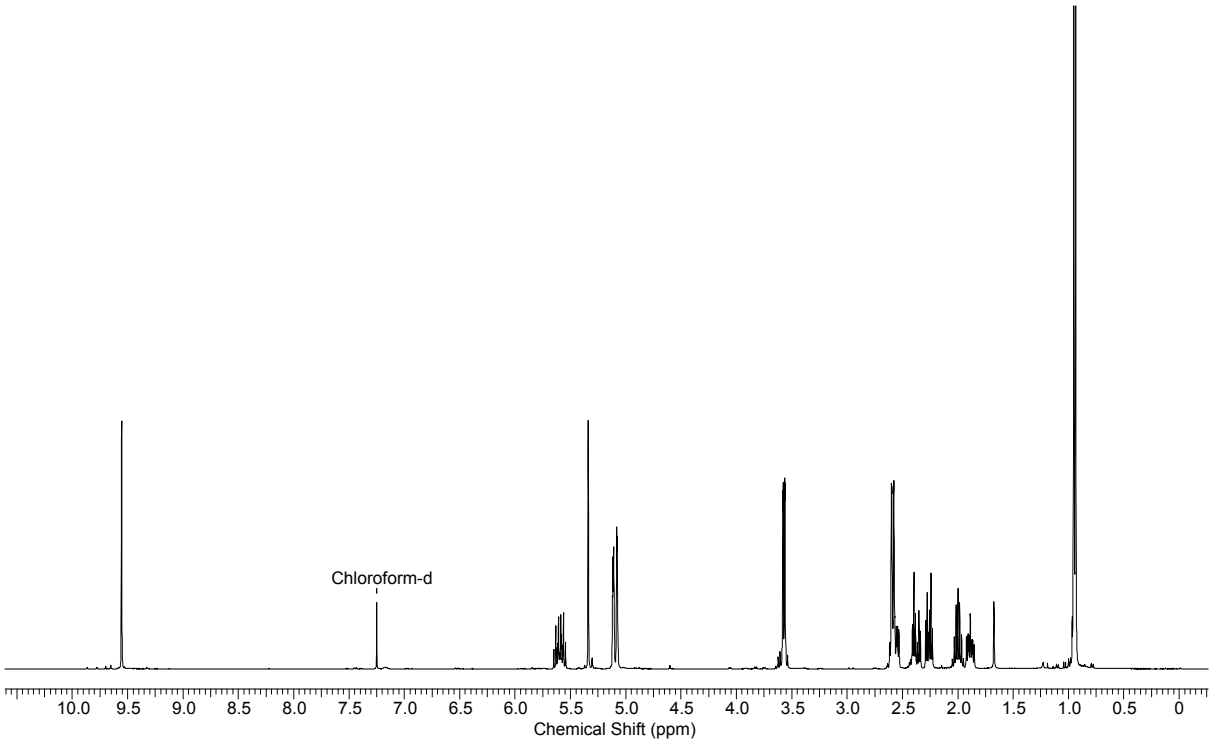
6-13

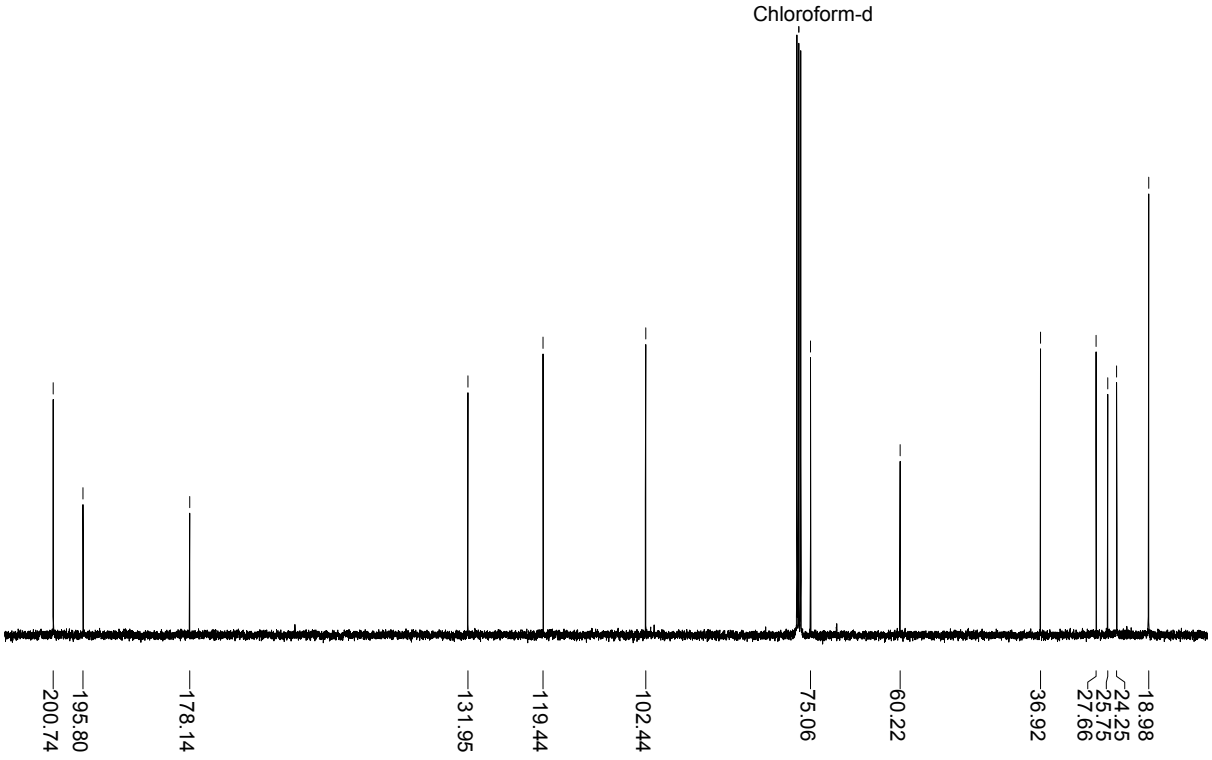

Chloroform-d
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

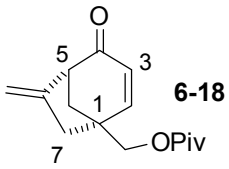

Chloroform-d
188.10
177.39
151.94
141.49
130.64
118.74
120.02
103.26
74.97
69.52
27.65
27.77
20.97
18.99


O
3
1
CHO
O
4

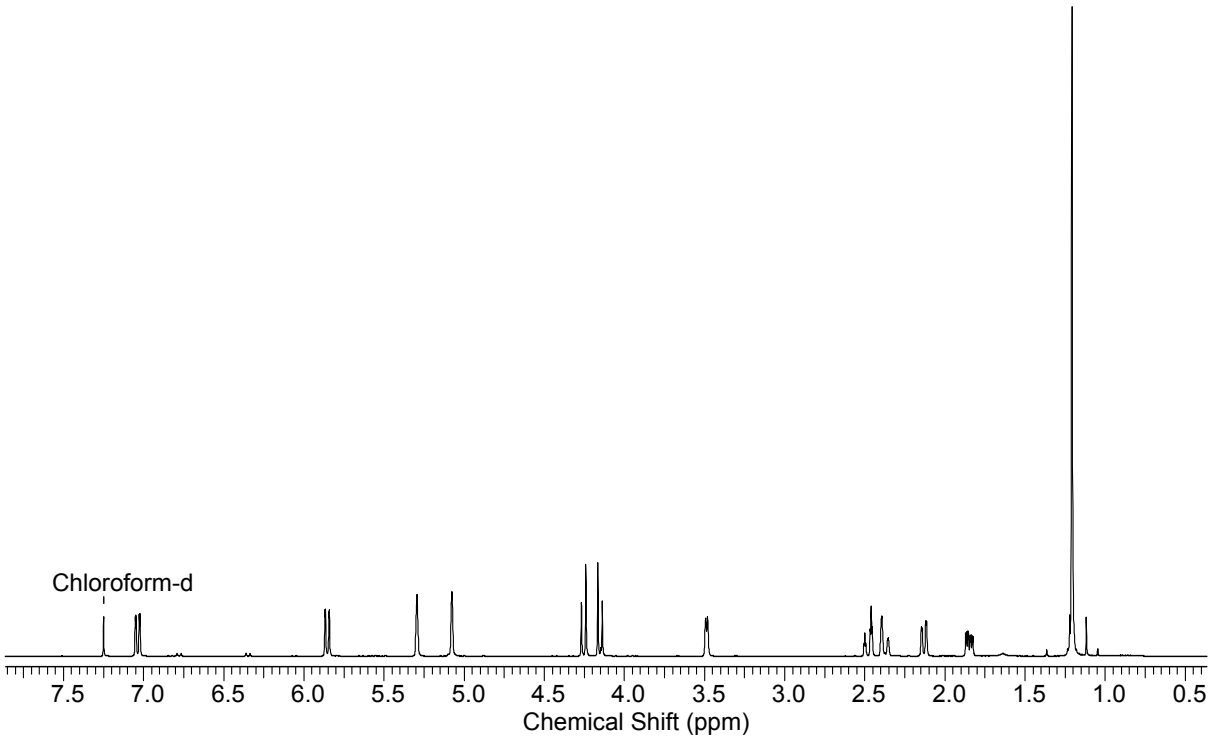
6-14

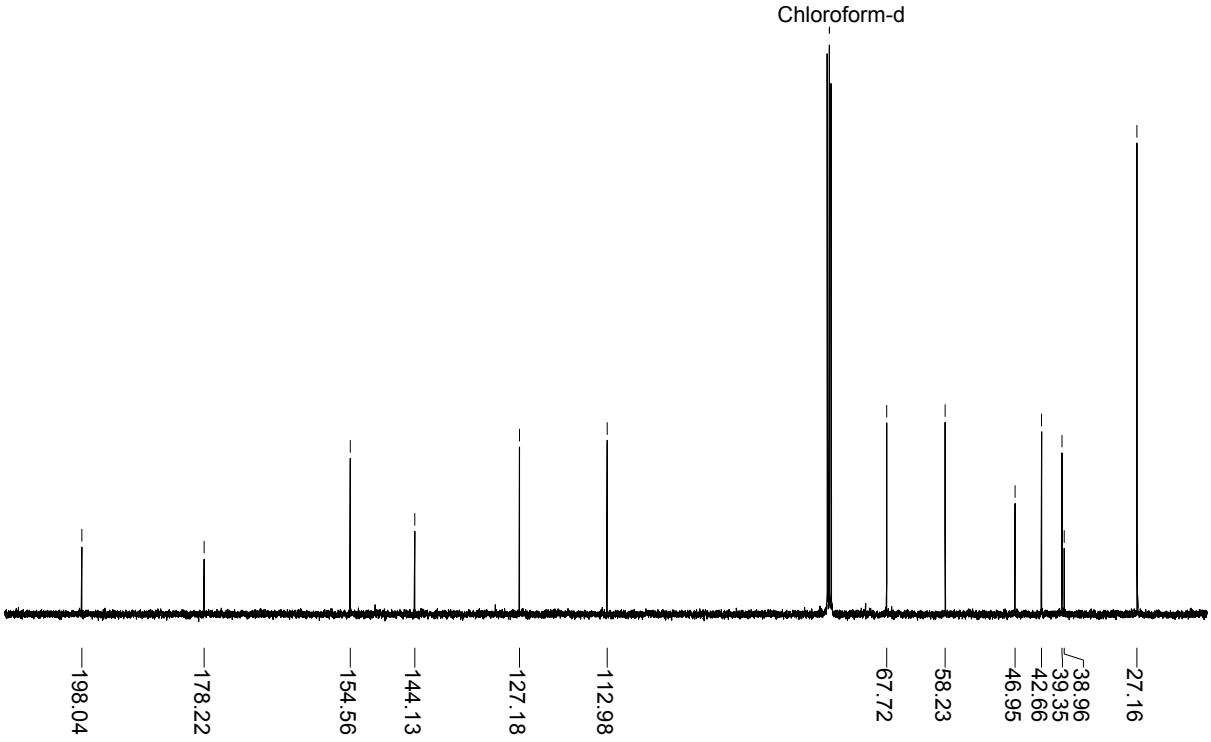

Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

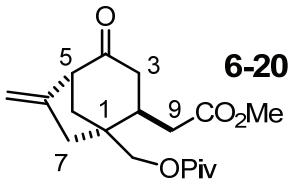

Chloroform-d
200.74
195.80
178.14
131.95
119.44
102.44
75.06
60.22
36.92
27.66
25.75
24.25
18.98


O
5
3
1
7
OPiv

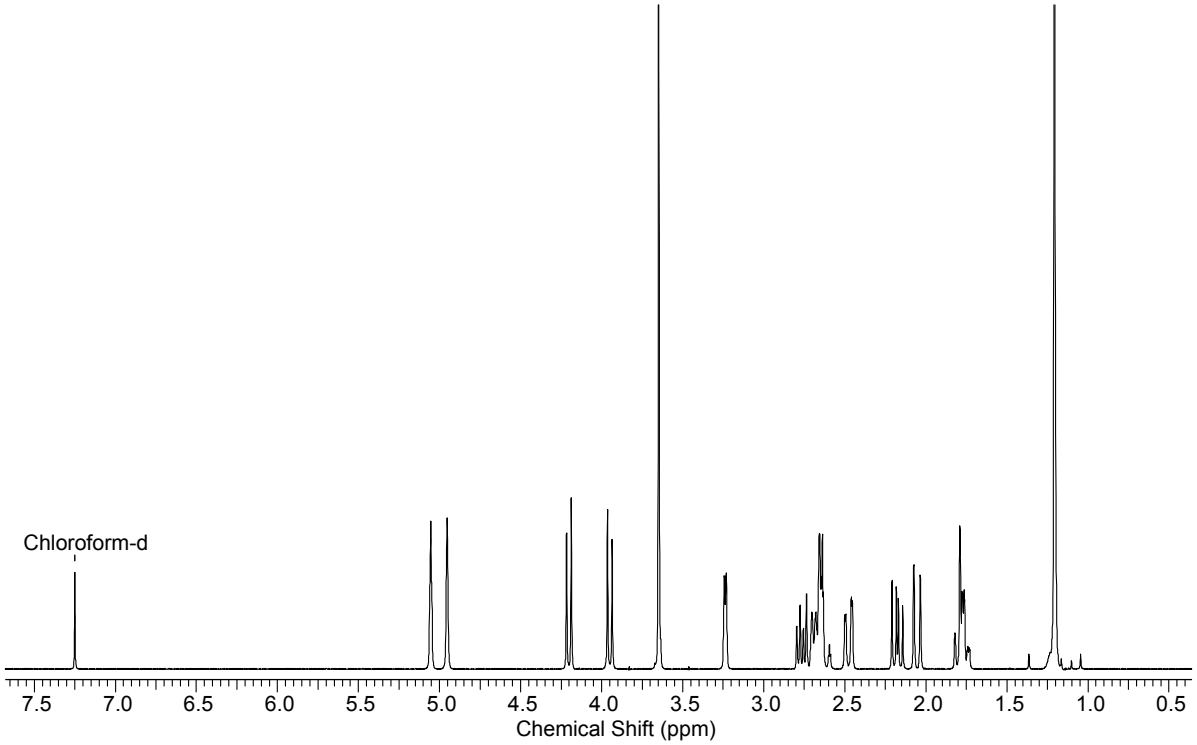
6-18

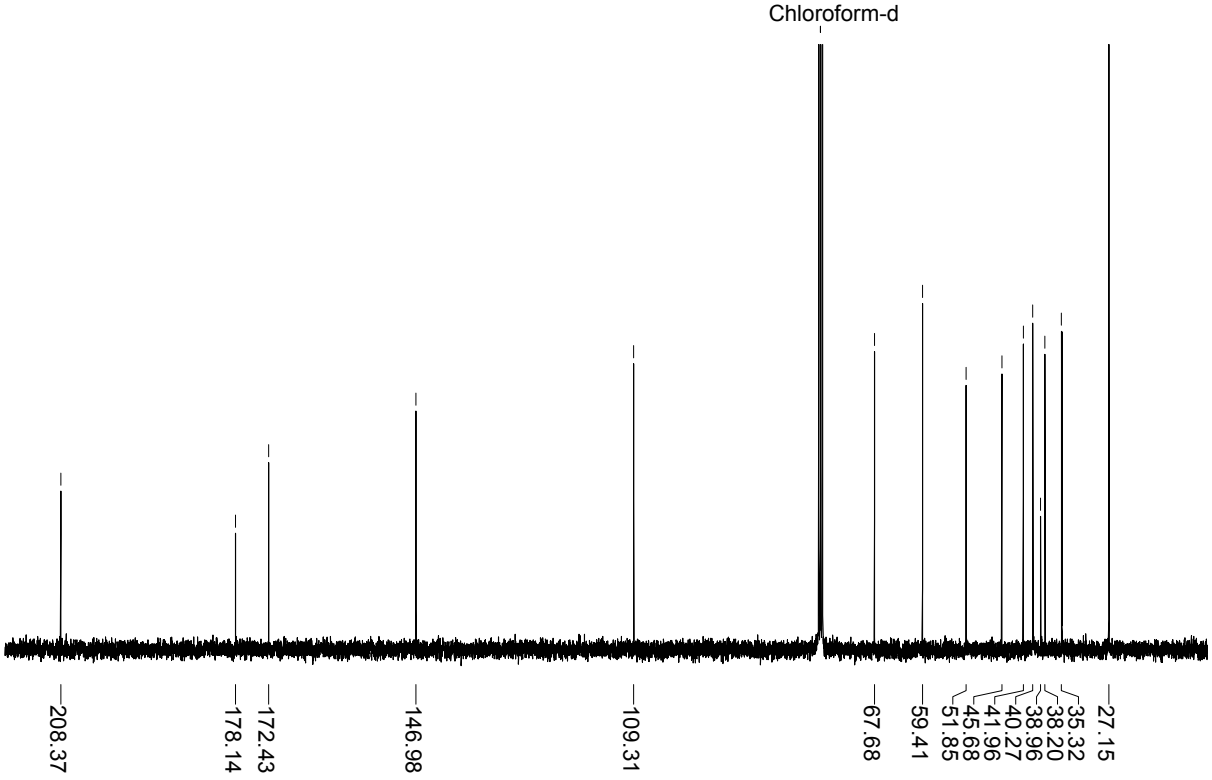

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

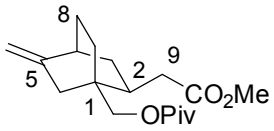

Chloroform-d
198.04
178.22
154.56
144.13
127.18
112.98
67.72
58.23
46.95
42.66
39.35
38.96
27.16


O
5
3
1
9
CO2Me
7
OPiv

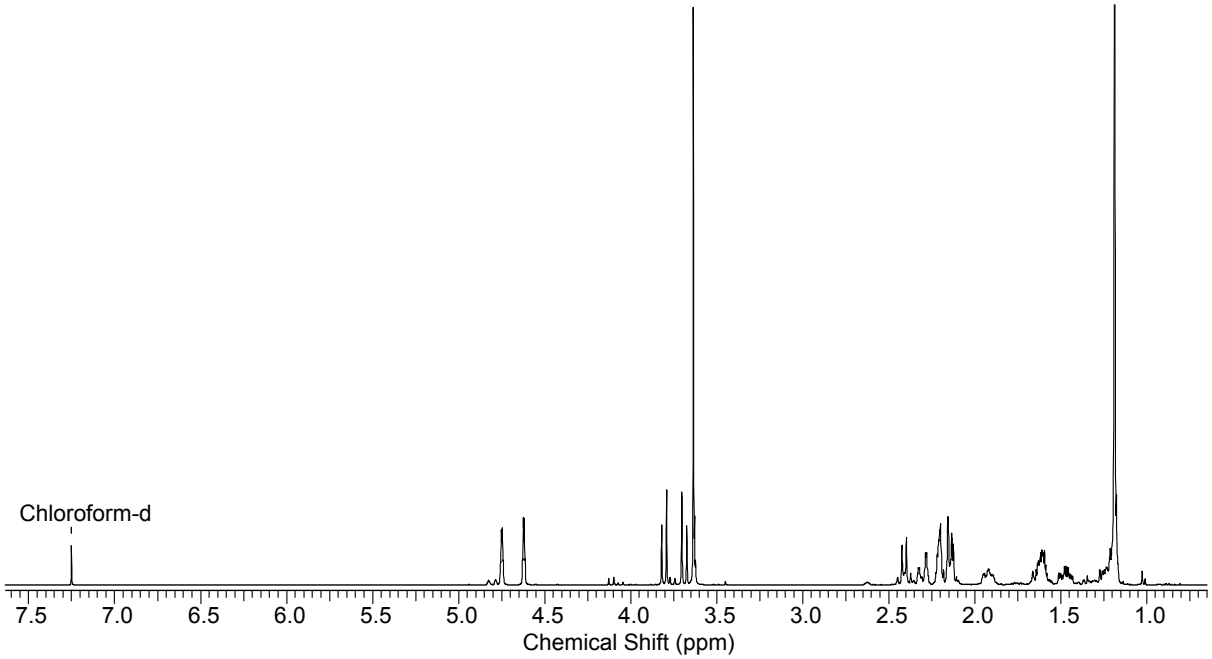
6-20

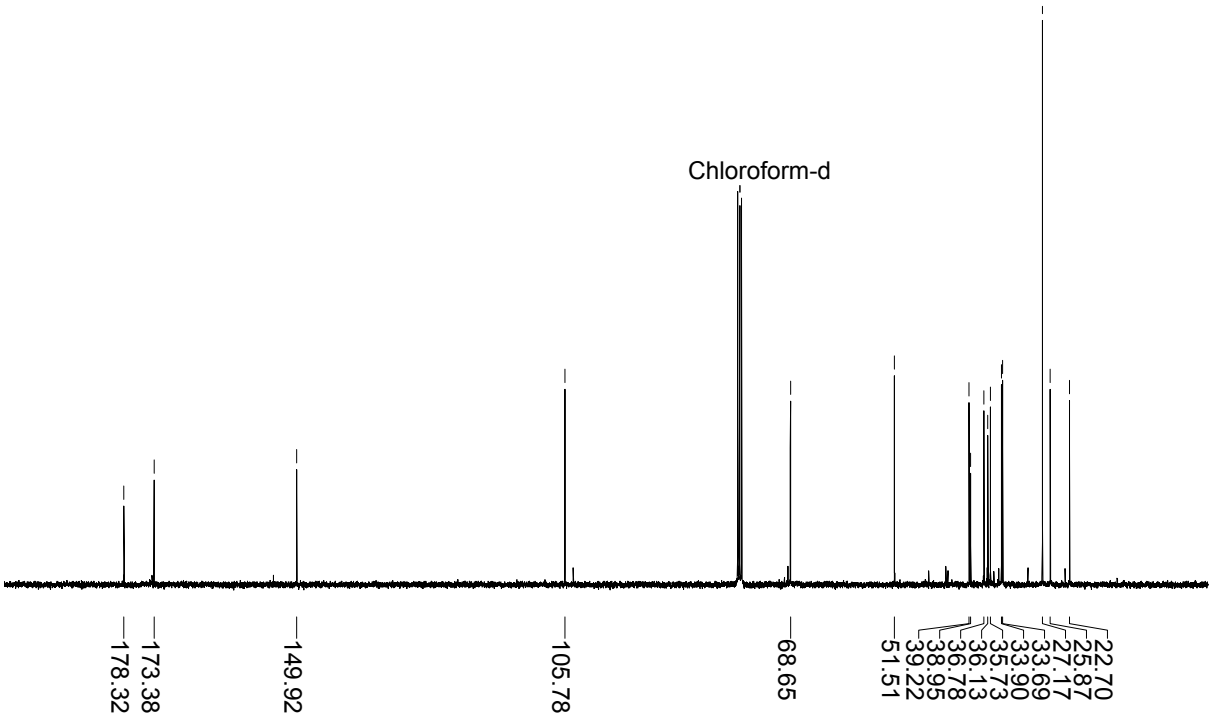

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

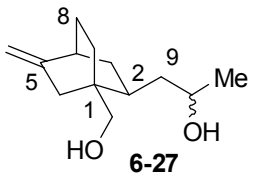

Chloroform-d
208.37
178.14
172.43
146.98
109.31
67.68
59.41
51.85
45.68
41.96
40.27
38.96
38.20
35.32
27.15


8
9
2
5
1
CO2Me
OPiv

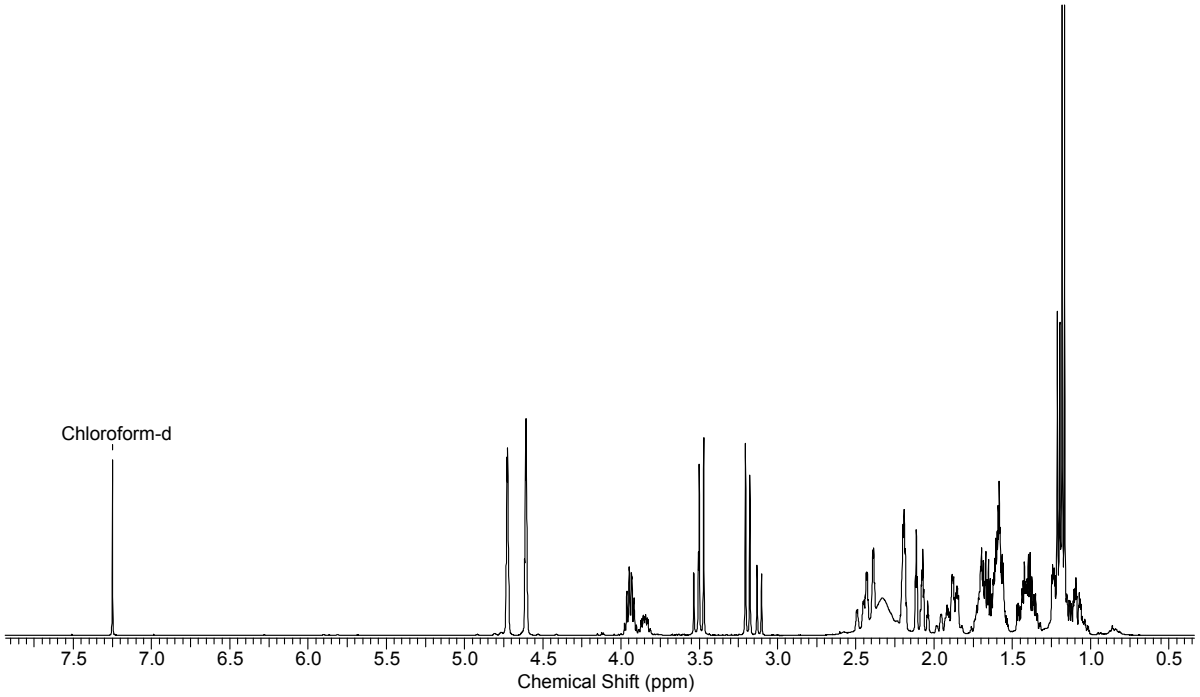
6-23

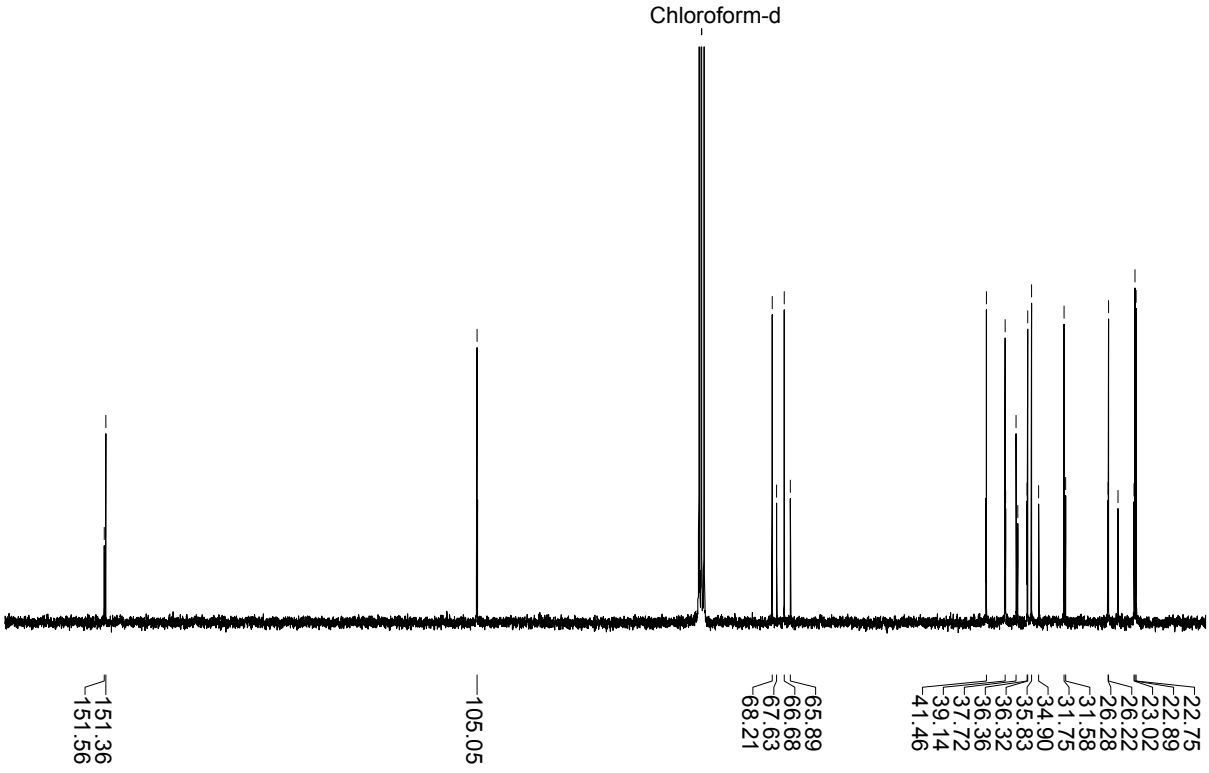

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

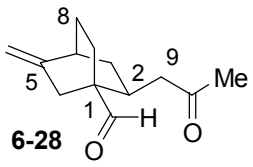

Chloroform-d
178.32
173.38
149.92
105.78
68.65
51.51
39.22
38.95
36.78
36.13
35.73
33.90
33.69
27.17
25.87
22.70


8
9
2
Me
5
1
OH
HO

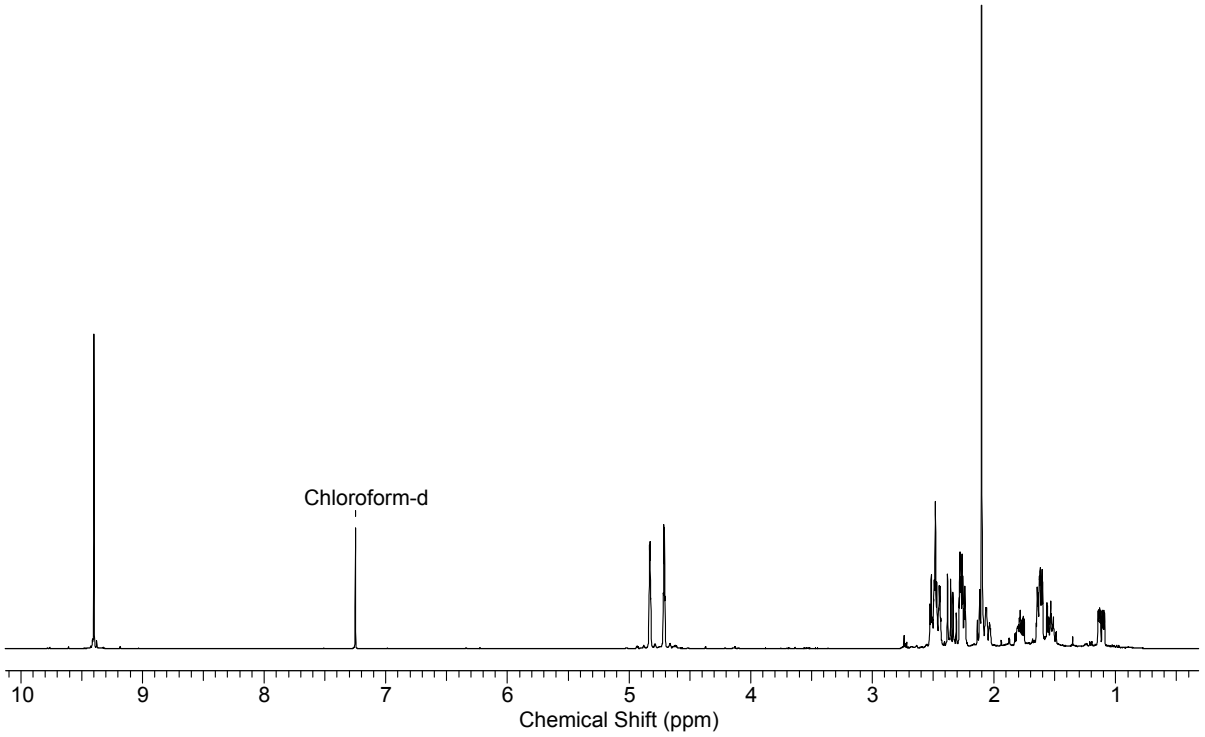
6-27

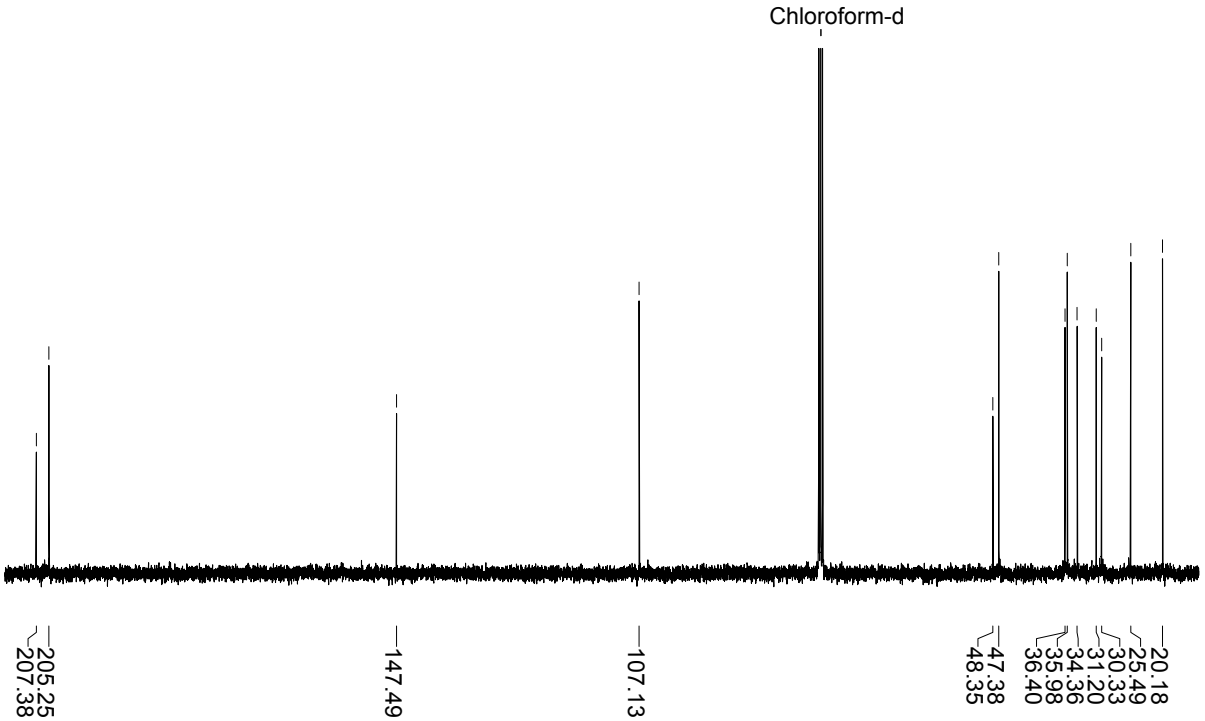

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

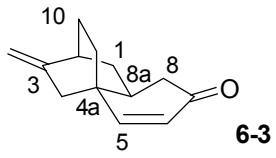

Chloroform-d
151.36
151.56
105.05
68.21
67.63
66.68
65.89
41.46
39.14
37.72
36.36
36.32
35.83
34.90
31.75
31.58
26.28
26.22
23.02
22.89
22.75


8
9
2
5
Me
1
H
O
O

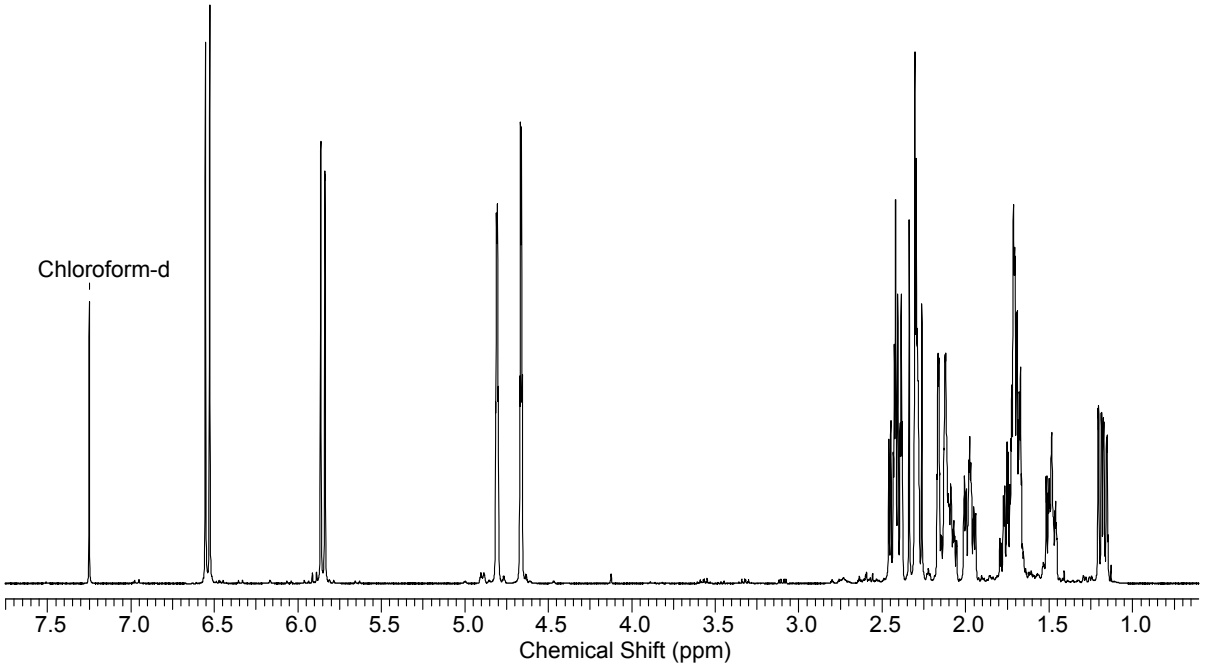
6-28

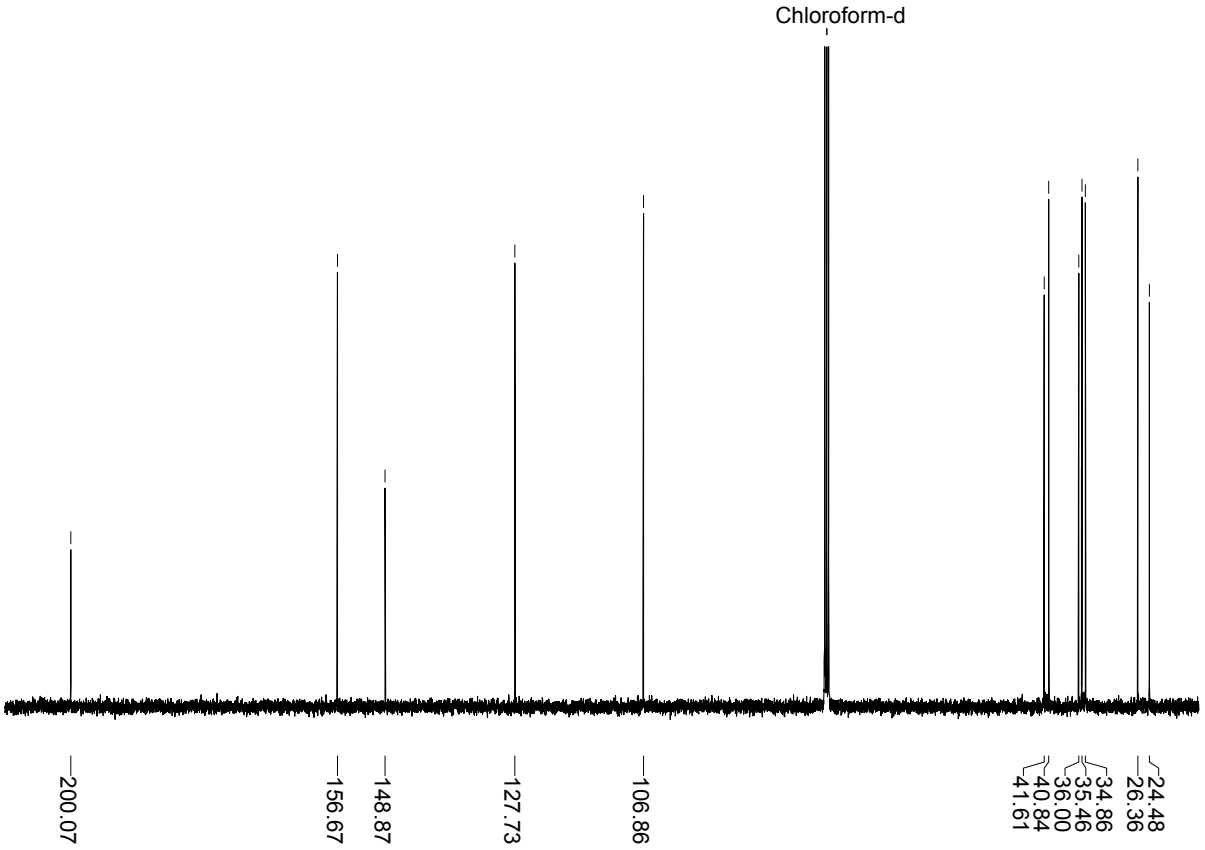

Chloroform-d
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


Chloroform-d
205.25
207.38
147.49
107.13
47.38
48.35
35.98
36.40
34.36
31.20
30.33
25.49
20.18


10
1
8
8a
3
O
4a
5

6-3


Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


Chloroform-d
200.07
156.67
148.87
127.73
106.86
41.61
40.84
36.00
35.46
34.86
26.36
24.48

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