Towards the Total Synthesis of Natural Products (–)-Englerin A and Crotogoudin

Studien zur Totalsynthese der Naturstoffe (–)-Englerin A und Crotogoudin

Dissertation

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my Daughter

Publications

1. Ushakov, D. B.; Maier, M. E. Studies towards the synthesis of crotogoudin. *Synlett* **2013**, *24*, in print. DOI: 10.1055/s-0032-1318366.

2. Ushakov, D. B.; Raja, A.; Franke, R.; Sasse, F.; Maier, M. E. Total synthesis of (±)-moluccanic acid methyl ester. *Synlett* **2012**, *23*, 1358–1360.

3. Ushakov, D. B.; Navickas, V.; Ströbele, M.; Maichle-Mössmer, C.; Sasse, F.; Maier, M. E. Total synthesis and biological evaluation of (–)-9-deoxy-englerin A. *Org. Lett*. **2011**, *13*, 2090–2093.

4. Navickas, V.; Ushakov, D. B.; Maier, M. E.; Ströbele, M.; Meyer, H.-J. Synthesis of the guaianolide ring system via cycloaddition of a bicyclic carbonyl ylide with allyl propiolate. *Org. Lett.* **2010**, *12*, 3418–3421. Highlighted in *ChemInform*, **2010**, *41* (48).

5. Morozkina, S. N.; Nikolaev, S. V.; Selivanov, S. I.; Ushakov, D. B.; Shavva, A. G. Catalytic hydrogenation on Raney nickel of estra-1,3,5(10),8,14-pentaenes with sterically accessible double bonds. *Russ. J. Org. Chem.* **2008**, *44*, 675−680. Highlighted in *ChemInform*, **2009**, *40* (2).

6. Morozkina, S. N.; Ushakov, D. B.; Eshenko, N. D.; Linder, S.; Shavva, A. G. Biological properties of 8α-steroid estrogens analogues with fluorine in position 2. *Russ. Biother. Jour*. **2008**, *7*, 65–65.

Table of Contents

Abbreviations

abs.	absolute
Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
ar. (arom.)	aromatic
A498	renal cancer cell line
Bn	benzyl
br	broad (NMR)
b.p.	boiling point
Bu	butyl
Bz	benzoyl
c	concentration
CDI	1,1'-carbonyldiimidazole
COSY	correlation spectroscopy
CSA	camphor sulfonic acid
δ	chemical shift in ppm (NMR)
d	doublet (NMR)
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHP	dihydropyran
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	Ethyleneglycoldimethylether
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio

E	*trans*
ee	enantiomeric excess
Eq.	equation
ESI	electronspray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation (NMR)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HUVEC	primary endothel cells
Hz	Hertz
IC_{50}	half maximal inhibitory concentration
IMDA	intramolecular Diels-Alder
Ipc	isopinocampheyl
*i*Pr	isopropyl
J	coupling constant
KB-3-1	HeLa cells
L	liter(s)
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
L929	mouse fibroblasts (cell line)
m	multiplet (NMR)
M	mol/L
MCF-7	breast cancer cells
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
mg	milligram
µg	microgram
MOM	methoxymethyl

Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Oct	octanoate
PCC	pyridinium chlorochromate
Piv	pivaloyl
Ph	phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
*p*TSA	*para*-toluenesulfonic acid
PtK2	potoroo kidney cell line
PTT	phenyltrimethylammonium tribromide
Py	pyridine
q	quartet (NMR)
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminiumhydride
R_f	retention factor (TLC)
r.t.	room temperature (ca. 23 °C)
s	singlet (NMR)
sec	secondary
t	triplet (NMR)
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TfO	trifluoromethanesulfonate

TMS	trimethylsilyl
Triflate	trifluoromethanesulfonate
Z	*cis*

Introduction and Goal of Research

Natural products play a highly significant role in the drug discovery and development process.[1] Only in 2005, plant-derived drugs sold for an established $ 18 billion.[2] For example, in the area of cancer treatment, 49% of the small molecules are either natural products or directly derived therefrom. Plants are a valuable source of new bioactive molecules that can also serve as structural "muse" for the design of small molecule libraries, in particular to define library scaffolds based on the activity of the parent molecule.[3] Although many natural products have impressive biological activity, they are usually presented in organisms in low quantities. This significantly hampers elucidation of the mode of action or extensive clinical research of these compounds. Thus, chemical synthesis is called to provide access to the required amounts as well as modified analogues that may have improved biological profile. Another important role of total synthesis is to prove the assigned structure and to determine absolute stereochemistry of the new molecule.[4] In recent decades several concepts like atom- and step-economy[5] or protecting group-free synthesis[6] have stimulated the development of powerful synthetic methodologies, which allow organic chemists to construct complex molecules in a more efficient manner. The desire to imitate nature has led to establishment of biomimetic approaches.

To this moment more than 50 000 terpenes are known and they represent one of the largest group of natural products, which often have intriguing biological activities. These natural products play important role in communication, defense and many other functions.[7] Selection of a specific molecule for the synthesis is dependent on many issues: impressive biological activity, challenging structural features, an idea to test scope and limitations of newly developed methods etc. Renal cancer is the cause of over 12 000 deaths every year in the United States.[8] Modern drugs used in chemotherapy (sorafenib, sutinib, everolimus) have moderate efficiency, require long-term administration for disease control, and have serious side effects.[9] Therefore, the identification of novel compounds that posses specific activity against renal cancer cells is highly desirable. Thus, the novel sesquiterpene englerin A with unique anticancer activity appeared as an interesting object for our studies that are highlighted in the first chapter. Crotogoudin – a new atisane diterpenoid attracted our synthetic interest due to its challenging structural features and interesting biological profile. Studies towards the synthesis of this novel diterpenoid are presented in the second chapter.

Chapter I
Studies Towards the Total Synthesis of Englerin A

1 Literature Review

1.1 Introduction

Terpenes can be divided into subgroups based on the number of isoprenoid units.[10] A large subgroup of the terpene family are sesquiterpenes (C_{15}) which originate from farnesyl diphosphate.[11] Among various ring systems that result from this precursor, the perhydroazulene skeleton, or bicyclo[5.3.0]decane, is quite common. The core structures might differ in the oxidation level and the relative stereochemistry at the ring fusion. Some of these guaiane-type terpenes feature an oxygen bridge in the seven-membered ring (**Figure 1**).[12]

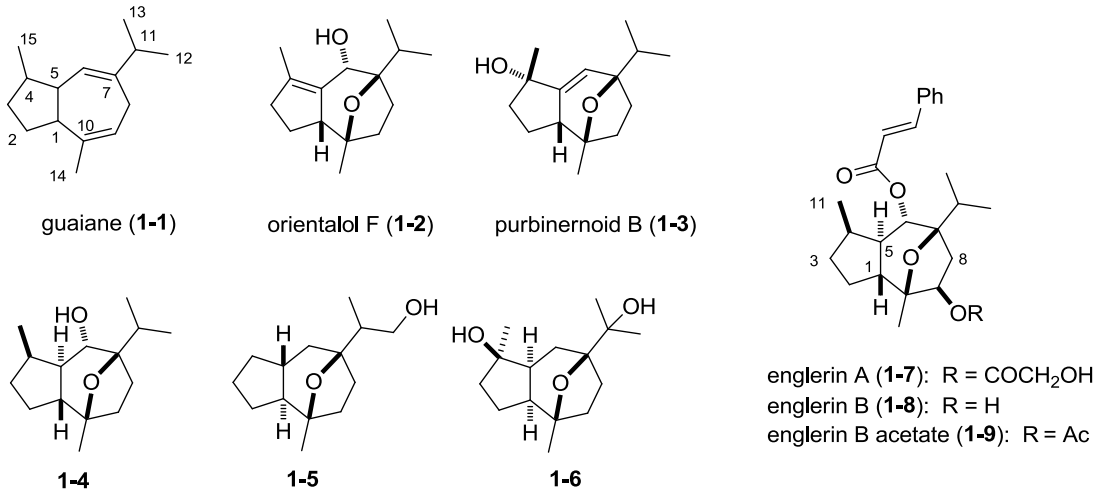


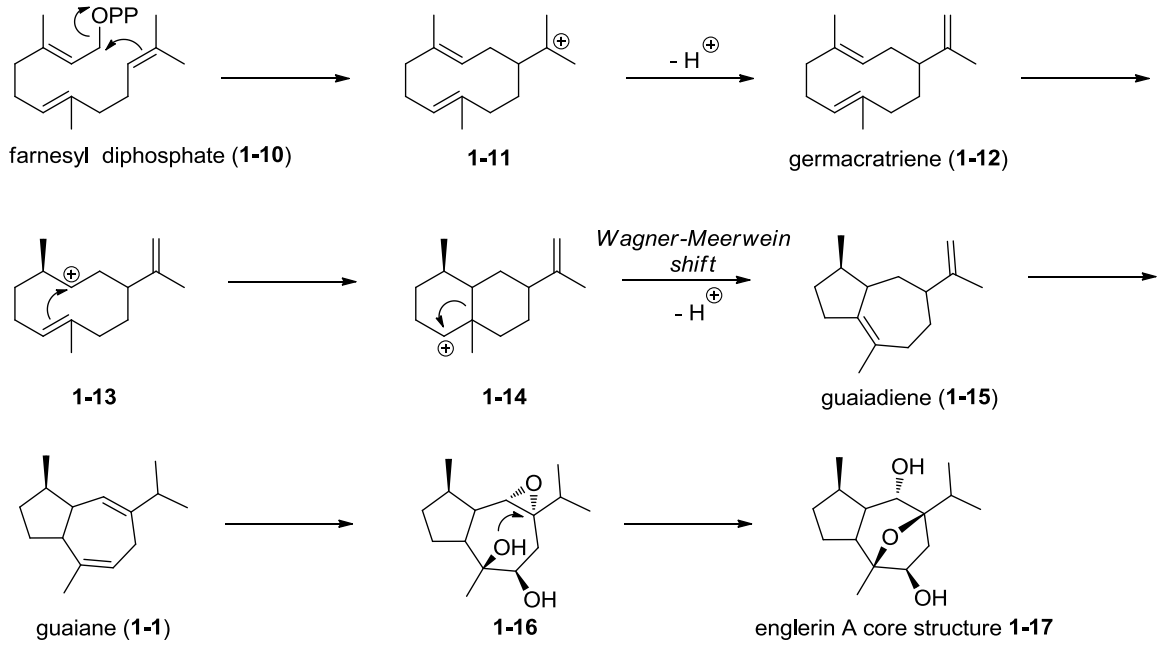
Figure 1. Examples for oxa-bridged guaiane-type natural products.

The guaiane sesquiterpene englerin A (**1-7**) was isolated from the plant extract of *Phyllanthus engleri* by Beutler *et al.*[13] The compound features an oxygen bridge in the seven-membered ring and seven contiguous stereocenters, including two quarternary centers. This novel guaianolide showed very high selectivity and potency against various cell lines that are involved in renal cancer having GI_{50} values under 20 nM (**Table 1**). Interestingly, englerin B (**1-8**) was significantly less active and less selective, while englerin B acetate (**1-9**) showed an approximately 400-fold selectivity against the renal cell line.

renal cell line	**1-7**	taxol
786–0	< 0.01	0.034
A498	< 0.01	0.10
ACHN	< 0.01	0.65
CAKI-1	15.5	0.35
RFX-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	< 0.01	0.45

Table 1. GI_{50} values in μM for englerin A (**1-7**) for different renal cancer cell lines, compared to average values for taxol.

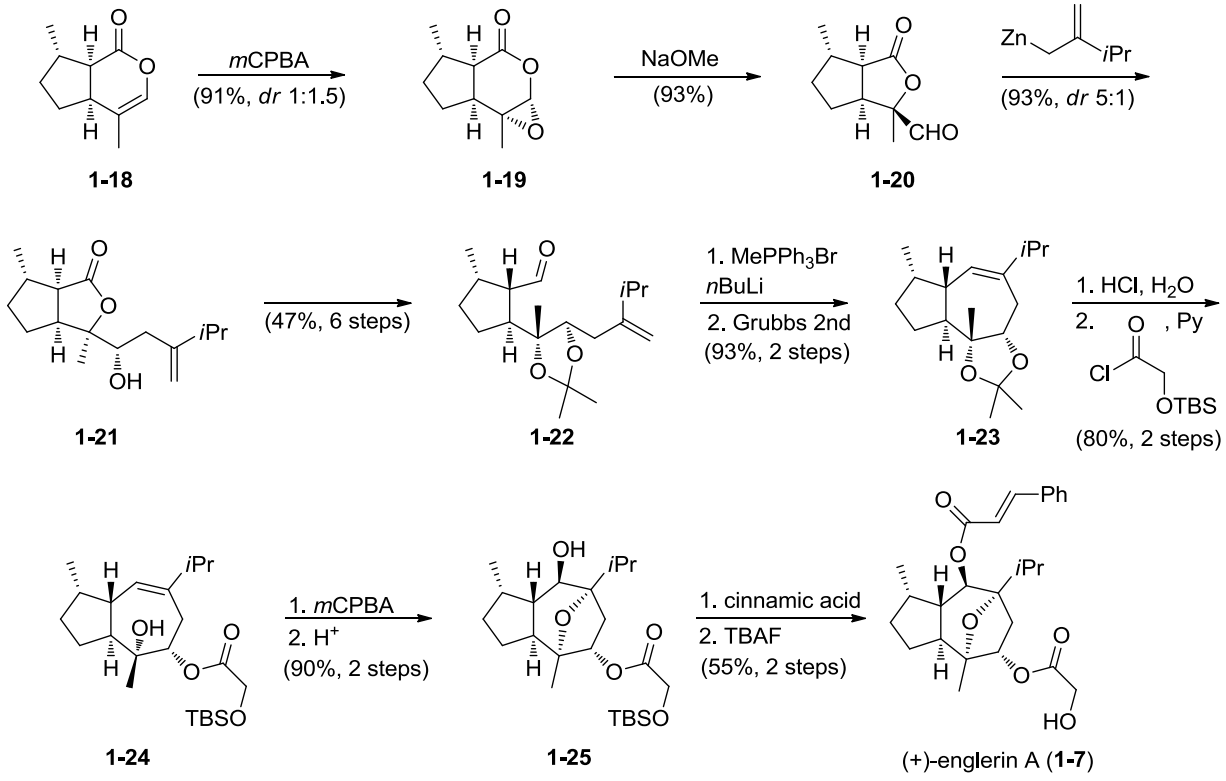
As it was mentioned above, the tricyclic core structure of guaiane sesquiterpenes originates from acyclic farnesyl diphosphate (**1-10**),[11] which undergoes cationic cyclization to decaline structure germacratriene (**1-12**) (**Scheme 2**). Protonation of the desired double bond, followed by intramolecular cyclization gives the 6,6-fused ring system **1-14**. Subsequent Wagner-Meerwein shift converts carbocation **1-14** to guaiadiene (**1-15**), from which the exocyclic double bond is moved into the cycle to give guaiane (**1-1**). The oxygen bridge possibly originates from transannular epoxide opening in **1-16**.



Scheme 2. Possible biosynthesis of oxa-bridged guaiane sesquiterpenes.

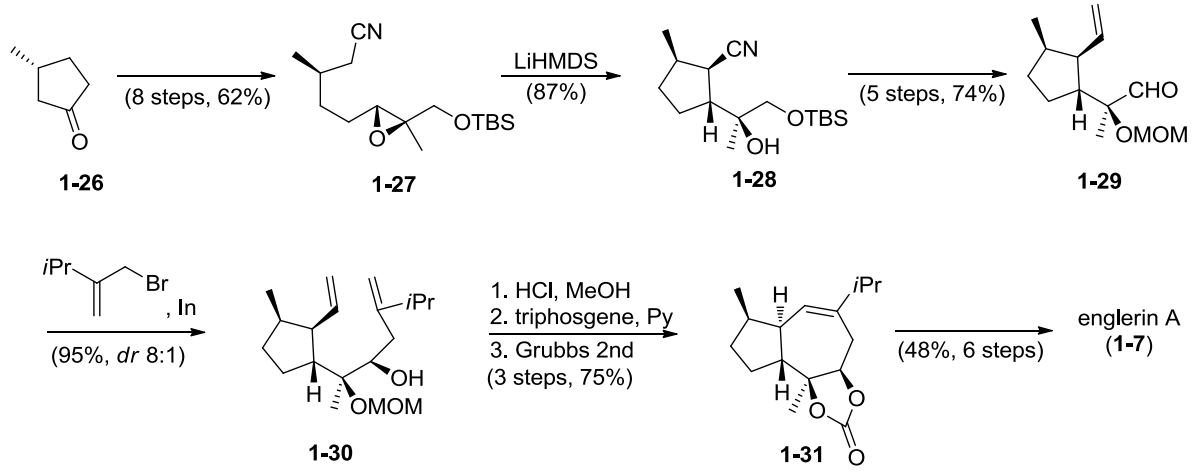
1.2 Overview of the Reported Studies Towards the Synthesis of Englerin A

The absolute stereochemistry of natural (–)-englerin A (**1-7**) was clarified by the group of Christmann.[14] They prepared *ent*-**1-7** [(+)-englerin A] from *cis*,*trans*-nepetalactone (**1-18**), a terpene which can be obtained by distillation of commercially available catnip oil (**Scheme 3**). Thus, lactone **1-18** was converted to aldehyde **1-20** in a two step sequence utilizing epoxidation followed by methanolysis via the corresponding alkoxyformyl ester. Protected diol **1-23** was synthesized in nine steps involving a diastereoselective Barbier reaction of aldehyde **1-20** with an organozinc species, epimerization at C-5 and Wittig olefination of aldehyde **1-22** followed by ring-closing metathesis. Regioselective esterification[15] of the secondary alcohol function gave glycolate ester **1-24**, whose stereoselective epoxidation and subsequent acid-catalyzed transannular epoxide opening[16] resulted in the oxygen bridge formation. This strategy for the ether formation certainly corresponds to the likely biosynthetic pathway (**Scheme 2**). In two further steps, including Yamaguchi esterification[17] and final deprotection the (+)-enantiomer of englerin A (**1-7**) was prepared, establishing the absolute stereochemistry of natural (–)-englerin A (**1-7**).



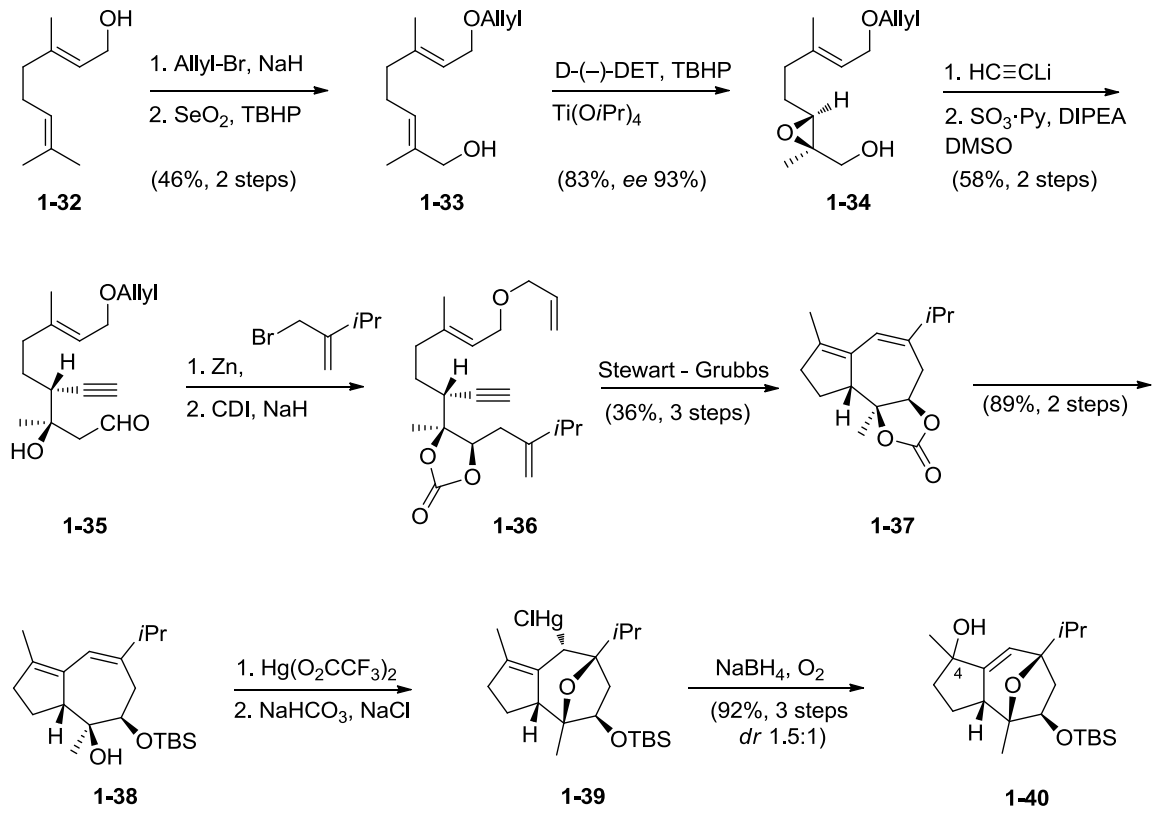
Scheme 3. Synthesis of *ent*-**1-7** by Christmann *et al*.

Application of a Barbier reaction/ring-closing metathesis strategy for the construction of englerin's 7-membered ring was also reported by Hatakeyama *et al.*[18] Highly functionalized cyclopentane **1-28** was prepared in a nine-step sequence from optically active 3-methylcyclopentenone (**1-26**) utilizing base-promoted cyclization[19] of epoxynitrile **1-27** to a cyclopentane **1-28** (**Scheme 4**). Barbier reaction on aldehyde **1-29** using an allylindium species afforded **1-30** in excellent yield. The high diastereoselectivity observed in the indium mediated allylation is attributable to a predominant attack of the allylindium to a nonchelation Felkin–Ahn model. Completion of the synthesis of (–)-englerin A (**1-7**) features a ring-closing metathesis, transannular epoxide opening and Yamaguchi esterification[17] with cinnamic acid, as previously reported by Christmann *et al.*[14]



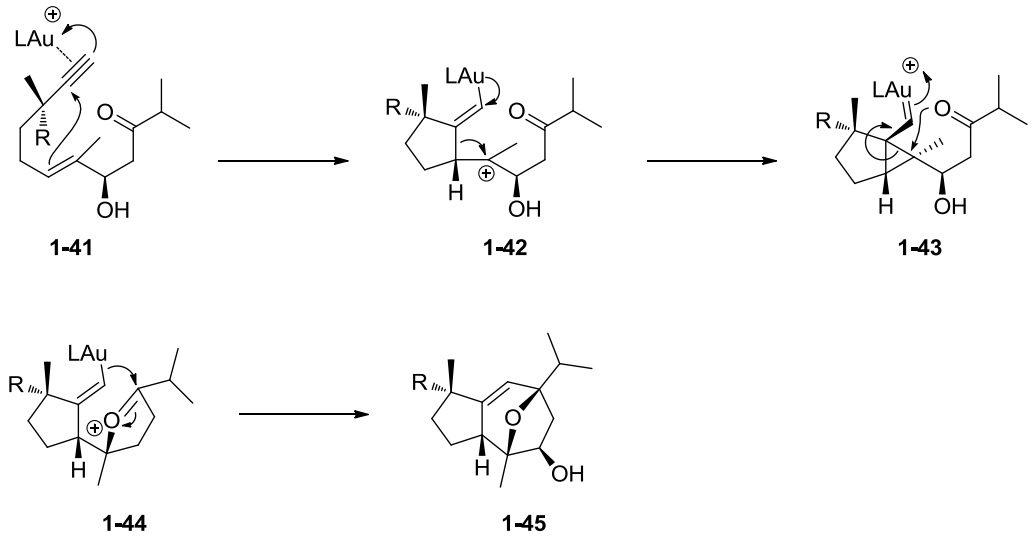
Scheme 4. Total synthesis of (–)-englerin A (**1-7**) by Hatakeyama *et al.*

Another example of a Barbier reaction/ring-closing metathesis strategy was reported by Parker *et al.*[20] Starting from geraniol (**1-32**) acyclic aldehyde **1-35** was prepared in a five step sequence involving a selective allylic oxidation, enantioselective Sharpless epoxidation of **1-33** and epoxide opening by lithium acetylide (**Scheme 5**). Barbier addition of 2-bromomethyl-3-methyl-1-butene to aldehyde **1-35** provided a substrate for the relay ene-yne-ene metathesis, which was achieved using the Stewart-Grubbs catalyst. This way, bicyclic diene **1-37**, that is disubstituted on the both ends and that contains a tetrasubstituted olefin, was prepared with good yield. Transannular etherification was achieved via regio- and stereoselective oxymercuration, followed by treatment with $NaCl/NaHCO_3$ leading to organomercurial intermediate **1-39**. Oxidative demercuration provided known tertiary alcohol **1-40**[21] as a mixture of diastereomers at C-4.



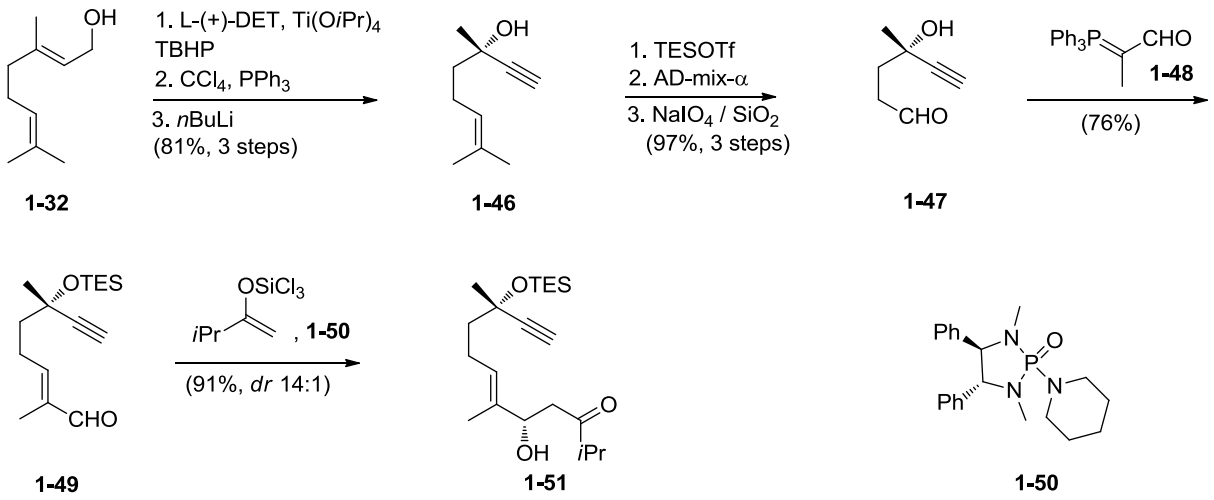
Scheme 5. A formal synthesis of (–)-englerin A (**1-7**) by Parker *et al.*

Two conceptually similar total syntheses of (–)-englerin A (**1-7**) appeared independently utilizing gold-catalysis for the cyclization of an acyclic precursor to a tricyclic englerin core structure.[21,22] In both cases the oxatricyclic core was fashioned by gold(I) catalyzed cyclization of an acyclic enyneketone **1-41**.[23] A clear analogy can be drawn between the biosynthetic route (**Scheme 1**) and the laboratory synthesis (**Scheme 6**).[24] The key gold-catalyzed domino process started with a 5-*exo*-dig cyclization leading to cyclopropyl gold carbene **1-43** which reacted with the carbonyl oxygen releasing the strain on the cyclopropane ring and producing oxonium ion **1-44**. Then, a Prins-cyclization took place followed by proto-deauration to give englerin's tricyclic skeleton. By this gold-catalyzed cyclization three new bonds and three stereocenteres were created in a highly selective fashion. Completion of the both syntheses relied on functionalization of **1-45** featuring allylic oxidation and stereoselective reduction of the double bond to establish a *trans*-fused ring orientation. Hoewever, one should mention that in both cases, conversion of **1-45** to englerin A (**1-7**) required a significant number of steps



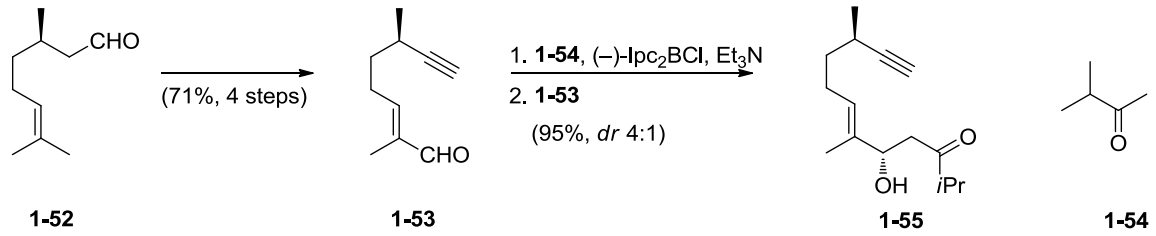
Scheme 6. The mechanism of gold-catalyzed domino cyclization reported by groups of Ma and Echavarren.

Echavarren's cyclization precursor[21] (R = OTES, **1-51**) was prepared in an eight step-sequence starting from geraniol (**1-32**) involving Sharpless asymmetric epoxidation followed by a stereoselective Denmark aldol reaction[25] (**Scheme 7**).



Scheme 7. Preparation of precursor **1-51**, according to Echavarren *et al*.

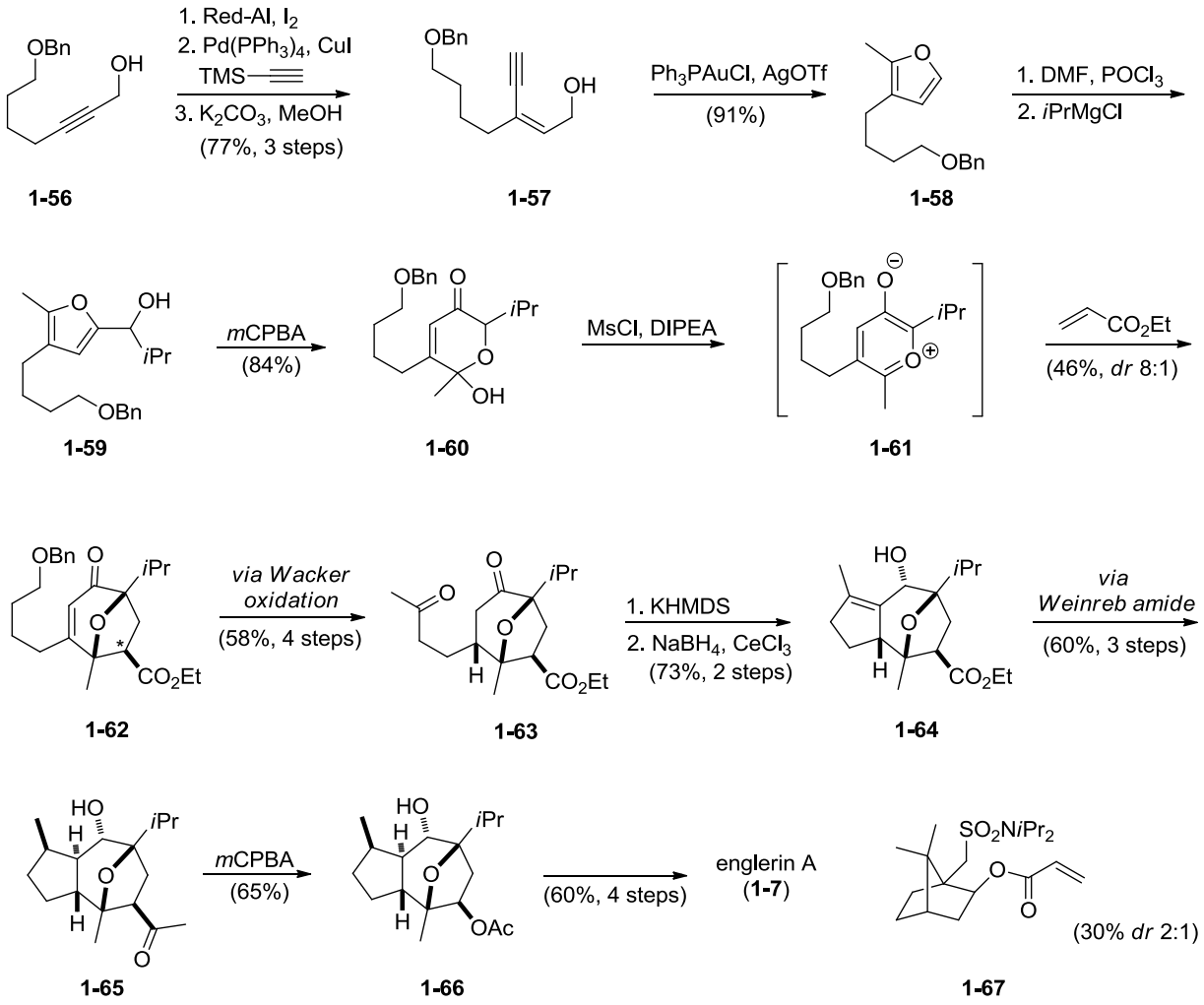
The precursor for Ma's approach[22] (R = H, **1-55**) was obtained in five steps from (*R*)-(+)-citronellal (**1-52**) utilizing a boron-aldol reaction (**Scheme 8**). Noteworthy is that this synthesis was performed without using protection groups.



1-52 **1-53** **1-55** **1-54**

Scheme 8. Preparation of precursor **1-55**, according to Ma *et al*.

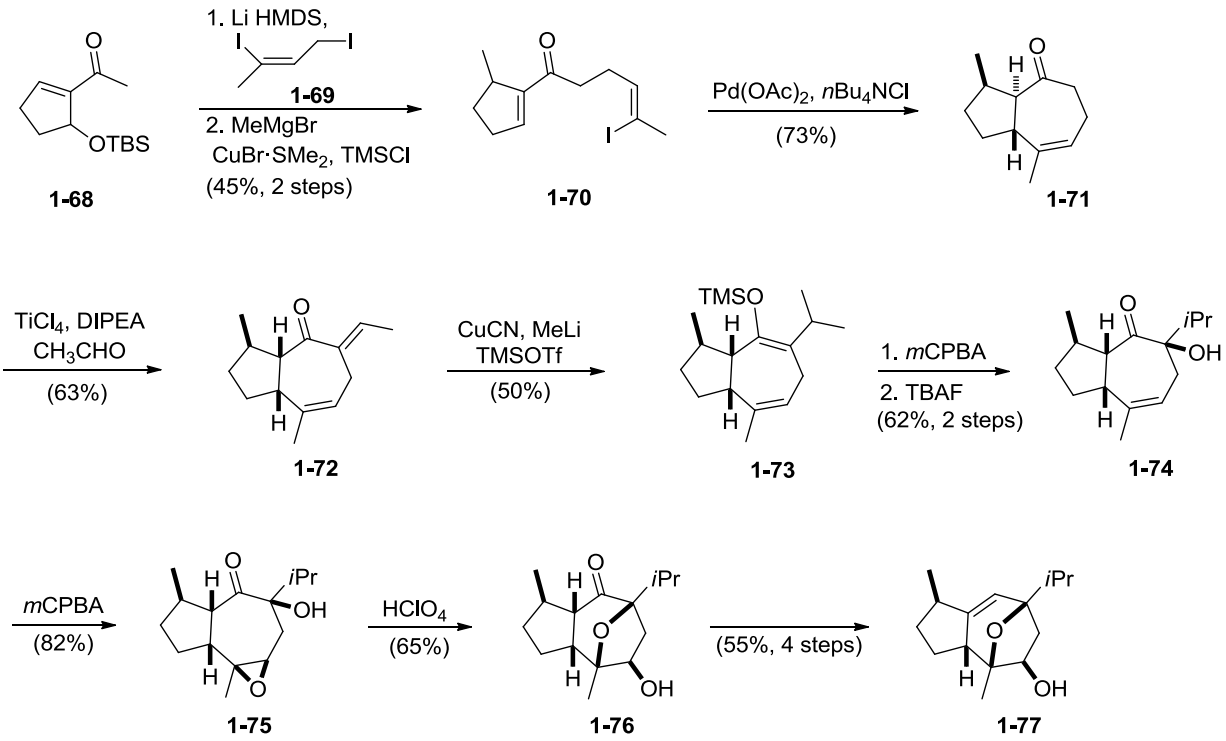
The Nicolaou/Chen group achieved the synthesis of englerin A (**1-7**) via a [5+2] cycloaddition to fashion the [3.2.1]oxabicyclic ring system followed by annulation of the cyclopentane ring (**Scheme 9**).[26] Starting from propargylic alcohol **1-56** furan **1-58** was prepared in four steps featuring a gold(I)-catalyzed furan formation.[27] Vilsmeier-Haack formylation[28] followed by Grignard addition and subsequent *m*CPBA mediated Achmatowicz rearrangement[29] provided key dihydropyranone **1-60**. Oxydopyrylium species **1-61** was formed by treatment of **1-60** with mesyl chloride and diisopropylethylamine and participated in a [5+2] cycloaddition reaction[30] with ethyl acrylate to afford oxabicyclic enone **1-62**. The five-membered ring was closed by intramolecular base-mediated aldol condensation. Baeyer-Villiger oxidation[31] was applied for degradation of methyl ketone **1-65** to acetate **1-66**. The authors also developed an asymmetric formal synthesis: camphor-derived acrylate **1-67** was used as a cycloaddition partner. Transformation of the resulting cycloadduct to (–)-**1-7** required additional four steps.



Scheme 9. Total synthesis of (±)-englerin A (**1-7**) via Achmatowicz rearrangement/[5+2] cycloaddition strategy.

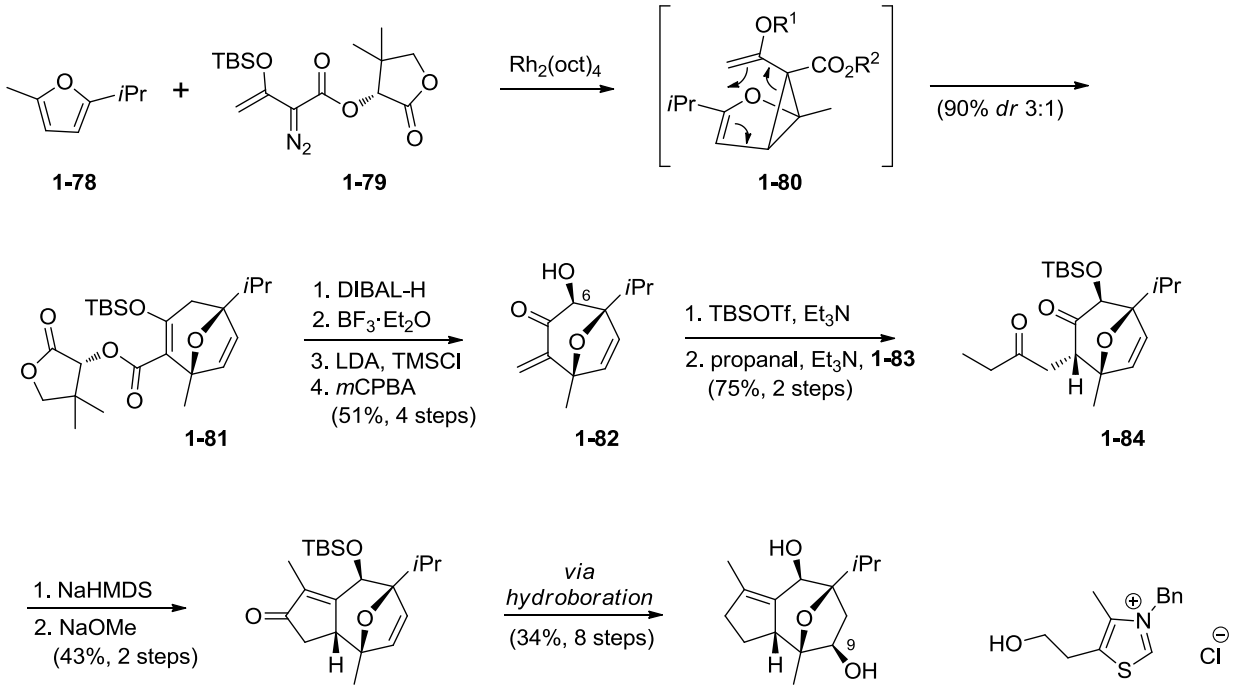
A reductive Heck reaction was applied for the synthesis of the hydroazulene ring system in a formal synthesis of (±)-englerin A (**1-7**) reported by Cook *et al.*[32] Starting from the known racemic α,β-unsaturated ketone **1-68**[33], *trans*-hydroazulene core **1-71** was prepared in a three-step sequence involving alkylation of the enolate, generated from **1-68,** with Wichterle iodide (**1-69**)[34] followed by copper-catalyzed Grignard addition and reductive Heck reaction (**Scheme 10**). During the installation of the isopropyl group on **1-71**, the desired *trans*-fused ring configuration was lost resulting in *cis*-hydroazulene derivative **1-72**. A hydroxyl function in an α-position to the carbonyl group was introduced via Rubottom oxidation.[35] Epoxidation of the double bond provided a substrate for an acid-mediated transannular epoxide opening furnishing the desired oxa-bridged englerin core **1-76**. This approach could be considered as an alternative to Christmann's[14] biomimetic ether formation. Alcohol **1-77**, prepared in

several steps from ketone **1-76** is a known compound, used in the synthesis of englerin A (**1-7**) by Ma *et al*.[22]



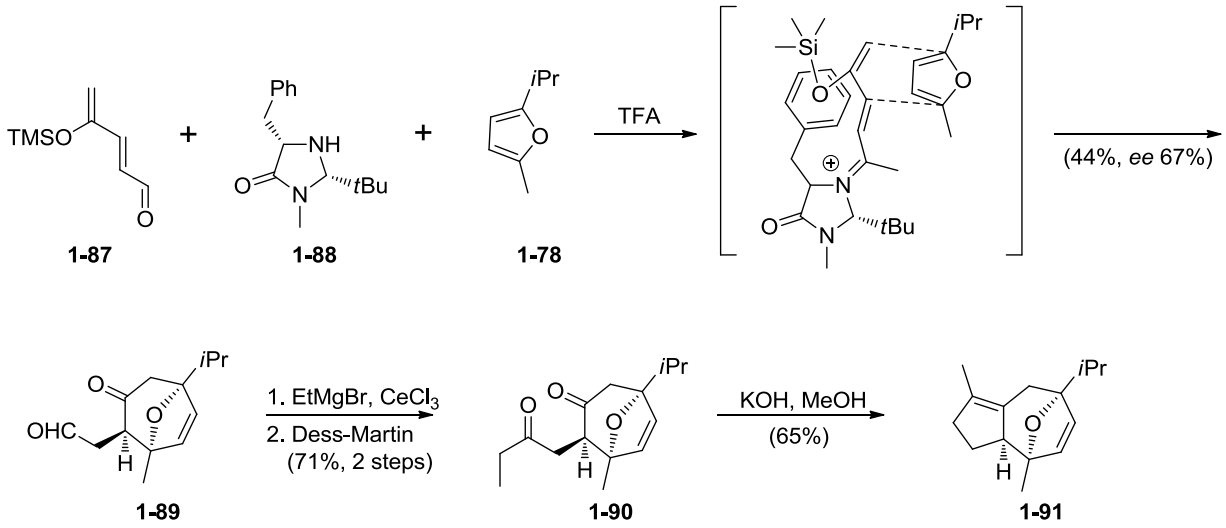
Scheme 10. A formal synthesis of (±)-englerin A (**1-7**) via reductive Heck reaction/transannular epoxide opening by Cook *et al*.

The group of Theodorakis achieved an enantioselective formal synthesis of (–)-englerin A (**1-7**) via a Rh-catalyzed [4+3] cycloaddition reaction.[36] The desired seven-membered oxabicycle **1-81** was obtained via a Rh-catalyzed cyclopropanation/Cope rearrangement sequence[37] from substituted furan **1-78** and chiral diazo ester **1-79** (**Scheme 11**). Removal of the chiral auxiliary, followed by Lewis acid-mediated rearrangement[38] resulted in exocyclic enone **1-82**. The hydroxyl group at C-6 was introduced via Rubottom oxidation.[35] Stetter reaction[39] provided substrate **1-84** for a base-induced intramolecular aldol condensation in order to construct the five-membered ring of **1-85**. Diol **1-86** is a known compound, and can be elaborated to (–)-englerin A (**1-7**) according to the method reported by Ma *et al*.[22]



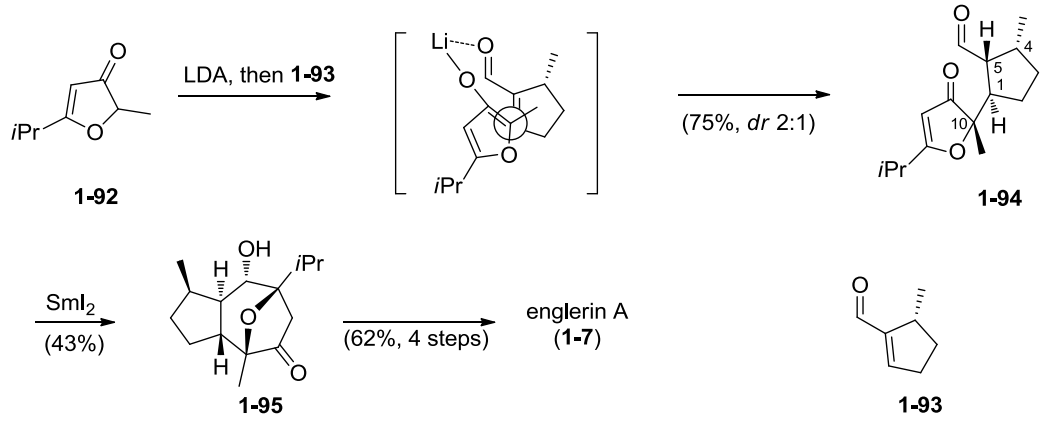
Scheme 11. A formal synthesis of (–)-Englerin A (**1-7**) via Rh-catalyzed [4+3] cycloaddition reaction.

Another approach towards the synthesis of (–)-englerin A (**1-7**) utlizing a [4+3] cycloaddition strategy was reported by Lin *et al.*[40] Organocatalyzed cycloaddition between furan **1-78** and iminium salt, generated from aldehyde **1-87** and MacMillan catalyst (**1-88**)[41] afforded cycloadduct **1-89** in moderate yield and enantioselectivity (**Scheme 12**). Englerin's core structure **1-91** was completed using base-mediated intramolecular aldol condensation.



Scheme 12. Studies towards the synthesis of Englerin A (**1-7**) utilizing organocatalytic [4+3] cycloaddition reaction.

A concise and elegant enantioselective total synthesis of (–)-englerin A (**1-7**) was reported by Chain *et al.*[42] Treatment of the lithium enolate, generated from 3-furanone **1-92**[43] with **1-93**[44] provided Michael adduct **1-94** in good yield (**Scheme 13**). Advantage of this strategy is a simultaneous establishment of the relative stereochemistry at C-1, C-4, C-5 and C-10 of the final natural product in the course of the Michael addition. Intramolecular reductive radical carbonyl-alkene cyclization mediated by samarium(II) iodide[45] was applied to furnish englerin's core structure **1-95**. Completion of the synthesis relies on the method reported by Ma *et al.*[22]



Scheme 13. A brief total synthesis of (–)-Englerin A (**1-7**) via Michael addition and Sm-mediated reductive carbonyl-alkene cyclization.

In summary, many different approaches were disclosed in the last 3 years to the intriguing englerin's architecture. Gold- and samarium(II)-mediated cyclizations reported by Ma/Echavaren[22,21] and Chain[42] respectively, together with Barbier reaction/ring closing metathesis sequence reported by Christmann,[13] seem to be the most efficient and elegant approaches to englerin A (**1-7**).

The first structure-activity relationship (SAR) investigations were reported together with racemic synthesis of englerin A (**1-7**) by Nicolaou/Chen.[26] One year letter Chen *et al.* published advanced SAR studies on analogues with modified cinnamate and glycolate domain.[46] It turned out that mostly analogues with the above-mentioned modifications showed significant loss of cytotoxic activity with selected renal cancer cell lines (UO31, A498). Albeit, some analogues were found to be promising (**Figure 2**, **Table 2**).

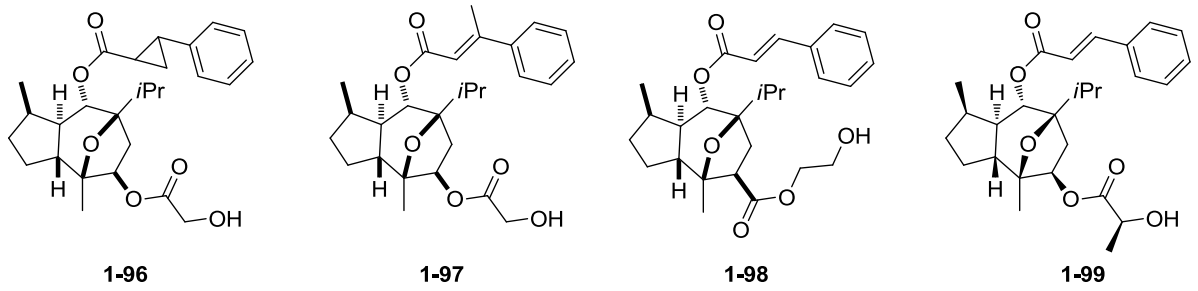


Figure 2. Synthetic analogues bearing improved activity profile.

Compd	GI_{50} in μM		
	UO31	A498	A549
1-96	0.007	0.049	> 10
1-97	0.014	0.086	> 10
1-98	0.035	0.048	> 10
1-99	0.047	0.020	> 10
(±)-**1-7**	0.037	0.045	> 10
Taxol	0.009	0.008	0.006

Table 2. Cytotoxicity of synthetic englerins against selected cancer cell lines.

Independent SAR studies on enantiomerically pure derivatives were reported by Christmann *et al.* together with an optimized multigram synthesis of (–)-englerin A (**1-7**),[47] based on their privous findings (**Figure 3**, **Table 3**).[14] It was found that the unnatural enantiomer of **1-7** showed diminished cytotoxicity (GI_{50} > 1 μM) against the A498 cell line. Substitution of the isopropyl group to a methyl or ethyl group led to loss of cytotoxic activity (4.64 and 2.93 μM

respectively). Analogues with modified glycolate domain did not show any enhanced activity in comparison with natural (–)englerin A (**1-7**), while some analogues (especially **1-101**) with a modified cinnamate domain showed improved cytotoxicity and selectivity.

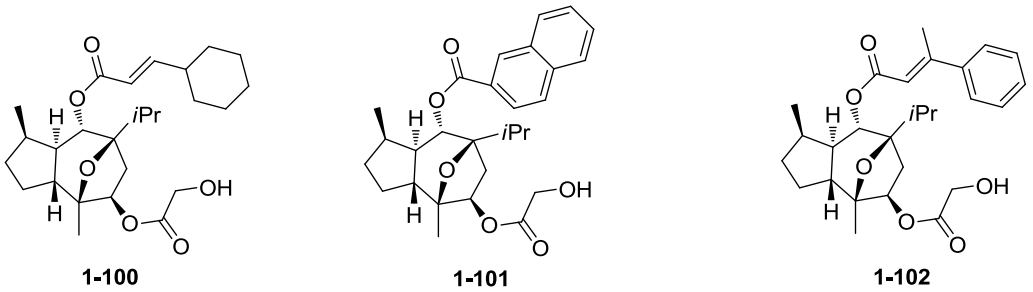


Figure 3. Synthetic analogues bearing improved activity profile.

Compd	GI_{50} in μM				
	Caki-1	A498	HEK293	HeLa	MD-AMB-468
1-7	–	0.045	24.8	15.9	17.7
1-100	–	0.025	29.2	> 30	> 30
1-101	–	0.024	> 30	> 30	> 30
1-102	–	0.026	13.9	15.2	19.4

Table 3. Cytotoxicity of synthetic englerins against selected cancer cell lines.

In conclusion, englerin A (**1-7**) – a novel guaianolide with unique anticancer activity and intriguing molecular architecture attracted a lot of interest within the synthetic community: to this moment the original publication by Beutler *et al.*[13] collected 36 citings. Taken together with six total, three formal syntheses and several approaches to the guaiane carbone backbone, englerin A (**1-7**) became a "hot topic" in natural product synthesis.[48] Several analogues with improved biological profile were developed. However so far, not much information regarding the mode of action nor the status in clinical development is available.[49] Recently the group of Neckers[50] found that englerin A (**1-7**) binds and activates protein kinase C-θ (PKCθ) that induces an insulin-resistant phenotype, limiting the access of tumor cells to glucose. At the same time, englerin A (**1-7**) causes PKCθ-mediated phosphorylation and activation of the transcription factor heat shock factor 1, an inducer of glucose dependence. By promoting glucose addiction, while simultaneously starving cells of glucose, englerin A (**1-7**) proves to be synthetically lethal to highly glycolytic tumors. Englerin A (**1-7**) remains one of the most promising drug candidates in development for curing kidney cancer without the severe side effects of other treatments.

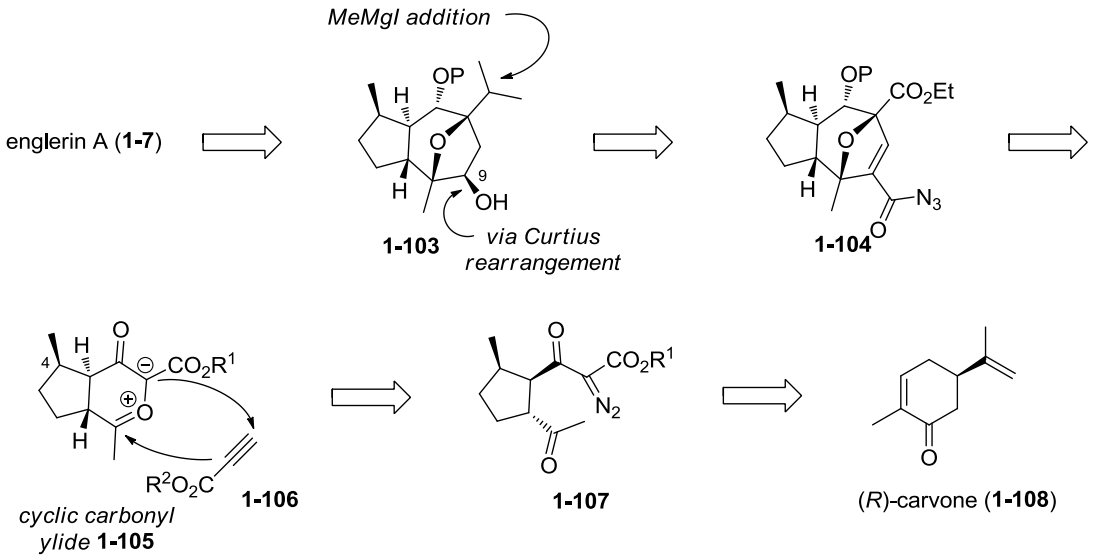
2 Results and Discussion

2.1 Towards the Synthesis of Englerin A via [3+2] Cycloaddition Reaction*

This project was started in October 2009, half a year after presentation of englerin A (**1-7**) to the synthetic community.[13] To that moment total syntheses or studies towards englerin A (**1-7**) mentioned in the literature review had not been reported as well as the absolute stereochemistry of the natural product.

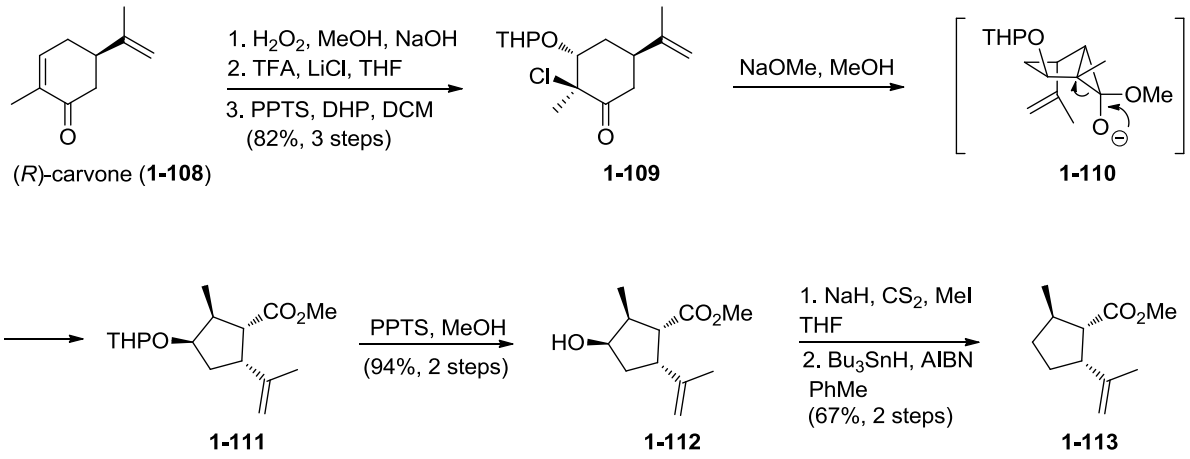
In our first retrosynthetic plan a bimolecular carbonyl ylide – alkyne cycloaddition reaction played a key role in formation of the guaiane skeleton.[51,52] As an advantage of this strategy appeared to us the simultaneous formation of the oxygen bridge in the course of the cycloaddition, where propiolate **1-106** would be expected to approach the carbonyl ylide **1-105** from the opposite site to the C-4 methyl group. The intermediate carbonyl ylide **1-105** should be available by rhodium(II)-catalyzed decomposition of diazoketoester **1-107**. The latter can be traced back to (*R*)-(–)-carvone (**1-108**). The hydroxyl group at C-9 in **1-103** would be generated from the acyl azide **1-104** via a Curtius rearrangement/vinyl isocyanate hydrolysis sequence. The isopropyl group would be installed via double Grignard addition to an ester function, followed by deoxygenation of a resulting tertiary alcohol.

* This work was done together with graduate student Vaidotas Navickas and some of the results presented in this chapter are already highlighted in his doctoral thesis (University of Tübingen, 2011)



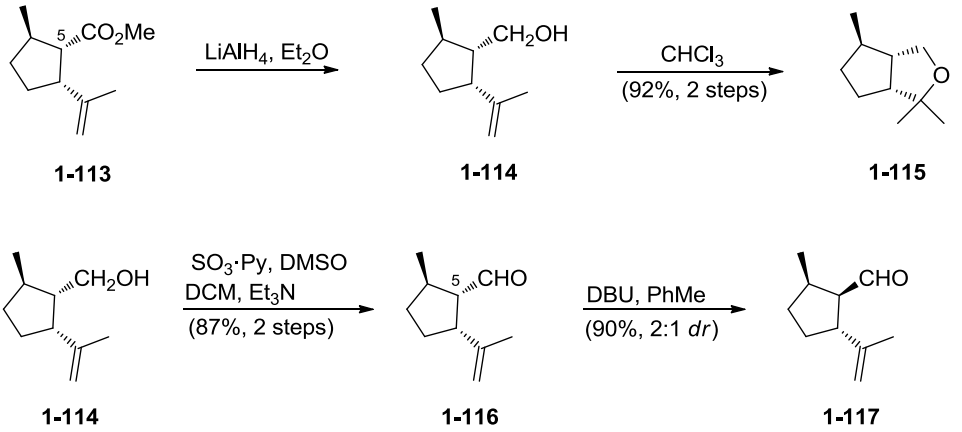
Scheme 14. Retrosynthetic disconnection of (–)-englerin A (**1-7**) utilizing a [3+2] cycloaddition reaction as a key step.

The synthesis commenced with commercially available (*R*)-(–)-carvone (**1-108**) (**Scheme 15**). Following known procedures,[53] this terpene was transformed into a highly functionalized cyclopentanecarboxylate **1-111** in a five-step sequence featuring stereoselective nucleophilic enone epoxidation, regioselective epoxide opening and a stereoselective Favorskii rearrangement on chlorohydrine **1-109** resulting in ring contraction. Use of THP as a protecting group made analysis and work up inconvenient (mixture of diastereomers on the acetal carbon), however other protecting groups were less satisfactory in the subsequent rearrangement reaction.[54] The hydroxyl group was then removed utilizing the Barton−McCombie protocol on the corresponding xanthogenate[55] giving ester **1-113** in 67% yield over two steps. Deoxygenation of the alcohol with tetrabutylammonium peroxydisulfate and formate ion[56] as a softer and tin-free method was not successful.



Scheme 15. Synthesis of cyclopentanecarboxylate **1-113** from (*R*)-(–)-carvone (**1-108**).

At this stage, epimerization at C-5 (englerin numbering) was considered. However, all attempts to invert the configuration on ester **1-113**, under basic conditions (DBU, DIPEA, LDA, Et_3N), gave inadequate results. Therefore, the ester **1-113** was successfully transformed into the corresponding aldehyde **1-116** utilizing a two step protocol, namely $LiAlH_4$ reduction and Parikh−Doering oxidation[57] (**Scheme 16**). We found that this two step procedure was more reliable to perform on a large scale (25 g, 87%), as DIBAL-H reduction gave just the corresponding alcohol which was then oxidized with Dess-Martin periodinane[58] (5.0 g, 49% over two steps). Also we found that primary alcohol **1-114** was not stable under acidic conditions ($CHCl_3$, overnight, r.t.) and underwent intramolecular ether formation leading to **1-115**. Base-induced epimerization of aldehyde **1-116** was achieved with DBU in refluxing toluene (**Table 4**) leading to *trans* orientation of the aldehyde group with respect to the larger isopropenyl group (*trans*/*cis* = 2:1).

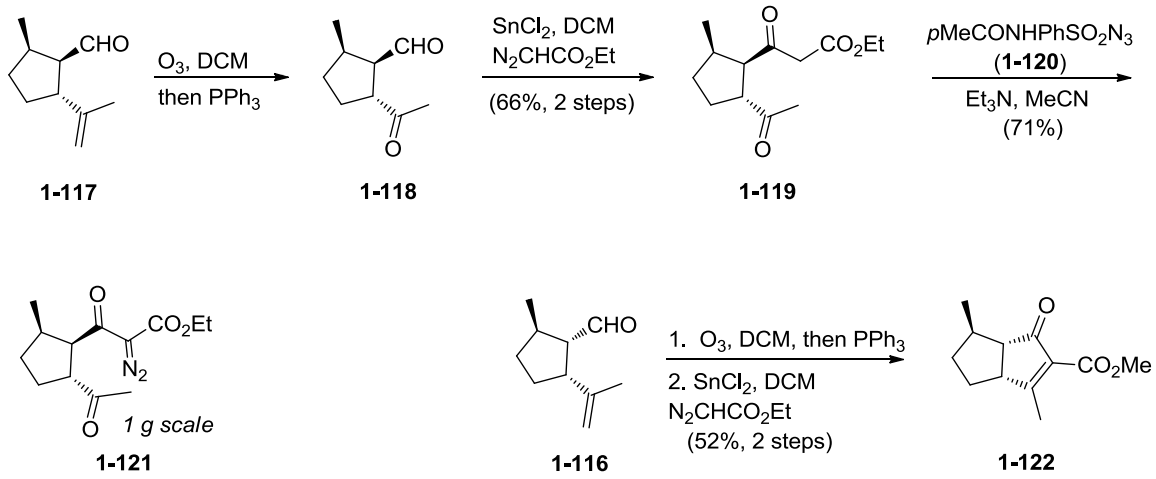


Scheme 16. Preparation of aldehyde **1-117**.

Entry	Base	Solvent	Temperature	Time, h	Ratio **1-117**:**1-116**
1	DIPEA	CH_2Cl_2	reflux	30	1:1
2	DBU	CH_2Cl_2	r.t.	30	1:4
3	DBU	CH_2Cl_2	reflux	48	1.3:1
4	DBU	toluene	reflux	48	2:1
5	LDA	THF	r.t.	20	1:1
6	LDA	THF	reflux	20	decomp.

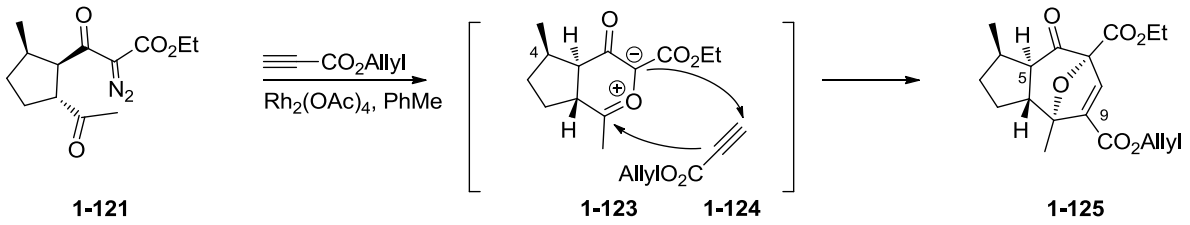
Table 4. Screening for the optimal epimerization conditions (**Scheme 16**).

An unseparable diastereomeric mixture of aldehydes **1-116** and **1-117** was used in the next step, where ozonolysis and reaction with ethyl diazoacetate catalyzed by tin (II) chloride[59] provided β-ketoester **1-119** as a single isomer in 66% yield over two steps (**Scheme 17**). Ketoaldehyde **1-118** turned out to be volatile and proceeding the reaction in one pot was found to be crucial to obtain β-ketoester **1-119** in good yield. One should mention that the other diastereomer of β-ketoester was not detected after work up (diastereomeric mixture of **1-117** and **1-116** was used in this sequence). As a control experiment we made ozonolysis with not epimerized (*cis*) aldehyde **1-116** followed by reaction with ethyl diazoacetate. After work up we isolated a new compound to which we assigned structure **1-122**. It seems, that an intramolecular Knovenagel-type condensation took place when ketone and β-ketoester groups are close to each other. Finally, a diazotransfer reaction with sulfonyl azide **1-120**[60] furnished diazoketone **1-121** in 71% yield. This thirteen step sequence allowed us to prepare gram quantities of **1-121** starting from (*R*)-(–)-carvone (**1-108**).



Scheme 17. Synthesis of diazoketone **1-121**.

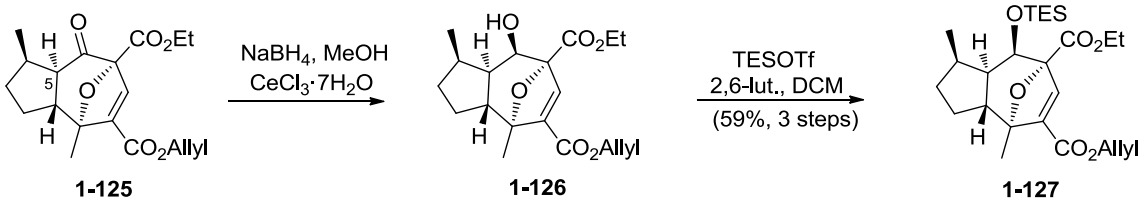
With diazoketone **1-121** in hand, we tested the proposed intramolecular carbonyl ylide formation of **1-123** promoted by Rh(II) and its subsequent cycloaddition with allyl propiolate (**1-124**) (**Scheme 18**). We chose **1-124**[61] as a dipolarophile due to ease of further functionalization and absence of a new stereocenter at C-9 in **1-125**. After careful experimentation, we found that heating of a mixture containing allyl ester **1-124**, 1 mol % of $Rh_2(OAc)_2$, and diazo compound **1-121** in toluene (100 °C) for 15 min led to the formation of cycloadduct **1-125** as a single isomer. Decreasing the temperature and/or increasing the reaction time led to lower yields of the cycloadduct **1-125**. When ethyl acrylate was used as a dipolarophile a mixture of diastereomers was isolated in 16% yield. In case of methyl vinyl ketone no desired product was detected.



Scheme 18. The key [3+2] cycloaddition step between cyclic carbonyl ylide **1-123** and allyl propiolate (**1-124**).

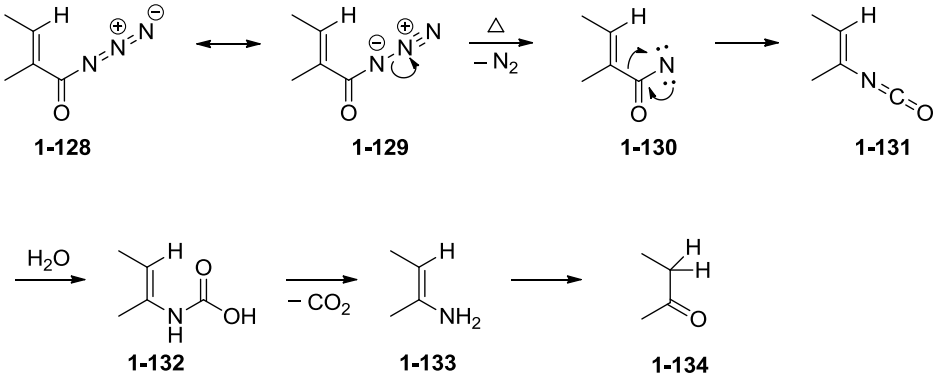
The cycloadduct **1-125** turned out to be sensitive to epimerization at C-5 even upon silica gel chromatography, leading exclusively to the corresponding *cis*-isomer. Therefore, crude ketodiester **1-125** was selectively reduced under Luche conditions[62] and the resulting alcohol converted to TES-ether **1-127** in 59% over three steps (starting from **1-121**) (**Scheme 19**). At

this stage we were not able to determine for sure the stereochemistry of the newly formed centres in **1-127** via NOESY experiments (orientation of the oxygen bridge).



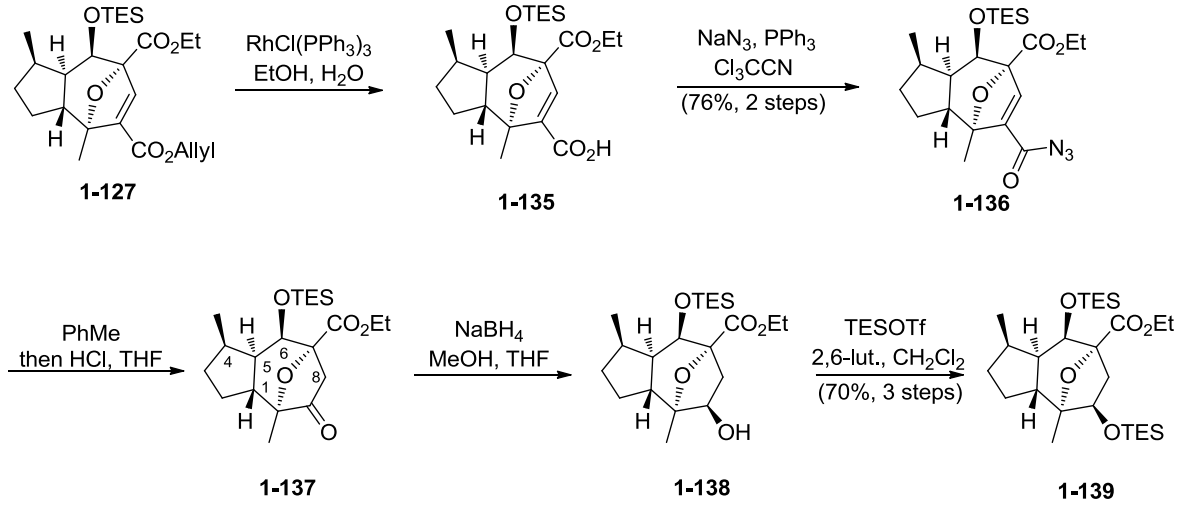
Scheme 19. Synthesis of silyl ether **1-127**.

Further functionalization of the seven-membered ring called for degradation of the acrylate to a keto function. This was achieved via a Curtius rearrangement/hydrolysis sequence.[63] The proposed mechanism for this sequence relies on the formation of vinyl isocyanate **1-131**, via the corresponding nitrene **1-130** (**Scheme 20**). It seems that isocyanate moiety in **1-131** hydrolyzes first, followed by the hydrolysis of the resulting enamine **1-132**.



Scheme 20. Mechanism of Curtius rearrangement/vinyl isocyanate hydrolysis.

It was found that the allyl ester in **1-127** could be easily removed using 10 mol% of Wilkinson's catalyst in an ethanol/water mixture (**Scheme 21**).[64] In contrast, palladium-based methods failed to provide carboxylic acid **1-135**. Now, acid **1-135** was converted to acyl azide **1-136** in presence of trichloracetonitrile and PPh_3.[65] Upon heating, azide **1-136** rearranged to the vinyl isocyanate which was selectively hydrolyzed to ketone **1-137** under acidic conditions. It should be noted that under this conditions (HCl aq. (5%), THF, r.t.) no deprotection of the TES group at C-6 was observed.



Scheme 21. Transformation of cycloadduct **1-127** into bis-silyl ether **1-139** via degradation of acrylate moiety.

At this stage, key NOESY cross peaks between 1-H/8-H, 4-H/5-H, and 5-H/6-H suggested a structure of **1-137** where the oxygen bridge is on the opposite site with respect to the C-4 methyl group (**Figure 4**).

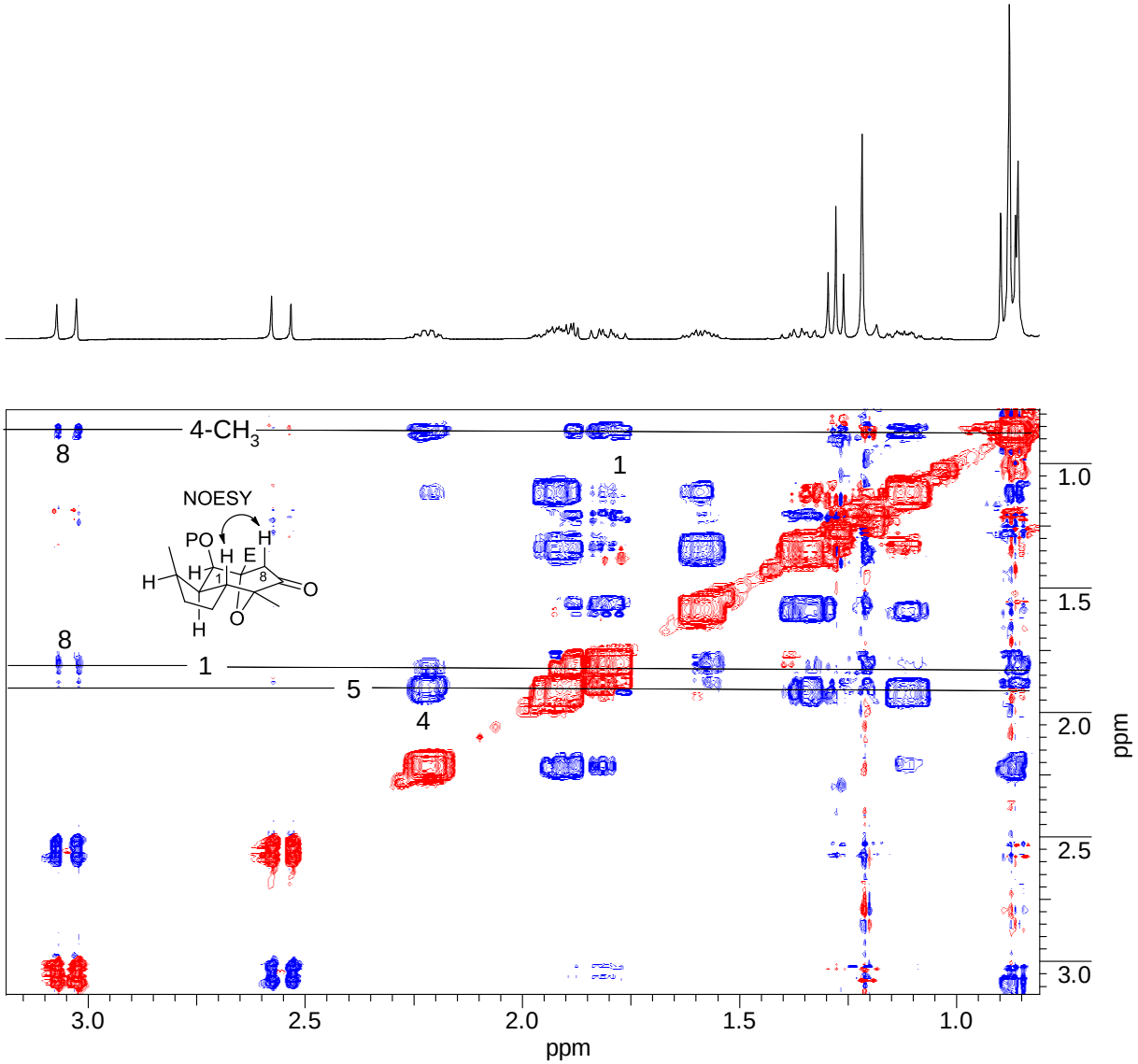
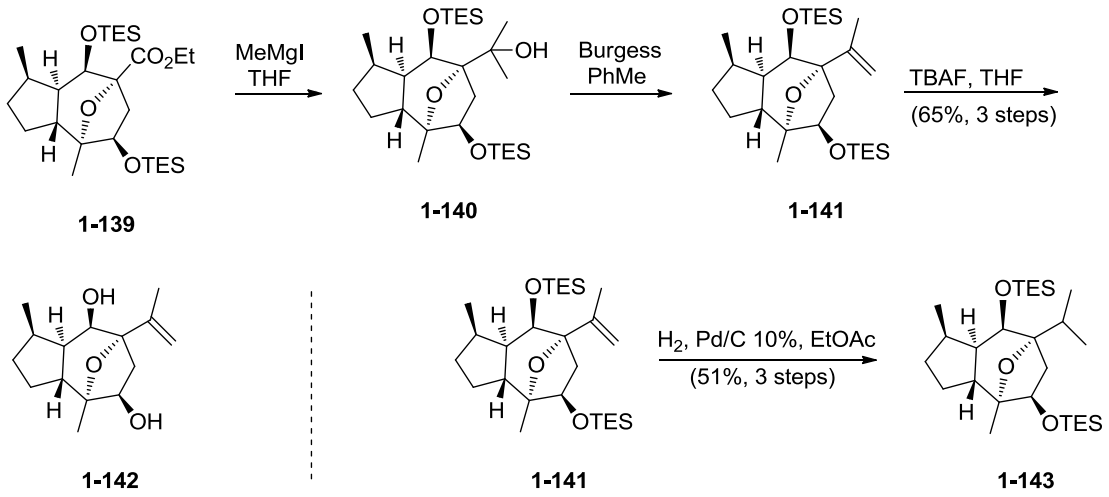


Figure 4. Key NOESY correlations between 1-H and 8-H in **1-137**.

Nevertheless, we continued with further functional group manipulations to prove the NMR studies by X-ray (the intensity of the cross peak between 8-H and 1-H was not very high in **Figure 4**) and to prepare a carbon backbone common of many other guaiane sesquiterpenes. Accordingly, reduction of the carbonyl group and TES-protection provided bis silyl ether **1-139** as a single diastereomer (**Scheme 21**).

Subsequent addition of freshly prepared MeMgI (6.0 equiv) to ester **1-139** at 0 °C gave tertiary alcohol **1-140** in quantitative yield (**Scheme 22**). As next, we thought to use the same radical deoxygenation conditions applied earlier (Barton-McCombie method). However,

neither the xanthogenate[55] nor the corresponding trifluoro acetate,[66] did undergo deoxygenation. On the other hand, Burgess reagent ($MeO_2CN^-SO_2N^+Et_3$)[67] did the job providing alkene **1-141** which led to silyl ether **1-143** via catalytic hydrogenation. TES deprotection on alkene **1-141** was achieved with TBAF to give alkenediol **1-142** in 65% yield.



Scheme 22. Transformation of ester function to the isopropylene group. Completion of the synthesis of guaianolides **1-142** and **1-143**.

Crystallization of **1-142** from a hexane/diethyl ether mixture provided crystals suitable for X-ray analysis (**Figure 5**) indicating the configuration of all stereocenters and conformation of the structure. The X-ray structure additionally proved the facial selectivity in the cycloaddition step which corroborated the NOESY data of ketone **1-137**.

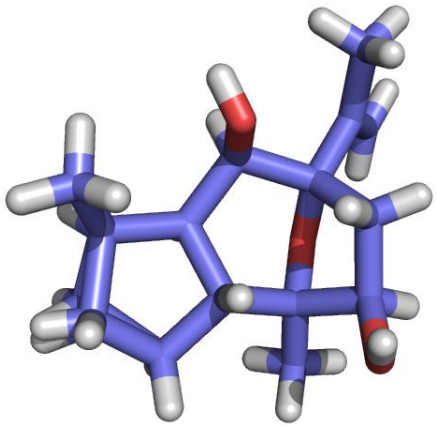
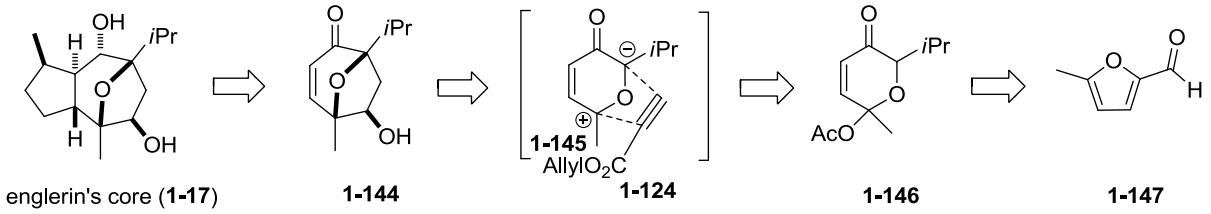


Figure 5. X-ray structure of diol **1-142**.

The synthesized analogue **1-142** was tested against five cancer cell lines (L929, A498, KB-3-1, MCF-7, HUVEC), using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[68] The obtained IC_{50} values were > 40 µg/mL with all tested cell lines.

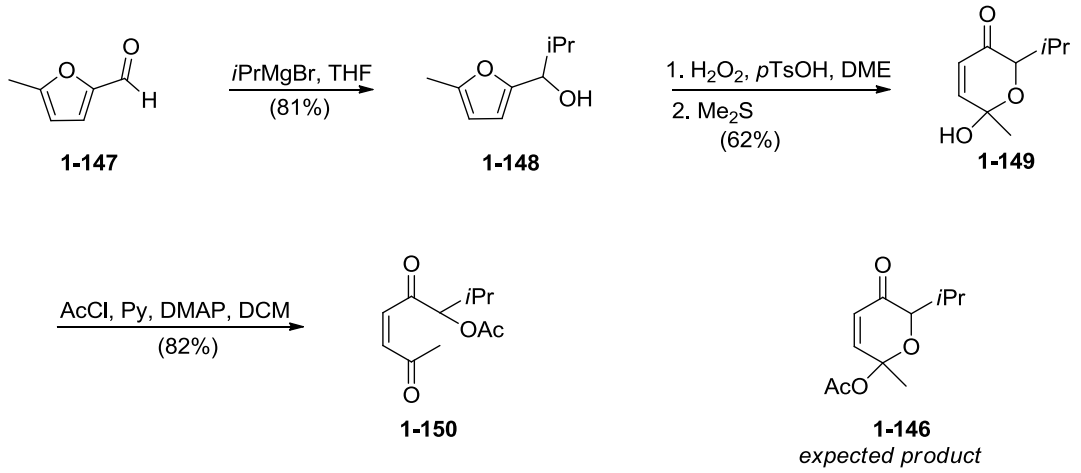
2.2 Construction of the Oxabicyclo[3.2.1]octane System of the Englerins via Oxidopyrylium/Alkyne [5+2] Cycloaddition

According to this approach, the oxygen-bridged seven-membered ring would be contracted first, followed by annulation of the five-membered ring. The retrosynthetic analysis features an oxidopyrylium/alkyne [5+2] cycloaddition reaction as a key step,[30,69] where 1,3-dipole **1-145** would be generated via elimination of acetic acid from **1-146** (**Scheme 23**). The required hydroxypyranone should be available from furan **1-147** via Achmatowicz rearrangement.[29,70]



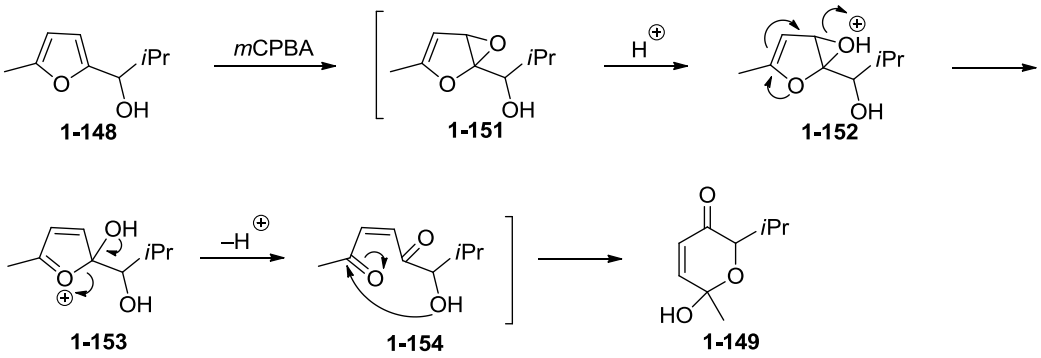
Scheme 23. Retrosynthetic analysis of englerin's core structure (**1-17**) utilizing [5+2] cycloaddition strategy.

Starting from commercially available furfural **1-147**, furfuryl alcohol **1-148** was prepared via Grignard addition of *i*PrMgBr to the carbonyl group of **1-147** (**Scheme 24**). Further oxidation with H_2O_2/*p*TSA induced the Achmatowicz rearrangement, resulting in hydroxypyranone **1-149**. During preparation of acetate **1-146** we faced the problem, that diketone **1-150** was formed under all tested conditions (AcCl, Py, DMAP, CH_2Cl_2; Ac_2O, Py; Ac_2O, AcOH, CH_2Cl_2; Ac_2O, Et_3N, CH_2Cl_2; Ac_2O, AcONa, THF etc.), and we were not able to observe any amounts of the desired **1-146**.



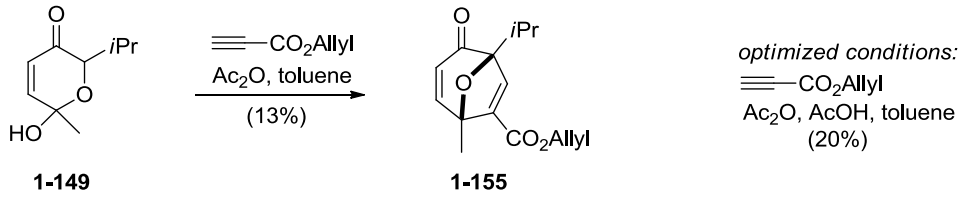
Scheme 24. Preparation of hydroxypyranone **1-149** via Achmatowicz rearrangement.

The proposed mechanism for the Achmatowicz rearrangement relies on directed electrophilic epoxidation of allylic double bond of the furan ring, protonation of epoxide, epoxide opening with formation of oxonium ion **1-153** and intramolecular hemiacetal formation **(Scheme 25)**.



Scheme 25. The proposed mechanism for H_2O_2/*p*TSA-mediated formation of hydroxypyranone **1-149**.

Finally, we decided to introduce hydroxypyranone **1-149** in the key cycloaddition reaction, suggesting that acetate would form *in situ*. In our first experiment, we were able to obtain the desired cycloadduct **1-144** in 13% yield (**Scheme 26**). Unfortunately, we could not significantly increase the yield during optimization studies (only up to 20%), due to the favored formation of diketone **1-150**.

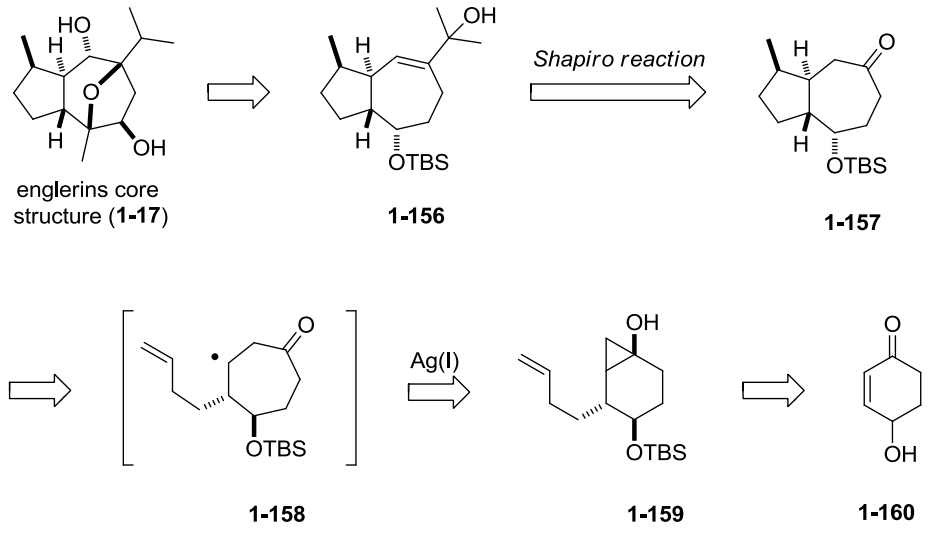


Scheme 26. Synthesis of oxygen-bridged seven-membered ring **1-155** via [5+2] cycloaddition.

One month after receiving the best results for the cycloaddition reaction Nicolaou *et al.*[26] published a conceptually similar synthesis of (±)-englerin A (**1-7**), where a mesylate was used instead of acetate as a leaving group (**Scheme 9**).

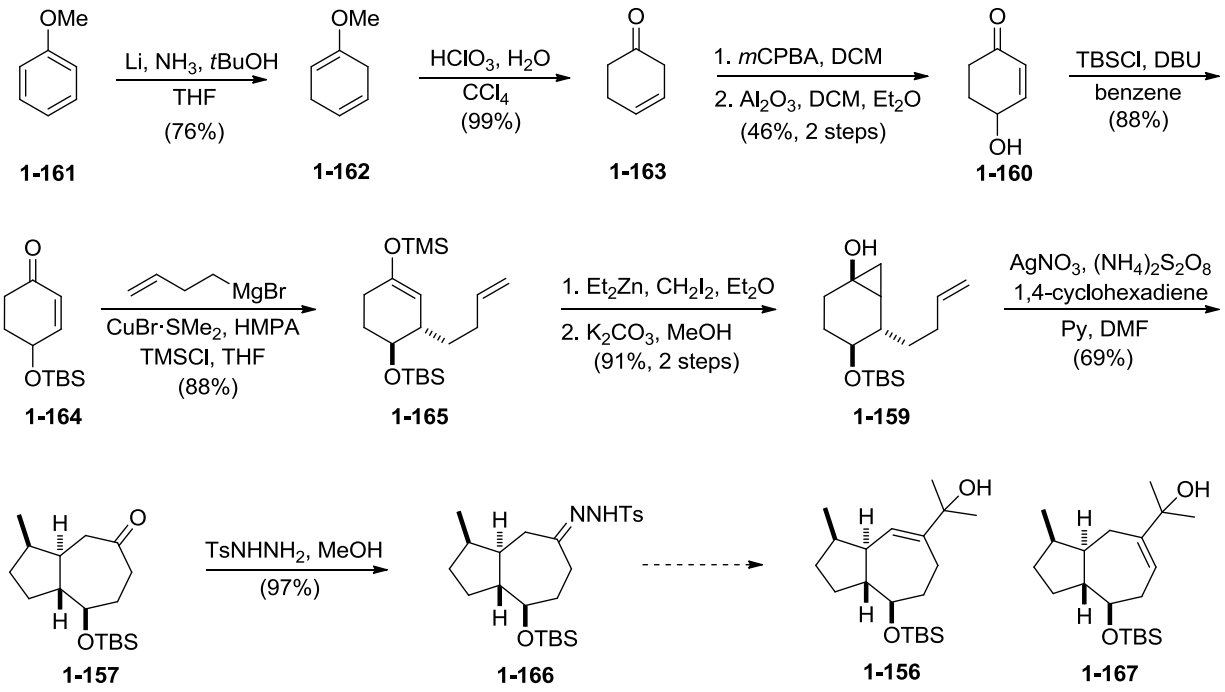
2.3 Studies Towards the Synthesis of Englerin A Exploiting Ag(I)-catalyzed Oxidative Radical Cyclization as a Key Step

Being impressed by the total synthesis of sordarin reported by Narasaka *et al.*,[71] where the authors used an Ag(I)-catalyzed oxidative radical cyclization of a cyclopropanol derivative for the construction of bicyclo[5.3.0]decan-3-one skeleton,[72] we decided to apply that strategy for our synthesis of (±)-englerin A (**1-7**). The retrosynthetic bond disconnections are presented below (**Scheme 27**).



Scheme 27. Retrosynthetic analysis for englerin's core structure (**1-17**), utilizing an Ag-catalyzed oxidative radical cyclization.

The synthesis commenced with Birch reduction of anisole (**1-161**),[73] followed by hydrolysis of methyl enol ether **1-162**.[74] A subsequent *m*CPBA-mediated epoxidation of nonconjugated enone **1-163** followed by epoxide ring opening by alumina gave allylic alcohol **1-160**,[75] whose hydroxyl group was protected as a TBS ether.[76] Copper-catalyzed 1,4-Grignard addition of 3-butenylmagnesium bromide, followed by treatment of the resulted enolate with TMSCl afforded silyl enol ether **1-165**.[77] Diastereoselective Simmons-Smith cyclopropanation[78] and hydrolysis of TMS-ether provided cyclopropanol **1-159**, which was introduced in the crucial Ag(I)-catalyzed oxidative radical cyclization. This way the bicyclo[5.3.0]decane skeleton **1-157** of the englerins was prepared.

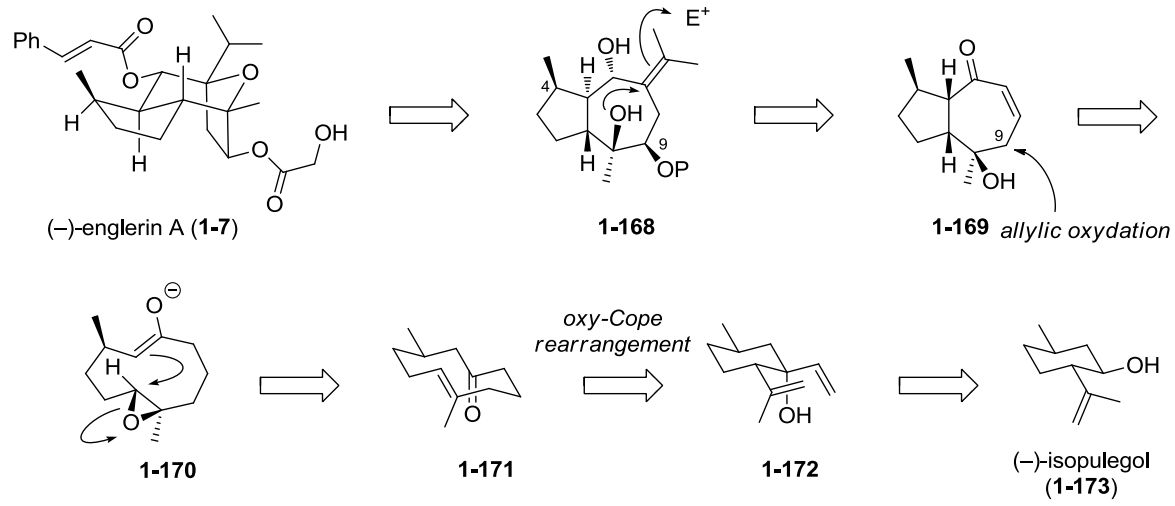


Scheme 28. Synthesis of hydrozone **1-166** via Ag-mediated oxidative radical cyclization.

Hydrazone **1-166**, prepared from ketone **1-157** in perfect yield, was introduced in a Shapiro reaction[79] with acetone. Unfortunately, we were not able to obtain the desired allylic alcohol **1-156** even in moderate yield. A mixture of regioisomers (1:1) was obtained in all experiments, using different bases (LDA, LiHMDS, KHMDS) and temperatures (r.t., –78 °C). Regioselective enolization of ketone **1-157** was also not fruitful.

2.4 Studies Towards the Synthesis of Englerin A via an Oxy-Cope Ring Expansion/Transannular Epoxide Opening Strategy

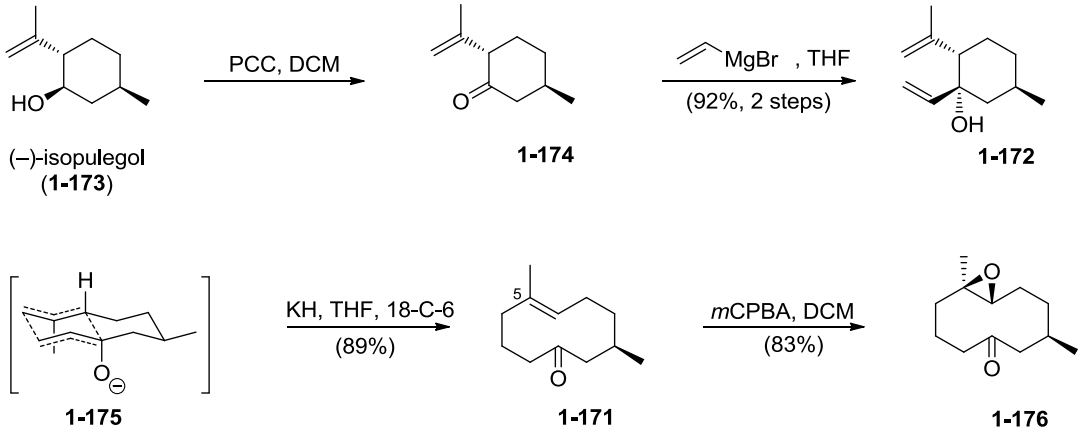
Our next retrosynthetic plan for (–)-englerin (**1-7**) featured a transannular ether formation leading to azulene derivative **1-168** (**Scheme 29**). This cyclization could be induced by acid or by activation of the double bond with mercurinium ion. The tetrasubstituted double bond of **1-168** could be possibly introduced via aldol condensation using acetone as a C_3 building block. Allylic oxidation of unsaturated enone **1-169** was considered to introduce the hydroxyl group at C-9. The annulated 5,7-ring system might originate from an intramolecular epoxide opening of a ketone enolate **1-170** which would be generated from cyclic enone **1-171**.[80] By considering an oxy-Cope rearrangement[81,82] on dienol **1-172** to generate cyclodec-5-enone **1-171**, (–)-isopulegol (**1-173**) appeared as a suitable starting material, providing stereochemical information for C-4 in (–)-englerin A (**1-7**).



Scheme 29. Retrosynthetic disconection of (–)-englerin A (**1-7**) utilizing transannular epoxide opening as a key step.

The synthesis commenced with commercially available (–)-isopulegol (**1-173**), which was converted to diene **1-172** in two steps utilizing a Corey-Suggs oxidation[83] followed by treatment of the resulting ketone with freshly prepared vinylmagnesium bromide[84] (**Scheme 30**). Only one diastereomer of **1-172** was formed, which could be expected from an equatorial attack of the nucleophile on the ketone. Anionic oxy-Cope rearrangement of vinyl carbinol **1-172** was achieved with KH in THF under reflux, resulting in ring expansion to cyclodecenone **1-171**. We found that addition of catalytic amounts of 18-crown-6 ether resulted in increase of

the rate and the yield up to 89% in 12 h (without 18-C-6, the reaction took 16 h and gave 71% of **1-171**).



Scheme 30. Transformation of (–)-isopulegol (**1-173**) to epoxide **1-176** via oxy-Cope rearrangement.

One should mention, that up to this step, purification of all compounds relied on a simple vacuum distillation. Several signals in the ^{1}H and ^{13}C NMR spectra of cyclodecenone **1-171** were rather broad, indicating the slow movement with regard to the NMR time scale (**Figure 6**).

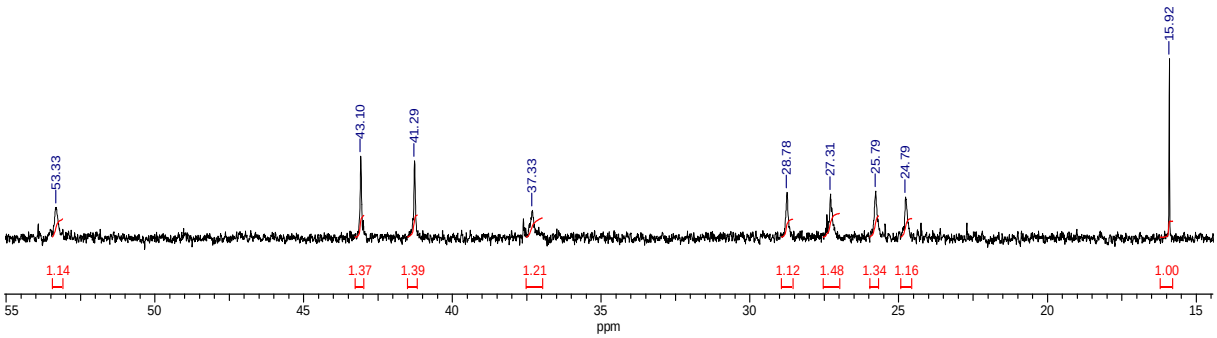


Figure 6. Broad signals in a fragment of the ^{13}C NMR spectrum of **1-171**.

Stereoselective *m*CPBA mediated epoxidation resulted in epoxide **1-176**, whose structure was confirmed by X-ray analysis (**Figure 7**). Explanation of the stereoselectivity in this step relies

on a macrocyclic control,[85] where the methyl group at C-5 prevents rotation of the double bond which would lead to diastereomers.

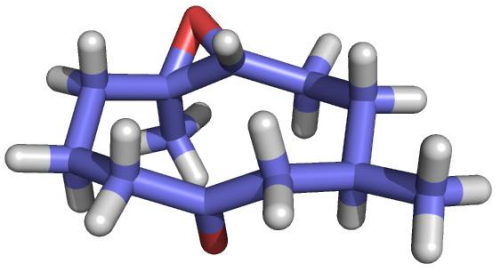
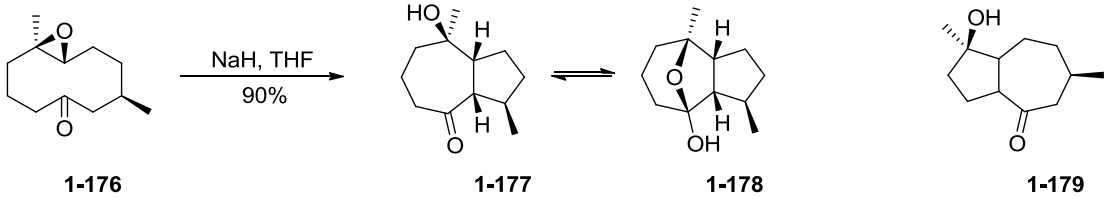


Figure 7. X-ray structure of epoxide **1-176**.

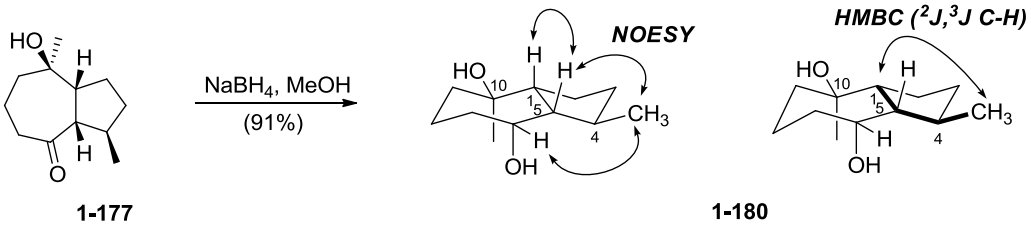
A regioselective enolate formation on keto epoxide **1-176**, in order to prepare the desired 5,7-fused ring system was found to be challenging. Thus, when a freshly prepared LDA solution was added dropwise to a stirred solution of ketone **1-176** at –78 °C a mixture of regioisomers **1-177** and **1-179** was obtained (1:4, 83%) (**Scheme 31**). Increase of the reaction temperature up to ambient conditions resulted in improved regioselectivity (1:0.7, 77%). Usage of LiHMDS provided similar results. Changeover from the big base to NaH and proceeding the reaction under reflux, resulted in formation of only the desired isomer **1-177** in perfect yield (90%). This way ketone **1-177** could be obtained on 6.0 g scale. The order of addition (base to ketone or ketone to base) did not influence the enolate formation: in all experiments the respective product ratios were the same.



1-176 **1-177** **1-178** **1-179**

Scheme 31. The optimized conditions for the transannular epoxide opening.

We were not able to prove the stereochemistry and constitution of **1-177** at that stage, while the hydroxyketone **1-177** exists in equilibrium with its cyclic hemiacetal **1-178** (3:7 ratio, $CDCl_3$, r.t.). Therefore we transformed a mixture of **1-177** and **1-178** into the derived diol **1-180** (**Scheme 32**).



Scheme 32. Reduction of **1-177**. Key NOESY and HMBC correlations in **1-180**.

The *cis*-orientation of 1-H, 5-H and the 4-CH_3 group could be inferred from the NOESY spectrum.

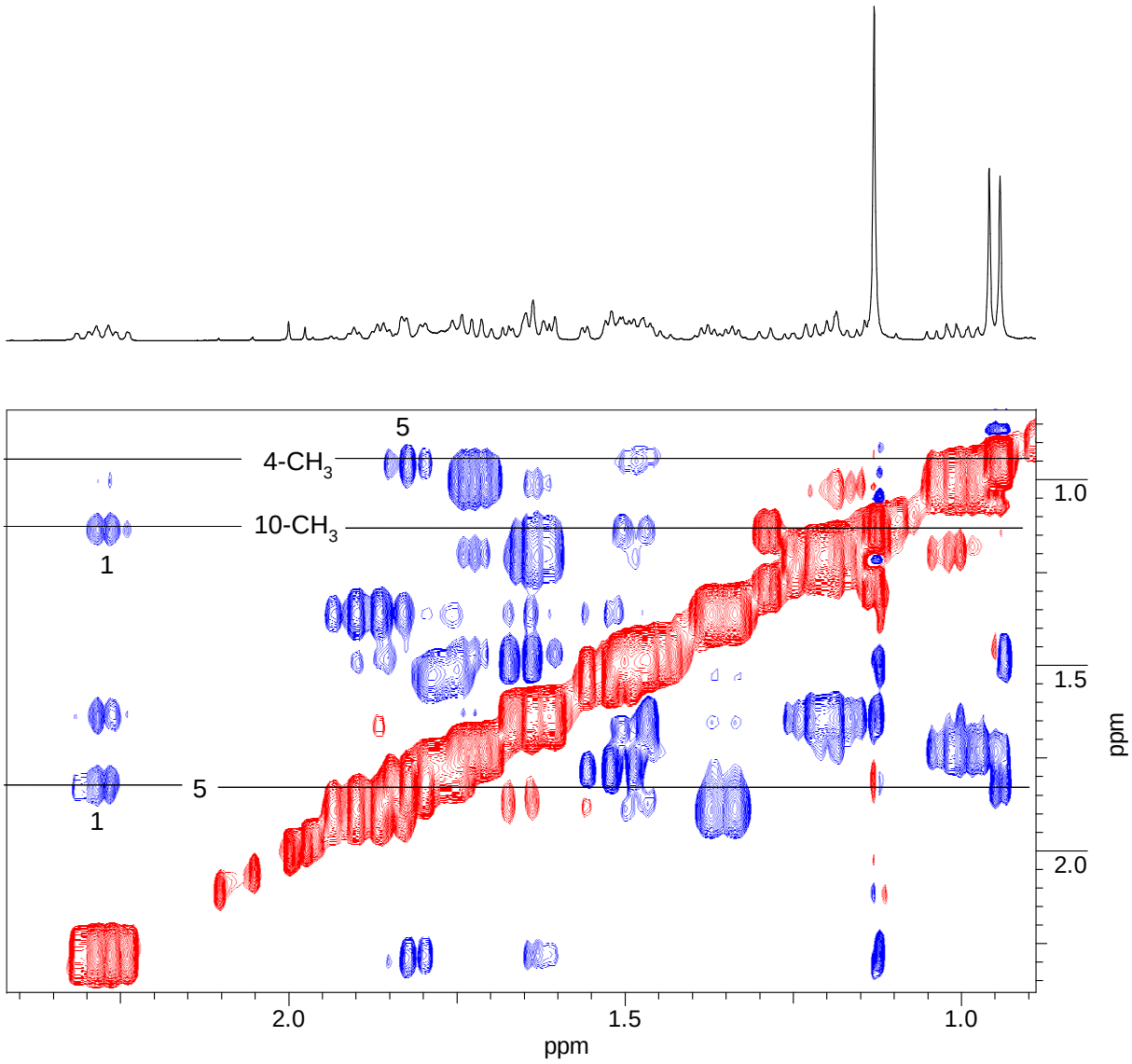


Figure 8. Fragment of the NOESY spectrum of **1-180**.

The connectivity in diol **1-180** was esteblished by a HMBC spectrum. Correlation between protons in 4-CH_3 and carbon C-1 and/or C-5 proved our assumption (**Figure 9**). Noteworthy, the chemical shift of C-1 and C-5 in ^{13}C NMR have the same value, resulting in one peak with higher intencity (confirmed by integration of peaks in ^{13}C spectra). With another constitution of 5,7-fused ring system (**1-179**), the 4-CH_3 group is too far from C-1 or C-5 (^5J) and the cross peaks would not be obeserved. Independent confirmation of the connectivity by X-ray analysis was performed after several steps.

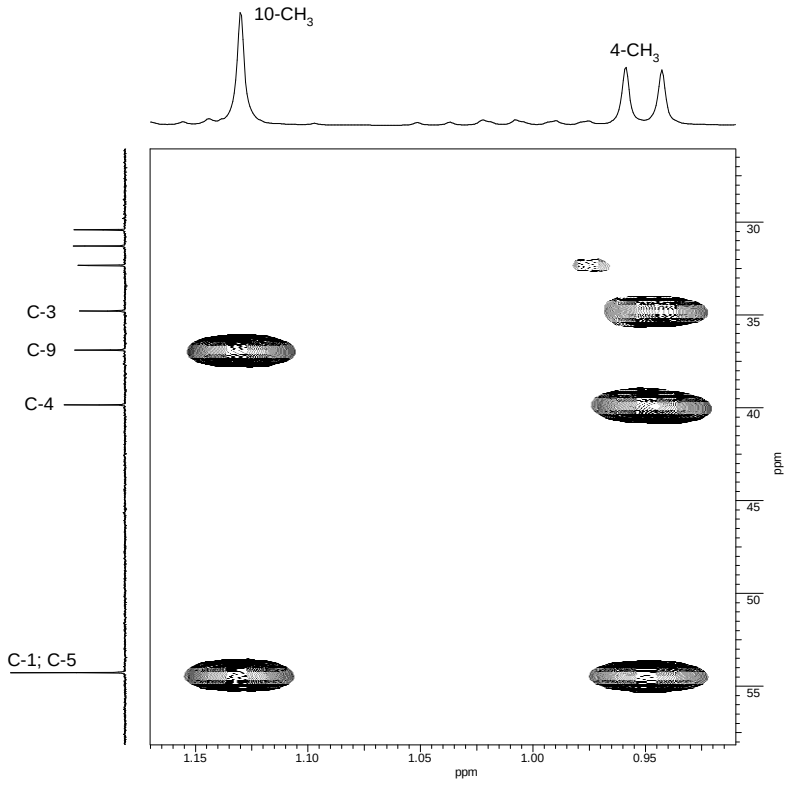
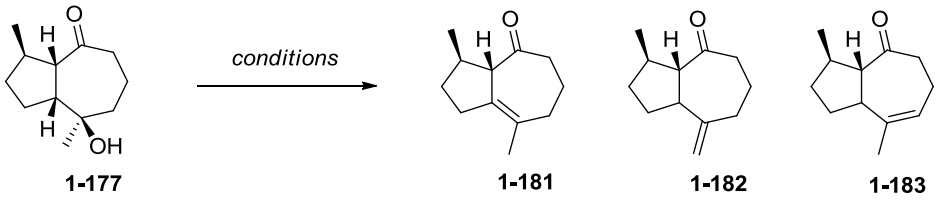


Figure 9. Fragment of the HMBC spectrum of **1-180**.

It turned out that for further functionalization of the seven-membered ring it was necessary to block the hydroxy group of **1-177**. Selective dehydration of hydroxyketone **1-177** to alkene **1-183**, in order to solve the problem with the hemiketal and to introduce a hydroxy group at C-9, was found to be challenging (**Scheme 33**).



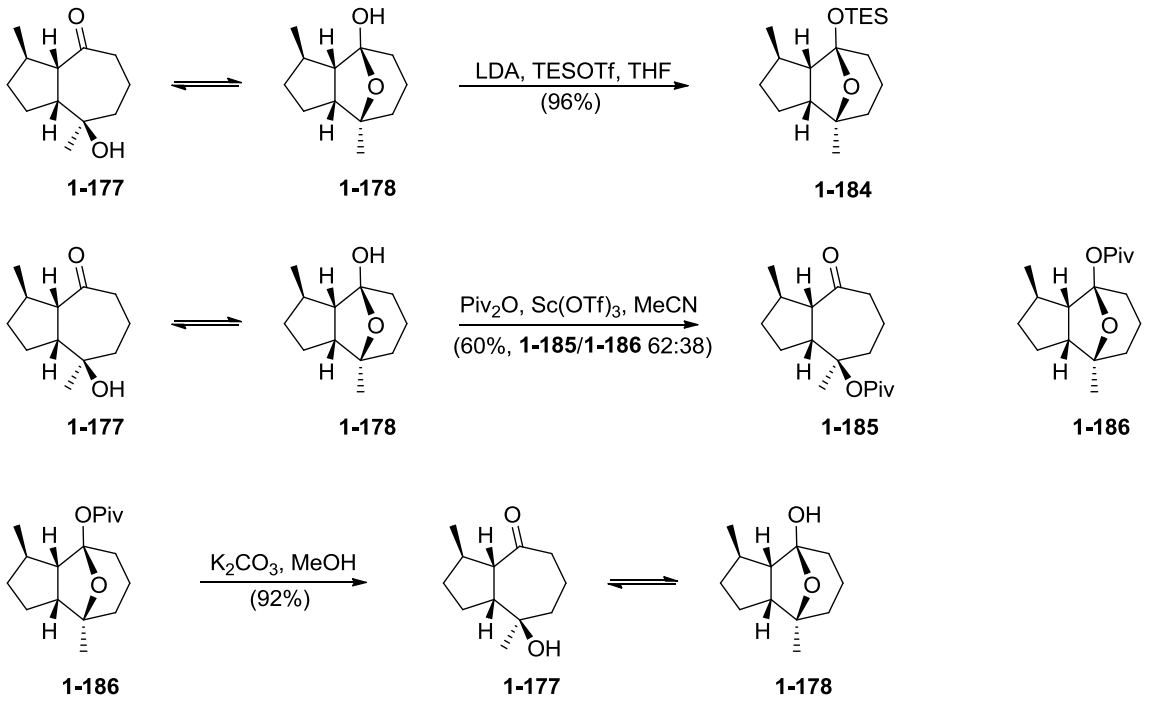
Scheme 33. Dehydration of **1-177** led to a mixture of alkenes.

Dehydration with Burgess reagent was found to be the most successful, however with low yield of the desired isomer **1-183**. Results are summarized in the **Table 5**. Transformation of the hydroxy group to a better leaving group (–OMs, –OTf etc.) under basic conditions was impossible, due to prevailing formation of the corresponding acetal.

Conditions	Ratio **1-181**/**1-182**/**1-183**	Yield of the 3 possible isomers
*p*TSA, benzene, reflux	complex mixture	0%
$KHSO_4$, toluene, reflux	no reaction	0%
Burgess, toluene, reflux	1.00 : 0.05 : 0.20	82%
DEAD, PhP_3, benzene, r.t.	no reaction	0%
$SOCl_2$, Py, CH_2Cl_2, r.t.	1.00 : 0.00 : 0.00	80%
$SOCl_2$, benzene, reflux	1.00 : 0.00 : 0.23	64%
a) Ac_2O, $Sc(OTf)_3$, MeCN, 0 °C; b) Et_3N, CH_2Cl_2, 0 °C	1.00 : 0.00 : 0.30	67%
b) THF, DBU, r.t.	no reaction	0%

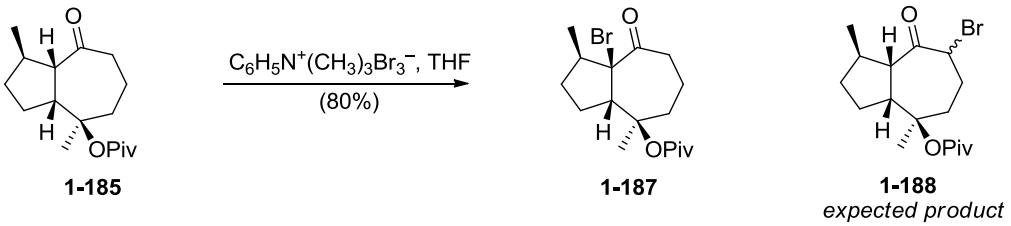
Table 5. Conditions for the dehydration reaction of **1-177**.

When the elimination of the hydroxy group did not work selectively, we concentrated our efforts on protection of the hydroxyl group in ketone **1-177**. We assumed that protection of the hydroxy function under basic conditions would shift the equilibrium towards hemiacetal **1-178**: for example, treatment of a mixture of **1-177** and **1-178** with TESOTf and LDA gave only **1-184** in nearly quantative yield (**Scheme 34**). Thus, esterification in presence of a catalytic amount of acid (or Lewis acid) would be optimal. Selective 4-OH protection as a pivalic ester[86] allowed us to separate ketone **1-185** in 60% yield from the oxygen bridged pivalic ester **1-186** by SiO_2 chromatography. Furthermore, hydroxy ketone **1-177** could be easily recycled via base mediated transesterification of **1-186** with methanol.



Scheme 34. Separation of hemiketal **1-178** and hydroxyketone **1-177** via acid catalyzed esterification.

With ketone **1-185** in hand, we tested various conditions in order to prepare enone **1-170**. The simpliest method for convertion of ketone **1-185** to the α,β-unsaturated enone relies on *o*-iodobenzoic acid (IBX) mediated oxidation,[87] which was not successful in our case in all possible modifications.[88] Our second attempt to introduce a double bond in α-position of ketone **1-185** utilized an α-bromination/base induced elimination sequnce. When ketone **1-185** was treated with phenyltrimethylammonium tribromide ($C_6H_5N^+(CH_3)_3Br_3^-$)[89] as a source of Br_2, a bromine atom was introduced at the most substituted position of the keto function to afford bromide **1-187** as a single regio- and stereoisomer (**Scheme 35**).



Scheme 35. Bromination of **1-185**.

Crystallization of **1-187** from a hexane/diethyl ether mixture provided crystals suitable for X-ray analysis, which additionally proved formation of the desired 5,7-fused ring system in the transannular epoxide opening step (**Figure 10**).

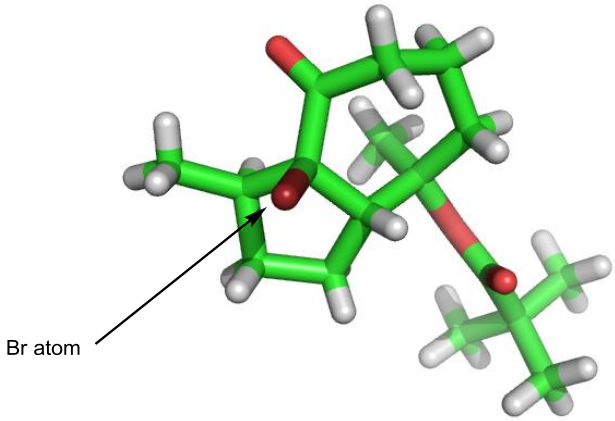
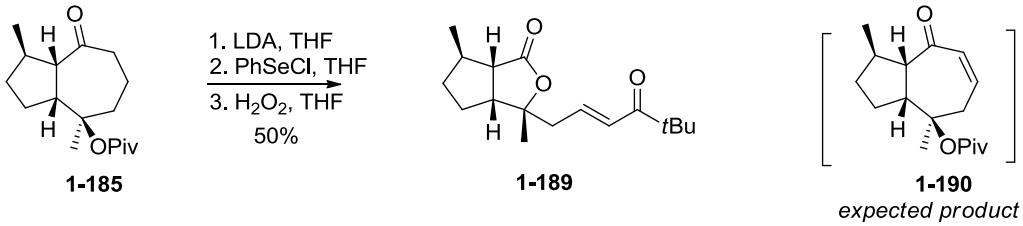


Figure 10. X-ray structure of **1-187**.

Next we tried generation of the kinetic enolate from **1-185**, followed by formation of phenylselenyl ether and subsequent elimination of phenylselenoxide (**Scheme 36**). Enolate generation at –78 °C was not successful, therefore we encreased the temperature to –5 °C. However, after work up we isolated unexpected product **1-189**, whose structure was assigned via X-ray analysis (**Figure 11**).



1-185 **1-189** **1-190**
expected product

Scheme 36. The unexpected formation of lactone **1-189**.

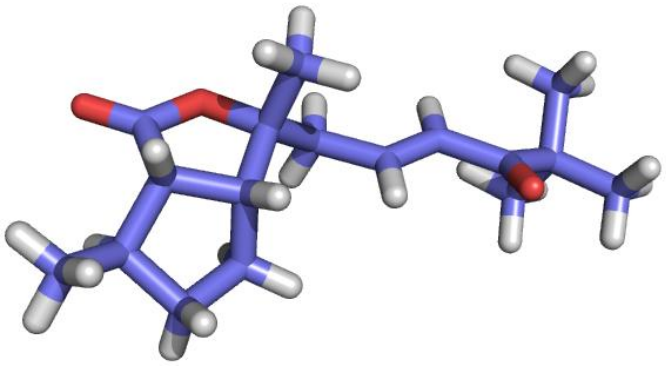
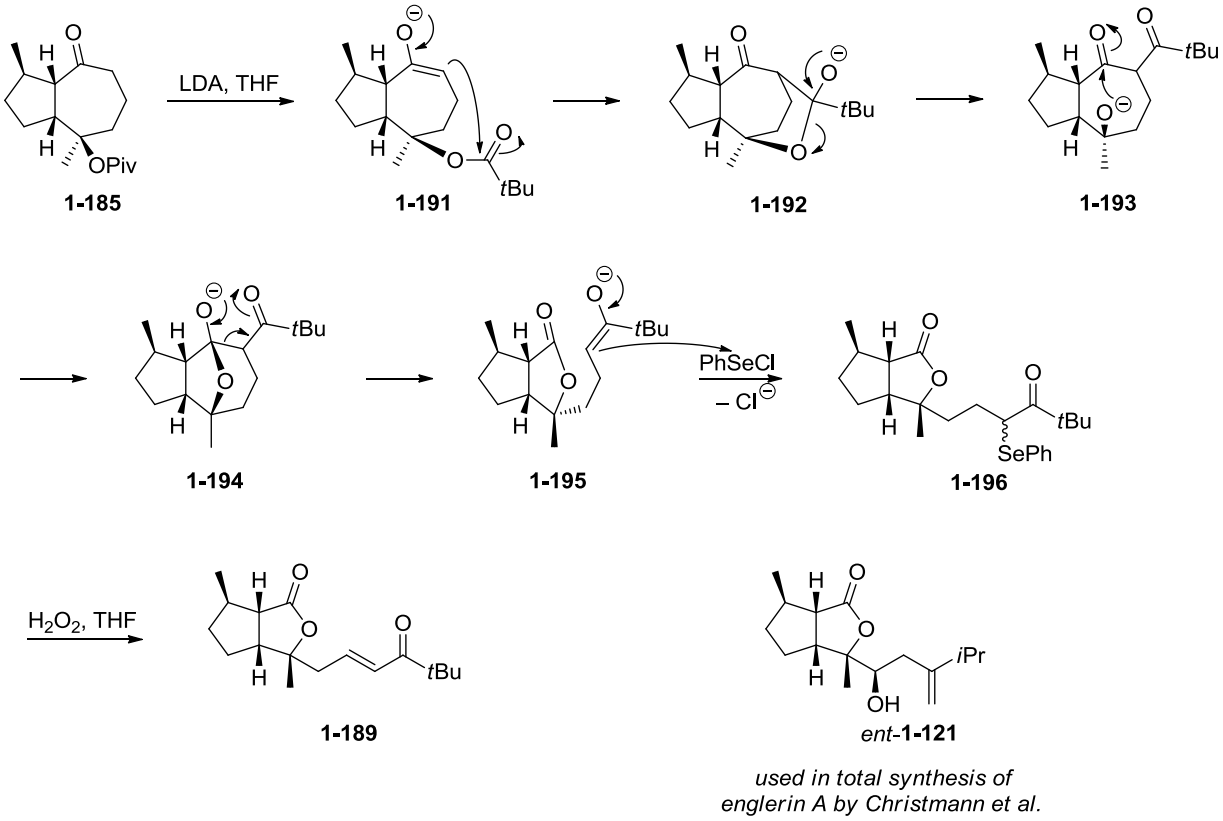


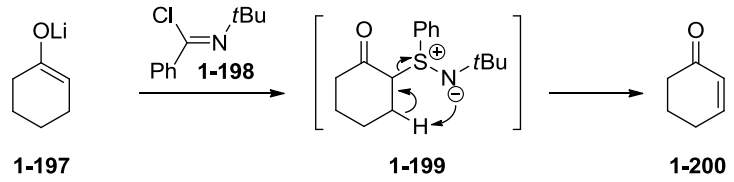
Figure 11. X-ray structure of **1-189**.

The following mechanism for **1-189** formation was proposed: upon treating ketone **1-185** with LDA at −20 °C and then warming the reaction mixture to −5 °C, a pivaloyl migration (Claisen condensation) occurred, followed by a *retro*-Claisen condensation (**Scheme 37**). The enolate **1-195** was quenched with PhSeCl to give a diastereomeric mixture of selenides **1-196**, which after oxidative elemination with hydrogen peroxide resulted in enone **1-189**. One can see the similarity between **1-189** and *ent*-**1-121**, which was used in Christmann's synthesis of englerin A.[14] We did not study this convertion, but application of this strategy in prepartion of related lactones seems to be promising.



Scheme 37. Proposed mechanism for the formation of **1-189**.

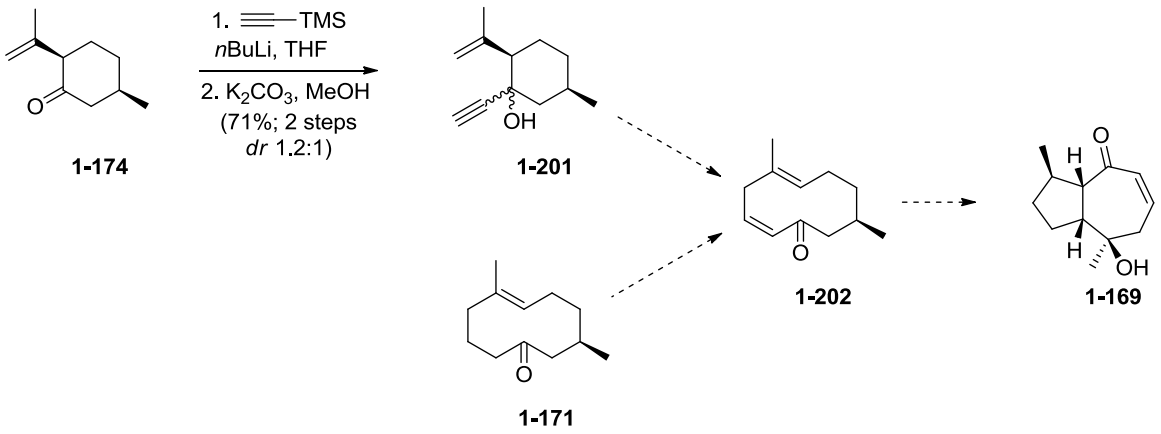
Another method for the synthesis of α,β-unsaturated ketones relies on treatment of an enolate with *N*-*tert*-butyl phenylsulfinimidoyl chloride (**1-198**) (**Scheme 38**).[90] In our case, this method was found to be unfruitful as well.



Scheme 38. One-pot dehydrogenation by *N*-*tert*-butyl phenylsulfinimidoyl chloride (**1-198**).

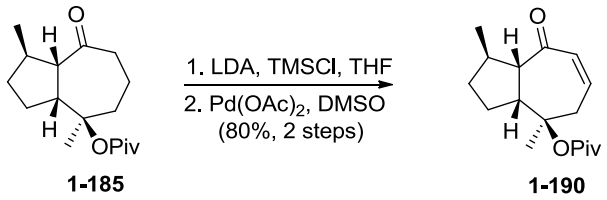
Being disappointed with the introduction of an α,β-unsaturated double bound on **1-185**, we checked the possibility of oxy-Cope rearrangement on alkyne **1-201**, which was prepared via treatment of isopulegone (**1-174**) with protected lithium acetylenide (**Scheme 39**). Interestingly, nucleophile addition to (–)-isopulegone (**1-174**) proceeded with poor stereoselectivity (1.2:1), that is in contrast to Grignard addition described above (**Scheme 30**). This could be possibly explained by the higher reactivity of lithium acetylide. The oxy-Cope

rearrangement was studied with both diastereomers of **1-201**, however no single experiment allowed us to make a ring extension. Introduction of α,β-unsaturated double bound on the earlier prepared cyclodecenone **1-171** by Se- or IBX-mediated procedures was not fruitful.



Scheme 39. Reversed strategies towards **1-168** via introduction of an α,β-unsaturated double bond on the earlier steps.

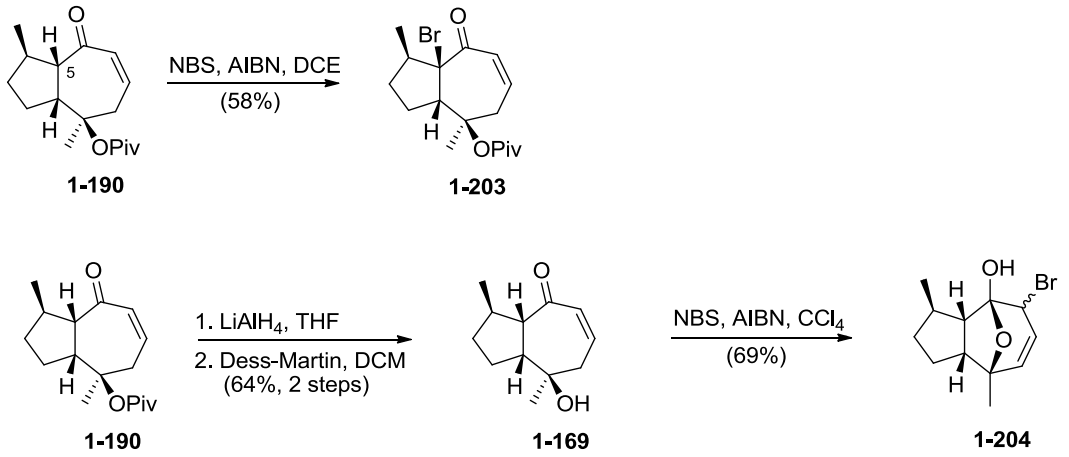
Finally, after careful experimentation we found that treatment of the kinetic enolate, generated from **1-185** under low temperatures (−40 °C), with TMSCl resulted in the corresponding silyl ether (**Scheme 40**). Subsequent Pd(II)-mediated Saegusa-Ito[91] oxidation gave desired enone **1-190**. We established that the temperature control was crucial in this reaction: at –78 °C no enolate could be generated from **1-185**, while at –5 °C Claisen rearrangement led to the lactone **1-189**.



Scheme 40. Preparation of α,β-unsaturated ketone **1-190** via Saegusa-Ito oxidation.

Now, allylic C-H activation was called for introduction of the hydroxyl group at C-9. Selenium(IV) dioxide is known as the most popular reagent for an allylic oxidation. To reduce the amount of metal, catalytical processes are known, involving co-oxidation by TBHP or H_2O_2.[92] Dirhodium(II) caprolactamate is also supposed to catalyze allylic oxidation with TBHP as a terminal oxidant.[93] Another way for generation of a *tert*-butylperoxy radical is by treatment of $PhI(OAc)_2$ with TBHP.[94] Kharasch-Sosnovsky reaction could be also used for an

allylic oxidation, where *tert*-butyl peroxybenzoate is used as an oxidizing agent in presence of copper(I) salt.[95] We tried all these methods, however we could not obtain even trace amounts of the desired allylic alcohol/diketone. Another well established approach for introduction of a hydroxyl group in allylic position utilizes a three step sequence, namely, Ziegler-Wohl bromination,[96] nucleophilic substitution of bromide with acetate,[97] followed by its saponification. It was found that bromine atom atacked C-5, the most substituted position, as it was observed on the ketone **1-185** (**Scheme 41**). In order to temporary deactivate the ketone as an intramolecular acetal we chose reductive removal of pivaloate with $LiAlH_4$, followed by reoxidation of the secondary alcohol with Dess-Martin reagent.[58] Interestingly, **1-169** does not exist in acetal form, which is in contrast to hydroxyketone **1-177**. Enone **1-169** was subjected to Ziegler-Wohl bromination, and the isolated product was assigned to structure **1-204**, where bromine added to a rearranged allyl radical.

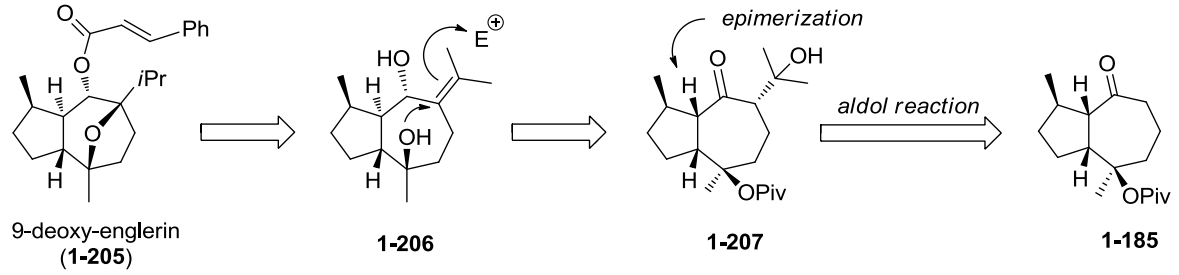


Scheme 41. Attempts to make Wohl-Ziegler bromination.

Thereby we were not able to perform a C-H activation at C-9 and we could not continue the synthesis of englerin A (**1-7**) with this strategy.

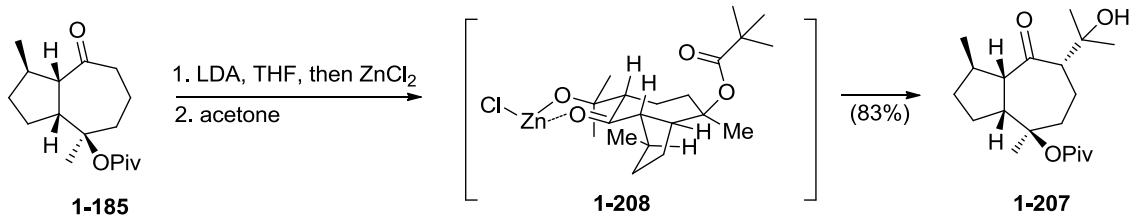
2.5 Total Synthesis of 9-Deoxy-englerin

To that moment several total syntheses of (–)-englerin A (**1-7**) were published, including SAR investigations, indicating the importance of the glycolate at C-9 (see literature review). In order to complete the core structure of englerins and to prove the significance of the glycolate domain, we decided to change the title compound to 9-deoxy-englerin (**1-205**), where the problematic functionalization at C-9 is not required. The revised retrosynthetic plan features a transannular ether formation as it was planned earlier for the natural englerin A (**1-7**) (**Scheme 42**). The tetrasubstituted double bond in **1-206** could be possibly introduced via aldol reaction between previously prepared ketone **1-185** and acetone. Base-induced epimerization should provide the desired *trans*-stereochemistry of the 5,7-fused ring system.



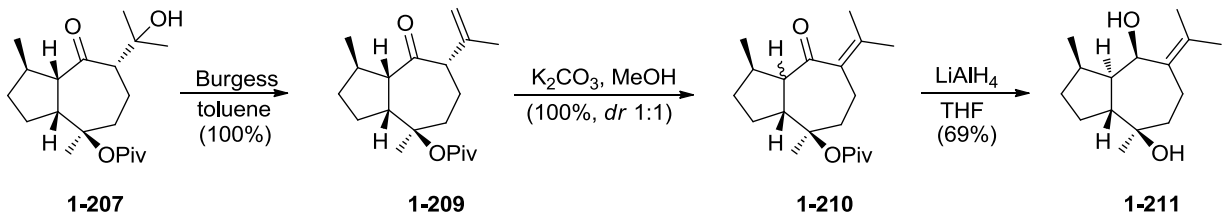
Scheme 42. Retrosynthetic plan for 9-deoxy-englerin (**1-205**).

The synthesis continued with aldol reaction between the kinetic zinc-enolate, generated from **1-185**, and acetone that yielded hydroxyketone **1-207** as a single diastereomer (**Scheme 43**). Chelation on the zinc provided control of the stereochemistry in this reaction.[98] This way, α-alkylation turned out to be more efficient, than quencing of the enolate with ethyl chloroformate that resulted in the corresponding β-keto ester (52% yield).



Scheme 43. Alkylation of the kinetic enolate, generated from **1-185**.

Subsequent dehydration of tertiary alcohol **1-207** under acidic conditions (*p*TSA, benzene, reflux) failed, whereas usage of thionyl chloride (benzene, reflux) resulted in **1-209** with nonconjugated double bond, however with moderate yield (52%). Dehydration with Burgess reagent[67] was found to be the most efficient method and the desired alkene **1-209** was prepared in quantitative yield (**Scheme 44**). By use of K_2CO_3 in methanol under reflux, migration of the double bond was observed with further epimerization at C-5 (*trans*/*cis* = 1:1).[99] The two stereoisomers were separated by flash chromatography, and the wrong isomer was reintroduced in the epimerization reaction. Interestingly, the pivalic ester remained untouched under the isomerization conditions. This is in contrast to pivalic ketal ester **1-186**, which underwent smooth transesterification under the same conditions. Saponification of the pivaloyl group with LiOH (water/MeOH, r.t.) or *t*BuOK (water/diethyl ether, r.t.) as well as acid mediated hydrolysis (3N HCl in water/dioxane, reflux) did not yield the desired free alcohol. Only reduction with $LiAlH_4$ led to the cleavage of pivalic ester **1-210**, but resulted in reduction of the keto group as well, providing diol **1-211** as a single diastereoisomer.

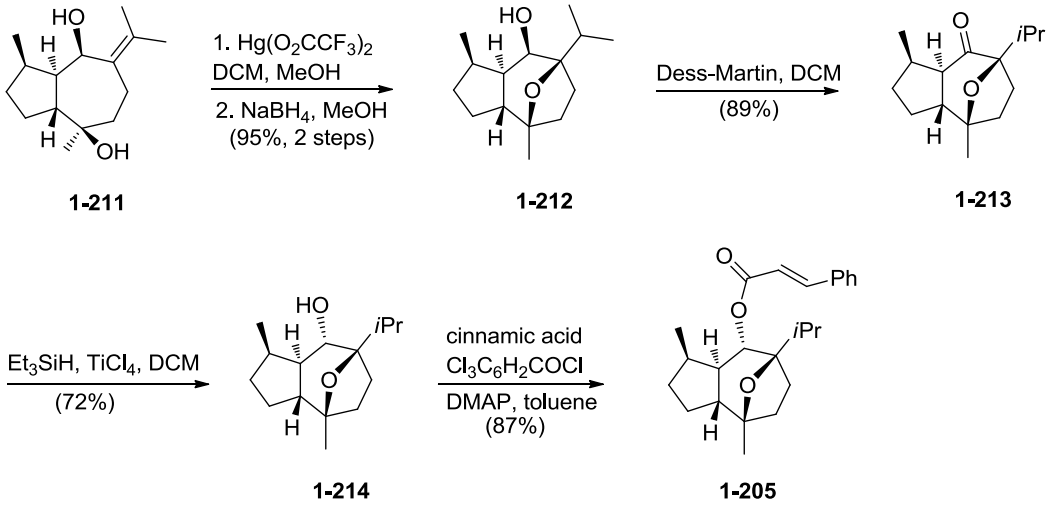


1-207 **1-209** **1-210** **1-211**

Scheme 44. Preparation of allylic alcohol **1-211**.

With dihydroxy alkene **1-211** in hand, we tested various conditions in order to promote the transannular cyclization. Acid-induced cyclization ($CHCl_3$, $SiO_2/CHCl_3$, TFA/CH_2Cl_2)[100] failed, as well as electrophile-mediated cyclization (PhSeCl, $SnCl_4$, CH_2Cl_2, followed by Bu_3SnH, AIBN, toluene).[101] After careful experimentation we found that reaction of alkene diol **1-211** with mercury(II) trifluoroacetate and reduction of the resulting organomercurial intermediate with $NaBH_4$ provided oxygen-bridged compound **1-212** in perfect yield (**Scheme 45**), whose structure was confirmed by X-ray analysis (**Figure 12**). As it was expected from the NOESY experiments on **1-212**, the hydroxyl group at C-6 had a wrong orientation with respect to the one required for C-6 of 9-deoxy-englerin (**1-205**). The *trans* orientation of the hydroxyl group at C-6 and 5-H results in a small coupling constant and the signal from 6-H in the ^{1}H-NMR spectrum looks like a broad singlet. Unfortunately, esterification of **1-212** under Mitsunobu conditions[102] (Ph_3P, DEAD, THF, –10 °C to r.t.) with cinnamic acid was

unsuccessful, as well as with other acids (AcOH, 4-nitrobenzoic acid). Therefore, inversion by an oxidation/reduction sequence was tried. Oxidation of alcohol **1-212** with Dess-Martin periodinane[58] provided ketone **1-213**, whose stereoselective reduction was found to be challenging. While various hydride reagents ($LiAlH_4$, $NaBH_4$, L-selectride, DIBAL-H), as well as reduction with SmI_2[45] provided again alcohol **1-212** as a single diastereomer, we discovered that ionic reduction with Et_3SiH and $TiCl_4$ proceeded with exclusive formation of the desired alcohol **1-214**.[103] Here coupling constant between 5-H and 6-H is big and the signal from 6-H in the ^1H NMR appears as a dublet (J = 10.4 Hz). Esterification of **1-214** with cinnamic acid under Yamaguchi conditions[17] provided (–)-9-deoxy-englerin (**1-205**).



Scheme 45. Completion of the synthesis of (–)-9-deoxy-englerin (**1-205**).

Albeit the stereochemistry of the hydroxyl group at C-6 in **1-212** was clear from the NMR spectra, we confirmed this additionally with an X-ray analysis.

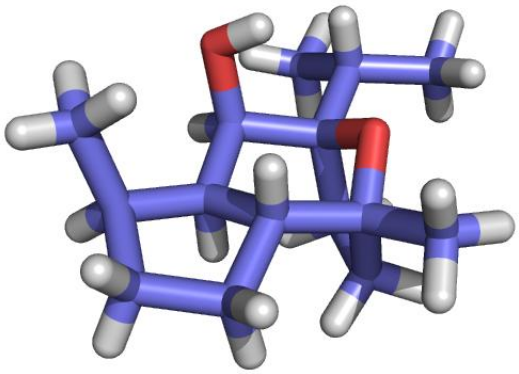


Figure 12. X-ray structure of **1-212**.

(–)-Englerin A (**1-7**),[104] (–)-9-deoxy-englerin (**1-205**) and ketone **1-213** were tested on different cell lines, using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[68] The results are summarized in **Table 6**.

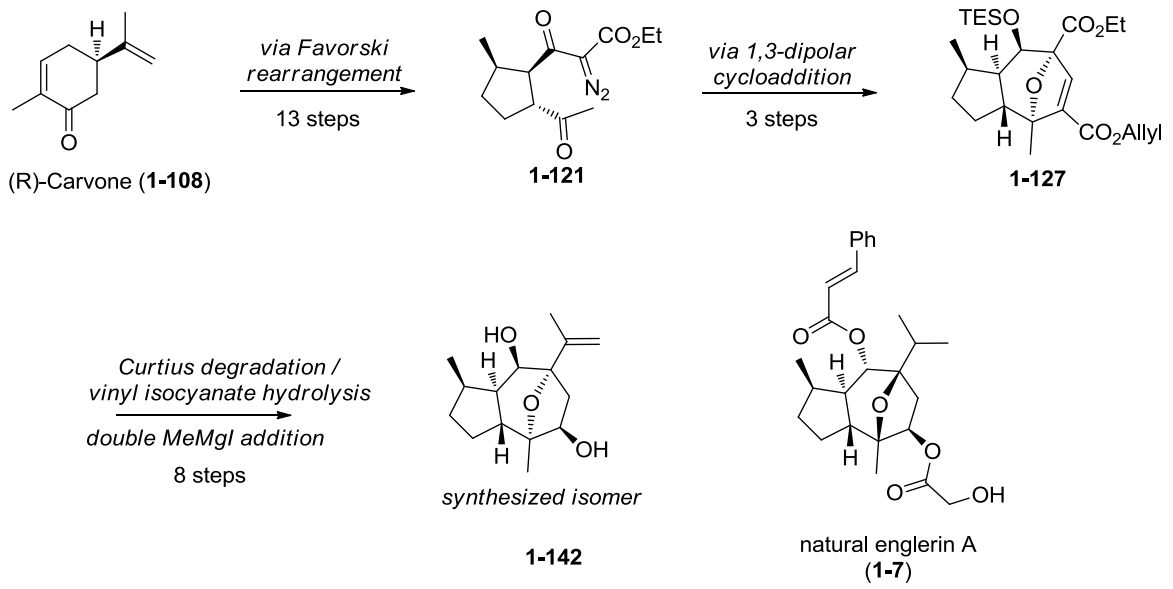
Compd	L929	A498	KB-3-1	MCF-7	HUVEC
1-7	29	0.4	12	18	4.3
1-213	> 170	> 170	> 170	> 170	> 170
1-205	65	35	41	41	9.8

Table 6. Cytotoxicity (IC_{50} in μM) of (–)-englerin A (**1-7**) and its analogues (**1-205**, **1-213**) against selected cell lines.

As expected, englerin A (**1-7**) was quite active with the renal cancer cell line (A498), while ketone **1-213** was essentially inactive. In general **1-7** was more active than **1-205** with the other cell lines as well, pointing to the importance of the glycolate at C-9. However, the difference in activity between **1-7** and **1-205** is much less pronounced with the other cell types. The inhibition curve of **1-7** with the A498 cells is actually rather shallow and the curves of **1-7** and **1-205** meet at 37 μg mL^{-1} (100% growth inhibition). Neither with **1-7** nor **1-205** a distinct phenotype could be seen which would provide hints regarding the mode of action.

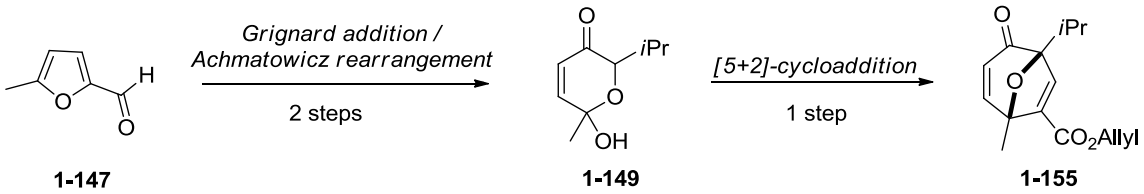
3 Conclusion

In summary, we developed four conceptually different approaches to the guainolide core structure of the englerins. The first generation approach to (–)-englerin A (**1-7**) features generation of a cyclic carbonyl ylide from diazoketone precursor **1-121** by a $Rh_2(OAc)_4$-catalyzed reaction which was trapped with allyl propiolate (**Scheme 46**). The 1,3-dipolar cycloaddition led to the stereoselective formation of an oxygen-bridged polycycle **1-127**. Via Curtius degradation, the cycloadduct **1-127** was transformed to the ring skeleton typical of the sesquiterpene family of guaianolides. X-ray of **1-142** showed the opposite stereochemistry of the ether bridge compared to natural (–)-englerin A (**1-7**). The guianolide structure common for many other terpenes was prepared in 3.9% overall yield in the longest linear sequence of 24 steps.



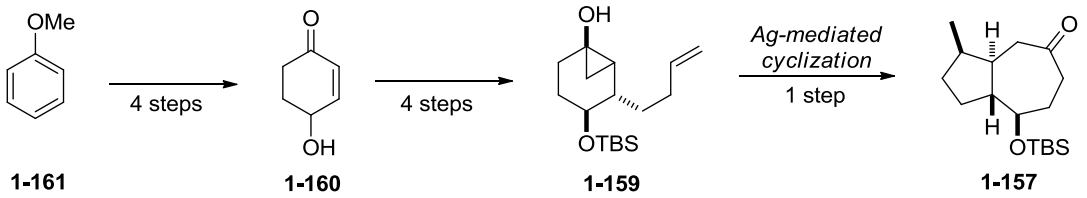
Scheme 46. Application of [3+2]-cycloaddition strategy for the synthesis of englerins core.

Our second approach to the guaianolide core features an oxidopyrylium/alkyne [5+2] cycloaddition reaction as a key step (**Scheme 47**). The desired hydroxypyranone **1-149** was prepared from furan **1-147** via *m*CPBA/*p*TSA-mediated Achmatowicz rearrangement. Racemic oxygen-bridged cycloheptenone **1-155** was prepared in 6.5% over 3 steps starting from commercially available furanal **1-147**. The poor yield in the cycloaddition step together with the similar approach, reported by Nicolaou *et al.* forced us to change the retrosynthetic plan.



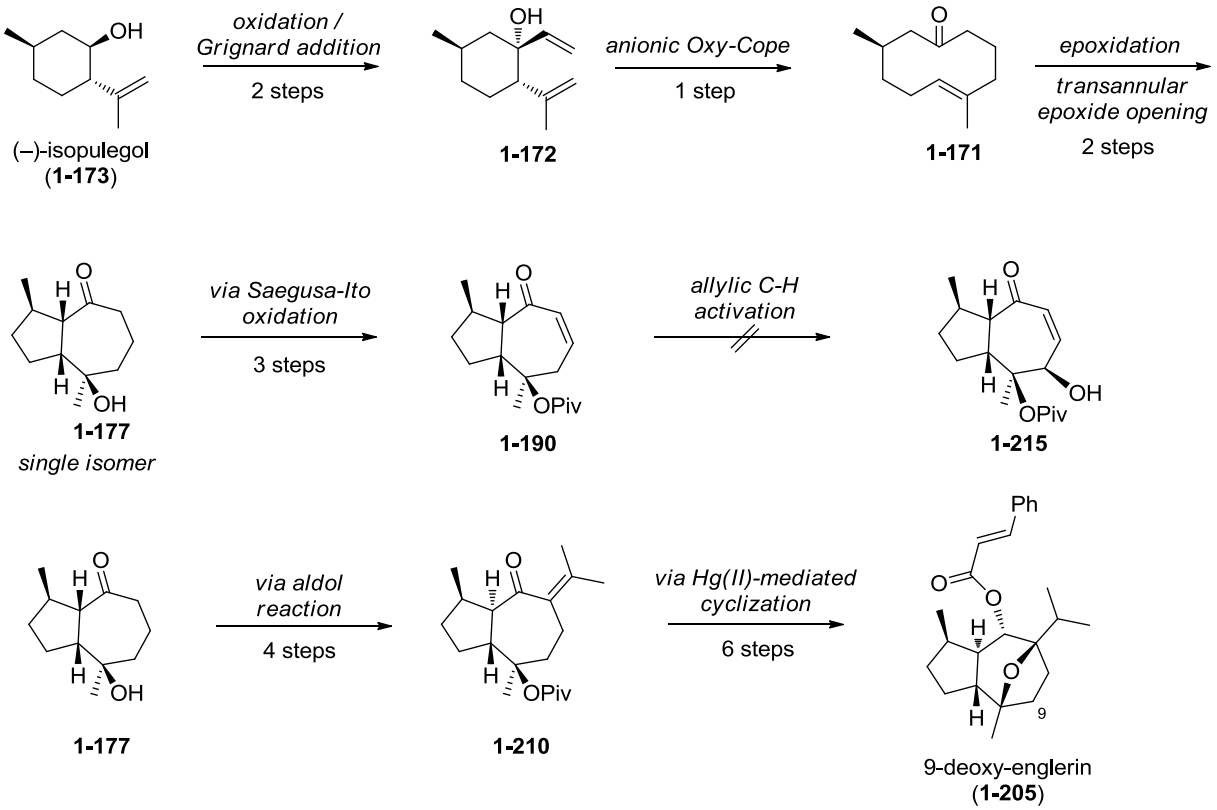
Scheme 47. Application of [5+2]-cycloaddition strategy for the synthesis of oxygen-bridged cycloheptenone **1-155**.

Next we tried to apply an Ag-catalyzed oxidative radical cyclization of cyclopropanol derivative **1-159** for the construction of the bicyclo[5.3.0]decan-3-one skeleton (**Scheme 48**). Unfortunately, further regioselective functionalization of the seven-membered ring in **1-157** was impossible. This way ketone **1-157** was prepared in 16.8% yield over 9 steps.



Scheme 48. Synthesis of *trans*-5,7-fused ring system via Ag-mediated oxidative radical cyclization.

Finally, a highly efficient synthesis of the 5,7-fused ring system **1-177** was achieved via an anionic oxy-Cope rearrangement/transannular epoxide opening sequence starting from (–)-isopulegol (**1-173**) (**Scheme 49**). Unfortunately, neither different allylic oxidations nor a Wohl-Ziegler bromination/substitution sequence did allow us to introduce an oxygen-containing functionality to the allylic position in enone **1-190**. To that moment several total syntheses of natural englerin A (**1-7**) were published including SAR, suggesting the important role of the glycolate at C-9. Therefore we decided to prepare 9-deoxy-englerin (**1-205**) to confirm the role of the glycolic acid at C-9. An effective synthesis of (–)-9-deoxy-englerin (**1-205**) has been achieved from **1-177**. Aldol reaction of **1-177** with acetone and subsequent dehydration followed by base-catalyzed migration of the double bond caused epimerization at C-5. Ether formation was achieved with mercury(II) trifluoroacetate from the corresponding hydroxyalkene followed by reduction with $NaBH_4$ of the resulting organomercurial intermediate. This way 9-deoxy-englerin (**1-205**) was prepared in 13.4% overall yield with a longest linear sequence of 15 steps, utilizing one protecting group.



Scheme 49. Synthesis of 9-deoxyenglerin (**1-205**) via an anionic oxy-Cope rearrangement/transannular epoxide opening sequence.

Studies on the cytotoxic activity of different englerin analogues proved the importance of the hydroxyl group and glycolic acid at C-9, as well as the orientation of the oxygen bridge.

Chapter II
Studies Towards the Total Synthesis of Crotogoudin

1 Literature Review

1.1 Introduction

The screening of plant extracts from Madagascan plants *Croton barorum* and *C. goudotii* with a cytotoxicity assay led to the discovery of two closely related 3,4-*seco*-atisane diterpenes: crotogoudin (**2-1**) and crotobarin (**2-2**) (**Figure 13**).[105] While the enone moiety presented in these two novel diterpenoids might prohibit their development as drugs, this functional group might help to elucidate the target in the cell by affinity-based methods.[106] Initial cell cycle analysis led to the conclusion, that these two compounds arrest the cells at the G2/M stage. We focused our research on the simpler of the two compounds, namely crotogoudin (**2-1**). This novel diterpene contains a polycyclic ring system with four contiguous stereocenters, where a six-membered ring is fused to a bicyclo[2.2.2]octane subunit.

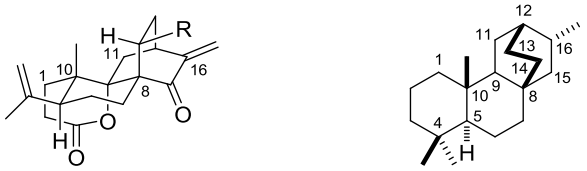
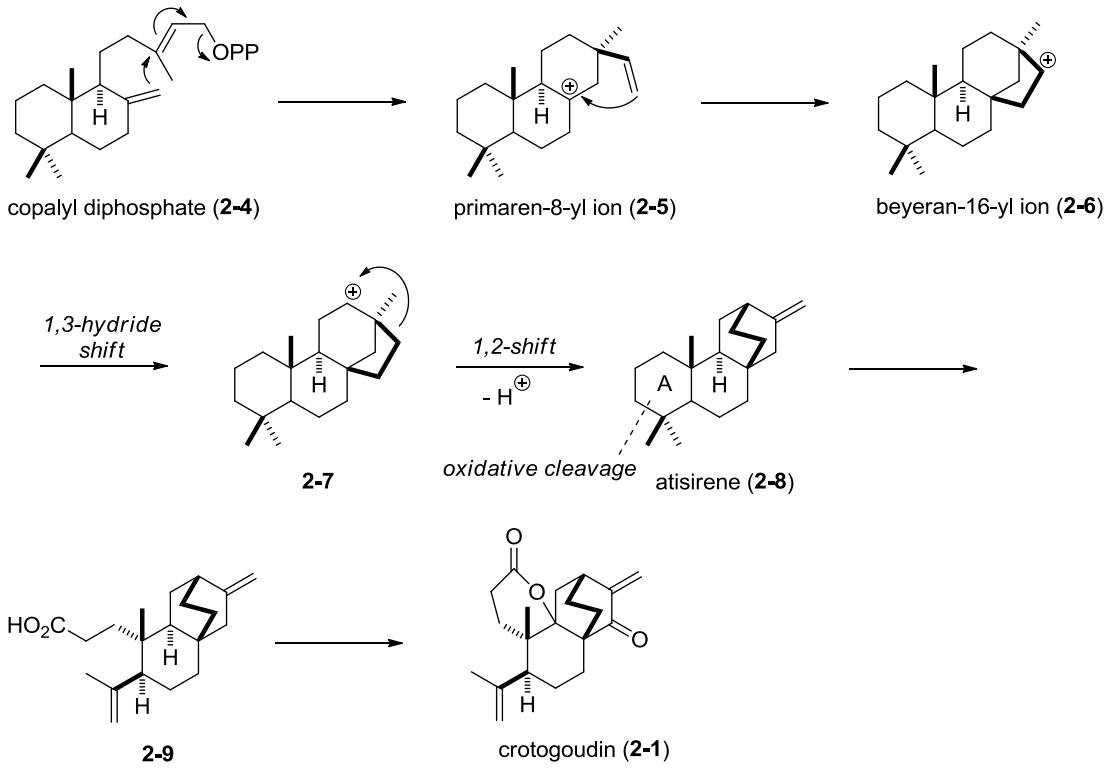


Figure **13**. The structures of crotogoudin (**2-1**), crotobarin (**2-2**) and atisane (**2-3**).

This new natural product belongs to a diterpene (C_{20}) family whose biosynthesis starts from copalyl diphosphate (**2-4**) leading to cation **2-6** (**Scheme 50**).[107] The sequence of 1,3-hydride shift and 1,2-shift gives atiserene (**2-8**) after elimination of a proton. The last steps require oxidative cleavage of the A ring and further oxidations to form the lactone and enone moieties.



Scheme 50. The proposed biosynthesis of crotogoudin (**2-1**).

A large number of 3,4-seco terpenoids have been reported in the literature[108] (**Figure 14**) and almost all of them are postulated to have been formed from 3-keto-4,4-dimethyl terpenoids by Baeyer-Villiger type oxidation to furnish the lactones which ultimately yielded the 3,4-*seco* compounds under some biogenetic conditions.[109]

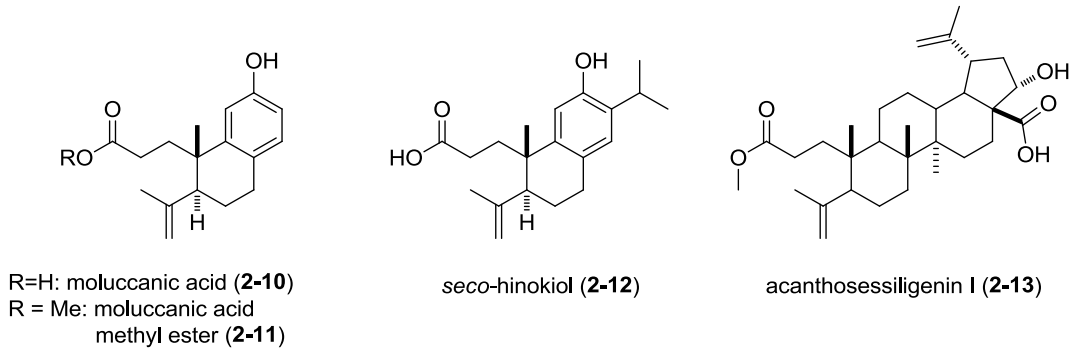
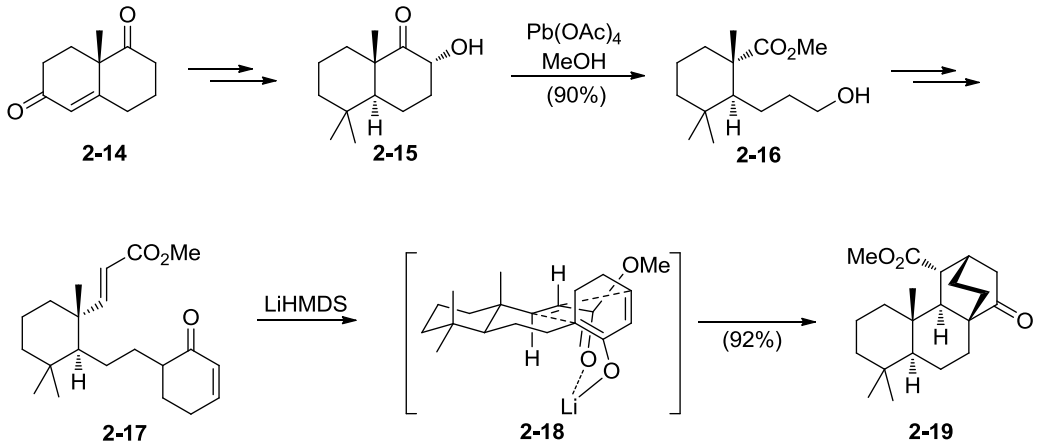


Figure 14. Some examples of 3,4-*seco* natural products.

To this moment neither a total synthesis of crotogoudin (**2-1**) nor its absolute stereochemistry have been published yet.

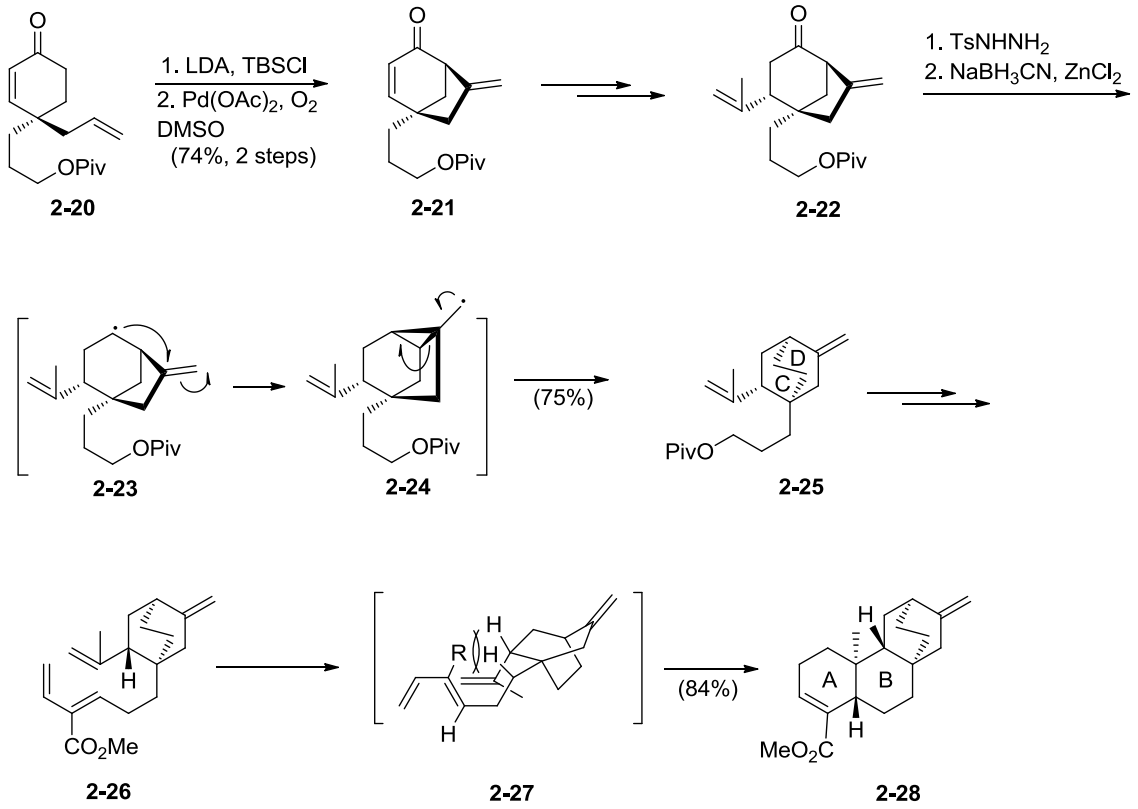
1.2 Literature Overview on the Approaches to the Bicyclo[2.2.2]octane Ring System

Three approaches towards atisane-type diterpenes are described in the literature. According to the first one, an intramolecular domino Michael reaction is applied for the late stage synthesis of bicyclo[2.2.2]octane ring system by Fukumoto *et al.*[110] For example, in the synthesis of atisirene[111] the key intermediate **2-17** was prepared from optically active Wieland-Miescher ketone (**2-14**), utilizing oxidative cleavage of α-hydroxy ketone **2-15** with lead tetra-acetate in methanol (**Scheme 51**). Enone **2-17** was subjected to a double Michael reaction resulting in tetracyclic compound **2-19**, as a single stereoisomer. The remarkable stereoselectivity could be explained by lithium-chelation in intermediate **2-18**.



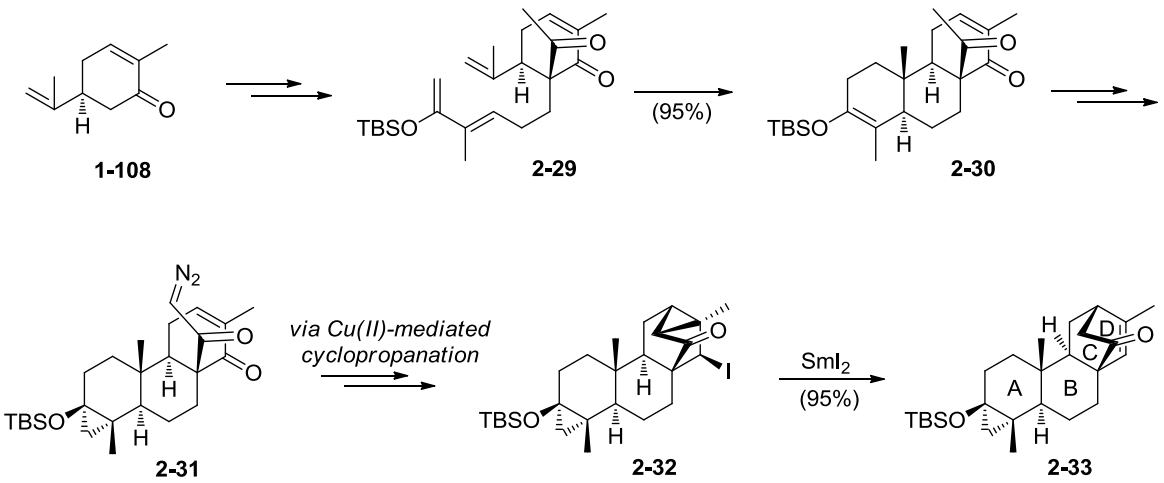
Scheme 51. Synthesis of atisane skeleton via intramolecular domino Michael reaction according to Fukumoto *et al.*

Another synthetic approach to atisane-type diterpenes relies on the homoallyl-homoallyl radical rearrangement to convert a bicyclo[3.2.1]octane to a bicyclo[2.2.2]octane motif in the CD rings, followed by intramolecular Diels-Alder reaction for the construction of the AB ring system.[112] According to the most recent application of this strategy reported by the Toyota/Ihara group,[113] serofendic acids A and B were synthesized utilizing the following sequence (**Scheme 52**). A palladium-catalyzed cycloalkenylation of TBS enol ether, generated from enone **2-20** and subsequent tin-free radical skeleton rearrangement resulted in the thermodynamically more stable bicyclo[2.2.2]octane **2-25**. Stereoselective intramolecular Diels-Alder reaction provided tetracyclic compound **2-28**.



Scheme 52. Application of a homoallyl-homoallyl radical rearrangement for the construction of bicyclo[2.2.2]octane motif by Ihara/Toyota *et al.*

An intramolecular Diels-Alder reaction was also used for the construction of rings A and B in the approach reported by Abad *et al.*[114] The formation of the bicyclo[2.2.2]octane ring system called for an intramolecular diazoketone cyclopropanation, followed by an endocyclic cyclopropane ring cleavage. By this unified method several atisane-related natural products were synthesized: for example, the synthesis of antiquorin,[115] commenced with transformation of (*S*)-(+)-carvone (**1-108**) to a advanced intermediate **2-29**, which underwent thermo-induced IMDA reaction (**Scheme 53**). The resulting tricyclic compound **2-30**, was converted to diazoketone **2-31**, which was used in an intramolecular copper(II)-catalyzed cyclopropanation reaction. SmI_2-mediated cyclopropane opening resulted in formation of the desired bicyclo[2.2.2]octane constitution of rings C and D. While in principle it seems possible to adopt the above strategies towards crotogoudin, the problem is the lack of functionality at C-9 (double bond, alcohol etc.) required for lactonization.



Scheme 53. The construction of atisane ring system according to Abad *et al*.

Platencin (**2-34**), a novel antibiotic isolated a few years ago[116] is structurally related to crotogoudin (**2-1**) (**Figure 15**). This molecule was a "hot topic" in synthetic organic chemistry and to this moment many strategies towards platencin or its core structure were presented in the literature.[117] Due to their structural similarity, synthetic approaches towards the platencin's core have to be also considered.

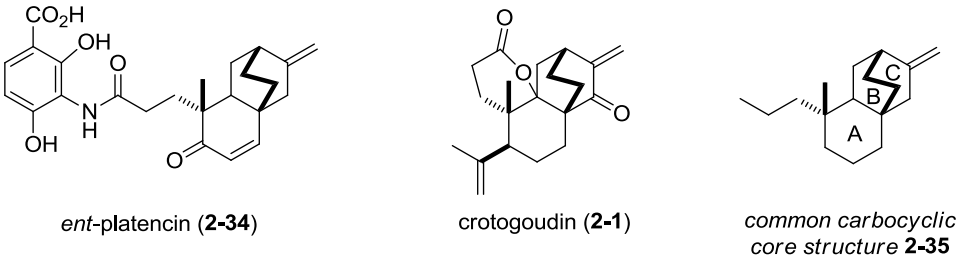
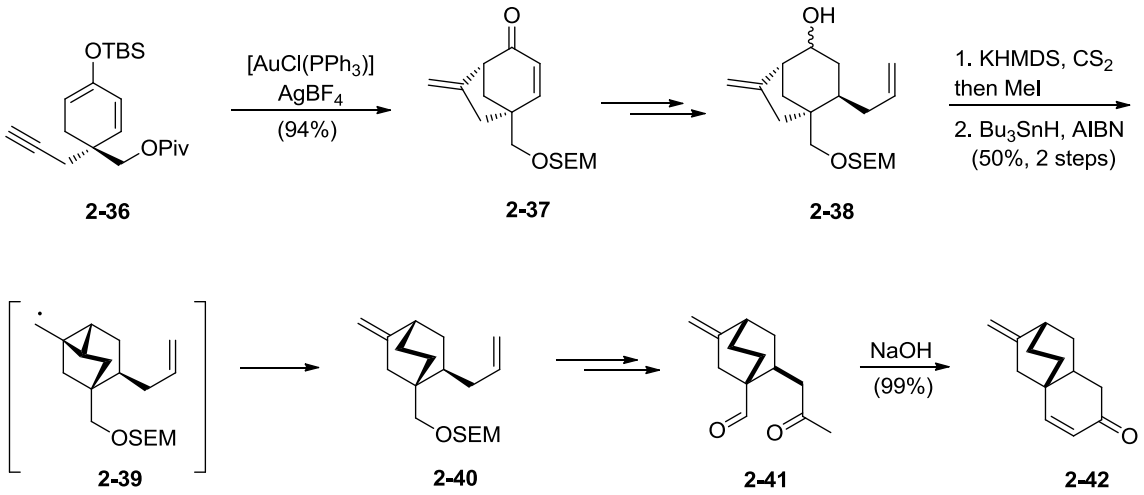


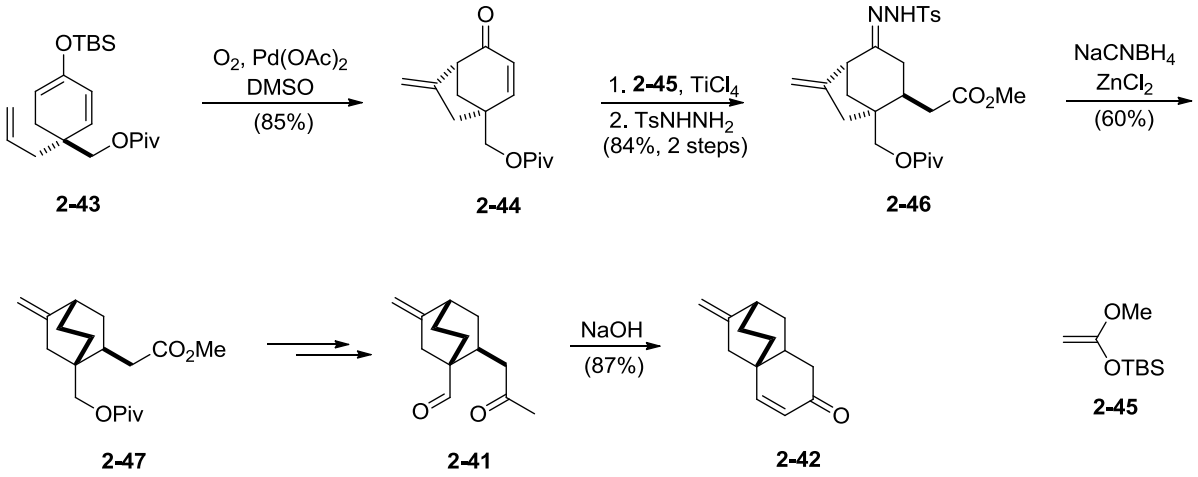
Figure 15. The comparison of the structures of crotogoudin (**2-1**) and *ent*-platencin (**2-34**).

Nicolaou *et al.*[118] used a gold-catalyzed cyclization of enol ether **2-36** to generate bicyclo[3.2.1]octane **2-37** (**Scheme 54**). Subsequent homoallyl radical rearrangement resulted in bicyclo[2.2.2]octane **2-40** via the corresponding xanthogenate. The closure of the A ring relied on a base-mediated intramolecular aldol condensation.



Scheme 54. The synthesis of platencin's core structure **2-42** according to Nicolaou *et al.*

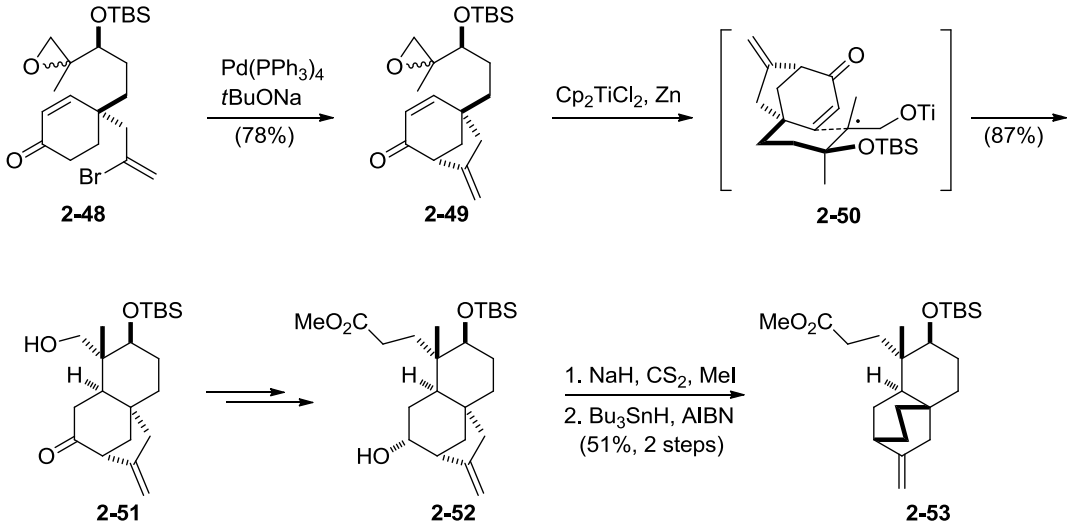
In the synthesis of platencin's core structure (**2-42**) reported by Maier *et al.*[119] a palladium(II)-catalyzed cycloalkenylation of the silyl enol ether **2-43** and radical-mediated reductive rearrangement of the tosylhydrazone **2-46** were used for the construction of the bicyclo[2.2.2]octane motif (**Scheme 55**). For the closure of the A ring an intramolecular aldol condensation was applied, previously utilized by Nicolaou *et al.*[118]



Scheme 55. The construction of the tricyclic core structure **2-42** according to Maier *et al.*

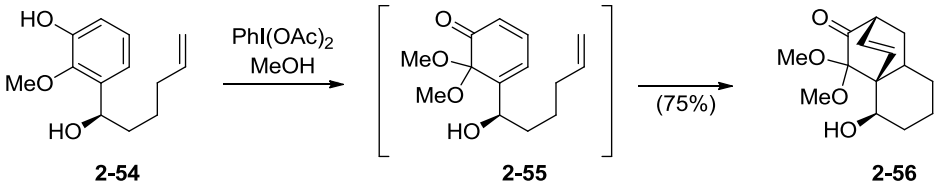
The total synthesis of (±)-platencin (**2-34**), reported by Yoshimitsu *et al.*[120] features a stereoselective titanium(IV)-mediated radical cyclization of epoxide **2-49**, prepared via Pd-catalyzed cyclization of enone **2-48** (**Scheme 56**). The diastereomeric mixture of epoxides **2-49** (*dr* 2:3) yielded **2-51** as a single isomer in 87% yield. Probably rapid epimerization of the radical center in **2-50** takes place, so that the bulky OTBS group is situated at the equatorial

position. Tricyclic compound **2-52** underwent homoallyl radical rearrangement via the corresponding xanthogenate resulting in the desired bicyclo[2.2.2]octane structure **2-53**. This is an example for a late stage formation of the bicyclic subunit.



Scheme 56. The construction of tricyclic core structure **2-53** via titanium(IV)-mediated radical cyclization and homoallyl radical rearrangement.

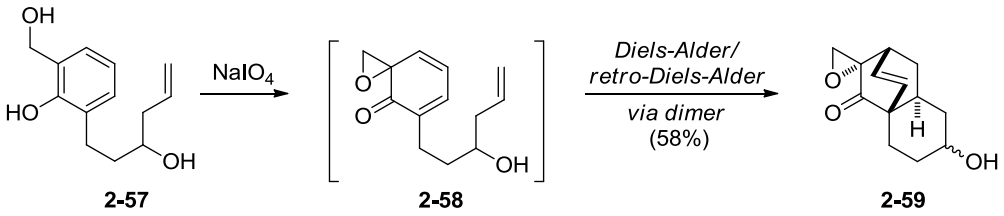
These three methods start with the formation of a bicyclo[3.2.1] ketone motif, which undergoes skeleton rearrangement to afford the required bicyclo[2.2.2]octane ring system. The next strategy involves an intramolecular Diels-Alder reaction for the formation of the bicyclo[2.2.2]octane framework. In the work published by Chen *et al.*[121] phenol **2-54** was converted to *o*-benzoquinone derivative **2-55**,[122] which *in situ* underwent the key Diels-Alder reaction (**Scheme 57**).



Scheme 57. Diels-Alder reaction approach according to Chen *et al.*

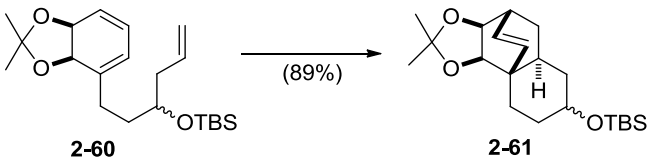
In situ formation of a cyclic diene by oxidative dearomatization of a phenol, followed by IMDA reaction was also reported by Singh *et al.* (**Scheme 58**).[123] Interestingly the reaction led not to the desired cycloadduct **2-59** directly, instead dimer was obtained, which was

introduced into a thermal retro-Diels-Alder reaction to give the required tricyclic compound **2-59**.



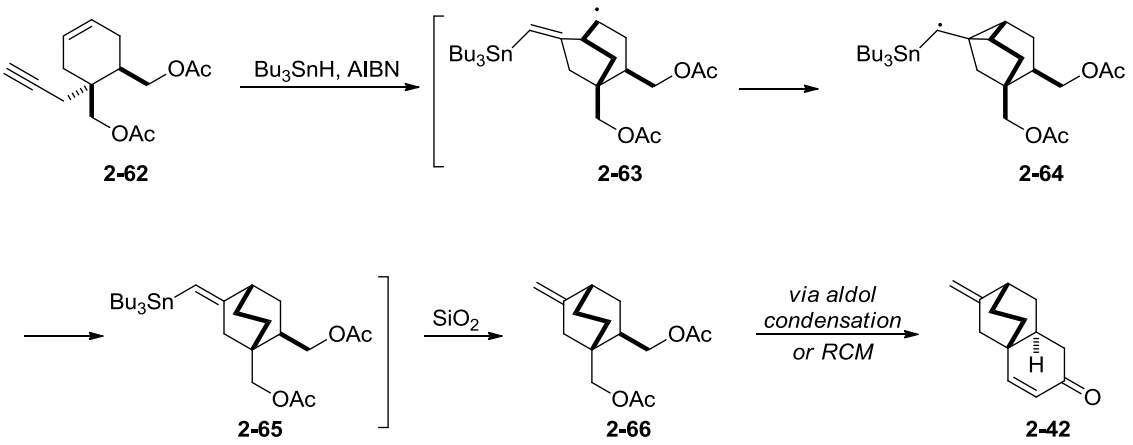
Scheme 58. Diels-Alder reaction approach according to Singh *et al.*

Another example for an IMDA reaction, where the substrate has aromatic origin is reported by Banwell *et al.* (**Scheme 59**).[124]



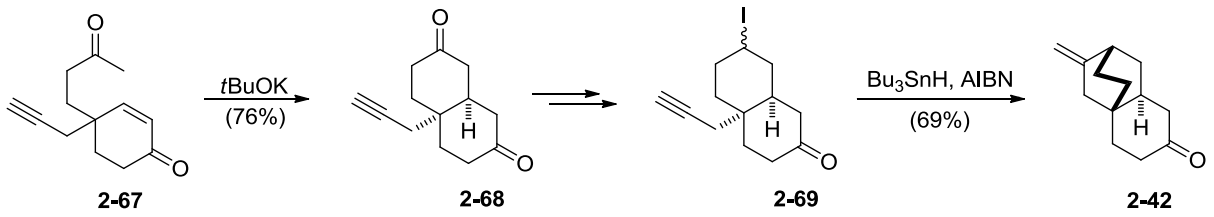
Scheme 59. Intramolecular Diels-Alder approach according to Banwell *et al.*

According to the next strategy a radical cyclization was called for the construction of a bicyclic system. Lee *et al.*[125] reported about an addition of tributylstannyl radical to the triple bond that resulted in formation of homoallyl radical **2-63**, which underwent skeletal rearrangement to the required bicyclo[2.2.2]octane **2-66** (**Scheme 60**).[126] Completion of the synthesis could be achieved either by an intramolecular aldol condensation or ring closing metathesis.



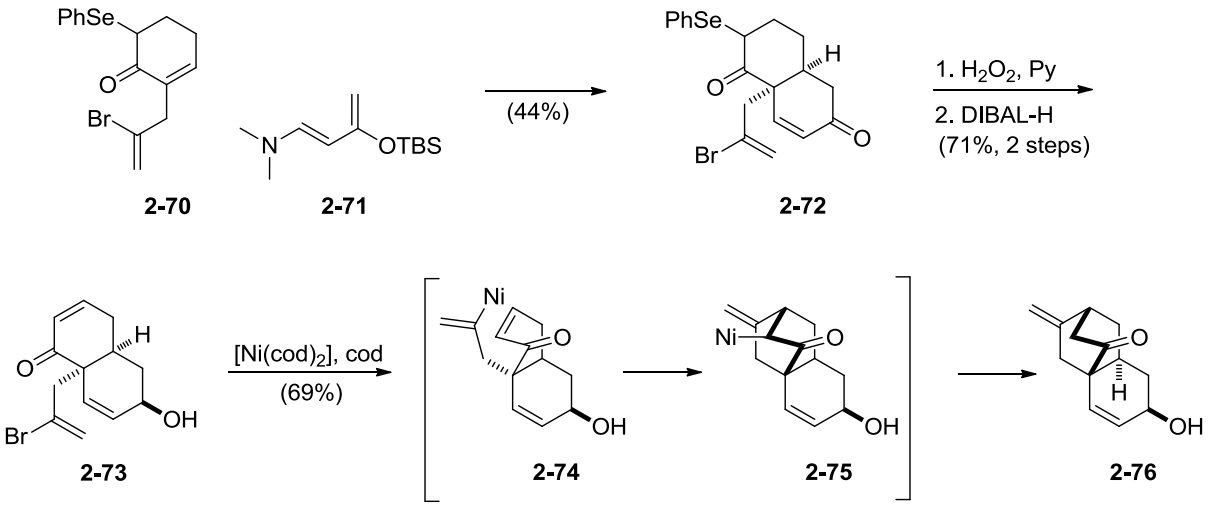
Scheme 60. Synthesis of the core structure **2-42**, according to Lee *et al.*

A late-stage radical cyclization approach was reported by Ghosh *et al.*[127] Their formal synthesis of platencin (**2-34**) features an intramolecular base-catalyzed Michael cyclization of enone **2-67**, followed by radical cyclization of iodoalkyne **2-69** (**Scheme 61**).



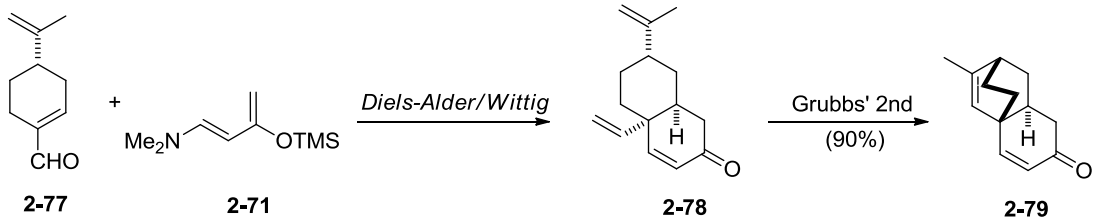
Scheme 61. Michael and radical cyclizations, reported by Ghosh *et al.*

In the strategy reported by Rawal *et al.*[128] *cis*-decaline **2-72**, available from a Diels-Alder reaction between Rawal diene (**2-71**)[129] and enone **2-70**, was introduced into a nickel-mediated intramolecular 1,4-conjugate addition[130] resulting in the desired bicyclo[2.2.2]octane skeleton (**Scheme 62**).



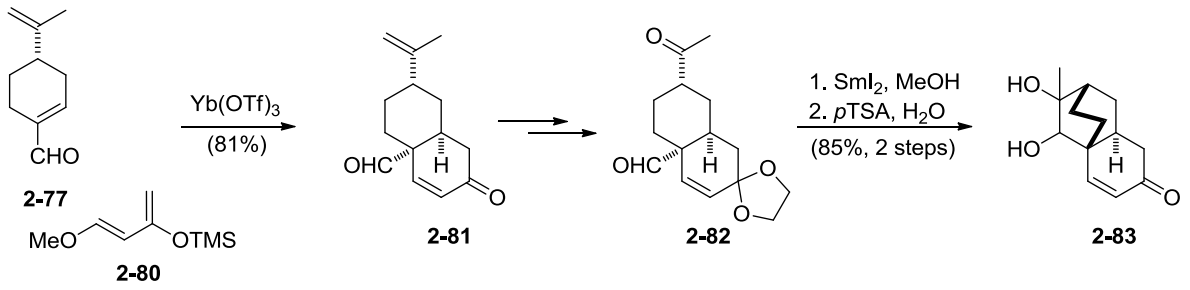
Scheme 62. The construction of bicyclo[2.2.2]octane framework via $[Ni(cod)_2]$-promoted cyclization.

Mulzer *et al.*[131] used the same diene **2-71**[129] for a Diels-Alder reaction in their formal synthesis of platencin (**2-34**) (**Scheme 63**). Wittig olefination of the cycloadduct resulted in decaline **2-78**, which was subjected to a ring-closing metathesis to afford tricyclic structure **2-79**.



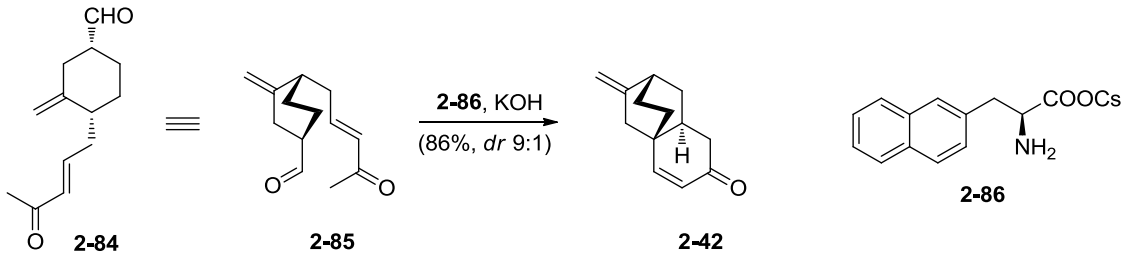
Scheme 63. Diels-Alder/ring-closing metathesis strategy towards platencin's core structure **2-79** according to Mulzer *et al.*

A similar Diels-Alder reaction of (–)-perillaldehyde (**2-77**) and Danishefsky's diene (**2-80**)[132] was applied for the synthesis of the platencin core by Rutjes *et al.* (**Scheme 64**).[133] The construction of the bicyclo[2.2.2]octane motif was then realized through a SmI_2-mediated pinacol coupling.[45]



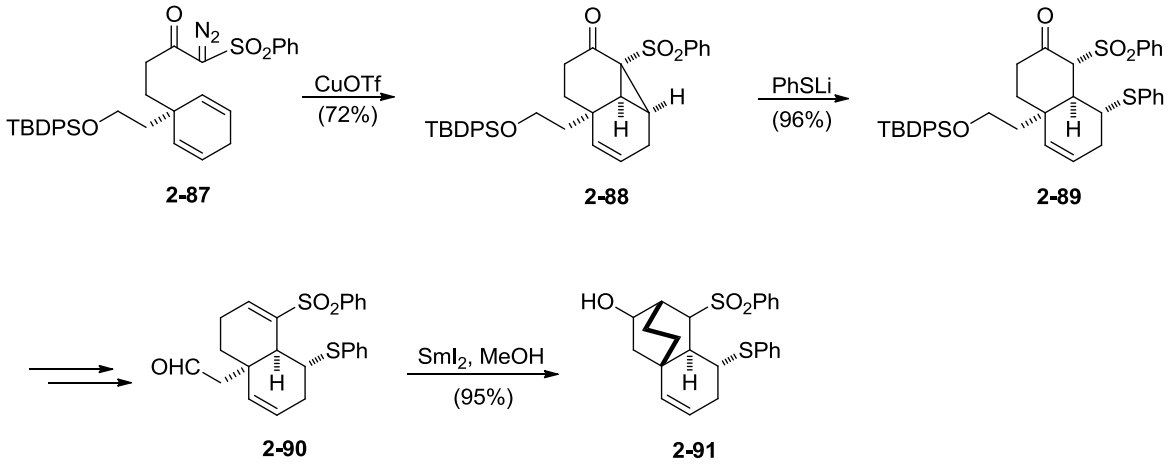
Scheme 64. Diels-Alder/pinacol coupling strategy towards platencin's core structure **2-83**, according to Rutjes *et al.*

Yamamoto *et al.*[134] applied an amino acid salt catalyzed (**2-86** as catalyst) intramolecular Robinson annulation for the construction of two rings (A and B) in one step (**Scheme 65**).



Scheme 65. Robinson annulation approach towards platencin's core structure **2-42**, according to Yamamoto *et al.*

The most recent approach to platencin (**2-34**) published by Nakada *et al.*[135] involves an intramolecular cyclopropanation to construct a decaline system **2-88**. After opening of the cyclopropane with thiophenolate,[136] a samarium(II)-mediated Michael addition of an aldehyde function to a vinylsulfone moiety resulted in **2-91**.



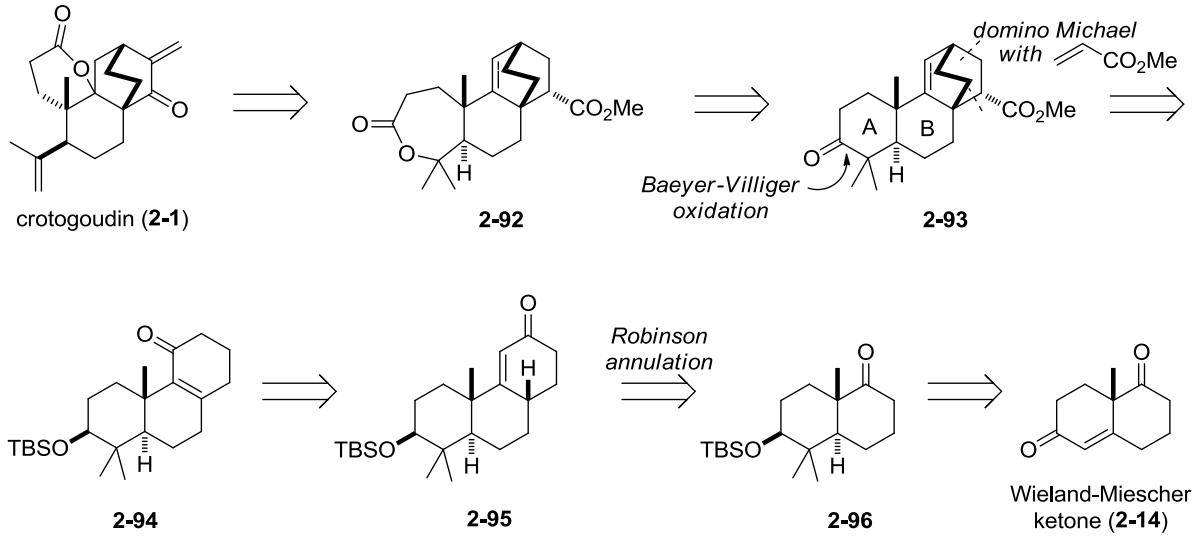
Scheme 66. Strategy towards platencin by Nakada *et al.*

In conclusion, many approaches towards a bicyclo[2.2.2]octane framework are described in literature. The high functionalization of crotogoudin's core structure including lactone, isopropenyl and enone moieties required the development of a flexible synthesis to access stereogenic and structural analogues that might help to identify the biological target. In this regard, we aimed to investigate the utility of the developed methodologies mentioned above for the total synthesis of crotogoudin (**2-1**).

2 Results and Discussion

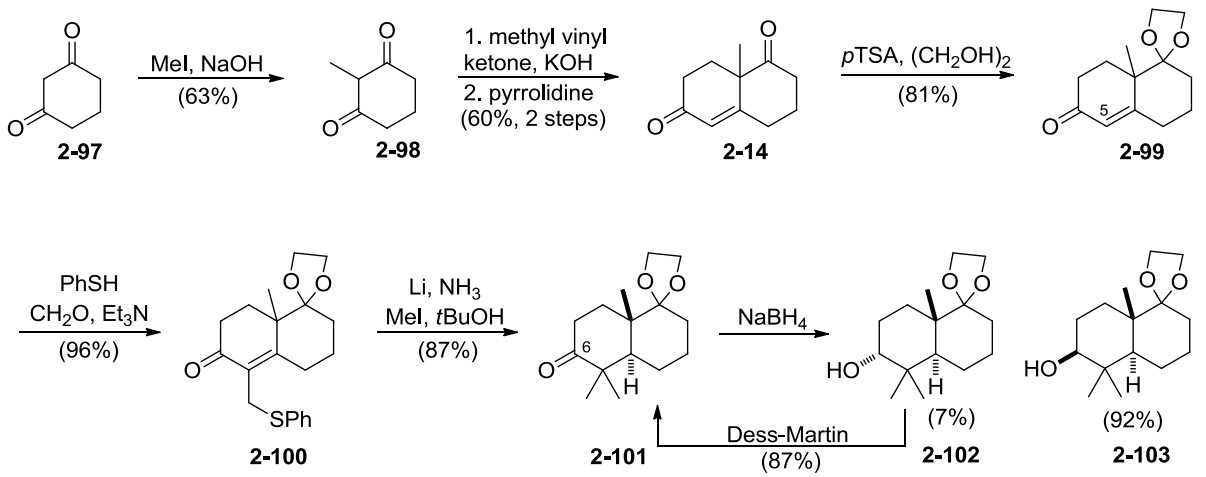
2.1 Studies Towards the Synthesis of Crotogoudin via a Late-stage Formation of Bicyclo[2.2.2]octane Ring System

Our first retrosynthetic plan for (±)-crotogoudin (**2-1**) features a Baeyer-Villiger-type oxidation, followed by translactonization leading to lactone **2-92**, which itself would originate from tricyclic ketone **2-93** (**Scheme 67**). This step certainly corresponds to the likely biosynthetic pathway. We were impressed by the excellent stereoselectivity, which was observed in intramolecular double Michael reactions, reported by Fukumoto *et al.* in their synthesis of atisirene and atisane.[110,111] For our retrosynthetic consideration we proposed an intermolecular version of the domino Michael reaction, which is called for the construction of a bicyclo[2.2.2]octane ring system from enone **2-94** and methyl acrylate. Construction of this bicyclic motif by intermolecular domino Michael reaction has been broadly described in the literature,[137] however application of this strategy for the synthesis of atisane-related compounds was unknown. Tricyclic enone **2-95** could be generated by Robinson annulation from decalinone derivative **2-96**. Wieland-Miescher ketone (**2-14**) appeared as an appropriate starting material for our synthesis.



Scheme 67. Retrosynthetic plan for the synthesis of crotogoudin (**2-1**).

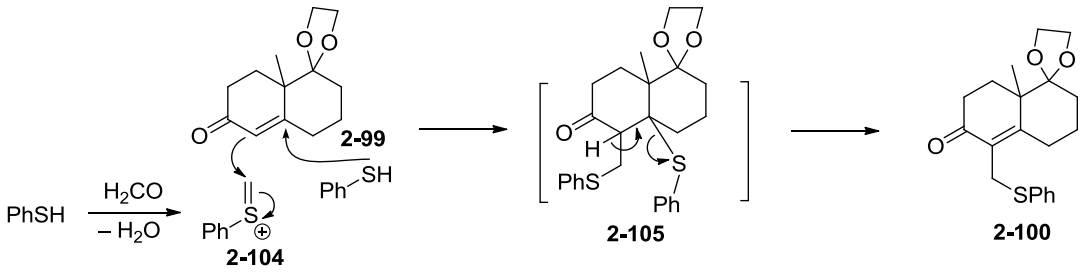
The synthesis commenced with monomethylation of 1,3-cyclohexadione (**2-97**) (**Scheme 68**).[138] Racemic Wieland-Miescher ketone (**2-14**) was prepared in a two step sequence involving intramolecular Michael reaction between dione **2-98** and methyl vinyl ketone, followed by pyrrolidine-catalyzed intramolecular aldol condensation.[139] We decided to investigate a racemic synthesis for initial studies, however optically active Wieland-Miescher ketone (**2-14**) can be prepared with high *ee* values.[140] Regioselective ketalization with ethylene glycol resulted in enone **2-99** with the α,β-unsaturated ketone remaining untouched.[141] Now, bis-methylation at C-5 can be achieved by alkylation of enone **2-99** with excess of methyl iodide in the presence of *t*BuOK that results in a concomitant migration of the double bond, which could be hydrogenated in the next step.[142] An alternative method was chosen, due to high yields, scalability and perfect stereoselectivity. Namely, a Kirk-Petrow reaction (reaction of the enone with thiophenol and formaldehyde in the presence of base)[143] was followed by Stork reductive methylation (reduction of the enone with lithium in liquid ammonia that results in the lithium enolate, which is quenched with methyl iodide) to furnish *trans*-decalone **2-101** as a single diastereomer.[144] Reduction of the ketone at C-6 with sodium borohydride in ethanol[145] resulted in a diastereomeric mixture of alcohols (**2-103**/**2-102** 13:1). Crystallization of this mixture from petroleum ether/ethyl acetate gave the desired alcohol **2-103**, while ketone **2-101** could be recycled from the mother liquor by reoxidation of **2-102** with Dess-Martin reagent.[58]



Scheme 68. Preparation of alcohol **2-103** from 1,3-cyclohexadion (**2-97**) via Wieland-Miescher ketone (**2-14**).

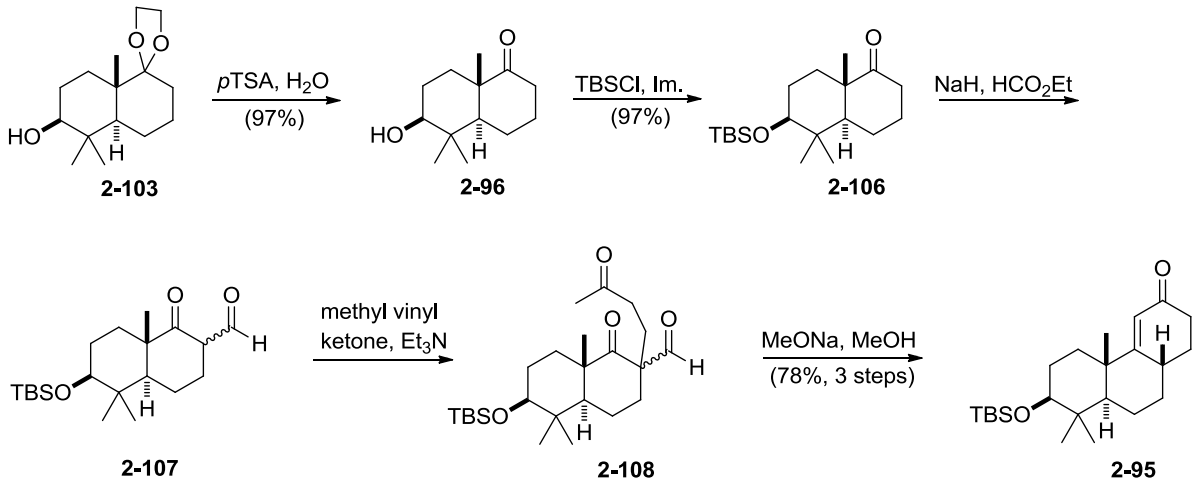
A proposed mechanism for the Kirk-Petrow reaction[143] involves a conjugated nucleophilic addition of thiophenol to an enone moiety and the resulting enolate is quenched with

intermediate **2-104**, which forms *in situ* from a second molecule of thiophenol and formaldehyde (**Scheme 69**). Further elimination of thiophenolate results in enone **2-100**.



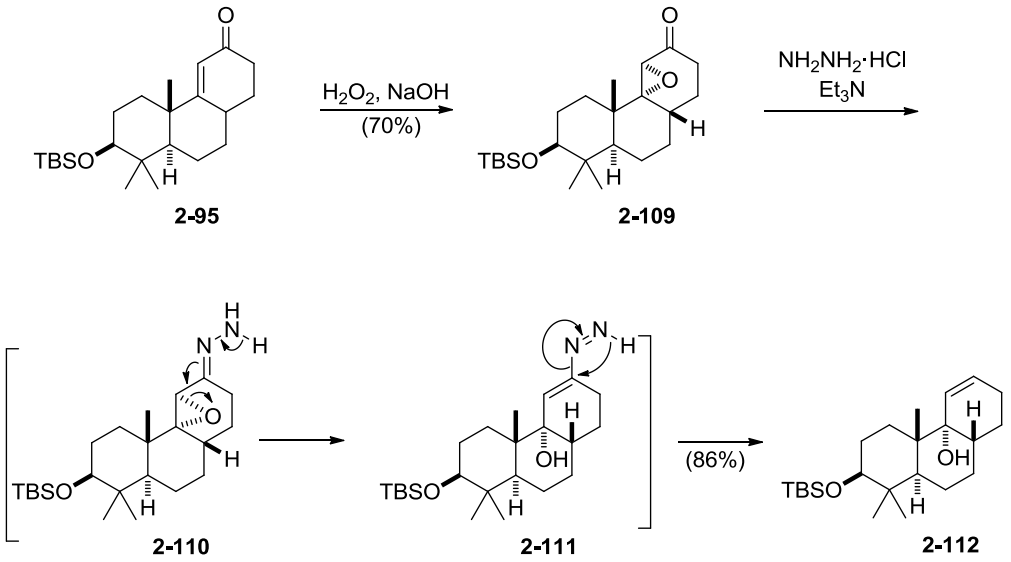
Scheme 69. The proposed mechanism for the Kirk-Petrow reaction.

Acid-mediated cleavage of the acetal protecting group resulted in ketone **2-96**, where the hydroxyl group was supposed to be protected as a silyl ether (**Scheme 70**). This transformation is known in the literature, however either expensive TBSOTf is used (TBSOTf, pyridine, CH_2Cl_2, r.t. (83%))[146] or moderate yield is observed (TBSCl, DMAP, Et_3N, reflux, 5 days (74%)).[147] It was found that protection of this sterically hindered secondary alcohol at C-6 proceeds nicely even at ambient temperature when dimethyl formamide is used as a solvent. Further annulation was achieved by formylation of the ketone **2-106**, followed by Robinson annulation employing methyl vinyl ketone, with concomitant removal of the formyl group, to afford the enone **2-95** in 78% overall yield.[148] Using LiHMDS as base the enolate of **2-106** reacted with methyl vinyl ketone (THF, –78 °C, to r.t.) directly to enone **2-95**, albeit in lower yield (43%).



Scheme 70. The synthesis of enone **2-95** via Robinson annulation.

The next challenge involved transposition of the enone functionality to set the stage for the key domino Michael reaction or preparation of a diene for a Diels-Alder reaction. Thus, a stereoselective nucleophilic epoxidation of α,β-unsaturated enone **2-95** resulted in desired epoxide **2-109** in 70% yield (**Scheme 71**). Wharton rearrangement[149] on the derived hydrazone provided allylic alcohol **2-112**.



Scheme 71. Synthesis of allylic alcohol **2-112** via Wharton rearrangement.

The stereochemical outcome in epoxidation step can be explained by steric hindrance of 4a-CH_3 blocking attack to the upper side (β-face) of the double bond (**Figure 15**).

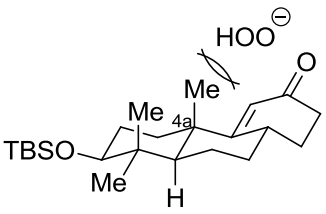


Figure 15. Epoxidation of **2-95**

It was found that allylic alcohol **2-112** was unstable under acidic conditions (*p*TSA, benzene, r.t.) and underwent smooth dehydration to a mixture of three dienes **2-113**, **2-114** and **2-115** (**Scheme 72**). Short reaction time (5 min, reflux) led to the formation of **2-113** and **2-114** in ratio 1.00:0.78 (**Figure 16**).

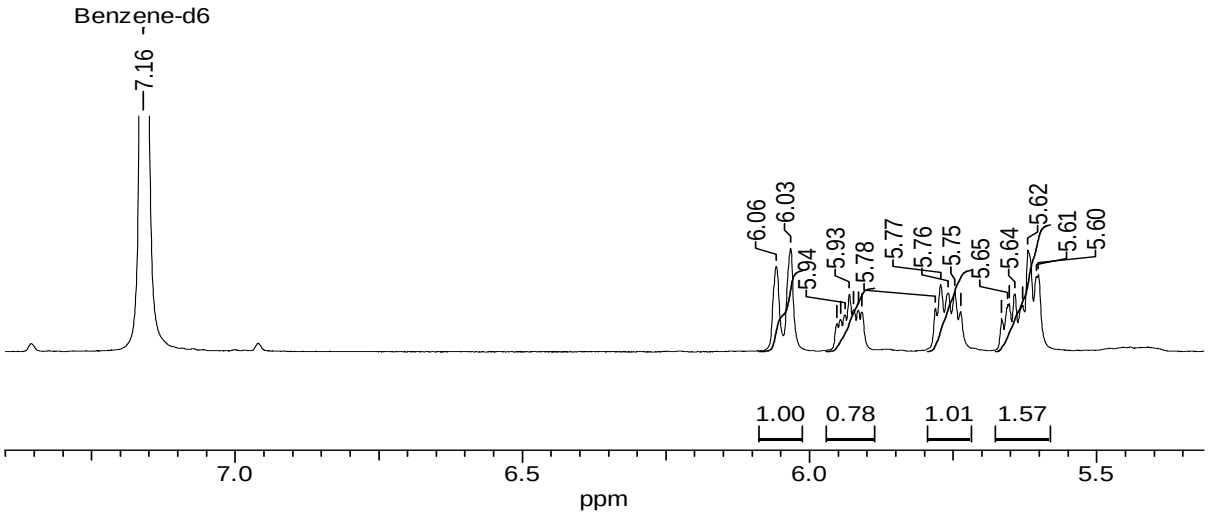
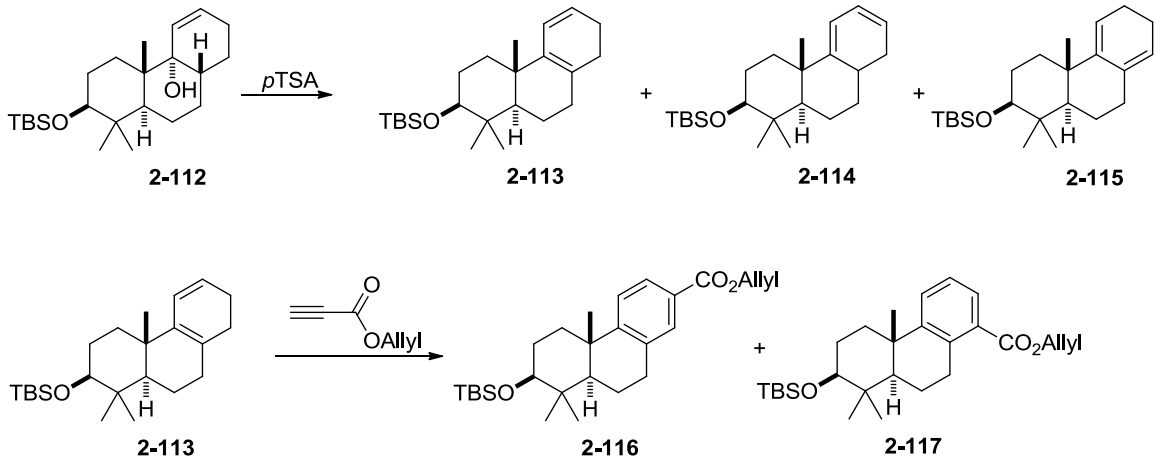


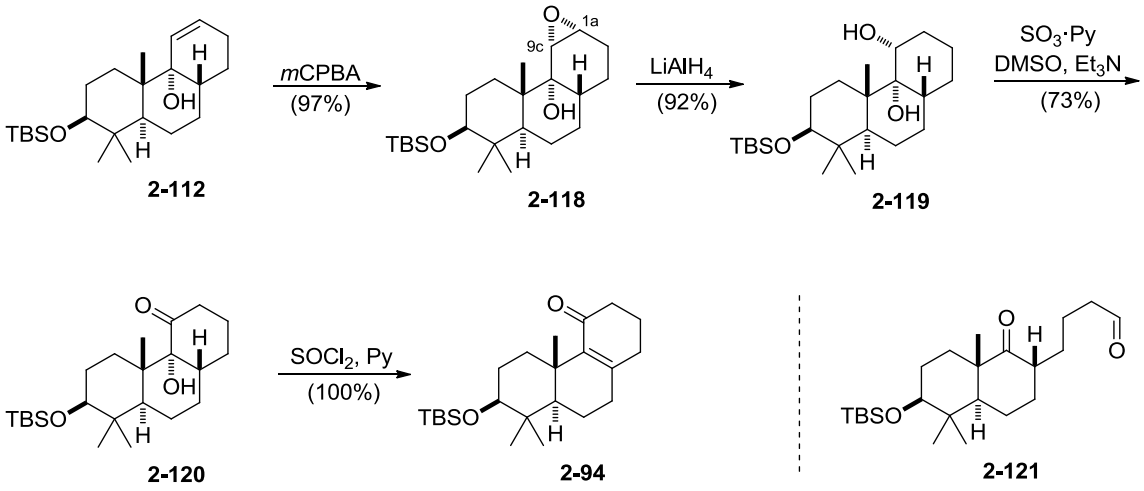
Figure 16. The fragment of ^{1}H NMR spectrum of the diene mixture **2-113** and **2-114**.

Longer stirring with acid (1 h, reflux) resulted in exclusive formation of the thermodynamically most stable diene **2-115** (**Scheme 72**). Thermo-induced Diels-Alder reaction between **2-113** and allyl propiolate resulted in a mixture of aromatic compounds **2-116** and **2-117**. The formation of these compounds can be explained from the sequence of Diels-Alder/retro Diels-Alder reactions with loss of ethylene.[150] Lewis-acid catalyzed ($AlCl_3$, $NbCl_5$, Me_2AlCl, $MeAlCl_2$) Diels-Alder reactions were not successful as well, and provided diene **2-115** as a main product. No reaction was observed, when methyl acrylate was used as a dienophile. The reaction between 2-chloroacrylonitrile[151] and **2-113** resulted in a complex mixture of products.

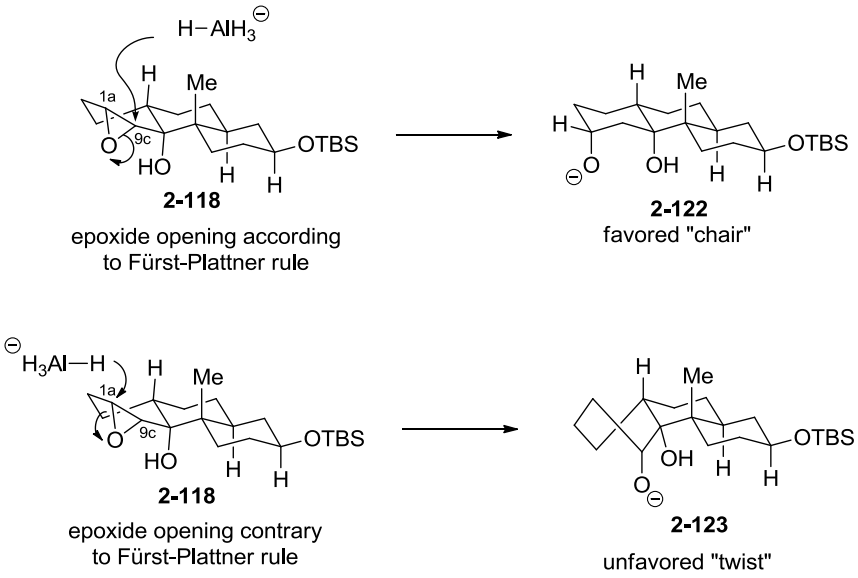


Scheme 72. Attemps to perform a Diels-Alder reaction.

As mentioned above, use of an intermolecular double Michael reaction could be an alternative way for the construction of the desired tetracyclic ring system. Thus, allylic alcohol **2-112** was subjected to a stereoselective *m*CPBA-mediated epoxidation (**Scheme 73**). Nucleophilic opening of the epoxide may occur either at C-1a or C-9c position (**Scheme 74**). According to the Fürst-Plattner rule[152] the major product formed results from attack at the C-9c position since the alternative attack at C-1a would give an unfavorable twist-boat transition state. However reductive epoxide opening with lithium aluminum hydride afforded diol **2-119** as a single regioisomer, whose constitution did not correspond to our expectations. This could be explained by the smaller steric hindrance of the C-1a position and ease of nucleophilic attack. With diol **2-119** in hand, we studied the regioselective oxidation of the secondary alcohol in presence of the tertiary hydroxyl group. While Dess-Martin oxidation of **2-119** resulted in keto aldehyde **2-121**,[153] Parikh-Doering oxidation[57] provided the desired α-hydroxy ketone **2-120** in 73% yield (**Scheme 73**). The next challenge involved dehydration of **2-120** to α,β-unsaturated ketone **2-94**. When Burgess reagent[67] was applied for this purpose, the required enone **2-94** was obtained only in 50% yield (Burgess regent, toluene, reflux, 1 min). After careful experimentation it was found that treatment of **2-120** in a pyridine solution with thionyl chloride (r.t., 20 min) provided enone **2-94** in 84% yield. These conditions were optimized (0 °C, 30 min) and the required α,β-unsaturated ketone **2-94** was prepared in quantitative yield.

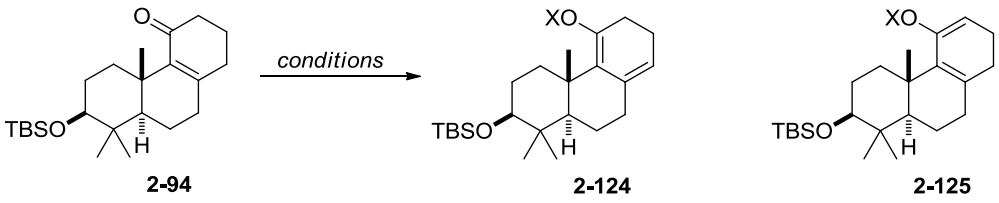


Scheme 73. Synthesis of enone **2-94**.



Scheme 74. Comparison of nuclephilic epoxide opening pathways.

Unfortunately generation of the desired enolate **2-125** from **2-94** by action of different bases failed. γ-Deprotonation took place under all tested conditions with different bases (LDA, LiHMDS, KHMDS) and temperatures (–78 °C, 0 °C) resulting in dienolate **2-124**. Treatment of **2-94** with TBSOTf in presence of triethylamine (CH_2Cl_2, –78 °C) provided mixture of enol ethers **2-124** and **2-125** that could not be separated by chromatography (ratio 1:0.9).



Scheme 75. Preparation of enolate **2-125** for a key domino Michael reaction.

Thus, we were not able to find conditions, that would generate the desired enolate for the key domino Michael reaction. Also we were not successful with the preparation of the required diene system for an intermolecular Diels-Alder reaction. The challenging late-stage construction of the bicyclo[2.2.2]octane motif forced us to reconsider our retrosynthetic plan (see 2.3).

2.2 Total Synthesis of Moluccanic Acid Methyl Ester

Enone **2-95** prepared in the previous part of this chapter (2.1) has a similar tricyclic motif as podocarpane (**2-126**) (**Figure 17**). We decided to apply our synthetic strategy described in 2.1 for the synthesis of one of the padocarpane diterpenes, where the problematic formation of the bicyclo[2.2.2]octane ring system is not required. It was also interesting for us to try the Baeyer-Villiger oxidation for the oxidative cleavage of the ring A, that could later be applied for the synthesis of crotogoudin (**2-1**). Thus, we selected the recently discovered 3,4-*seco*-podocarpane trinorditerpenoid moluccanic acid methyl ester (**2-11**) as a title compound for our spin-off synthesis. This molecule was isolated from plant extracts of *Aleurites moluccana* in 2008.[154] Methyl ester **2-11** displays moderate cytotoxic activity against the HepG2 cell line with an IC_{50} value of 32 μM, while the free acid **2-10** was essentially inactive (IC_{50} > 360 μM).

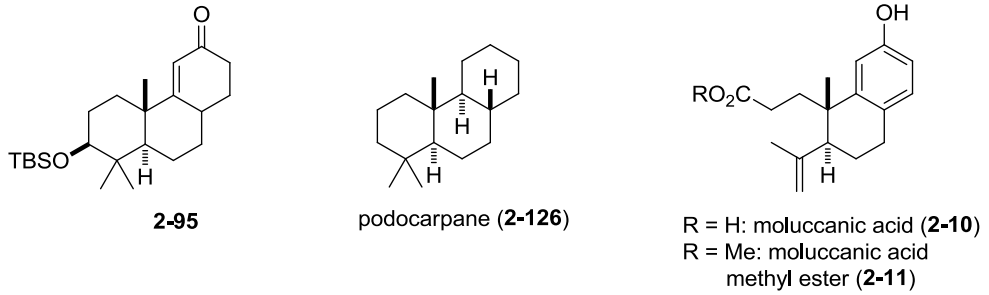
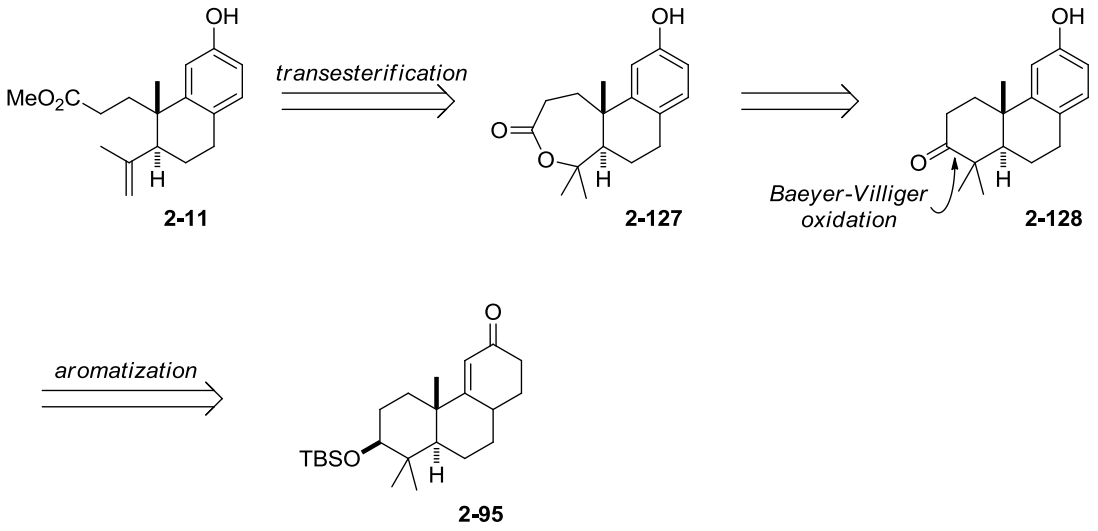


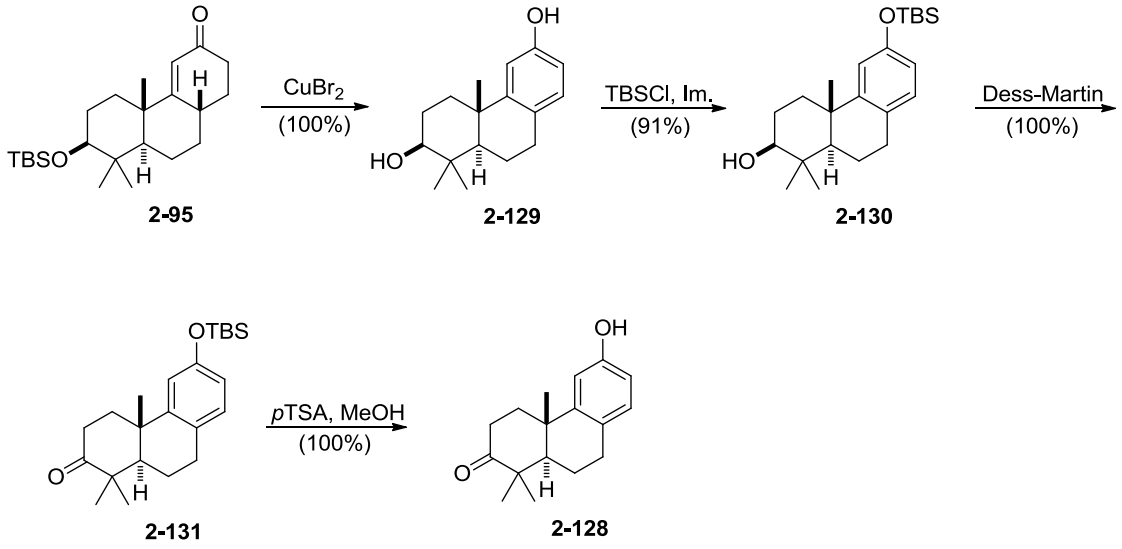
Figure 17. The structures of moluccanic acid (**2-10**), its methyl ester (**2-11**) and podocarpane (**2-126**).

Our retrosynthetic plan for (±)-moluccanic acid methyl ester (**2-11**) features a Baeyer-Villiger-type oxidation leading to lactone **2-127**, which itself would originate from ketone **2-128** (S**cheme 76**). The aromatic ring in ketone **2-128** could be introduced via aromatization[155] of the previously prepared tricyclic enone **2-95**.



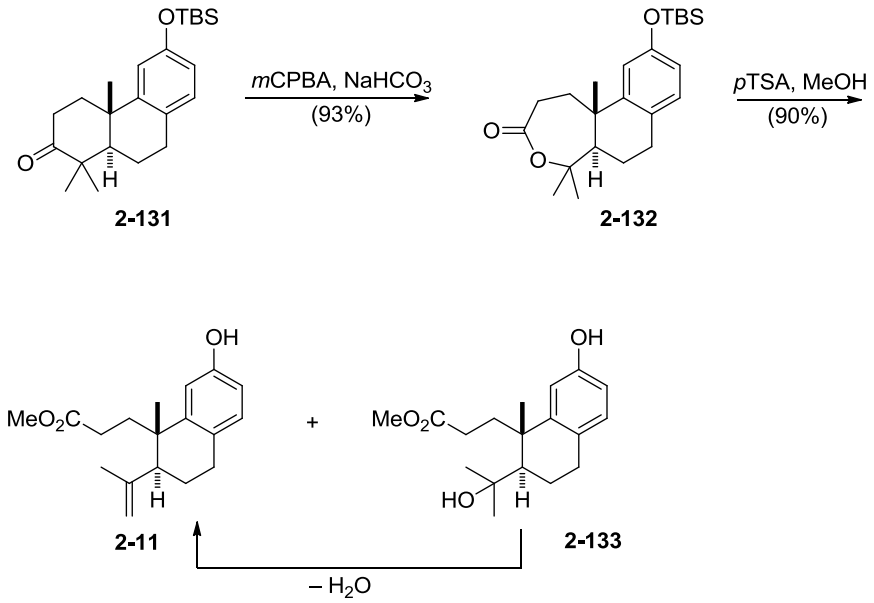
Scheme 76. Retrosynthetic analysis of moluccanic acid methyl ester (**2-11**).

The synthesis commenced with treatment of earlier prepared enone **2-95** with catalytic amounts of $CuBr_2$ (5 mol%, CH_3CN, r.t.). However, only TBS deprotection was observed.[156] Addition of excess (1.7 equiv) $CuBr_2$ provided phenol **2-129** in quantitative yield (**Scheme 77**).[157] With hydroxyphenol **2-129** in hand we tested various conditions in order to promote the oxidation of the secondary hydroxyl group in the presence of the phenol. Standard procedures for oxidation of alcohols to ketones (Dess-Martin, Swern, PCC, Parikh-Doering oxidations) failed.[158] After careful experimentation we found that selective TBS protection of the phenol to give silyl ether **2-130** was possible. This was followed by oxidation with Dess-Martin periodinane,[58] which provided ketone **2-131** in 91% yield over two steps. Then the silyl protecting group was smoothly removed by *p*TSA in methanol to afford phenol **2-128** in quantitative yield.



Scheme 77. Preparation of phenol **2-128** via Cu(II)-mediated aromatization.

The crucial Baeyer-Villiger oxidation of ketone **2-131** was achieved with *m*CPBA and $NaHCO_3$ leading to lactone (**Scheme 78**).[159,31] Gratifyingly, transesterification[160] with MeOH in presence of *p*TSA completed the synthesis of (±)-moluccanic acid methyl ester (**2-11**) as an amorphous solid. In addition, a second product was isolated from the transesterification reaction. The structure of this by-product was assigned to the hydroxyester **2-133** (combined yield 90%, ratio **2-11**/**2-133** = 1:2), that upon standing overnight as a chloroform solution underwent dehydration to give the desired alkene **2-11** in quantitative yield.



Scheme 78. Synthesis of moluccanic acid methyl ester (**2-11**) via Baeyer-Villiger oxidation.

Moluccanic acid methyl ester (**2-11**), as well as the phenols **2-128**, **2-129** and **2-133** were tested against three cancer cell lines using an MTT assay (**Table 7**).[161]

compound	cell line		
	L-929	KB-3-1	PtK2
2-129	96	15	104
2-128	124	109	105
2-133	>130	46	>130
2-11	80	19	66

Table 7. Cytotoxicity (IC_{50} in µM) of (±)-moluccanic acid methyl ester (**2-11**) and its possible precursors **2-128**, **2-129** and **2-133** against selected cell lines.

The cancer cell line KB-3-1 turned out to be the most sensitive against all compounds tested. For this cell line, ester **2-11** and the phenol **2-129** showed similar IC_{50} values. The other two compounds, ketone **2-128** and hydroxyester **2-133** did not show any significant cytotoxicity. For phenol **2-128** and ester **2-11** also impedance curves were recorded since the course of these curves is characteristic for the mode of action of a particular compound.[162] The two compounds were found to cluster with microtubule effecting compounds. Ester **2-11** clustered with taxol and epothilone (**Figure 18**). One the other hand phenol **2-129** seems to be similar to tubulysin, griseofulvin, and nocodazole in the cluster analysis.

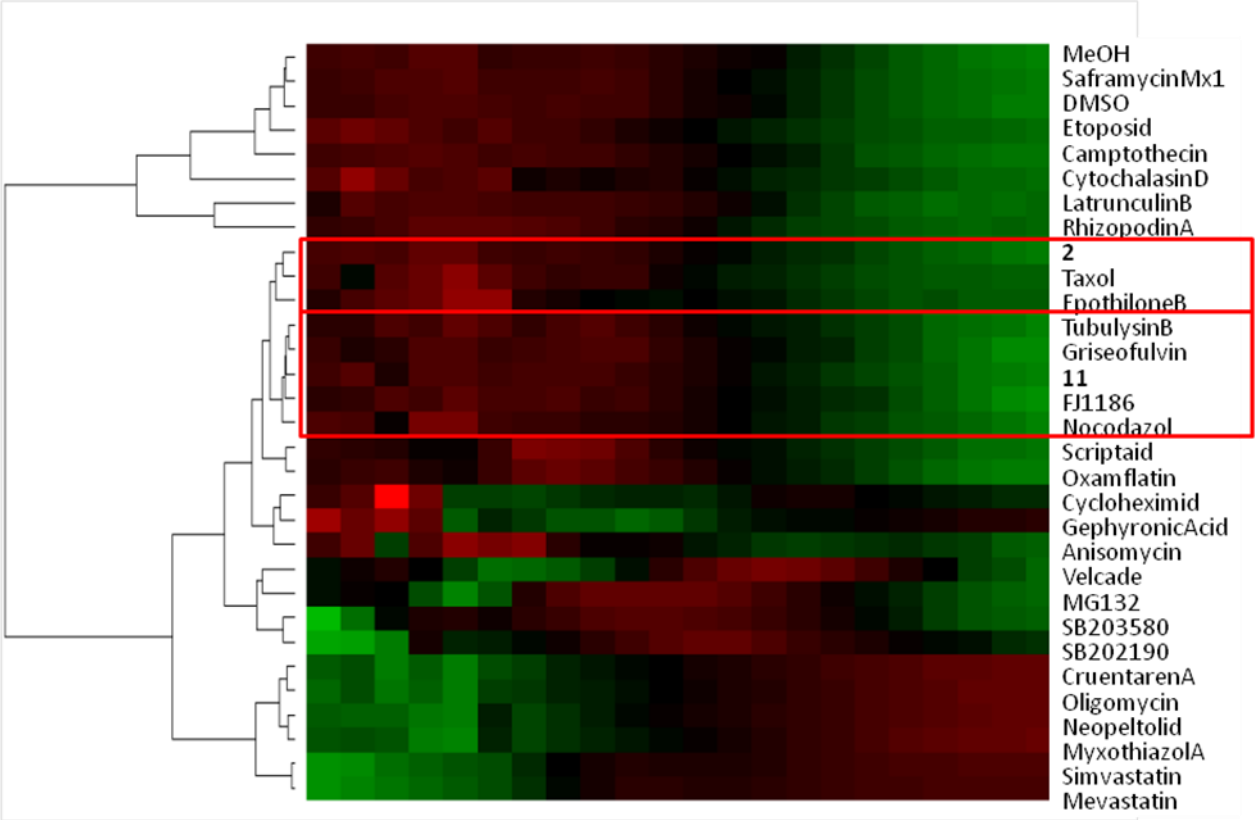


Figure 18. Hierarchical cluster analysis of the reference compounds together with the compounds with unknown mode of action.

Finally, these compounds were tested for their effect on actin (**Figure 19**). Potoroo kidney cells PtK2 were incubated with **2-11** (69 µM) (right) or the vehicle only (left) for 24 h and stained for microtubules. With compound **2-11** we observed weak and bended mitotic spindles.

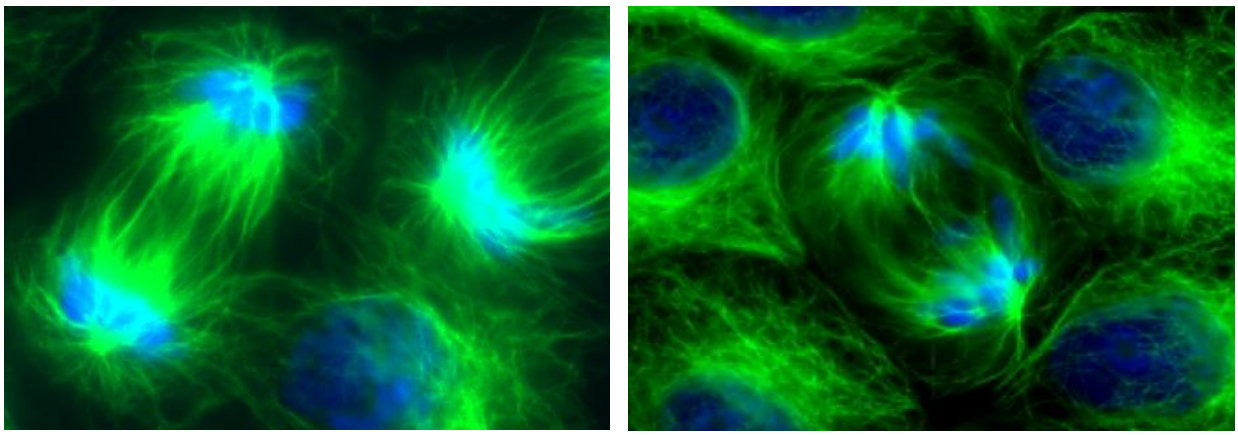
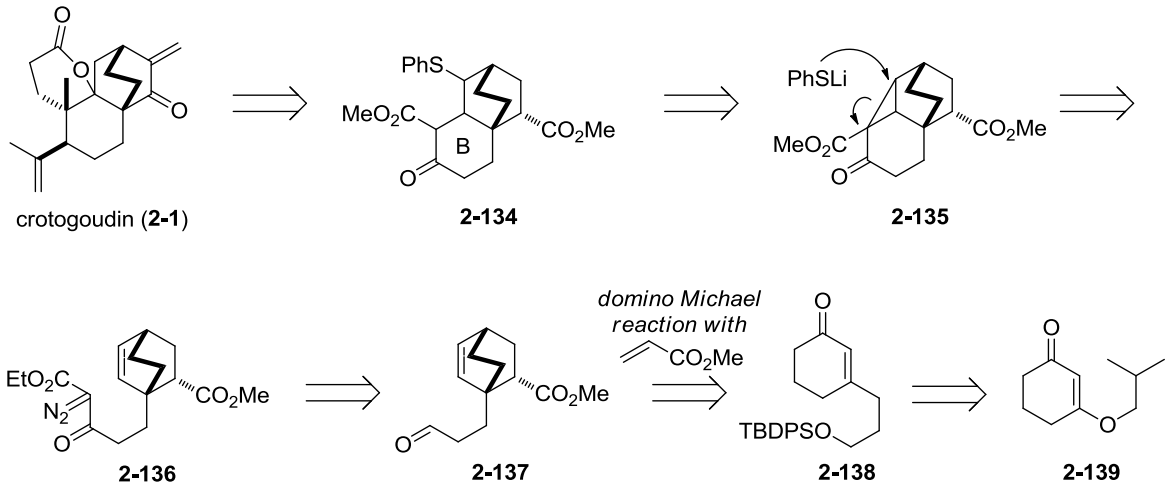


Figure 19. Effect of **2-11** on microtubules.

2.3 Studies Towards the Synthesis of Crotogoudin via an Early-stage Formation of the Bicyclo[2.2.2]octane Ring System

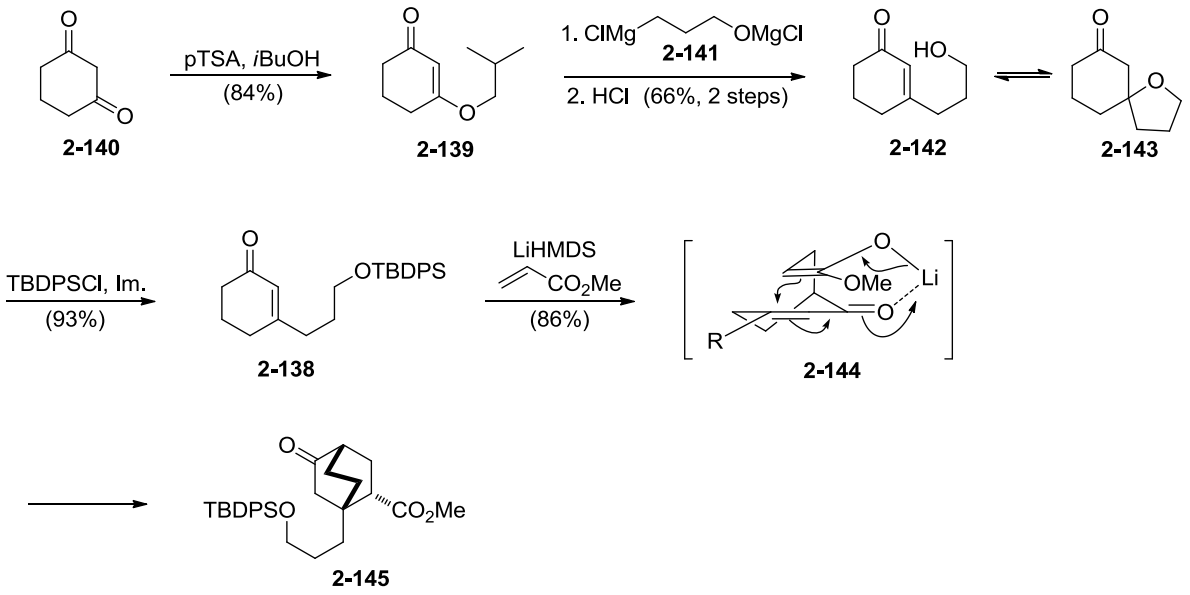
Our second retrosynthetic plan towards crotogoudin (**2-1**) features an early-stage formation of the bicyclo[2.2.2]octane motif via a double Michael reaction (**Scheme 79**). The ring B could be constructed by intramolecular cyclopropanation/thiophenolate-mediated cyclopropane opening strategy, which was applied by Nakada *et al.* in the synthesis of platencin (**2-34**).[136] For this purpose diazo β-keto ester **2-136** could be prepared from aldehyde **2-137**, according to the sequence used in our studies towards the synthesis of englerin A (**1-7**) (**Scheme 17**). Vinylogous ester **2-139** appeared as an appropriate starting material for our plan (**Scheme 79**).



Scheme 79. Retrosynthetic analysis of crotogoudin (**2-1**).

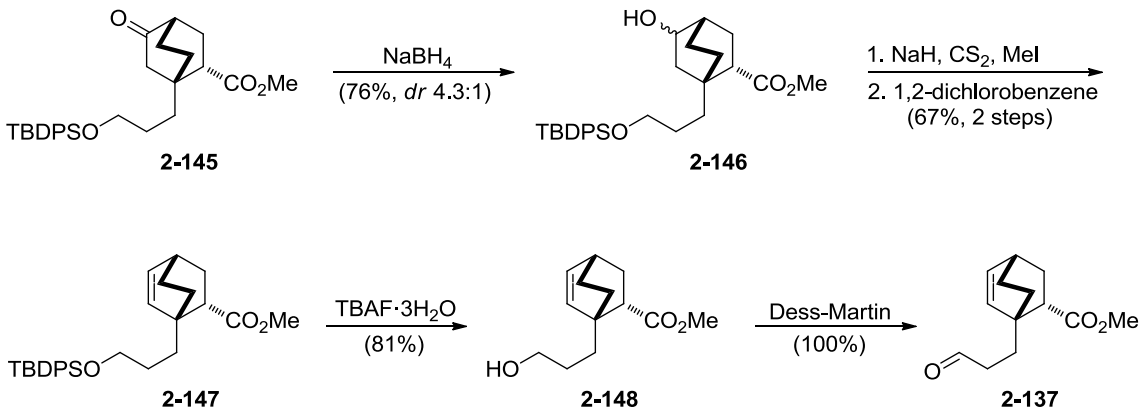
The synthesis commenced with Grignard addition of readily available 3-chloropropan-1-ol with temporary protected hydroxyl group **2-141** to vinylogous ester **2-139**,[163] which can be prepared in one step from commercially available 1,3-cyclohexadione (**Scheme 80**).[164] Acid-mediated hydrolysis of the enol ether obtained from the Grignard reaction led to enone **2-142** in 86% yield. Enone **2-142** exists in equilibrium with ether **2-143**. Protection of primary hydroxyl group in enone **2-142** as a silyl ether resulted in **2-138** in 93% yield. Oxa-Michael product from the previous step was not detected after this reaction. Treatment of the lithium enolate, generated from **2-138** using LiHMDS as a base with methyl acrylate resulted in formation of bicyclic compound **2-145** as a single stereoisomer.[165] A remarkable

stereoselectivity in this reaction arises from the chelation effect of the enone oxygen with lithium enolate in intermediate **2-144**.



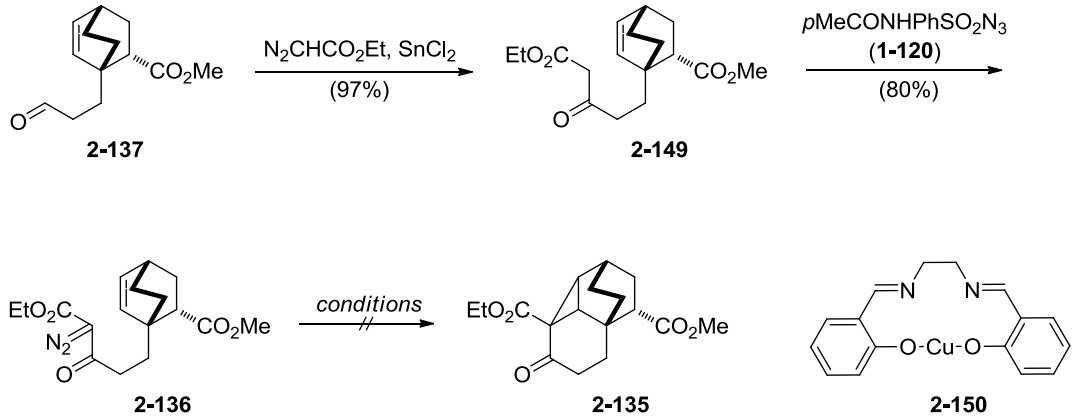
Scheme 80. Synthesis of bicyclo[2.2.2]octane derivative **2-145** via domino Michael reaction.

The further functionalization called for a conversion of the carbonyl group to an endocyclic double bond. Thus, the carbonyl group in **2-145** was reduced by $NaBH_4$ to afford a diastereomeric mixture of diols **2-146** (ratio 4.3:1) (**Scheme 81**). With hydroxyester **2-146** we tried various conditions in order to promote the dehydration reaction. Water elimination by Burgess reagent[67] failed as well as reaction with $MsCl/Et_3N$. After careful experimentation we found that a Chugaev reaction[166] (xanthogenate formation, followed by *syn*-elimination) resulted in the desired alkene **2-147** in good overall yield. Fluoride-mediated cleavage of the silyl ether converted ester **2-147** to primary alcohol **2-148**, which was then oxidized with Dess-Martin reagent[58] to afford aldehyde **2-137** in quantitative yield.



Scheme 81. Synthesis of aldehyde **2-137** via Chugaev dehydration.

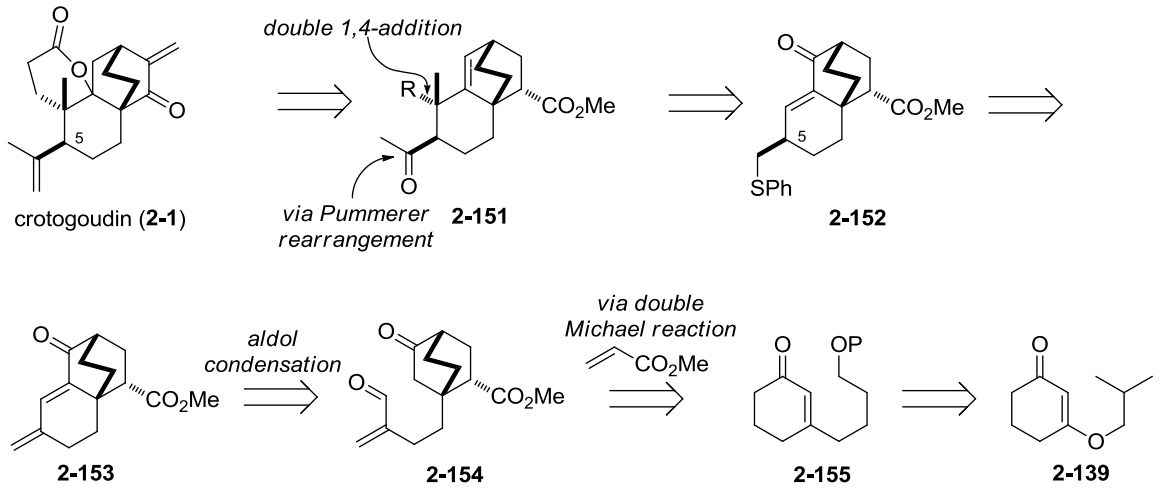
Aldehyde **2-137** was subjected to reaction with ethyl diazoacetate, catalyzed by tin (II) chloride,[59] and provided β-ketoester **2-149** in nearly quantitative yield (**Scheme 82**). Diazotransfer reaction with sulfonyl azide **1-120**[60] furnished diazoketone **2-136** in 80% yield. Intramolecular cyclopropanation reaction was found to be challenging. Several rhodium- or copper-based catalysts ($Rh_2(OAc)_4$; $Cu(acac)_2$; $CuSO_4$; CuI; $Rh(PPh_3)_3Cl$; $Rh(cod)_2Cl$; **2-150**[167]) were used in order to promote carbene formation and its reaction with the double bond. However, we were not able to detect even trace amounts of the desired cycloadduct **2-135**. A complex mixture of different C-H insertion products was obtained in all experiments. Most likely the desired cyclopropane **2-135** cannot be formed, because the double bond and carbene generated from **2-136** are too far from each other. Possible cyclopropanation is possible by an intermolecular reaction.



Scheme 82. Synthesis of diazo β-keto ester **2-136** and attempts to perform an intramolecular cyclopropanation.

Although we were not able to perform the key intramolecular cyclopropanation, we found that the bicyclo[2.2.2]octane ring system can be constructed via domino Michael reaction with high yield and stereoselectivity. The double bond could be installed via Chugaev reaction. These findings could be used in the following studies, where construction of the B ring relies on another method, namely intramolecular aldol condensation.

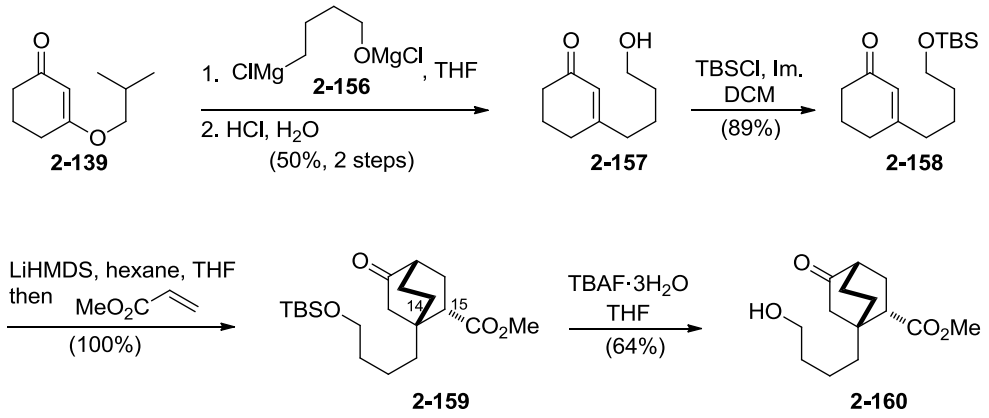
Our revised retrosynthetic approach features a Pummerer rearrangement[168] to install the isopropenyl group at C-5 (**Scheme 83**). The quaternary center at C-10 could be constructed via double copper-catalyzed 1,4-Grignard addition. The desired tricyclic ring system would originate from intramolecular aldol condensation of aldehyde **2-154** that has an additional methylene group in the side chain in comparison to the earlier prepared **2-137**. The synthesis of aldehyde **2-154** relies on a domino Michael reaction between enolate generated from **2-155** and methyl acrylate under the conditions disclosed before.



Scheme 83. Retrosynthetic plan for the synthesis of crotogoudin (**2-1**) via domino Michael reaction/intramolecular aldol condensation.

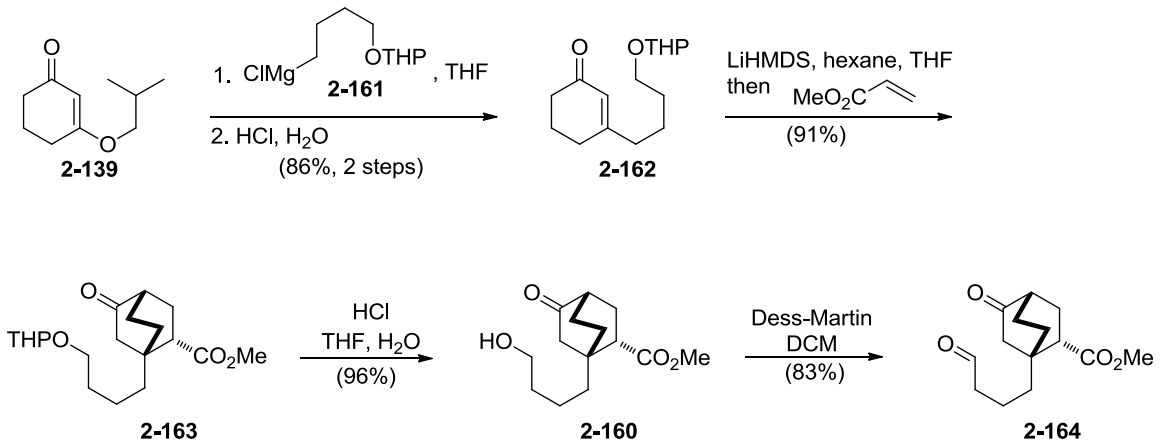
Starting from vinylogous ester **2-139**, hydroxy ester **2-160** was prepared by the previously described five-step sequence (**Scheme 84**). The moderate yield observed in the Grignard addition could be explained from intramolecular cyclization of **2-156** to a tetrahydrofuran during its preparation. In a contrast to the use of 3-cloropropan-1-ol (**Scheme 80**) the intramolecular oxa-Michael product was not detected and **2-157** was isolated as a single compound (**Scheme 84**). The protecting group for the primary hydroxyl group was changed to a smaller TBS, that was supposed to survive under the planned reaction conditions. The key intermolecular domino Michael reaction proceeded with quantitative yield and resulted in

stereoselective formation of ester **2-159**. The orientation of the ester group could be inferred from the NOESY spectrum which shows a cross-peak between 15-H and 14-H (atisane numbering). This assignment was confirmed by X-ray analysis on a similar compound in the synthesis of the core structure of palhinine A.[165]



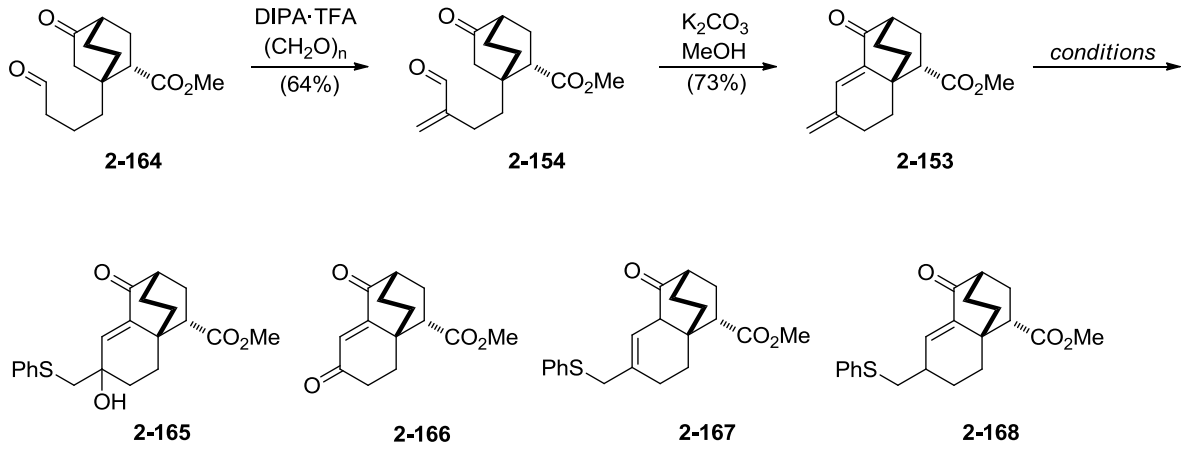
Scheme 84. Synthesis of hydroxy ester **2-160**.

To avoid furan formation during preparation of the Grignard reagent we investigated a slightly modified route to **2-160** which utilizes readily available THP-protected 4-chlorobutan-1-ol **2-161** for the Grignard addition to vinylogous ester **2-139** (**Scheme 85**).[169] We were not able to prepare a Grignard reagent from a readily available TBS-protected 4-chlorobutanol. Acid-mediated hydrolysis of the vinylogous hemiacetal obtained from the Grignard reaction led to enone **2-162** in 86% yield. Treatment of the lithium enolate, generated from **2-162** using LiHMDS as base with methyl acrylate resulted in formation of bicyclic compound **2-163** also in high yield and as a single isomer (diastereomers on the acetal carbon of the THP group). Acid-induced cleavage of the THP-protecting group provided alcohol **2-160** as well. Although the use of THP as a protecting group made work up and NMR analysis inconvenient (diastereomeric mixture at the acetal carbon), the yields were higher in comparison to the use of the previous method (**Scheme 84**). Subsequent Dess-Martin oxidation[58] of primary alcohol **2-160** gave keto aldehyde **2-164** in good yield (**Scheme 85**).



Scheme 85. Synthesis of keto aldehyde **2-164** via improved method.

The next challenge involved α-methylenation of the aldehyde group in **2-164**. This was achieved by Mannich-type reaction on a transiently formed methyleneammonium salt (**Scheme 86**).[170] Subsequent base-mediated aldol condensation provided enone **2-153**, while acid-mediated condesation (*p*TSA, benzene, reflux) failed. Intramolecular Michael adduct as well as the intermediate β-hydroxyketone (aldol reaction product) were not detected in that reaction. Treatment of dienone **2-153** with thiophenol resulted in formation of several products, however formation of the required enone **2-168** was not observed. Allylic oxidation by traces of oxygen (all reactions were performed under N_2 with degassed reagents and absolute solvents) proceeded smoothly and **2-165** and **2-166** were formed in almost all experiments even as main products in some of them. It was found that deconjugation of the double bond took place as well. This could probably be explained from release of strain if the double bond shifts.

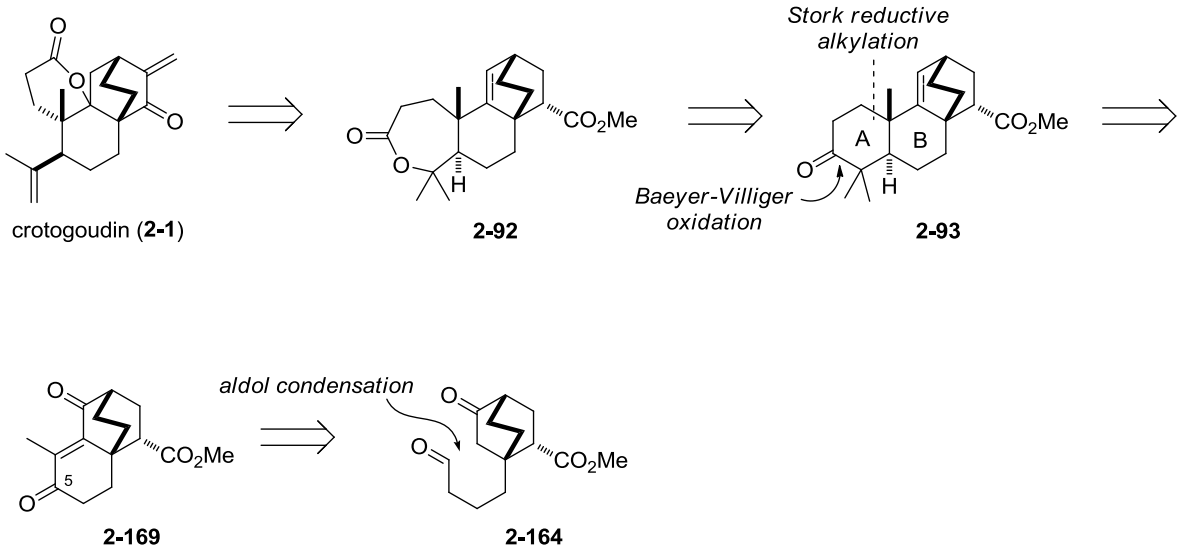


Scheme 86. Synthesis of dienone **2-153** and its treatment with thiophenol.

Conditions	Yields			
	2-165	**2-166**	**2-167**	**2-168**
PhSH, Et_3N, benzene, air	70	20	0	0
PhSH, Et_3N, benzene, $CHCl_3$ air	68	17	0	0
Et_3N, benzene, air	0	0	0	0
PhSH, K_2CO_3, MeOH, air	36	0	44	0
PhSH, K_2CO_3, MeOH, N_2	10	0	61	0

Table 7. Conditions for conjugated addition of thiophenol to dienone **2-153**.

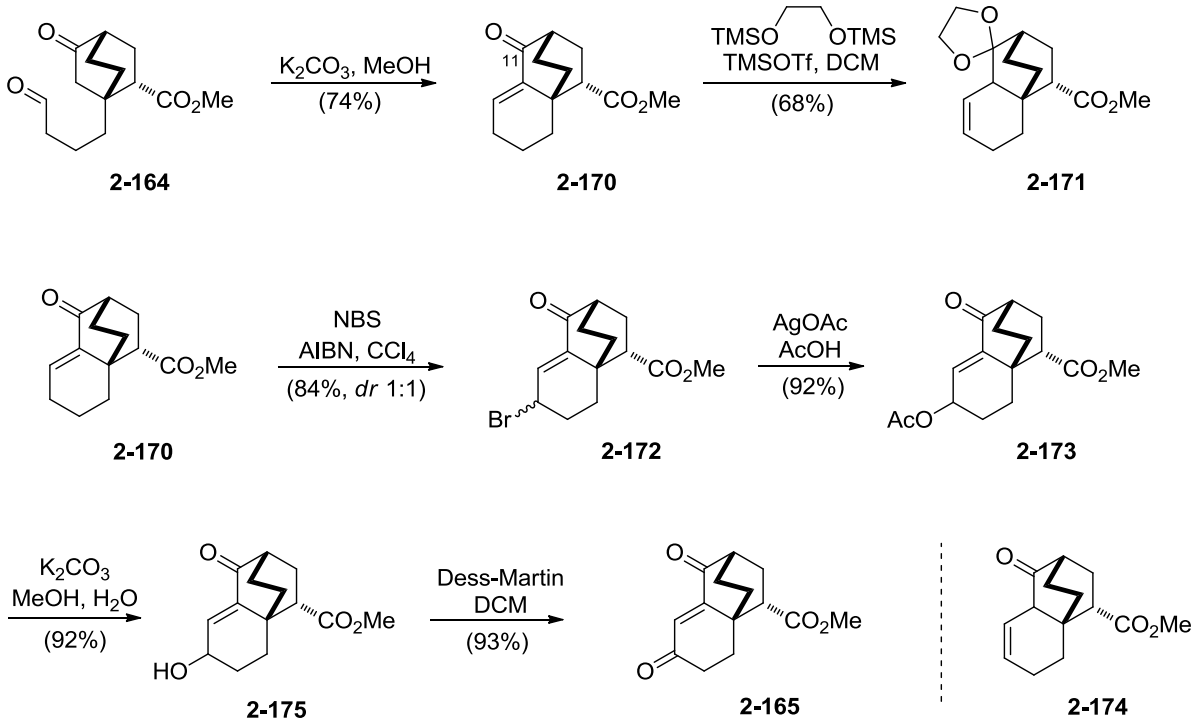
Thus, we found a very efficient strategy for construction of the tricyclic core structure of crotogoudin, however further functionalization via 1,4-Grignard addition and Pummerer rearrangement was found to be challenging due to deconjugation of the enone system. Thus, we proposed a new revised retrosynthetic plan for the completion of the synthesis of crotogoudin (**2-1**), where deconjugation would be impossible due to tetrasubstitution at C-5. According to this plan a biomimetic Baeyer-Villiger oxidation and intramolecular translactonization leads to ketone **2-93** (**Scheme 86**). The A ring in ketone **2-93** could be introduced via a Stork reductive alkylation strategy on an advanced intermediate **2-169**.[171] The latter could be prepared from previously synthesized keto aldehyde **2-164**.



Scheme 87. Retrosynthetic analysis of crotogoudin (**2-1**)

The first challenge involved allylic C-H activation on enone **2-170**, which is readily available by base-mediated aldol condensation from keto aldehyde **2-164** (**Scheme 88**). Being disappointed by inefficiency of different selenium and chromium-based methods in order to introduce a carbonyl moiety in the allylic position of enone **2-164**, we tried to deactivate the

carbonyl group at C-11 by its protection as an acetal. Transposition of the double bond was observed, which parallels our findings about the stability of this double bond in the previous approach (**Scheme 86**). However, we were successful with a four-steps sequence starting with allylic bromination of enone **2-170** in order to functionalize the allylic position (**Scheme 88**). Thus, a diastereomeric mixture of bromides **2-172** (1:1), prepared utilizing Ziegler-Wohl bromination, was transformed to the corresponding acetate **2-173**. It was found that the stereochemistry of the products in the nucleophilic substitution strongly depends on the reaction conditions. The results are summarized in the **Table 8**. With the use of silver acetate in presence of acid we prepared acetate **2-173** as a single stereoisomer with high yield. We attribute this to a S_N1-type mechanism. At this stage we tried to introduce a methyl group at C-10 via copper-catalyzed 1,4-Grignard addition, however we isolated the unexpected product **2-174** with a deconjugated double bond.[172] Migration of the double bond and formation of **2-174** was also observed when bromides **2-172** were heated with indium and acetone in order to introduce the isopropyl functionality in C-5. Saponification of acetate **2-173** led to allylic alcohol **2-175** and a final Dess-Martin oxidation resulted in diketone **2-165** (66%, 4 steps).

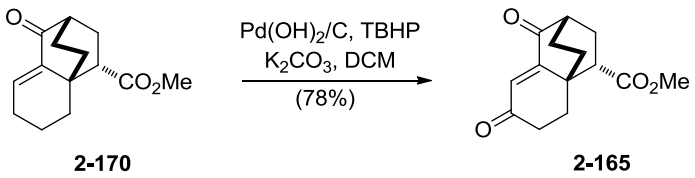


Scheme 88. Introduction of carbonyl group at C-5.

Conditions	Yields (*dr*)
AcONa, DMF, 80 °C	90 (1:1)
AcONa, DMF, r.t.	0
AcOH, $NaHCO_3$, DMF, 80 °C	90 (1:1)
AgOAc, AcOH, r.t.	**92 (1:0)**
AgOAc, dioxane, r.t.	88 (1:1)
AcOK, KI, 18-C-6, acetone, 80°C	22 (1:0)
AcOK, KI, Et_4NCl, acetone, 80 °C	10 (1:0)
AcOH, Et_3N, acetone, 80 °C	87 (1:1)

Table 8. Conditions for the nucleophilic substitution on bromide **2-172**.

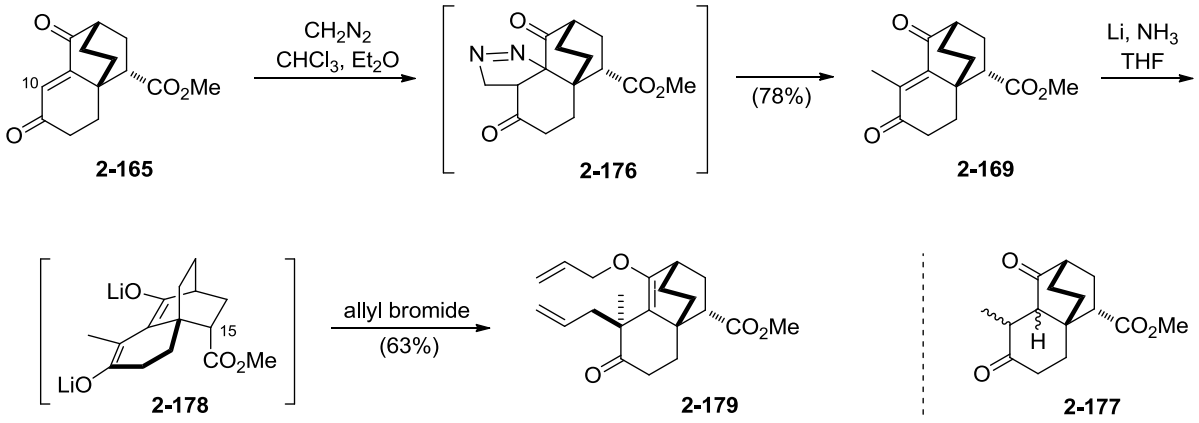
After further experimentation we found even a single step procedure for the desired transformation of enone **2-170** to 1,4-enedione **2-165**, namely a Pd-catalyzed oxidation using *tert*-butylhydroperoxide (**Scheme 89**).[173]



2-170 **2-165**

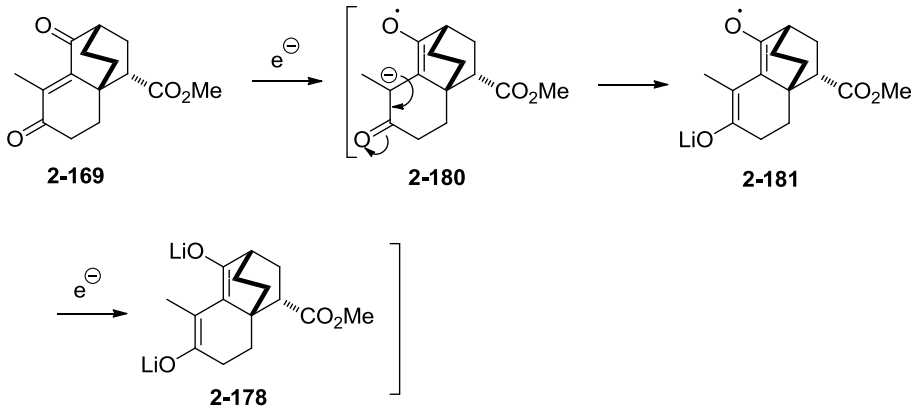
Scheme 89. Single-step allylic oxidation.

We next faced the challenge of introducing substituents at C-10. This was achieved by [3+2]-cycloaddition of freshly prepared diazomethane to the electron poor double bond of enedione **2-165** (**Scheme 90**).[174] This resulted in formation of a pyrazoline derivative, which underwent nitrogen elimination even under ambient temperature to give diketone **2-169**. Hydrogenation of the double bond with zinc in glacial acid furnished diketone **2-177** as a mixture of two diastereomers (1.6:1). Unfortunately acid-mediated Robinson annulation neither with ethyl vinyl ketone nor with 1-chloropentan-3-one was fruitful;[175] therefore a Stork reductive alkylation strategy was applied for the construction of ring A. Accordingly, dienolate **2-178**, prepared by treatment of diketone **2-169** with lithium in liquid ammonia, was quenched with allyl bromide. After work up only one regio- and stereoisomer was detected and its structure was assigned to **2-179**. As it can be seen, *C*-alkylation took place on the less hindered carbon atom (C-10), while the other enolate underwent *O*-alkylation. Unfortunately the stereochemistry of the newly formed stereocenter was opposite with respect to the one required for C-10 of crotogoudin (**2-1**). This can be explained by shielding of the enolate face *syn* to the ester group at C-15.



Scheme 90. Functionalization at C-10.

A proposed mechanism for the reductive alkylation of enedione **2-169** involves single electron reduction of enone moiety leading to radical **2-181**, followed by second single electron reduction resulting in dienolate **2-178** (**Scheme 91**).



Scheme 91. The proposed mechanism for the reduction of enedione **2-169**.

Confirmation of the stereochemistry at C-10 in **2-179** was possible through a NOESY experiment, where we observed a relatively strong cross peak between the allyl CH and 14-H (methylene group) (**Figure 20**). In addition, the other 14-H showed a NOE correlation with 15-H, confirming the endo orientation of the ester group at C-4 and that it remained untouched during the synthesis.

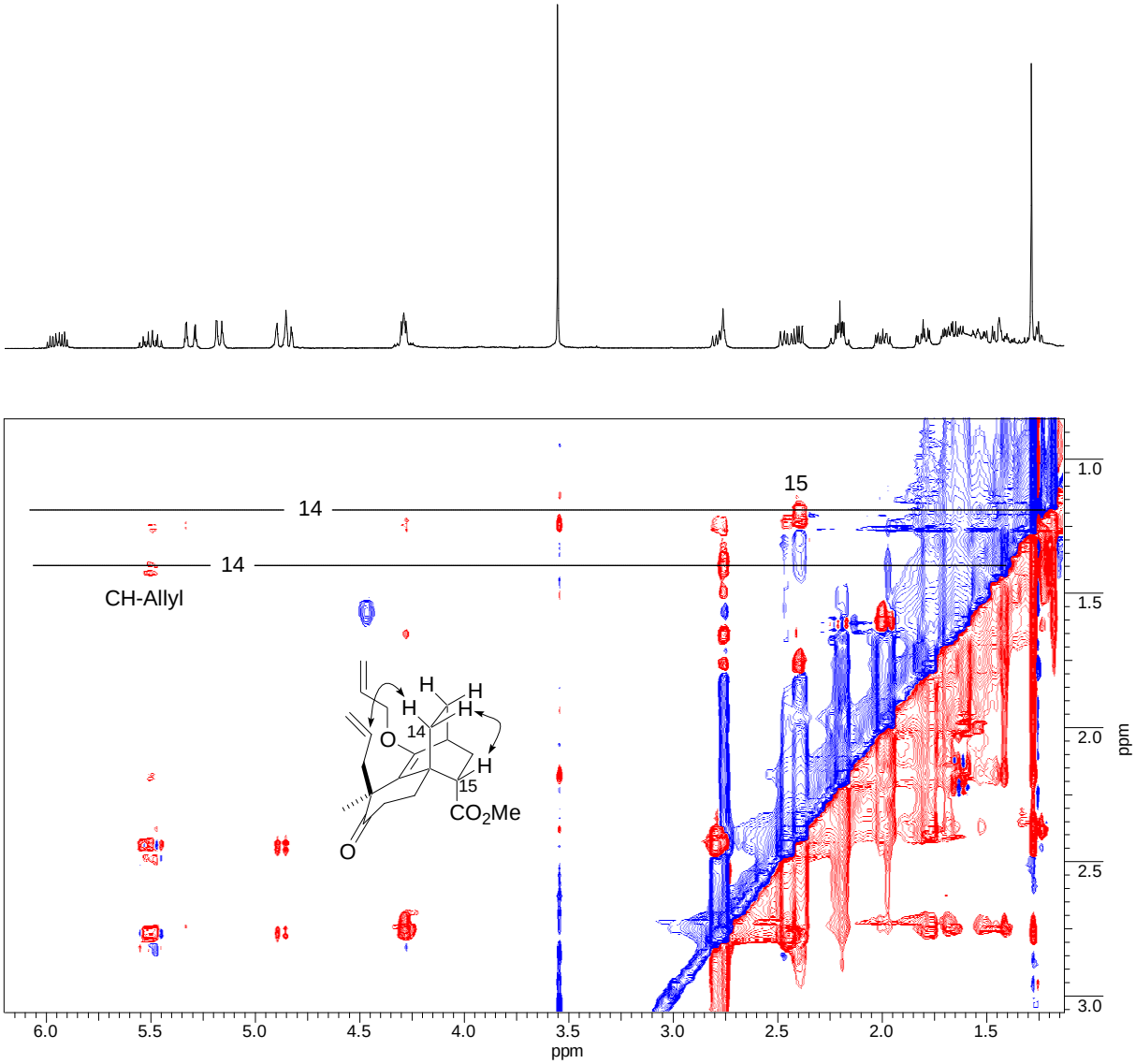
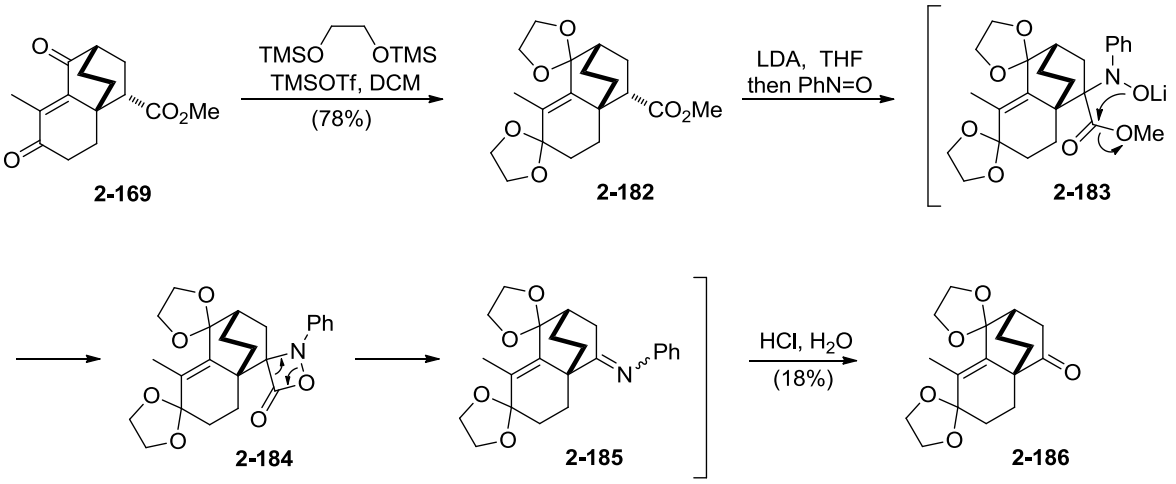


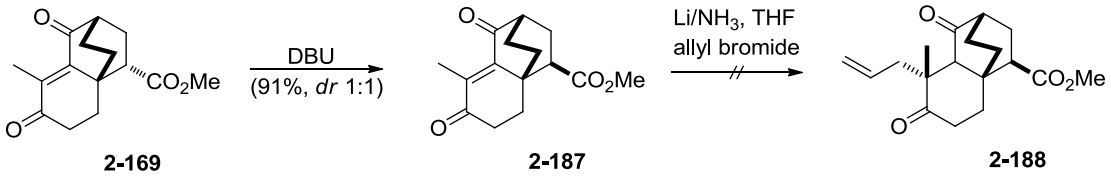
Figure 20. The fragment of NOESY spectrum of **2-179**.

In order to reverse the stereochemical outcome in the alkylation step we tried a degradation of the ester group at C-15. We were inspired by the work of Yamamoto *et al*,[176] where they describe a nitrosobenzene-mediated C-C bond cleavage via formation of an oxazetidin-4-one. Protection of the two keto groups was necessary to generate a selective enolate from the carboxyl group. Thus, double protected ester **2-182** was treated with LDA, followed by addition of nitrosobenzene (**Scheme 92**). The resulting oxazetidin-4-one underwent smooth fragmentation to imine **2-185**. Subsequent acid-mediated hydrolysis furnished the desired ketone **2-186** albeit with poor yield.



Scheme 92. Nitrosobenzene-mediated decarboxylation.

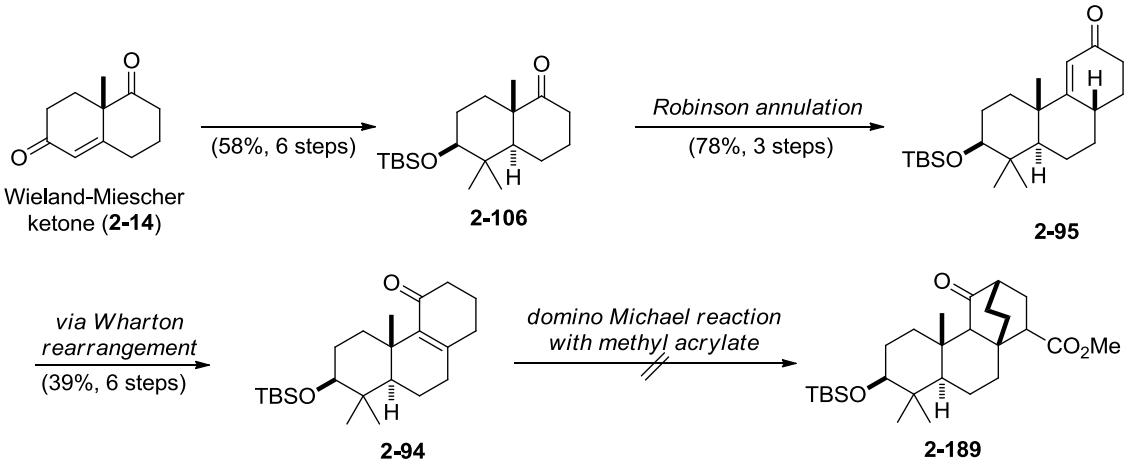
Next we tried epimerization of the ester group at C-15 in order to release the space on the α-side of the molecule. This was achieved with the use of DBU as base (ratio 1:1) (**Scheme 93**). The two stereoisomers were separated by SiO_2 column chromatography, and recovered **2-169** was reintroduced in the epimerization reaction again. A key reductive Stork allylation led to a complex mixture of overreduced products, and the desired product **2-188** was not detected.



Scheme 93. Epimerization at C-15.

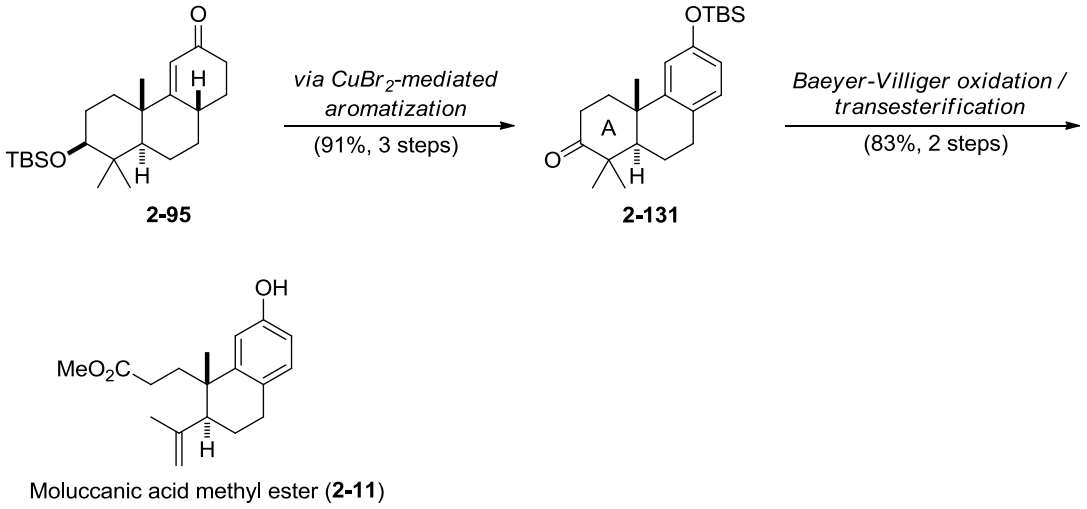
3 Conclusion

In summary, we investigated several approaches to the carbocyclic core structure of crotogoudin (**2-1**), based on a domino Michael reaction. A late- or early stage formation of the bicyclo[2.2.2]octane subunit can be chosen. The first generation approach to crotogoudin (**2-1**) features generation of the bicyclic motif at the end of the synthesis. The synthesis commenced with the transformation of readily available Wieland-Miescher ketone to a double methylated derivative **2-106** (**Scheme 94**). Its Robinson annulation with methyl vinyl ketone, followed by transposition of the enone moiety via Wharton rearrangement resulted in tricyclic compound **2-94**. Unfortunately, a domino Michael addition with methyl acrylate to get bicylo[2.2.2]octane derivative **2-189** failed as well as Diels-Alder reactions of the derived diene with different dienophiles. This way tricyclic enone **2-94** was prepared in 17.6% overall yield in the longest linear sequence of 15 steps.



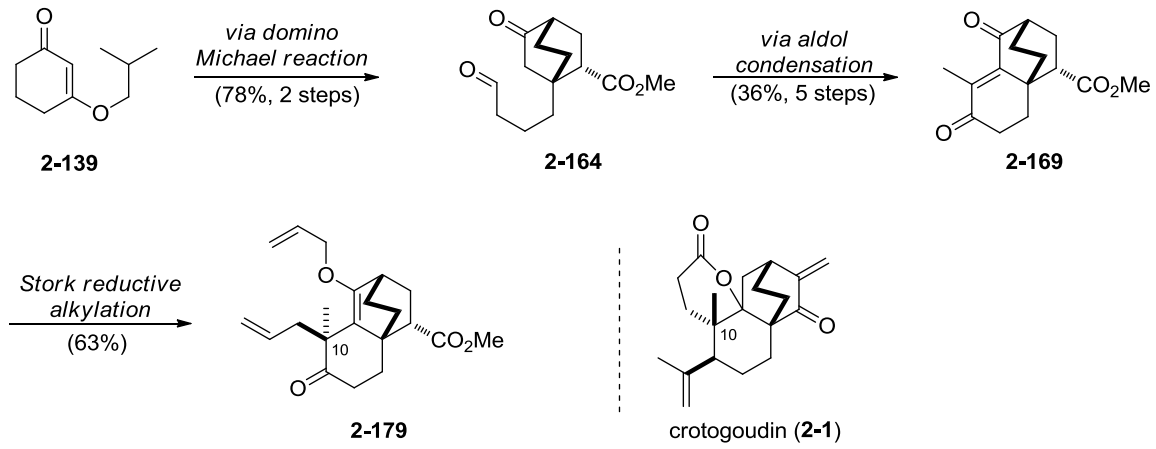
Scheme 94. Studies towards the synthesis of crotogoudin (**2-1**), utilizing a late stage bicyclo[2.2.2]octane formation.

As a spin-off of this project, an effective total synthesis of the trinorditerpene moluccanic acid methyl ester (**2-11**) has been achieved from common intermediate **2-95** (**Scheme 95**). The synthesis features a $CuBr_2$-mediated aromatization of enone **2-95** and Baeyer-Villiger oxidation of the A ring to finish the target molecule **2-11**. The route to **2-11** proceeded in 35.2% overall yield with a longest linear sequence of 14 steps from Wieland-Miescher ketone (**2-14**). Methyl ester **2-11** and its possible biosynthetic precursors were tested against different cancer cell lines and showed interesting activity.



Scheme 95. Synthesis of (±)-moluccanic acid methyl ester (**2-11**).

Due to the challenges faced in the first approach towards crotogoudin (**2-1**), the bicyclo[2.2.2.]octane motif was constructed in the beginning of the synthesis via domino Michael reaction between a cyclohexenone, which was available from vinylogous ester **2-139**, and methyl acrylate (**Scheme 96**). Ring B was introduced by intramolecular aldol condensation of **2-164**. Reductive Stork alkylation of the dienolate, generated from **2-169** furnished **2-179**, where the stereochemistry of the newly formed stereocenter was opposite with respect to the one required for C-10 of crotogoudin (**2-1**). The route to **2-169** proceeded in 30% overall yield starting from vinylogous ester **2-139** with a longest linear sequence of seven steps utilizing a single protecting group (THP) and one oxidation reaction (from alcohol to aldehyde).



Scheme 96. Synthesis of the tricyclic core structure of crotogoudin (**2-1**).

Experimental Section

General Remarks

Chemicals and Working Techniques

Unless otherwise noted, all reactions were performed in oven-dried glassware. All solvents used in the reactions were purified before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, dimethylformamide, methanol, ethyl acetate, benzene, chloroform, pyridine, diisopropylamine and triethylamine were distilled from CaH_2; acetone by distillation from phosphorus pentoxide. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under nitrogen atmosphere. All commercially available compounds (Acros, Aldrich, Fluka, Merck, Avocado, Applichem and Strem) were used without purification.

NMR Spectroscopy

All spectra were measured on a Bruker Avance 400 spectrometer, which operates at 400 MHz for ^1H and 100 MHz for ^{13}C nuclei. The spectra were recorded at 295 K in $CDCl_3$, C_6D_6, MeOD-d_4 or in DMSO-d_6; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (^1H 7.25, ^{13}C 77.0 ppm), C_6D_6 (^1H 7.16, ^{13}C 128.1 ppm), MeOD-d_4 (^1H 3.31, ^{13}C 49.0 ppm), DMSO (^1H 2.50, ^{13}C 39.5 ppm).[177]

Mass Spectrometry

Mass spectra were recordered on a Bruker Daltonic APEX 2 with electron spray ionization (ESI). High resolution mass (HRMS) are reported as follows: (ESI): calcd mass, for the related compound followed by found mass.

Chromatographic Methods

Thin-layer chromatography (TLC) was performed on precoated with silica gel Machery-Nagel Polygram Sil G/UV_{254}. The compounds were visualized by UV_{254} light and the chromatography plates were developed with an aqueous solution of ceric ammonium molybdate or an aqueous solution of potassium permanganate (heating with hot gun). For preparation of the molybdate solution 20.0 g ammoinium 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. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 mL water.

Polarimetry

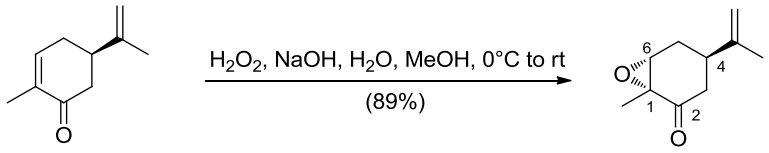
Optical rotations were measured on a JASCO Polarimeter P-1020. They are reported as follows: $[\alpha]^{temperature}_D$ (concentration, solvent). *c* = g per 100 mL. Anhydrous CH_2Cl_2, $CHCl_3$ or MeOH were used as solvents. For the measurement the sodium D line = 589 nm was used.

Melting points

Melting points were determined with a Büchi Melting Point B-540 apparatus.

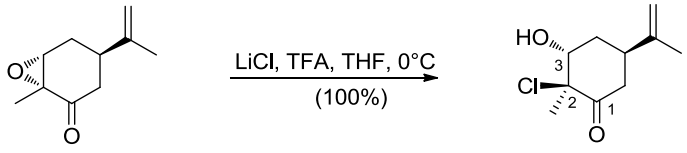
Experimental Procedures

All the experimental procedures are arranged to reflect the synthetic sequences shown in the schemes.



1-108 **1-108a**

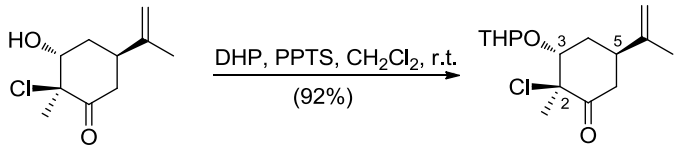
(1*R*,4*R*,6*R*)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (1-108a).[178] A solution of H_2O_2 in water (30%, 160 mL, 1.42 mol) was added dropwise to a solution of (*R*)-carvone (**1-108**) (70.0 g, 0.47 mol) in methanol (500 mL) at 0 °C over a period of 10 min. A solution of NaOH in water (2M, 120 mL, 0.24 mol) was added over a period of 30 min at the same temperature. The resulting mixture was stirred for 2 h at room temperature before it was treated with half-saturated Na_2SO_3 solution (500 mL) and extracted with diethyl ether (4 × 300 mL). The combined organic layers were washed with water (2 × 300 mL) and saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give epoxide **1-108a** (69.1 g, 89%) as a colorless oil. R_f = 0.38 (petroleum ether/EtOAc, 9:1). $[\alpha]^{20}_D$ = –77.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.33 (d, *J* = 3.2 Hz, 3H, 1-CH_3), 1.62 (s, 3H, H_2C=C–C*H*$_3$), 1.84 (ddd, *J* = 14.9, 12.0, 1.0 Hz, 1H, 5-H), 1.95 (ddd, *J* = 13.5, 11.8, 2.8 Hz, 1H, 5-H), 2.25–2.34 (m, 1H, 4-H), 2.47–2.53 (m, 1H, 3-H), 2.62–2.68 (m, 1H, 3-H), 3.37 (d, *J* = 2.1 Hz, 1H, 6-H), 4.65 (s, 1H, *H*$_2$C=C–CH_3), 4.71 (s, *H*$_2$C=C–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 15.2 (1-CH_3), 20.5 (H_2C=C–*C*H_3), 28.4 (C-5), 34.8 (C-4), 41.7 (C-3), 58.5 (C-1), 61.1 (C-6), 110.4 (H_2*C*=C–CH_3), 146.1 (H_2C=*C*–CH_3), 205.1 (C-2).



1-108a **1-108b**

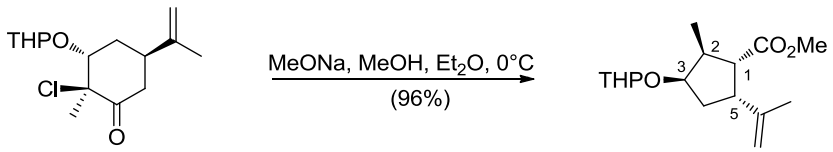
(2*S*,3*R*,5*R*)-2-Chloro-3-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexenone (1-108b).[178] TFA (70 mL, 0.41 mol) was added dropwise to a mixture of epoxide **1-108a** (50 g, 0.30 mol) and LiCl (130 g, 3.07 mol) in THF (900 mL) at 0 °C. The resulting mixture was stirred for 1 h at the same temperature before it was treated with saturated $NaHCO_3$ solution (900 mL) at 0 °C and stirred for additional 1 h at room temperature and extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with water (2 × 200 mL) and saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give ketone **1-108b** (69.1 g, 89%) as a colorless oil. R_f = 0.29 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –45.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.66 (s, 3H, 2-CH_3), 1.78 (s, 3H,

H_2C=C–CH_3), 1.82–1.91 (m, 1H, 5-H), 2.07 (br s, 1H, OH), 2.40–2.45 (m, 2H, 2 × 4-H), 2.76–2.85 (m, 1H, 6-H), 3.03 (dd, *J* = 13.9, 13.1 Hz, 1H, 6-H), 4.25 (dd, *J* = 3.5, 2.9 Hz, 1H, 3-H), 4.75–4.82 (m, 2H, H_2C=C–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 20.2 (H_2C=C–CH_3), 22.2 (2-CH_3), 32.8 (C-4), 39.1 (C-5), 41.2 (C-6), 68.2 (C-3), 77.1 (C-2), 110.8 (H_2C=C–CH_3), 146.6 (H_2C=C–CH_3), 204.7 (C-1).



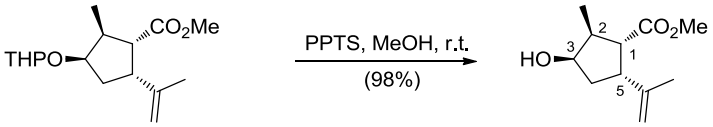
1-108b **1-109**

(2*S*,3*R*,5*R*)-2-Chloro-2-methyl-5-(prop-1-en-2-yl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)cyclohexenone (1-109).[178] PPTS (0.9 g, 3.6 mmol) was added to a stirred solution of alcohol **1-108b** (61.0 g, 0.34 mol) and dihydropyran (110 mL, 1.21 mol) in CH_2Cl_2 (400 mL). The mixture was stirred for 2 d at room temperature before it was treated with saturated $NaHCO_3$ solution (300 mL) and extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with water (200 mL) and saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 30:1 to 15:1) to give ketone **1-109** (89.0 g, 92%) as a colorless oil. R_f = 0.44 (petroleum ether/EtOAc, 9:1); NMR: mixture (1:1) of two diastereomers on acetal carbon.

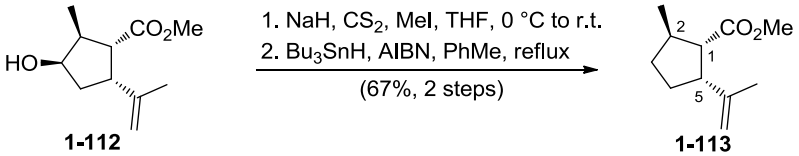


1-109 **1-111**

(1*R*,2*S*,3*R*,5*R*)-Methyl 2-methyl-5-(prop-1-en-2-yl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)cyclopentanecarboxylate (1-111).[178] A solution of MeONa in methanol (1M, 220 mL, 0.22 mol) was added dropwise to a solution of chloroketone **1-109** (40.0 g, 0.14 mol) in diethyl ether (400 mL) at 0 °C. The resulting mixture was stirred for 1 h at the same temperature before it was treated with saturated NH_4Cl solution (100 mL) and stirred for additional 1 h at room temperature. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (200 mL) and saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give carboxylate **1-111** (38.0 g, 96%) as a colorless oil. R_f = 0.36 (petroleum ether/EtOAc, 9:1); NMR: mixture (1:1) of two diastereomers on acetal carbon.



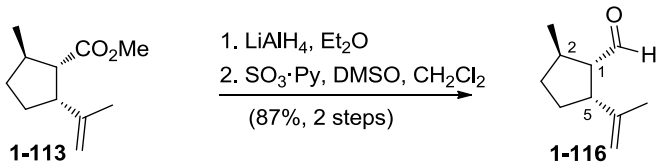
(1*R*,2*S*,3*R*,5*R*)-Methyl 3-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclopentanecarboxylate (1-112).[178] PPTS (0.9 g, 3.6 mmol) was added to a stirred solution of THP-protected alcohol **1-111** (38.0 g, 0.14 mol) in methanol (500 mL). The resulting mixture was stirred for 20 h at room temperature before it was concentrated in vacuo to ca. 100 mL, treated with saturated $NaHCO_3$ solution (300 mL), diluted with water (150 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1 to 2:1) to give carboxylate **1-112** (26.3 g, 98%) as a colorless oil. R_f = 0.08 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +5.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.08 (d, *J* = 7.2 Hz, 3H, 2-CH_3), 1.74 (s, 3H, CCH_3), 1.85 (ddd, *J* = 13.7, 7.1, 1.4 Hz, 1H, 4-H), 2.06 (ddd, *J* = 13.7, 10.9, 4.4 Hz, 1H, 4-H), 2.46–1.54 (m, 1H, 2-H), 2.84 (dd, *J* = 10.3, 8.9 Hz, 1H, 1-H), 3.29 (ddd, *J* = 10.3, 7.1, 6.4 Hz, 1H, 5-H), 3.63 (s, 3H, OCH_3), 4.28 (dd, *J* = 4.5, 4.6 Hz, 1H, 3-H), 4.75 (s, 1H, H_2C=C), 4.83 (br s, 1H, H_2C=C); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 13.5 (2-CH_3), 22.5 (CCH_3), 39.5 (C-4), 42.5 (C-5), 46.8 (C-2), 51.3 (C-1), 53.3 (OCH_3), 75.1 (C-3), 111.4 (H_2C=C), 145.2 (H_2C=*C*), 174.6 (ester).



(1*S*,2*R*,5*R*)-Methyl 2-methyl-5-(prop-1-en-2-yl)cyclopentanecarboxylate (1-113). NaH (60% dispersion in oil, 22.0 g, 550 mmol) was added to a stirred solution of alcohol **1-112** (11.2 g, 57.0 mmol) and imidazole (ca. 300 mg) in THF (200 mL) at 0 °C. The cooling bath was removed. After 15 min the reaction was recooled to 0 °C and CS_2 (38 mL, 612 mmol) was added dropwise. The mixture was allowed to warm to ambient temperature and after 1 h recooled to 0 °C before MeI (40 mL, 600 mmol) was added dropwise. After 3 h the reaction was quenched by careful addition of water (200 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in petroleum ether) to give the titled xanthate (16.2 g, 98%) as a yellow oil which was directly introduced to the next step. R_f = 0.43 (petroleum ether/EtOAc, 9:1).

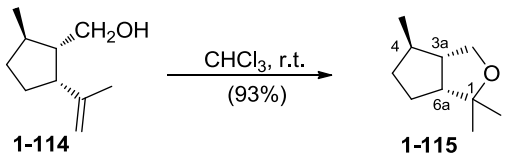
Tributylstannane (20.0 mL, 77.0 mmol) was added to a stirred solution of xanthate (16.2 g, 56.0 mmol) in dry toluene (200 mL) under N_2. The mixture was stirred for 5 min, and then AIBN (ca. 100 mg) was added. The resulting mixture was heated under reflux for 1 h and then the reaction was allowed to cool to ambient temperature, washed with water (3 × 100 mL) and saturated NaCl solution (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting colorless oil was distilled under reduced pressure (b.p. 90–95 °C, 25 mbar) to afford the title compound **1-113** (6.9 g, 67%, over 2 steps) as a

colorless oil. R_f = 0.60 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +19.8 (*c* 1.00, diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.02 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.16 (dddd, *J* = 12.5, 10.5, 8.7, 7.8 Hz, 1H, 3-H), 1.71 (s, 3H, CH_2=CC*H*$_3$), 1.71–1.77 (m, 1H, 4-H), 1.83 (dddd, *J* = 12.6, 10.2, 10.2, 7.6 Hz, 1H, 4-H), 2.02 (dddd, *J* = 12.5, 7.7, 7.7, 2.4 Hz, 1H, 3-H), 2.41 (dddq, *J* = 14.2, 14.2, 6.6, 6.6 Hz, 1H, 2-H), 2.56 (dd, *J* = 8.9, 6.1 Hz, 1H, 1-H), 2.76 (ddd, *J* = 9.4, 9.4, 6.7 Hz, 1H, 5-H), 3.55 (s, 3H, OCH_3), 4.67 (br s, 1H, C*H*$_2$=CCH_3), 4.72 (br s, 1H, C*H*$_2$=CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.2 (CH*C*H$_3$), 22.6 (CH_2=C*C*H$_3$), 29.7 (C-4), 33.7 (C-3), 36.9 (C-2), 49.7 (C-5), 51.0 (OCH_3), 55.6 (C-1), 110.7 (*C*H$_2$=CCH_3), 145.5 (CH_2=*C*CH_3), 175.1 (*C*O$_2$$CH_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{11}H_{18}O_2Na$ 205.11990, found 205.11972; The spectral data are identical to those previously reported.[179]



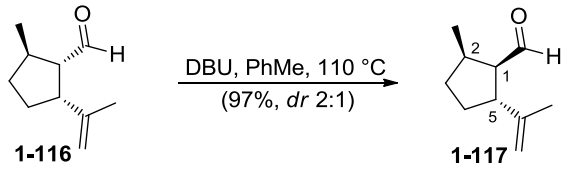
(1*S*,2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclopentanecarbaldehyde (1-116). A solution of ester **1-113** (25.1 g, 0.14 mol) in diethyl ether (200 mL) was added dropwise to the suspension of lithium aluminium hydride (6.3 g, 0.17 mol) in diethyl ether (300 mL) at 0 °C. The mixture was stirred at room temperature for 2 d and then was carefully treated with 15% aqueous NaOH soultion (70 mL) and water (200 mL). Stirring was continued for 15 min, before $MgSO_4$ was added, the mixture stirred for additional 15 min, and filtered to remove salts. Evaporation of the solvent yielded crude alcohol **1-114** (21.0 g), which was introduced to the next reaction without further purification. R_f = 0.25 (petroleum ether/EtOAc, 9:1).

To a stirred solution of the foregoing alcohol **1-114** (21.0 g, 0.14 mol) in CH_2Cl_2 (700 mL) were added at room temperature Et_3N (230 mL, 1.66 mol) and a solution of SO_3×Py (125 g, 0.78 mol) in DMSO (400 mL). The reaction mixture was stirred for 1 h before it was treated with water (300 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water (200 mL), 1 N HCl (2 × 200 mL), water (2 × 200 mL), saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled at low pressure (b.p. 100–105 °C, 25 mbar) to give aldehyde **1-116** as a colorless oil (18.0 g, 87%, over 2 steps). R_f = 0.65 (petroleum ether/EtOAc, 9:1); The spectral data are identical to those previously reported.[180]



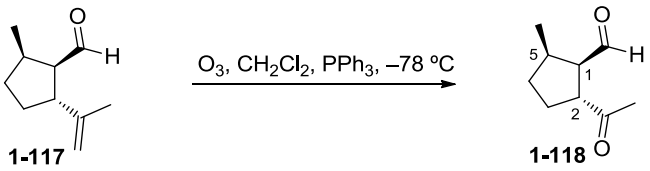
(3a*S*,4*R*,6a*R*)-1,1,4-Trimethylhexahydro-1*H*-cyclopenta[c]furan (1-115). A solution of an alcohol **1-114** (100 mg, 0.65 mmol) in chloroform (3 mL) was stirred overnight at room temperature. The solvent was removed in vacuo to afford tetrahydrofuran **1-115** (100 mg, quant.) as a colorless oil. R_f = 0.55 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz,

$CDCl_3$): δ[ppm] = 0.97 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.03–1.13 (m, 1H, 5-H), 1.11 (s, 3H, CCH_3), 1.19 (s, 3H, CCH_3), 1.38–1.48 (m, 1H, 4-H), 1.57–1.72 (m, 2H, 4-H, 6-H), 1.77 (dddd, *J* = 11.9, 6.1, 6.0, 3.0 Hz, 1H, 5-H), 2.18–2.33 (m, 2H, 3a-H, 6a-H), 3.49 (dd, *J* = 9.1, 3.0 Hz, 1H, 1-H), 3.86 (dd, *J* = 9.0, 7.4 Hz, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 20.0 (6-CH_3), 23.8 (3-CH_3), 27.1 (3-CH_3), 28.1 (C-4), 36.4 (C-5), 42.2 (C-6), 52.9 (C-3a), 53.8 (C-6a), 71.3 (C-1), 81.8 (C-3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{11}H_{18}O_2Na$ 205.11990, found 205.11972;



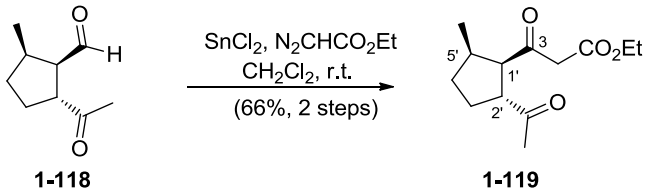
1-116 **1-117**

(1*R*,2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclopentanecarbaldehyde (1-117). DBU (0.2 mL) was added to a stirred solution of aldehyde **1-116** (17.0 g, 0.11 mol) in toluene (150 mL). The resulting mixture was stirred under reflux for 2 d. Then the solvent was carefully evaporated to afford a mixture of two stereoisomers **1-117/1-116** in a ratio of 2:1 (16.5 g, 97%) [as determined by ^{1}H NMR spectroscopy via integration of the aldehyde signals (**1-116**: 9.48 ppm, **1-117**: 9.72 ppm)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.98 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.13–1.34 (m, 2H), 1.43–1.54 (m, 1H), 1.84–2.02 (m, 1H), 1.63 (s, 3H, C*H*$_3$C=CH_2), 2.41–2.49 (m, 1H, 2-H), 2.62 (ddd, *J* = 8.7, 8.7, 3.4 Hz, 1H, 1-H), 2.98 (ddd, *J* = 8.5, 8.5, 8.5 Hz, 1H, 5-H), 4.64 (br s, 1H, CH_3C=C*H*$_2$), 4.65 (br s, 1H, CH_3C=C*H*$_2$), 9.72 (d, *J* = 3.8 Hz, 1H, CH=O).



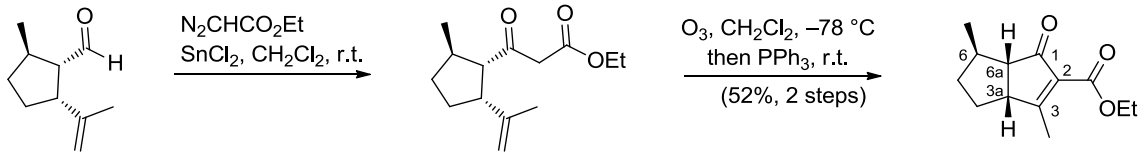
1-117 **1-118**

(1*R*,2*R*,5*R*)-2-Acetyl-5-methylcyclopentanecarbaldehyde (1-118). Ozone was bubbled through a solution of aldehyde **1-117** (4.0 g, 27 mmol) in CH_2Cl_2 (40 ml) at –78 °C until a deep blue color was observed. Nitrogen was applied until no blue color remained. After the addition of PPh_3 (10.5 g, 40 mmol) the reaction mixture was stirred overnight at room temperature. R_f ketoaldehyde **1-118** = 0.43 (petroleum ether/EtOAc, 4:1). This solution was used as such for the subsequent keto ester formation. An analytical sample was prepared after evaporation of the solvent followed by flash chromatography (petroleum ether/diethyl ether, 9:1). $[\alpha]^{20}_D$ = +25.5 (*c* 0.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.03 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.32 (ddd, *J* = 15.4, 12.5, 7.6 Hz, 1H, 4-H), 1.65 (ddd, *J* = 16.1, 12.8, 8.0 Hz, 1H, 3-H), 1.88 (dddd, *J* = 12.6, 7.8, 6.4, 5.0 Hz, 1H, 4-H), 2.10 (dddd, *J* = 9.9, 7.5, 5.0, 2.5 Hz, 1H, 3-H), 2.17 (s, 3H, CH_3C=O), 2.56 (app dddq, *J* = 14.5, 14.5, 7.4, 7.1 Hz, 1H, 5-H), 3.25 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1H, 1-H), 3.48 (ddd, *J* = 9.5, 7.6, 7.5 Hz, 1H, 2-H), 9.81 (d, *J* = 0.8 Hz, 1H, CH=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.4 (CH*C*H$_3$), 27.7 (C-3), 29.1 (*C*H$_3$C=O), 34.2 (C-4), 36.6 (C-5), 49.5 (C-2), 56.4 (C-1), 203.1 (CH=O), 209.0 (CH_3*C*=O); HRMS (ESI): $[M+Na+MeOH]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.11429, found 209.11450.



1-118 1-119

Ethyl 3-((1'*R*,2'*R*,5'*R*)-2'-acetyl-5'-methylcyclopentyl)-3-oxopropanoate (1-119). Anhydrous tin (II) chloride[181] (9.0 g, 47 mmol) was added, followed by dropwise addition of ethyl diazoacetate (8 mL, 73 mmol) to the foregoing solution of crude ketoaldehyde **1-118** in CH_2Cl_2 (40 mL) (the quenched ozonolysis solution). Stirring was continued for 2 h, and then the mixture was transferred to a separatory funnel, containing saturated NaCl (100 mL) and diethyl ether (200 mL). After separation of the layers, the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 4:1) to give β-keto ester **1-119** (2.5 g, 66%, over 2 steps) as a colorless oil. R_f = 0.30 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = –11.7 (*c* 1.02, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.83 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$), 1.24 (dd, *J* = 7.3, 7.3 Hz, 3H, OCH$_2$C*H*$_3$), 1.42–1.50 (m, 1H, 4'-H), 1.58–1.67 (m, 1H, 3'-H), 1.82–1.92 (m, 1H, 4'-H), 2.07–2.20 (m, 1H, 3'-H), 2.13 (s, 3H, CH_3C=O), 2.54 (app dddq, *J* = 13.7, 11.3, 7.0, 7.0 Hz, 1H, 5'-H), 3.40–3.48 (m, 2H, 1'-H, 2'-H), 3.47 (s, 2H, 2-H), 4.11–4.30 (m, 2H, OC*H*$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.0 (OCH$_2$*C*H$_3$), 16.4 (CH*C*H$_3$), 27.0 (C-3'), 29.3 (*C*H$_3$C=O), 33.8 (C-4'), 37.0 (C-5'), 49.8 (C-3), 51.2 (C-1'), 57.0 (C-2'), 61.3 (O*C*H$_2$CH$_3$), 166.8 (C-1), 203.3 (C-3), 209.2 (CH$_3$*C*=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{20}O_4Na$ 263.12538, found 263.12538.

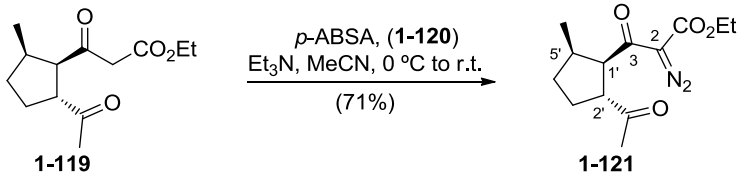


1-116 1-116a 1-122

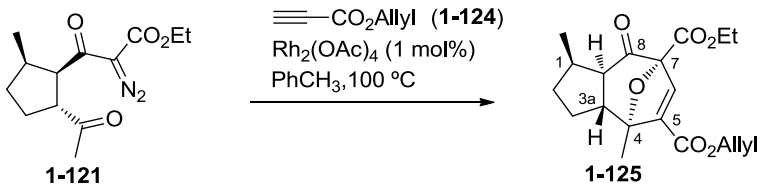
(3a*R*,6*R*,6a*S*)-Ethyl 3,6-dimethyl-1-oxo-1,3a,4,5,6,6a-hexahydropentalene-2-carboxylate (1-122). Anhydrous tin (II) chloride[181] (160 mg, 0.83 mmol) was added, followed by dropwise addition of ethyl diazoacetate (0.27 mL, 2.5 mmol) to the solution of aldehyde **1-116** (200 mg, 1.30 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 2 h, and then the mixture was transferred to a separatory funnel, containing saturated NaCl (100 mL) and diethyl ether (200 mL). After separation of the layers, the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The obtained β-keto ester **1-116a** (240 mg, 78%) was used in next step without further purification. R_f = 0.55 (petroleum ether/EtOAc, 4:1);

Ozone was bubbled through a solution of β-keto ester **1-116a** (240 mg, 1.01 mmol) in CH_2Cl_2 (15 ml) at –78 °C until a deep blue color was observed. Nitrogen was applied until no blue color remained. After the addition of PPh_3 (420 mg, 1.60 mmol) the reaction mixture was

stirred overnight at room temperature. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 9:1) to give β-keto ester **1-122** (173 mg, 52% over 2 steps). R_f = 0.53 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.05 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.29 (dd, *J* = 7.1, 7.1 Hz, 3H, CH_2CH_3), 1.30–1.36 (m, 1H, 5-H), 1.48–1.61 (m, 2H, 4-H; 5-H), 1.98–2.06 (m, 1H, 4-H), 2.13–2.19 (m, 1H, 6-H), 2.36 (dd, *J* = 6.3, 3.8 Hz, 1H, 6a-H), 3.16–3.21 (m, 1H, 3a-H), 4.24 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.1 (CH_2CH_3), 17.1 (3-CH_3), 20.0 ($CHCH_3$), 27.2 (C-4), 33.2 (C-5), 37.1 (C-6), 49.4 (C-3a), 58.3 (C-6a), 60.6 (CH_2CH_3), 131.3 (C-2), 163.3 (C-3), 185.7 (ester), 205.2 (C-1).

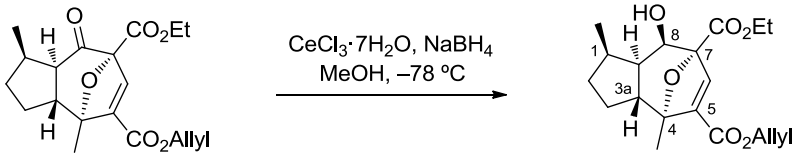


Ethyl 3-((1'*R*,2'*R*,5'*R*)-2'-acetyl-5'-methylcyclopentyl)-2-diazo-3-oxopropanoate (1-121). Triethylamine (3.9 mL, 28.0 mmol) was added dropwise at 0 °C to a solution of β-keto ester **1-119** (3.4 g, 14 mmol) and *p*-acetamidobenzenesulfonyl azide[182] (*p*-ABSA, **1-120**) (4.3 g, 18 mmol) in acetonitrile (60 mL). The mixture was stirred for 2 h and treated with saturated NH_4Cl solution (30 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give diazo compound **1-121** (2.7 g, 71%) as a yellow oil. R_f = 0.70 (petroleum ether/EtOAc, 2:1); $[\alpha]^{20}_D$ = –39.2 (*c* 1.76, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.80 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.30 (dd, *J* = 7.2, 7.2 Hz, 3H, OCH_2CH_3), 1.39 (dddd, *J* = 12.8, 7.6, 7.4, 5.8 Hz, 1H, 4'-H), 1.63 (dddd, *J* = 12.5, 8.9, 8.8, 8.2 Hz, 1H, 3'-H), 1.94 (dddd, *J* = 12.4, 8.6, 6.8, 5.0 Hz, 1H, 4'-H), 2.07–2.13 (m,1H, 3'-H), 2.12 (s, 3H, CH_3C=O), 2.61 (app dddq, *J* = 14.2, 14.2, 6.9, 6.8 Hz, 1H, 5'-H), 3.56 (ddd, *J* = 18.7, 9.4, 9.4 Hz, 1H, 2'-H), 4.07 (dd, *J* = 8.6 Hz, 1H, 1'-H), 4.23–4.31 (m, 2H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.2 (OCH_2CH_3), 16.8 ($CHCH_3$), 27.4 (C-3'), 29.1 (CH_3C=O), 34.0 (C-4'), 36.2 (C-5'), 52.6 (C-2'), 53.1 (C-1'), 61.4 (OCH_2CH_3), 160.9 (C-1), 192.9 (C-3), 209.2 (CH_3C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{18}O_4N_2Na$ 289.11588, found 289.11592.



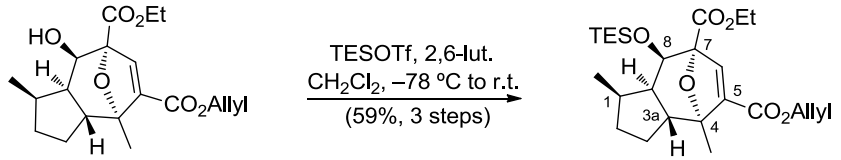
(1*R*,3a*R*,4*R*,7*R*,8a*R*)-5-Allyl 7-ethyl 1,4-dimethyl-8-oxo-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (1-125). $Rh_2(OAc)_4$ (30 mg, 1 mol%) was added to a mixture of diazo compound **1-121** (1.0 g, 3.8 mmol) and allyl propiolate[183] (**1-124**) (2 mL) in toluene (50 mL) at room temperature. Then the closed Schlenk tube was transferred to a preheated oil bath (100 ºC) and kept with stirring at this temperature for 15 min. The mixture

was allowed to cool to room temperature and filtered through a pad of Celite, using diethyl ether as a rinse. The filtrate was concentrated in vacuo to afford crude cycloadduct **1-125** (1.32 g) as a yellowish oil, which was used in the next step without further purification. R_f = 0.50 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = +74.4 (*c* 1.84, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.95 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.31 (dd, *J* = 7.1, 7.1Hz, 3H, OCH$_2$C*H*$_3$), 1.69 (s, 3H, OCCH$_3$), 3.28 (dd, *J* = 11.7, 6.4 Hz, 8a-H), 1.27–1.42 (m, 2H, OC*H*$_2$CH$_3$), 4.67 (dd, *J* = 5.8, 5.8 Hz, 2H, OC*H*$_2$CH=CH$_2$), 5.26 (dd, *J* = 10.4, 1.0 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.33 (dd, *J* = 17.0, 1.3 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.92 (dddd, *J* = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH$_2$C*H*=CH$_2$), 6.93 (s, 1H, 6-H); further protons could not be assigned. ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.1 (OCH$_2$*C*H$_3$), 17.7 (OC*C*H$_3$), 18.8 (CH*C*H$_3$), 27.0 (C-3), 29.0 (C-2), 29.8 (C-1), 47.1 (C-3a), 57.0 (C-8a), 62.5 (O*C*H$_2$CH$_3$), 65.6 (O*C*H$_2$CH=CH$_2$), 87.2 (C-4), 93.2 (C-7), 118.9 (OCH$_2$CH=*C*H$_2$), 131.4 (OCH$_2$*C*H=CH$_2$), 137.2 (C-6), 146.0 (C-5), 162.0 (CO_2Allyl), 164.3 (CO_2Et), 201.4 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{19}H_{24}O_6Na$ 371.14651, found 371.14627.



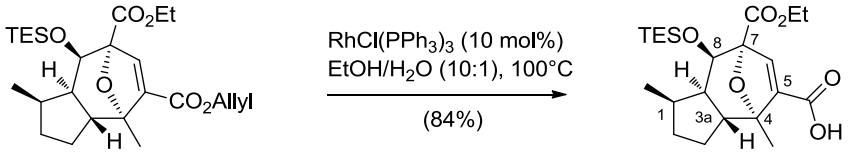
1-125 **1-126**

(1*R*,3a*R*,4*R*,7*R*,8*S*,8a*R*)-5-Allyl 7-ethyl 8-hydroxy-1,4-dimethyl-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (1-126). Cerium (III) chloride heptahydrate (3.5 g, 9.5 mmol) was added to the solution of crude ketone **1-125** (1.1 g, 3.2 mmol) in methanol (20 mL) and the mixture stirred for 30 min at room temperature, before it was cooled to –78 °C and sodium borohydride (240 mg, 6.4 mmol) was added in portions. Stirring was continued for 2 h at the same temperature. The reaction was quenched by slow addition of water, and most of methanol was removed in vacuo. Diethyl ether (100 mL) and water (100 mL) were added, the layers separated, and the aqueous layer was extracted with diethyl ether (4 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude alcohol **1-126** (1.1 g) as a yellowish oil, which was used in the next step without further purification. R_f = 0.20 (petroleum ether/EtOAc, 4:1); An analytical sample was obtained by flash chromatography (petroleum ether/EtOAc, 9:1). $[\alpha]^{20}_D$ = +17.0 (*c* 2.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.95 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 0.98–1.03 (m, 1H, 2-H), 1.23–1.34 (m, 1H, 3-H), 1.31 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.56 (s, 1H, OCC*H*$_3$), 1.72–1.78 (m, 1H, 3-H), 1.87 (ddd, *J* = 12.1, 12.1, 6.5 Hz, 1H, 3a-H), 1.94–2.02 (m, 2H, 2-H, OH), 2.17 (ddd, *J* = 12.5, 7.4, 4.6 Hz, 1H, 8a-H), 2.25 (app dddq, *J* = 7.4, 7.4, 2.9 Hz, 1H, 1-H), 4.28 (2 app dq, *J* = 14.2, 7.1, 2H, OC*H*$_2$CH$_3$), 4.51 (dd, *J* = 4.7, 4.7 Hz, 1H, 9-H), 4.66 (dd, *J* = 13.3, 5.7 Hz, 2H, OC*H*$_2$CH=CH$_2$), 5.24 (dd, *J* = 10.4, 1.0 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.33 (dd, *J* = 17.0, 1.3 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.93 (dddd, *J* = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH$_2$C*H*=CH$_2$), 7.02 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.2 (OCH$_2$*C*H$_3$), 19.1 (OC*C*H$_3$), 20.1 (CH*C*H$_3$), 25.8 (C-3), 31.1 (C-2), 32.5 (C-1), 35.7 (C-3a), 47.8 (C-8a), 61.9 (O*C*H$_2$CH$_3$), 65.3 (O*C*H$_2$CH=CH$_2$), 73.5 (C-8), 87.2 (C-4), 88.4 (C-7), 118.5 (OCH$_2$CH=*C*H$_2$), 131.7 (OCH$_2$*C*H=CH$_2$), 141.9 (C-6), 144.6 (C-5), 162.6 (CO_2Allyl), 170.2 (CO_2Et); HRMS (ESI): $[M+Na]^+$ calcd for $C_{19}H_{26}O_6Na$ 373.16216, found 373.16217.



1-126 **1-127**

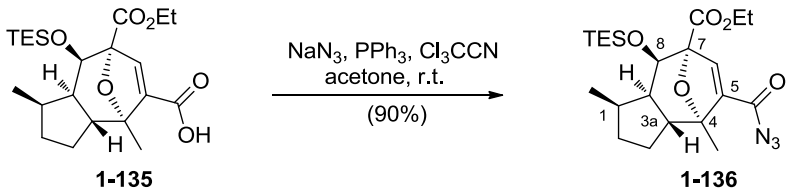
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-5-Allyl 7-ethyl 1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5,7-dicarboxylate (1-127). 2,6-Lutidine (0.2 mL, 1.7 mmol) was added dropwise to a solution of alcohol **1-126** (150 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) at –78 °C. Then TES-triflate (0.2 mL, 0.8 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature, filtered through a pad of silica gel, washed with 50% solution of ethyl acetate in petroleum ether, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give TES-ether **1-127** (118 mg, 59% over 3 steps) as a colorless oil. R_f = 0.53 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +28.2 (*c* 2.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.61 (ddd, *J* = 15.8, 7.6, 7.6 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.88 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 0.93 (dd, *J* = 7.9, 7.9 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.97–1.05 (m, 1H, 2-H), 1.24–1.33 (m, 1H, 3-H), 1.33 (dd, *J* = 7.4, 7.4 Hz, 3H, OCH$_2$C*H*$_3$), 1.54 (s, 3H, OCCH$_3$), 1.68–1.75 (m, 1H, 3-H), 1.87–1.96 (m, 2H, H-2, 3a-H), 2.07 (ddd, *J* = 12.5, 6.4, 4.3 Hz, 1H, 8a-H), 2.15–2.25 (m, 1H, 1-H), 4.28 (2 app dq, *J* = 10.9, 7.4 Hz, 2H, OC*H*$_2$CH$_3$), 4.60–4.75 (m, 3H, 8-H, OC*H*$_2$CH=CH$_2$), 5.24 (dd, *J* = 10.4, 0.8 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.33 (dd, *J* = 17.3, 1.3 Hz, 1H, OCH$_2$CH=C*H*$_2$), 5.93 (dddd, *J* = 16.8, 10.9, 5.8, 5.5 Hz, 1H, OCH$_2$C*H*=CH$_2$), 6.98 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.8 (Si(*C*H$_2$CH$_3$)$_3$), 6.8 (Si(CH$_2$*C*H$_3$)$_3$), 14.2 (OCH$_2$*C*H$_3$), 19.4 (OC*C*H$_3$), 19.6 (CH*C*H$_3$), 24.8 (C-3), 31.1 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.3 (C-8a), 61.9 (O*C*H$_2$CH$_3$), 65.0 (O*C*H$_2$CH=CH$_2$), 73.3 (C-8), 86.8 (C-4), 89.2 (C-7), 118.0 (OCH$_2$CH=*C*H$_2$), 132.0 (OCH$_2$*C*H=CH$_2$), 142.8 (C-6), 143.1 (C-5), 162.8 (CO_2Allyl), 170.1 (CO_2Et); HRMS (ESI): $[M+Na]^+$ calcd for $C_{25}H_{40}O_6SiNa$ 487.24864, found 487.24857.



1-127 **1-135**

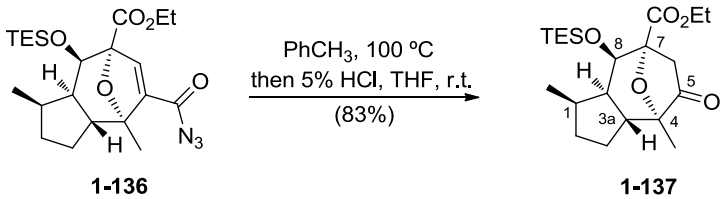
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-7-(Ethoxycarbonyl)-1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-5-carboxylic acid (1-135). $RhCl(PPh_3)_3$ (10 mg) was added to a solution of allyl ester **1-127** (42 mg, 0.09 mmol) in a mixture of water/ethanol (2 mL, 1:10). Then the closed flask was transferred to a preheated (100 °C) oil bath. The mixture was stirred for 1 h at this temperature, cooled, and then the solvents were removed in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether/AcOH (glac.), 4:1:0.01) to give carboxylic acid **1-135** (32 mg, 84%) as a colorless oil. R_f = 0.2 (petroleum ether/diethyl ether/AcOH (glac.), 4:1:0.01); $[\alpha]^{20}_D$ = +50.6 (*c* 3.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.62 (ddd, *J* = 15.9, 7.8, 7.8 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.90 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 0.94 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.99–1.07 (m, 1H, 2-H), 1.26–1.37 (m, 1H, 3-H), 1.33 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.55 (s, 3H, OCCH$_3$), 1.68–1.76 (m, 1H, 3-H), 1.88–1.96 (m, 2H, 3a-H, 2-H), 2.09 (ddd, *J* = 12.4, 6.4, 4.4 Hz, 1H, 8a-H), 2.17–2.26 (m, 1H, 1-H), 4.29 (2 app dq, *J* = 10.9, 7.4 Hz, 2H,

OC*H*$_2$CH$_3$), 4.67 (d, *J* = 4.3 Hz, 1H, 8-H), 7.14 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.8 (Si(*C*H$_2$CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 14.1 (OCH$_2$*C*H$_3$), 19.4 (OC*C*H$_3$), 19.6 (CH*C*H$_3$), 24.8 (C-3), 31.0 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.4 (C-8a), 61.9 (O*C*H$_2$CH$_3$), 73.4 (C-8), 86.7 (C-4), 89.2 (C-7), 142.8 (C-5), 145.7 (C-6), 168.2 (CO_2Et), 169.9 (CO_2H); HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{36}O_6SiNa$ 447.21734, found 447.21730.



1-135 **1-136**

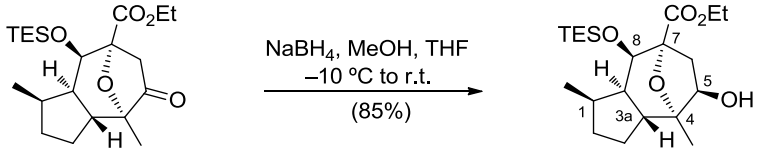
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-Ethyl 5-(azidocarbonyl)-1,4-dimethyl-8-((triethylsilyl)oxy)-1,2,3,3a,4,7,8,8a-octahydro-4,7-epoxyazulene-7-carboxylate (1-136). Trichloroacetonitrile (0.03 mL, 0.33 mmol) was added dropwise to a stirred solution of carboxylic acid **1-135** (70 mg, 0.16 mmol), sodium azide (16 mg, 0.25 mmol), PPh_3 (86 mg, 0.33 mmol) in acetone (2 mL) at room temperature. After 30 min the solvent was removed by a flow of nitrogen and the residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give azide **1-136** (66 mg, 90%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +40.1 (*c* 1.63, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.61 (ddd, *J* = 15.9, 7.8, 7.8 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.88 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 0.94 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.97–1.05 (m, 1H, 2-H), 1.25–1.37 (m, 1H, 3-H), 1.32 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.54 (s, 3H, OCCH$_3$), 1.68–1.76 (m, 1H, 3-H), 1.81–1.95 (m, 2H, 3a-H, 2-H), 2.06 (ddd, *J* = 12.4, 6.4, 4.4 Hz, 1H, 8a-H), 2.15–2.25 (m, 1H, 1-H), 4.28 (2 app dq, *J* = 10.9, 7.4 Hz, 2H, OC*H*$_2$CH$_3$), 4.66 (d, *J* = 4.3 Hz, 1H, 8-H), 7.06 (s, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ[ppm] = 4.8 (Si(*C*H$_2$CH$_3$)$_3$), 6.8 (Si(CH$_2$*C*H$_3$)$_3$), 14.1 (OCH$_2$*C*H$_3$), 19.2 (OC*C*H$_3$), 19.5 (CH*C*H$_3$), 24.7 (C-3), 31.0 (C-2), 32.9 (C-1), 35.2 (C-3a), 48.3 (C-8a), 62.0 (O*C*H$_2$CH$_3$), 73.4 (C-8), 86.9 (C-4), 89.2 (C-7), 144.4 (C-5), 145.8 (C-6), 168.4 (CO_2Et), 169.7 (CON_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{35}N_3O_5SiNa$ 472.22382, found 472.22384.



1-136 **1-137**

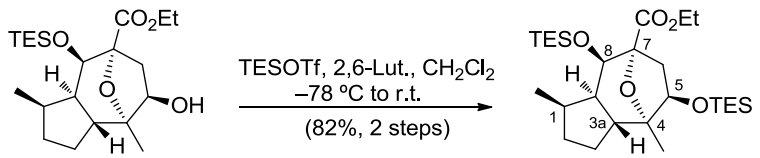
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-Ethyl 1,4-dimethyl-5-oxo-8-((triethylsilyl)oxy)decahydro-4,7-epoxyazulene-7-carboxylate (1-137). Azide **1-136** (66 mg, 0.15 mmol) was dissolved in toluene (2 mL) and stirred for 1 h at 100 °C. Then the solvent was removed in vacuo, the residue was dissolved in THF (2 mL) followed by the addition of 5% HCl (0.5 mL) and THF (0.5 mL). Stirring was continued for 15 min, then the reaction was quenched with triethylamine (0.5 mL) and the solvents were evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give ketone **1-137** (48 mg, 83%) as a colorless oil. R_f = 0.53 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +0.5 (*c* 0.98, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.60 (dddd, *J* = 16.8, 9.9, 8.4, 1.8 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$),

0.92 (d, *J* = 9.4 Hz, 3H, CHC*H*$_3$), 0.93 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.13–1.21 (m, 1H, 2-H), 1.26 (s, 3H, OCCH$_3$), 1.32 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.40 (ddd, *J* = 10.9, 7.2, 1.3 Hz, 1H, 3-H), 1.60–1.68 (m, 1H, 3-H), 1.85 (ddd, *J* = 13.2, 10.7, 7.4 Hz, 1H, 3a-H), 1.92–2.02 (m, 2H, 2-H, 8a-H), 2.22–2.31 (m, 1H, 1-H), 2.60 (d, *J* = 18.1 Hz, 1H, 6-H), 3.10 (d, *J* = 18.1 Hz, 1H, 6-H), 4.28 (2 app dq, *J* = 10.8, 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4,73 (d, *J* = 4.1 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ[ppm] = 4.8 (Si(*C*H$_2$CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 14.1 (OCH$_2$*C*H$_3$), 16.5 (OC*C*H$_3$), 19.2 (CH*C*H$_3$), 24.0 (C-3), 32.4 (C-1), 32.6 (C-2), 36.4 (C-3a), 38.8 (C-6), 45.2 (C-8a), 62.0 (O*C*H$_2$CH$_3$), 71.2 (C-8), 83.0 (C-4), 84.2 (C-7), 171.4 (CO$_2$Et), 214.6 (C=O); HRMS (ESI): [M+Na]$^+$ calcd for C$_{21}$H$_{36}$O$_5$SiNa 419.22242, found 419.22238.



1-137 **1-138**

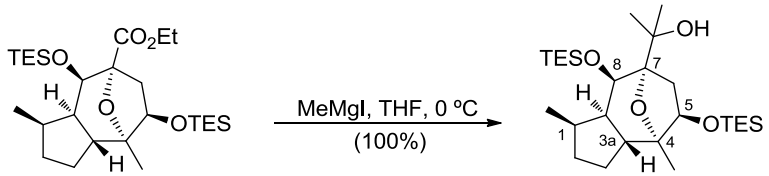
(1*R*,3a*R*,4*R*,5*R*,7*R*,8*R*,8a*R*)-Ethyl 5-hydroxy-1,4-dimethyl-8-((triethylsilyl)oxy)decahydro-4,7-epoxyazulene-7-carboxylate (1-138). Sodium borohydride (21 mg, 0.55 mmol) was added in portions to a stirred solution of ketone **1-137** (150 mg, 0.38 mmol) in methanol/THF (6.6 mL, 1:10) at –10 °C. The mixture was allowed to warm to room temperature, and then carefully treated with water (5 mL). Most of the organic solvents were evaporated in vacuo, the residue was diluted with water (10 mL), and the mixture extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give alcohol **1-138** (150 mg, 85%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 4:1); [α]$^{20}_D$ = +5.8 (*c* 2.46, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, DMSO): δ[ppm] = 0.48–0.55 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.88 (dd, *J* = 8.1, 8.1 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.96 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.09 (s, 3H, OCCH$_3$), 1.10–1.35 (m, 2H, 2-H, 3-H), 1.21 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.47 (dddd, *J* = 12.4, 8.3, 8.3, 4.3 Hz, 1H, 3-H), 1.71 (ddd, *J* = 13.8, 6.2, 6.1, 1H, 8a-H), 1.87–1.96 (m, 1H, 2-H), 2.14 (dd, *J* = 13.3, 8.0 Hz, 1H, 6-H), 2.19–2.35 (m, 3H, 1-H, 3a-H, 6-H), 3.60 (ddd, *J* = 8.6, 8.6, 4.3 Hz, 1H, 5-H), 4.10 (2 app dq, *J* = 10.9, 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.63 (d, *J* = 6.1 Hz, 1H, 8-H), 5.20 (d, *J* = 4.3 Hz, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$): δ[ppm] = 4.3 (Si*C*H$_2$CH$_3$), 6.7 (SiCH$_2$*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$), 18.8 (CH*C*H$_3$), 19.9 (OC*C*H$_3$), 23.8 (C-3), 32.0 (C-1), 32.7 (C-3a), 32.8 (C-6), 33.6 (C-2), 44.2 (C-8a), 61.0 (O*C*H$_2$CH$_3$), 70.8 (C-8), 76.8 (C-5), 82.5 (C-4), 83.3 (C-7), 171.8 (CO$_2$Et); HRMS (ESI): [M+Na]$^+$ calcd for C$_{21}$H$_{38}$O$_5$SiNa 421.23807, found 421.23845.



1-138 **1-139**

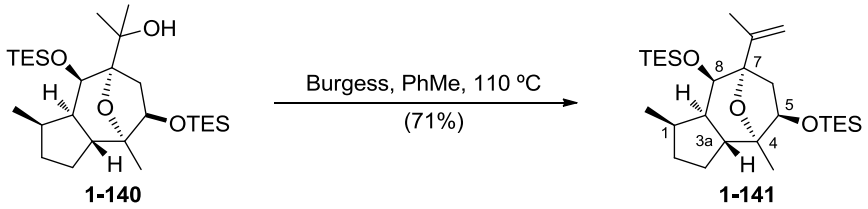
(1*R*,3a*R*,4*R*,5*R*,7*R*,8*R*,8a*R*)-Ethyl 1,4-dimethyl-5,8-bis((triethylsilyl)oxy)decahydro-4,7-epoxyazulene-7-carboxylate (1-139). 2,6-Lutidine (0.13 mL, 1.15 mmol) was added

dropwise to a solution of alcohol **1-138** (150 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) at –78 °C. Then TES-triflate (0.13 mL, 0.58 mmol) was added at the same temperature. The mixture was allowed to warm to room temperature (ca 3 h), filtered through a pad of silica gel, the filter cake was washed with mixture of petroleum ether/EtOAc (1:1), and the filtrates concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to afford TES-ether **1-139** (159 mg, 82% over 2 steps). R_f = 0.55 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +2.0 (*c* 6.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.51–0.61 (m, 12H, $(Si(CH_2CH_3)_3)_2$), 0.92 (dd, *J* = 7.9, 7.9 Hz, 9H, $(Si(CH_2CH_3)_3)$), 0.95 (dd, *J* = 8.1, 8.1 Hz, 9H, $(Si(CH_2CH_3)_3)$), 1.00 (d, *J* = 7.1 Hz, 3H, $CHCH_3$), 1.18–1.26 (m, 1H, 2-H), 1.20 (s, 3H, $OCCH_3$), 1.30 (dd, *J* = 7.1, 7.1 Hz, 3H, OCH_2CH_3), 1.30–1.39 (m, 1H, 3-H), 1.53 (dddd, *J* = 16.9, 8.8, 8.5, 4.7 Hz, 1H, 3-H), 1.81 (ddd, *J* = 14.0, 6.1, 6.1 Hz, 1H, 8a-H), 1.87–1.96 (m, 1H, 2-H), 2.22–2.51 (m, 4H, 1-H, 3a-H, 6-H, 6-H), 3.77 (dd, *J* = 9.3, 7.5 Hz, 1H, 5-H), 4.21 (2 app dq, *J* = 10.8, 7.1 Hz, 2H, OCH_2CH_3), 4.66 (d, *J* = 5.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.8 ($SiCH_2CH_3$), 4.9 ($SiCH_2CH_3$), 6.7 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 14.1 (OCH_2CH_3), 18.7 ($CHCH_3$), 20.2 ($OCCH_3$), 24.2 (C-3), 32.7 (C-1), 33.2 (C-3a), 34.1 (C-6), 44.6 (C-2), 61.5 (OCH_2CH_3), 71.6 (C-8), 78.1 (C-5), 83.2 (C-4), 84.4 (C-7), 172.7 (CO_2Et); HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{52}O_5Si_2Na$ 535.32455, found 535.325022.



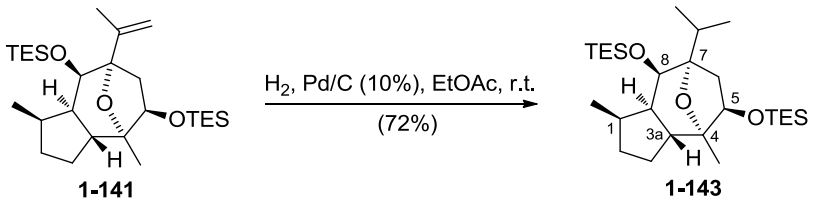
1-139 **1-140**

2-((1*R*,3a*R*,4*R*,5*R*,7*R*,8*R*,8a*R*)-1,4-Dimethyl-5,8-bis((triethylsilyl)oxy)decahydro-4,7-epoxyazulen-7-yl)propan-2-ol (1-140). Freshly prepared methylmagnesium iodide (0.12 mL, 1M solution in diethyl ether, 0.12 mmol) was added dropwise to a stirred solution of ester **1-139** (10 mg, 0.019 mmol) in THF (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and treated with saturated NH_4Cl (0.5 mL), diluted with water (2 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give tertiary alcohol **1-140** (9.7 mg, 100%) as a colorless oil. R_f = 0.48 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +3.4 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.57 (ddd, *J* = 16.7, 8.6, 1.3 Hz, 6H, $Si(CH_2CH_3)_3$), 0.65 (ddd, *J* = 15.9, 7.9, 2.3 Hz, 6H, $Si(CH_2CH_3)_3$), 0.94 (dd, *J* = 7.8, 7.8 Hz, 9H, $Si(CH_2CH_3)_3$), 0.96 (dd, *J* = 8.1, 8.1 Hz, 9H, $Si(CH_2CH_3)_3$), 1.00 (d, *J* = 7.1 Hz, 3H, $CHCH_3$), 1.14 (s, 3H, $OCCH_3$), 1.16 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.22–1.28 (m, 1H, 2-H), 1.35 (dddd, *J* = 12.2, 10.3, 10.3, 6.2 Hz, 1H, 3-H), 1.49–1.58 (m, 1H, 3-H), 1.69 (ddd, *J* = 13.6, 6.4, 4.7 Hz, 1H, 8a-H), 1.88 (dddd, *J* = 12.1, 10.5, 7.1, 4.9 Hz, 1H, 2-H), 1.98 (dd, *J* = 13.0, 9.7 Hz, 1H, 6-H), 2.15–2.24 (m, 2H, 1-H, 6-H), 2.55 (ddd, *J* = 13.6, 10.0, 9.0 Hz, 1H, 3a-H), 3.66 (dd, *J* = 9.6, 6.6 Hz, 1H, 5-H), 4.45 (d, *J* = 4.6 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 4.9 ($SiCH_2CH_3$), 5.9 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 7.2 ($SiCH_2CH_3$), 18.6 ($CHCH_3$), 21.2 ($OCCH_3$), 24.0 (C-3), 24.8 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$), 32.6 (C-1), 32.7 (C-6), 33.1 (C-3a), 34.9 (C-2), 45.9 (C-8a), 71.0 (C-8), 73.3 ($C(CH_3)_2$), 79.6 (C-5), 81.4 (C-4), 89.1 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{54}O_4Si_2Na$ 521.34528, found 521.345436.



1-140 **1-141**

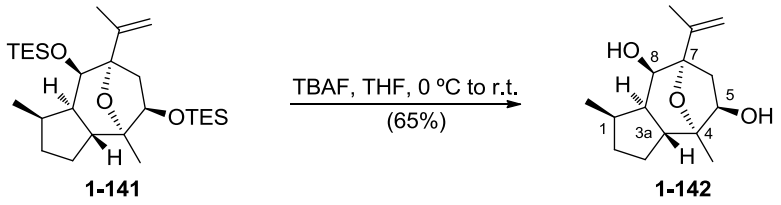
(((1*R*,3a*R*,4*R*,5*R*,7*S*,8*R*,8a*R*)-1,4-Dimethyl-7-(prop-1-en-2-yl)decahydro-4,7-epoxyazulene-5,8-diyl)bis(oxy))bis(triethylsilane) (1-141). Burgess reagent (10 mg, 0.040 mmol) was added to a stirred solution of alcohol **1-140** (5 mg, 0.010 mmol) in toluene (1 mL) and the mixture stirred at 110 °C for 5 min. Then the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 30:1) to afford the tittled alkene **1-141** (3.4 mg, 71%) as a colorless oil. R_f = 0.31 (petroleum ether/EtOAc, 33:1); $[\alpha]^{20}_D$ = +4.8 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.50–0.60 (m, 12H, $(Si(CH_2CH_3)_3)_2$), 0.92 (dd, *J* = 7.8, 7.8 Hz, 9H, $Si(CH_2CH_3)_3$), 0.95 (dd, *J* = 8.1, 8.1 Hz, 9H, $Si(CH_2CH_3)_3$), 1.00 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.16 (s, 3H, $OCCH_3$), 1.21–1.27 (m, 1H, 2-H), 1.30–1.39 (m, 1H, 3-H), 1.49–1.58 (m, 1H, 3-H), 1.73 (ddd, *J* = 14.0, 5.9, 5.8 Hz, 1H, 8a-H), 1.77 (s, 3H, $CH_2=CCH_3$), 1.84–1.93 (m, 1H, 2-H), 2.04 (dd, *J* = 13.0, 9.2 Hz, 1H, 6-H), 2.19–2.24 (m, 1H, 1-H), 2.29 (dd, *J* = 13.1, 7.3 Hz, 1H, 6-H), 2.49 (ddd, *J* = 14.0, 10.1, 8.7 Hz, 1H, 3a-H), 3.68 (dd, *J* = 9.3, 7.3 Hz, 1H, 5-H), 4.25 (d, *J* = 6.1 Hz, 1H, 8-H), 4.88 (dd, *J* = 1.4, 1.4 Hz, 1H, $C=CH_2$), 4.91 (br.s, 1H, $C=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 5.0 ($SiCH_2CH_3$), 5.4 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 7.0 ($SiCH_2CH_3$), 18.4 ($CH_3C=CH_2$), 18.6 ($CHCH_3$), 20.7 ($OCCH_3$), 23.9 (C-3), 32.8 (C-3a), 32.9 (C-1), 34.0 (C-2), 35.0 (C-6), 45.7 (C-8a), 72.4 (C-8), 78.7 (C-5), 80.9 (C-4), 85.9 (C-7), 112.1 ($CH_3C=CH_2$), 147.0 ($CH_3C=CH_2$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{52}O_3Si_2Na$ 503.33472, found 503.33510.



1-141 **1-143**

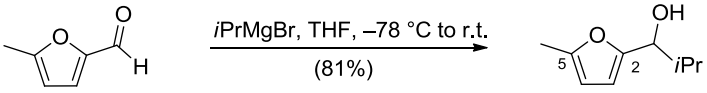
(((1*R*,3a*R*,4*R*,5*R*,7*S*,8*R*,8a*R*)-1,4-Dimethyl-7-(prop-2-yl)decahydro-4,7-epoxyazulene-5,8-diyl)bis(oxy))bis(triethylsilane) (1-143). A 5 mL round-bottom flask was charged with alkene **1-141** (3.40 mg, 0.007 mmol) and a stirring bar. Ethyl acetate (1 mL) and Pd/C 10% (4.00 mg) were added with stirring. The reaction was placed under H_2 atmosphere and stirred for 2 h at room temperature. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 100:1) to afford the title compound **1-143** (2.5 mg, 72%) as a colorless oil. R_f = 0.60 (petroleum ether/ EtOAc, 60:1); $[\alpha]^{20}_D$ = +2.7 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.52–0.64 (m, 12H, $(Si(CH_2CH_3)_3)_2$), 0.92–1.01 (m, 27H, $(Si(CH_2CH_3)_3)_2$, $(CHCH_3)_3$, 1.12 (s, 3H, $OCCH_3$), 1.17–1.35 (m, 2H, 2-H, 3-H), 1.47–1.52 (m, 1H, 3-H), 1.60–1.74 (m, 3H, 8a-H, 6-H $CH(CH_3)_2$), 1.85–1.94 (m, 1H, 2-H), 2.17–2.24 (m, 2H, 6-H, 1-H), 2.40 (ddd, *J* = 13.8, 10.4, 8.6 Hz, 1H, 3a-H), 3.52 (dd, *J* = 8.6, 8.6 Hz, 1H, 5-H), 4.36 (d, *J* = 6.1 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 5.0 ($SiCH_2CH_3$), 5.3 ($SiCH_2CH_3$), 6.8 ($SiCH_2CH_3$), 7.0 ($SiCH_2CH_3$), 16.6 ($CH(CH_3)_2$), 16.8 ($CH(CH_3)_2$), 18.9

(CH*C*H$_3$), 20.4 (OC*C*H$_3$), 24.0 (*C*H(CH$_3$)$_2$), 31.6 (C-3), 32.6 (C-3a), 33.6 (C-1), 34.1 (C-2), 34.7 (C-6), 46.0 (C-8a), 71.3 (C-8), 78.9 (C-5), 80.6 (C-4), 85.4 (C-7); HRMS (ESI): [M+Na]$^+$ calcd for $C_{27}H_{54}O_3SiNa$ 505.35037, found 505.35007.



1-141 **1-142**

(1*R*,3a*R*,4*R*,5*R*,7*S*,8*R*,8a*R*)-1,4-Dimethyl-7-(prop-1-en-2-yl)decahydro-4,7-epoxyazulene-5,8-diol (1-142). TBAF × 3H$_2$O (38.5 mg, 0.120 mmol) was added in one portion to a stirred solution of silyl ether **1-141** (6.9 mg, 0.012 mmol) in anhydrous THF (1 mL) at 0 °C. Then the cooling bath was removed and the mixture stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give alcohol **1-142** (2.0 mg, 65%) as white crystals. R_f = 0.32 (petroleum ether/EtOAc, 2:1); $[\alpha]^{20}_D$ = +2.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.08 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$), 1.19–1.27 (m, 1H, 2-H), 1.27 (s, 3H, OCCH$_3$), 1.36 (dddd, *J* = 11.6, 11.6, 9.2, 9.1 Hz, 1H, 3-H), 1.58–1.65 (m, 1H, 3-H), 1.75 (dd, *J* = 1.4, 0.9 Hz, 3H, C*H*$_3$C=CH$_2$), 1.86 (ddd, *J* = 13.6, 8.0, 4.2 Hz, 1H, 8a-H), 1.97 (dd, *J* = 13.4, 9.6 Hz, 1H, 6-H), 2.07–2.15 (m, 1H, 2-H), 2.24–2.37 (m, 3H, 1-H, 3a-H, 6-H), 3.91 (dd, *J* = 9.6, 4.8 Hz, 1H, 5-H), 4.17 (d, *J* = 4.3 Hz, 1H, 8-H), 4.70 (ddd, *J* = 3.2, 1.5, 1.4 Hz, 1H, CH$_3$C=C*H*$_2$), 4.93 (dd, *J* = 1.9, 0.9 Hz, 1H, CH$_3$C=C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 18.5 (*C*H$_3$C=CH$_2$), 20.4 (CH*C*H$_3$), 21.5 (OC*C*H$_3$), 26.0 (C-3), 31.4 (C-3a), 33.8 (C-1), 34.4 (C-2), 38.4 (C-6), 44.8 (C-8a), 73.8 (C-8), 78.9 (C-5), 81.7 (C-4), 86.0 (C-7), 107.9 (CH$_3$C=*C*H$_2$), 148.4 (CH$_3$*C*=CH$_2$); HRMS (ESI): [M+Na]$^+$ calcd for $C_{15}H_{24}O_3Na$ 275.16177, found 275.16169.



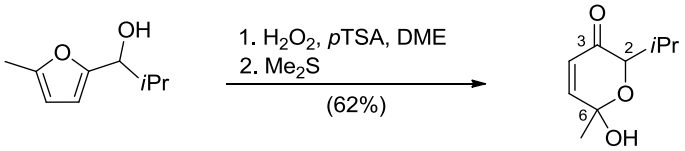
1-147 **1-148**

2-Methyl-1-(5-methylfuran-2-yl)propan-1-ol (1-148). *Preparation of isopropylmagnesium bromide.* A solution of isopropyl bromide (35.7 mL, 0.38 mol) in THF (200 mL) was added dropwise to a stirred mixture of Mg (9.7 g, 0.40 mmol) in THF (40 mL) maintaining a temperature 45 °C. The resulting mixture was stirred for 1 h at the same temperature. The concentration was found to be 1.7M in THF by titration of a THF solution of menthol in presence of 1,10-phenantroline.

General procedure for the titration of Grignard reagents. A Grignard reagent solution was added dropwise to a stirred solution of menthol (312 mg, 2.00 mmol) and 1,10-phenantroline (4 mg, 0.02 mmol) in THF (15 mL) at room temperature until a distinct violet color persisted for longer than one minute. C[RMgX] in M = mmol of menthol/volume of RMgX in mL.[184]

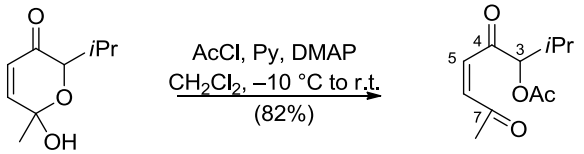
Grignard reaction. Isopropylmagnesium bromide (200 mL, 0.35 mol) was added dropwise to a stirred solution of 5-methylfurfural (**1-147**) (15.0 g, 0.14 mol) in THF (200 mL) at –78 °C.

The resulting mixture was allowed to warm to room temperature, then again cooled to –78 °C and treated with saturated NH_4Cl solution (50 mL), diluted with water (200 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give alcohol **1-148** (17.0 g, 81%) as a colorless oil. R_f = 0.60 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.82 (d, *J* = 6.9 Hz, 3H, *i*Pr), 0.99 (d, *J* = 6.6 Hz, 3H, *i*Pr), 2.02–2.10 (m, 2H, OH, *i*Pr), 2.24 (s, 3H, CCH_3), 4.24 (dd, *J* = 6.9, 1.8 Hz, 1H, C*H*OH), 5.85–5.87 (m, 1H, 3-H), 6.05 (d, *J* = 3.0 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 13.4 (5-CH_3), 18.3 (*i*Pr), 18.8 (*i*Pr), 33.1 (*i*Pr), 73.5 (CHOH), 105.8 (C-4), 107.2 (C-3), 151.2 (C-5), 154.3 (C-2); HRMS (ESI): $[M+Na]^+$ calcd for $C_9H_{14}O_2Na$ 177.08860, found 177.088595.



1-148 **1-149**

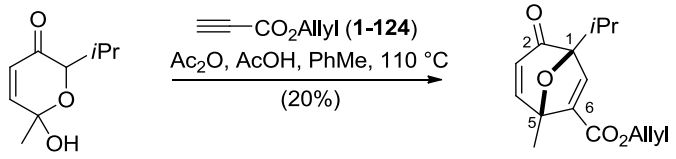
6-Hydroxy-2-isopropyl-6-methyl-2*H*-pyran-3(6*H*)-one (1-149).[70] An aqueous solution of H_2O_2 (30%, 5 mL, 38 mmol) was added dropwise to a stirred solution of alcohol **1-148** (3.0 g, 19 mmol) and *p*TSA (1.4 g, 7.6 mmol) in dimethoxyethane (190 mL) at room temperature. The resulting mixture was stirred overnight before it was treated with Me_2S (5.5 mL, 76 mmol), stirred for additional 1 h, diluted with diethyl ether (100 mL), washed with saturated NaCl solution (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give hydroxypyranone **1-149** (2.0 g, 62%) as a colorless oil. R_f = 0.25 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$):[185] δ[ppm] = 0.84 (d, *J* = 6.9, 3H, *i*Pr), 1.02 (d, *J* = 7.1 Hz, 3H, *i*Pr), 1.62 (s, 3H, CCH_3), 2.38–2.44 (m, 1H, *i*Pr), 2.61 (s, 1H, OH), 4.34 (d, *J* = 2.8 Hz, 1H, 2-H), 6.00 (d, *J* = 10.2 Hz, 1H, 4-H), 6.80 (d, *J* = 10.2 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.0 (*i*Pr), 19.0 (*i*Pr), 28.6 (*i*Pr), 28.8 (6-CH_3), 78.3 (C-2), 92.6 (C-6), 127.1 (C-4), 147.8 (C-5), 196.9 (C-6); HRMS (ESI): $[M+Na]^+$ calcd for $C_9H_{14}O_3Na$ 193.08352, found 193.083436.



1-149 **1-150**

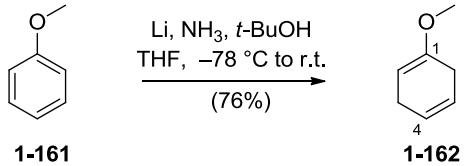
(*Z*)-2-Methyl-4,7-dioxooct-5-en-3-yl acetate (1-150). Acetyl chloride (0.28 mL, 3.9 mmol) was added dropwise to a stirred solution of hydroxypyranone **1-149** (330 mg, 2.0 mmol), DMAP (50 mg, 0.4 mmol) and pyridine (0.5 mL) in CH_2Cl_2 (2.5 mL) at –10 °C. The resulting mixture was allowed to warm to room temperature and stirred for 2 h before it was treated with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1M HCl solution (2 × 30 mL), saturated NaCl solution (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash

chromatography (petroleum ether/EtOAc, 9:1) to give acetate **1-150** (350 mg, 82%) as a colorless oil. R_f = 0.27 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.89 (d, *J* = 6.8, 3H, *i*Pr), 0.97 (d, *J* = 6.8 Hz, 3H, *i*Pr), 2.11 (s, 3H, acetate), 2.18–2.23 (m, 1H, *i*Pr) 2.32 (s, 3H, 7-CH_3), 4.96 (d, *J* = 5.0 Hz, 1H, 3-H), 6.94 (br s, 2H, 5-H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.9 (*i*Pr), 18.9 (*i*Pr), 20.4 (CH_3COO), 28.8 (*i*Pr), 29.4 (C-8), 82.1 (C-3), 132.7 (C-5), 137.6 (C-6), 170.6 (CH_3*C*OO), 196.4 (C-4), 197.5 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{11}H_{16}O_4Na$ 235.23211, found 235.23203.



1-149 1-155

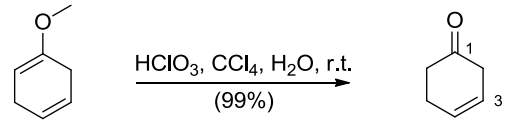
(1*S*,5*S*)-Allyl 1-isopropyl-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (1-155). Allyl propiolate (**1-124**) (320 mg, 2.9 mmol), acetic anhydride (0.22 mL, 2.36 mmol), hydroxypyranone **1-149** (100 mg, 0.59 mmol) and one drop of glacial acid were dissolved in toluene (5 mL). The mixture was stirred for 10 h at 110 °C in a closed Schlenk tube before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give enone **1-155** (30 mg, 20%) as a colorless oil. R_f = 0.78 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.96 (d, *J* = 6.9, 3H, *i*Pr), 0.97 (d, *J* = 7.1 Hz, 3H, *i*Pr), 1.71 (s, 3H, 5-CH_3), 2.50 (ddd, *J* = 13.7, 6.9, 6.9 Hz, 1H, *i*Pr), 4.61–4.71 (m, 2H, C*H*$_2$CH=CH$_2$), 5.25–5.35 (m, 2H, CH$_2$CH=C*H*$_2$), 5.49 (d, *J* = 9.9 Hz, 1H, 3-H), 5.88–5.97 (m, 1H, CH$_2$C*H*=CH$_2$), 6.93 (s, 1H, 7-H), 7.25 (d, *J* = 9.7 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.4 (C-5), 16.9 (*i*Pr), 20.2 (*i*Pr), 28.5 (*i*Pr), 65.6 (*C*H$_2$CH=CH$_2$), 84.7 (C-1), 97.6 (C-5), 118.9 (CH$_2$CH=*C*H$_2$), 122.9 (C-3), 131.6 (CH$_2$*C*H=*C*H$_2$), 144.0 (C-7), 147.8 (C-6), 154.5 (C-4), 162.5 (ester), 194.3 (C-2); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{18}O_4Na$ 285.29079, found 285.29081.



1-161 1-162

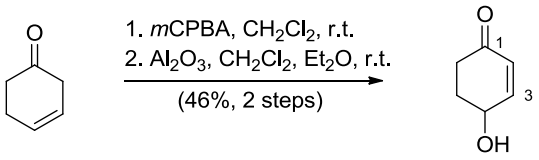
1-Methoxycyclohexa-1,4-diene (1-162).[73] A 1-liter, three-necked flask, equipped with an inlet tube and mechanic stirrer was charged with anisol (**1-161**) (15.0 g, 0.17 mol), THF (45 mL), *tert*-butanol (75 mL) and liquid ammonia (ca. 500 mL). The resulting mixture was carefully treated with lithium (5.0 g, 0.71 mol) in small portions at –78 °C. When the addition was complete, the mixture was allowed to warm to room temperature and stirred overnight before it was carefully treated with methanol (45 mL) and water (250 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL) saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo (40 °C, 800 mbar). The residue was distilled at low pressure (b.p. 45–50 °C, 26 mbar) to give diene **1-162** as a colorless oil (11.6 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 2.47–2.56 (m, 2H, 2 × 5-H), 2.81–2.93 (m, 2H, 2 × 2H), 3.46 (s, 3H, OCH_3), 4.52 (m, 1H, 6-H),

5.67 (m, 2H, 3-H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 26.3 (C-5), 28.4 (C-2), 53.6 (OCH_3), 90.5 (C-6), 123.1 (C-4), 124.5 (C-3), 152.8 (C-1).



1-162 **1-163**

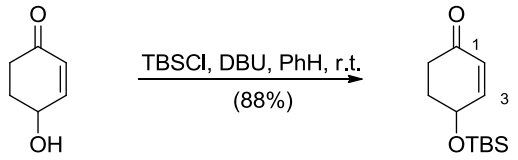
Cyclohex-3-enone (1-163).[74] Perchloric acid (60%, 5 drops) was added to a stirred suspension of diene **1-162** (22.5 g, 0.21 mol) in CCl_4 (55 mL) and water (140 mL). The two phase system was stirred vigorously for 20 h at room temperature, before the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo (30 °C, 600 mbar) to afford enone **1-163** (20.1 g, 99%) as a colorless oil, which was used in the next step without further purification.



1-163 **1-160**

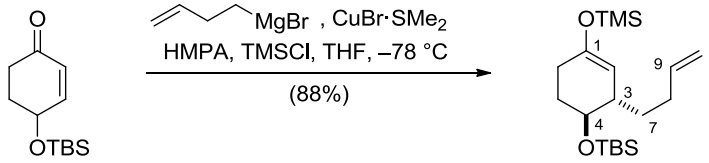
4-Hydroxycyclohex-2-enone (1-160).[76] A solution of *m*CPBA (70%, 34.3 g, 0.140 mol) in CH_2Cl_2 (200 mL) was added dropwise to a stirred solution of enone **1-163** (12.2 g, 0.127 mol) in CH_2Cl_2 (200 mL). The resulting mixture was stirred for 15 h at room temperature before it was filtered and treated with $Na_2S_2O_3$ solution (10%, 250 mL). After additional stirring for 1 h, the organic phase was separated and washed with saturated $NaHCO_3$ solution (200 mL), water (100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$ and concentrated in vacuo.

The residue was dissolved in CH_2Cl_2/diethyl ether mixture (1:1, 250 mL) and stirred for 1 h with basic alumina (17 g). The resulting mixture was filtered from alumina, solvents were removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:2) to give allylic alcohol **1-160** (6.5 g, 46%) as a colorless oil. R_f = 0.40 (petroleum ether/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 2.04 (ddd, *J* = 12.5, 9.1, 4.2 Hz, 1H, 5-H), 2.32–2.44 (m, 2H, 5-H, 6-H), 2.57 (ddd, *J* = 15.9, 4.2, 1.0 Hz, 1H, 6-H), 4.51 (dddd, *J* = 9.1, 4.3, 2.0, 1.7 Hz, 1H, 4-H), 5.95 (ddd, *J* = 10.3, 2.2, 1.0 Hz, 1H, 2-H), 6.91 (ddd, *J* = 10.4, 2.2, 1.3 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 32.5 (C-5), 35.9 (C-6), 69.3 (C-4), 129.1 (C-2), 154.5 (C-3), 199.5 (C-1).



1-160 1-164

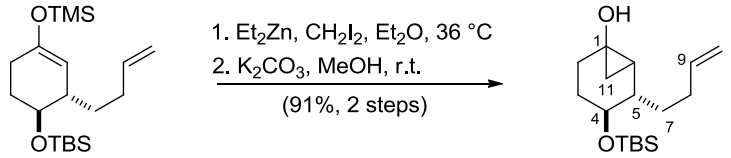
4-((*tert*-Butyldimethylsilyl)oxy)cyclohex-2-enone (1-164).[76] DBU (9.5 mL, 64 mmol) was added dropwise to a stirred solution of allylic alcohol **1-160** (6.5 g, 58 mmol) and TBSCl (9.2 g, 61 mmol) in benzene (120 mL). The resulting solution was stirred for 2 h at room temperature before it was diluted with diethyl ether (200 mL), washed with water (100 mL), 0.1M HCl solution (2 × 100 mL), saturated $NaHCO_3$ solution (100 mL), water (100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give allylic alcohol **1-164** (11.5 g, 88%) as a colorless oil. R_f = 0.95 (petroleum ether/EtOAc, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.11 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 2.01 (ddd, *J* = 12.8, 4.2, 1.9 Hz, 1H, 5-H), 2.20 (ddd, *J* = 12.8, 4.2, 1.9 Hz, 1H, 5-H), 2.34 (ddd, *J* = 15.9, 12.8, 4.2, 1H, 6-H), 2.62 (ddd, *J* = 15.9, 4.2, 1.0 Hz, 1H, 6-H), 4.51 (dddd, *J* = 9.3, 4.2, 2.2, 2.1 Hz, 1H, 4-H), 5.91 (ddd, *J* = 10.3, 2.2, 1.0 Hz, 1H, 2-H), 6.82 (ddd, *J* = 10.4, 2.2, 1.3 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.8 ($SiCH_3$), –4.3 ($SiCH_3$), 18.0 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 32.1 (C-5), 35.4 (C-6), 66.9 (C-4), 128.6 (C-2), 153.8 (C-3), 198.8 (C-1).



1-164 1-165

(((3*S*,4*S*)-3-(But-3-en-1-yl)-4-((*tert*-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)oxy)trimethylsilane (1-165).[71] A solution of $CuBr{\cdot}SMe_2$ (1.0 g, 0.005 mol) in HMPA (21 mL) was added to a THF solution (80 mL) of 3-butenylmagnesium bromide, prepared from 3-butenyl bromide (10.5 g, 0.077 mol) and magnesium (2.1 g, 0.085 mol), over 5 min at –78 °C. The mixture was stirred for additional 30 min at –78 °C and a THF solution (50 mL) of enone **1-164** (11.5 g, 0.051 mol) and TMSCl (10.9 g, 0.100 mol) was added dropwise over 30 min at –78 °C. The mixture was stirred for 1 h before it was treated with triethylamine (6.4 mL), followed by addition of hexane (100 mL) and pH 7 phosphate buffer solution (100 mL). The resulting mixture was filtered through a celite pad and the filtrate was extracted with diethyl ether (100 mL). The organic layer was separated and washed with water (2 × 100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 30:1, + 0.5% Et_3N) to give silyl enol ether **1-165** (15.1 g, 88%) as a colorless oil. R_f = 0.45 (petroleum ether/EtOAc, 30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.06 (s, 6H, $Si(CH_3)_2$), 0.19 (s, 9H, $Si(CH_3)_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.25–1.33 (m, 1H, 7-H), 1.54–1.62 (m, 1H, 7-H), 1.64–1.68 (m, 1H, 6-H), 1.72–1.77 (m, 1H, 6-H), 1.97–2.05 (m, 2H, 2 × 5-H), 2.06–2.13 (m, 3H, 3-H, 2 × 8-H), 3.55 (ddd, *J* = 9.2, 6.1, 2.8 Hz, 1H, 4-H), 4.70 (s, 1H, 2-H), 4.95 (d, *J* = 10.8 Hz, 1H, 10-H), 5.02 (d, *J* = 17.7 Hz, 1H, 10-H), 5.81 (dddd, *J* = 17.7, 13.2, 10.8, 6.1 Hz, 1H, 9-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.8 ($Si(CH_3)_2$), –4.3 ($Si(CH_3)_2$), 0.2 ($Si(CH_3)_3$), 18.1

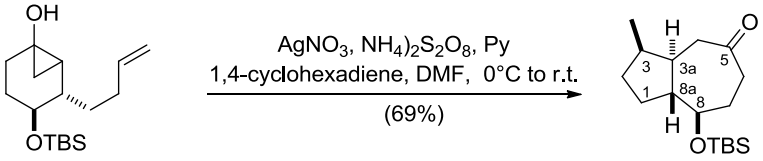
(Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 27.5 (C-8), 29.8 (C-6), 30.9 (C-5), 32.9 (C-7), 42.3 (C-3), 70.8 (C-4), 106.0 (C-2), 114.4 (C-10), 139.0 (C-9), 149.7 (C-1).



1-165 **1-159**

(4*S*,5*S*)-5-(But-3-en-1-yl)-4-(*tert*-butyldimethylsilyl)oxy)bicyclo[4.1.0]heptane-1-ol (1-159).[71] A hexane solution of diethyl zinc (1M, 22 mL, 22.0 mmol) was added to a stirred solution of silyl enol ether **1-165** (5.2 g, 15.4 mmol) in diethyl ether (50 mL), followed by slow addition of diiodomethane (2.7 mL, 33.2 mmol). The resulting mixture was stirred under reflux for 13 h before it was cooled to 0 °C, treated with saturated NH_4Cl solution (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was used in the next step without further purification.

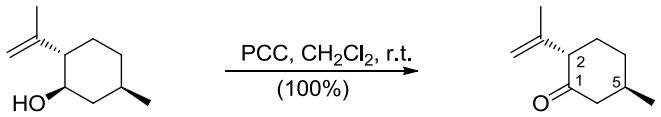
A solution of previously prepared cyclopropane in methanol (60 mL) was treated with potassium carbonate (80 mg). The mixture was stirred for 1 h at room temperature before it was treated with pH 7 phosphate buffer solution (50 mL). After most of the methanol was removed under reduced pressure, the residue was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 6:1) to give cyclopropanol **1-159** (4.2 g, 91% over 2 steps) as a colorless oil. R_f = 0.2 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.06 (s, 3H, Si(C*H*$_3$)$_2$), 0.47 (dd, *J* = 5.4, 5.7 Hz, 1H, 11-H), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 0.93–0.98 (m, 1H, 11-H), 1.05–1.11 (m, 1H, 6-H), 1.22–1.31 (m, 2H, 2 × 7-H), 1.61–1.67 (m, 1H, 2-H), 1.81–1.86 (m, 2H, 2-H, 3-H), 1.93–2.02 (m, 1H, 3-H), 2.06–2.12 (m, 1H, 5-H), 2.22–2.32 (m, 2H, 2 × 8-H), 3.28 (ddd, *J* = 11.0, 8.9, 3.3 Hz, 1H, 4-H), 4.92 (d, *J* = 10.8 Hz, 1H, 10-H), 5.06 (d, *J* = 17.8 Hz, 1H, 10-H), 5.81 (dddd, *J* = 17.8, 13.0, 10.8, 6.4 Hz, 1H, 9-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.8 (Si(CH$_3$)$_2$), –4.0 (Si(CH$_3$)$_2$), 18.0 (Si*C*(CH$_3$)$_3$), 19.4 (C-11), 23.6 (C-6), 25.9 (SiC(*C*H$_3$)$_3$), 30.4 (C-3), 30.5 (C-7), 30.8 (C-8), 33.1 (C-2), 45.6 (C-5), 55.4 (C-1), 73.2 (C-4), 114.2 (C-10), 138.8 (C-9).



1-159 **1-157**

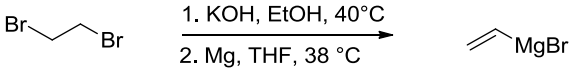
(3*R*,3a*R*,8*R*,8a*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-3-methyloctahydroazulen-5(1*H*)-one (1-157).[71] $AgNO_3$ (240 mg, 1.41 mmol) and $(NH_4)_2S_2O_8$ (4.9 g, 21 mmol) were added to a solution of cyclopropanol **1-159** (4.2 g, 14.2 mmol), pyridine (2.3 mL, 28 mmol) and 1,4-cyclohexadiene (4.1 mL, 43 mmol) in dimethylformamide (120 mL) at 0 °C. The resulting mixture was stirred for 4 h at room temperature before it was carefully treated with saturated

$NaHCO_3$ solution (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give ketone **1-157** (2.9 g, 69%) as a colorless oil. R_f = 0.78 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.05 (s, 3H, Si(C*H*$_3$)$_2$), 0.06 (s, 3H, Si(C*H*$_3$)$_2$), 0.83 (d, *J* = 7.2 Hz, 3H, 3-CH_3), 0.87 (s, 9H, SiC(C*H*$_3$)$_3$), 1.24–1.33 (m, 1H, H-2), 1.33–1.42 (m, 1H, H-2), 1.69–1.92 (m, 4H, 2 × 1-H, 2 × 7-H), 1.92–1.98 (m, 1H, 3a-H), 2.06 (dddd, *J* = 19.0, 8.5, 5.5, 5.5 Hz, 1H, 3-H), 2.18 (ddd, *J* = 10.3, 7.7, 3.9 Hz, 1H, 8a-H), 2.37–2.59 (m, 4H, 2 × 4-H, 2 × 6-H), 3.44 (ddd, *J* = 9.9, 9.9, 3.7 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.7 (Si(C*H*$_3$)$_2$), –4.1 (Si(C*H*$_3$)$_2$), 15.8 (3-C*H*$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 30.4 (C-1), 31.9 (C-7), 33.8 (C-2), 37.8 (C-3a), 39.0 (C-6), 40.3 (C-4), 44.7 (C-3), 53.0 (C-8a), 78.5 (C-8), 213.8 (C-5).

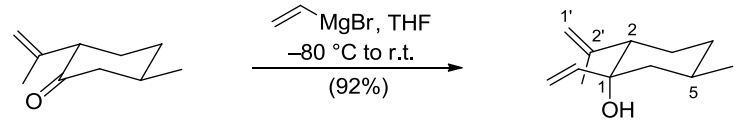


1-173 **1-174**

Isopulegone (1-174).[186] (–)-Isopulegol (**1-173**) (50 g, 0.32 mol) was added dropwise to a stirred solution of PCC (110 g, 0.51 mol) in CH_2Cl_2 (1300 mL) at room temperature. The resulting mixture was stirred overnight before it was filtered through a silica-Celite pad, which was then washed with CH_2Cl_2. The solvent was removed under reduced pressure. The residue was distilled at low pressure (b.p. 40–42 °C, 1 × 10^{-2} mbar) to give isopulegone (**1-174**) as a colorless oil (48.6 g, 100%). R_f = 0.57 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.01 (d, *J* = 6.3 Hz, 3H, 5-CH_3), 1.42 (m, 1H, 4-H), 1.72 (s, 3H, CCH_3), 1.75–2.06 (m, 5H, 2 × 3H, 4-H, 5-H, 6-H), 2.38 (ddd, *J* = 13.2, 3.6, 2.0 Hz, 1H, 6-H), 2.93 (dd, *J* = 12.0, 3.5 Hz, 1H, 2-H), 4.69 (s, 1H, C=C*H*$_2$), 4.91 (s, 1H, C=C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.3 (CCH_3), 22.3 (5-CH_3), 31.2 (C-3), 33.8 (C-4), 35.3 (C-5), 50.5 (C-6), 57.7 (C-2), 112.8 (C=*C*H$_2$), 143.4 (*C*=CH$_2$), 210.2 (C-1).

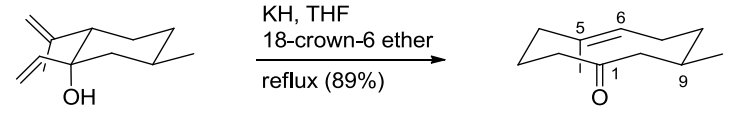


Vinylmagnesium bromide. 1,2-Dibromoethane (72 mL, 0.80 mol) was added dropwise (1 h) to a stirred solution of KOH (60 g, 1.05 mol) in ethanol (400 mL) at 40 °C. The resulting vinyl bromide was distilled from the reaction mixture (b.p. 16 °C) through a Vigreux column (30 cm) and collected in a nitrogen cooled flask. Distillation over $CaCl_2$ (2 times) gave vinyl bromide (60 g, 70%) as a colorless liquid. Vinyl bromide should be stored at –20 °C and handled in a well ventilated hood. A solution of vinyl bromide (12.9 g, 121 mmol) in THF (50 mL) was added dropwise to a suspension of magnesium turnings (2.9 g, 130 mmol) in THF (10 mL), activated with a single iodine crystal, maintaining the temperature at 38 °C. After complete addition of vinyl bromide, the reaction mixture was stirred for 1 h at the same temperature. The concentration was found to be 1.7M in THF by titration of a THF solution of menthol in presence of 1,10-phenantroline. For the exact procedure, see titration of isopropylmagnesium bromide, described earlier.



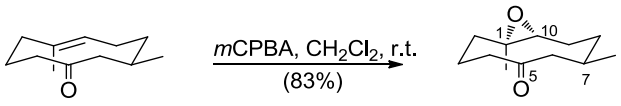
(–)-isopulegone (**1-174**) **1-172**

(1*R*,2*S*,5*R*)-5-Methyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (1-172). Freshly prepared vinylmagnesium bromide (250 mL, 1.7M solution in THF, 0.42 mol) was added dropwise to a stirred solution of ketone **1-174** (47.0 g, 0.33 mol) in THF (300 mL) at –80 °C. The reaction mixture was allowed to warm to room temperature within 1 h and treated with saturated NH_4Cl solution (50 mL), diluted with water (200 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled at low pressure (b.p. 45–50 °C, 6 × 10^{-3} mbar) to give alcohol **1-172** as a colorless oil (55.7 g, 92%). R_f = 0.69 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +17.2 (*c* 2.49, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.86 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 0.90–1.01 (m, 1H, 4-H), 1.10 (ddd, *J* = 14.0, 12.2, 2.0 Hz, 1H, 6-H), 1.47 (ddd, *J* = 13.2, 6.4, 3.6 Hz, 1H, 3-H), 1.61 (ddd, *J* = 13.7, 3.3, 2.3 Hz, 1H, 6-H), 1.74 (s, 3H, 2'-CH_3), 1.76–1.83 (m, 4H, 3-H, 4-H, 5-H, OH), 1.98 (dd, *J* = 13.0, 3.3 Hz, 1H, 2-H), 4.73 (s, 1H, 1'-H), 4.87 (s, 1H, 1'-H), 4.96 (dd, *J* = 10.7, 1.3 Hz, 1H, CH_2 vinyl), 5.16 (dd, *J* = 17.2, 1.1 Hz, 1H, CH_2 vinyl), 5.86 (dd, *J* = 17.0, 10.7 Hz, 1H, CH vinyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.2 (5-CH_3), 25.7 (2'-CH_3), 27.4 (C-5, C-3), 34.8 (C-4), 46.5 (C-6), 52.0 (C-2), 73.2 (C-1), 110.6 (CH_2 vinyl), 111.7 (C-1'), 146.2 (CH vinyl), 148.1 (C-2'); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}ONa$ 203.14064, found 203.140504.



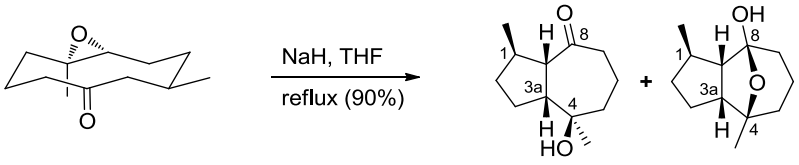
1-172 **1-171**

(9*R*,*E*)-5,9-Dimethylcyclodec-5-enone (1-171). A solution of alcohol **1-172** (26.7 g, 0.15 mol) and 18-crown-6 ether (3.9 g, 0.015 mol) in abs. THF (100 mL) was added to a stirred suspension of KH (17.8 g, 0.45 mol) in THF (250 mL). The resulting mixture was stirred under reflux for 12 h. Then the reaction mixture was treated with ethanol (30 mL) at –78 °C, diluted with water (300 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled at low pressure (55−60 °C, 10^{-2} mbar) to give ketone **1-171** as a colorless oil (23.9 g, 89%). R_f = 0.59 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +2.9 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.92 (d, *J* = 6.8 Hz, 3H, 9-CH_3), 1.17–1.23 (m, 1H), 1.43 (s, 3H, 5-CH_3), 1.60–1.68 (m, 2H), 1.80–1.85 (m, 1H), 1.95–2.15 (m, 6H), 2.20–2.35 (m, 2H), 2.57–2.63 (m, 1H), 5.12–5.14 (m, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 15.9 (5-CH_3), 24.8 (9-CH_3), 25.8, 27.3 (CH_2), 28.8 (C-9), 37.3, 41.3, 43.1, 53.3 (CH_2), 126.4 (C-6), 138.0 (C-5), 208.7 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}ONa$ 203.14064, found 203.140461.



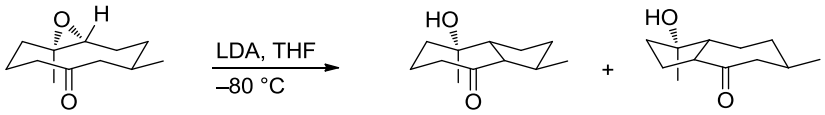
1-171 **1-176**

(1*R*,7*R*,10*R*)-1,7-Dimethyl-11-oxa-bicyclo[8.1.0]undecan-5-one (1-176). *m*CPBA (11.5 g, 47.0 mmol, 70–75%) was added to a stirred solution of ketone **1-171** (7.0 g, 39 mmol) in abs. CH_2Cl_2 (400 mL) and the mixture stirred overnight at ambient temperature. The reaction mixture was treated with saturated $Na_2S_2O_3$ solution (100 mL) and stirred for additional 1 h. The organic layer was separated and washed with saturated $NaHCO_3$ solution (2 × 100 mL), water (100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give epoxide **1-176** (6.3 g, 83%) as white crystals (m.p. 66–67.5 °C). R_f = 0.24 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –0.4 (*c* 1.29, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.84–0.92 (ddd, *J* = 13.7, 13.7, 3.3 Hz, 1H, 2-H), 0.96 (d, *J* = 7.4 Hz, 3H, 7-CH_3), 1.15 (s, 3H, 1-CH_3), 1.25–1.45 (m, 2H, 8-H, 9-H), 1.55–1.65 (m, 1H, 3-H), 1.79–1.85 (m, 2H, 8-H, 9-H), 2.10–2.20 (m, 2H, 2-H, 3-H), 2.24–2.43 (m, 4H, 4-H, 4-H, 6-H, 7-H), 2.56 (dd, *J* = 17.5, 10.3 Hz, 1H, 6-H), 2.63 (dd, *J* = 7.5, 0.9 Hz, 1H, 10-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.1 (1-CH_3), 20.2 (C-3), 23.4 (7-CH_3), 26.4 (C-9), 28.8 (C-7), 35.9 (C-8), 40.5 (C-2), 43.2 (C-4), 52.3 (C-6), 61.5 (C-1), 63.2 (C-10), 210.3 (C=O); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}O_2Na$ 219.13555, found 219.135501.



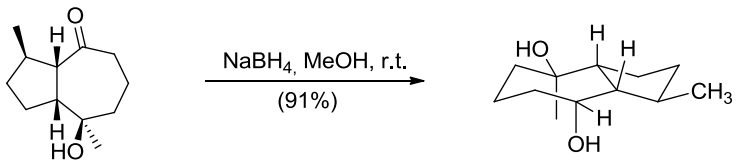
1-176 **1-177** **1-178**

(1*R*,3a*R*,4*R*,8a*S*)-4-Hydroxy-1,4-dimethyl-octahydroazulen-4(2*H*)-one (1-177) and (1*R*,3a*R*,4*R*,8*S*,8a*S*)-1,4-dimethyldecahydro-4,8-epoxyazulen-8-ol (1-178). A solution of epoxy ketone **1-176** (7.0 g, 35.7 mmol) in THF (50 mL) was added to the suspension of NaH (6.0 g, 150.0 mmol, 60% dispersed in mineral oil) in THF (200 mL) and stirred under reflux for 1 h. Then the reaction mixture was cooled to –10 °C and carefully treated with saturated NH_4Cl solution (50 mL). The mixture was diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 1M HCl solution (50 mL), water (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give an inseparable mixture of ketone **1-177** and hemiketal **1-178** (**1-177**/**1-178** = 30:70) which was introduced in the next step without further purification (6.0 g, 90%).



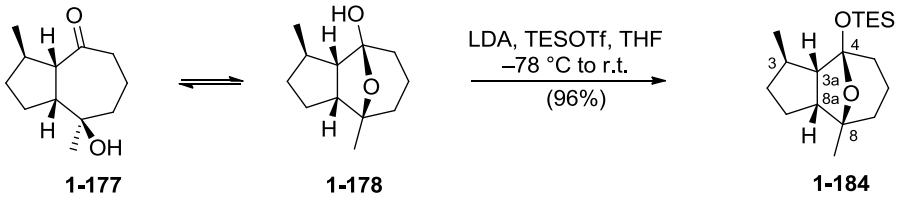
1-176 **1-177** (20%) **1-179** (80%)

(1*S*,3a*R*,6*R*,8a*R*)-1-Hydroxy-1,6-dimethyl-octahydroazulen-4(1*H*)-one (14). A freshly prepared solution of LDA in THF (1.0 mL, 0.5M, 0.50 mmol) was added dropwise to a solution of epoxy ketone **1-176** (25 mg, 0.13 mmol) in THF (1 mL) at –80 °C followed by stirring of the mixture for 24 h at the same temperature. The reaction mixture was treated with saturated NH_4Cl solution (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with water (10 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give a mixture of ketone **1-177**/hemiketal **1-178** (4 mg, 20%) and ketone **1-179** (21 mg, 80%). R_f = 0.18 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = –16.8 (*c* 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.83 (dddd, *J* = 13.1, 13.1, 12.0, 1.3 Hz, 1H, 8-H), 0.97 (d, *J* = 6.6 Hz, 3H, 6-H), 1.12–1.20 (m, 1H, 7-H), 1.45–1.54 (m, 1H, 2-H), 1.59–1.68 (m, 3H, 2-H, 6-H, OH), 1.70–1.80 (m, 2H, 3-H, 8-H), 1.87–1.93 (m, 1H, 7-H), 2.09–2.20 (m, 2H, 3-H, 8a-H), 2.32 (ddd, *J* = 10.2, 2.8, 1.8 Hz, 1H, 5-H), 2.42 (dd, *J* = 11.4, 10.2 Hz, 1H, 5-H), 3.42 (ddd, *J* = 9.4, 9.4, 7.4 Hz, 1H, 3a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.8 (C-3), 23.6 (4-CH_3), 24.1 (1-CH_3), 27.5 (C-8), 34.4 (C-6), 38.6 (C-2), 38.6 (C-7), 52.2 (C-5), 52.3 (C-8a), 55.4 (C-3a), 82.4 (C-1), 213.2 (C-4); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}O_2Na$ 219.13555, found 219.135579.



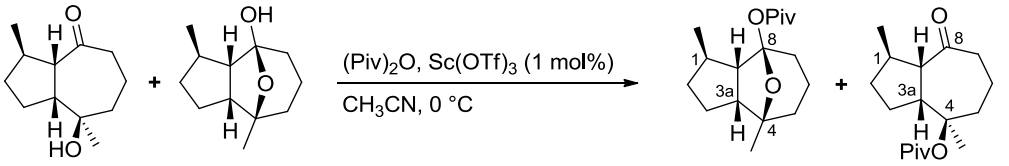
1-177 **1-180**

(1*R*,3a*R*,4*R*,8*R*,8a*S*)-1,4-Dimethyldecahydroazulene-4,8-diol (1-180). $NaBH_4$ (50 mg, 1.30 mmol) was added to a solution of ketone **1-177** (170 mg, 0.87 mmol) in a THF/MeOH mixture (10 mL/1 mL) at –78 °C. The resulting mixture was allowed to warm to ambient temperature and stirred for 1 h at room temperature. Then the reaction mixture was cooled to 0 °C and carefully treated with water (10 mL). The mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give diol **1-180** (155 mg, 91%) as a colorless oil. R_f = 0.34 (petroleum ether/EtOAc, 1:1); $[\alpha]^{20}_D$ = –14.0 (*c* 2.35, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.99 (d, *J* = 6.3 Hz, 3H, 1-CH_3), 1.05 (ddd, *J* = 12.3, 5.8 Hz, 1H, 2-H), 1.17 (s, 3H, 4-CH_3), 1.20–1.30 (m, 1H, 3-H), 1.40 (dddd, *J* = 14.7, 7.6, 3.8, 3.7 Hz, 1H, 6-H), 1.46–1.60 (m, 3H, 1-H, 5-H, 7-H), 1.65–1.94 (m, 6H, 2-H, 3-H, 5-H, 6-H, 7-H, 8a-H), 2.32 (ddd, *J* = 11.2, 11.2, 7.1 Hz, 1H, 3a-H), 3.91 (dd, *J* = 6.6, 3.0 Hz, 1H, 8-H), 4.64 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 17.4 (C-6), 19.5 (1-CH_3), 30.2 (C-7), 31.1 (C-3), 32.2 (4-CH_3), 34.6 (C-2), 36.7 (C-5), 39.7 (C-1), 54.1 (C-3a, C-8a), 71.7 (C-8), 75.5 (C-4); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{22}O_2Na$ 221.115120, found 221.151057.



1-177 **1-178** **1-184**

(3*R*,3a*S*,4*S*,8*R*,8a*R*)-3,8-Dimethyl-4-((triethylsilyl)oxy)-decahydro-4,8-epoxyazulen (1-184). A freshly prepared LDA solution (0.5M in THF, 1.0 mL, 0.50 mmol) was added drowise to a stirred solution of **1-177** and **1-178** (25 mg, 0.13 mmol) in THF (1 mL) at –78 °C. The resulting mixture was stirred for 1 h at the same temperature before it was treated with TESOTf (86 µL, 0.38 mmol). After being stirred overnight, the reaction mixture was diluted with petroleum ether/EtOAc mixture (1:1, 3 mL) and filtered through a pad of silica (eluent petroleum ether/EtOAc 1:1). Solvents were removed under reduced pressure to afford acetal **1-184** (39 mg, 96%) as a colorless oil. R_f = 0.78 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.56–0.67 (m, 6H, Si(C*H*$_2$CH$_3$)$_3$); 0.94 (dd, *J* = 7.8, 7.8 Hz, 12H, Si(C*H*$_2$CH$_3$)$_3$); 0.98 (d, *J* = 6.1 Hz, 3H, 3-CH$_3$), 1.17 (s, 3H, 8-CH$_3$), 1.36–1.53 (m, 5H, 2 × 2-H, 2 × 5-H, 6-H), 1.57–1.67 (m, 2H, 1-H, 6-H), 1.78–1.93 (2 × 7-H), 2.03–2.13 (m, 2H, 1-H, 3-H), 2.21 (dd, *J* = 13.6, 8.6 Hz, 1H, 3a-H), 2.65 (ddd, *J* = 13.8, 9.1, 9.1 Hz, 1H, 8a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 6.3 (Si(*C*H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 18.5 (3-CH$_3$), 20.5 (C-6), 25.3 (8-CH$_3$), 28.1 (C-1), 31.8 (C-2), 33.4 (C-7), 33.7 (C-3), 41.2 (C-5), 54.4 (C-3a), 64.5 (C-8a), 80.9 (C-8), 105.2 (C-4); HRMS (ESI): $[M+Na]^+$ calcd for $C_{18}H_{34}O_2SiNa$ 333.22203, found 333.222230.



1-177 **1-178** **1-186** (37%) **1-185** (61%)

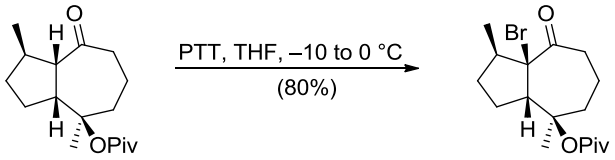
(1*R*,3a*R*,4*R*,8a*S*)-1,4-Dimethyl-8-oxo-decahydroazulen-4-yl-pivalate (1-185) and (3*R*,3a*S*,4*R*,8*R*,8a*R*)-3,8-Dimethyldecahydro-4,8-epoxyazulen-4-yl pivalate (1-186). Pivalic anhydride (16 ml, 79.1 mmol) was added dropwise to a stirred solution of **1-177** and **1-178** mixture (4.3 g, 21.9 mmol) in dry acetonitrile (90 mL) at –10 °C, followed by addition of Sc(OTf)$_3$ (0.1 g, 0.2 mmol) dissolved in acetonitrile (1 mL) at the same temperature. The resulting mixture was stirred overnight at 0 °C, treated with saturated NaHCO$_3$ solution (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with saturated NaCl solution (50 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give pivalic ketone **1-185** (3.7 g, 61%) and protected hemiketal **1-186** (2.3 g, 37%) as colorless oils.

Pivalic ketone **1-185**: R_f = 0.65 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = +22.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.01 (d, *J* = 6.4 Hz, 3H, 1-CH$_3$), 1.08 (s, 9H, (CH$_3$)$_3$), 1.16–1.26 (m, 1H, 2-H), 1.41 (s, 3H, 4-CH$_3$), 1.50–1.86 (m, 5H, 2 × 3-H, 5-H, 2 × 6-H), 1.93–2.07 (m, 2H, 1-H, 2-H), 2.28–2.39 (m, 3H, 5-H, 7-H, 8a-H), 2.57 (ddd, *J* = 11.7, 11.7, 3.3 Hz,

1H, 7-H), 2.95 (ddd, *J* = 11.2, 11.2, 7.1 Hz, 1H, 3a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.9 (1-CH_3), 21.2 (C-6), 26.2 (4-CH_3), 27.1 (CO(*C*H_3)$_3$), 29.4 (C-3), 35.3 (C-5), 35.4 (C-2), 39.2 (C-1), 39.6 (*C*O(CH$_3$)$_3$), 41.5 (C-7), 49.4 (C-3a), 61.3 (C-8a), 86.1 (C-4), 177.7 (C=O ester), 212.4 (C=O ketone). HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{28}O_3Na$ 303.19307, found 303.192921.

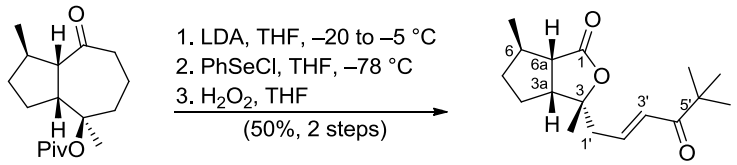
Hemiketal pivalate **1-186**: R_f = 0.75 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.99 (d, *J* = 6.1 Hz, 3H, 1-CH_3), 1.15 (s, 9H, CO(CH$_3$)$_3$), 1.26 (s, 3H, 4-CH_3), 1.40–1.68 (m, 7H, 5-H, 2-H), 1.88–1.99 (m, 2H), 2.14–2.22 (m, 2H, 3-H), 2.31–2.35 (ddd, *J* = 11.9, 11.7, 6.2 Hz, 1H), 2.46 (dd, *J* = 13.8, 8.2 Hz, 1H, 3a-H), 2.79 (ddd, *J* = 13.6, 8.6, 8.6 Hz, 1H, 8a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 17.9 (1-CH_3), 20.9 (C-6), 25.0 (4-CH_3), 27.0 (CO(*C*H_3)$_3$), 27.9 (C-3), 28.9 (C-5), 31.8 (C-2), 33.7 (C-1), 38.5 (*C*O(CH$_3$)$_3$), 39.0 (C-7), 41.1 (C-3a), 54.5 (C-8a), 62.5 (C-3a), 82.1 (C-4), 110.0 (C-8), 176.0 (*C*O(*C*H$_3$)$_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{28}O_3Na$ 303.19307, found 303.193064.

Recycling of 1-177+1-178 via pivalic ester cleavage: K_2CO_3 (4.20 g, 30.4 mmol) was added to a stirred solution of ester **1-186** (2.85 g, 10.2 mmol) in methanol (70 mL). The resulting mixture was stirred for 10 h at 60 °C, treated with water (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give a mixture **1-177**+**1-178** (1.83 g, 92%) as a colorless oil.



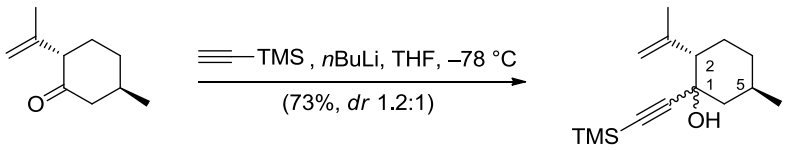
1-185 **1-187**

(1*R*,3a*S*,4*R*,8a*R*)-8a-Bromo-1,4-dimethyl-8-oxodecahydroazulen-4-yl pivalate (1-187). Phenyltrimethylammonium tribromide (PTT)[89] (48 mg, 0.13 mmol) was added to a stirred solution of ketone **1-185** (30 mg, 0.11 mmol) in THF (1 mL) at –10 °C. The resulting mixture was allowed to warm to 0 °C and stirred for 30 min before it was filtered through a pad of silica (3 cm) using a mixture of petroleum ether/EtOAc (5:1, 20 mL) as a rinse. The solvents were removed under reduced pressure to give bromide **1-187** (31 mg, 80%) as white crystals. R_f = 0.45 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.08 (d, *J* = 5.8 Hz, 1H, 1-CH_3), 1.12 (s, 9H, C(CH$_3$)$_3$), 1.13 (s, 3H, 4-CH_3), 1.58–2.01 (m, 8H, 2 × 2-H, 2 × 3-H, 5-H, 2 × 6-H, 7-H), 2.45–2.53 (m, 2H, 5-H, 7-H), 3.38 (ddd, *J* = 12.1, 12.1, 3.3 Hz, 1H, 1-H), 4.00 (dd, *J* = 9.4, 6.4 Hz, 1H, 3a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 18.0 (1-CH_3), 19.8 (C-6), 22.7 (C-3), 24.6 (4-CH_3), 27.1 (C(*C*H$_3$)$_3$), 31.7 (C-2), 39.1 (C-5), 39.4 (*C*(CH$_3$)$_3$), 40.8 (C-7), 43.6 (C-1), 58.4 (C-3a), 84.2 (C-4), 86.4 (C-8a), 177.2 (ester), 204.4 (C-8).



1-185 **1-189**

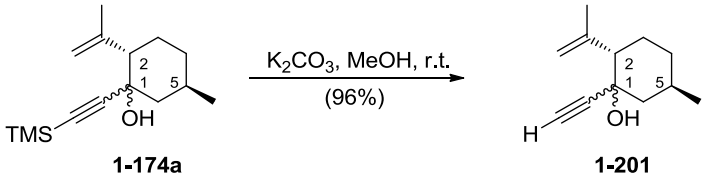
(3*R*,3a*R*,6*R*,6a*S*)-3-((*E*)-5,5-Dimethyl-4-oxohex-2-enyl)-3,6-dimethylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (1-189). *n*-BuLi (0.20 mL, 2.5M in THF) was added to a flask containing abs. THF (1.0 mL). The resulting solution was cooled to –20 °C and then DIPA (0.07 mL, 0.40 mmol) was added. The resulting LDA solution was stirred at –20 °C for 1 h. Then a solution of ketone **1-185** (30.0 mg, 0.11 mmol) in abs. THF (1.0 mL) was added at –20 °C. The resulting solution was warmed to –5 °C and stirred for 40 min. After this time, the reaction mixture was recooled to –78 °C and a solution of PhSeCl (57.4 mg, 0.33 mmol) in THF (0.5 mL) was added dropwise. The resulting yellow solution was allowed to stir overnight at –40 °C and then treated with saturated NH_4Cl solution (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organics were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in THF (1 mL) and H_2O_2 (0.1 mL, 1.1 mmol, 30% in water) was added in one portion. The resulting solution was stirred overnight and then diluted with water (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organics were washed with saturated $Na_2S_2O_3$ solution (2 × 10 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give enone **1-189** (15 mg, 50%) as a colorless oil. R_f = 0.42 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +10.7 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.13–1.14 (m, 12H, 5'-$(CH_3)_3$, 6-CH_3), 1.17–1.25 (m, 1H, 5-H), 1.35 (s, 3H, 3-CH_3), 1.52–1.57 (m, 1H, 5-H), 1.80–1.96 (m, 2H, 4-H), 2.33–2.40 (m, 1H, 6-H), 2.53–2.69 (m, 3H, 1'-H, 3a-H), 2.76 (dd, *J* = 8.6, 4.1 Hz, 1H, 6a-H), 6.60 (app d, *J* = 15.2 Hz, 1H, 3'-H), 6.83 (ddd, *J* = 15.2, 7.6, 7.6, 1H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.3 (6-CH_3), 26.0 (5-$(CH_3)_3$), 27.0 (3-CH_3), 27.6 (C-4), 35.4 (C-5), 37.7 (C-6), 40.0 (C-1'), 42.9 (C-5'), 49.8 (C-3a), 53.5 (C-6a), 84.7 (C-3), 128.2 (C-3'), 140.2 (C-2'), 179.3 (C=O ester), 203.7 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{26}O_3Na$ 301.17742, found 301.177335.



1-174 **1-174a**

(2*R*,5*R*)-5-Methyl-2-(prop-1-en-2-yl)-1-((trimethylsilyl)ethynyl)cyclohexanol (1-174a). *n*-BuLi (2.5M in hexane, 5.8 mL, 14.5 mmol) was added dropwise to a stirred solution of mono-TMS-acetylene (1.6 mL, 14.5 mmol) in THF (100 mL) at –78 °C over 15 min. The resulting solution was stirred for 15 min before a solution of isopulegone (**1-174**) (2.0 g, 13.2 mmol) in THF (20 mL) was added dropwise and stirring continued for additional 1 h at the same temperature. The reaction was treated with saturated NH_4Cl solution (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give a diastereomeric

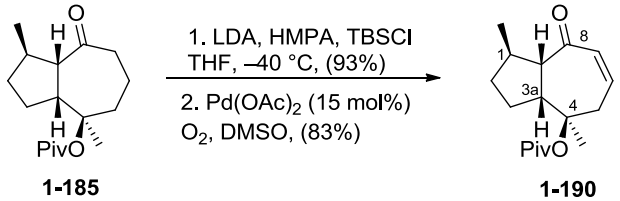
mixture of two alcohols **1-174a** (2.4 g, 73%, *dr* 1.2:1) as a colorless oil, which was used in next step without separation. R_f = 0.58, 0.68 (petroleum ether/EtOAc, 9:1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{26}OSiNa$ 273.164513, found 273.164250.



(2*R*,5*R*)-1-Ethynyl-5-methyl-2-(prop-1-en-2-yl)cyclohexanol (1-201). The diastereomeric mixture of alcohols **1-174a** (1.2:1, 70 mg, 0.28 mmol) was dissolved in methanol (1 mL) and treated with K_2CO_3 (58 mg, 0.42 mmol) at room temperature. The resulting mixture was stirred for 2 h before it was diluted with diethyl ether (10 mL), treated with water (10 mL) and extracted with diethyl ether (3 × 10 mL).The combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give alcohols **1-201** (47 mg, 96%, *dr* 1.2:1) as colorless oils.

R_f = 0.53 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.88 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 0.85–0.99 (m, 2H, 3-H, 4-H), 1.24–1.39 (m, 2H, 3-H, 4-H), 1.45–1.50 (m, 1H, 5-H), 1.66–1.82 (m, 2H, 2-H, 6-H), 1.98 (s, 3H, CH_2=CCH_3), 2.11–2.18 (m, 1H, 6-H), 2.22 (br s, 1H, OH), 2.41 (s, C≡CH), 4.84 (br s, CH_2=CCH_3), 5.00 (dd, *J* = 1.5, 1.5 Hz, 1H, CH_2=CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.8 (CH_2=CCH_3), 25.9 (5-CH_3), 26.6 (C-3), 26.7 (C-5), 34.4 (C-4), 48.0 (C-6), 52.1 (C-2), 67.4 (C-1), 71.2 (C≡CH), 88.6 (*C*≡CH), 112.4 (CH_2=CCH_3), 148.0 (CH_2=CCH_3).

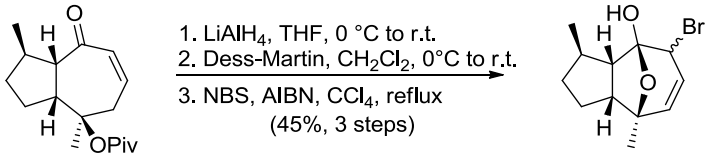
R_f = 0.63 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.94 (d, *J* = 6.8 Hz, 3H, 5-CH_3), 0.88–1.02 (m, 1H, 3-H), 1.17–1.28 (m, 1H, 4-H), 1.60–1.90 (m, 4H, 6-H, 5-H, 3-H, 4-H), 1.87 (s, 3H, CH_2=CCH_3), 2.04–2.11 (m, 2H, 6-H, 2-H), 2.47 (s, 1H, OH), 2.71 (s, C≡CH), 4.92 (s, CH_2=CCH_3), 4.99 (dd, *J* = 1.5, 1.5 Hz, 1H, CH_2=CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 20.9 (CH_2=CCH_3), 21.8 (5-CH_3), 28.0 (C-3), 30.2 (C-5), 34.3 (C-4), 48.6 (C-6), 55.7 (C-2), 69.6 (C-1), 74.2 (C≡CH), 86.2 (*C*≡CH), 115.1 (CH_2=CCH_3), 145.3 (CH_2=CCH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{18}ONa$ 201.124986, found 201.124935.



(1*R*,3a*R*,4*R*,8a*S*)-1,4-Dimethyl-8-oxo-1,2,3,3a,4,5,8,8a-octahydroazulen-4-yl pivalate (1-190). *TBS enol ether formation*. *n*-BuLi (0.43 mL, 2.5M in THF) was added to a flask containing THF (1.5 mL). The resulting solution was cooled to –20 °C and then DIPA (0.17 mL, 1.18 mmol) was added. The resulting LDA solution was stirred at –20 °C for 1 h and

recooled to –40 °C. A solution of ketone **1-185** (100 mg, 0.36 mmol) in abs. THF (1.0 mL) was introduced dropwise at –40 °C. The resulting solution was stirred at the same temperature for 2 h and then a solution of TBSCl (217 mg, 1.44 mmol) in abs. THF (1.0 mL) was added followed by HMPA (0.1 mL, 0.54 mmol). The reaction mixture was allowed to warm to room temperature. After being stirred overnight, water (10 mL) was added. The organic layer was separated and the water phase extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc/Et_3N, 40:1:0.12) to give TBS enol ether (131 mg, 93%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 33:1). The compound was directly introduced to the next step.

Saegusa-Ito oxidation. To a solution of TBS enol ether obtained above in dry DMSO (3.0 mL) was added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol). The reaction mixture was placed under oxygen (balloon) and stirred at 50 °C for 24 h. After this time, the reaction mixture was diluted with diethyl ether (10 mL) followed by water addition (5 mL). The layers were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo.The residue was purified via flash chromatography (petroleum ether/EtOAc, 9:1) to give enone **1-190** (76 mg, 83%) as a colorless oil. R_f = 0.42 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –21.3 (*c* 0.39, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.97 (d, *J* = 5.8 Hz, 3H, 1-CH_3), 1.06 (s, 9H, *t*Bu), 1.15–1.24 (m, 2H, CH_2), 1.46 (s, 3H, 4-CH_3), 1.86–2.03 (m, 2H, 3a-H, CH_2), 2.50 (dd, *J* = 10.6, 10.6 Hz, 1H, CH_2), 2.61–2.67 (m, 1H, 5-H), 2.80–2.87 (m, 1H, 8a-H), 3.26–3.32 (m, 1H, 5-H), 5.90 (dd, *J* = 12.1, 2.9 Hz, 1H, 7-H), 6.10 (ddd, *J* = 12.1, 6.7, 2.7 Hz 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 18.2 (1-CH_3), 25.0 (4-CH_3), 27.0 (C(*C*H_3)$_3$), 28.5 (CH_2), 34.8 (CH_2), 36.9 (C-1), 39.4 (*C*(CH_3)$_3$), 40.8 (C-5), 50.6 (C-3a), 63.7 (C-8a), 85.0 (C-4), 130.9 (C-7), 137.0 (C-6), 177.9 (C=O ester), 204.2 (C=O ketone). HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{26}O_3Na$ 301.17742, found 301.177335.



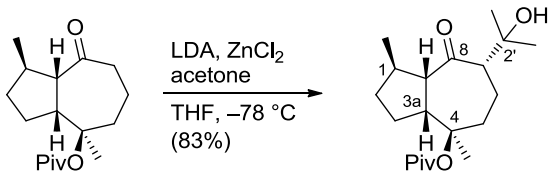
1-190 **1-204**

(1*R*,3a*R*,4*RS*,8a*S*)-1,4-Dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulene-4,8-diol (1-204). A solution of pivalate **1-190** (20 mg, 0.072 mmol) in THF (1.5 mL) was added to a stirred suspension of $LiAlH_4$ (27 mg, 0.72 mmol) in THF (1 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h before it was carefully treated with water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give the corresponding diol (12 mg, 86%) as a colorless oil. R_f = 0.32 (petroleum ether/EtOAc, 1:2).

The crude diol (12 mg, 0.061 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with Dess-Martin periodinane (30 mg, 0.070 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h before it was carefully treated with water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with

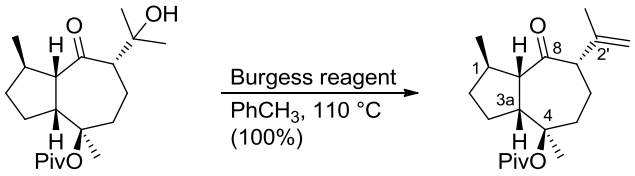
saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give the enone **1-169** (9 mg, 75%) as a colorless oil. R_f = 0.46 (petroleum ether/EtOAc, 2:1).

The crude enone **1-169** (9 mg, 0.046 mmol) was dissolved in CCl_4 (1 mL) and treated with NBS (9 mg, 0.50 mmol) and AIBN (cat.) at room temperature. The resulting mixture was stirred for 3 h under reflux before the solvent was removed. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7:1) to give bromide **1-204** (9 mg, 69%) as a colorless oil. R_f = 0.55 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.98 (d, *J* = 6.4 Hz, 3H, 1-CH_3), 1.23–1.33 (m, 2H, 2-H, 3-H), 1.37 (s, 3H, 4-CH_3), 1.59–1.76 (m, 2H, 1-H, 3-H), 1.91–1.97 (m, 1H, 2-H), 2.66 (dd, *J* = 11.7, 9.7 Hz, 1H, 8a-H), 2.90 (ddd, *J* = 11.8, 8.3, 8.1 Hz, 1H, 3a-H), 3.75 (s, 1H, OH), 4.71 (d, *J* = 4.3 Hz, 1H, 7-H), 5.84 (d, *J* = 9.4 Hz, 1H, 5-H), 6.06 (dd, *J* = 9.4, 4.3 Hz, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.9 (1-CH_3), 23.1 (4-CH_3), 24.7 (C-3), 36.0 (C-1), 40.1 (C-2), 56.7 (C-7), 58.2 (C-3a), 61.5 (C-8a), 83.5 (C-4), 100.7 (C-8), 126.9 (C-6), 138.0 (C-5).



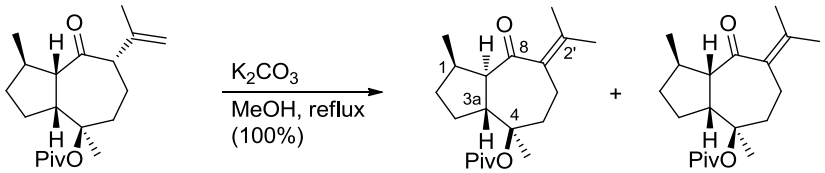
1-185 **1-207**

(1*R*,3a*R*,4*R*,7*S*,8a*S*)-7-(2-Hydroxypropan-2-yl)-1,4-dimethyl-8-oxodecahydroazulen-4-yl pivalate (1-207). A solution of ketone **1-185** (200 mg, 0.71 mmol) in THF (6 mL) was added dropwise to freshly prepared LDA (4.7 mL, 2.14 mmol, 0.45M solution in THF) at –45 °C. The resulting mixture was stirred for 1 h before $ZnCl_2$ (0.85 mL, 0.85 mmol, 1M solution in diethyl ether) was added dropwise at –78 °C, followed by addition of acetone (0.6 mL, 8.17 mmol). After 30 min the reaction mixture was treated with saturated NH_4Cl solution (5 mL), diluted with water (15 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give aldol product **1-207** (193 mg, 83%) as a colorless oil. R_f = 0.53 (petroleum ether/EtOAc, 2:1); $[\alpha]^{20}_D$ = +50.4 (*c* 0.76, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.06 (d, *J* = 6.6 Hz, 3H, 1-CH_3), 1.12 (s, 9H, $COC(CH_3)_3$), 1.21 (s, 6H, 2 × 2'-CH_3), 1.26−1.36 (m, 1H, CH_2), 1.46−1.89 (m, 7H, 4-CH_3, 2 × CH_2), 2.02−2.08 (m, 1H, CH_2), 2.12−2.23 (m, 1H, 1-H), 2.39−2.44 (m, 2H, 8a-H, CH_2), 2.58 (dd, *J* = 12.1, 2.0 Hz, 1H, 7-H), 2.95 (ddd, *J* = 12.8, 11.3, 6.4 Hz, 1H, 3a-H), 3.87 (br. s, 1H, 2'-OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.8 (1-CH_3), 22.9 (CH_2), 27.1 ($COC(CH_3)_3$), 27.1 (2'-CH_3), 27.6 (4-CH_3), 29.0 (2'-CH_3), 30.2 (CH_2), 34.1, 35.7 (CH_2), 39.0 (C-1), 39.6 ($COC(CH_3)_3$), 50.1 (C-3a), 56.9 (C-7), 62.5 (C-8a), 71.9 (C-2'), 85.3 (C-4), 177.7 (C=O ester), 217.1 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{20}H_{34}O_4Na$ 361.23493, found 361.235157.



1-207 **1-209**

(1*R*,3a*R*,4*R*,7*R*,8a*S*)-1,4-Dimethyl-8-oxo-7-(prop-1-en-2-yl)decahydroazulen-4-yl pivalate (20). Burgess reagent (42 mg, 0.177 mmol) was added to a stirred solution of alcohol **1-207** (15 mg, 0.044 mmol) in abs. toluene (3 mL) and the mixture stirred at 110 °C for 5 min. After cooling, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/EtOAc, 15:1) providing alkene **1-209** (14 mg, quant.) as a colorless oil. R_f = 0.56 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = +89.5 (*c* 12.7, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.05 (d, *J* = 6.5 Hz, 3H, 1-CH_3), 1.11 (s, 9H, $COC(CH_3)_3$), 1.27−1.35 (m, 1H, 2-H), 1.54 (s, 3H, 4-CH_3), 1.59−1.87 (m, 8H, 2'-CH_3, 2 × 3-H, 5-H, 2 × 6-H), 2.04−2.07 (m, 1H, 2-H), 2.17−2.23 (m, 1H, 1-H), 2.42−2.52 (m, 2H, 5-H, 8a-H), 2.92 (ddd, *J* = 12.5, 11.1, 6.6 Hz, 1H, 3a-H), 3.31 (dd, *J* = 12.2, 2.3 Hz, 1H, 7-H), 4.78 (s, 1H, 1'-H), 4.93 (s, 1H, 1'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.7 (1-CH_3), 22.3 (2'-CH_3), 25.7 (CH_2), 27.1 ($COC(CH_3)_3$), 27.1 (4-CH_3), 30.0 (CH_2), 33.9 (CH_2), 35.5 (CH_2), 39.3 (C-1), 39.6 ($COC(CH_3)_3$), 50.1 (C-3a), 55.7 (C-7), 61.5 (C-8a), 85.5 (C-4), 111.9 (C-1'), 144.2 (C-2'), 177.8 (C=O ester), 210.9 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{20}H_{32}O_3Na$ 343.22437, found 343.224348.



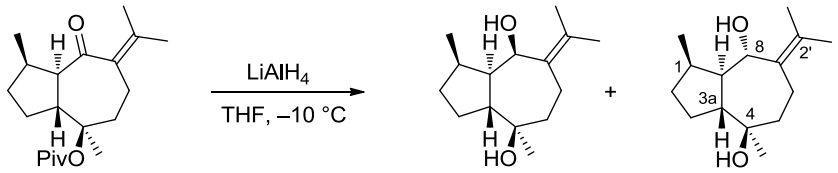
1-209 **1-210** ***epi*-1-210**

(1*R*,3a*R*,4*R*,8a*R*)-1,4-Dimethyl-8-oxo-7-(propan-2-ylidene)decahydroazulen-4-yl pivalate (1-210). K_2CO_3 (18 mg, 0.131 mmol) was added to a stirred solution of ketone **1-209** (14 mg, 0.044 mmol) in methanol (2 mL). The resulting mixture was stirred at 70 °C for 4 h, treated with water (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (10 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give enone **1-210** (7 mg, 50%) as a colorless oil and enone *epi*-**1-210** (7 mg, 50%), which was introduced again in this step without further purification.

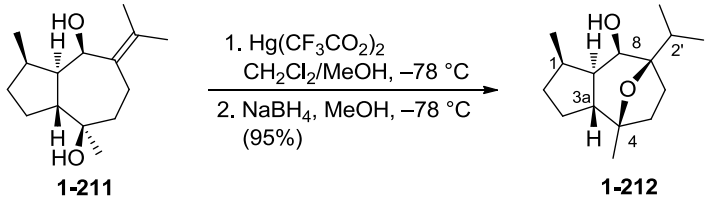
1-210: R_f = 0.33 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –99.2 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.86 (d, *J* = 6.9 Hz, 3H, 1-CH_3), 1.16 (s, 9H, $COC(CH_3)_3$), 1.40−1.45 (m, 1H, 2-H), 1.43 (s, 3H, 4-CH_3), 1.62−1.75 (m, 2H, 2-H, 3-H),1.74 (s, 3H, 2'-CH_3), 1.83 (s, 3H, 2'-CH_3), 1.86−1.95 (m, 2H, 3-H, 6-H), 2.03 (ddd, *J* = 13.9, 8.8, 1.6 Hz, 1H, 5-H), 2.41 (ddd, *J* = 13.6, 11.2, 1.9 Hz, 1H, 5-H), 2.48−2.55 (m, 1H, 6-H), 2.54 (dd, *J* = 11.9, 6.6 Hz, 1H, 8a-H), 2.62−2.69 (m, 1H, 1-H), 2.93 (ddd, *J* = 11.2, 11.2, 5.8 Hz, 1H, 3a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 15.9 (1-CH_3),18.4 (4-CH_3), 20.8 (2'-CH_3), 21.9 (2'-CH_3), 23.9 (C-6), 24.6 (C-3), 27.2 ($COC(CH_3)_3$), 32.6 (C-2), 36.7 (C-5), 37.4 (C-1), 39.5 ($COC(CH_3)_3$), 44.6 (C-3a), 56.5 (C-8a), 86.5 (C-4), 136.8 (C-2'), 137.9 (C-7), 177.6 (C=O

ester), 209.6 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{20}H_{32}O_3Na$ 343.22437, found 343.224401.

epi-**1-210**[187]: R_f = 0.45 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.05 (d, *J* = 6.6 Hz, 3H, 1-CH_3), 1.13 (s, 9H, $COC(CH_3)_3$), 1.20−2.44 (m, 9H), 1.43 (s, 3H, 4-CH_3), 1.71 (s, 3H, 2'-CH_3), 1.73 (s, 3H, 2'-CH_3), 2.56 (dd, *J* = 10.0, 7.0 Hz, 1H, 8a-H), 2.91 (ddd, *J* = 12.0, 10.1, 6.9 Hz, 1H, 3a-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 20.3, 20.8, 22.3, 24.1, 25.3, 27.1, 28.1, 33.7, 34.4, 36.9, 49.6 44.6 (C-3a), 61.4 (C-8a), 85.6 (C-4), 132.6 (C-2'), 136.1 (C-7), 177.6 (C=O ester), 210.0 (C=O ketone); HRMS (ESI): $[M+Na]^+$ calcd for $C_{20}H_{32}O_3Na$ 343.22437, found 343.224399.

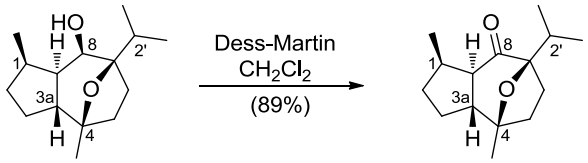


(1*R*,3a*R*,4*R*,8*R*,8a*R*)-1,4-Dimethyl-7-(propan-2-ylidene)decahydroazulene-4,8-diol (1-211). A solution of ketone **1-210** (20 mg, 0.062 mmol) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (30 mg, 0.789 mmol) in THF (1 mL) at –10 °C. The resulting mixture was allowed to warm to ambient temperature during 2 h and then carefully treated with 20% aqueous NaOH solution (0.5 mL) and water (10 mL). Stirring was continued for 15 min, before the mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with water (10 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 3:1) to give diol **1-211** (25 mg, 69%) and diol *epi*-**1-211** (8 mg, 22%) as white crystals. *epi*-**1-211**: R_f = 0.54 (petroleum ether/EtOAc, 2:3). **1-211**: R_f = 0.48 (petroleum ether/EtOAc, 2:3); $[\alpha]^{20}_D$ = –29.1 (*c* 0.35, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.09 (d, *J* = 7.3 Hz, 3H, 1-CH_3), 1.11 (s, 3H, 4-CH_3), 1.24−1.30 (m, 1H, 2-H), 1.41−1.56 (m, 3H, 3-H, 5-H, 8a-H), 1.65 (s, 3H, 2'-CH_3), 1.68−1.82 (m, 2H, 2-H, 3-H), 1.76 (s, 3H, 2'-CH_3), 1.93 (ddd, *J* = 14.3, 10.0, 1.8 Hz, 1H, 5-H),2.02−2.13 (m, 1H, 1-H), 2.21 (app dd, *J* = 10.1, 15.4 Hz, 1H, 6-H), 2.38 (app dd, *J* = 9.1, 15.7 Hz, 1H, 6-H), 2.66 (ddd, *J* = 10.0, 10.0, 8.0 Hz, 1H, 3a-H), 4.89 (br.s, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.3 (1-CH_3), 20.4 (2'-CH_3), 20.7 (2'-CH_3), 22.3 (C-6), 22.7 (4-CH_3) 25.9 (C-3), 34.4 (C-2), 38.1 (C-1), 43.4 (C-5), 46.3 (C-3a), 46.5 (C-8a), 68.6 (C-8), 74.6 (C-4), 126.8 (C-2'), 136.4 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{26}O_2Na$ 261.18250, found 261.182581.



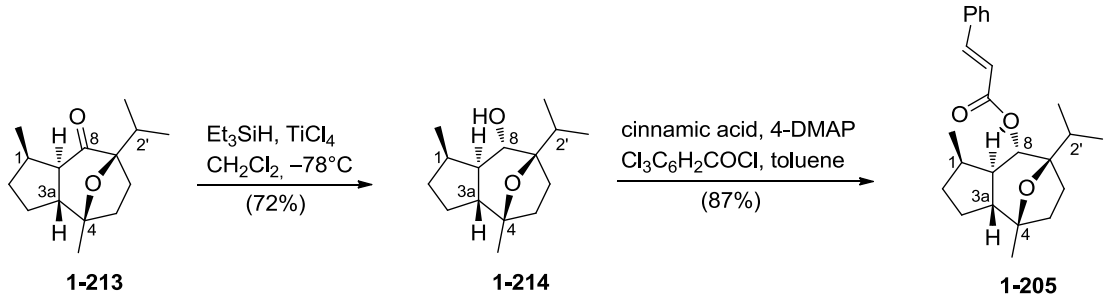
(1*R*,3a*R*,4*R*,7*R*,8*R*,8a*R*)-7-Isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-ol (1-212). Mercury (II) trifluoroacete (90 mg, 0.21 mmol) was added in one portion to a stirred

solution of alkenediol **1-211** (40 mg, 0.17 mmol) in CH_2Cl_2/MeOH (5 mL / 10 μL) at –78 °C. The mixture was stirred overnight at the same temperature, treated with water (20 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with water (10 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in MeOH (5 mL), cooled to –78 °C and $NaBH_4$ (120 mg, 3.16 mmol) was added in one portion. The resulting mixture was allowed to warm to ambient temperature within 3 h, treated with water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give epoxyazulene **1-212** (38 mg, 95%) as white crystals. R_f = 0.66 (petroleum ether/EtOAc, 4:1); $[\alpha]^{20}_D$ = –36.7 (*c* 0.55, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.83 (d, *J* = 6.8 Hz, 3H, 2'-CH_3), 0.89 (d, *J* = 6.8 Hz, 3H, 2'-CH_3), 0.92−0.96 (m, 1H, 3-H), 1.00 (d, *J* = 7.3 Hz, 3H, 1-CH_3), 1.13 (dddd, *J* = 13.2, 8.3, 8.3, 2.8 Hz, 1H, 2-H), 1.25 (s, 3H, 4-CH_3), 1.24−1.36 (m, 2H, 5-H, 6-H), 1.42 (ddd, *J* = 13.5, 7.2, 2.8 Hz, 1H, 8a-H), 1.60−1.67 (m, 1H, 3-H), 1.70−1.86 (m, 4H, 3a-H, 5-H, 6-H, 8-OH), 1.93 (dddd, *J* = 13.4, 10.8, 8.2, 2.8 Hz, 1H, 2-H), 2.23 (app ddd, *J* = 15.0, 7.4, 2.6 Hz, 1H, 1-H), 2.34 (app. sept, *J* = 6.8 Hz, 1H, 2'-H), 3.80 (br s, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 15.9 (2'-CH_3), 17.8 (2'-CH_3), 19.8 (1-CH_3), 24.5 (C-3), 24.6 (4-CH_3), 27.6 (C-6), 28.2 (C-9), 30.1 (C-5), 32.5 (C-2), 33.8 (C-1), 44.3 (C-3a), 44.5 (C-8a), 70.5 (C-8), 84.0 (C-4), 88.9 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{26}O_2Na$ 261.18250, found 261.182896.



1-212 **1-213**

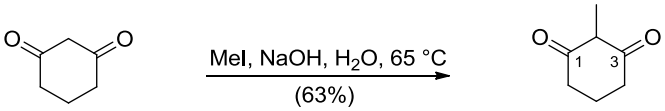
(1*R*,3a*R*,4*R*,7*R*,8a*R*)-7-Isopropyl-1,4-dimethyloctahydro-4,7-epoxyazulen-8(2*H*)-one (1-213). Dess-Martin periodinane (19.8 mg, 0.047 mmol) was added to a stirred solution of alcohol **1-212** (10.0 mg, 0.042 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature and then saturated $Na_2S_2O_3$ solution (1 mL) was added, followed by addition of saturated $NaHCO_3$ solution (1 mL) after 15 min. The resulting mixture was stirred for additional 15 min, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (10 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 33:1) to give ketone **1-213** (8.8 mg, 89%) as white crystals. R_f = 0.50 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –94.8 (*c* 0.92, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.94 (d, *J* = 6.9 Hz, 6H, 2 × 2'-CH_3), 0.99 (d, *J* = 7.1 Hz, 3H, 1-CH_3), 1.11−1.24 (m, 2H, 2-H, 3-H), 1.36 (s, 3H, 4-CH_3), 1.57−1.70 (m, 3H, 3-H, 5-H, 6-H), 1.91−2.07 (m, 3H, 2-H, 5-H, 6-H), 2.17−2.25 (m, 3H, 3a-H, 8a-H, 9-H), 2.37 (app ddd, *J* = 13.3, 13.3, 6.5 Hz, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.6 (1-CH_3), 17.6 (2'-CH_3), 18.4 (2'-CH_3), 23.9 (4-CH_3), 25.5 (C-3), 29.3 (C-2`), 30.1 (C-1), 30.5 (C-5), 31.0 (C-2), 31.5 (C-6), 52.1 (C-8a), 54.2 (C-3a), 83.8 (C-4), 89.8 (C-7); 207.6 (C-8); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{24}O_2Na$ 236.34991, found 236.34987.



1-213 **1-214** **1-205**

(1*R*,3a*R*,4*R*,7*R*,8*S*,8a*R*)-7-Isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-yl cinnamate (9-deoxy-englerin) (1-205). $TiCl_4$ (5 µL, 46 µmol) was added to a stirred solution of triethylsilane (24 µL, 152 µmol) and ketone **1-213** (8.8 mg, 38 µmol) in CH_2Cl_2 (2 mL) at –78 °C. The mixture was stirred for 30 min at this temperature, before it was treated with saturated $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with water (10 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 4:1) to give alcohol **1-214** (6.4 mg, 72%) as white crystals.

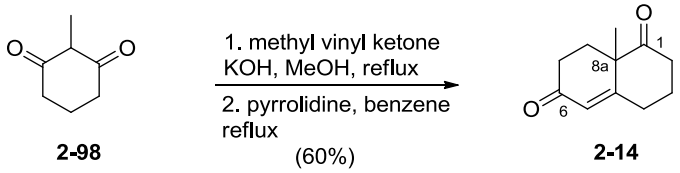
Triethylamine (11 µL, 81 µmol) and 2,4,6-trichlorobenzoyl chloride (10 µL, 67 µmol) were added successively to a stirred solution of alcohol **1-214** (6.4 mg, 27 µmol) and cinnamic acid (8.0 mg, 54 µmol) in dry toluene (1 mL), followed by addition of 4-DMAP (0.2 mg, cat. amounts) after 10 min. The reaction mixture was stirred for 12 h, diluted with diethyl ether (10 mg), and the organic phase was extracted with 1M HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL), saturated NaCl solution (5 mL), before it was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 33:1) to give 9-deoxy-englerin (**1-205**) (8.5 mg, 63% over 2 steps) as a colorless oil. R_f = 0.61 (petroleum ether/EtOAc, 9:1); $[\alpha]^{20}_D$ = –20.6 (*c* 0.32, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.94 (d, *J* = 7.1 Hz, 3H, 1-CH_3), 0.95 (d, *J* = 6.9 Hz, 3H, 2'-CH_3), 1.00 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 1.00−1.10 m (1H, 3-H), 1.18−1.23 (m, 1H, 2-H), 1.27 (s, 3H, 4-CH_3), 1.42−1.50 (m, 1H, 5-H), 1.59−1.68 (m, 2H, 6-H, 8a-H), 1.75−1.86 (m, 4H, 3a-H, 5-H, 6-H, 2'-H), 1.93 (dddd, *J* = 13.4, 10.8, 8.2, 2.8 Hz, 1H, 2-H), 1.99−2.12 (m, 2H, 1-H, 3-H), 5.17 (d, *J* = 10.4 Hz, 1H, 8-H); 6.40 (d, *J* = 16.0 Hz, 1H, 4'-H); 7.35−7.39 (m, 3H, 2 × meta-, para); 7.51−7.53 (m, 2H, 2 × ortho), 7.65 (d, *J* = 15.8 Hz, 1H, 5'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 17.3 (1-CH_3), 17.6 (2'-CH_3), 18.4 (2'-CH_3), 24.4 (4-CH_3), 25.0 (C-3), 30.4 (C-6), 31.1 (C-5), 31.2 (C-2), 31.5 (C-1), 33.3 (C-2'), 47.5 (C-8a), 49.0 (C-3a), 72.6 (C-8), 83.2 (C-4), 86.0 (C-7), 118.4 (C-4'), 128.1 (2 × orto), 128.8 (2 × meta), 130.2 (para), 134. 4 (C-6'), 144.7 (C-5'), 165.8 (C=O ester); HRMS (ESI): $[M+Na]^+$ calcd for $C_{24}H_{32}O_3$ 391.22437, found 391.224232.



2-97 **2-98**

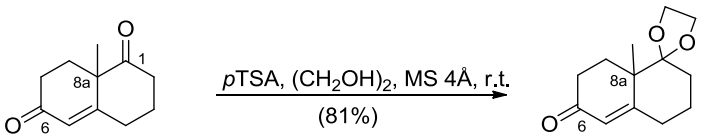
2-Methylcyclohexane-1,3-dione (2-98).[138] Cyclohexa-1,3-dione (**2-97**) (42.0 g, 0.38 mol) was dissolved in a solution of NaOH (14 g, 0.35 mol) in water (70 mL). Methyl iodide (46 mL, 0.74 mmol) was added in one portion and the resulting solution was stirred for 20 h at 65

°C before it was cooled to 0 °C. The precipitate was filtered and washed with cold petroleum ether (50 mL) and cold water (40 mL) to give diketone (29.8, 63%) **2-98** as white crystals (m.p. 198–201 °C (lit.[188] 204–205 °C)). ^{1}H NMR (400 MHz, DMSO-d_6; 100% enol tautomer): δ[ppm] = 1.52 (s, 3H, CH_3), 1.80 (m, 2H, 2 × 5-H), 2.29 (dd, *J* = 6.5, 6.5 Hz, 4H, 2 × 4-H, 2 × 6-H); ^{13}C NMR (100 MHz, DMSO-d6): δ[ppm] = 7.7 (CH_3), 21.0 (C-5), 33.0 (C-4, C-6), 110.0 (C-1, C-3) C-2 was not observed.



2-98 **2-14**

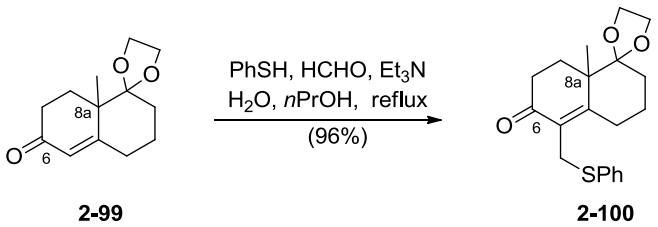
8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (2-14).[139] A solution of diketone **2-98** (42.0 g, 0.33 mol), methyl vinyl ketone (35.0 g, 0.50 mol) and potassium hydroxide (0.4 g, 0.01 mmol) in methanol (160 mL) was stirred for 3 h under reflux. The volatiles were removed under reduced pressure and the residue was dissolved in benzene (650 mL) and treated with pyrrolidine (2 mL). The resulting mixture was stirred under reflux with a Dean-Stark condenser for 1 h before it was cooled to room temperature, diluted with diethyl ether (200 mL), washed with 1M HCl solution (200 mL), saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from petroleum ether/diethyl ether (1:1, 300 mL) to give Wieland-Miescher ketone (**2-14**) (35.6 g, 60%) as white crystals (m.p. 46–49.5 °C (lit.[139] 48.6–50 °C)). R_f = 0.22 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] = 1.42 (s, 3H, CH_3), 1.67 (qt, *J* = 13.3, 4.4 Hz, 1H, 3-H), 2.05–2.13 (m, 3H, 3-H, 2 × 8-H), 2.41–2.49 (m, 4H, 2-H, 4-H, 2 × 7-H), 2.62–2.71 (m, 2H, 2-H, 4-H), 5.82 (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ[ppm] = 23.0 (C-3), 23.3 (CH_3), 29.7 (C-8), 31.8 (C-4), 33.7 (C-7), 37.7 (C-2),50.7 (C-8a), 126.9 (C-5), 166.0 (C-4a), 198.4 (C-6), 211.1 (C-1).



2-14 **2-99**

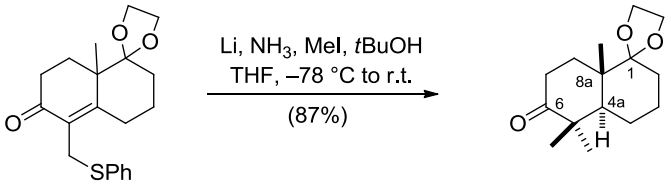
8a'-Methyl-3',4',8',8a'-tetrahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'*H*)-one (2-99).[141] *p*TSA (115.3 g, 0.61 mol) was added to a stirred mixture of diketone **2-14** (107.8 g, 0.60 mol) and molecular sieves (4Å, 200 g) in ethylene glycol (2.7 L) at room temperature. After stirring for 23 min the reaction mixture was poured into a saturated $NaHCO_3$ solution (3 L) and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with water (500 mL), saturated NaCl solution (300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from petroleum ether/diethyl ether (20:1, 600 mL) to give enone **2-99** (108.5 g, 81%) as white crystals (m.p. 50–51.5 °C (lit.[141] 51–52 °C)). R_f = 0.34 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.34 (s, 3H, CH_3), 1.64–1.93 (m, 4H, 2 × 3-H, 8-H, 2 × 2-H), 2.24–2.28 (m, 2H, 8-H, 4-H), 2.34–2.46 (m, 3H, 4-H, 2 × 7-H), 3.93–4.08 (m, 4H, $(CH_2O)_2$), 5.80 (s, 1H, 5-H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ[ppm] = 20.6 (C-3), 21.9 (CH_3), 27.0 (C-8), 30.2 (C-4), 31.6 (C-7), 34.0 (C-2), 45.2 (C-8a), 65.2 (($CH_2O)_2$), 65.5 (($CH_2O)_2$), 112.5 (C-1), 125.8 (C-5), 167.9 (C-4a), 199.4 (C-6).



2-99 **2-100**

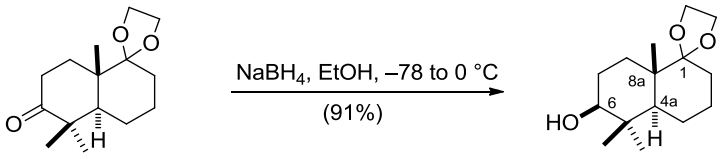
8a'-Methyl-5'-((phenylthio)methyl)-3',4',8',8a'-tetrahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one (2-100).[144] Enone **2-99** (103.0 g, 0.45 mmol), thiophenol (76.6 g, 0.70 mol), formaline (57 mL, 0.74 mol) and triethylamine (84 mL, 0.60 mol) were dissolved in propan-1-ol (350 mL). The resulting mixture was stirred for 24 h under reflux, before it was cooled down to ambient temperature and filtered. The mother liquor was treated with an aqueous solution of KOH (5%, 1 L) and extracted with diethyl ether (3 × 500 mL). The combined organic layers were washed with KOH solution (5%, 3 × 250 mL), saturated NaCl solution (300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give enone **2-100** (153.0 g, 96%) as a colorless oil. R_f = 0.37 (petroleum ether/ EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.31 (s, 3H, CH_3), 1.49–1.60 (m, 1H, 3-H), 1.63–1.78 (m, 3H, 2-H, 3-H, 8-H), 1.85 (ddd, *J* = 13.5, 13.5, 4.6 Hz, 1H, 2-H), 1.98–2.07 (m, 1H, 4-H), 2.24 (ddd, *J* = 13.5, 13.5, 4.8 Hz, 1H, 8-H), 2.37 (ddd, *J* = 14.9, 14.9, 5.1 Hz, 1H, 7-H), 2.49 (ddd, *J* = 15.9, 15.9, 4.4 Hz, 1H, 7-H), 2.66 (d, *J* = 15.5 Hz, 1H, 4-H), 3.76 (d, *J* = 11.6 Hz, 1H, CH_2S), 3.90–3.99 (m, 5H, ($CH_2O)_2$, CH_2S), 7.19–7.28 (m, 3H, 2 × $H_{Ar\text{-}m}$, $H_{Ar\text{-}p}$), 7.35–7.43 (m, 2H, $H_{Ar\text{-}o}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.4 (CH_3), 21.7 (C-3), 26.5 (C-8), 27.1 (C-4), 29.4 (CH_2S), 29.8 (C-2), 33.9 (C-7), 45.8 (C-8a), 65.2 (($CH_2O)_2$), 65.4 (($CH_2O)_2$), 112.8 (C-1), 126.7 ($C_{Ar\text{-}p}$), 128.8 ($C_{Ar\text{-}m}$), 130.4 (C-5), 131.5 ($C_{Ar\text{-}o}$), 136.4 ($C_{Ar\text{-}ipso}$), 164.3 (C-4a), 197.0 (C-6).



2-100 **2-101**

(4a'*S*,8a'*S*)-5',5',8a'-trimethylhexahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'*H*)-one (2-101).[144] Lithium (13.1 g, 1.88 mol) was added to liquid ammonia (2 L) at –78 °C in small portions. The resulting blue solution was stirred for 1 h, before it was treated with a solution of enone **2-100** (108.0 g, 0.31 mol) and *tert*-butanol (58 mL, 0.61 mol) in THF (1 L) at –78 °C over a period of 2 h. The reaction mixture was stirred for additional 1 h and then methyl iodide (196 mL, 3.14 mol) was added at the same temperature. The resulting mixture was allowed to warm to room temperature, stirred overnight, carefully treated with water (1 L) and extracted with diethyl ether (3 × 250 mL). The combined organic layers were washed with saturated NaCl solution (3 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to

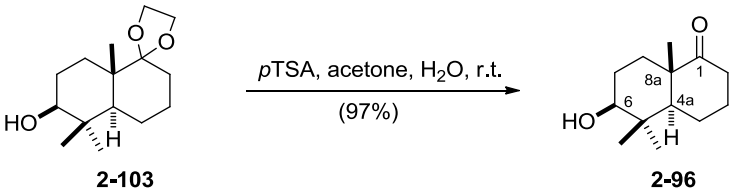
give ketone **2-101** (69.1 g, 87%) as a colorless oil. R_f = 0.62 (petroleum ether/ EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.03 (s, 3H, 5-CH_3), 1.06 (s, 3H, 5-CH_3), 1.22 (s, 3H, 8a-CH_3), 1.44–1.55 (m, 4H, 2-H, 3-H, 2 × 4-H), 1.62–1.74 (m, 3H, 2-H, 3-H, 8-H), 1.81–1.89 (m, 1H, 4a-H), 1.93 (ddd, J = 13.4, 13.4, 5.3 Hz, 1H, 8-H), 2.28–2.36 (m, 1H, 7-H), 2.57–2.63 (m, 1H, 7-H), 3.82–3.93 (m, 4H, $(CH_2O)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.2 (8a-CH_3), 21.8 (5-CH_3), 21.9 (C-4), 23.0 (C-3), 25.6 (5-CH_3), 30.0 (C-2), 30.4 (C-8), 34.6 (C-7), 42.8 (C-8a), 47.8 (C-5), 49.3 (C-4a), 65.0 $(CH_2O)_2$), 65.3 $(CH_2O)_2$), 113.0 (C-1), 216.8 (C-6).



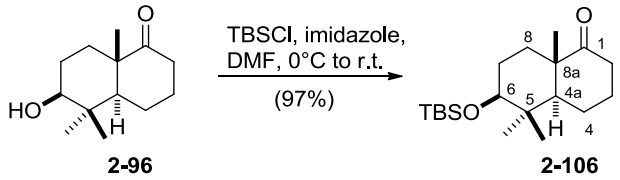
2-101 **2-103**

(4a'*S*,6'*S*,8a'*S*)-5',5',8a'-Trimethyloctahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'-ol (2-103). Sodium borohydride (0.12 g, 3.2 mmol) was added in one portion to a stirred solution of ketone **2-101** (0.81 g, 3.2 mmol) in ethanol (10 mL) at –78 °C. The resulting mixture was allowed to warm to 0 °C and stirred for 0.5 h before it was carefully treated with water (10 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from petroleum ether/ethyl acetate (9:1, 10 mL) to give desired diastereomer **2-103** (0.74 g, 91%) as white crystals. R_f = 0.68 (petroleum ether/ EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.79 (s, 3H, 8a-CH_3), 0.98 (s, 3H, 5-CH_3), 1.05 (s, 3H, 5-CH_3), 1.25–1.72 (m, 11H, 2 × 2-H, 2 × 3-H, 2 × 4-H, 4a-H, 2 × 7-H, 2 × 8-H), 3.24 (dd, J = 11.1, 4.3 Hz, 1H, 6-H), 3.79–3.94 (m, 4H, $(CH_2O)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 15.4 (5-CH_3), 16.5 (8a-CH_3), 20.6 (5-CH_3), 23.1 (C-4), 27.1 (C-3), 28.0 (C-2), 28.7 (C-7), 30.4 (C-8), 38.8 (C-5), 43.1 (C-8a), 48.2 (C-4a), 64.8 $(CH_2O)_2$), 65.3 $(CH_2O)_2$), 78.7 (C-6), 113.3 (C-1).

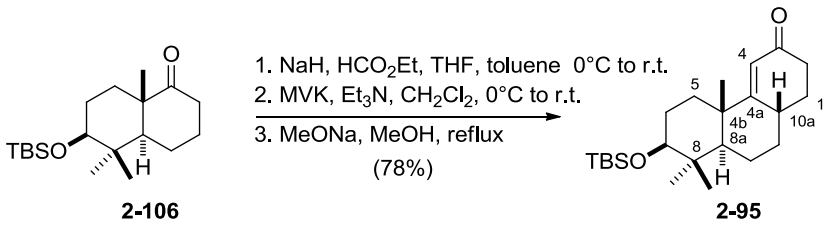
Recycling of ketone XX from the mother liquor. The mother liqior after filtration was concentrated in vacuo to give a diastereomeric mixture of alcohols **2-103/2-102** in a ratio 1:7 (55 mg, 0.22 mmol). A CH_2Cl_2 solution (2 mL) of these alcohols was treated with Dess-Martin reagent (101 mg, 0.24 mmol) and the resulting solution was stirred for 2 h at room temperature before it was treated with saturated $Na_2S_2O_3$ solution (1 mL) and stirred for additional 15 min. The resulting mixture was washed with saturated $NaHCO_3$ solution (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL).The combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give ketone **2-101** (48 mg, 87%) as white crystals.



(4a*S*,6*S*,8a*S*)-6-Hydroxy-5,5,8a-trimethyloctahydronaphthalen-1(2*H*)-one (2-96).[189] *p*TSA monohydrate (0.61 g, 3.2 mmol) was added to a stirred solution of acetal **2-103** (0.82 g, 3.2 mmol) in an acetone/water mixture (1:1, 20 mL). The resulting mixture was stirred overnight before it was treated with saturated $NaHCO_3$ solution (20 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from petroleum ether/ethyl acetate (9:1, 10 mL) to give ketone **2-96** (0.66 g, 97%) as white crystals. R_f = 0.37 (petroleum ether/ EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.87 (s, 3H, 5-CH_3), 0.99 (s, 3H, 8a-CH_3), 1.12 (s, 3H, 5-CH_3), 1.42–1.79 (m, 8H, H-4a, 2 × 4-H, 2 × 3-H, 7-H, 2 × 8-H), 2.02–2.10 (m, 1H, 7-H), 2.10–2.18 (m, 1H, 2-H), 2.54 (ddd, *J* = 14.0, 14.0, 7.0 Hz, 1H, 2-H), 3.16–3.20 (m, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 15.8 (C-4), 18.6 (5-CH_3), 20.7 (8a-CH_3), 26.2 (5-CH_3), 26.9 (C-3), 27.8 (C-7), 30.9 (C-8), 31.2 (C-2), 37.4 (C-5), 48.6 (C-8a), 52.6 (C-4a), 78.1 (C-6), 215.4 (C-1).



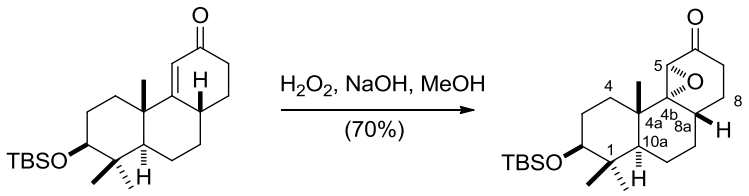
(4a*S*,6*S*,8a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-5,5,8a-trimethyloctahydronaphthalen-1(2*H*)-one (2-106). TBSCl (7.9 g, 52.4 mmol) was added in one portion to a stirred solution of alcohol **2-96** (10.0 g, 47.6 mmol) and imidazole (7.1 g, 104.8 mmol) in DMF (100 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight, treated with water (200 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (200 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give ketone **2-106** (15.0 g, 97%) as white crystals. R_f = 0.68 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.03 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.86 (s, 3H, 5-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.92 (s, 3H, 8a-CH_3), 1.14 (s, 3H, 5-CH_3), 1.47–1.80 (m, 8H, H-4a, 2 × 4-H, 2 × 3-H, 7-H, 2 × 8-H), 2.03–2.09 (m, 1H, 7-H), 2.11–2.22 (m, 1H, 2-H), 2.56 (ddd, *J* = 14.0, 14.0, 7.0 Hz, 1H, 2-H), 3.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –5.0 ($Si(CH_3)_2$), –3.8 ($Si(CH_3)_2$), 16.3 (C-4), 18.1 (Si*C*$(CH_3)_3$), 18.7 (5-CH_3), 21.0 (8a-CH_3), 25.9 ($SiC(CH_3)_3$), 26.4 (5-CH_3), 27.3 (C-3), 28.4 (C-7), 31.1 (C-8), 37.5 (C-2), 40.3 (C-5), 48.6 (C-8a), 52.7 (C-4a), 78.7 (C-6), 215.5 (C-1).



(4b*S*,7*S*,8a*R*,10a*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-4b,8,8-trimethyl-1,4b,5,6,7,8,8a,9,10,10a-decahydrophenanthren-3(2H)-one (2-95). NaH (60% suspension in mineral oil; 3.2 g, 80.0 mmol) was added portionwise to a stirred solution of ketone **2-106** (20.0 g, 61.5 mmol) in a THF/toluene (200 mL/80 mL) mixture at 0 °C. The resulting suspension was stirred 30 min at the same temperature followed by addition of ethyl formate (10 mL). The resulting mixture was allowed to warm to room temperature, stirred overnight and carefully treated with water (200 mL) at 0 °C. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo.

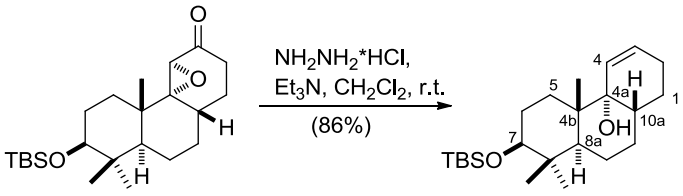
The obtained formylketone **2-107** was dissolved in CH_2Cl_2 (100 mL) and treated with triethylamine (17.2 mL, 123.0 mmol) and methyl vinyl ketone (15.4 mL, 215.2 mmol) at 0 °C. The resulting solution was stirred for 2 h at room temperature, and then diluted with water (200 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo.

This residue was dissolved in methanol (100 mL) and treated with MeONa (16.6 g, 307.5 mmol). The resulting solution was stirred under reflux for 1 h, treated with water and concentrated in vacuo. Additional 200 mL of water was added and the mixture extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give tricyclic enone **2-95** (18.1 g, 78%) as white crystals. R_f = 0.37 (petroleum ether/ EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.03 (s, 3H, Si-CH_3), 0.05 (s, 3H, Si-CH_3), 0.82 (s, 3H, 8-CH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.91 (s, 3H, 8-CH_3), 1.02 (dd, *J* = 12.1, 2.8 Hz, 1H, 8a-H), 1.11 (s, 3H, 4b-CH_3), 1.14–1.21 (m, 1H, 10-H), 1.49–1.77 (m, 7H, 1-H, 2 × 5-H, 2 × 6-H, 2 × 9-H), 1.98–2.11 (m, 2H, H-1, H-10), 2.23 (ddd, *J* = 16.4, 12.7, 5.0 Hz, 1H, 2-H), 2.36 (ddd, *J* = 16.4, 5.0, 5.0 Hz, 1H, 2-H), 2.49–2.58 (m, 1H, 10a-H), 3.17 (dd, *J* = 10.2, 4.9 Hz, 1H, 7-H), 5.80 (d, *J* = 1.8 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –5.0 (Si-CH_3), –3.8 (Si-CH_3), 16.1 (8-CH_3), 18.1 (Si-C), 21.3 (4b-CH_3, C-9), 25.9 (C(CH_3)$_3$), 27.7 (C-6), 28.5 (8-CH_3), 29.3 (C-1), 34.2 (C-10a), 34.7 (C-5), 35.1 (C-10), 35.9 (C-2), 40.1 (C-8), 40.6 (C-4b), 52.2 (C-8a), 78.8 (C-7), 119.8 (C-4), 176.0 (C-4a), 201.3 (C-3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{40}O_2SiNa$ 399.268978, found 399.268854.



2-95 2-109

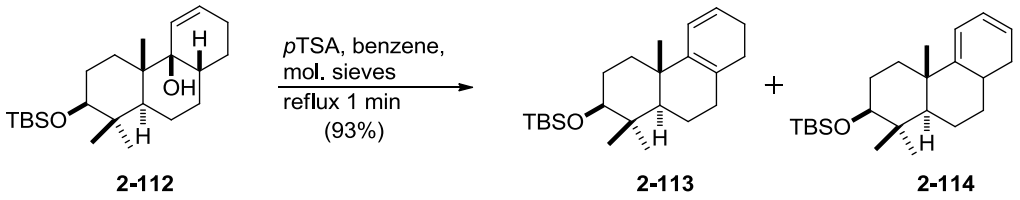
(2*S*,4a*S*,4b*R*,5*S*,8a*S*,10a*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1,1,4a-trimethyldecahydro-1*H*-phenanthro[4,4a-b]oxiren-6(5a*H*)-one (2-109). Hydrogen peroxide (30% aqueous solution; 10 mL, 88.2 mmol) was added to a stirred solution of enone **2-95** (5.8 g, 15.4 mmol) in methanol at –40 °C followed by addition of NaOH (10% aqueous solution; 6 mL, 15.0 mmol) at the same temperature. The resulting mixture was stirred overnight, treated with saturated $Na_2S_2O_3$ solution (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give epoxide **2-109** (4.2 g, 70%) as white crystals. R_f = 0.60 (petroleum ether/ EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.00 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), 0.75 (s, 3H, 1-CH_3), 0.85 (s, 9H, $C(CH_3)_3$), 0.89 (s, 3H, 1-CH_3), 1.04 (ddd, *J* = 12.9, 3.4, 3.4 Hz, 1H, 4-H), 1.10 (s, 3H, 4a-CH_3), 1.19 (dd, *J* = 12.4, 2.5 Hz, 1H, 10a-H), 1.23–1.39 (m, 2H, 4-H, 9-H), 1.45–1.86 (m, 5H, 2 × 3-H, 2 × 8-H, 10-H), 1.70–1.77 (m, 1H, 10-H), 1.89 (ddd, *J* = 12.8, 7.6, 3.5 Hz, 1H, 9-H), 2.00–2.18 (m, 2H, 7-H, 8a-H), 2.40 (ddd, *J* = 19.0, 5.1, 1.6 Hz, 1H, 7-H), 3.14 (dd, *J* = 10.9, 4.8 Hz, 1H, 2-H), 3.18 (s, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –5.0 ($Si(CH_3)_2$), –3.9 ($Si(CH_3)_2$), 15.8 (1-CH_3), 18.0 ($C(CH_3)_3$), 19.5 (4a-CH_3), 21.2 (C-10), 23.6 (C-8), 25.8 ($C(CH_3)_3$), 26.8 (C-3), 28.0 (1-CH_3), 28.6 (C-4), 32.0 (C-8a, C-9), 36.2 (C-7), 37.6 (C-4a), 39.6 (C-1), 50.0 (C-10a), 57.6 (C-5), 71.1 (C-4b), 78.2 (C-2), 206.7 (C-6); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{40}O_3SiNa$ 415.263893, found 415.264016.



2-109 2-112

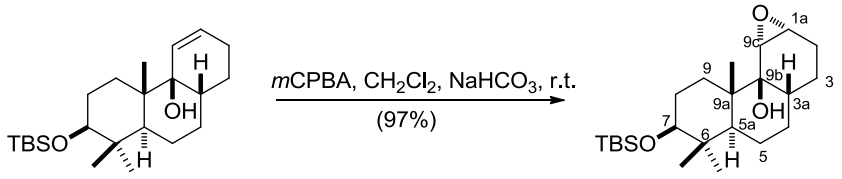
(4a*S*,4b*S*,7*S*,8a*S*,10a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-4b,8,8-trimethyl-1,2,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydrophenanthren-4a-ol (2-112). Hydrazine monohydrochloride (1.3 g, 19.1 mmol) and triethylamine (4 mL, 28.5 mmol) were sonicated in CH_2Cl_2 (20 mL) for 0.5 h before a solution of ketone **2-109** (2.5 g, 6.4 mmol) in dichlormethane (10 mL) was added at room temperature. The resulting solution was stirred for 2 h, then the solvent was removed in vacuo and the residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give allylic alcohol **2-112** (2.2 g, 86%) as a colorless oil. R_f = 0.66 (petroleum ether/ EtOAc 9:1); ^{1}H NMR (400 MHz, C_6D_6): δ[ppm] = 0.07 (s, 3H, $Si(CH_3)_2$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.88 (s, 3H, 4b-CH_3), 0.94 (s, 3H, 8-CH_3), 1.02 (br s, 12H, $SiC(CH_3)_3$, 8-CH_3), 1.15–1.20 (m, 1H, 1-H), 1.26–1.40 (m, 4H, 1-H, 5-H, 9-H, 10-H), 1.50 (ddd, *J* = 12.2, 12.2, 2.9 Hz, 1H, 10a-H), 1.55–1.97 (m, 8H, 2 × 2-H, 5-H, 2 × 6-H, 8a-H, 9-H, 10-H), 3.30 (dd, *J* = 11.1, 4.8 Hz, 1H, 7-H), 5.61 (ddd, *J* = 6.6, 6.6, 3.3 Hz, 1H, 3-H), 5.73 (d, *J* = 10.1 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, C_6D_6): δ[ppm] = –4.7

($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 16.1 (8-CH_3), 17.4 (4b-CH_3), 18.4 ($SiC(CH_3)_3$), 21.9 (C-10), 25.3 (C-1), 26.1 (C-2), 26.2 ($SiC(CH_3)_3$), 28.2 (C-6), 28.7 (8-CH_3), 29.2 (C-5, C-9), 37.1 (C-10a), 39.8 (C-8), 40.5 (C-4b), 44.6 (C-8a), 73.7 (C-4a), 79.5 (C-7), 130.3 (C-4), 131.7 (C-3).



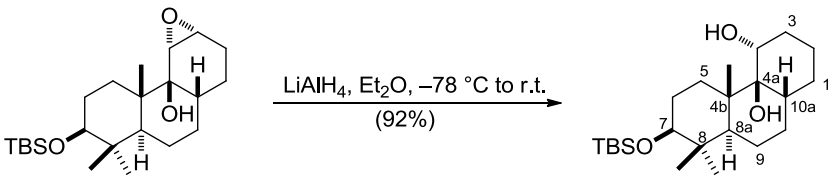
2-112 **2-113** **2-114**

(2*S*,4a*S*,10a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1,1,4a-trimethyl-1,2,3,4,4a,7,8,9,10,10a-decahydrophenanthrene (2-113). Molecular sieves (4Å, 0.2 g) were added to a stirred solution of allylic alcohol **2-112** (500 mg, 1.28 mmol) in benzene (15 mL) followed by addition of *p*TSA monohydrate (10 mg). Then the flask was transferred to a preheated oil bath (100 °C) and stirred there for 1 minute. The resulting mixture was concentrated in vacuo and the residue was purified by flash chromatography (petroleum ether/EtOAc, 33:1) to give a mixture of dienes **2-113** and **2-114** (490 mg, 1.27 mmol) as a colorless oil. R_f = 0.69 (petroleum ether/ EtOAc 33:1).

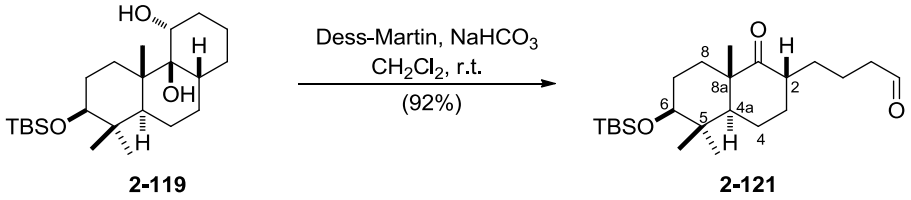


2-112 **2-118**

(1a*R*,3a*S*,5a*S*,7*S*,9a*S*,9b*S*,9c*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-6,6,9a-trimethyltetradecahydrophenanthro[3,4-b]oxiren-9b-ol (2-118). *m*CPBA (70%, 500 mg, 2.90 mmol) was added to a stirred suspension of $NaHCO_3$ (100 mg) and alcohol **2-112** (650 mg, 1.72 mmol) in CH_2Cl_2 (6 mL) at room temperature. The resulting mixture was stirred for 5 h before it was treated with saturated $Na_2S_2O_3$ solution (10 mL) and stirred for additional 1 h. The organic layer was separated and washed with saturated $NaHCO_3$ solution (2 × 10 mL), water (10 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give epoxide **2-118** (660 mg, 97%) as a colorless oil. R_f = 0.64 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.06 (s, 3H, $Si(CH_3)_2$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.77 (s, 3H, 9a-CH_3), 0.71–0.84 (m, 1H, 3-H), 0.93 (s, 3H, 6-CH_3), 0.99 (s, 3H, 6-CH_3), 1.02 (s, 9H, $SiC(CH_3)_3$), 0.95–1.00 (m, 1H, 3a-H), 1.12–1.38 (m, 5H, 2-H, 3-H, 4-H, 5-H, 9-H), 1.55–1.71 (m, 5H, 4-H, 5-H, 2 × 8-H), 1.80 (ddd, *J* = 14.3, 2.0, 2.0 Hz, 1H, 2-H), 1.87 (dd, *J* = 12.5, 2.4 Hz, 1H, 5a-H), 2.14 (ddd, *J* = 12.9, 12.9, 5.3 Hz, 1H, 9-H), 2.59 (s, OH), 2.87–2.92 (m, 1H, 1a-H), 2.96 (d, *J* = 3.8 Hz, 1H, 9c-H), 3.30 (dd, *J* = 10.6, 5.3 Hz, 1H, 7-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.7 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 16.2 (6-CH_3), 16.4 (4a-CH_3), 18.4 ($SiC(CH_3)_3$), 20.9 (C-3), 21.8 (C-5), 25.4 (C-2), 26.2 ($SiC(CH_3)_3$), 28.0 (C-4, C-8), 28.5 (6-CH_3), 28.9 (C-9), 37.6 (C-3a), 39.7 (C-6), 40.6 (C-9a), 45.2 (C-5a), 56.0 (C-1a, C-9c), 71.5 (C-9b), 79.3 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{42}O_3SiNa$ 417.279543, found 417.279957.

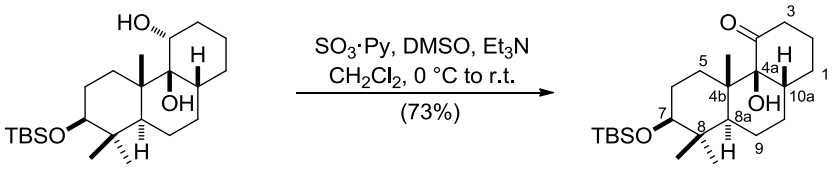


(4*R*,4a*S*,4b*S*,7*S*,8a*S*,10a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-4b,8,8-trimethyltetradecahydrophenanthrene-4,4a-diol (2-119). A solution of epoxide **2-118** (660 mg, 1.68 mmol) in diethyl ether (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in diethyl ether (20 mL) at –78 °C. The resulting mixture was allowed to warm to room temperature, stirred for 2 h before it was treated with isopropanol (1 mL) and water (50 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL).). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give diol **2-119** (610 mg, 92%) as a colorless oil. R_f = 0.21 (petroleum ether/ EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.06 (s, 6H, $Si(CH_3)_2$), 0.79 (s, 3H, 8-CH_3), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 3H, 8-CH_3), 1.05 (s, 3H, 4b-CH_3), 1.09–1.72 (m, 15H, 2 × 1-H, 2 × 2-H, 2 × 3-H, 5-H, 2 × 6-H, 8a-H, 2 × 9-H, 2 × 10-H, 10a-H), 1.98–2.04 (m, 1H, 5-H), 2.85 (s, 1H, 4a-OH), 3.20–3.24 (m, 1H, 7-H), 3.37 (d, *J* = 5.0 Hz, 1H, 4-OH), 3.71 (ddd, *J* = 10.2, 5.2, 5.2 Hz, 1H, 4-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.7 ($Si(CH_3)_2$), –3.5 ($Si(CH_3)_2$), 16.6 (8-CH_3), 17.0 (4b-CH_3), 18.8 (Si*C*$(CH_3)_3$), 22.7 (C-9), 24.7 (C-2), 26.4 ($SiC(CH_3)_3$), 29.1 (C-6), 29.5 (8-CH_3), 30.1 (C-1), 30.8 (C-10), 33.6 (C-5), 34.1 (C-3), 39.5 (C-10a), 40.5 (C-8), 44.0 (C-4b), 46.8 (C-8a), 71.4 (C-4), 77.6 (C-4a), 80.2 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{44}O_3SiNa$ 419.295193, found 419.295294.



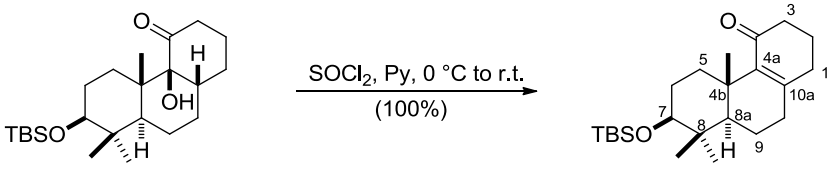
4-((2*R*,4a*S*,6*S*,8a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-5,5,8a-trimethyl-1-oxodecahydronaphthalen-2-yl)butanal (2-121). Dess-Martin reagent[58] (43 mg, 0.103 mol) was added in one portion to a stirred suspension of diol **2-119** (37 mg, 0.093 mol) and $NaHCO_3$ (50 mg, 0.595 mmol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred for 2 h before it was treated with saturated $Na_2S_2O_3$ solution (5 mL) and stirred for additional 15 minutes. The resulting suspension was washed with saturated $NaHCO_3$ solution (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give ketone **2-121** (34 mg, 92%) as a colorless oil. R_f = 0.27 (petroleum ether/ EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.06 (s, 6H, $Si(CH_3)_2$), 0.79–0.89 (m, 3H, 3-H, 4a-H, 1'-H), 0.84 (s, 3H, 5-CH_3), 0.86 (br s, 6H, 5-CH_3, 8a-CH_3), 1.00 (s, 9H, $C(CH_3)_3$), 1.33–1.92 (m, 10H, 3-H, 2 × 4-H, 2 × 7-H, 1'-H,

2 × 2'-H, 2 × 3'-H), 2.16 (ddd, *J* = 12.8, 12.8, 6.2 Hz, 1H, 2-H), 3.02 (dd, *J* = 11.0, 4.4 Hz, 1H, 6-H), 9.36 (dd, *J* = 1.5, 1.5 Hz, 1H, 4'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.8 ($Si(CH_3)_2$), –3.7 ($Si(CH_3)_2$), 16.4 (5-CH_3), 18.3 ($SiC(CH_3)_3$), 18.6 (8a-CH_3), 20.1 (C-2), 21.3 (C-4), 26.1 ($SiC(CH_3)_3$), 27.7 (C-7), 28.3 (5-CH_3), 29.7 (C-1'), 31.6 (C-8), 33.7 (C-3), 40.4 (C-5), 44.1 (C-3'), 45.0 (C-4a), 48.4 (C-8a), 53.2 (C-2), 79.0 (C-6), 200.7 (C-4'), 213.5 (C-1).



2-119 **2-120**

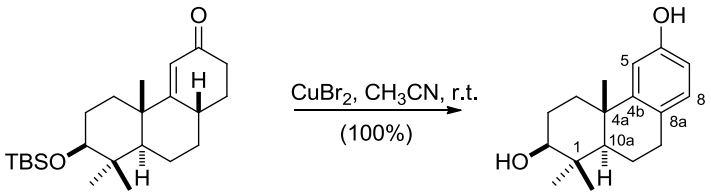
(4a*S*,4b*S*,7*S*,8a*S*,10a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-4a-hydroxy-4b,8,8-trimethyldodecahydrophenanthren-4(4a*H*)-one (2-120). To a stirred solution of diol **2-119** (600 mg, 1.51 mmol) in CH_2Cl_2 (20 mL) were added at room temperature Et_3N (2.1 mL, 15.1 mmol) and a solution of SO_3·Py (1.2 g, 7.55 mmol) in DMSO (20 mL). The reaction mixture was stirred for 1 h before it was treated with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL), 1 N HCl (2 × 100 mL), water (2 × 100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give ketone **2-120** as a colorless oil (430 mg, 73%). R_f = 0.32 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.10 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 3H, 8-CH_3), 0.99 (s, 3H, 8-CH_3), 1.02 (s, 9H, $SiC(CH_3)_3$), 1.11 (s, 3H, 4b-CH_3), 1.18–1.57 (m, 11H, 2 × 1-H, 2 × 2-H, 5-H, 6-H, 8a-H, 2 × 9-H, 2 × 10-H), 1.61–1.77 (m, 2H, 6-H, 10a-H), 2.06–2.12 (m, 3-H), 2.21 (ddd, *J* = 13.4, 3.5, 3.5 Hz, 1H, 5-H), 2.62 (ddd, *J* = 12.7, 11.7, 6.2 Hz, 1H, 3-H), 3.17 (dd, *J* = 11.5, 4.4 Hz, 1H, 7-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.7 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 16.4 (8-CH_3), 16.5 (4b-CH_3), 18.4 ($SiC(CH_3)_3$), 21.4 (C-9), 24.9 (C-2), 26.2 ($SiC(CH_3)_3$), 27.2 (C-1), 28.0 (C-6), 28.5 (C-10), 28.9 (8-CH_3), 29.8 (C-5), 39.5 (C-3), 39.9 (C-8), 40.4 (C-10a), 41.0 (C-4b), 46.2 (C-8a), 79.5 (C-7), 81.4 (C-4a), 210.9 (C-4); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{42}O_3SiNa$ 417.279543, found 417.279653.



2-120 **2-94**

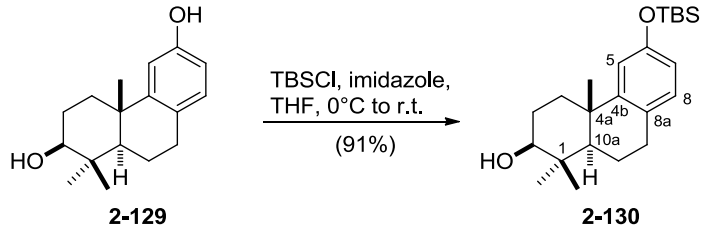
(4b*S*,7*S*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-4b,8,8-trimethyl-2,3,4b,5,6,7,8,8a,9,10-decahydrophenanthren-4(1*H*)-one (2-94). Thionyl chloride (0.23 mL, 3.17 mmol) was added dropwise to a stirred solution of alcohol **2-120** (230 mg, 0.58 mmol) in pyridine (5 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 20 min before it was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give enone **2-94** as a colorless oil (220 mg, 100%). R_f = 0.52 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.09 (s, 3H,

$Si(CH_3)_2$), 0.11 (s, 3H, $Si(CH_3)_2$), 0.84 (dd, *J* = 12.2, 1.6 Hz, 1H, 8a-H), 0.94 (s, 3H, 8-CH_3), 1.00 (s, 3H, 8-CH_3), 1.03 (s, 9H, $SiC(CH_3)_3$), 1.03–1.08 (m, 1H, 5-H),1.23–1.49 (m, 4H, 2 × 2-H, 2 × 9-H), 1.39 (s, 3H, 4b-CH_3), 1.58–1.69 (m, 3H, 2 × 1-H, 6-H), 1.75–1.86 (m, 3H, 6-H, 2 × 10-H), 2.06 (ddd, *J* = 16.2, 9.3, 7.1 Hz, 1H, 3-H), 2.27–2.34 (m, 1H, 3-H), 3.19–3.28 (m, 2H, 5-H, 7-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.8 ($Si(CH_3)_2$), –3.6 ($Si(CH_3)_2$), 16.6 (8-CH_3), 18.3 (C-9), 18.4 ($SiC(CH_3)_3$), 19.6 (4b-CH_3), 22.3 (C-2), 26.2 ($SiC(CH_3)_3$), 28.7 (C-6), 28.9 (8-CH_3), 31.8 (C-1), 34.6 (C-10), 34.7 (C-5), 37.8 (C-4b), 39.8 (C-8), 40.0 (C-3), 51.8 (C-8a), 79.8 (C-7), 142.8 (C-4a), 154.8 (C-10a), 196.7 (C-4); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{40}O_2SiNa$ 377.287034, found 377.286828.



2-95 **2-129**

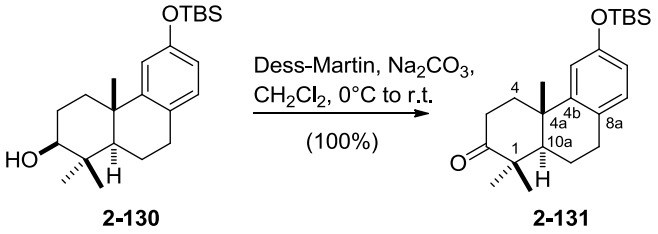
(2*S*,4a*S*,10a*R*)-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,6-diol (2-129). To a solution of enone **2-95** (1.00 g, 2.65 mmol) in acetonitrile (50 mL) was added a solution of $CuBr_2$ (1.00 g, 4.48 mmol) in acetonitrile (50 mL) added dropwise over 2 h at room temperature. The resulting mixture was stirred for additional 1 h, treated with phosphate buffer (pH = 7; 200 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to give phenol **2-129** (690 mg, quant.) as yellowish crystals. R_f = 0.45 (petroleum ether/ EtOAc 1:1); ^{1}H NMR (400 MHz, CD_3OD): δ[ppm] = 0.86 (s, 3H, 1-CH_3), 1.03 (s, 3H, 1-CH_3), 1.15 (s, 3H, 4a-CH_3), 1.19–1.25 (m, 1H, 10a-H), 1.35 (ddd, *J* = 12.9, 12.9, 4.4 Hz, 1H, 4-H), 1.63–1.87 (m, 4H, 2 × 3-H, 2 × 10-H), 2.22 (ddd, *J* = 13.0, 13.5, 3.4 Hz, 1H, 4-H), 2.64–2.84 (m, 2H, 2 × 9-H), 3.20 (dd, *J* = 11.1, 5.0 Hz, 1H, 2-H), 6.47 (dd, *J* = 8.1, 2.5 Hz, 1H, 7-H), 6.65 (d, *J* = 2.5 Hz, 1H, 5-H), 6.79 (d, *J* = 8.1 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, CD_3OD): δ[ppm] = 16.1 (1-CH_3), 20.2 (C-10), 25.3 (4a-CH_3), 28.8 (C-3, 1-CH_3), 31.0 (C-9), 38.5 (C-4), 39.1 (C-4a), 40.1 (C-1), 51.5 (C-10a), 79.4 (C-2), 111.8 (C-5), 113.9 (C-7), 126.9 (C-8a), 130.7 (C-8), 151.7 (C-4b), 156.1 (C-6); HRMS (ESI): $[M–H]^–$ calcd for $C_{17}H_{23}O_2$ 259.170354, found 259.170369.



2-129 **2-130**

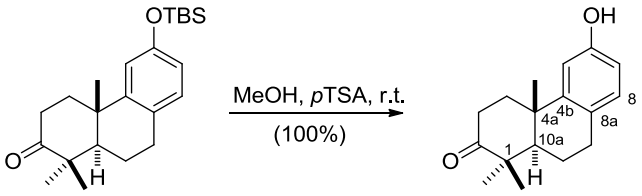
(2*S*,4a*S*,10a*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (2-130). TBSCl (140 mg, 0.93 mmol) was added in one portion to a stirred solution of phenol **2-129** (220 mg, 0.85 mmol) and imidazole (125 mg, 1.86 mmol) in THF (10 mL) at 0 °C. The resulting mixture was allowed to warm to room

temperature and stirred overnight, diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to give mono-TBS-protected compound **2-130** (290 mg, 91%) as a colorless oil. R_f = 0.43 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, CD_3OD): δ[ppm] = 0.15 (2 × s, 6H, $Si(CH_3)_2$), 0.87 (s, 3H, 1-CH_3), 0.96 (s, 9H, $C(CH_3)_3$), 1.05 (s, 3H, 1-CH_3), 1.16 (s, 3H, 4a-CH_3), 1.25 (dd, *J* = 12.2, 2.1 Hz, 1H, 10a-H), 1.45 (ddd, *J* = 12.8, 12.8, 4.7 Hz, 1H, 4-H), 1.69–1.90 (m, 4H, 2 × 3-H, 2 × 10-H), 2.22 (ddd, *J* = 12.9, 12.9, 3.5 Hz, 1H, 4-H), 2.67–2.88 (m, 2H, 2 × 9-H), 3.21 (dd, *J* = 11.0, 5.2 Hz, 1H, 2-H), 6.53 (dd, *J* = 8.3, 2.5 Hz, 1H, 7-H), 6.67 (d, *J* = 2.3 Hz, 1H, 5-H), 6.84 (d, *J* = 8.3 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, CD_3OD): δ[ppm] = –4.2 ($Si(CH_3)_2$), 16.1 (1-CH_3), 19.1 (SiC), 20.2 (C-10), 25.4 (4a-CH_3), 26.3 ($C(CH_3)_3$), 28.8 (C-3, 1-CH_3), 31.1 (C-9), 38.4 (C-4), 38.7 (C-4a), 40.1 (C-1), 51.4 (C-10a), 79.4 (C-2), 116.8 (C-5), 118.6 (C-7), 129.0 (C-8a), 130.8 (C-8), 151.7 (C-4b), 154.8 (C-6); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{39}O_2Si$ 375.271383, found 375.271019.



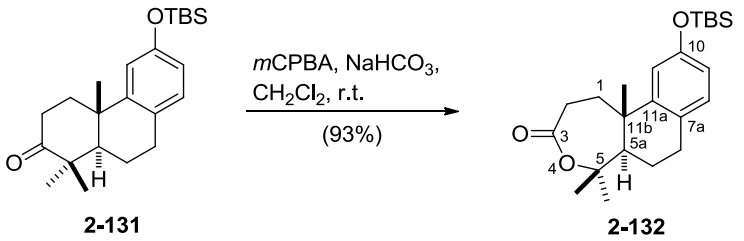
2-130 **2-131**

(4a*S*,10a*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-1,1,4a-trimethyl-1,4,4a,9,10,10a-hexahydrophenanthren-2(3*H*)-one (2-131). Dess-Martin reagent (500 mg, 1.17 mmol) was added to a stirred suspension of alcohol **2-130** (400 mg, 1.07 mmol) and Na_2CO_3 (400 mg) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, treated with saturated $Na_2S_2O_3$ (5 mL) followed by addition of saturated $NaHCO_3$ (20 mL) solution. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 12:1 to 6:1) to give ketone **2-131** (400 mg, quant.) as a colorless oil. R_f = 0.77 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, CD_3OD): δ[ppm] = 0.15 (s, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $Si(CH_3)_3$), 1.11 (s, 3H, 1-CH_3), 1.14 (s, 3H, 1-CH_3), 1.25 (s, 3H, 4a-CH_3), 1.72–1.93 (m, 4H, 3-H, 10a-H, 2 × 10-H), 2.41 (m, 1H, 3-H), 2.57–2.87 (m, 4H, 2 × 4-H, 2 × 9-H), 6.57 (dd, *J* = 8.1, 2.5 Hz, 1H, 7-H), 6.70 (d, *J* = 2.5 Hz, 1H, 5-H), 6.89 (d, *J* = 8.1 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, CD_3OD): δ[ppm] = –4.2 ($Si(CH_3)_2$), 19.1 (SiC), 21.4 (1-CH_3, C-10), 25.0 (4a-CH_3), 26.2 ($C(CH_3)_3$), 27.4 (1-CH_3), 31.1 (C-9), 35.5 (C-4), 38.5 (C-4a), 38.7 (C-3), 48.4 (C-1), 51.9 (C-10a), 117.8 (C-5), 119.1 (C-7), 129.0 (C-8a), 130.9 (C-8), 149.7 (C-4b), 155.0 (C-6), 219.9 (C-2); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{36}O_2SiNa$ 395.237678, found 395.237858.



2-131 **2-128**

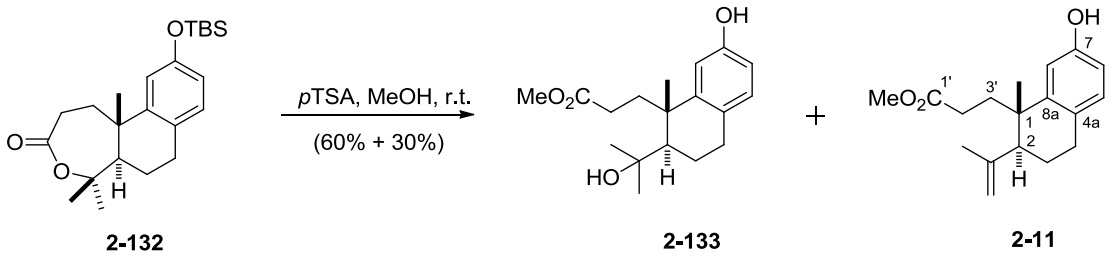
(4a*S*,10a*R*)-6-Hydroxy-1,1,4a-trimethyl-1,4,4a,9,10,10a-hexahydrophenanthren-2(3*H*)-one (5). *p*TsOH monohydrate (23 mg, 0.12 mmol) was added to a stirred solution of ketone **2-131** (30 mg, 0.08 mmol) in methanol (2 mL) at room temperature. The resulting solution was stirred overnight at the same temperature, poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 6:1 to 2:1) to give phenol **2-128** (20 mg, quant.) as a colorless oil. R_f = 0.19 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, CD_3OD): δ[ppm] = 1.12 (s, 3H, 1-CH_3), 1.14 (s, 3H, 1-CH_3), 1.25 (s, 3H, 4a-CH_3), 1.65–1.93 (m, 4H, 10a-H, 3-H, 2 × 10-H), 2.34 (ddd, *J* = 13.1, 7.8, 4.3 Hz, 1H, 3-H), 2.55–2.86 (m, 4H, 2 × 4-H, 2 × 9-H), 6.52 (dd, *J* = 8.3, 2.5 Hz, 1H, 7-H), 6.69 (d, *J* = 2.5 Hz, 1H, 5-H), 6.79 (d, *J* = 8.3 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, CD_3OD): δ[ppm] = 21.5 (1-CH_3, C-10), 25.0 (4a-CH_3), 27.4 (1-CH_3), 31.1 (C-9), 35.6 (C-4), 38.7 (C-4a), 38.7 (C-3), 48.9 (C-1), 52.0 (C-10a), 112.7 (C-5), 114.4 (C-7), 126.9 (C-8a), 130.8 (C-8), 149.6 (C-4b), 156.4 (C-6), 220.2 (C-2); HRMS (ESI): $[M–H]^-$ calcd for $C_{17}H_{21}O_2$ 257.154703, found 257.154736.



2-131 **2-132**

(5a*R*,11b*S*)-10-((*tert*-Butyldimethylsilyl)oxy)-5,5,11b-trimethyl-1,5,5a,6,7,11b-hexahydronaphtho[2,1-c]oxepin-3(2*H*)-one (2-132). *m*CPBA (70%; 790 mg, 3.22 mmol) was added to a stirred suspension of ketone **2-131** (600 mg, 1.61 mmol) and $NaHCO_3$ (135 mg, 1.61 mmol) in CH_2Cl_2 (10 mL) at room temperature. The resulting mixture was stirred overnight, treated with saturated $Na_2S_2O_3$ (5 mL) followed by addition of saturated $NaHCO_3$ (30 mL) solution. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 12:1 to 6:1) to give lactone **2-132** (580 mg, 93%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.16 (s, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $C(CH_3)_3$), 1.46 (s, 3H, 5-CH_3), 1.47 (s, 3H, 11b-CH_3), 1.56 (s, 3H, 5-CH_3), 1.70–1.76 (m, 2H, 2 × 6-H), 1.96 (ddd, *J* = 14.2, 6.0, 3.8 Hz, 1H, 1-H), 2.22–2.34 (m, 2H, 1-H, 5a-H), 2.53–2.80 (m, 4H, 2 × 2-H, 2 × 7-H), 6.58 (dd, *J* = 8.3, 2.5 Hz, 1H, 9-H), 6.66 (d, *J* = 2.3 Hz, 1H, 11-H), 6.84 (d, *J* = 8.3 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –4.4 ($Si(CH_3)_2$), 18.9 (SiC), 24.8 (C-6), 25.7 ($C(CH_3)_3$), 26.4 (5-CH_3), 26.5 (11b-CH_3), 30.1 (C-7), 30.2 (5-CH_3), 32.7 (C-2), 39.0 (C-1), 39.5 (C-11b), 49.3 (C-5a), 85.8 (C-5), 117.9 (C-9), 118.1 (C-11), 126.5 (C-7a), 129.1 (C-8),

149.4 (C-11a), 154.1 (C-11b), 174.1 (C-3); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{37}O_3Si$ 389.250648, found 389.250822.

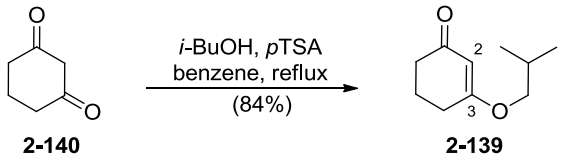


2-132 **2-133** **2-11**

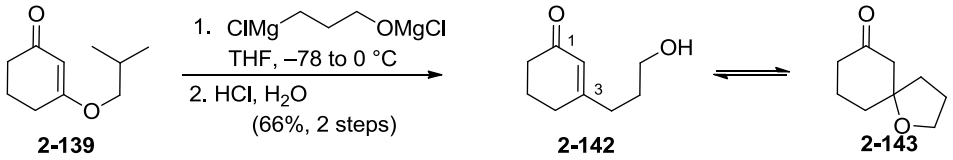
Methyl 3-((1*S*,2*R*)-7-hydroxy-2-(2-hydroxypropan-2-yl)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate (2-133) and methyl 3-((1*S*,2*S*)-7-hydroxy-1-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate (2-11). *p*TsOH monohydrate (2.03 g, 10.7 mmol) was added in one portion to a stirred solution of lactone **2-132** (520 mg, 1.34 mmol) in methanol (10 mL) at room temperature. The resulting solution was stirred overnight, treated with saturated $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to give the two esters **2-133** and **2-11** (**2-133**: 320 mg, 60%); (**2-11**: 160 mg, 30%) as colorless oils.

2-11: R_f = 0.33 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.19 (s, 3H, 1-CH_3), 1.77 (s, 3H, CH_3C=CH_2), 1.56 (s, 3H, 5-CH_3), 1.80–2.15 (m, 5H, 2′-H, 2 × 3′-H, 2 × 3-H), 2.21–2.29 (m, 1H, 2'-H), 2.38 (dd, *J* = 11.4, 3.0 Hz, 1H, 2-H), 2.68–2.75 (m, 2H, 2 × 4-H), 3.61 (s, 3H, OCH_3), 4.69 (br s, 1H, =CH_2), 4.94 (br s, 1H, =CH_2), 6.61 (dd, *J* = 8.1, 2.5 Hz, 1H, 6-H), 6.75 (d, *J* = 2.5 Hz, 1H, 5-H), 6.89 (d, *J* = 8.1 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 22.8 (*C*H_3C=CH_2), 24.7 (C-3), 27.8 (1-CH_3), 29.5 (C-2′, C-4), 34.6 (C-3′), 41.1 (C-1), 47.0 (C-2), 51.7 (OCH_3), 112.9 (C-8), 113.3 (C-6), 114.3 (C=*C*H_2), 129.1 (C-4a), 130.1 (C-5), 144.5 (C-8a), 146.6 (*C*=CH_2), 154.0 (C-7), 175.0 (ester); HRMS (ESI): $[M+Na]^+$ calcd for $C_{18}H_{24}O_3Na$ 311.161766, found 311.161980.

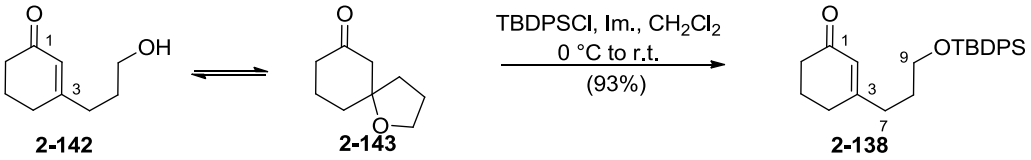
2-133: R_f = 0.10 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.29 (s, 3H, C(CH_3)$_2$), 1.35 (s, 3H, 1-CH_3), 1.47 (s, 3H, C(CH_3)$_2$), 1.50–1.76 (m, 3H, 2 × 3-H, 2-H), 1.92–2.10 (m, 3H, 2 × 3′-H, 2′-H), 2.17 (s, 1H, OH), 2.56–2.69 (m, 2H, 2′-H, 4-H), 2.82–2.88 (m ,1H, 4-H), 3.60 (s, 3H, OCH_3), 6.58 (dd, *J* = 8.3, 2.5 Hz, 1H, 6-H), 6.79 (d, *J* = 2.3 Hz, 1H, 8-H), 6.85 (d, *J* = 8.3 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 24.5 (C-3), 26.8 (C(*C*H_3)$_2$), 27.2 (1-CH_3), 29.6 (C-4), 30.7 (C(*C*H_3)$_2$), 33.2 (C-2′), 36.6 (C-3′), 43.4 (C-1), 48.7 (C-2), 51.8 (OCH_3), 75.5 (C(CH_3)$_2$), 112.9 (C-6), 113.2 (C-8), 129.6 (C-4a), 129.8 (C-5), 146.4 (C-8a), 154.4 (C-7), 176.3 (C-1′); HRMS (ESI): $[M+Na]^+$ calcd for $C_{18}H_{26}O_4Na$ 329.172330, found 329.172482.



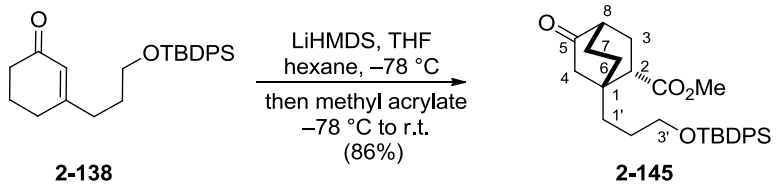
3-Isobutoxycyclohex-2-enone (2-139).[190] *p*TSA (0.2 g, 1.3 mmol) was added to a stirred solution of cyclohexan-1,3-dione (**2-140**) (25.0 g, 0.22 mol) and isobutanol (62 mL, 0.67 mol) in benzene (300 mL) at room temperature. The reaction mixture was stirred under reflux for 3.5 h before it was cooled to room temperature, treated with triethylamine (1 mL) and concentrated in vacuo. The residue was destilled at low pressure (b.p. 106–108 °C, 1×10^{-1} mbar) to give vinylogous ester **2-139** as a colorless oil (31.4 g, 84%). R_f = 0.33 (petroleum ether/ EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.03 (d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$), 1.90–2.02 (m, 3H, 2 × 5-H, $CH(CH_3)_2$), 2.28–2.38 (m, 4H, 2 × 4-H, 2 × 6-H), 3.55 (d, *J* = 6.4 Hz, 2H, OCH_2), 5.29 (s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.0 ($CH(CH_3)_2$), 21.2 (C-5), 27.7 ($CH(CH_3)_2$), 29.0 (C-4), 36.7 (C-6), 74.7 (OCH_2), 102.7 (C-2), 178.1 (C-3), 199.8 (C-1).



3-(3-Hydroxy-propyl)cyclohex-2-en-1-one (2-142). To a solution of 3-chloro-1-propanol (1.0 mL, 12.0 mmol) in THF (15 mL) a solution of MeMgCl in THF (20%, 4.4 mL, 12.0 mmol) was added at –78 °C. The mixture was allowed to warm to room temperature, magnesium turnings (0.32 g, 13.1 mmol) were added and the mixture was heated under reflux for 3 h before it was cooled to –10 °C and treated with 3-isobutoxycyclohex-2-en-1-one (**2-139**) (1.30 g, 8.0 mmol). After 1.5 h the reaction was allowed to warm to 0 °C and treated with saturated NH_4Cl solution (5 mL). The reaction mixture was partitioned between aqueous hydrochloric acid (2N, 50 mL) and cold ethyl acetate (30 mL). The aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo, followed by flash chromatography (petroleum ether/EtOAc, 1:1) to give a mixture of **2-142** and **2-143** (0.83 g, 66%) as a colorless oil. R_f = 0.25 (EtOAc). Hydroxy enone **2-142**: ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.68–1.79 (m, 2H, 2'-H), 1.91–2.00 (m, 2H, 5-H), 2.24–2.37 (m, 7H, 1'-H, 4-H, 6-H, OH), 3.62 (t, *J* = 6.3 Hz, 2H, 3'-H), 5.83-5.89 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 22.6 (C-5), 29.7 (C-1'), 29.7 (C-2'), 34.2 (C-4), 37.2 (C-6), 61.8 (C-3'), 125.5 (C-2), 166.4 (C-3), 200.13 (C-1).

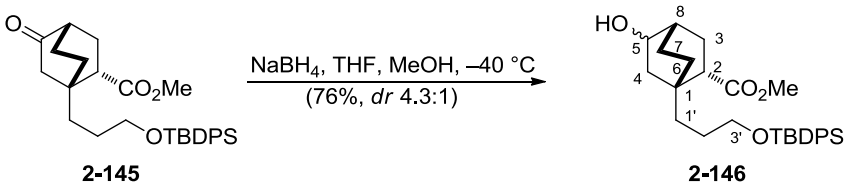


3-[3-(*tert*-Butyldiphenylsilyl)oxy-propyl]cyclohex-2-en-1-on (2-138). A solution of **2-142** and **2-143** (2.0 g, 13.0 mmol) in CH_2Cl_2 (20 mL) was treated with imidazol (1.8 g, 26 mmol) at 0 °C followed by dropwise addition of TBDPSCl (3.7 mL, 14.3 mmol) at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred for 4 h before it was treated with water (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 4:1) to give enone **2-138** (4.70 g, 93%) as a colorless oil. R_f = 0.46 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.07 (s, 9H, $C(CH_3)_3$), 1.71–1.78 (m, 2H, 2 × 8-H), 1.89–1.97 (m, 2H, 2 × 5-H), 2.23 (dd, *J* = 5.8, 5.8 Hz, 2H, 2 × 4-H), 2.30–2.34 (m, 4H, 2 × 6-H, 2 × 7-H), 3.69 (dd, *J* = 6.2, 6.2 Hz, 2H, 2 × 9-H), 7.35–7.43 (m, 6H, H_{Ar}), 7.65–7.70 (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 19.0 ($C(CH_3)_3$), 22.5 (C-5), 26.7 ($C(CH_3)_3$), 29.5 (C-4), 29.6 (C-8), 34.2 (C-7), 37.1 (C-6), 62.8 (C-9), 125.5 (C-2), 127.5 (C_{Ar}), 129.5 (C_{Ar}), 133.5 (C_{Ar}), 135.3 (C_{Ar}), 165.9 (C-3), 199.4 (C-1); HRMS: calcd for $C_{25}H_{32}O_2Si$ 415.20638 $[M+Na]^+$, found 415.206436.



(1*R*,2*S*,4*S*)-Methyl 1-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-5-oxobicyclo[2.2.2]octane-2-carboxylate (2-145). A solution of enone **2-138** (4.7 g, 12.1 mmol) in hexane (40 mL) was added dropwise to a stirred solution of LiHMDS (1M in THF, 15.7 mL, 15.7 mmol) in hexane (20 mL) at –78 °C. The resulting mixture was stirred for 45 min before it was treated with methyl acrylate (2.2 mL, 24.1 mmol) at the same temperature. The cooling bath was removed, the the reaction mixture was allowed to warm to room temperature and stirred for additional 2 h before it was treated with saturated NH_4Cl solution (10 mL). The aqueous layer was diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 9:1) to give ester **2-145** (4.9 g, 86%) as white crystals (m.p. 99.7–100.2 °C (*n*-hexane)). R_f = 0.46 (petroleum ether/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.03 (s, 9H, $C(CH_3)_3$), 1.23–1.34 (m, 2H, 2 × 1'-H), 1.36–1.50 (m, 2H, 2'-H, 6-H), 1.52–1.67 (m, 2H, 2'-H, 6-H), 1.74–1.90 (m, 2H, 2 × 7-H), 1.95 (dd, *J* = 18.8, 1.5 Hz, 1H, 4-H), 2.04 (dd, *J* = 8.8 Hz, 2.7 Hz, 2H, 2 × 3-H), 2.33 (ddd, *J* = 5.9, 2.9, 2.9 Hz, 1H, 8-H), 2.61–2.69 (m, 2H, 4-H, 2-H), 3.57–3.64 (m, 2H, 2 × 3'-H), 3.60 (s, 3H, OCH_3), 7.35–7.44 (m, 6H, H_{Ar}), 7.63–7.65 (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.2 ($C(CH_3)_3$), 23.0 (C-7), 26.5 (C-2'), 26.8 ($C(CH_3)_3$), 28.0 (C-3), 29.9 (C-6), 33.9 (C-1'), 38.4 (C-1), 41.8 (C-8), 44.2 (C-2), 44.7 (C-4), 51.6 (OCH_3), 64.1 (C-3'), 127.6 (C_{Ar}), 129.6 (C_{Ar}), 133.9 (C_{Ar}), 135.5

(C_{Ar}), 175.4 (CO_2Me), 215.2 (C-5); HRMS: calcd for $[M+Na]^+$ $C_{29}H_{38}O_4Si$ 501.24316, found 501.243420.

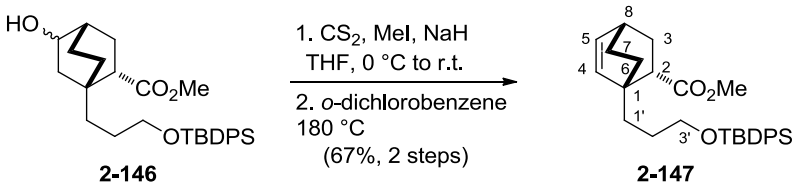


2-145 **2-146**

(1*R*,2*S*,4*S*,5*RS*)-Methyl 1-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-5-hydroxybicyclo[2.2.2]octane-2-carboxylate (2-146). Sodium borohydride (36 mg, 0.95 mmol) was added to a stirred solution of ketone **2-145** (228 mg, 0.5 mmol) in a THF/methanol mixture (22 mL, 10:1) at –40 °C. The resulting mixture was stirred for 1 h at room temperature before it was diluted with diethyl ether (20 mL) and treated with water (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 4:1) to give alcohols **2-146-A** (144 mg, 62%) and **2-146-B** (34 mg, 14%) as colorless oils.

Diastereomer A: R_f = 0.55 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.03 (s, 9H, $C(CH_3)_3$), 1.08–1.37 (m, 4H, 2 × 6-H, 2 × 2'-H), 1.37–1.51 (m, 3H, 4-H, 7-H, 2'-H), 1.52–1.69 (m, 3H, 4-H, 7-H, 2'-H), 1.70–1.83 (m, 2H, 4-H, 8-H), 2.07–2.15 (m, 1H, 3-H), 2.49–2.57 (m, 1H, 2-H), 3.60 (s, 3H, OCH_3), 3.55–3.63 (m, 2H, 2 × 3'-H), 3.79–3.84 (m, 1H, 5-H), 7.34–7.44 (m, 6H, H_{Ar}), 7.62–7.67 (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.2 ($C(CH_3)_3$), 23.3 (C-3, C-7), 26.3 (C-2'), 26.8 ($C(CH_3)_3$), 29.5 (C-6), 31.1 (C-8), 34.4 (C-1), 35.5 (C-1'), 38.9 (C-4), 44.5 (C-2), 51.7 (OCH_3), 64.5 (C-3'), 68.5 (C-5), 127.6 (C_{Ar}), 129.5 (C_{Ar}), 134.0 (C_{Ar}), 135.5 (C_{Ar}), 178.9 (Ester); HRMS (ESI): $[M+Na]^+$ calcd for $C_{29}H_{40}O_4SiNa$ 503.25881, found 503.259225.

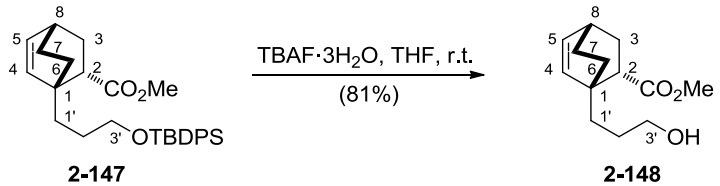
Diastereomer B: R_f = 0.50 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.03 (s, 9H, $C(CH_3)_3$), 1.06–1.66 (m, 9H, 4-H, 6-H_2, 7-H, 2 × 1'-H, 2 × 2'-H), 1.66–1.75 (m, 2H, 3-H, 8-H), 1.76–1.85 (m, 1H, 3-H), 1.92–2.02 (m, 1H, 7-H), 2.07–2.18 (m, 1H, 4-H), 2.38–2.48 (m, 1H, 2-H), 3.56 (s, 3H, OCH_3), 3.30–3.44 (m, 2H, 2 × 3'-H), 4.10–4.18 (m, 1H, 5-H), 7.33–7.44 (m, 6H, H_{Ar}), 7.62–7.69 (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 18.6 (C-7), 19.2 ($C(CH_3)$, 26.5 (C-2), 26.8 ($C(CH_3)$, 28.4 (C-3), 30.3 (C-6), 31.5 (C-8), 34.4 (C-1), 34.8 (C-1'), 38.5 (C-4), 44.1 (C-2), 51.2 (OCH_3), 64.5 (C-3'), 68.9 (C-5), 127.6 (C_{Ar}), 129.5 (C_{Ar}), 134.0 (C_{Ar}), 135.5 (C_{Ar}), 176.4 (Ester); $[M+Na]^+$ calcd for $C_{29}H_{40}O_4SiNa$ 503.25881, found 503.259104.



2-146 **2-147**

(1*R*,2*S*,4*S*)-Methyl 1-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)bicyclo[2.2.2]oct-5-ene-2-carboxylate (2-147). *Xanthogenate preparation.* A solution of alcohols **2-146** (150 mg, 0.31 mmol) in THF (5 mL) was added dropwise to a stirred suspension of sodium hydride (60%, 125 mg, 3.12 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h before it was treated with CS_2 (0.38 mL, 6.24 mmol) at 0 °C. The resulting mixture was stirred for 3 h at room temperature before it was treated with methyl iodide (0.78 mL, 12.48 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h before it was carefully treated with water (20 mL) at 0 °C. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 9:1) to give a diastereomeric mixture of xanthogenates (138 mg, 78%) as an yellow oil. R_f = 0.47 (petroleum ether/EtOAc 9:1).

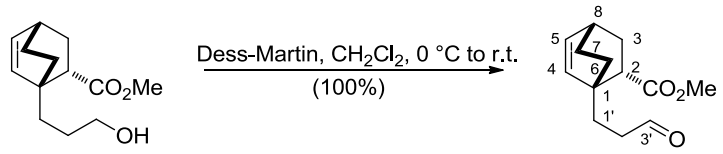
Chugaev reaction. A solution of the foregoing xanthogenates (138 mg, 0.24 mmol) in *o*-dichlorobenzene was stirred for 20 h at 180 °C before it was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 15:1) to give alkene **2-147** (96 mg, 86%) as an yellow oil. R_f = 0.53 (petroleum ether/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.04 (s, 9H, $C(CH_3)_3$), 1.11–1.19 (m, 1H, 6-H), 1.28–1.38 (m, 2H, 6-H, 7-H), 1.42–1.68 (m, 6H, 2 × 1'-H, 2 × 2'-H, 3-H, 7-H), 1.85 (ddd, *J* = 12.4, 9.8, 2.8 Hz, 1H, 3-H), 2.53 (dd, *J* = 9.8, 5.8 Hz, 1H, 2-H), 2.55–2.59 (m, 1H, 8-H), 3.54 (s, 3H, OCH_3), 3.65 (ddd, *J* = 9.8 Hz, 6.1, 4.3 Hz, 2H, 2 × 3'-H), 6.94 (d, *J* = 8.3 Hz, 1H, 4-H), 6.33 (dd, *J* = 8.1, 6.8 Hz, 1H, 5-H), 7.35–7.43 (m, 6H, H_{Ar}), 7.63–7.67 (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.2 ($C(CH_3)_3$), 25.3 (C-7), 26.9 ($C(CH_3)_3$), 27.5 (C-2'), 29.7 (C-8), 30.6 (C-6), 32.5 (C-1'), 33.4 (C-3), 39.1 (C-1), 47.1 (C-2), 51.2 (OCH_3), 64.5 (C-3'), 127.6 (C_{Ar}), 129.5 (C_{Ar}), 133.9 (C_{Ar}), 134.1 (C-5), 134.9 (C-4), 135.6 (C_{Ar}), 176.1 (ester); HRMS (ESI): $[M+Na]^+$ calcd for $C_{29}H_{38}O_3SiNa$ 485.24824, found 485.247910.



2-147 **2-148**

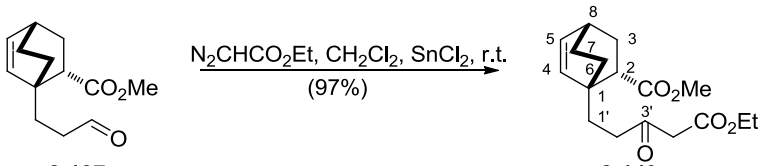
(1*R*,2*S*,4*R*)-Methyl 1-(3-hydroxypropyl)bicyclo[2.2.2]oct-5-ene-2-carboxylate (2-148). $TBAF·3H_2O$ (800 mg, 2.53 mmol) was added in one portion to a stirred solution of ester **2-147** (760 mg, 1.64 mmol) in THF (50 mL) at room temperature. The resulting solution was stirred for 3 h before it was treated with water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 2:1) to give alcohol **2-148** (298 mg, 81%) as a colorless oil. R_f = 0.17 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] =

1.14–1.70 (m, 9H, 2 × 1'-H, 2 × 2'-H, 3-H, 2 × 6-H, 2 × 7-H), 1.86 (ddd, *J* = 12.5, 9.8, 2.6 Hz, 1H, 3-H), 2.54–2.60 (m, 2H, 2-H, 8-H), 3.60 (s, 3H, OCH_3), 3.61–3.67 (m, 2H, 2 × 3'-H), 5.95 (d, *J* = 8.3 Hz, 1H, 4-H), 6.34 (dd, *J* = 8.3, 6.8 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 25.3 (C-7), 27.6 (C-2'), 29.7 (C-8), 30.6 (C-6), 32.4 (C-1'), 33.3 (C-3), 38.9 (C-1), 46.9 (C-2), 51.3 (OCH_3), 63.6 (C-3'), 134.8 (C-5), 134.0 (C-4), 176.1 (ester).



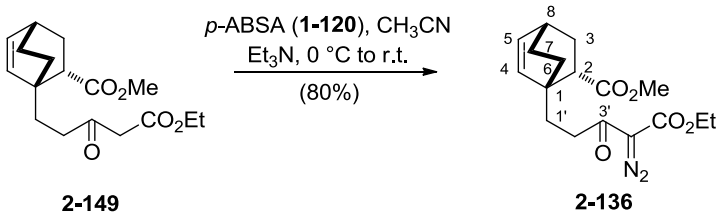
2-148 **2-137**

(1*R*,2*S*,4*S*)-Methyl 1-(3-oxopropyl)bicyclo[2.2.2]oct-5-ene-2-carboxylate (2-137). Dess-Martin reagent[58] (620 mg, 1.46 mmol) was added in one portion to a stirred solution of alcohol **2-148** (298 mg, 1.33 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature before it was treated with saturated $Na_2S_2O_3$ solution (30 mL) and stirred for additional 15 min. The resulting mixture was washed with saturated $NaHCO_3$ solution (100 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL).The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give aldehyde **2-137** (295 mg, 100%) as a colorless oil. R_f = 0.64 (petroleum ether/ EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.05–1.12 (m, 1H, 6-H), 1.29–1.39 (m, 2H, 1'-H, 6-H, 7-H), 1.47–1.56 (m, 2H, 3-H, 7-H), 1.78–1.94 (m, 3H, 1'-H, 2 × 2'-H), 2.44–2.61 (m, 3H, 2-H, 8-H, 3-H), 3.60 (OCH_3), 5.91 (d, *J* = 8.3 Hz, 1H, 4-H), 6.36 (dd, *J* = 8.3, 6.8 Hz, 1H, 5-H), 9.79 (dd, *J* = 1.6, 1.6 Hz, 1H, 3'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 25.2 (C-7), 28.1 (C-2'), 29.6 (C-8), 30.6 (C-6), 33.1 (C-1'), 38.7 (C-3), 39.3 (C-1), 46.6 (C-2), 51.4 (OCH_3), 133.9 (C-5), 134.6 (C-4), 175.6 (ester), 202.2 (C-3'); HRMS (ESI): $[M+Na+MeOH]^+$ calcd for $C_{14}H_{22}O_4Na$ 277.14103, found 277.14121.

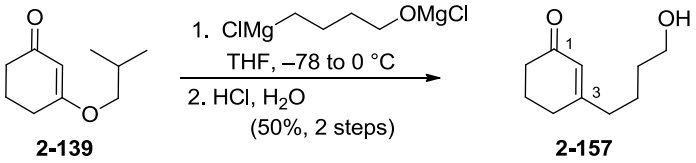


2-137 **2-149**

(1*R*,2*S*,4*S*)-Methyl 1-(5-ethoxy-3,5-dioxopentyl)bicyclo[2.2.2]oct-5-ene-2-carboxylate (2-149). Anhydrous tin (II) chloride[181] (270 mg, 1.42 mmol) was added, followed by dropwise addition of ethyl diazoacetate (0.4 mL, 3.73 mmol) to the stirred solution of crude aldehyde **2-137** (280 mg, 1.26 mmol) in CH_2Cl_2 (30 mL) at room temperature. Stirring was continued for 1 h before the reaction was treated with water (100 mL) and the mixture extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 4:1) to give β-keto ester **2-149** (377 mg, 97%) as a colorless oil. R_f = 0.57 (petroleum ether/EtOAc, 2:1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{24}O_5Na$ 331.15159, found 331.151403.

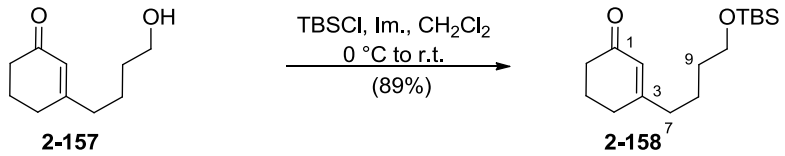


(1*R*,2*S*,4*S*)-Methyl 1-(4-diazo-5-ethoxy-3,5-dioxopentyl)bicyclo[2.2.2]oct-5-ene-2-carboxylate (2-136). *p*-ABSA (**1-120**, 340 mg, 1.40 mmol) was added in one portion to a stirred solution of β-keto ester **2-149** (360 mg, 1.17 mmol) and triethylamine (0.32 mL, 2.34 mmol) in acetonitrile (20 mL) at 0 °C. The resulting mixture was stirred 20 h at room temperature before it was treated with water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ diethyl ether, 4:1) to give diazo ester **2-136** (310 mg, 80%) as a yellowish oil. R_f = 0.65 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.12 (ddd, *J* = 11.6, 11.6, 4.7 Hz, 1H, 6-H), 1.25–1.53 (m, 4H, 6-H, 7-H, 3-H), 1.29 (dd, *J* = 7.1, 7.1 Hz, 3H, $OCH_2C\mathit{H_3}$), 1.75–1.90 (m, 3H, 1'-H, 2'-H, 7-H), 2.52–2.56 (m, 2H, 2'-H, 8-H), 2.91 (ddd, *J* = 9.8, 6.5, 4.4 Hz, 2H, 2-H, 3-H), 4.26 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H, $OC\mathit{H_2}CH_3$), 5.94 (d, *J* = 8.3 Hz, 1H, 4-H), 6.31 (dd, *J* = 8.3, 6.8 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 14.3 ($OCH_2\mathit{C}H_3$), 25.2 (C-7), 29.5(C-8), 30.4 (C-6), 33.1 (C-1'), 35.4 (C-3), 38.8 (C-1), 46.6 (C-2), 51.2 (OCH_3), 61.3 (C-2'), 134.2 (C-5), 161.2 (C-4), 175.6 (ester), 192.8 (C-3'); HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{22}N_2O_5Na$ 357.14209, found 357.141973.



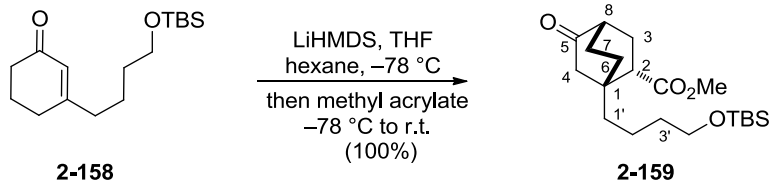
3-(4-Hydroxybutyl)cyclohex-2-enone (2-157). A solution of MeMgCl in THF (20%, 13.0 mL, 35.6 mmol) was added to a stirred solution of 4-chloro-1-butanol (3.86 g, 35.6 mmol) in THF (10 mL) at –78°C. The mixture was allowed to warm to room temperature, then magnesium turnings (0.92 g, 38.0 mmol) were added and the mixture was heated under reflux for 3 h before it was cooled to –10 °C and treated with 3-isobutoxycyclohex-2-en-1-one (**2-139**) (4.0 g, 23.8 mmol). After 1.5 h the reaction mixture was allowed to warm to 0 °C and treated with saturated NH_4Cl solution (10 mL). The mixture was partitioned between aqueous hydrochloric acid (2N, 50 mL) and cold diethyl ether (50 mL). The aqueous phase was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with saturated NaCl solution (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:2) to give alcohol **2-157** (2.00 g, 50%) as a colorless oil. R_f = 0.35 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.54–1.62 (m, 4H, 2 × 3'-H, 2 × 2'-H), 1.97 (ddd, *J* = 12.8, 6.3, 6.3 Hz, 2H, 2 × 1'-H), 2.22–2.29 (m, 4H, 2 × 5-H, 2 × 6-H), 2.35 (dd, *J* = 6.7, 6.7 Hz, 2H, 2 × 4-H), 3.65 (dd, *J* = 5.9, 5.9 Hz, 2H, 2 × 4'-H), 5.87 (dd, *J* = 1.3, 1.3 Hz, 1H, 2-H); ^{13}C NMR (100

MHz, $CDCl_3$): δ[ppm] = 22.7 (C-5), 23.2 (C-2'), 29.6 (C-3'), 32.1 (C-1'), 37.3 (C-4), 37.7 (C-6), 62.4 (C-4'), 125.8 (C-2), 166.1 (C-3), 199.9 (C-1).



2-157 **2-158**

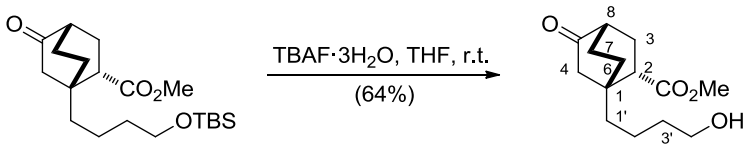
3-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)cyclohex-2-enone (2-158). A solution of alcohol **2-157** (0.70 g, 4.2 mmol) in CH_2Cl_2 (20 mL) was treated with imidazole (0.57 g, 8.34 mmol) at 0 °C followed by addition of TBSCl (0.68 g, 4.59 mmol) at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred for 1 h before it was treated with water (50 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 4:1) to give enone **2-158** (1.04 g, 89%) as a colorless oil. R_f = 0.51 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.03 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.49–1.61 (m, 4H, 2 × 2'-H, 2 × 3'-H), 1.97 (ddd, *J* = 12.8, 6.3, 6.3 Hz, 2H, 2 × 5-H), 2.22 (dd, *J* = 6.9, 6.9 Hz, 2H, 2 × 1'-H), 2.27 (dd, *J* = 5.9, 5.9, Hz, 2H, 2 × 4-H), 2.35 (dd, *J* = 7.3, 7.3 Hz, 2H, 2 × 6-H), 3.61 (dd, *J* = 5.9, 5.9 Hz, 2H, 2 × 4'-H), 5.86 (br. s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = –5.3 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 22.7 (C-5), 23.3 (C-2'), 25.9 ($SiC(CH_3)_3$), 29.6 (C-3'), 32.3 (C-4), 37.4 (C-6), 37.8 (C-1'), 62.6 (C-4'), 125.7 (C-2), 166.5 (C-3), 200.0 (C-1).



2-158 **2-159**

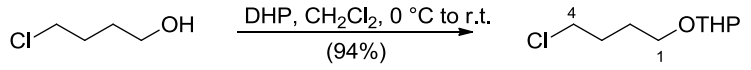
(1*R*,2*S*,4*S*)-Methyl 1-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-5-oxobicyclo[2.2.2]octane-2-carboxylate (2-159). A solution of enone **2-158** (1.0 g, 3.55 mmol) in hexane (5 mL) was added dropwise to a stirred solution of LiHMDS (1M in THF, 4.6 mL, 4.60 mmol) in hexane (6 mL) at –78 °C. The resulting mixture was stirred for 30 min before it was treated with methyl acrylate (0.64 mL, 7.10 mmol) at the same temperature. The cooling bath was removed, then the reaction mixture was allowed to warm to room temperature and stirred for additional 1 h before it was treated with saturated NH_4Cl solution (10 mL). The aqueous layer was diluted with water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 9:1) to give ketoester **2-159** (1.3 g, 100%) as a colorless oil. R_f = 0.47 (petroleum ether/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.03 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.20–1.49 (m, 9H, 2 × 1'-H, 2 × 2'-H, 2 × 3'-H, 2 × 7-H, 6-H), 1.78–1.86 (m, 2H), 1.96 (dd, *J* = 18.8, 1.6 Hz, 1H, 6-H), 2.03 (app dd, *J* = 8.7, 2.9 Hz, 2H, 2 × 3-H), 2.32 (ddd, *J* = 6.0, 2.9, 2.9 Hz, 1H, 4-H), 2.67 (ddd, *J* = 8.5, 8.5, 1.8 Hz, 1H, 2-H), 3.58 (dd, *J* = 6.3, 6.3 Hz, 2H, 2 × 4'-H), 3.66 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm]

= –4.3 ($Si(CH_3)_2$), 18.8 ($SiC(CH_3)_3$), 19.5 (C-2'), 23.0 (C-8), 25.4 ($SiC(CH_3)_3$), 27.9 (C-3), 29.9 (C-7), 33.1 (C-3'), 37.4 (C-1'), 38.7 (C-1), 41.8 (C-4), 44.0 (C-2), 45.0 (C-6), 51.7 (OCH_3), 62.4 (C-4'), 175.4 (ester), 215.2 (C-5).



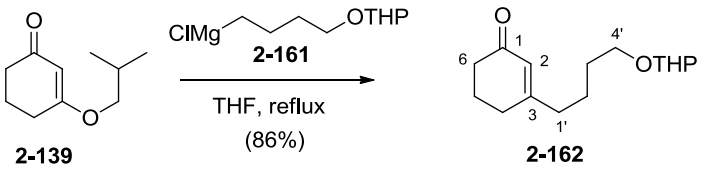
2-159 **2-160**

(1*R*,2*S*,4*R*)-Methyl 1-(4-hydroxybutyl)bicyclo[2.2.2]octane-2-carboxylate (2-160). $TBAF{\cdot}3H_2O$ (2.95 g, 9.35 mmol) was added in one portion to a stirred solution of ester **2-159** (3.11 g, 8.50 mmol) in THF (100 mL) at room temperature. The resulting solution was stirred for 1 h before it was treated with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 1:2) to give alcohol **2-160** (1.37 g, 64%) as a colorless oil. R_f = 0.27 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.19–1.26 (m, 9H, 2 × 1'-H, 2 × 2'-H, 2 × 3'-H, 2 × 7-H, OH), 1.74–1.87 (m, 2H, 8-H), 1.96 (dd, *J* = 18.8, 1.6 Hz, 1H, 6-H), 2.03 (app dd, *J* = 8.5, 2.9 Hz, 2H, 2 × 3-H), 2.32 (ddd, *J* = 6.0, 2.9, 2.9 Hz, 1H, 4-H), 2.63 (dd, *J* = 19.0, 3.2 Hz, 1H, 6-H), 2.70 (ddd, *J* = 8.5, 8.5, 1.8 Hz, 1H, 2-H), 3.62 (dd, *J* = 6.3, 6.3 Hz, 2H, 2 × 4'-H), 3.67 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.5 (C-2'), 23.0 (C-8), 27.9 (C-3), 29.9 (C-7), 33.1 (C-3'), 37.4 (C-1'), 38.7 (C-1), 41.8 (C-4), 44.0 (C-2), 45.0 (C-6), 51.7 (OCH_3), 62.4 (C-4'), 175.4 (ester), 215.2 (C-5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{22}O_4Na$ 277.141030, found 277.140944.

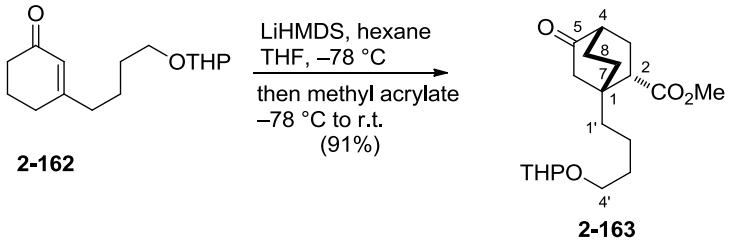


2-161a **2-161b**

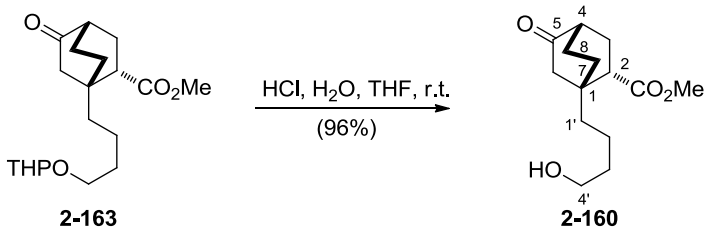
2-(4-Chlorobutoxy)tetrahydro-2*H*-pyran (2-161b).[191] Dihydropyran (28.0 g, 0.33 mol) was added dropwise to a stirred solution of 4-chlorobutan-1-ol (**2-161a**) (30.0 g, 0.28 mmol) in CH_2Cl_2 (200 mL) at 0 °C.[192] The resulting mixture was stirred for 2 h, before it was treated with triethylamine (10 mL) and washed with water (2 × 100 mL), and saturated NaCl solution (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was distilled under reduced pressure to give the THP ether (49.9 g, 94%) as a colorless oil (b.p. 65–70 °C, 4 mbar). ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.29–1.99 (m, 10H, 2 × 2-H, 2 × 3-H, 6 × THP-H), 3.41 (ddd, *J* = 9.8, 9.8, 6.2 Hz, 1H, 1-H), 3.45–3.55 (1H, m, CH_2O^{THP}), 3.79 (ddd, *J* = 9.7, 6.6, 6.4 Hz, 1H, 1-H), 3.87 (ddd, *J* = 11.2, 7.7, 3.5 Hz, 1H, CH_2O^{THP}), 4.56 (1H, m, CHO_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 20.4 (CH_2^{THP}), 25.4 (CH_2^{THP}), 27.4 (C-2), 29.3 (C-3), 30.5 (CH_2^{THP}), 44.7 (C-4), 63.3 (CH_2O^{THP}), 67.7 (C-1), 106.3 (CHO_2).



3-(4'-((Tetrahydro-2*H*-pyran-2-yl)oxy)butyl)cyclohex-2-enone (2-162). THP protected chlorobutanol **2-161b** (38.5 g, 0.20 mol) was added in one portion to a stirred mixture of magnesium (5.3 g, 0.22 mol) and THF (300 mL), which was preactivated with I_2. The mixture was stirred under reflux for 5 h and then vinylogous ester[Error! Bookmark not defined.] **2-139** (26.7 g, 0.16 mol) was added in one portion. The resulting solution was stirred under reflux for 8 h, cooled to –10 °C and carefully treated with half-saturated NH_4Cl solution (100 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give enone **2-162** (34.3 g, 86%) as a colorless oil. R_f = 0.18 (petroleum ether/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.43–1.78 (m, 10H, 2 × 2'-H, 2 × 3'-H, 6 × CH_2^{THP}), 1.91 (ddd, *J* = 12.8, 6.4, 6.4 Hz, 2H, 2 × 5-H), 2.18 (dd, *J* = 6.6, 6.6 Hz, 2H, 2 × 1'-H), 2.22 (dd, *J* = 6.1, 6.1 Hz, 2H, 2 × 4-H), 2.28 (dd, *J* = 6.3, 6.3 Hz, 2H, 2 × 6-H), 3.30–3.35 (m, 1H, 4'-H), 3.40–3.45 (m, 1H, CH_2O^{THP}), 3.65–3.71 (m, 1H, 4'-H), 3.75–3.81 (m, 1H, CH_2O^{THP}), 4.49 (dd, *J* = 3.5, 3.5 Hz, 1H, CHO_2^{THP}), 5.81 (dd, *J* = 1.3, 1.3 Hz, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.5 (CH_2^{THP}), 22.6 (C-5), 23.5 (C-2'), 25.3 (CH_2^{THP}), 29.1 (C-3'), 29.5 (C-4), 30.6 (CH_2^{THP}), 37.2 (C-6), 37.6 (C-1'), 62.2 (CH_2O^{THP}), 66.9 (C-4'), 98.8 (CHO_2^{THP}), 125.6 (C-2), 166.2 (C-3), 199.7 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{24}O_3Na$ 275.161766, found 275.161567.

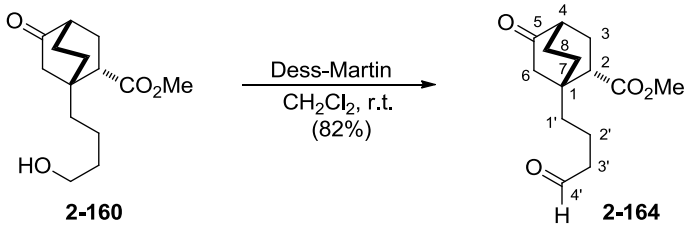


(1*S*,2*S*,4*S*)-Methyl 5-oxo-1-(4'-((tetrahydro-2*H*-pyran-2-yl)oxy)butyl)bicyclo[2.2.2]octane-2-carboxylate (2-163). A solution of *n*BuLi in hexane (2.5M, 133 mL, 0.332 mol) was added dropwise to a stirred solution of bis(trimethylsilyl)amine (55.7 g, 0.346 mol) in a hexane/THF mixture (2:3, 500 mL) at –78 °C. The resulting mixture was allowed to warm to room temperature and stirred for 30 min. and then again cooled to –78 °C. Then, a solution of enone **2-162** (33.6 g, 0.133 mol) in hexane (40 mL) was added dropwise during a 30 min period. Stirring was continued for additional 30 min followed by dropwise addition of methyl acrylate (30 mL, 0.33 mol) at the same temperature. The reaction was allowed to warm to room temperature, and treated with half-saturated NH_4Cl solution (100 mL). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give ester **2-163** (41.0 g, 91%) as a colorless oil. R_f = 0.20 (petroleum ether/EtOAc 4:1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{19}H_{30}O_5Na$ 361.198545, found 361.198321.



2-163 **2-160**

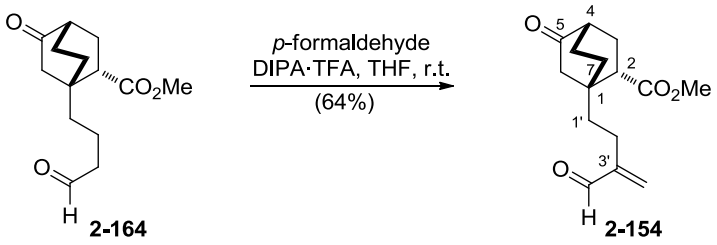
(1*S*,2*S*,4*S*)-Methyl 1-(4'-hydroxybutyl)-5-oxobicyclo[2.2.2]octane-2-carboxylate (2-160). Aqueous HCl (3M, 70 mL) was added to a stirred solution of ester **2-163** (30.6 g, 0.091 mol) in THF (200 mL) at room temperature. The mixture was stirred for 12 h at this temperature, treated with water (100 mL) and diethyl ether (100 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL).The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give alcohol **2-160** (22.1 g, 96%) as a colorless oil. R_f = 0.20 (petroleum ether/ EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.19–1.26 (m, 9H, 2 × 1'-H, 2 × 2'-H, 2 × 3'-H, 2 × 7-H, OH), 1.74–1.87 (m, 2H, 8-H), 1.96 (dd, *J* = 18.8, 1.6 Hz, 1H, 6-H), 2.03 (app dd, *J* = 8.5, 2.9 Hz, 2H, 2 × 3-H), 2.32 (ddd, *J* = 6.0, 2.9, 2.9 Hz, 1H, 4-H), 2.63 (dd, *J* = 19.0, 3.2 Hz, 1H, 6-H), 2.70 (ddd, *J* = 8.5, 8.5, 1.8 Hz, 1H, 2-H), 3.62 (dd, *J* = 6.3, 6.3 Hz, 2H, 2 × 4'-H), 3.67 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 19.5 (C-2'), 23.0 (C-8), 27.9 (C-3), 29.9 (C-7), 33.1 (C-3'), 37.4 (C-1'), 38.7 (C-1), 41.8 (C-4), 44.0 (C-2), 45.0 (C-6), 51.7 (OCH_3), 62.4 (C-4'), 175.4 (ester), 215.2 (C-5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{22}O_4Na$ HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{22}O_4Na$ 277.141030, found 277.140944.



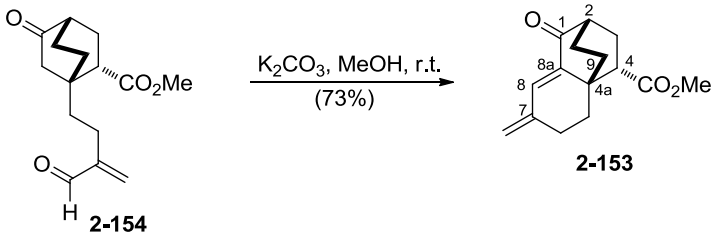
2-160 **2-164**

(1*S*,2*S*,4*S*)-Methyl 5-oxo-1-(4'-oxobutyl)bicyclo[2.2.2]octane-2-carboxylate (2-164). Dess-Martin reagent (44.2 g, 0.104 mol) was added in one portion to a stirred solution of alcohol **2-160** (24.1 g, 0.095 mol) in CH_2Cl_2 (300 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 5 h before it was treated with saturated $Na_2S_2O_3$ solution (30 mL) and stirred for additional 15 min. The resulting mixture was washed with saturated $NaHCO_3$ solution (100 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to give aldehyde **2-164** (19.6 g, 82%) as a colorless oil. R_f = 0.40 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.21 (ddd, *J* = 13.0, 13.0, 5.3 Hz, 1H, 1'-H), 1.34 (ddd, *J* = 13.1, 13.1, 4.6 Hz, 1H, 1'-H), 1.43–1.90 (m, 6H, 2 × 2'-H, 2 × 7-H, 2 × 8-H), 1.96 (dd, *J* = 19.0, 1.8 Hz, 1H, 6-H), 2.04 (dd, *J* = 9.1, 3.0 Hz, 2H, 2 × 3-H), 2.33 (ddd, *J* = 6.0, 2.9, 2.9 Hz, 1H, 4-H), 2.40 (dd, *J* = 7.1, 7.1 Hz, 2H, 2 × 3'-H), 2.64 (dd, *J* = 18.8, 3.2 Hz, 1H, 6-H), 2.67–2.72

(m, 1H, 2-H), 3.67 (s, 3H, OCH_3), 9.74 (dd, *J* = 1.5, 1.5 Hz, 1H, 4'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 16.0 (C-2'), 22.9 (C-8), 27.9 (C-3), 29.7 (C-7), 37.2 (C-1'), 38.6 (C-1), 41.7 (C-4), 43.8 (C-2), 44.2 (C-3'), 44.9 (C-6), 51.7 (OCH_3), 175.2 (ester), 201.8 (C-4'), 214.8 (C-5); HRMS (ESI): $[M+Na+MeOH]^+$ calcd for $C_{15}H_{24}O_5Na$ 307.15159, found 307.151322.

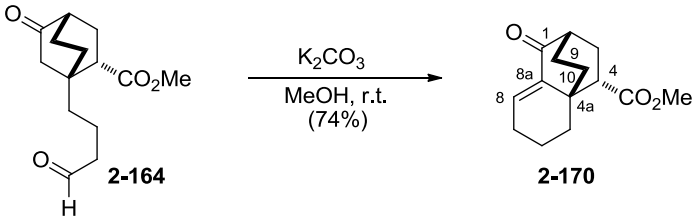


(1*R*,2*S*,4*S*)-Methyl 1-(3-formylbut-3-en-1-yl)-5-oxobicyclo[2.2.2]octane-2-carboxylate (2-154). A freshly prepared solution of DIPA·TFA in THF[193] (0.61M, 1.38 mL, 0.84 mmol) was added dropwise to a stirred solution of aldehyde **2-164** (210 mg, 0.84 mmol) and *p*-formaldehyde (100 mg, 3.36 mmol) in THF (3 mL) at room temperature. The resulting mixture was stirred for 1 h before it was treated with water (20 mL) and diethyl ether (10 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL).The combined organic layers were washed with saturated NaCl solution (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give aldehyde **2-154** (140 mg, 64%) as a colorless oil. R_f = 0.31 (petroleum ether/ EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.33 (ddd, *J* = 13.1, 13.1, 4.9 Hz, 1H, 1'-H), 1.42–1.53 (m, 2H, 1'-H, 7-H), 1.66–1.74 (m, 1H, 7-H), 1.77–1.90 (m, 2H, 2 × 8-H), 1.98 (dd, *J* = 18.8, 1.6 Hz, 1H, 6-H), 2.02–2.07 (m, 2H, 2 × 3-H), 2.17 (ddd, *J* = 13.3, 13.3, 4.9 Hz, 1H, 2'-H), 2.25–2.35 (m, 2H, 2'-H, 4-H), 2.67 (dd, *J* = 18.8, 3.2 Hz, 1H, 6-H), 2.71–2.76 (m, 1H, 2-H), 3.67 (s, 3H, OCH_3), 5.99 (s, 1H, $C=CH_2$), 6.22 (s, 1H, $C=CH_2$), 9.51 (s, 1H, 4'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 22.0 (C-2'), 22.9 (C-8), 27.9 (C-3), 29.6 (C-7), 35.9 (C-1'), 38.6 (C-1), 41.7 (C-4), 43.6 (C-2), 45.0 (C-6), 51.7 (OCH_3), 134.0 ($C=CH_2$), 150.0 ($C=CH_2$), 175.2 (ester), 194.3 (C-4'), 214.7(C-5).

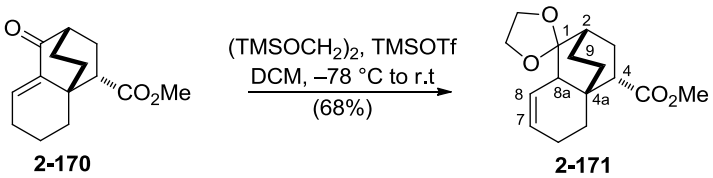


(2*S*,4*S*,4a*S*)-Methyl 7-methylene-1-oxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-153). K_2CO_3 (200 mg, 1.45 mmol) was added in one portion to a stirred solution of keto aldehyde **2-154** (140 mg, 0.53 mol) in methanol (5 mL) at room temperature. The mixture was stirred for 4 h at the same temperature, before it was treated with water (20 mL) and diethyl ether (10 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (2 × 10 mL), dried over $MgSO_4$, filtered, and

concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give dienone **2-153** (95 mg, 73%) as a colorless oil. R_f = 0.34 (petroleum ether/ EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.55 (ddd, *J* = 13.9, 8.8, 5.0 Hz, 1H, 5-H), 1.61–1.65 (m, 2H, 2 × 9-H), 1.81–1.90 (m, 3H, 5-H, 2 × 10-H), 2.02–2.14 (m, 3H, 2 × 3-H, 6-H), 2.26–2.33 (m, 1H, 6-H), 2.47 (ddd, *J* = 6.0, 2.9, 2.9 Hz, 1H, 2-H), 2.67 (dd, *J* = 10.1, 6.1 Hz, 1H, 4-H), 3.59 (s, 3H, OCH_3), 5.17 (s, 1H, C=CH_2), 5.24 (s, 1H, C=CH_2), 7.04 (s, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 23.3 (C-10), 26.5 (C-6), 28.4 (C-3), 30.8 (C-5), 33.2 (C-9), 38.1 (C-4a), 41.1 (C-2), 47.3 (C-4), 51.7 (OCH_3), 120.0 (C-11), 131.8 (C-8), 137.4 (C-8a), 141.1 (C-7), 174.9 (ester), 202.4 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{18}O_3Na$ 269.11482, found 269.114841.

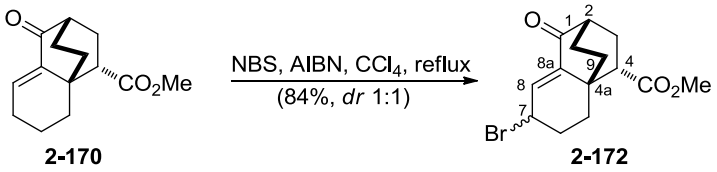


(2*S*,4*S*,4a*R*)-Methyl 1-oxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-170). K_2CO_3 (37.8 g, 0.274 mol) was added in one portion to a stirred solution of aldehyde **2-164** (23.0 g, 0.091 mol) in methanol (300 mL) at room temperature. The mixture was stirred for 5 h at the same temperature, before it was treated with water (200 mL) and diethyl ether (100 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give tricyclic enone **2-170** (15.8 g, 74%) as a colorless oil. R_f = 0.41 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.36–1.48 (m, 2H, 5-H, 6-H), 1.51–1.69 (m, 3H, 6-H, 2 × 10-H), 1.75–1.84 (m, 3H, 5-H, 2 × 9-H), 2.00–2.12 (m, 4H, 2 × 3-H, 2 ×7-H), 2.42 (ddd, *J* = 6.1, 3.0, 3.0 Hz, 1H, 2-H), 2.63 (dd, *J* = 10.6, 5.8 Hz, 1H, 4-H), 3.61 (s, 3H, OCH_3), 6.92 (dd, *J* = 4.2, 4.2 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 18.9 (C-6), 23.2 (C-9), 25.1 (C-7), 28.3 (C-3), 31.4 (C-5), 33.8 (C-10), 37.9 (C-4a), 41.0 (C-2), 47.4 (C-4), 51.6 (OCH_3), 134.8 (C-8), 137.8 (C-8a), 175.1 (ester), 201.7 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{18}O_3Na$ 257.114820, found 257.114860.



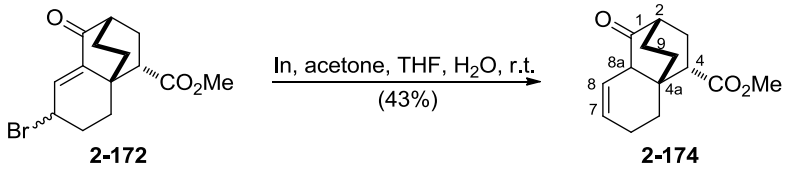
(2*S*,4*S*,4a*S*)-Methyl 2,3,4,5,6,8a-hexahydrospiro[2,4a-ethanonaphthalene-1,2'-[1,3]dioxolane]-4-carboxylate (2-171). TMSOTf (3 µL, 0.02 mmol) was added to a stirred solution of 1,2-bistrimethylsiloxyethane (80 µL, 0.32 mmol) and enone **2-170** (35 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) at –78 °C. The resulting mixture stirred overnight at room temperature before it was treated with half saturated $NaHCO_3$ solution (20 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated

NaCl solution (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give acetal **2-171** (31 mg, 68%) as a colorless oil. R_f = 0.62 (petroleum ether/ EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 0.96 (ddd, *J* = 10.8, 10.8, 1.9 Hz, 1H, 10-H), 1.25–1.39 (m, 3H, 2 ×5-H, 9-H), 1.71–1.94 (m, 5H, 2-H, 3-H, 6-H, 9-H, 10-H), 1.97–2.14 (m, 2H, 3-H, 6-H), 2.38–2.43 (m, 1H, 4-H), 3.09 (ddd, *J* = 4.2, 2.3, 2.1 Hz, 1H, 8a-H), 3.63 (s, 3H, OCH_3), 3.77–4.02 (m, 4H, $CH_2O)_2$), 5.52 (br.d., *J* = 10.1 Hz, 1H, 8-H), 5.70 (ddd, *J* = 7.6, 5.1, 2.6 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.2 (C-9), 21.7 (C-6), 25.8 (C-3), 26.2 (C-10), 30.5 (C-5), 33.6 (C-2), 34.9 (C-4a), 41.8 (C-8a), 46.4 (C-4), 51.3 (OCH_3), 63.4 ($CH_2O)_2$), 65.5 (($CH_2O)_2$), 111.5 (C-1), 124.2 (C-8), 125.8 (C-7), 175.7 (ester); HRMS (ESI): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$ 301.14103, found 301.146766.



2-170 **2-172**

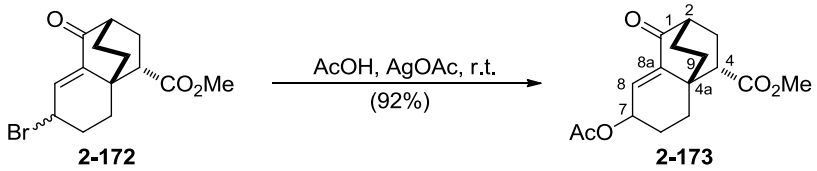
(2*S*,4*S*,4a*S*)-Methyl 7-bromo-1-oxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-172). AIBN (10 mg) was added to a stirred solution of enone **2-170** (800 mg, 3.45 mmol) and NBS (610 mg, 3.45 mmol) in CCl_4 (10 mL) at room temperature. The resulting mixture was stirred under reflux for 1 h before it was treated with water (50 mL) and diethyl ether (20 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give diastereomeric mixture of bromides **2-172** (1:1, 900 mg, 84%) as a colorless oil. R_f = 0.38; 0.50 (petroleum ether/EtOAc 2:1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{17}BrO_3Na$ 335.02533, found 335.025012.



2-172 **2-174**

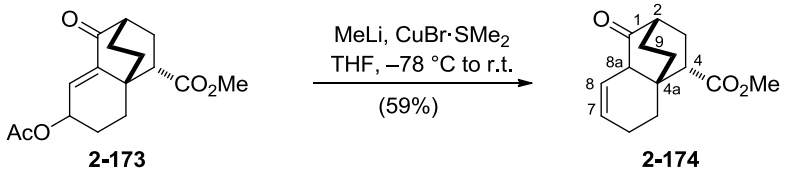
(2*S*,4*S*,4a*S*)-Methyl 1-oxo-2,3,4,5,6,8a-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-174). Acetone (31 µL, 0.42 mmol) was added to a stirred suspension of bromides **2-172** (13.0 mg, 0.042 mmol) and indium powder (5.8 mg, 0.050 mmol) in THF/water (1:1, 0.2 mL) at room temperature. The resulting mixture was stirred for 24 h before the solvents were removed and the residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give ketone **2-174** (4.2 mg, 43%) as a colorless oil. R_f = 0.55 (petroleum ether/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.15–1.23 (m, 1H, 10-H), 1.40 (ddd, *J* = 13.1, 10.8, 7.4 Hz, 1H, 5-H), 1.49–1.54 (m, 1H, 5-H), 1.72–1.90 (m, 3H, 2 × 9-H, 10-H), 2.02–2.10 (m, 3H, 3-H, 2 × 6-H), 2.17 (dddd, *J* = 13.9, 8.2, 2.0, 1.9 Hz, 1H, 3-H), 2.38 (ddd, *J* = 5.6, 3.7, 2.0 Hz, 1H, 2-H), 2.70 (dd, *J* = 10.1, 8.3 Hz, 1H, 4-H), 3.38–3.42 (m, 1H, 8a-H), 5.71 (ddd, *J* = 10.1, 6.7, 3.4 Hz, 1H, 7-H), 5.87 (ddd, *J* = 10.1, 4.0, 2.0 Hz, 1H,

8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 22.1 (C-6), 24.0 (C-9), 26.4 (C-10), 26.9 (C-3), 29.5 (C-5), 37.7 (C-4a), 42.3 (C-2), 45.8 (C-4), 48.0 (C-8a), 51.6 (OCH_3), 122.2 (C-8), 126.9 (C-7), 175.4 (ester), 215.0 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{18}O_3Na$ 257.11482, found 257.114654.



2-172 **2-173**

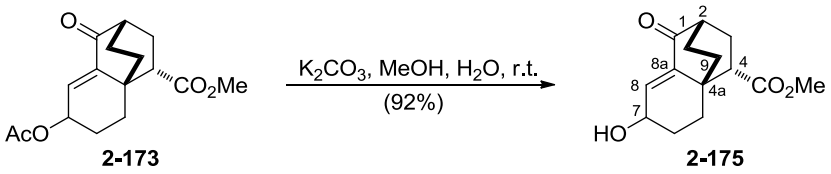
(2*S*,4*S*,4a*S*)-Methyl 7-acetoxy-1-oxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-173). A solution of bromide **2-172** (700 mg, 2.25 mmol) in glacial acetic acid (10 mL) was treated with silver acetate (750 mg, 4.50 mmol) at room temperature. The resulting mixture was stirred for 2 h before it was diluted with diethyl ether (50 mL), treated with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give acetate **2-173** (604 mg, 92%) as a colorless oil (one stereoisomer). R_f = 0.62 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.34–2.15 (m, 10H, 2 × 3-H, 2 × 5-H, 2 × 6-H, 2 × 9-H, 2 × 10-H), 2.03 (s, 3H, $OCOCH_3$), 2.47 (ddd, *J* = 5.8, 2.9, 2.9 Hz, 1H, 2-H), 2.67 (dd, *J* = 10.4, 5.8 Hz, 1H, 4-H), 3.64 (s, 3H, OCH_3), 5.28–5.31 (m, 1H, 7-H), 6.71 (d, *J* = 3.5 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 21.0 ($OCOCH_3$), 23.1 (C-6), 24.8 (C-10), 27.9 (C-3), 28.2 (C-5), 33.4 (C-9), 37.8 (C-4), 40.7 (C-2), 47.3 (C-4a), 51.7 (OCH_3), 67.4 (C-7), 130.5 (C-8), 140.0 (C-8a), 170.4 ($OCOCH_3$), 174.6 (4-ester), 201.2 (C-1).



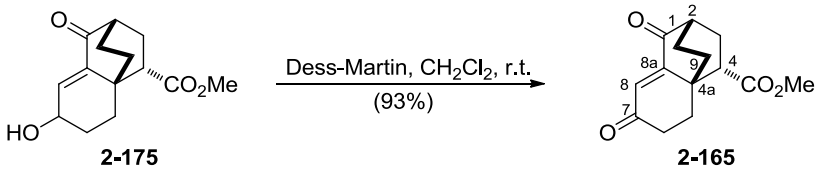
2-173 **2-174**

(2*S*,4*S*,4a*S*)-Methyl 1-oxo-2,3,4,5,6,8a-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-174). A solution of MeLi (1.6M in diethyl ether, 0.42 mL, 0.68 mmol) was added dropwise to a stirred suspension of $CuBr{\cdot}SMe_2$ (70 mg, 0.34 mmol) in THF (2 mL) at –78 °C. The resulting mixture was allowed to warm to room temperature and then cooled again to –78 °C and treated with a solution of acetate **2-173** (33 mg, 0.11 mmol) in THF (2 mL). The mixture was slowly warmed to room temperature, stirred for 1 h, treated with half saturated NH_4Cl solution (20 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give enone **2-174** (15.6 mg, 59%) as a colorless oil. R_f = 0.55 (petroleum ether/ EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.15–1.23 (m, 1H, 10-H), 1.40 (ddd, *J* = 13.1, 10.8, 7.4 Hz, 1H, 5-H), 1.49–1.54 (m, 1H, 5-H), 1.72–1.90 (m, 3H, 2 × 9-H, 10-H), 2.02–2.10 (m, 3H, 3-H, 2 × 6-H), 2.17 (dddd, *J* = 13.9, 8.2, 2.0, 1.9 Hz, 1H, 3-H), 2.38 (ddd, *J* = 5.6, 3.7, 2.0 Hz, 1H, 2-H), 2.70 (dd, *J* = 10.1, 8.3

Hz, 1H, 4-H), 3.38–3.42 (m, 1H, 8a-H), 5.71 (ddd, *J* = 10.1, 6.7, 3.4 Hz, 1H, 7-H), 5.87 (ddd, *J* = 10.1, 4.0, 2.0 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 22.1 (C-6), 24.0 (C-9), 26.4 (C-10), 26.9 (C-3), 29.5 (C-5), 37.7 (C-4a), 42.3 (C-2), 45.8 (C-4), 48.0 (C-8a), 51.6 (OCH_3), 122.2 (C-8), 126.9 (C-7), 175.4 (ester), 215.0 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{18}O_3Na$ 257.11482, found 257.114654.

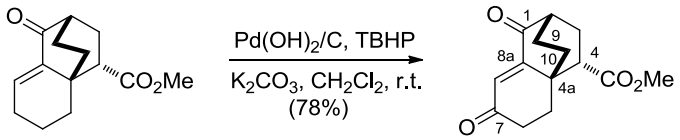


(2*S*,4*S*,4a*S*)-Methyl 7-hydroxy-1-oxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-175). Potassium carbonate (50 mg, 0.36 mmol) was added in one portion to a stirred solution of acetate **2-173** (100 mg, 0.34 mmol) in methanol/H_2O (25:1, 5.2 mL) at room temperature. The resulting mixture was stirred for 30 min before it was diluted with diethyl ether (10 mL), treated with water (20 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give alcohol **2-175** (82 mg, 92%) as a colorless oil. R_f = 0.27 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, benzene-d_6): δ[ppm] = 1.04–1.61 (m, 9H, 2 × 5-H, 2 × 6-H, 2 × 9-H, 2 × 10-H, OH), 1.95–2.06 (m, 2H, 2 × 3-H), 2.31–2.37 (m, 2H, 2-H, 4-H), 3.35 (s, 3H, OCH_3), 4.02–4.07 (m, 1H, 7-H), 7.09–7.11 (m, 1H, 8-H); ^{13}C NMR (100 MHz, benzene-d_6): δ[ppm] = 23.0 (C-6), 28.1 (C-10), 28.2 (C-3), 28.4 (C-5), 33.2 (C-9), 37.6 (C-4), 41.2 (C-2), 46.9 (C-4a), 51.4 (OCH_3), 64.6 (C-7), 134.4 (C-8), 138.5 (C-8a), 175.0 (ester), 200.4 (C=O).



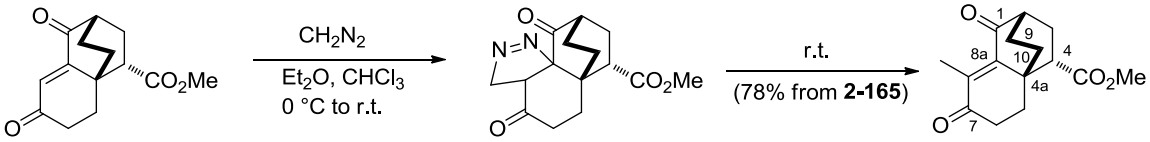
(2*S*,4*S*,4a*S*)-Methyl 1,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-165). Dess-Martin reagent (260 mg, 0.62 mol) was added in one portion to a stirred solution of alcohol **2-175** (140 mg, 0.056 mol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred for 2 h before it was treated with saturated $Na_2S_2O_3$ solution (5 mL) and stirred for additional 15 min. The resulting mixture was washed with saturated $NaHCO_3$ solution (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give ketone **2-165** (130 mg, 93%) as a colorless oil. R_f = 0.40 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.74–1.79 (m, 1H, 10-H), 1.84–1.99 (m, 4H, 5-H, 10-H, 2 × 9-H), 2.11–2.21 (m, 3H, 2 × 3-H, 5-H), 2.30 (ddd, *J* = 16.8, 7.3, 5.3 Hz, 1H, 6-H), 2.45 (ddd, *J* = 16.7, 9.9, 5.8 Hz, 1H, 6-H), 2.60 (ddd, *J* = 5.8, 3.0, 3.0 Hz, 1H, 2-H), 2.79 (dd, *J* = 9.6, 6.1 Hz, 1H, 4-H), 3.63 (s, 3H, OCH_3), 6.50 (s, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] =

22.7 (C-9), 28.0 (C-3), 29.8 (C-5), 31.1 (C-10), 34.4 (C-6), 38.6 (C-4a), 40.4 (C-2), 46.7 (C-4), 52.2 (OCH_3), 125.4 (C-8), 152.4 (C-8a), 174.3 (ester), 198.8 (C-7), 201.8 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{16}O_4Na$ 271.094080, found 271.094073.



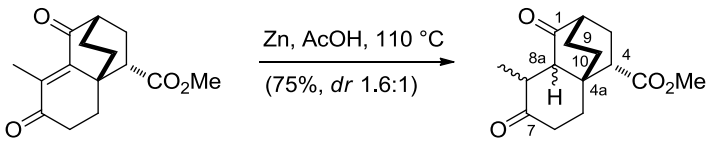
2-170 **2-165**

(2*S*,4*S*,4a*S*)-Methyl 1,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-165). $Pd(OH)_2/C$ (Pearlman's catalyst,[194] 20%, 1.1 g, 2.0 mmol) was added to a stirred suspension of enone **2-170** (10.0 g, 43.0 mmol), K_2CO_3 (1.5 g. 10.0 mmol) in CH_2Cl_2 (200 mL) followed by addition of *tert*-butylhydroperoxide (5.0–6.0M in decaline, 43 mL, 215.0 mmol) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction mixture was then filtered through a short pad of silica gel, washed with CH_2Cl_2 and concentrated in vacuo at room temperature. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give 1,4-diketone **2-165** (8.3 g, 78%) as a colorless oil. R_f = 0.40 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.74–1.79 (m, 1H, 10-H), 1.84–1.99 (m, 4H, 5-H, 10-H, 2 × 9-H), 2.11–2.21 (m, 3H, 2 × 3-H, 5-H), 2.30 (ddd, *J* = 16.8, 7.3, 5.3 Hz, 1H, 6-H), 2.45 (ddd, *J* = 16.7, 9.9, 5.8 Hz, 1H, 6-H), 2.60 (ddd, *J* = 5.8, 3.0, 3.0 Hz, 1H, 2-H), 2.79 (dd, *J* = 9.6, 6.1 Hz, 1H, 4-H), 3.63 (s, 3H, OCH_3), 6.50 (s, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 22.7 (C-9), 28.0 (C-3), 29.8 (C-5), 31.1 (C-10), 34.4 (C-6), 38.6 (C-4a), 40.4 (C-2), 46.7 (C-4), 52.2 (OCH_3), 125.4 (C-8), 152.4 (C-8a), 174.3 (ester), 198.8 (C-7), 201.8 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{16}O_4Na$ 271.094080, found 271.094073.



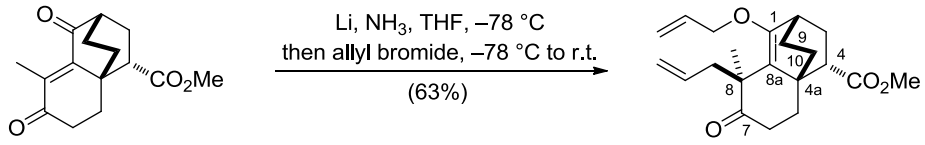
2-165 **2-176** **2-169**

(2*S*,4*S*,4a*S*)-Methyl 8-methyl-1,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-169). A solution of diazomethane[195] in diethyl ether (200 mL) was added to a stirred solution of enedione **2-165** (4.7 g, 0.019 mol) in chloroform (150 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 6 h before the solvents were removed with a flow of nitrogen. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to give enedione **2-169** (3.9 g, 78 %) as white crystals (m.p. 97–98.5 °C).[196] R_f = 0.45 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.61–1.68 (m, 1H, 10-H), 1.78–2.00 (m, 4H, 5-H, 10-H, 2 × 9-H), 2.06–2.14 (m, 3H, 2 × 3-H, 5-H), 2.17 (s, 3H, 8-CH_3) 2.34 (ddd, *J* = 16.4, 6.8, 5.0 Hz, 1H, 6-H), 2.49 (ddd, *J* = 16.4, 10.9, 5.8 Hz, 1H, 6-H), 2.55 (ddd, *J* = 6.1, 3.0, 3.0 Hz, 1H, 2-H), 2.69 (dd, *J* = 8.6, 7.3 Hz, 1H, 4-H), 3.60 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 12.0 (C*C*H_3), 22.6 (C-9), 28.1 (C-3), 29.8 (C-5), 31.1 (C-10), 34.0 (C-6), 39.8 (C-4a), 42.2 (C-2), 47.2 (C-4), 52.0 (OCH_3), 138.2 (C-8), 144.6 (C-8a), 174.6 (ester), 199.6 (C-7), 204.7 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{18}O_4Na$ 285.109730, found 285.109658.



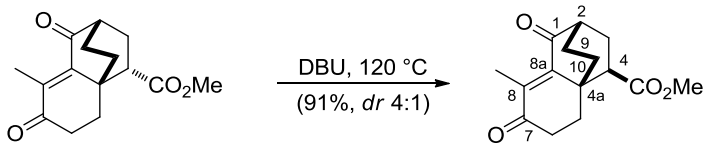
2-169 **2-177**

(2*S*,4*S*,4a*R*,8*RS*,8a*RS*) Methyl 8-methyl-1,7-dioxooctahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-177). A solution of diketone **2-169** (630 mg, 2.39 mmol) in glacial acetic acid (6 mL) was treated with zinc powder (930 mg, 14.32 mmol) at room temperature and stirred for 4 h under reflux. After concentration in vacuo the residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to give compound **2-177** (470 mg, 75%) as white crystals (mixture of two diastereomers in ratio 1.6:1). R_f = 0.45 (petroleum ether/EtOAc 1:1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{20}O_4Na$ 287.125380, found 287.125493.



2-169 **2-179**

(2*S*,4*S*,4a*S*,8*S*)-Methyl 8-allyl-1-(allyloxy)-8-methyl-7-oxo-3,4,5,6,7,8-hexahydro-2*H*-2,4a-ethanonaphthalene-4-carboxylate (2-179). Lithium (60 mg, 8.82 mmol) was added in small portions to stirred liquid ammonia (10 mL) at –78 °C. The resulting blue solution was stirred for 1 h before it was treated with a solution of diketone **2-169** (50 mg, 0.19 mmol) in THF (4 mL). After complete addition stirring was continued for 2 h at the same temperature. Then, allyl bromide (1.6 mL, 18.90 mmol) was added dropwise at –78 °C and the mixture stirred for 30 min before the cooling bath was removed and the ammonia was allowed to evaporate. The resulting white suspension was diluted with water (20 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give ketone **2-179** (41 mg, 63%) as a colorless oil. R_f = 0.64 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.29–1.76 (m, 7H, 2 × 3-H, 5-H, 2 × 9-H, 2 × 10-H), 1.33 (s, 3H, 8-CH_3), 1.85 (ddd, *J* = 12.6, 9.7, 2.8 Hz, 1H, 3-H), 2.01–2.08 (m, 1H, 5-H), 2.25 (ddd, *J* = 8.5, 5.1, 2.9 Hz, 2H, 2 × 6-H), 2.45 (dd, *J* = 9.8, 5.8 Hz, 1H, 4-H), 2.51 (dd, *J* = 13.1, 7.6 Hz, 1H, 8-(C*H*$_2$CH=CH$_2$)), 2.80–2.86 (m, 2H, 2-H, 8-(C*H*$_2$CH=CH$_2$)), 3.60 (s, 3H, OCH_3), 4.30–4.39 (m, 2H, 1-(OC*H*$_2$CH=CH$_2$)), 4.87–4.89 (m, 2H, 8-(CH$_2$CH=C*H*$_2$)), 5.22 (ddd, *J* = 12.1, 1.5, 1.5 Hz, 1H, 1-(OCH$_2$CH=C*H*$_2$)), 3.56 (ddd, *J* = 17.2, 3.3, 1.6 Hz, 1H, 1-(OCH$_2$CH=C*H*$_2$)), 5.55 (dddd, *J* = 17.2, 10.0, 7.4, 7.4 Hz, 1H, 8-(CH$_2$C*H*=CH$_2$)), 5.99 (dddd, *J* = 17.2, 10.4, 5.2, 5.0 Hz, 1H, 1-(OCH$_2$C*H*=CH$_2$)); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 24.8 (8-CH_3), 26.1 (C-9), 30.4 (C-2), 30.8 (C-5), 32.4 (C-3), 34.7 (C-10), 37.3 (C-6), 41.0 (C-4a), 42.9 (8-(*C*H$_2$CH=CH$_2$)), 49.2 (C-4), 51.6 (OCH_3, C-8), 68.8 (1-(O*C*H$_2$CH=CH$_2$)), 116.8 (8-(CH$_2$CH=*C*H$_2$), 1-(OCH$_2$CH=*C*H$_2$)), 118.5 (C-8a), 134.2 (1-(OCH$_2$*C*H=CH$_2$)), 136.1 ((8-(CH$_2$*C*H=CH$_2$)), 154.5 (C-1), 175.9 (ester), 215.2 (C-7); HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{30}O_4Na$ 393.203631 found 393.203799.

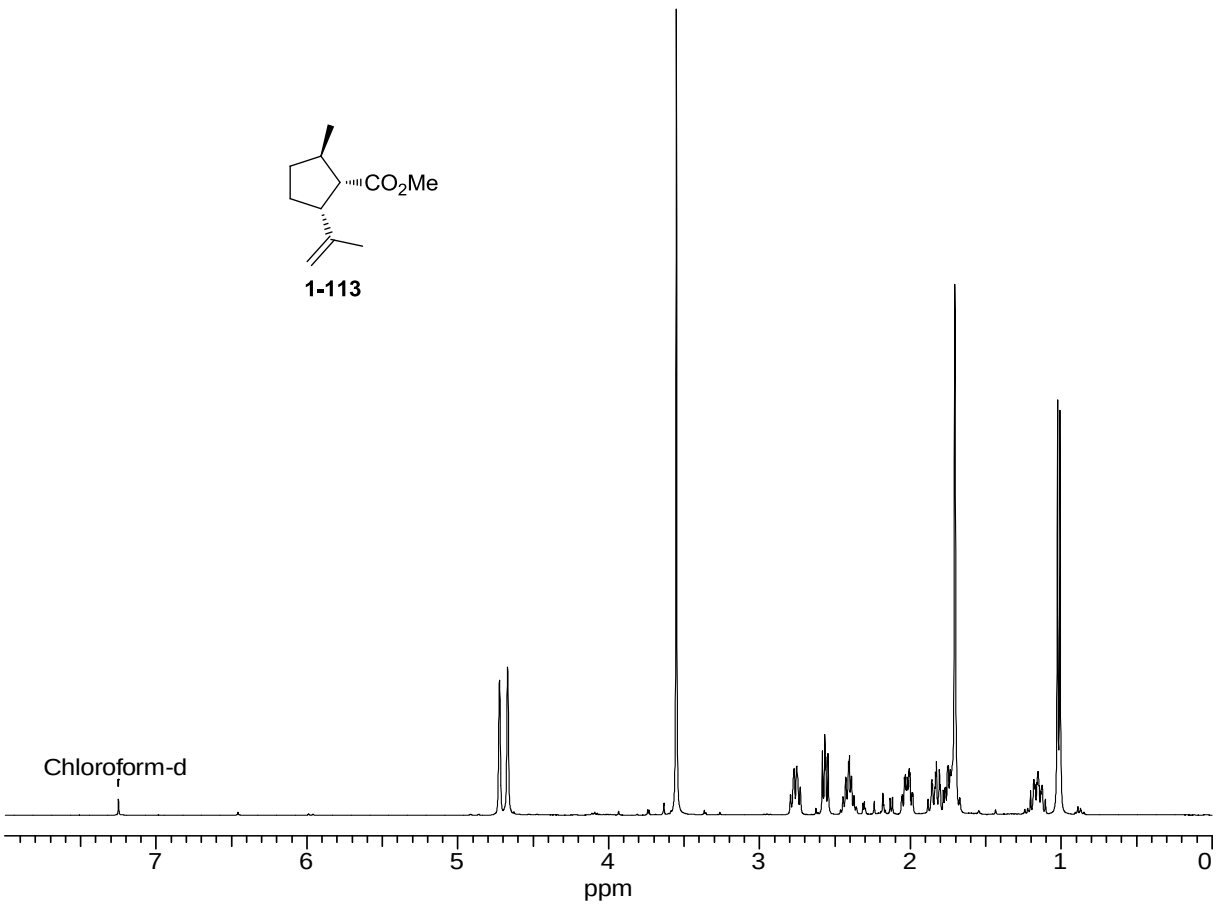


2-169 **2-187**

(2*S*,4*R*,4a*S*)-Methyl 8-methyl-1,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-2,4a-ethanonaphthalene-4-carboxylate (2-187). A solution of ester **2-169** (75 mg, 0.28 mmol) in DBU (1 mL) was stirred for 30 min at 120 °C before it was diluted with water (50 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with 1M HCl solution (2 × 20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give ketone **2-187** (41 mg, 63%) as a colorless oil. R_f = 0.64 (petroleum ether/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 1.58–1.67 (m, 1H, 10-H), 1.75 (ddd, *J* = 14.1, 9.0, 5.2 Hz, 1H, 5-H), 1.82–1.91 (m, 1H, 9-H), 1.97–2.10 (m, 4H, 3-H, 5-H, 9-H, 10-H), 2.16 (s, 3H, CCH_3), 2.21 (ddd, *J* = 13.9, 5.8, 2.5 Hz, 1H, 3-H), 2.46–2.62 (m, 3H, 2-H, 2 × 6-H), 2.83 (ddd, *J* = 10.7, 5.9, 1.8 Hz, 1H, 4-H), 3.73 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 11.9 (CCH_3), 23.1 (C-9), 25.5 (C-10), 27.1 (C-3), 29.9 (C-5), 33.9 (C-6), 39.8 (C-4a), 43.2 (C-2), 43.7 (C-4), 52.0 (OCH_3), 137.0 (C-8), 146.6 (C-8a), 174.1 (ester), 199.5 (C-7), 206.1 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{18}O_4Na$ 285.109730, found 285.109658.

Selected NMR Spectra for Important Compounds

Additional spectra are included in the supporting information of the published papers from this work and are available free of charge via Internet at http://www.pubs.acs.org and http://www.thieme-chemistry.com/products/journals/synlett.html.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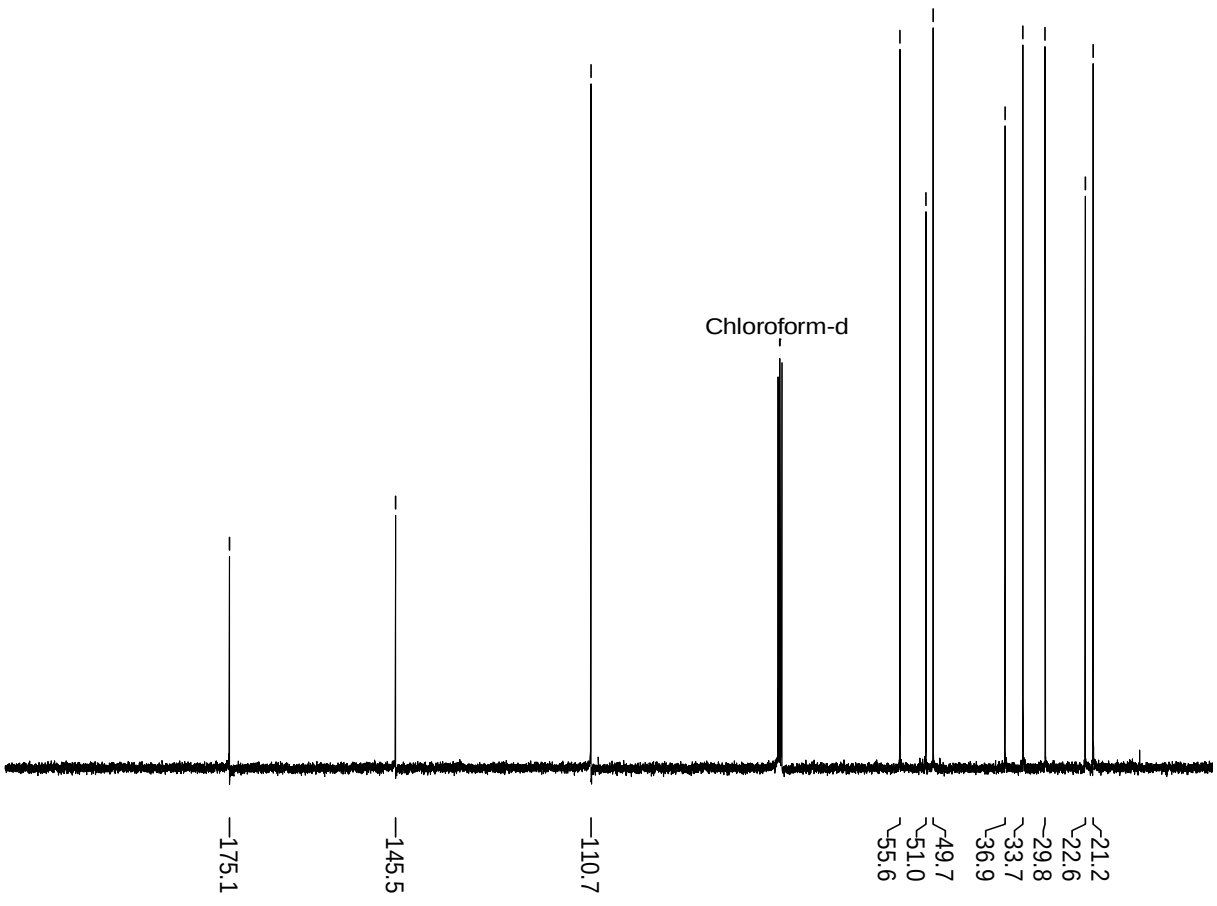
6
5
4
3
2
1
0
ppm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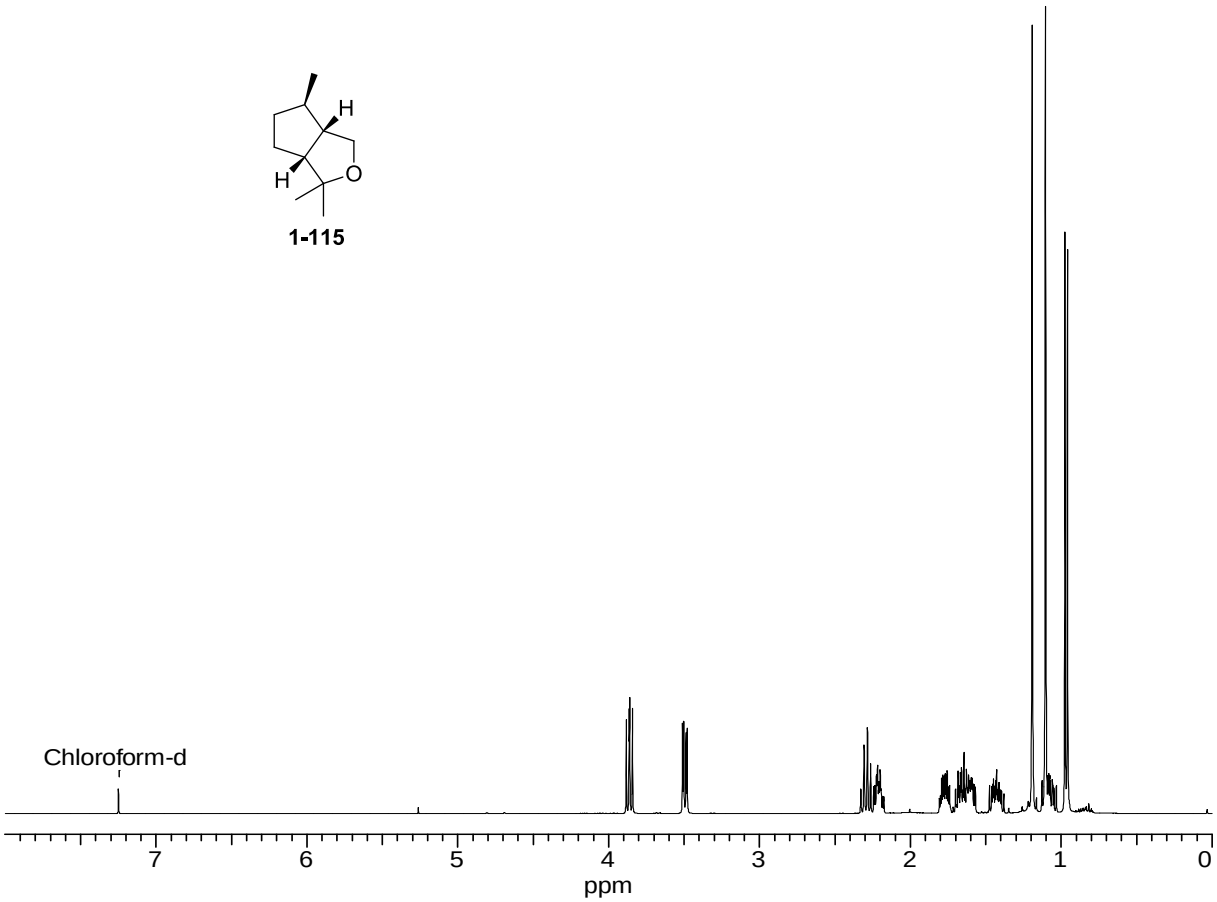
49.7
36.9
33.7
29.8
22.6
21.2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H
O
1-115
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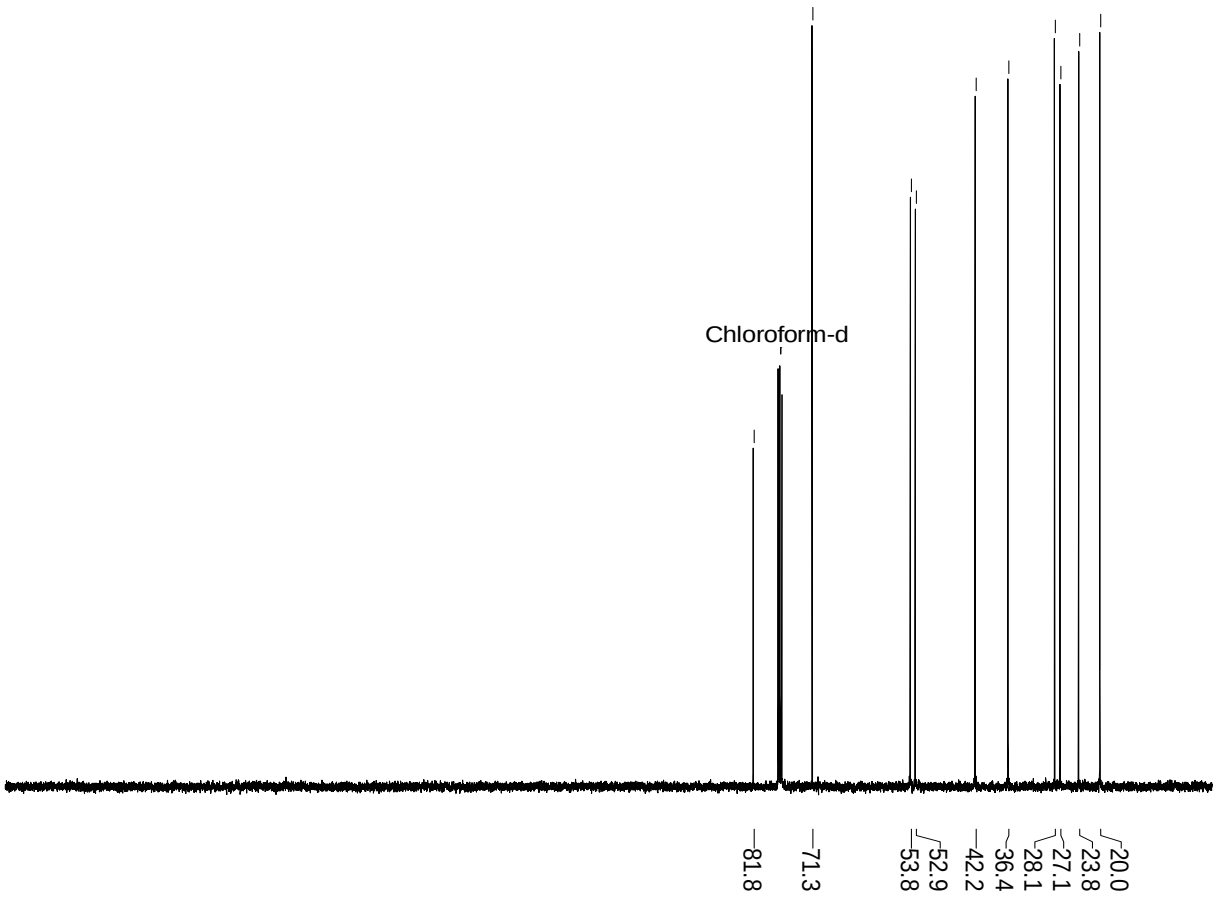
6
5
4
3
2
1
0
ppm


Chloroform-d
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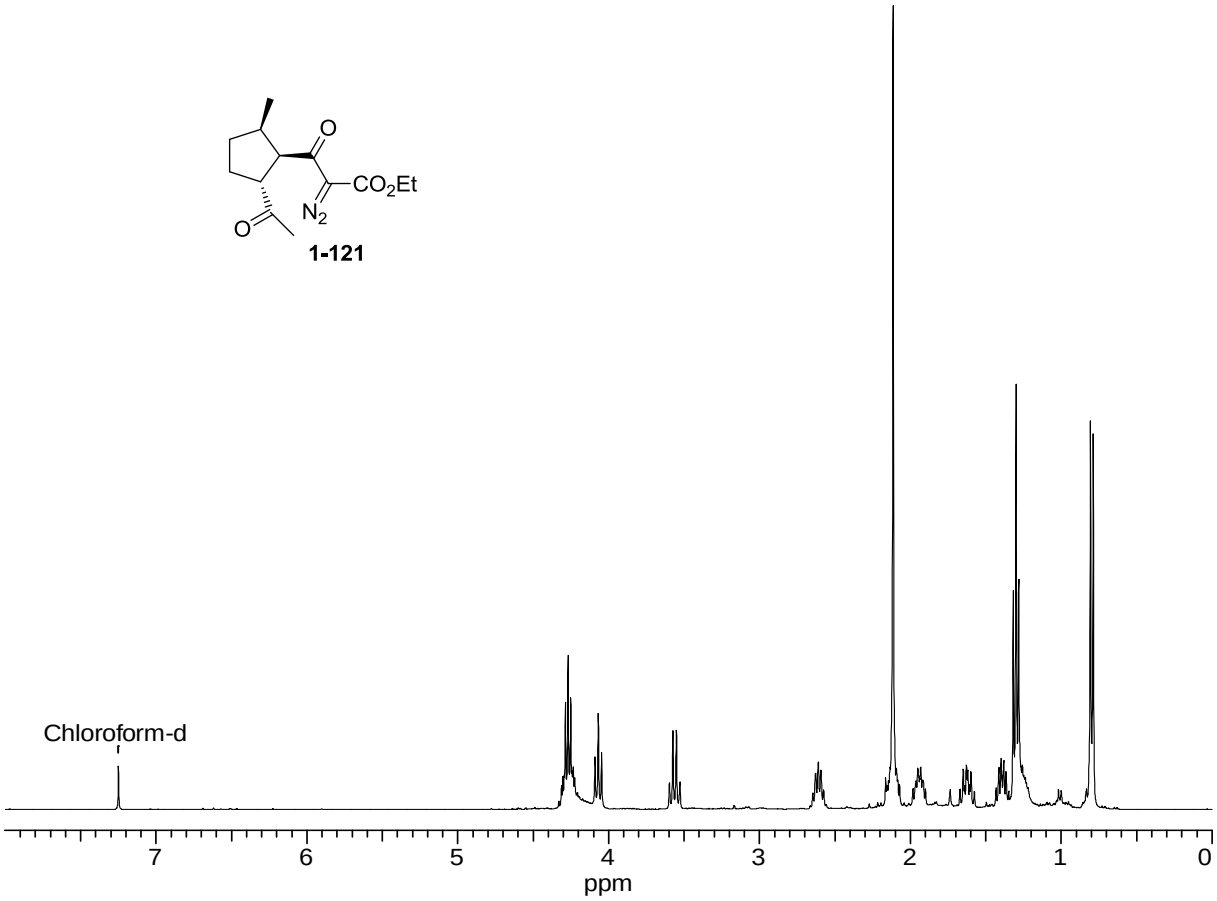
53.8
52.9
42.2
36.4
28.1
27.1
23.8
20.0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N2
O
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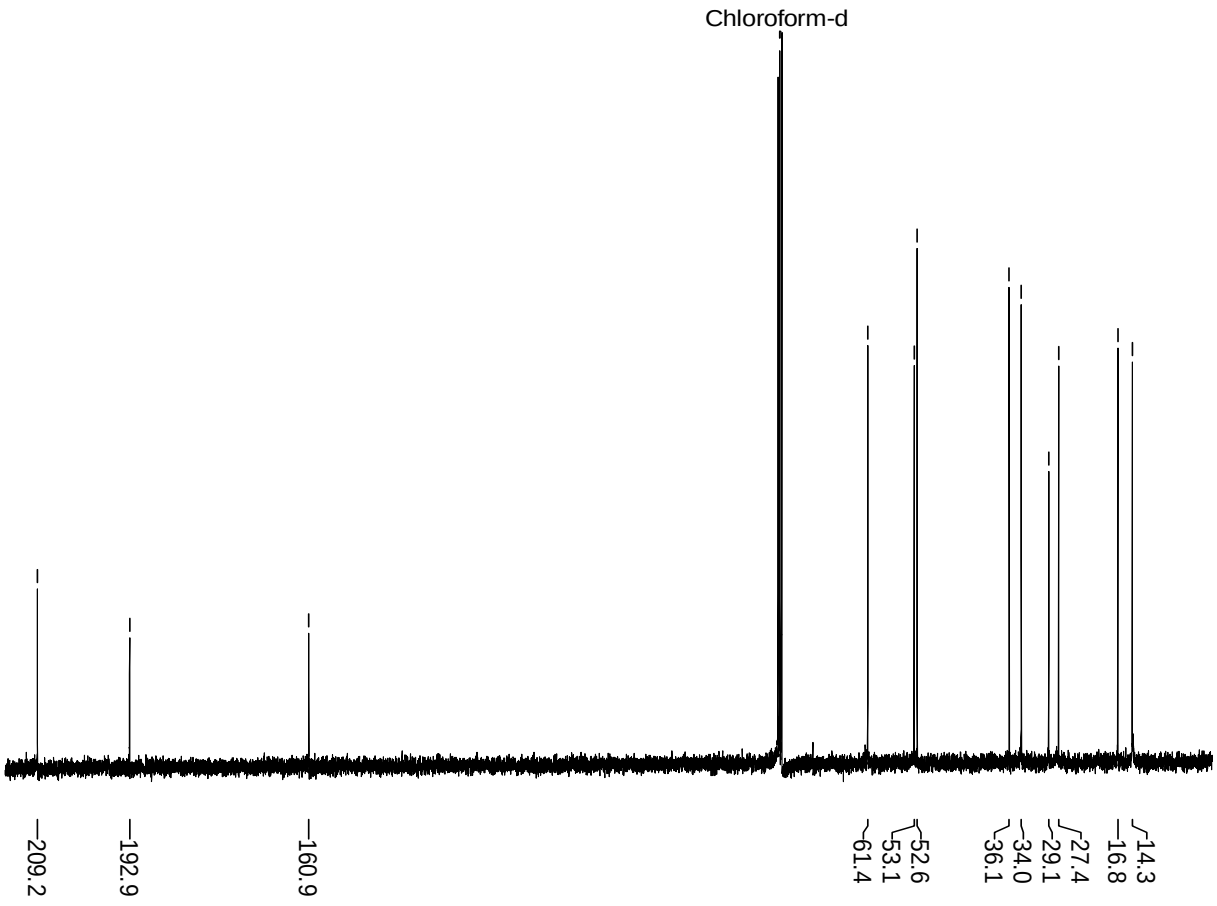
7
6
5
4
3
2
1
0
ppm


Chloroform-d
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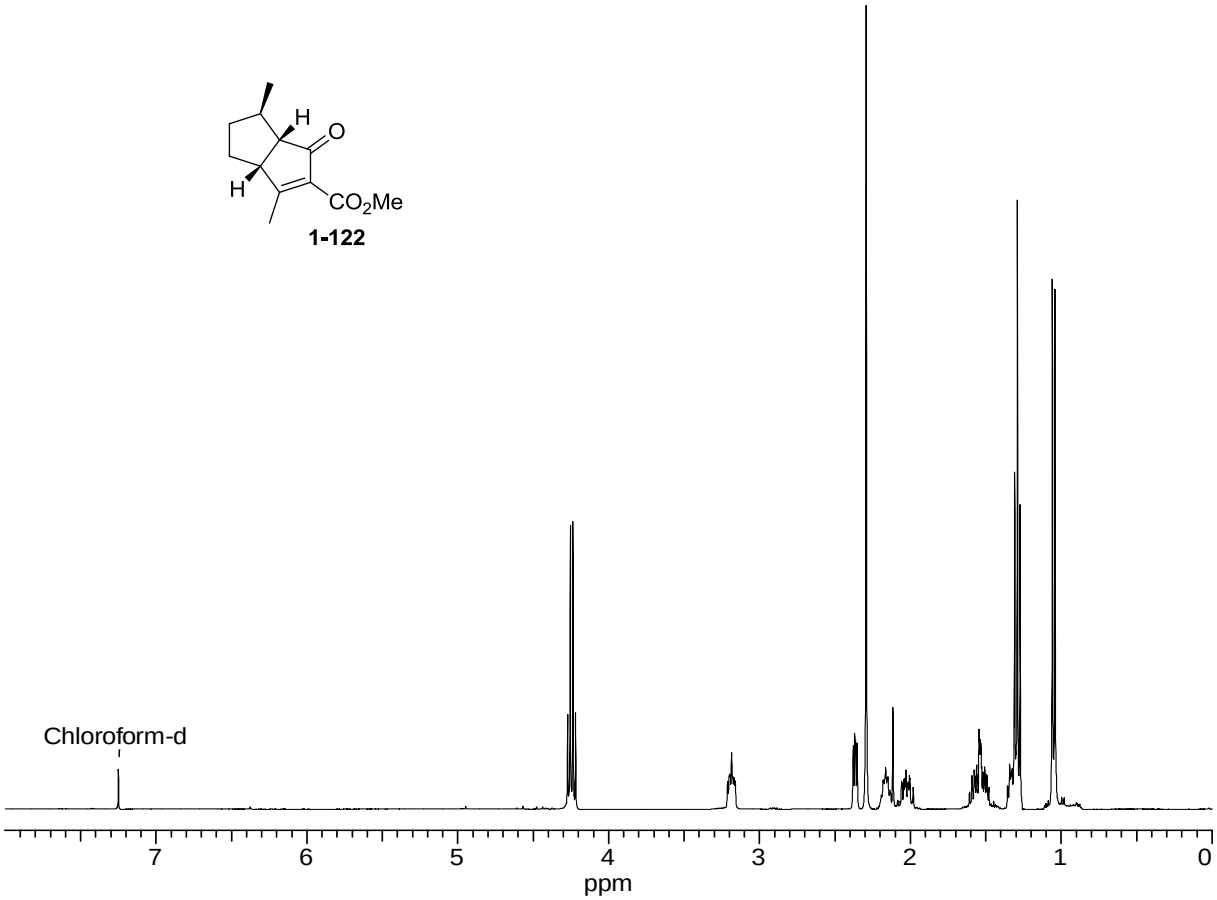
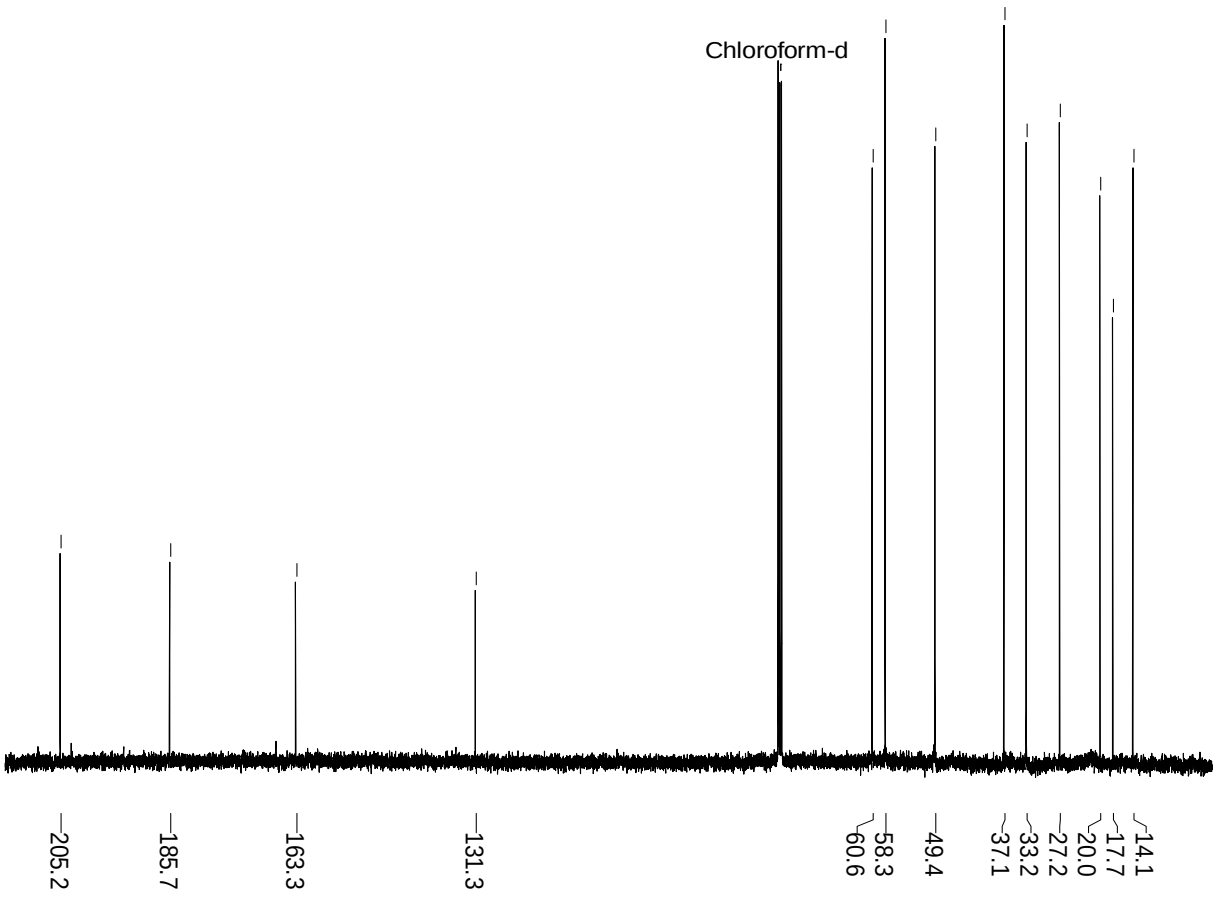
53.1
52.6
36.1
34.0
29.1
27.4
16.8
14.3


H
O
H
CO2Me
1-122
Chloroform-d
7
6
5
4
3
2
1
0
ppm


Chloroform-d
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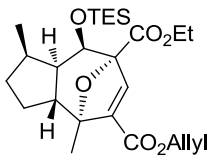
131.3
60.6
58.3
49.4
37.1
33.2
27.2
20.0
17.7
14.1


OTES
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O
H
CO2Allyl

1-127

Chloroform-d
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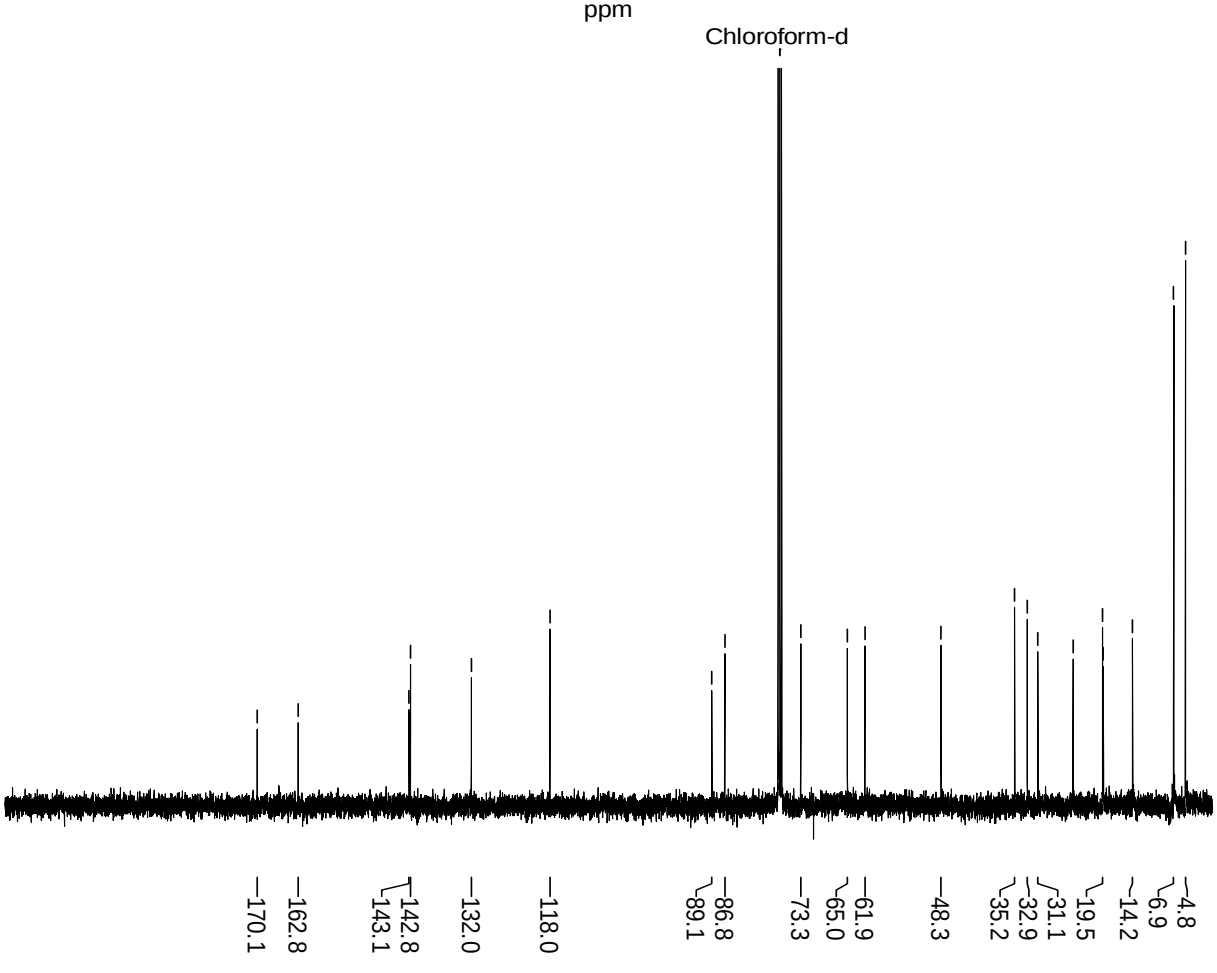
6
5
4
3
2
1
0
ppm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32.9
31.1
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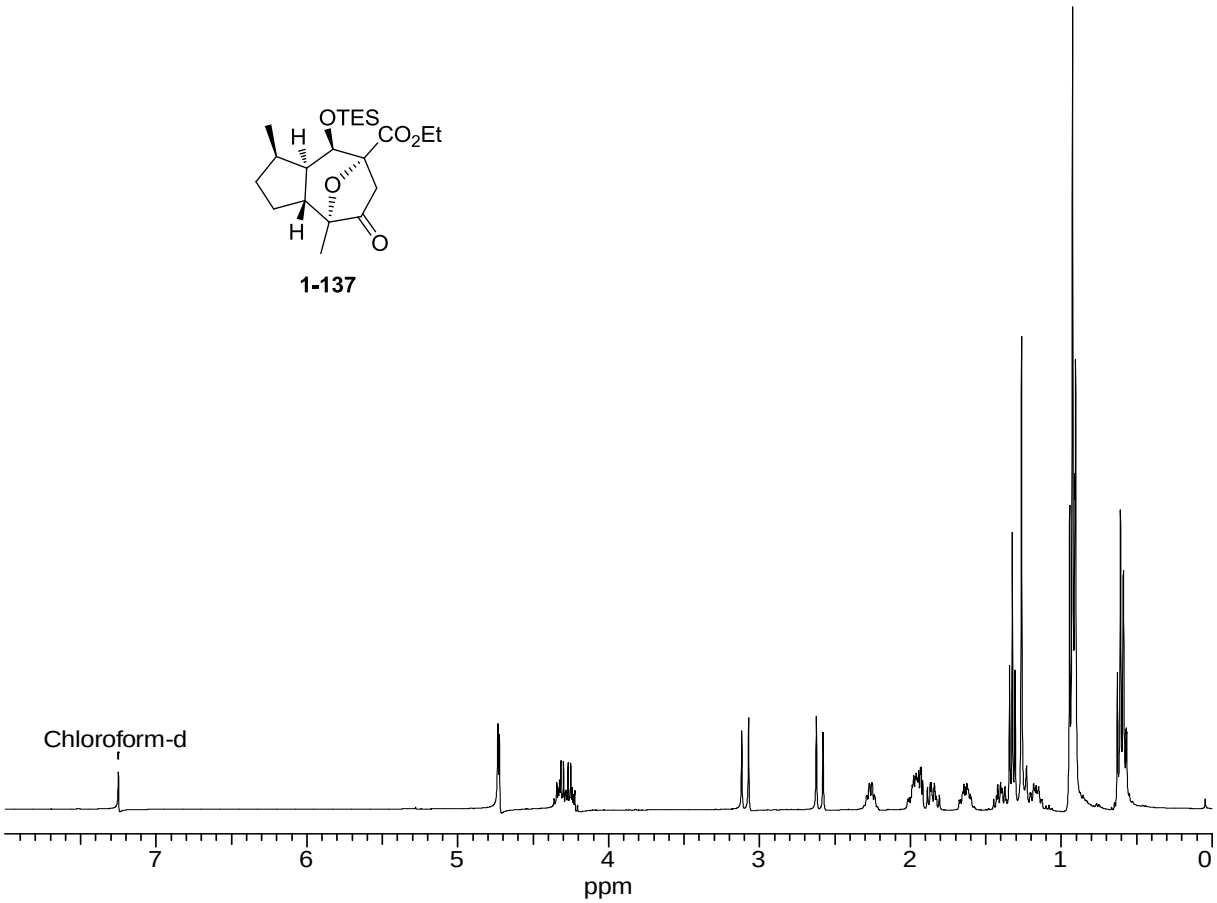
14.2
6.9
4.8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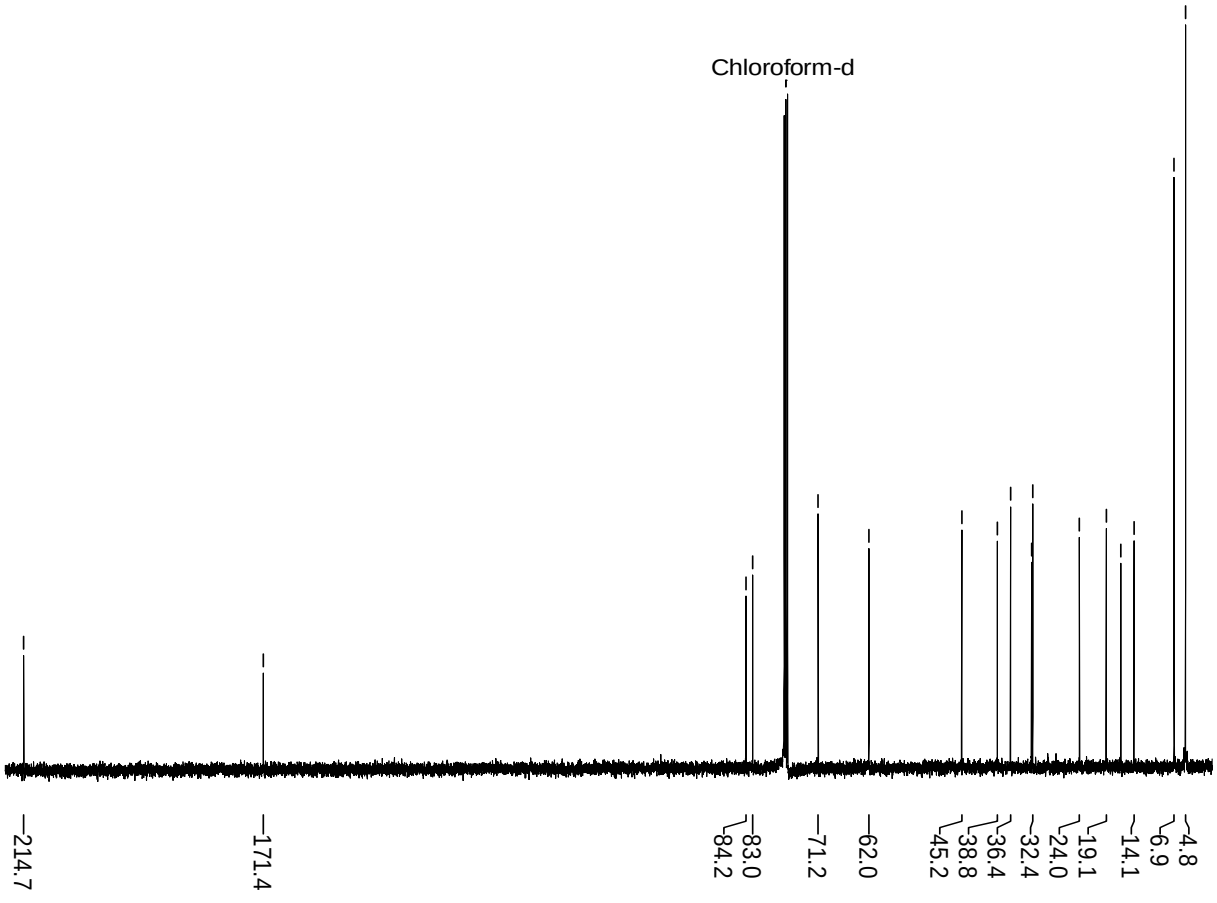
O
H
O
1-137
Chloroform-d
7
6
5
4
3
2
1
0
ppm


Chloroform-d
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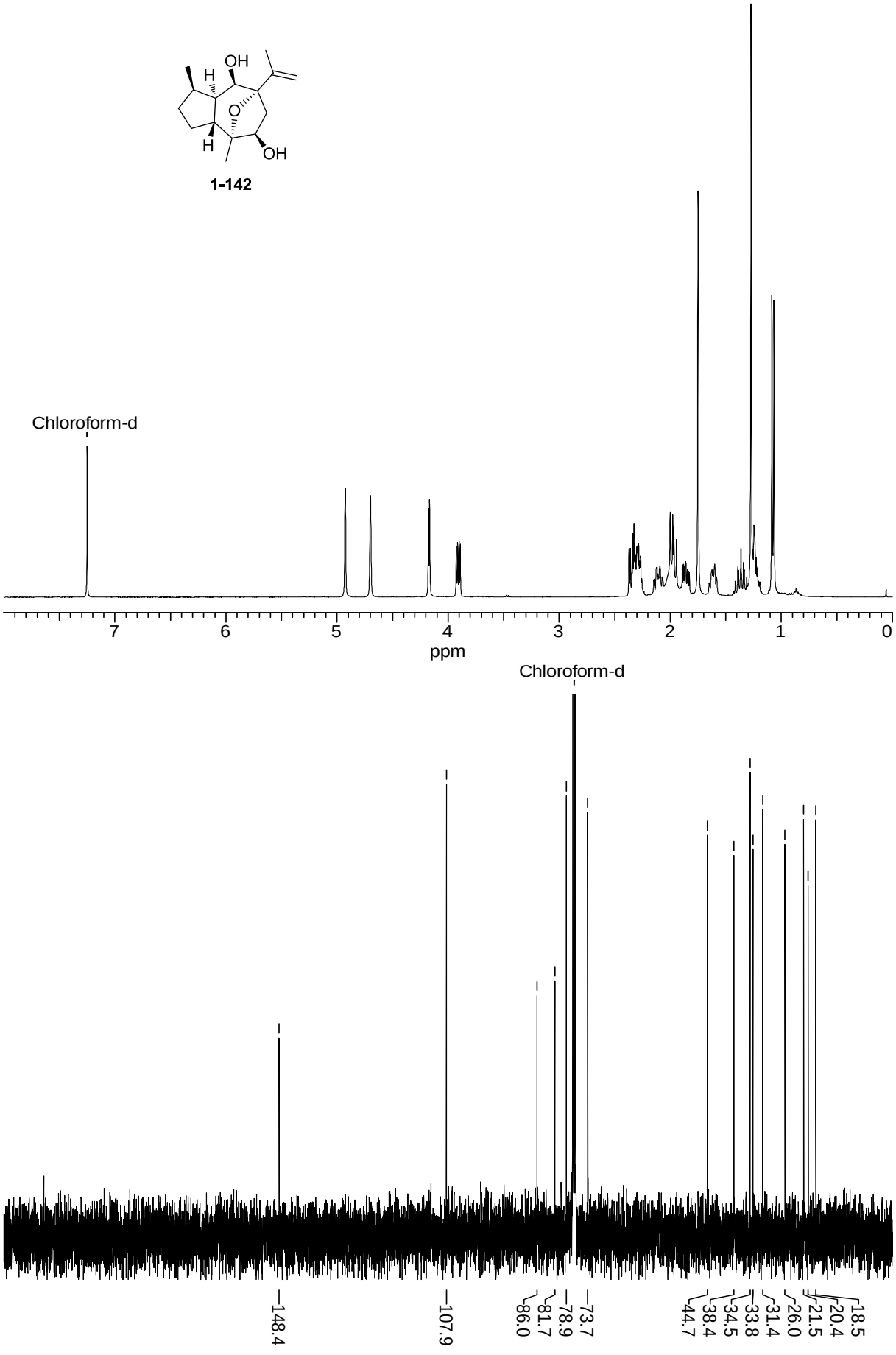
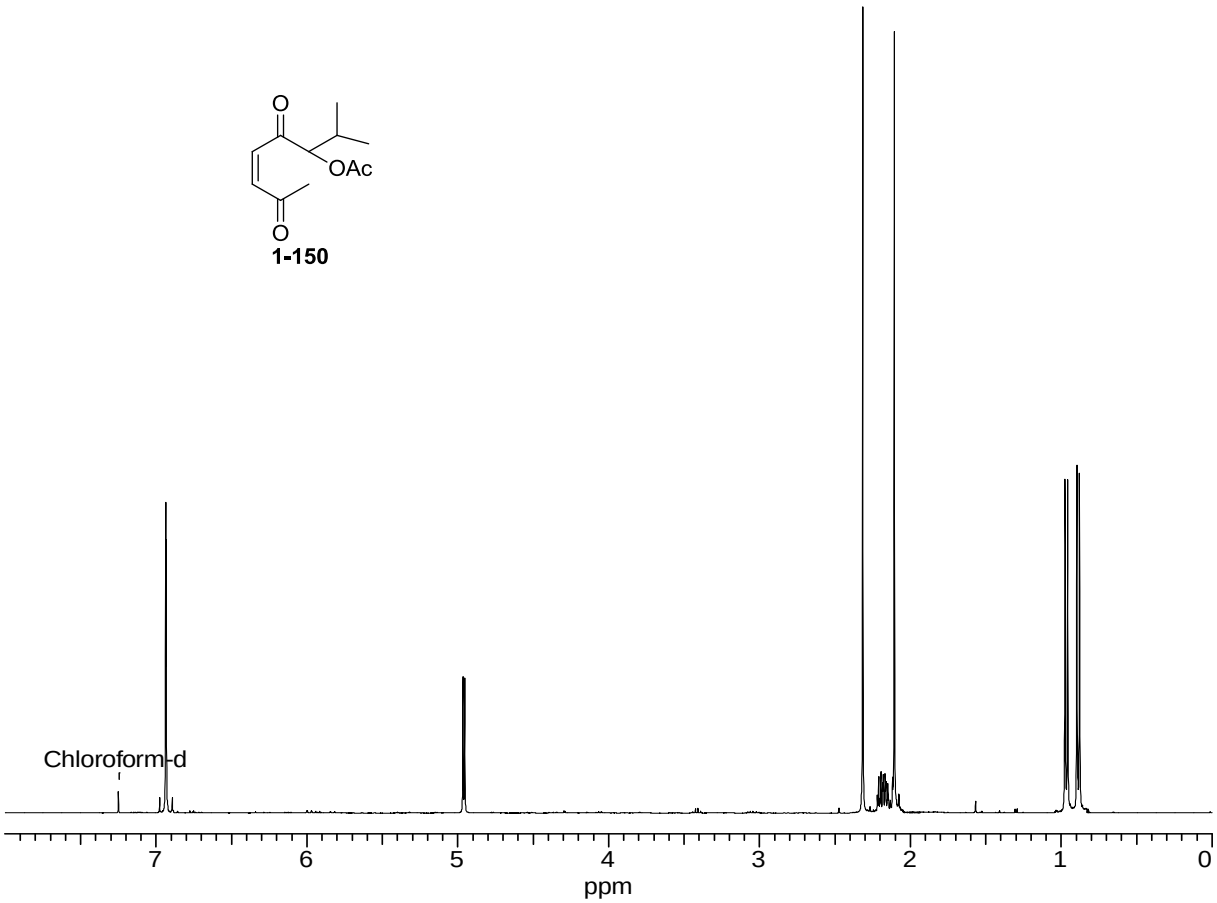
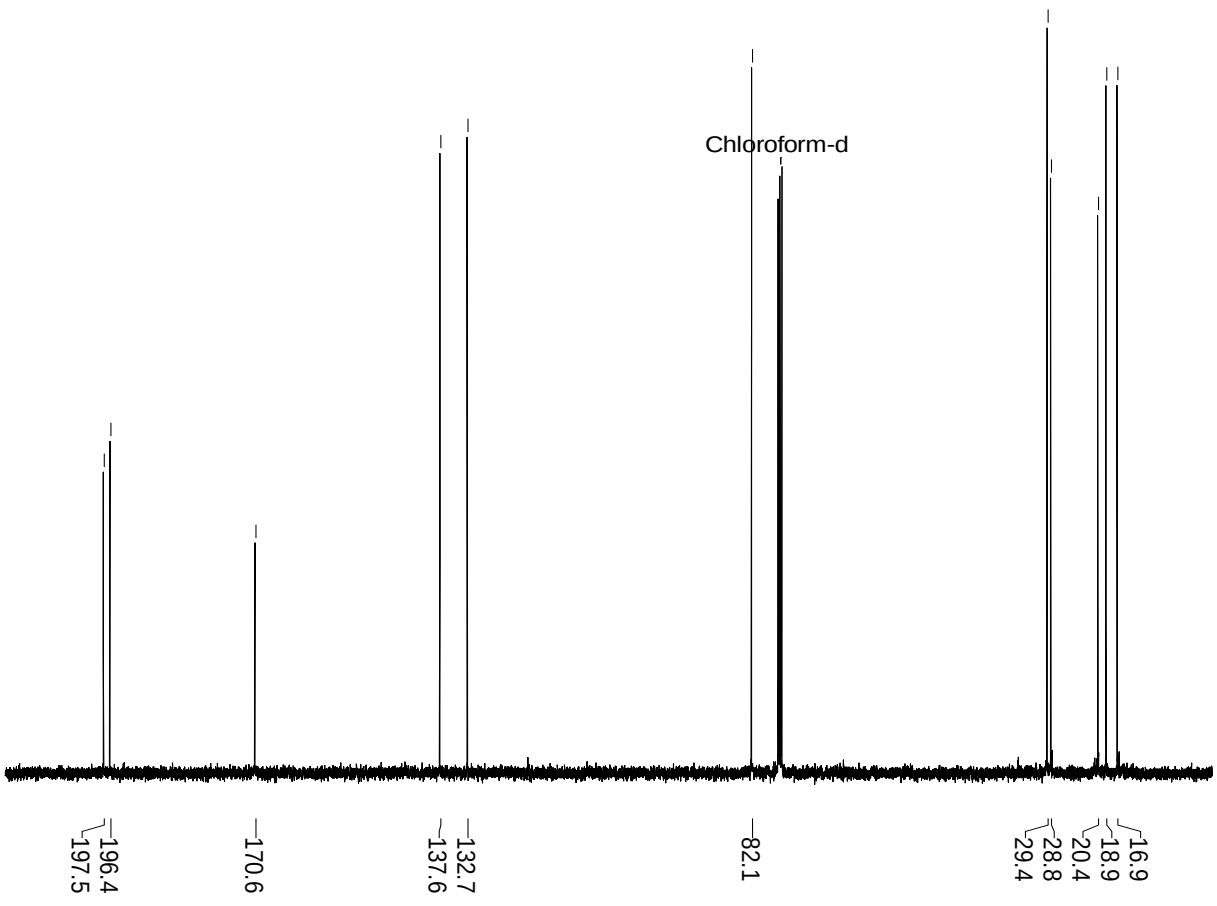
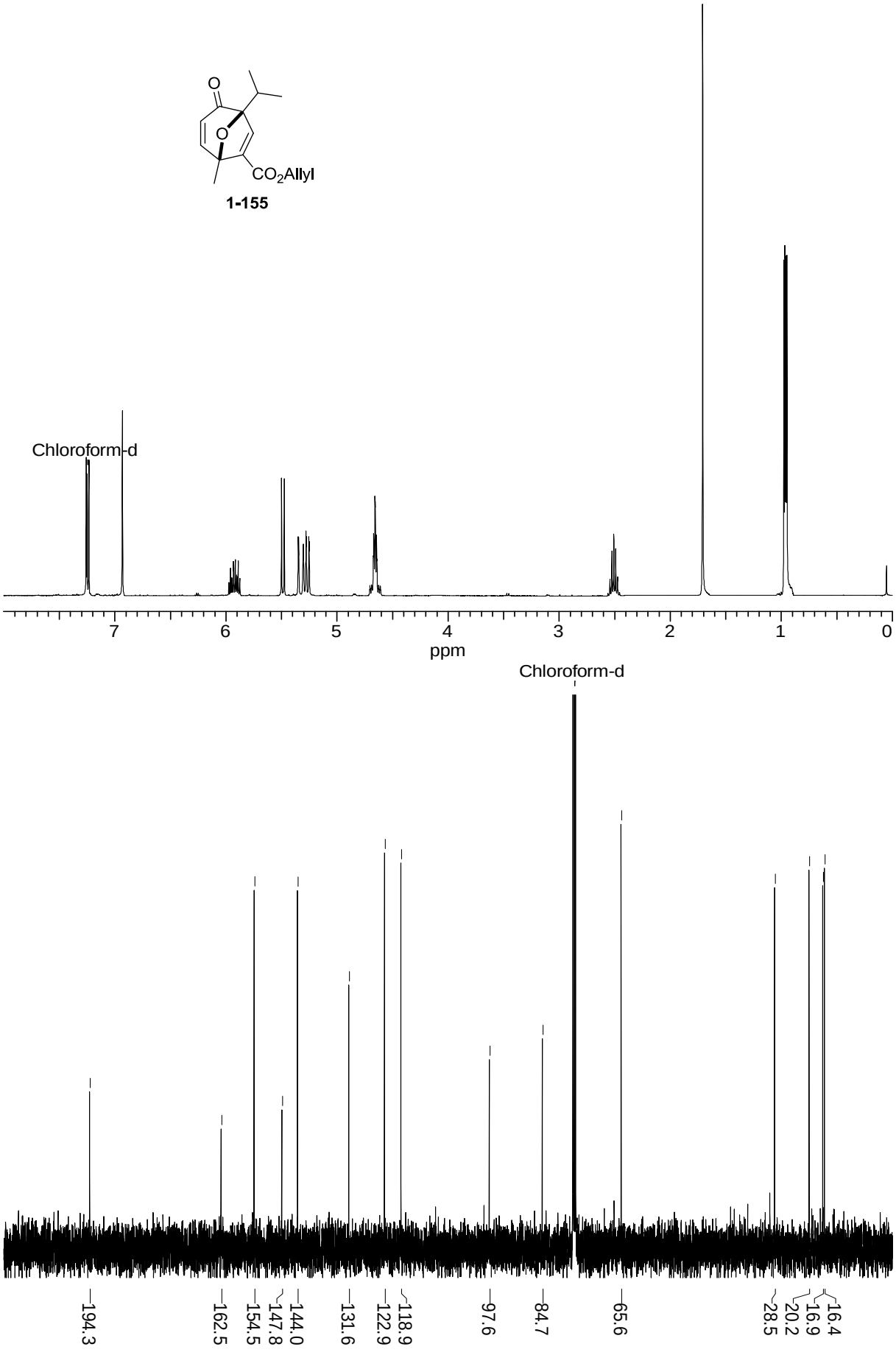
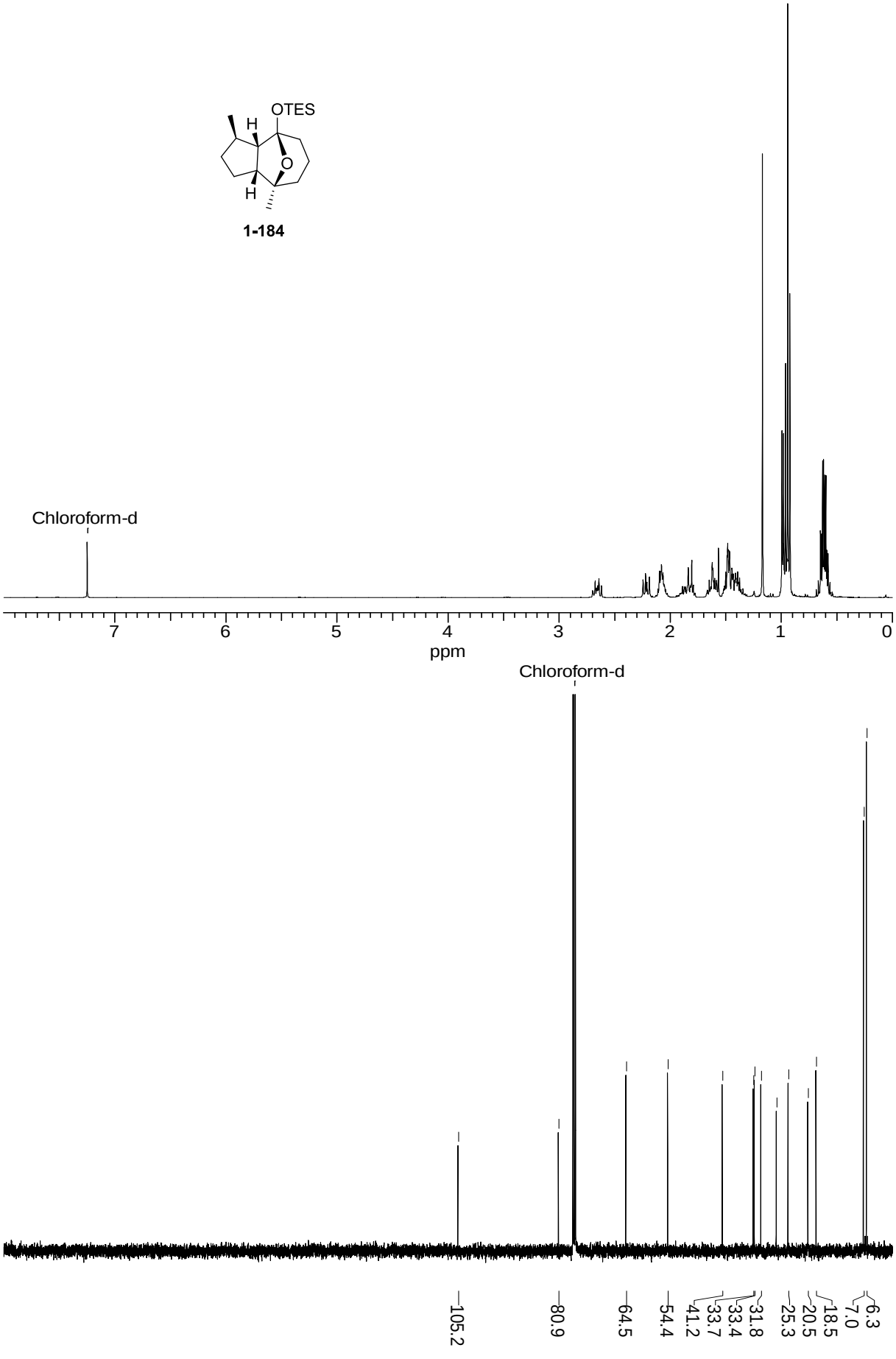
171.4
84.2
83.0
71.2
62.0
45.2
38.8
36.4
32.4
24.0
19.1
14.1
6.9
4.8

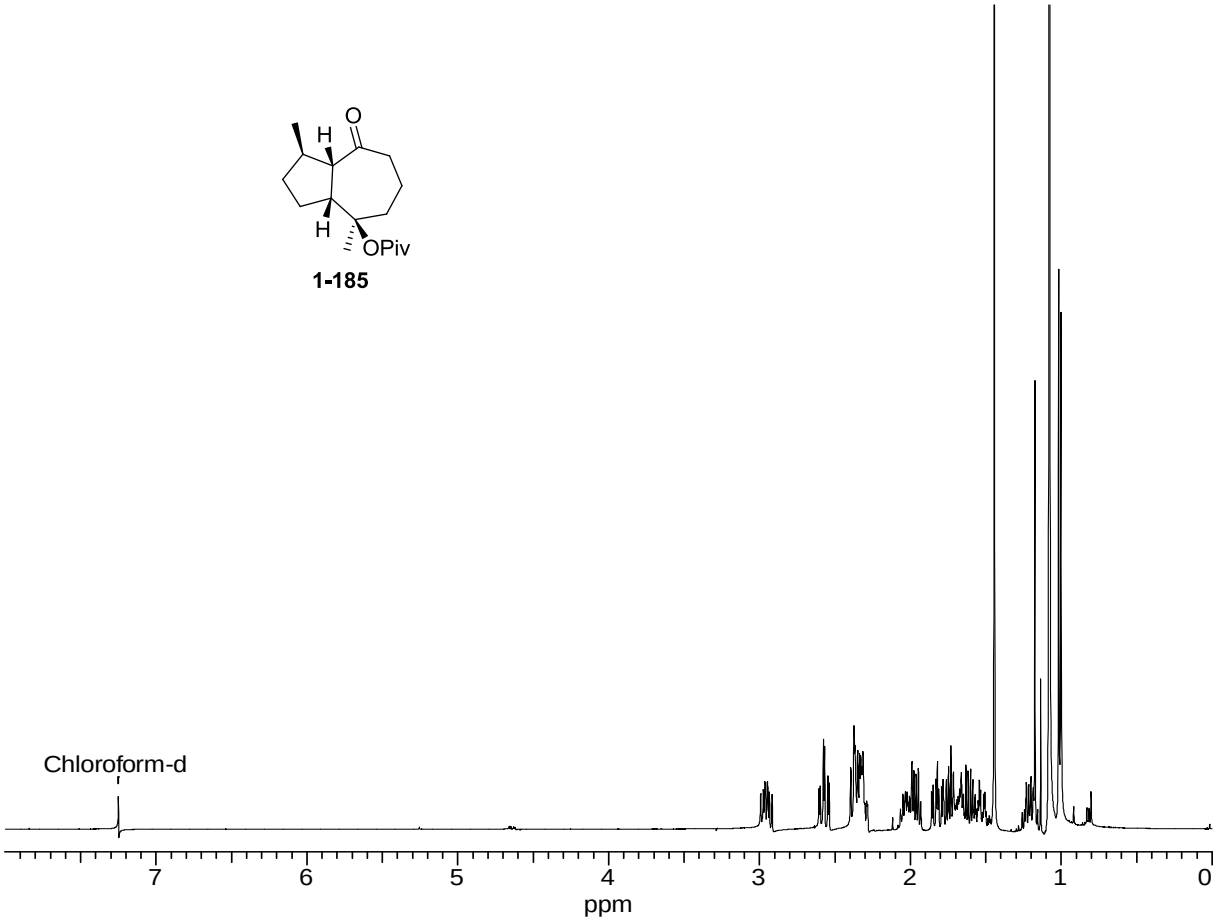

OH
H
O
H
OH
1-142
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
148.4
107.9
86.0
81.7
78.9
73.7
44.7
38.4
34.5
33.8
31.4
26.0
21.5
20.4
18.5

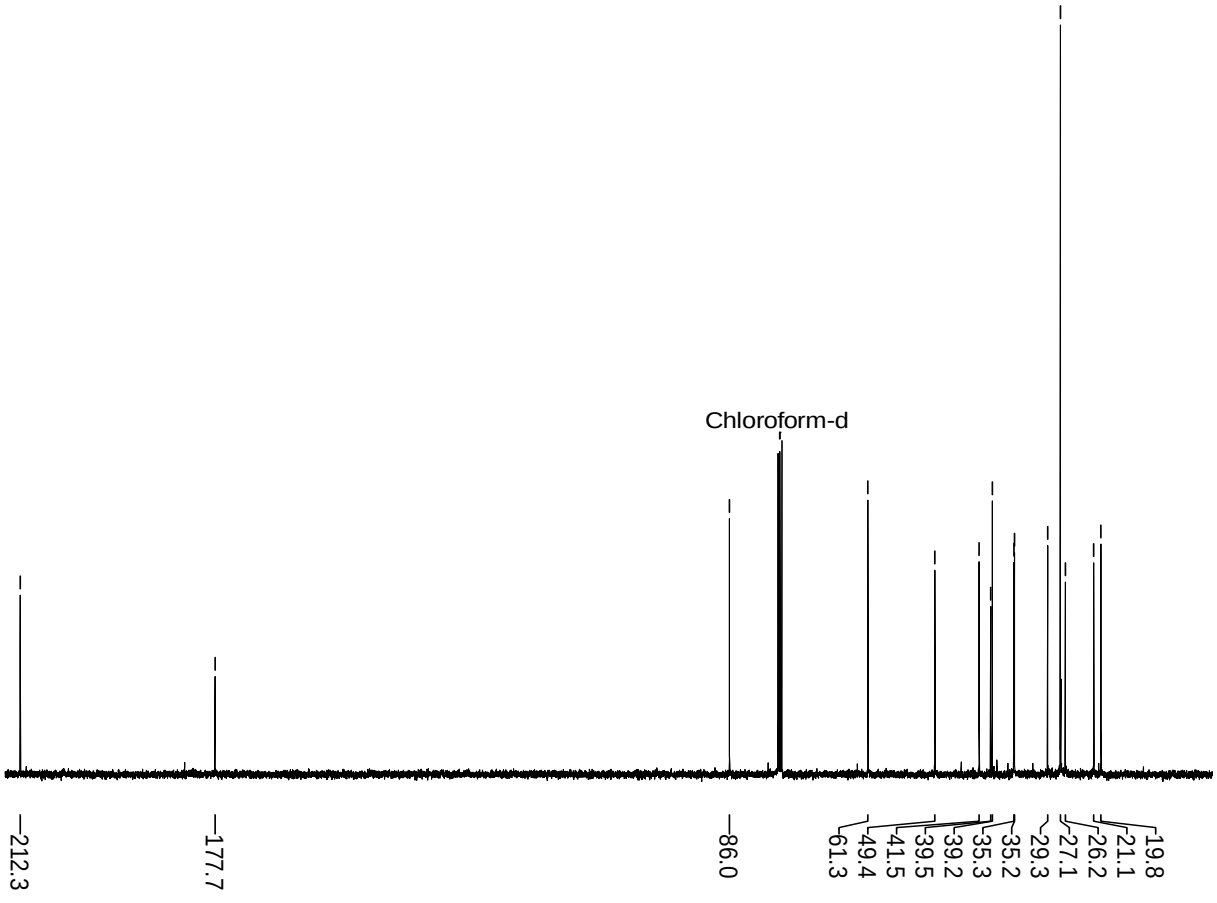

O
OAc
O
1-150
Chloroform-d
7
6
5
4
3
2
1
0
ppm

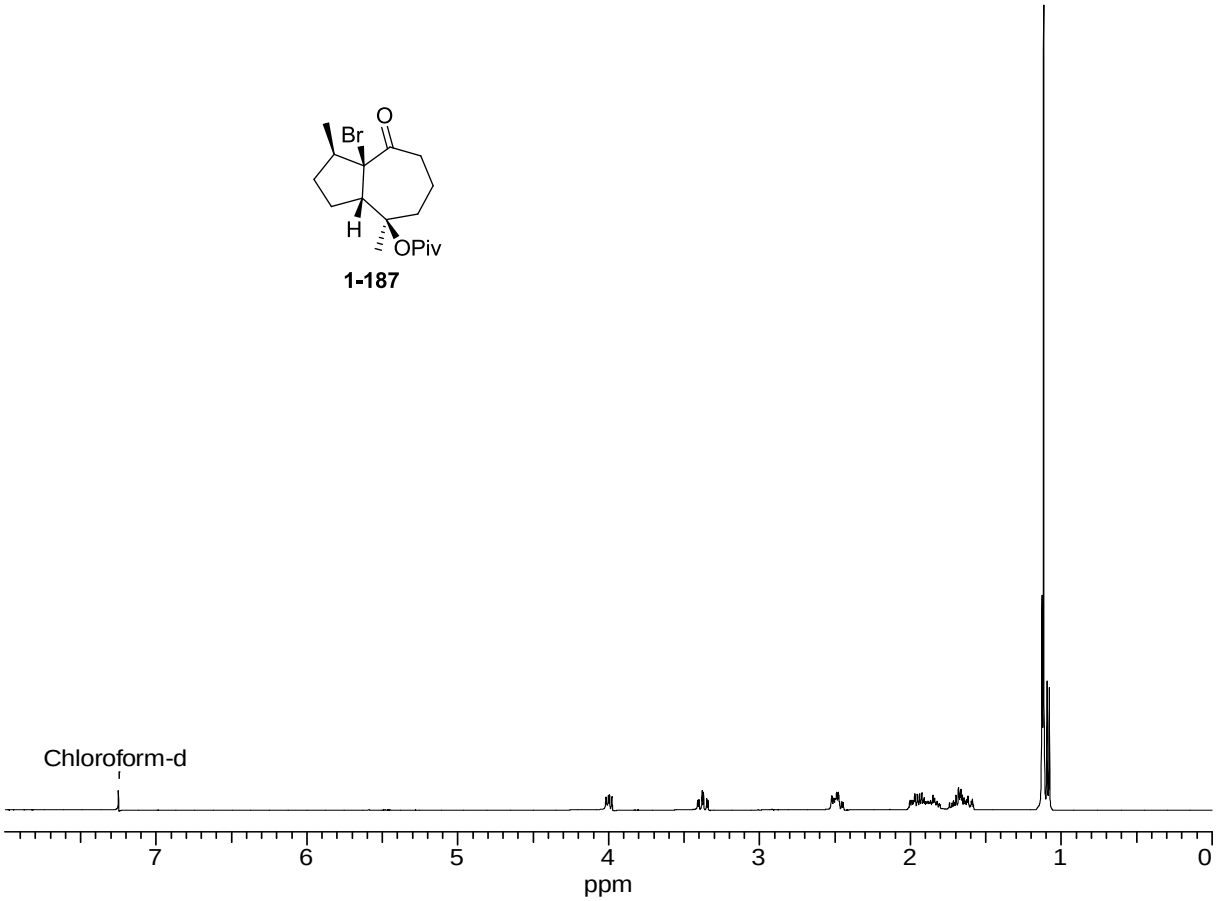

Chloroform-d
196.4
197.5
170.6
132.7
137.6
82.1
28.8
29.4
20.4
18.9
16.9

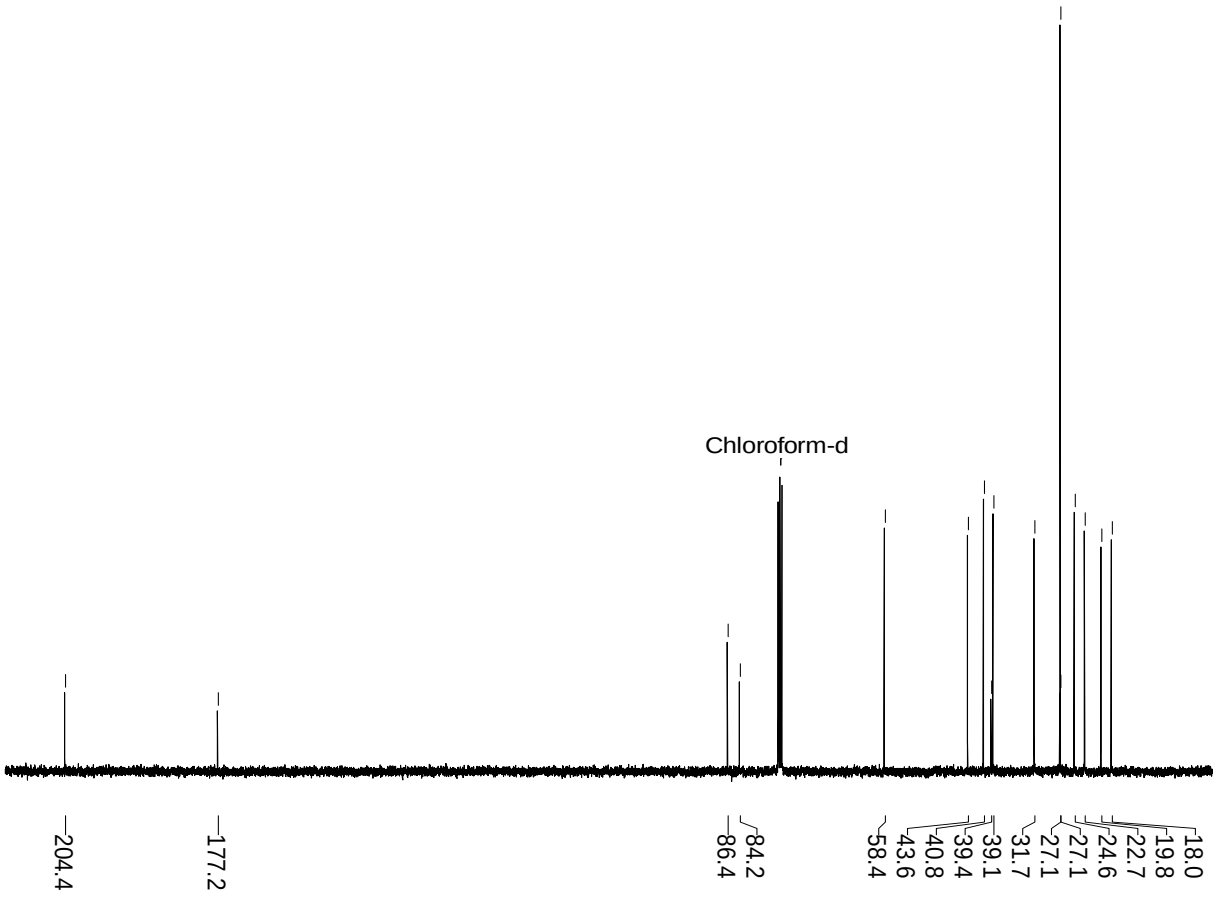

O
O
CO2Allyl
1-155
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
194.3
162.5
154.5
147.8
144.0
131.6
122.9
118.9
97.6
84.7
65.6
28.5
20.2
16.9
16.4

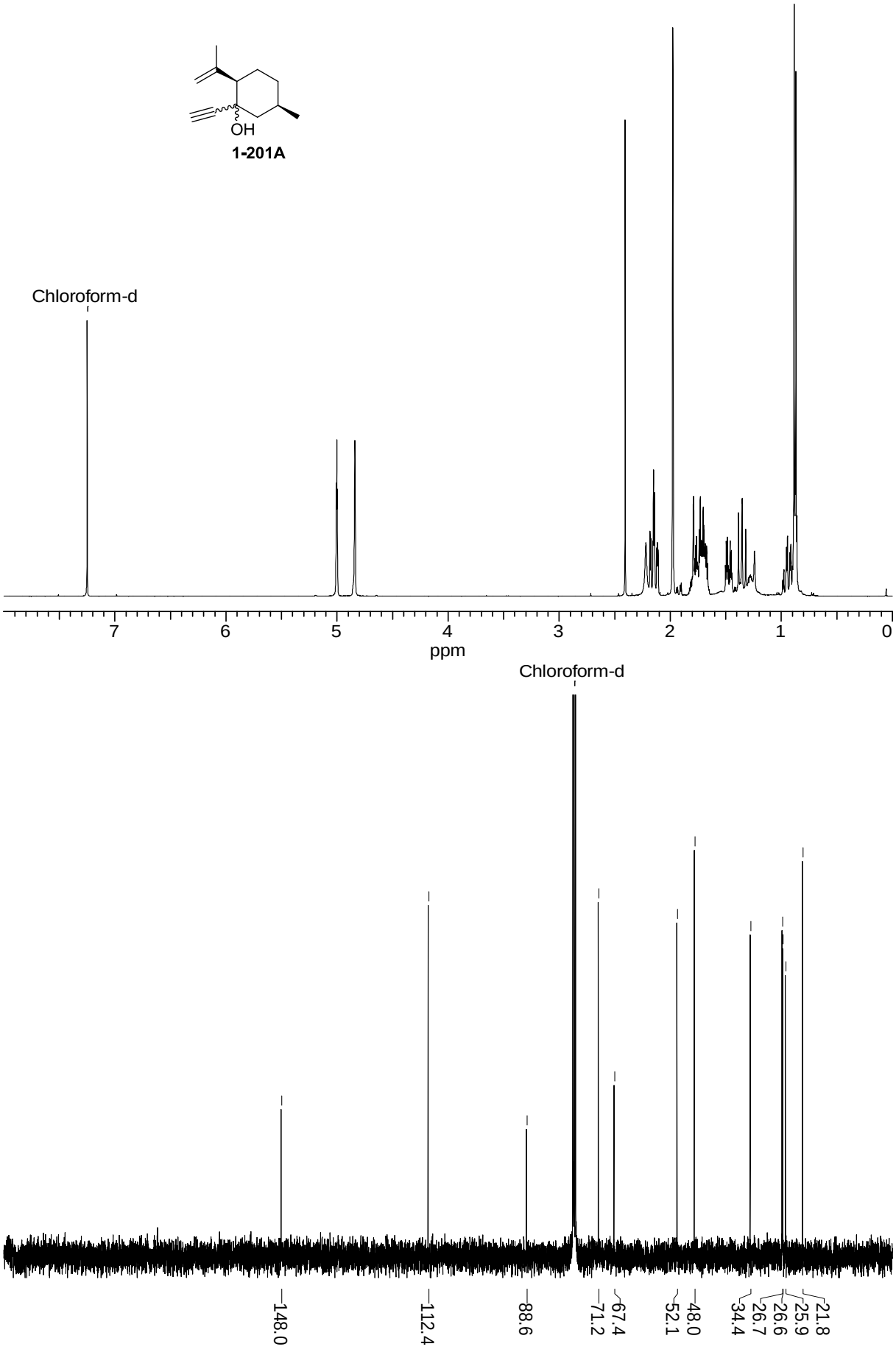

OTES
H
O
H
1-184
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
105.2
80.9
64.5
54.4
41.2
33.7
33.4
31.8
25.3
20.5
18.5
7.0
6.3

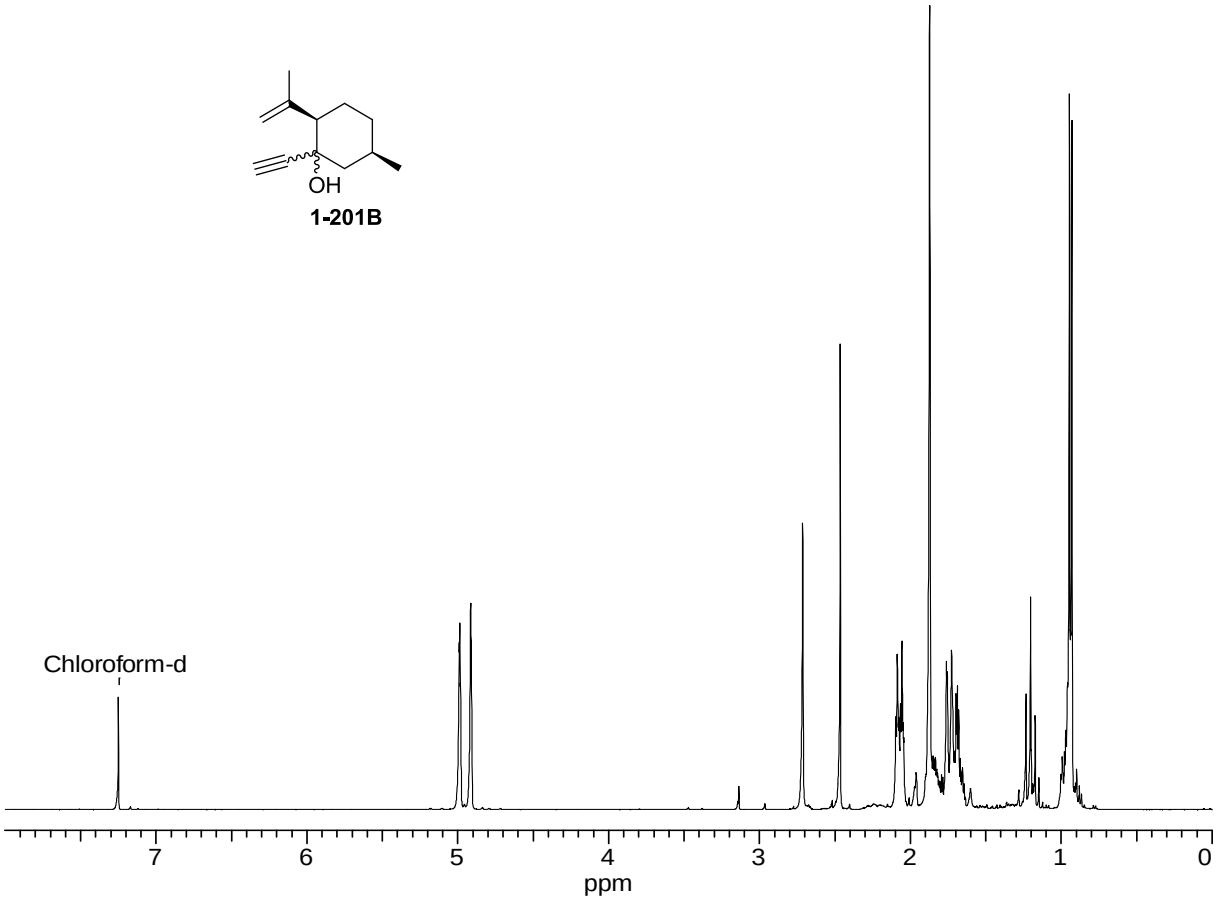

O
H
H
OPiv
1-185
Chloroform-d
7
6
5
4
3
2
1
0
ppm

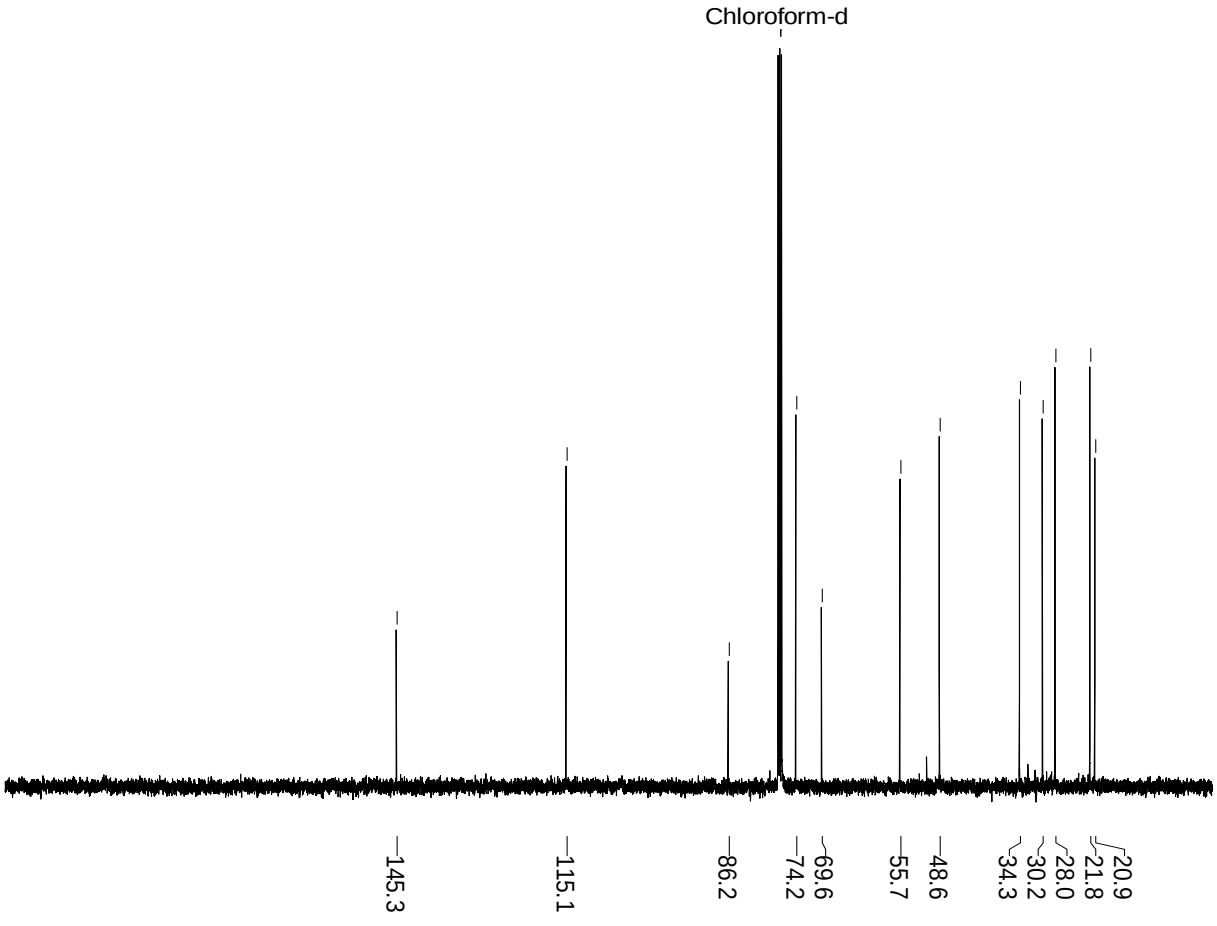

Chloroform-d
212.3
177.7
86.0
61.3
49.4
41.5
39.5
39.2
35.3
35.2
29.3
27.1
26.2
21.1
19.8

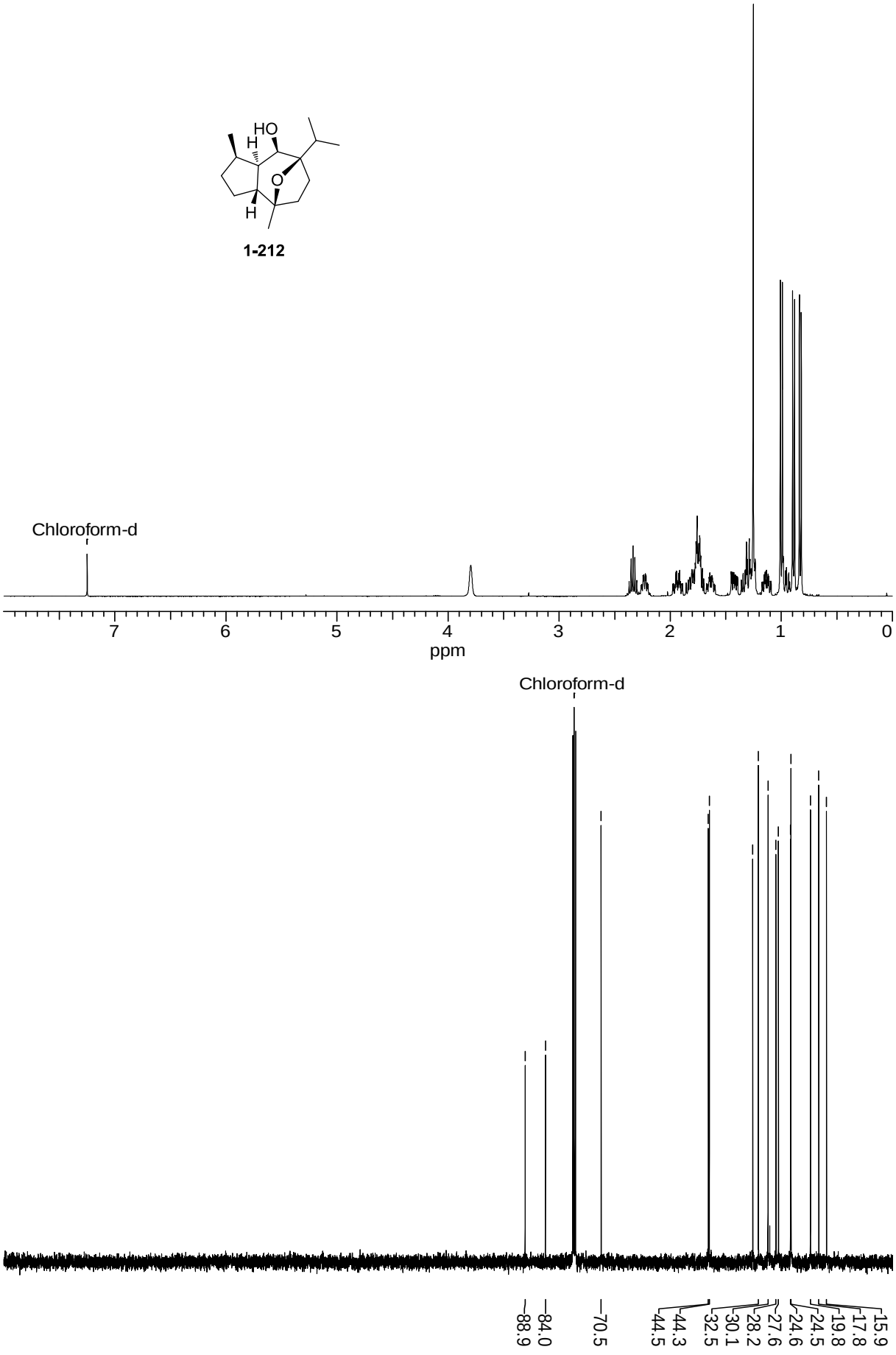

Br
O
H
OPiv
1-187
Chloroform-d
7
6
5
4
3
2
1
0
ppm

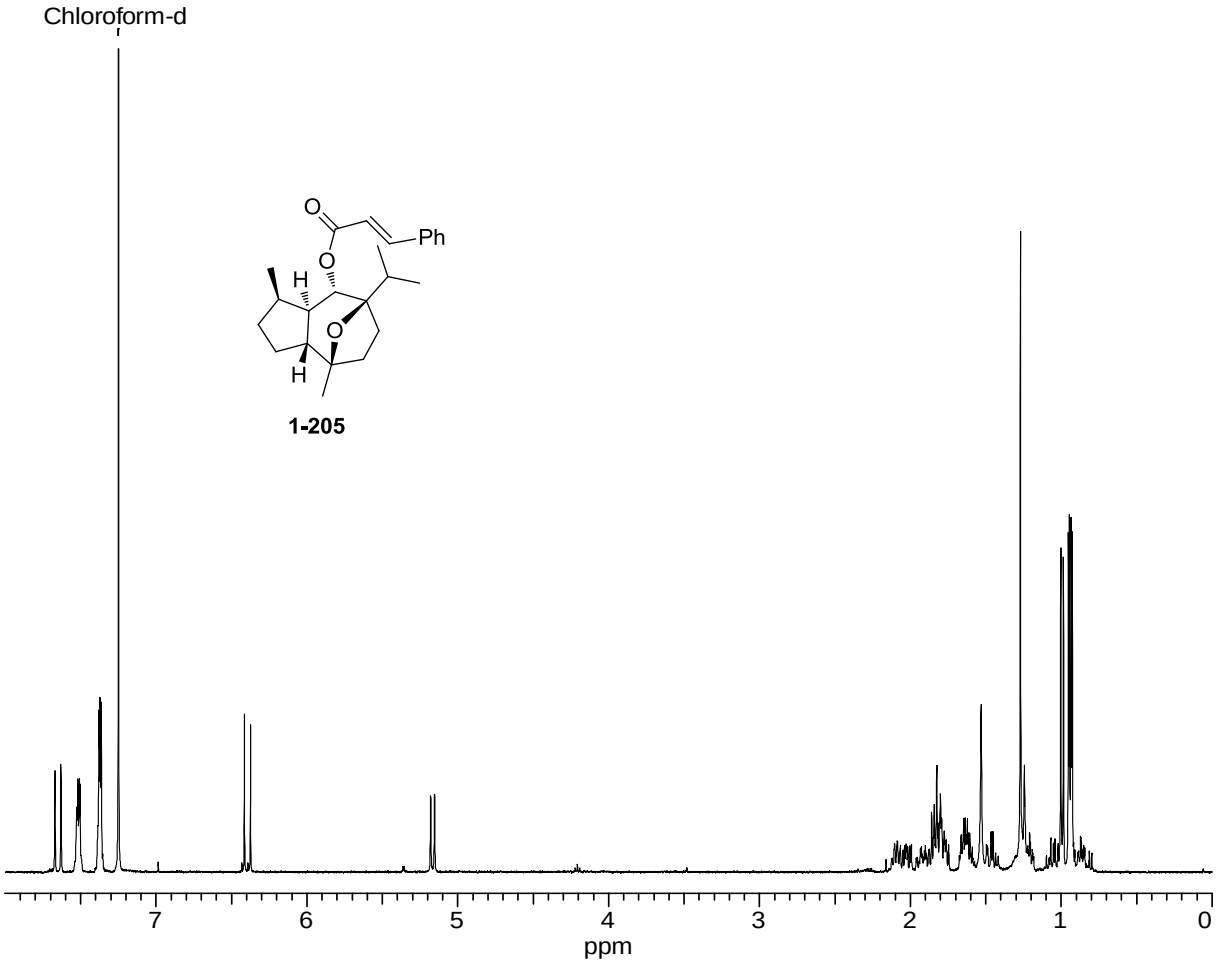

Chloroform-d
204.4
177.2
86.4
84.2
58.4
43.6
40.8
39.4
39.1
31.7
27.1
27.1
24.6
22.7
19.8
18.0

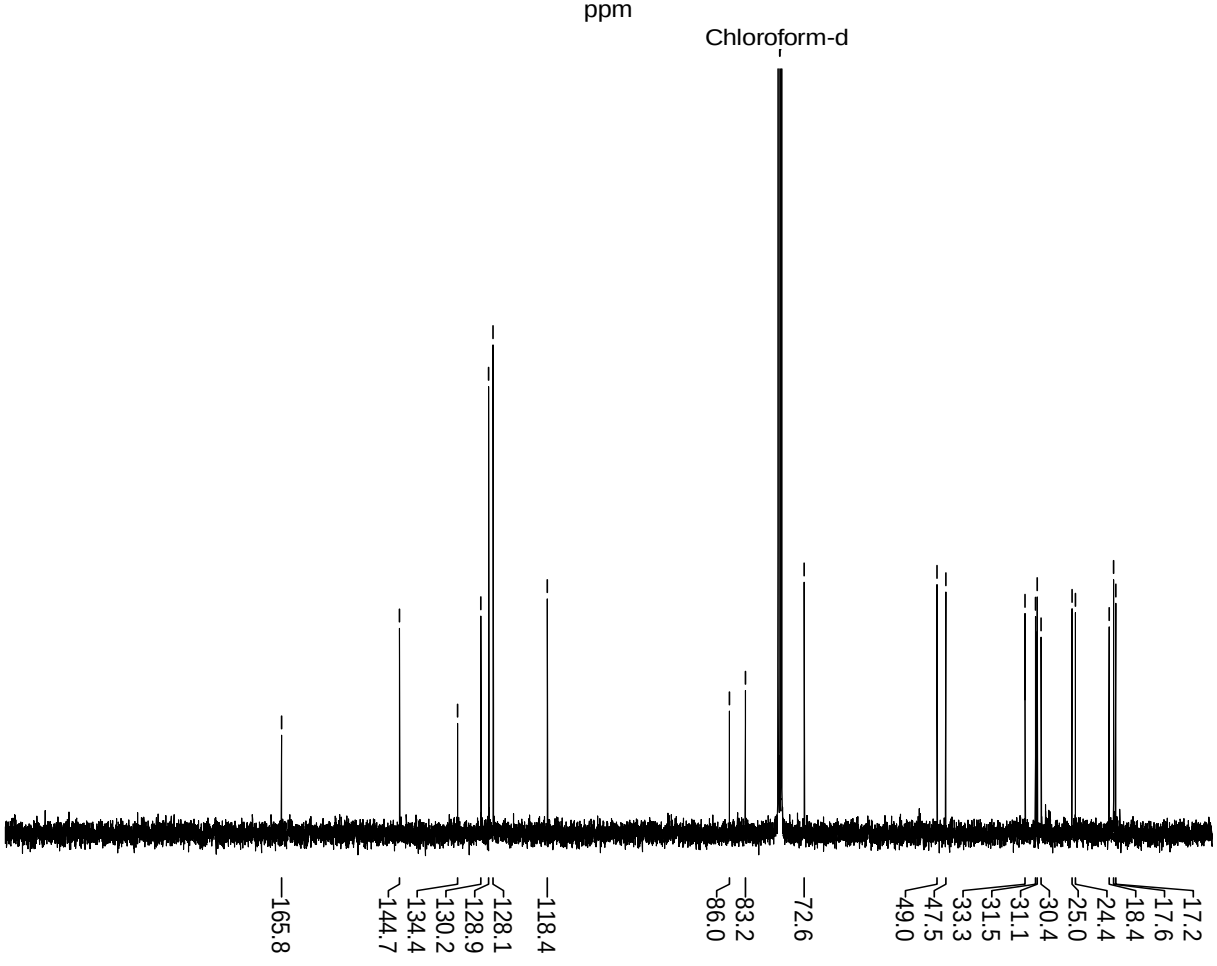

OH
1-201A
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
148.0
112.4
88.6
71.2
67.4
52.1
48.0
34.4
26.7
26.6
25.9
21.8

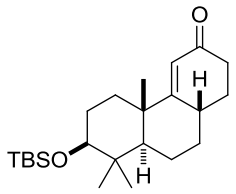

OH
1-201B
Chloroform-d
7
6
5
4
3
2
1
0
ppm


Chloroform-d
145.3
115.1
86.2
74.2
69.6
55.7
48.6
34.3
30.2
28.0
21.8
20.9


HO
H
O
H
1-212
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
88.9
84.0
70.5
44.5
44.3
32.5
30.1
28.2
27.6
24.6
24.5
19.8
17.8
15.9

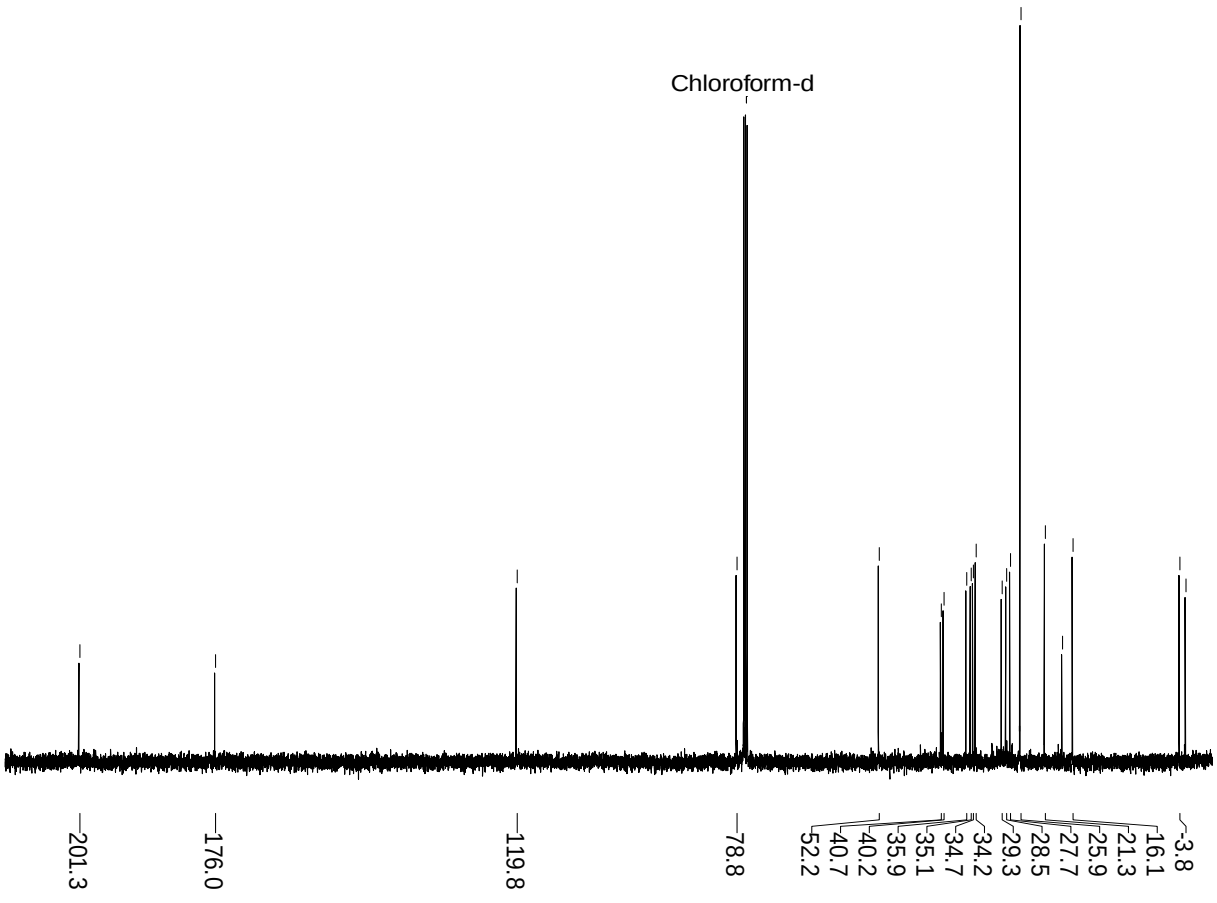

Chloroform-d
O
Ph
O
H
O
H
1-205
7
6
5
4
3
2
1
0
ppm

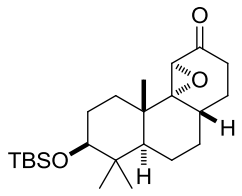

Chloroform-d
165.8
144.7
134.4
130.2
128.9
128.1
118.4
86.0
83.2
72.6
49.0
47.5
33.3
31.5
31.1
30.4
25.0
24.4
18.4
17.6
17.2


O
H
TBSO
H

2-95

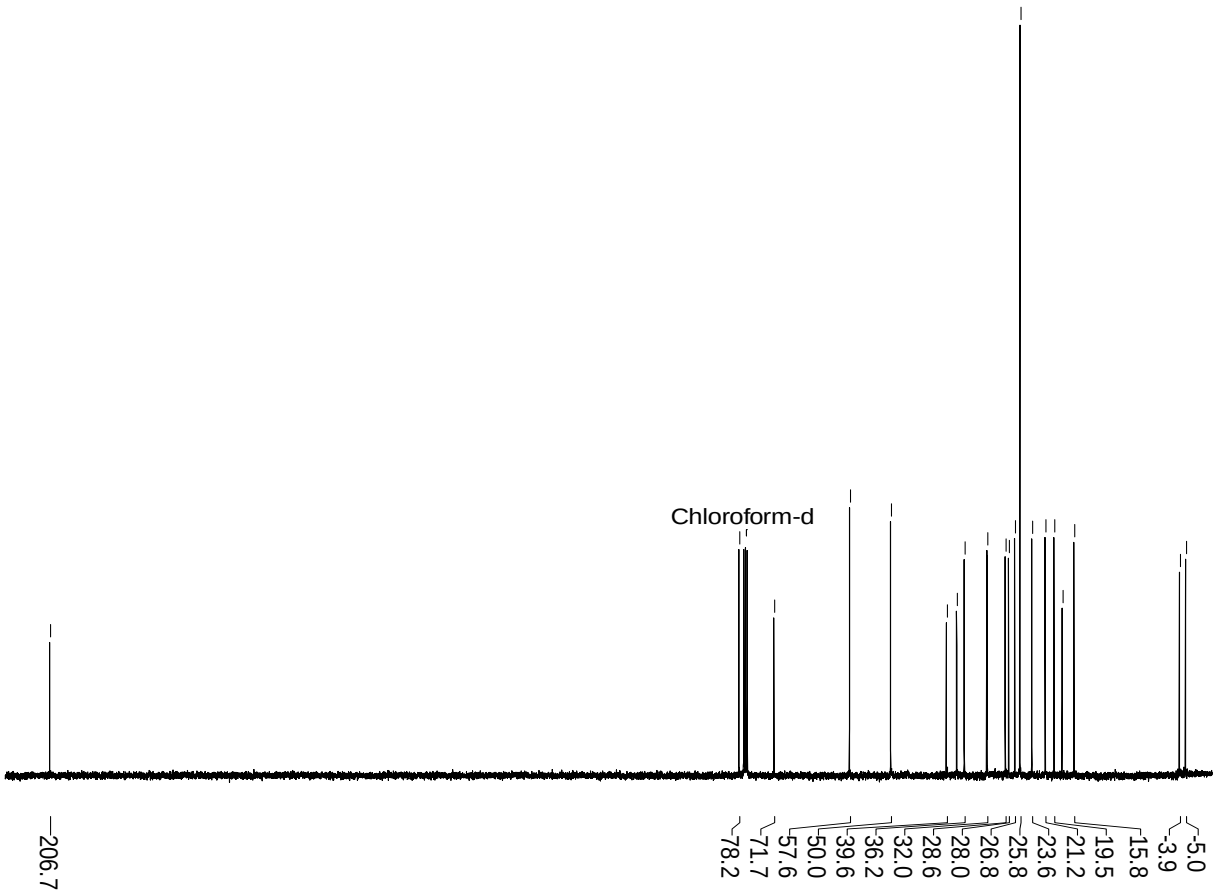
Chloroform-d
7
6
5
4
3
2
1
0
ppm

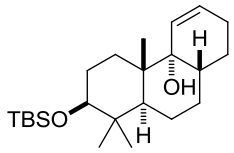

Chloroform-d
201.3
176.0
119.8
78.8
52.2
40.7
40.2
35.9
35.1
34.7
34.2
29.3
28.5
27.7
25.9
21.3
16.1
-3.8


O
O
H
TBSO
H

2-109

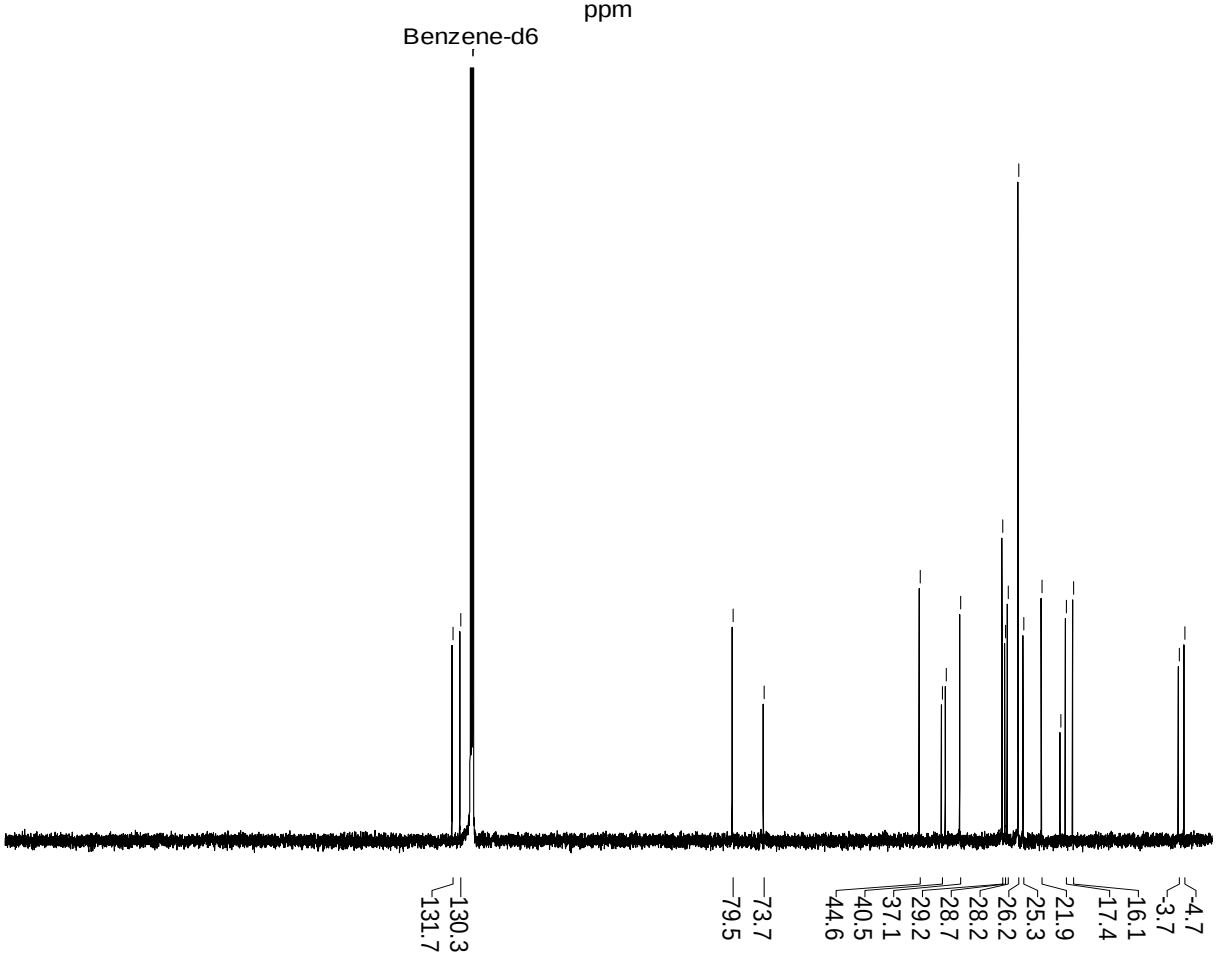
Chloroform-d
7
6
5
4
3
2
1
0
ppm

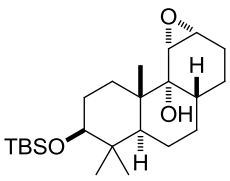

Chloroform-d
206.7
78.2
71.7
57.6
50.0
39.6
36.2
32.0
28.6
28.0
26.8
25.8
23.6
21.2
19.5
15.8
-3.9
-5.0


H
OH
TBSO
H

2-112

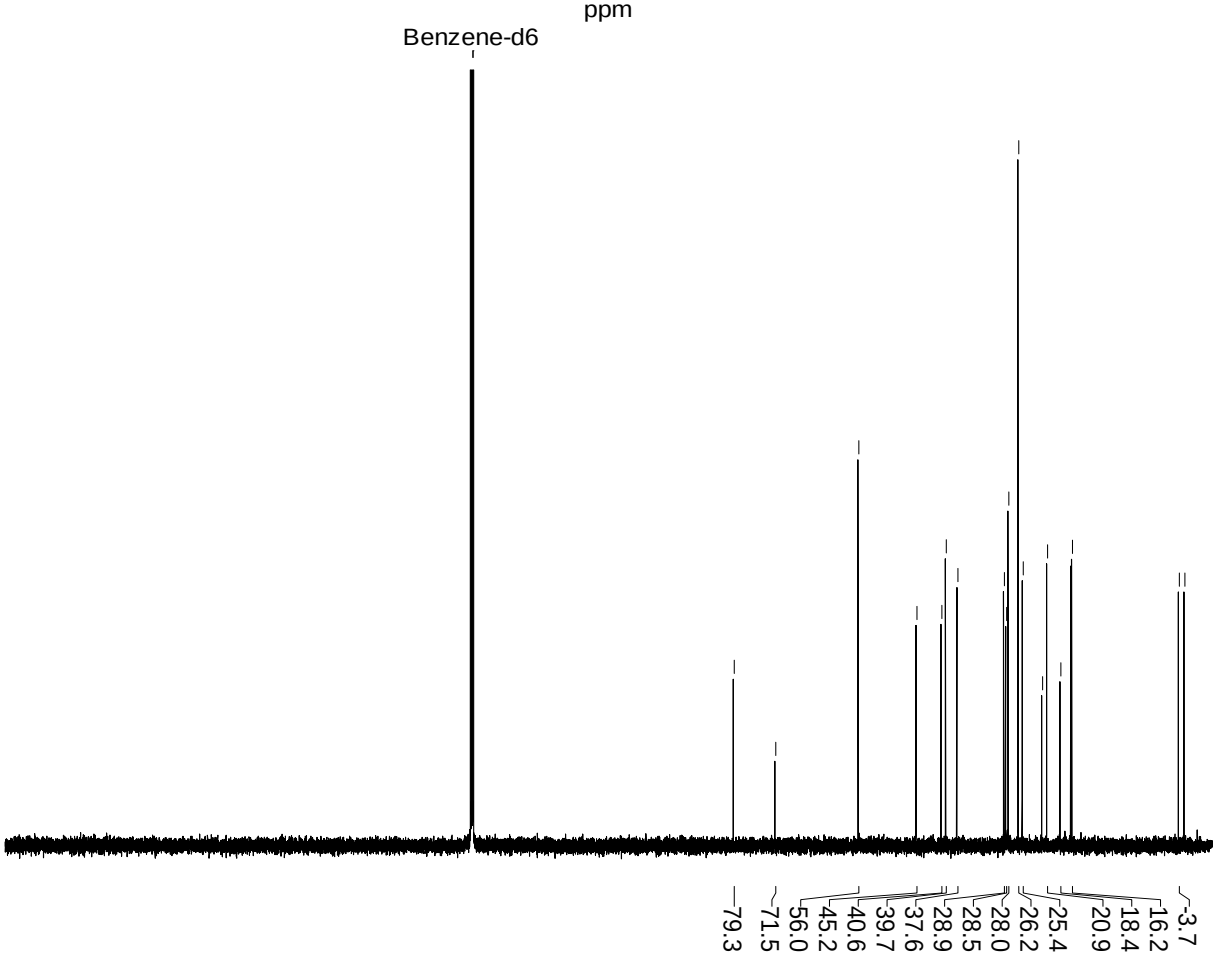
Benzene-d6
7
6
5
4
3
2
1
0
ppm

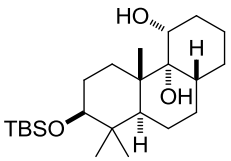

Benzene-d6
131.7
130.3
79.5
73.7
44.6
40.5
37.1
29.2
28.7
28.2
26.2
25.3
21.9
17.4
16.1
-3.7
-4.7


O
H
OH
TBSO
H

2-118

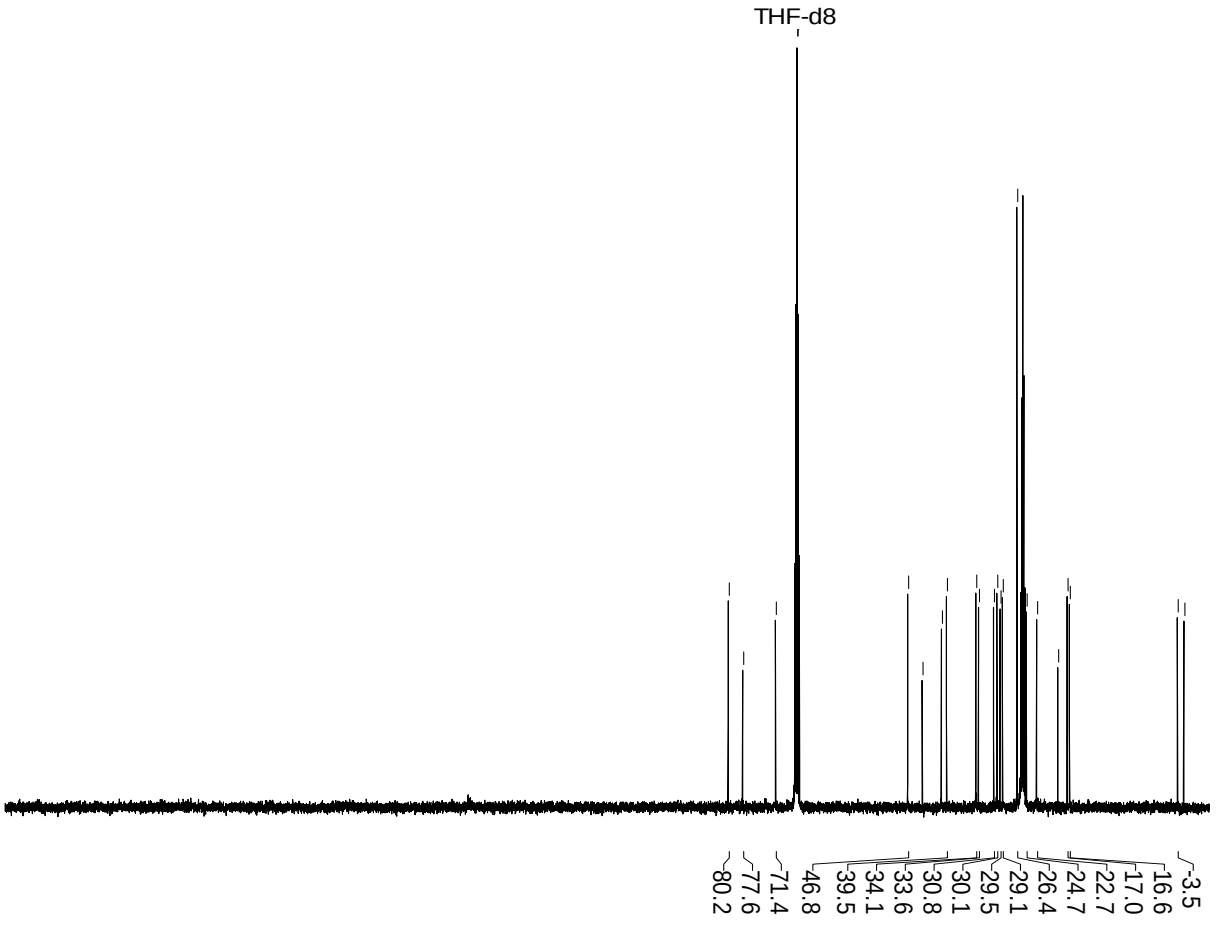
Benzene-d6
7
6
5
4
3
2
1
0
ppm

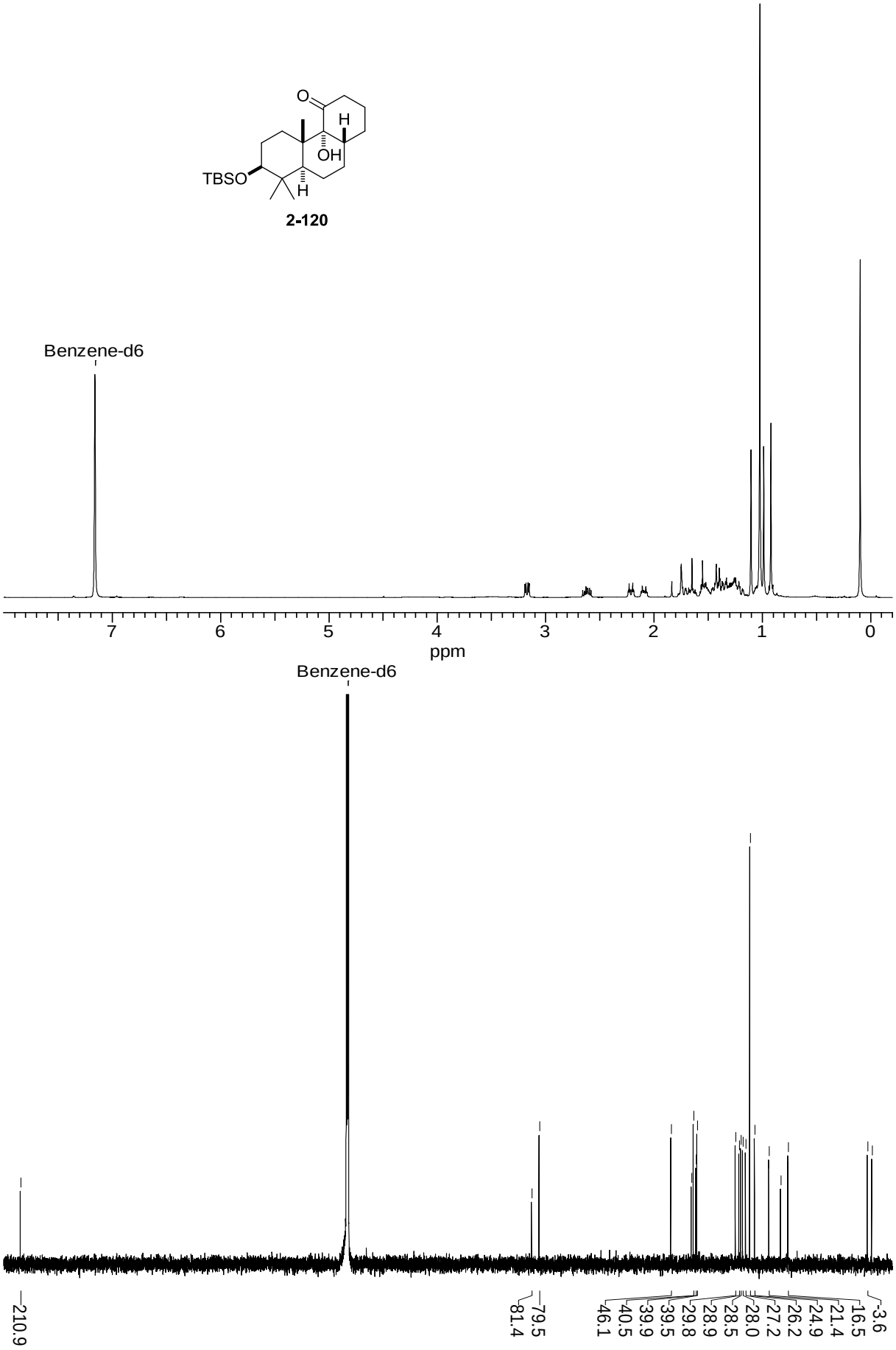

Benzene-d6
79.3
71.5
56.0
45.2
40.6
39.7
37.6
28.9
28.5
28.0
26.2
25.4
20.9
18.4
16.2
-3.7

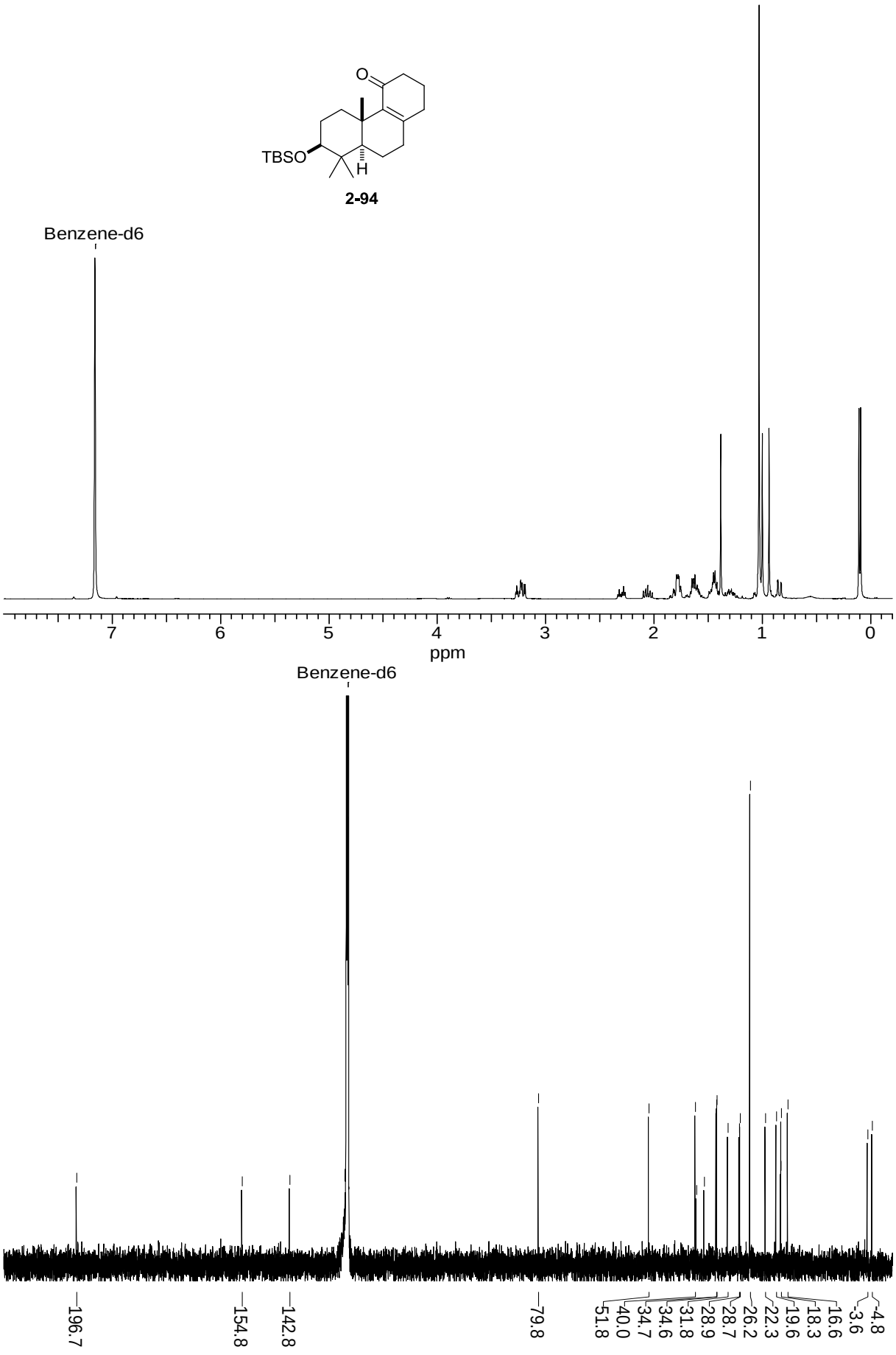

HO
H
OH
TBSO
H

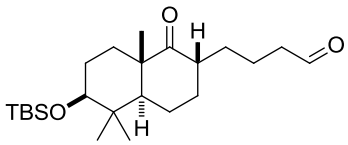
2-119

THF-d8
7
6
5
4
3
2
1
0
ppm


THF-d8
80.2
77.6
71.4
46.8
39.5
34.1
33.6
30.8
30.1
29.5
29.1
26.4
24.7
22.7
17.0
16.6
-3.5

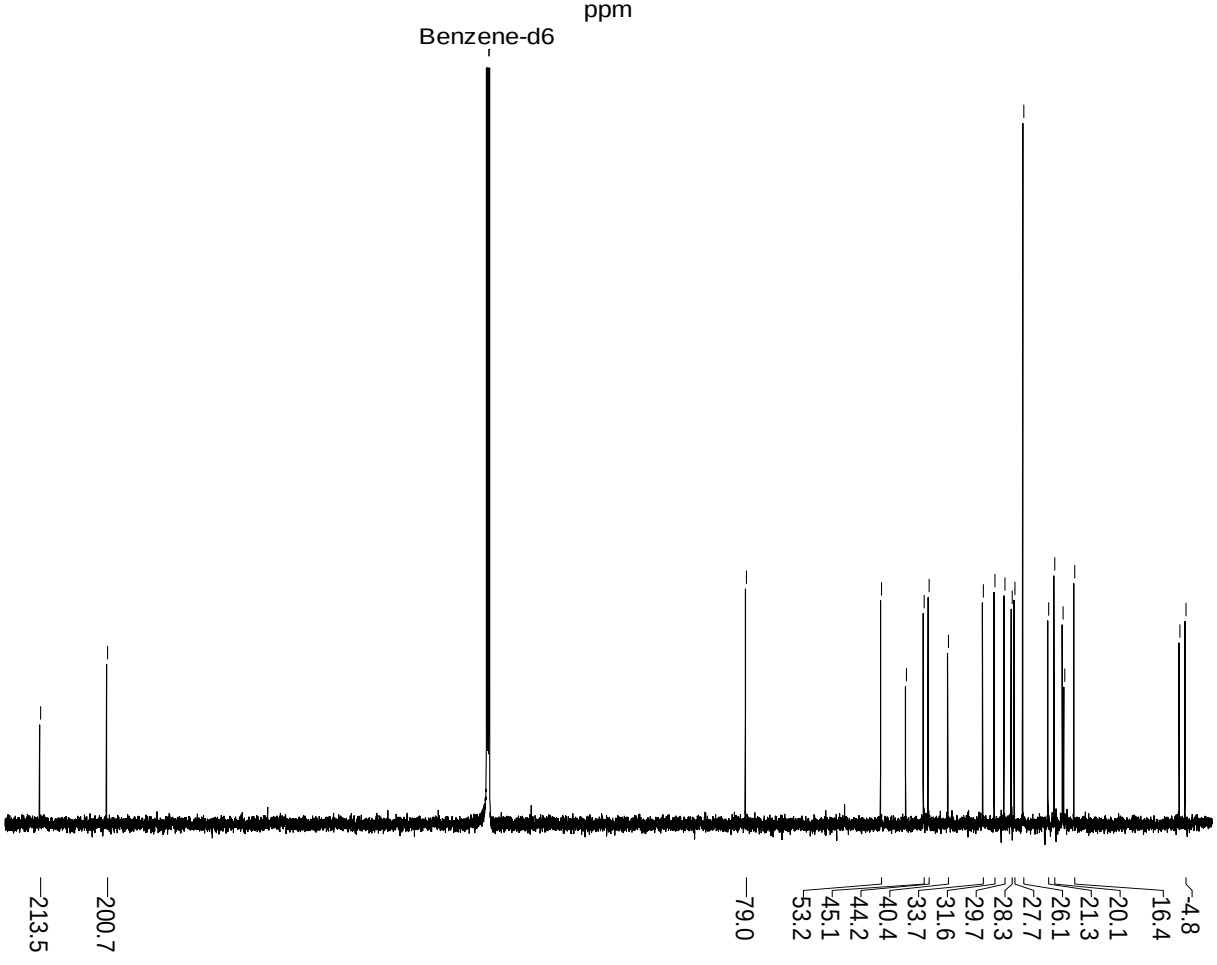

O
H
OH
TBSO
H
2-120
Benzene-d6
7
6
5
4
3
2
1
0
ppm
Benzene-d6
210.9
81.4
79.5
46.1
40.5
39.9
39.5
29.8
28.9
28.5
28.0
27.2
26.2
24.9
21.4
16.5
-3.6

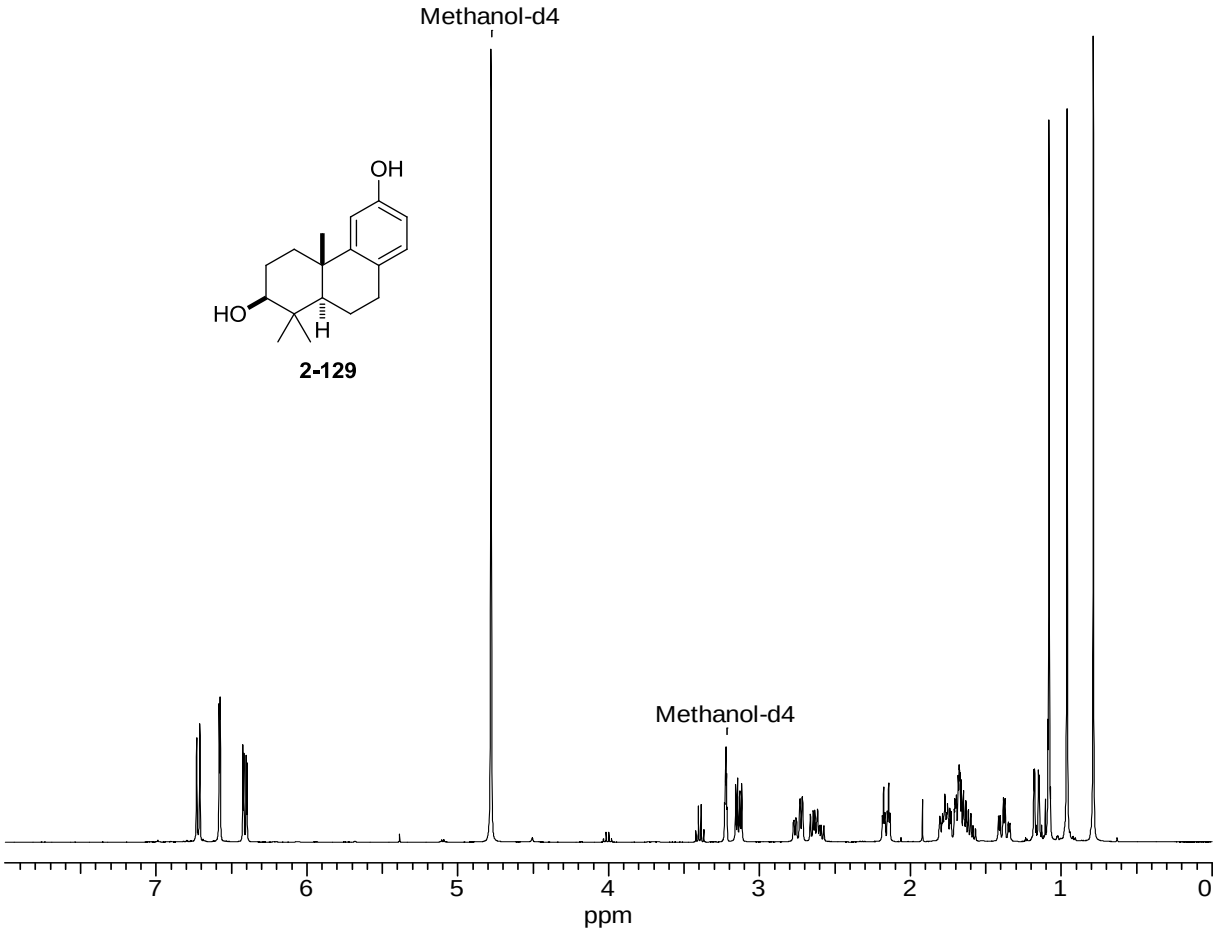

O
TBSO
H
2-94
Benzene-d6
7
6
5
4
3
2
1
0
ppm
Benzene-d6
196.7
154.8
142.8
79.8
51.8
40.0
34.7
34.6
31.8
28.9
28.7
26.2
22.3
19.6
18.3
16.6
-3.6
-4.8

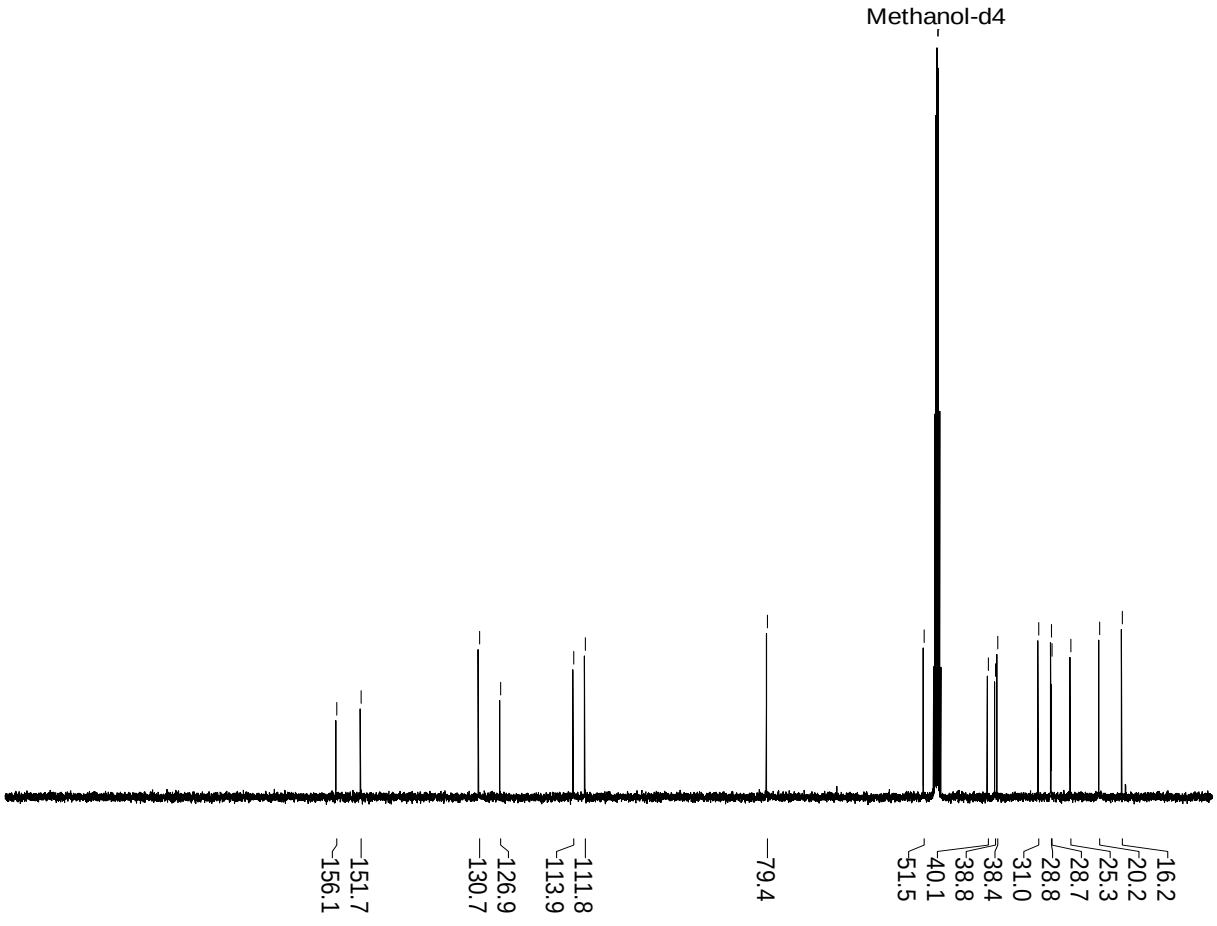

O
H
O
TBSO
H

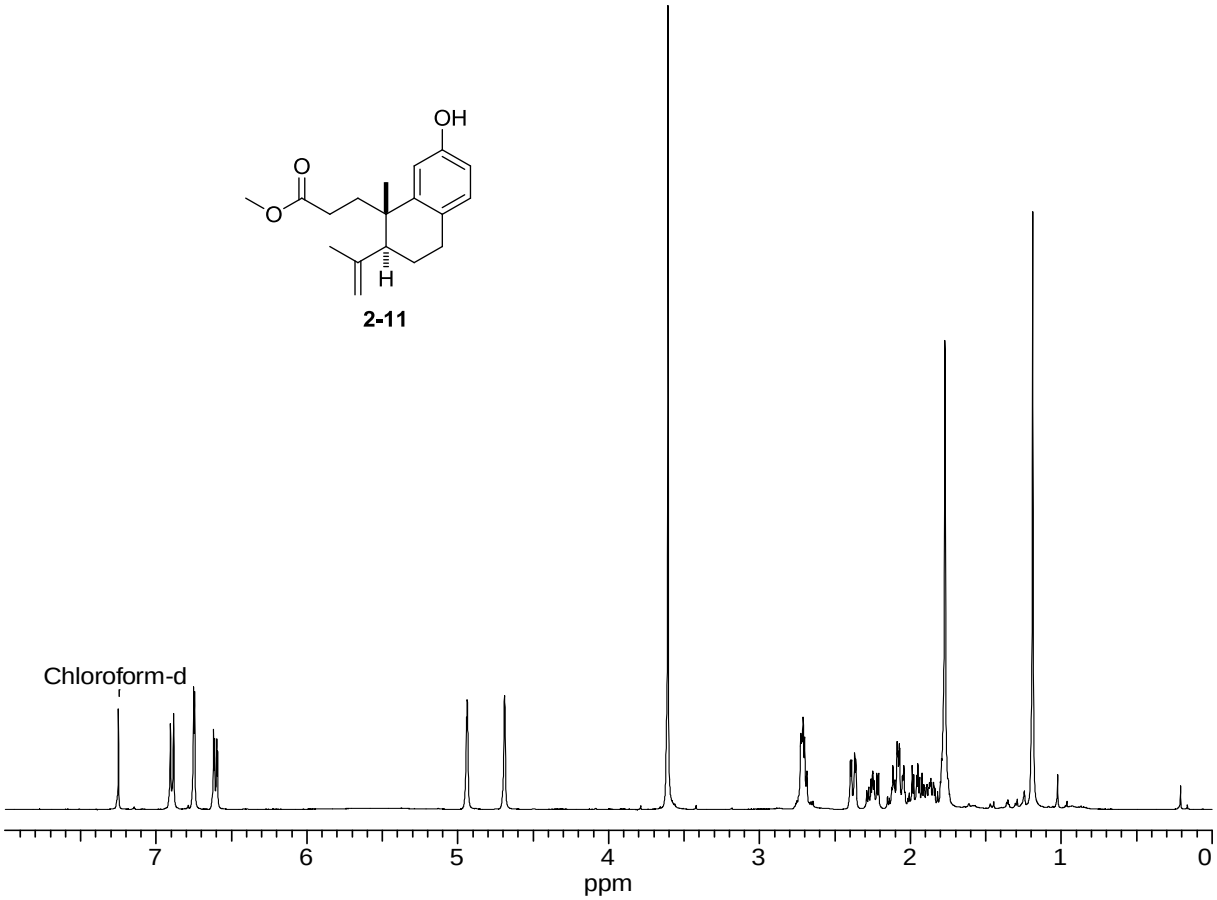
2-121

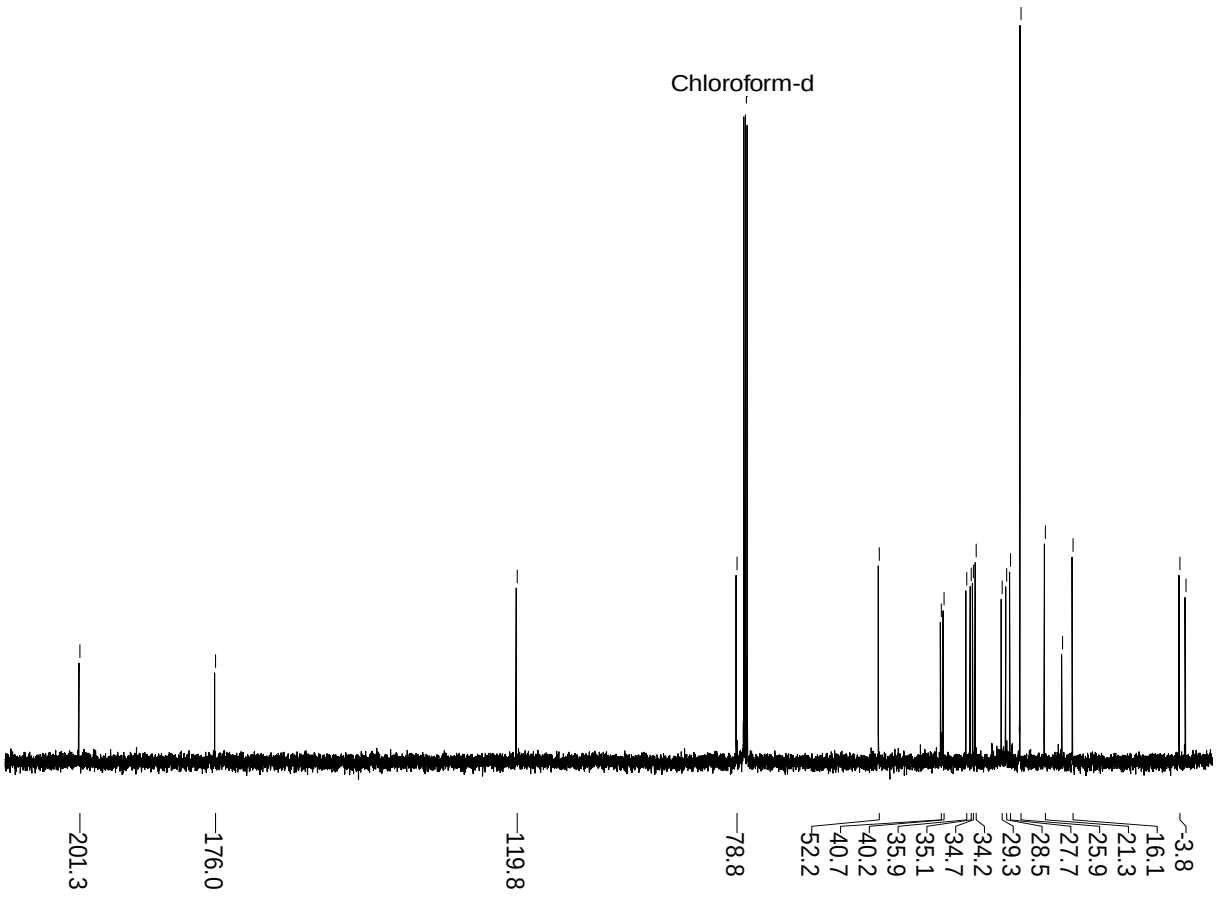
Benzene-d6
9
8
7
6
5
4
3
2
1
0
ppm

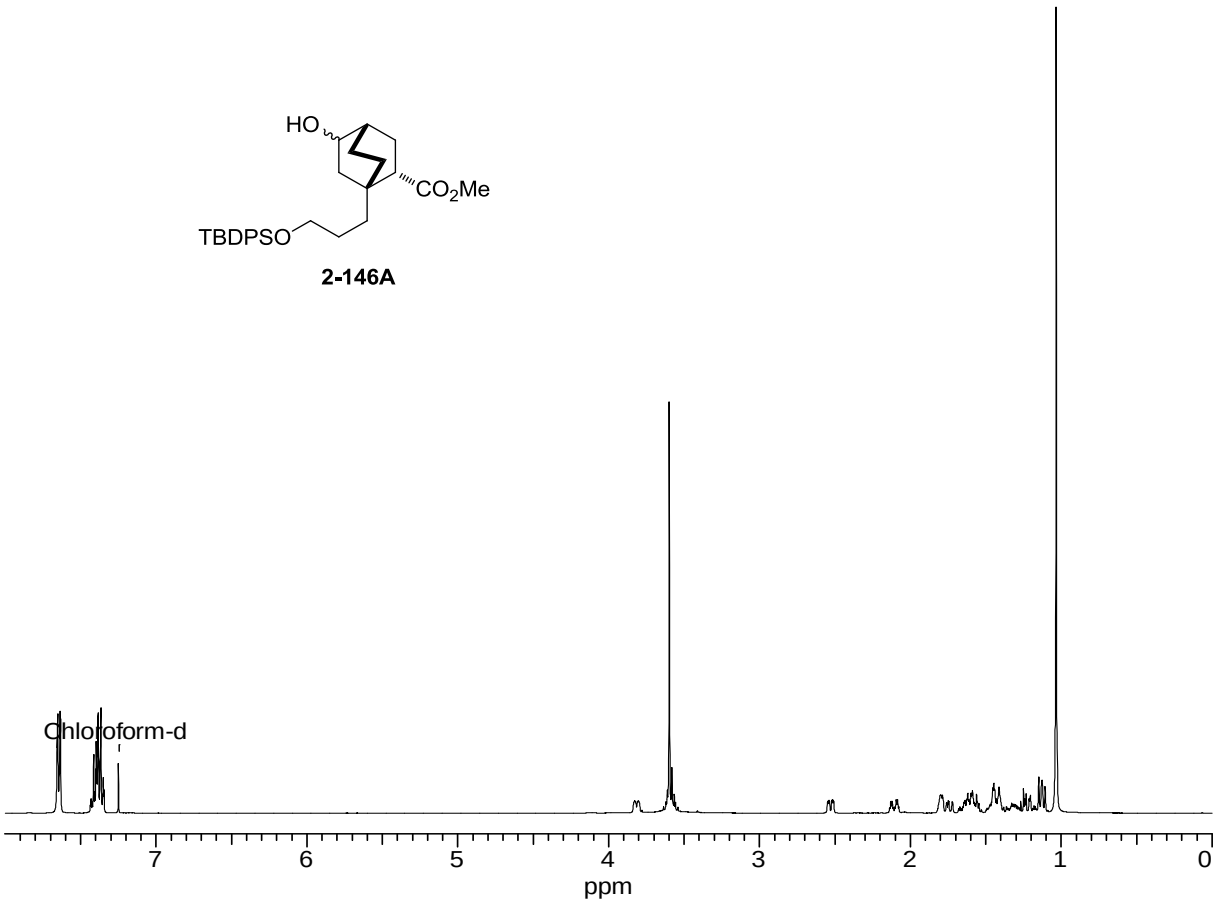

Benzene-d6
213.5
200.7
79.0
53.2
45.1
44.2
40.4
33.7
31.6
29.7
28.3
27.7
26.1
21.3
20.1
16.4
-4.8

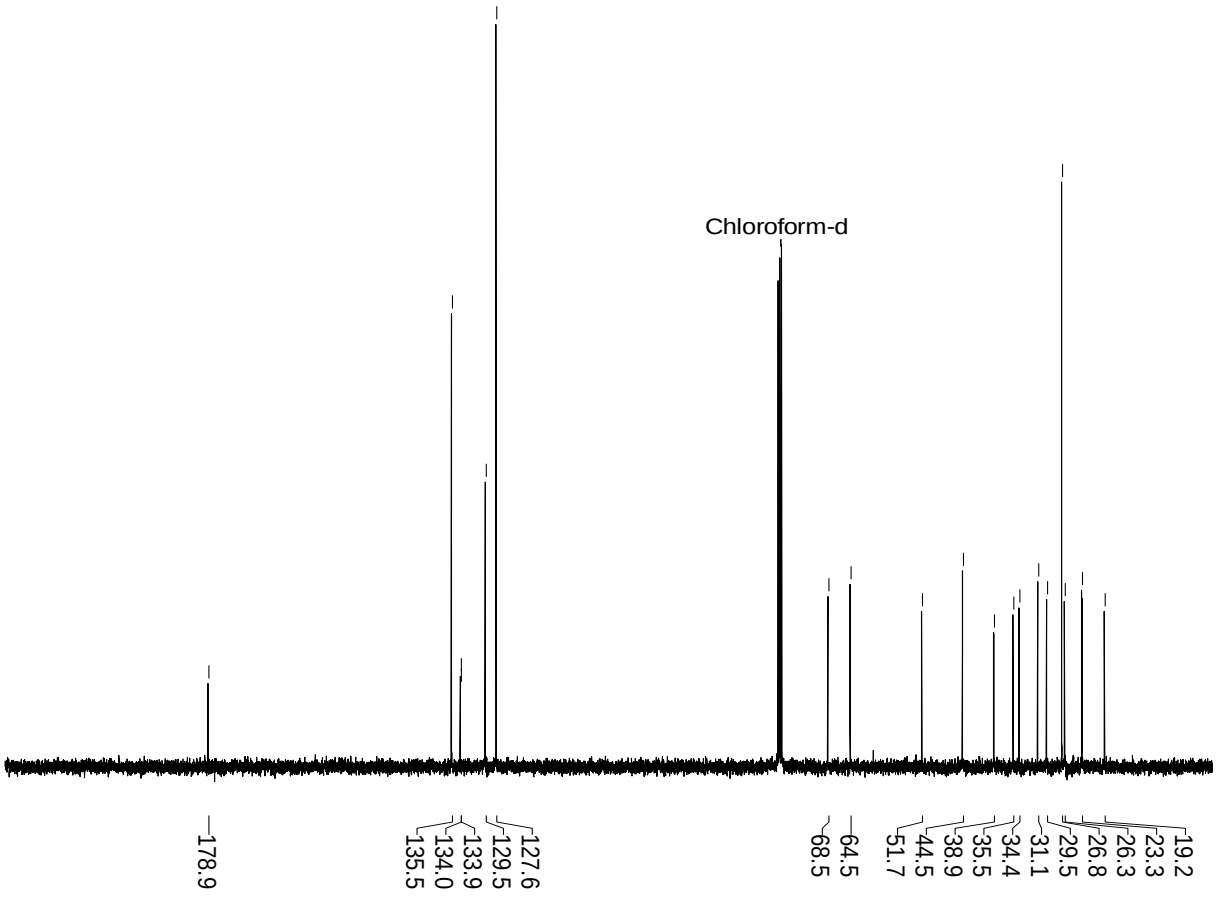

Methanol-d4
OH
HO
H
2-129
Methanol-d4
7
6
5
4
3
2
1
0
ppm

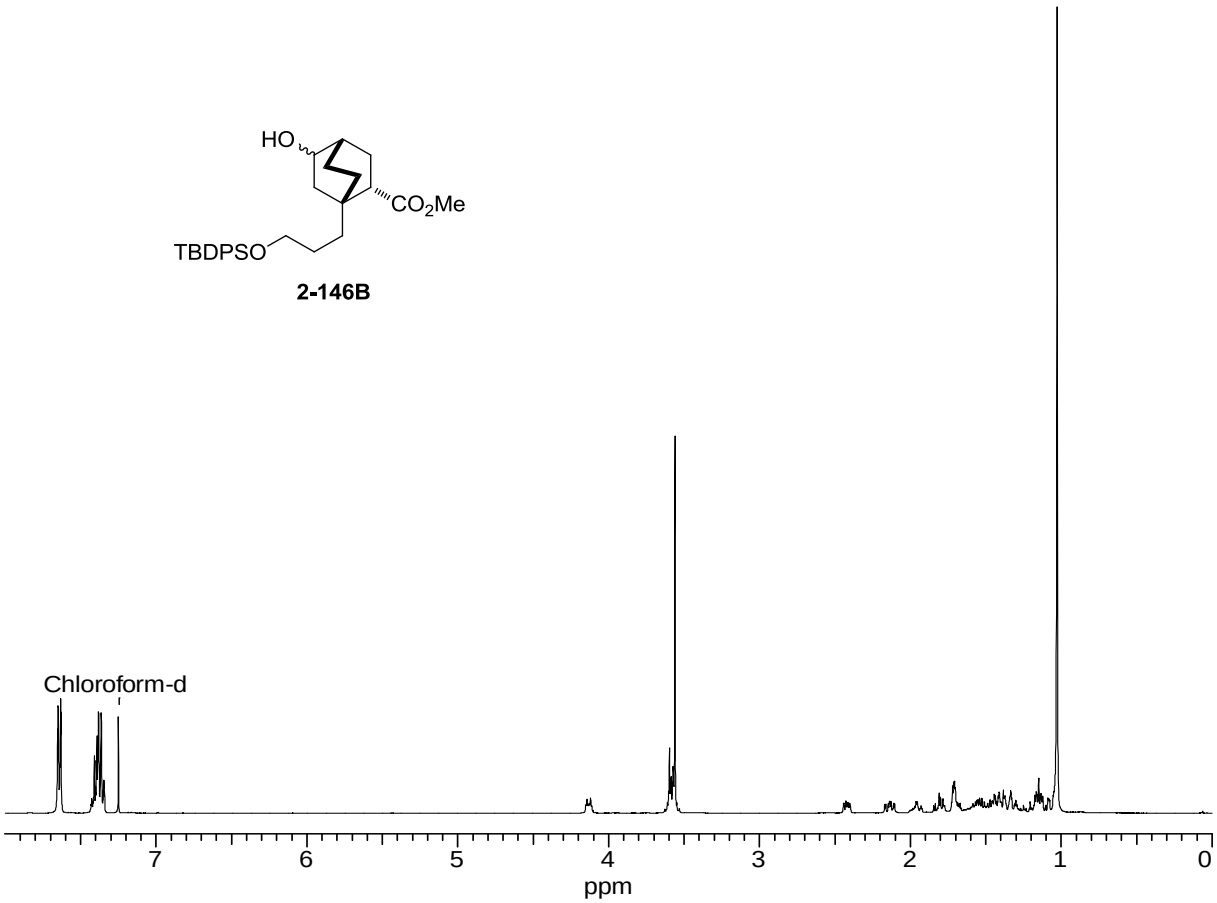

Methanol-d4
156.1
151.7
130.7
126.9
113.9
111.8
79.4
51.5
40.1
38.8
38.4
31.0
28.8
28.7
25.3
20.2
16.2


OH
O
O
H
2-11
Chloroform-d
7
6
5
4
3
2
1
0
ppm

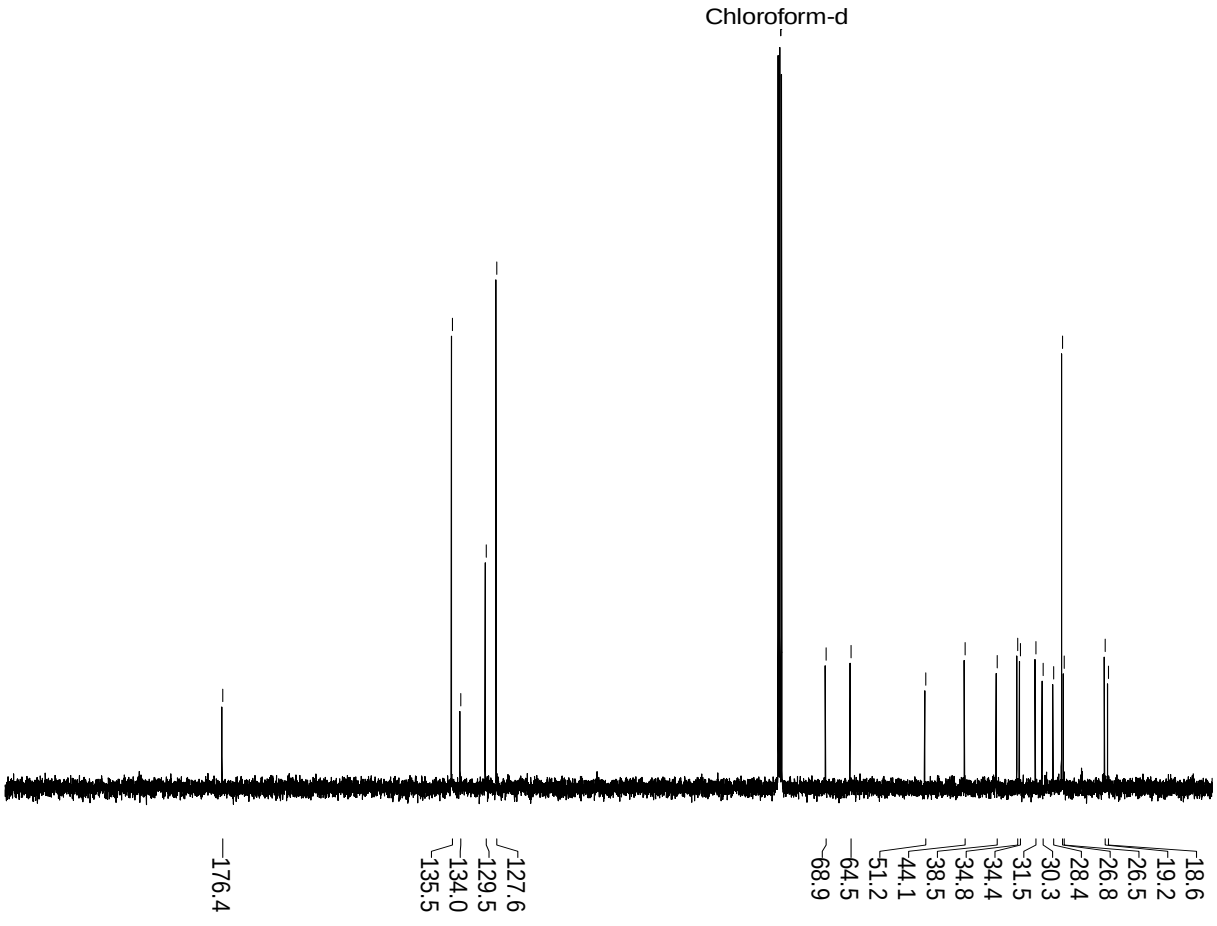

Chloroform-d
201.3
176.0
119.8
78.8
52.2
40.7
40.2
35.9
35.1
34.7
34.2
29.3
28.5
27.7
25.9
21.3
16.1
3.8

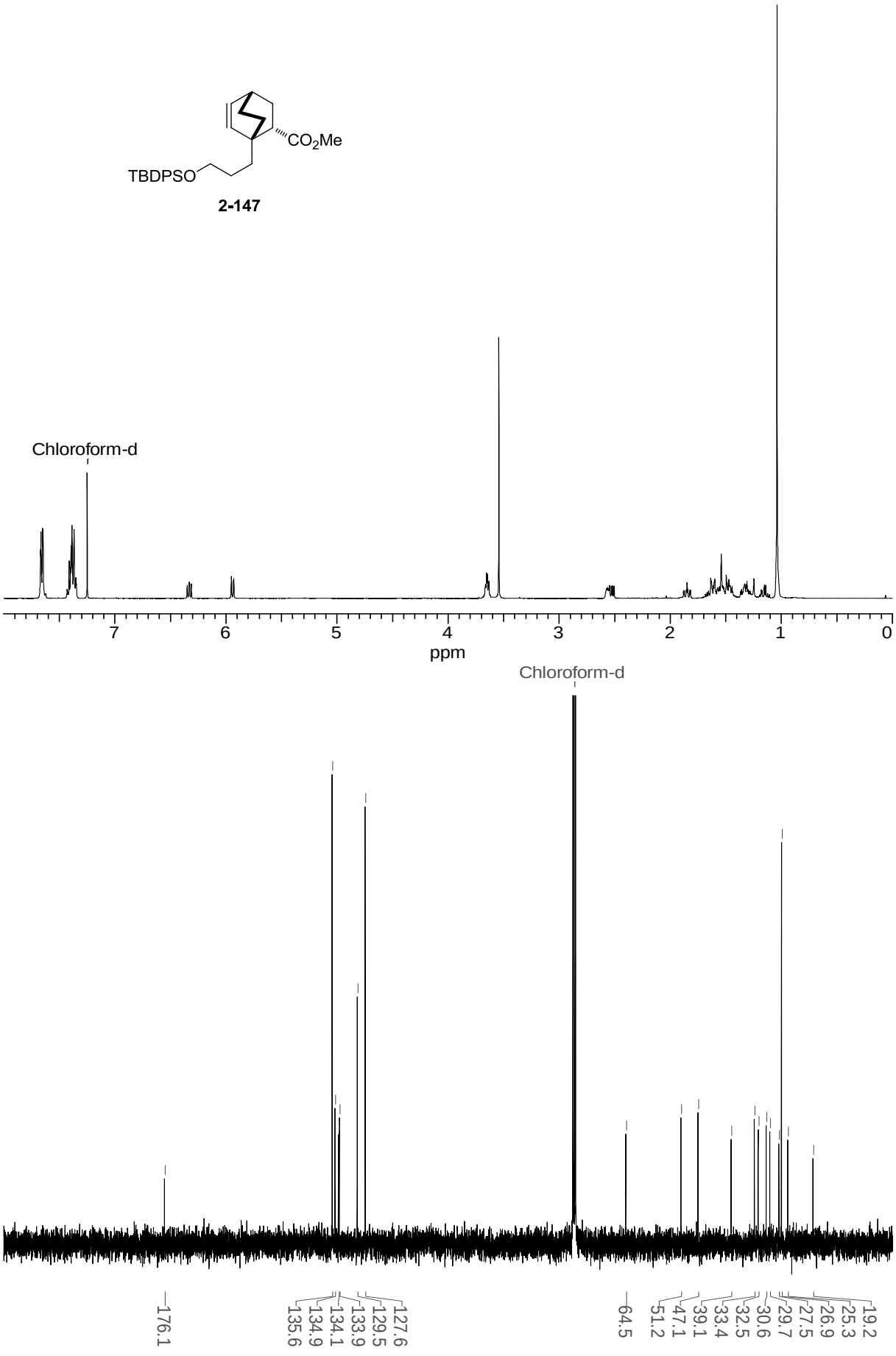

HO
CO2Me
TBDPSO
2-146A
Chloroform-d
7
6
5
4
3
2
1
0
ppm

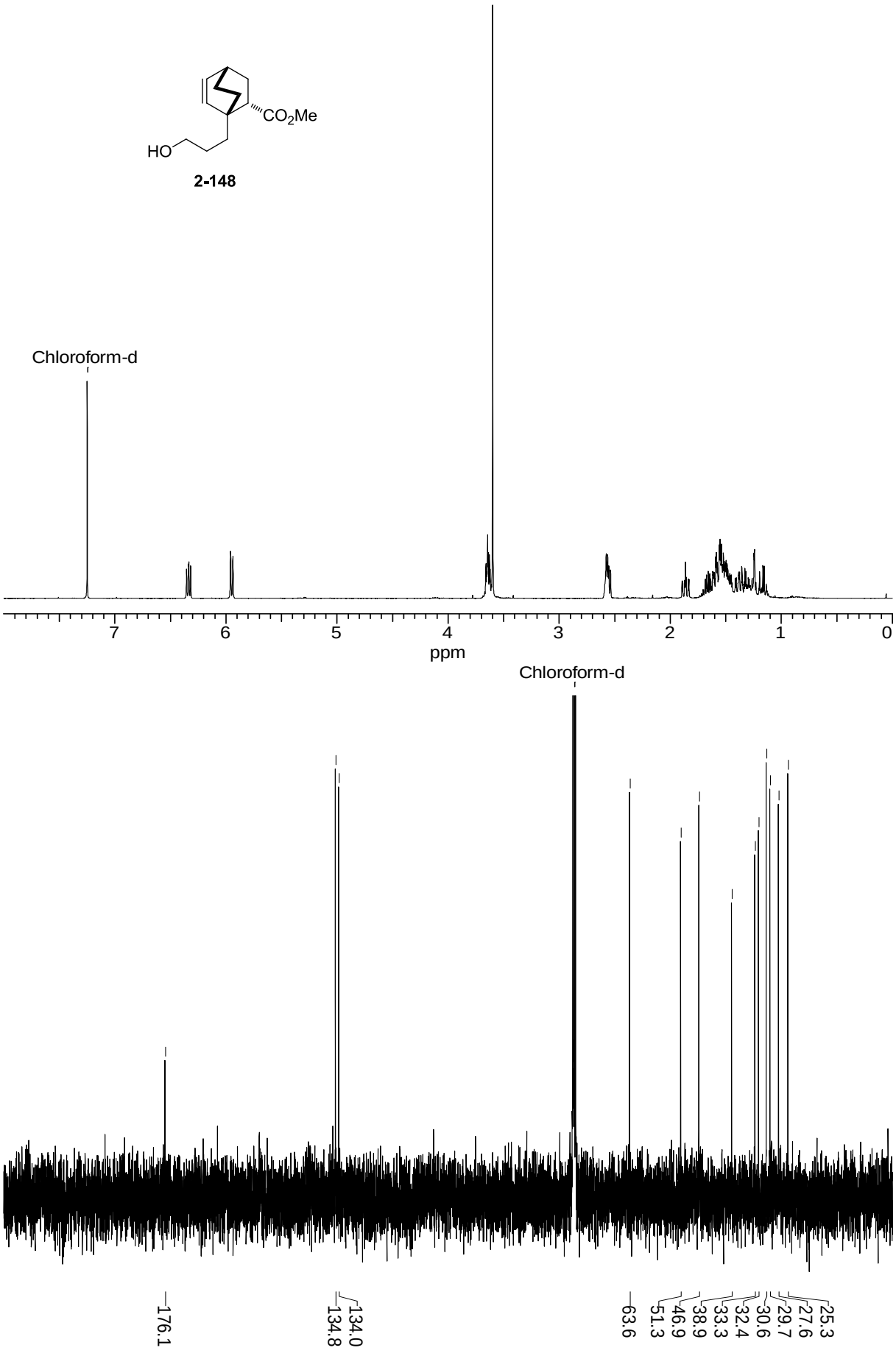

Chloroform-d
178.9
135.5
134.0
133.9
129.5
127.6
68.5
64.5
51.7
44.5
38.9
35.5
34.4
31.1
29.5
26.8
26.3
23.3
19.2

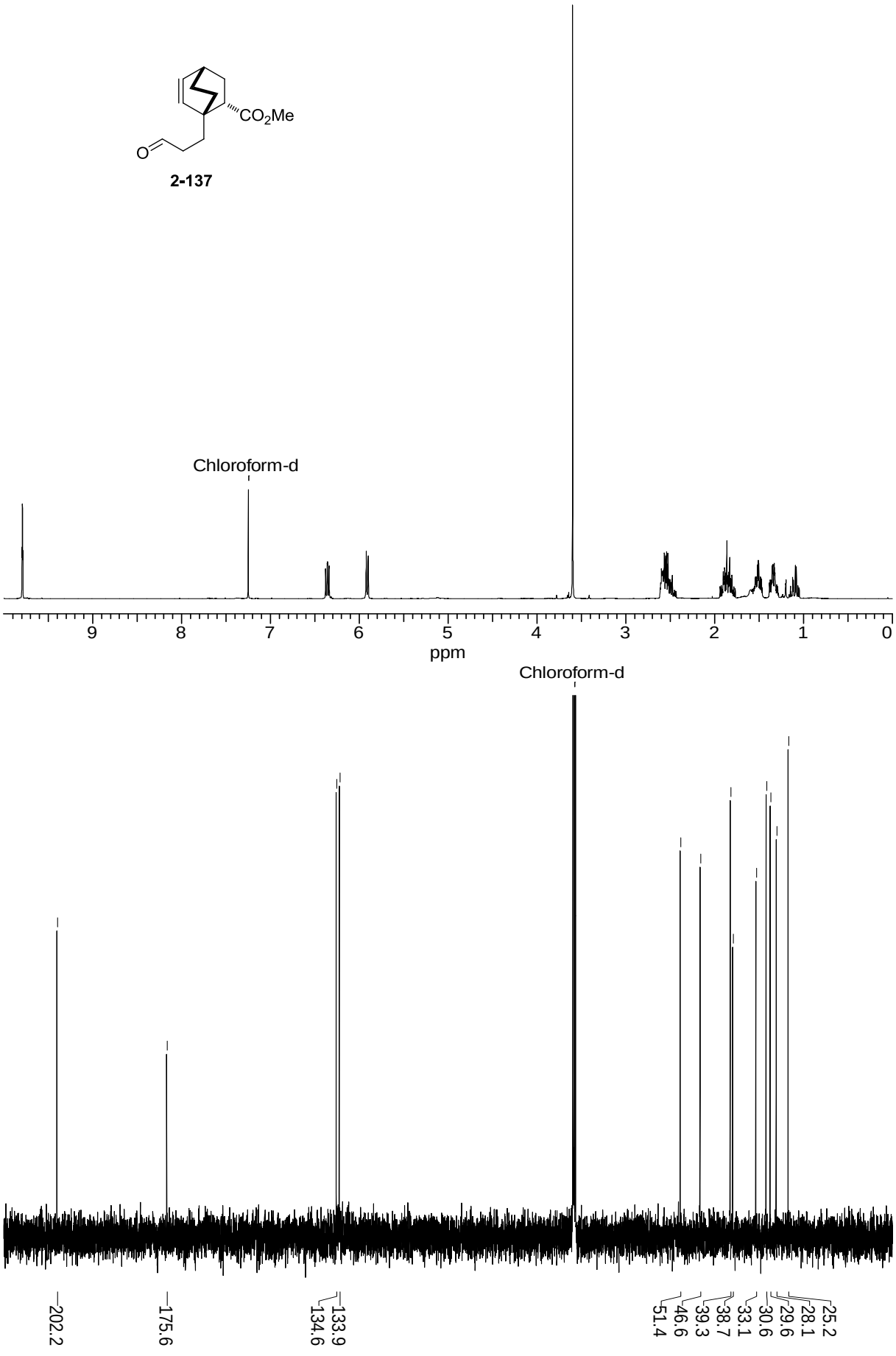

HO
CO2Me
TBDPSO
Chloroform-d
7
6
5
4
3
2
1
0
ppm

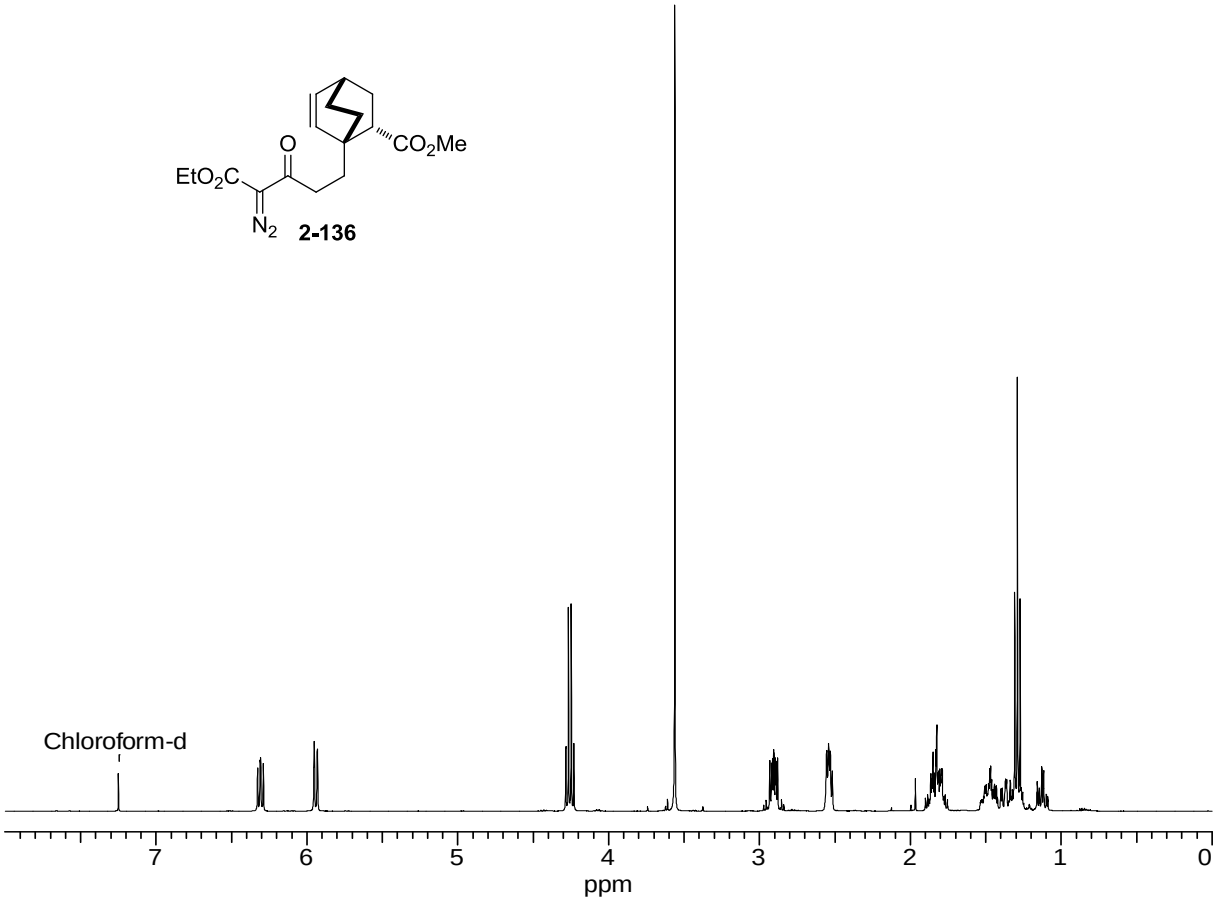
2-146B

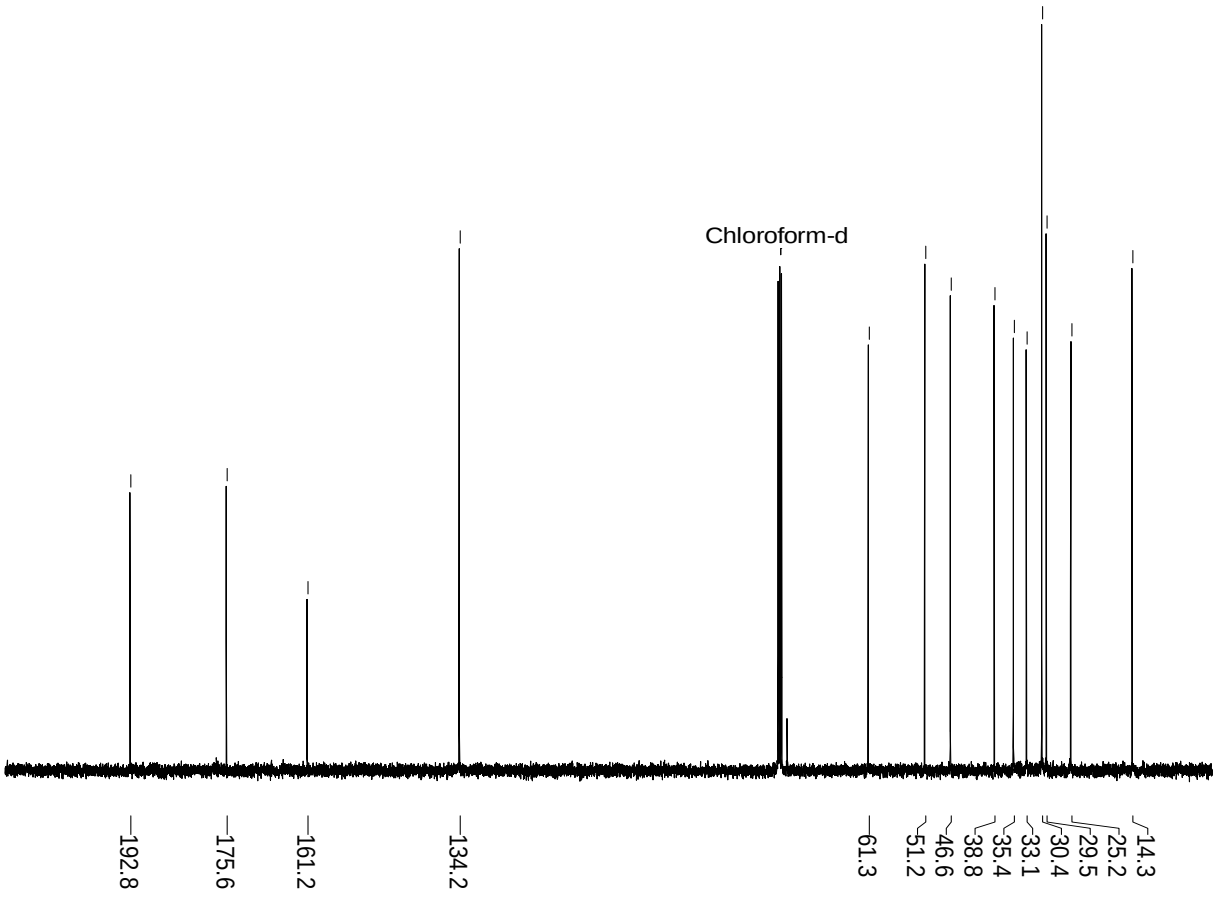

Chloroform-d
176.4
135.5
134.0
129.5
127.6
68.9
64.5
51.2
44.1
38.5
34.8
34.4
31.5
30.3
28.4
26.8
26.5
19.2
18.6

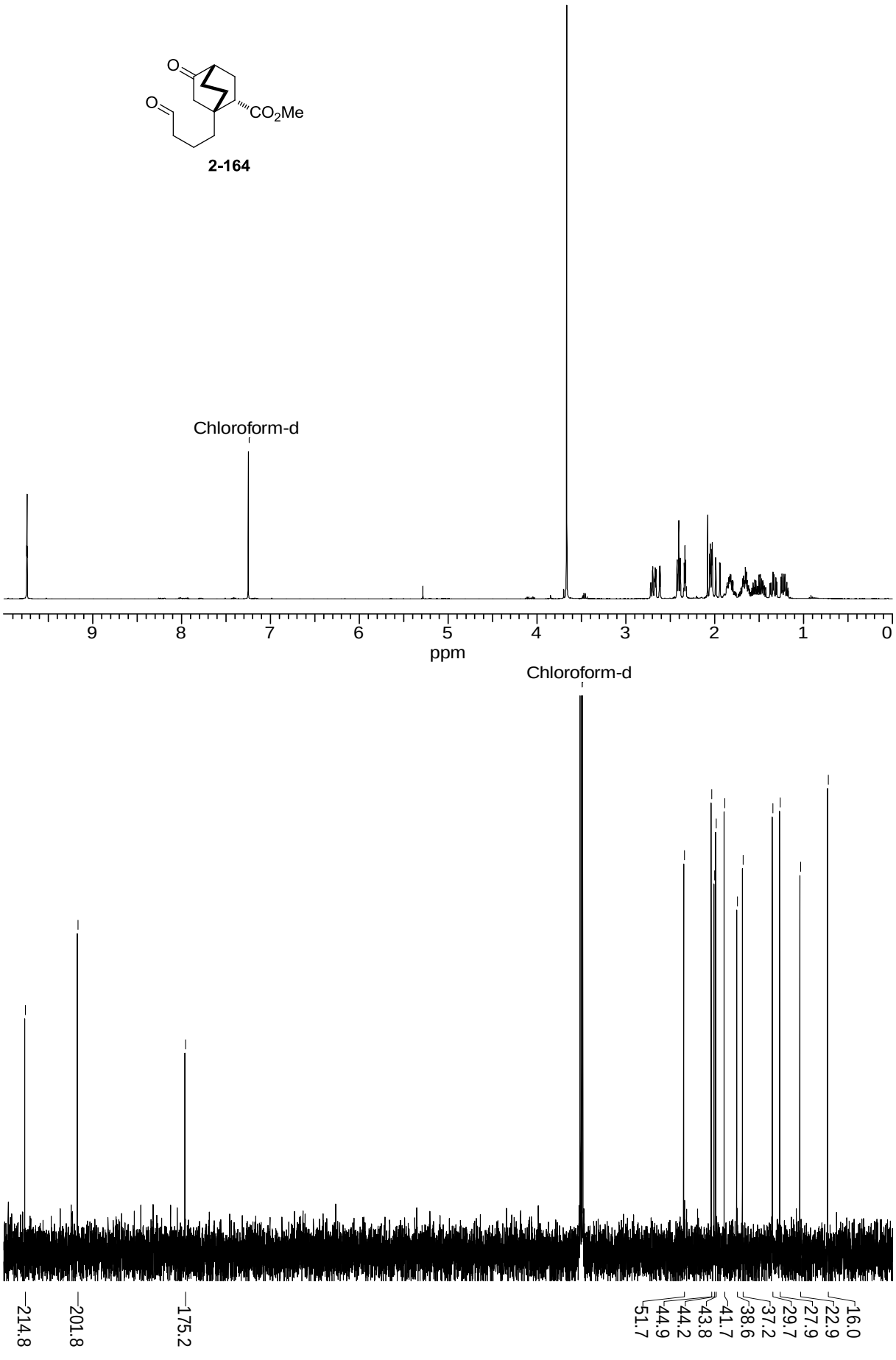

CO2Me
TBDPSO
2-147
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
176.1
135.6
134.9
134.1
133.9
129.5
127.6
64.5
51.2
47.1
39.1
33.4
32.5
30.6
29.7
27.5
26.9
25.3
19.2

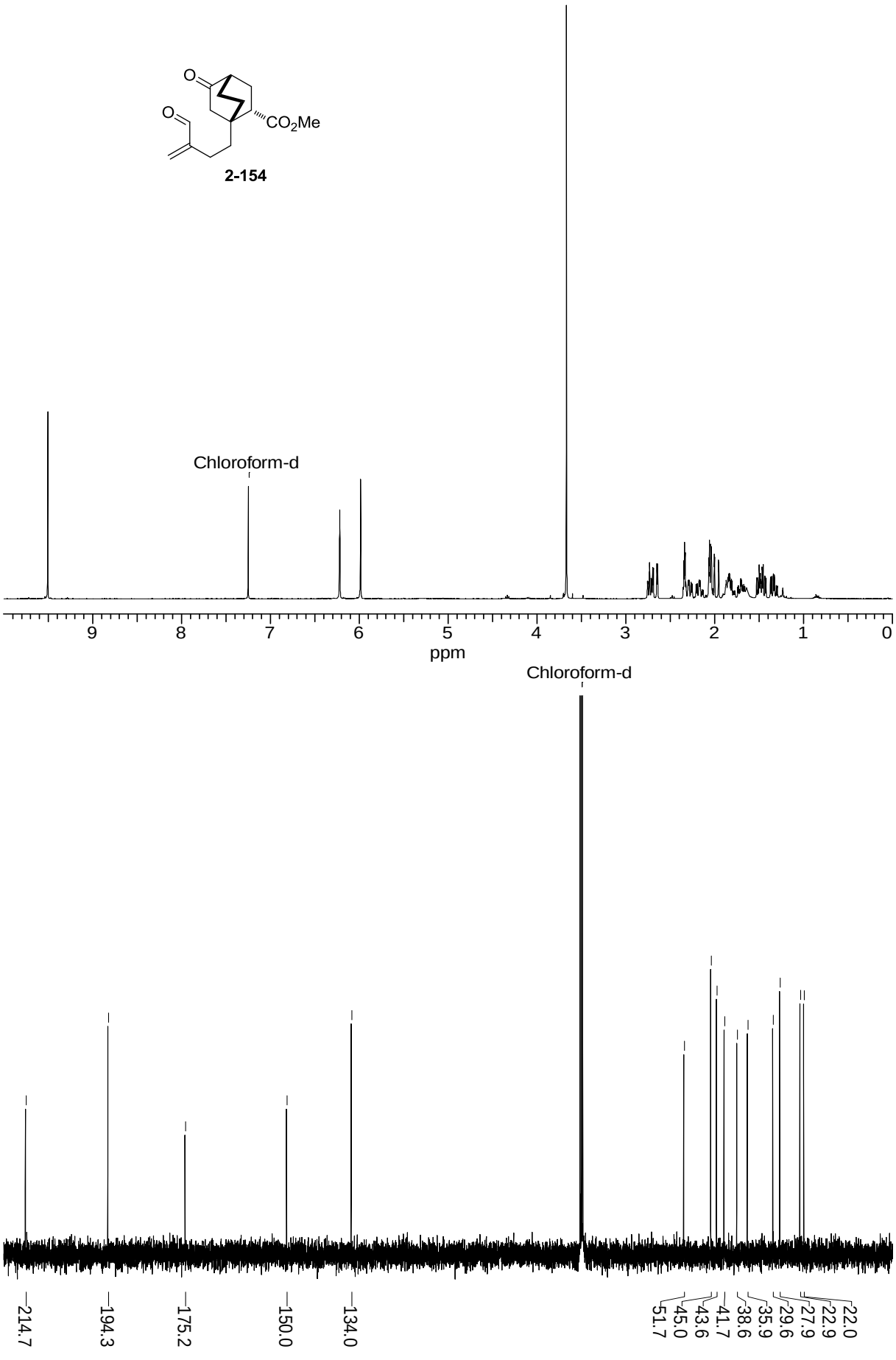

CO2Me
HO
2-148
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
176.1
134.8
134.0
63.6
51.3
46.9
38.9
33.3
32.4
30.6
29.7
27.6
25.3

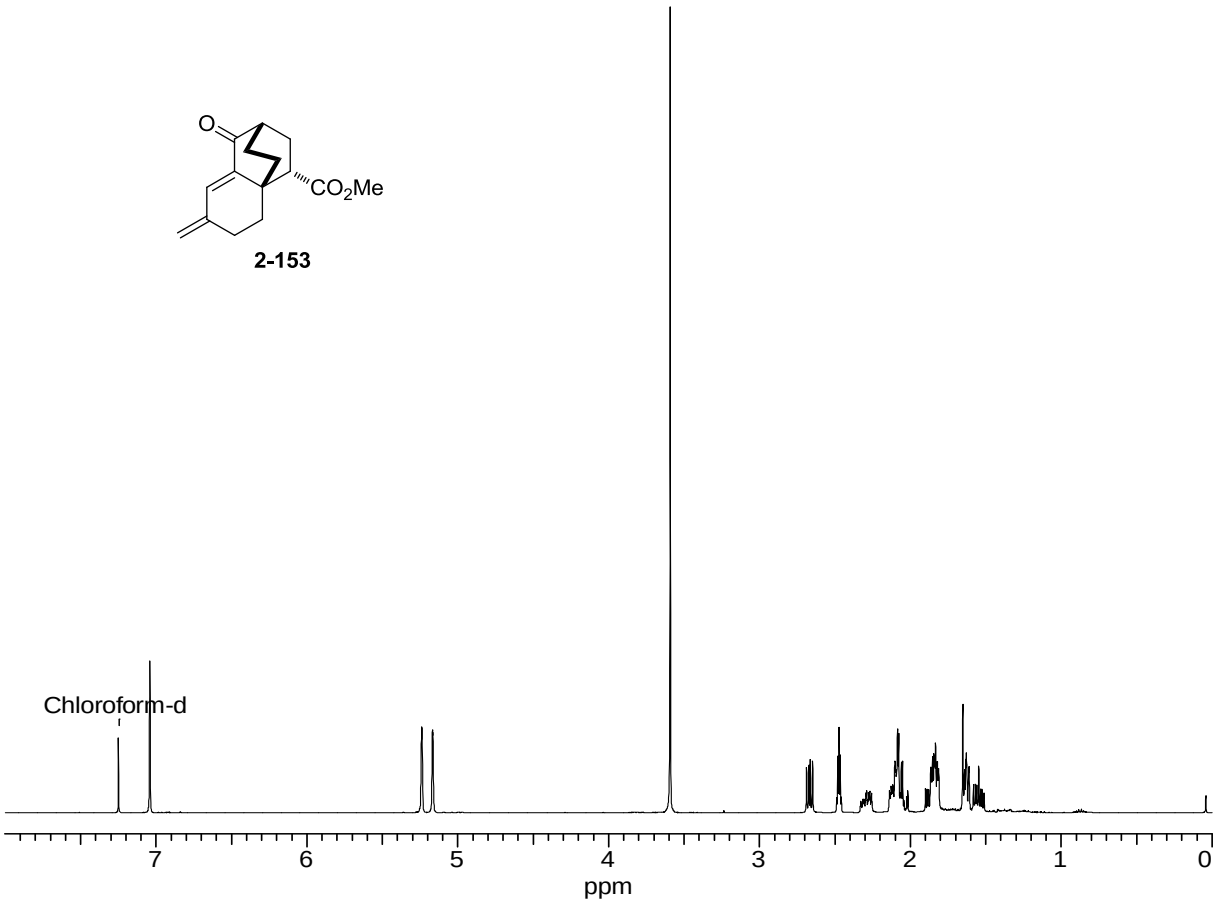

CO2Me
O
2-137
Chloroform-d
9
8
7
6
5
4
3
2
1
0
ppm
Chloroform-d
202.2
175.6
134.6
133.9
51.4
46.6
39.3
38.7
33.1
30.6
29.6
28.1
25.2

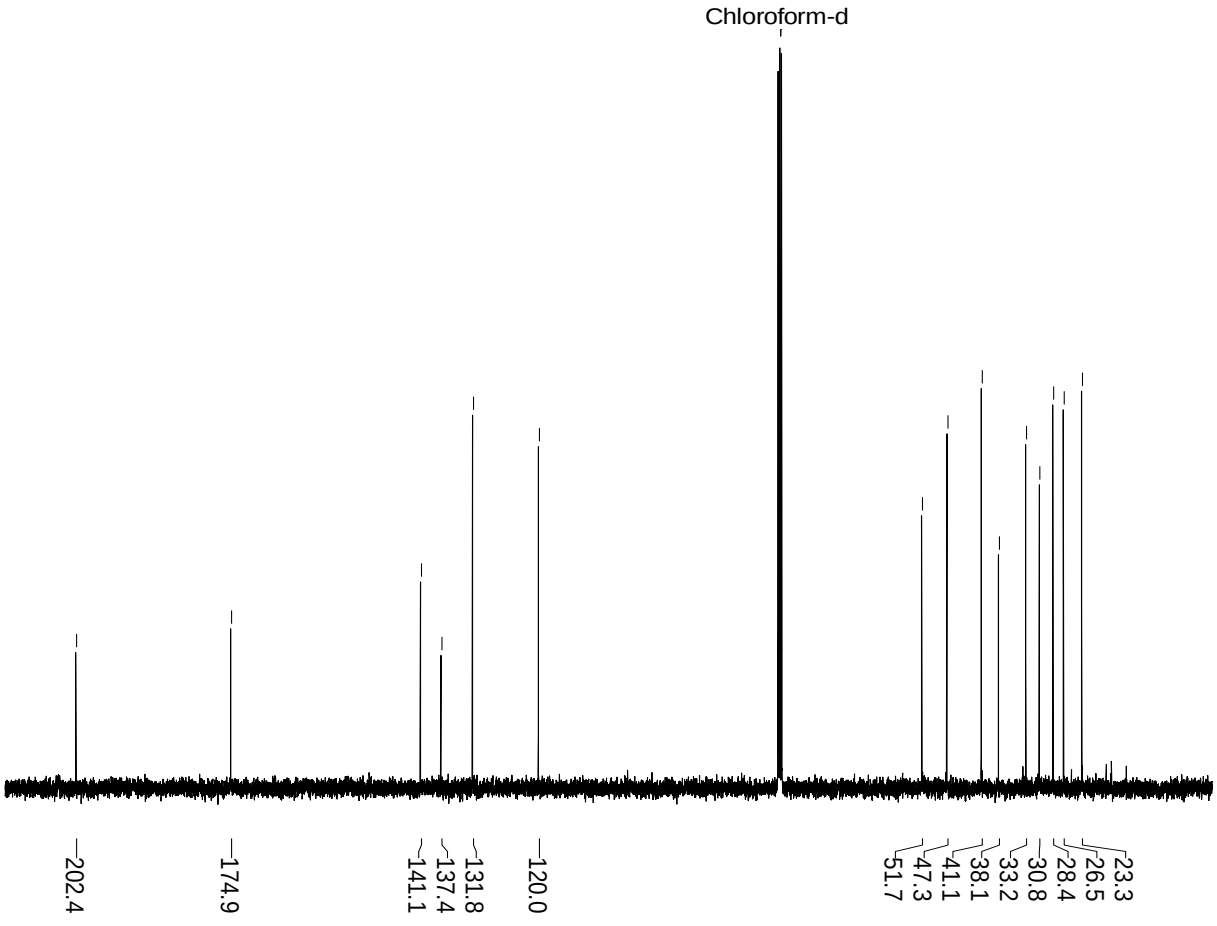

EtO2C
O
CO2Me
N2
2-136
Chloroform-d
7
6
5
4
3
2
1
0
ppm

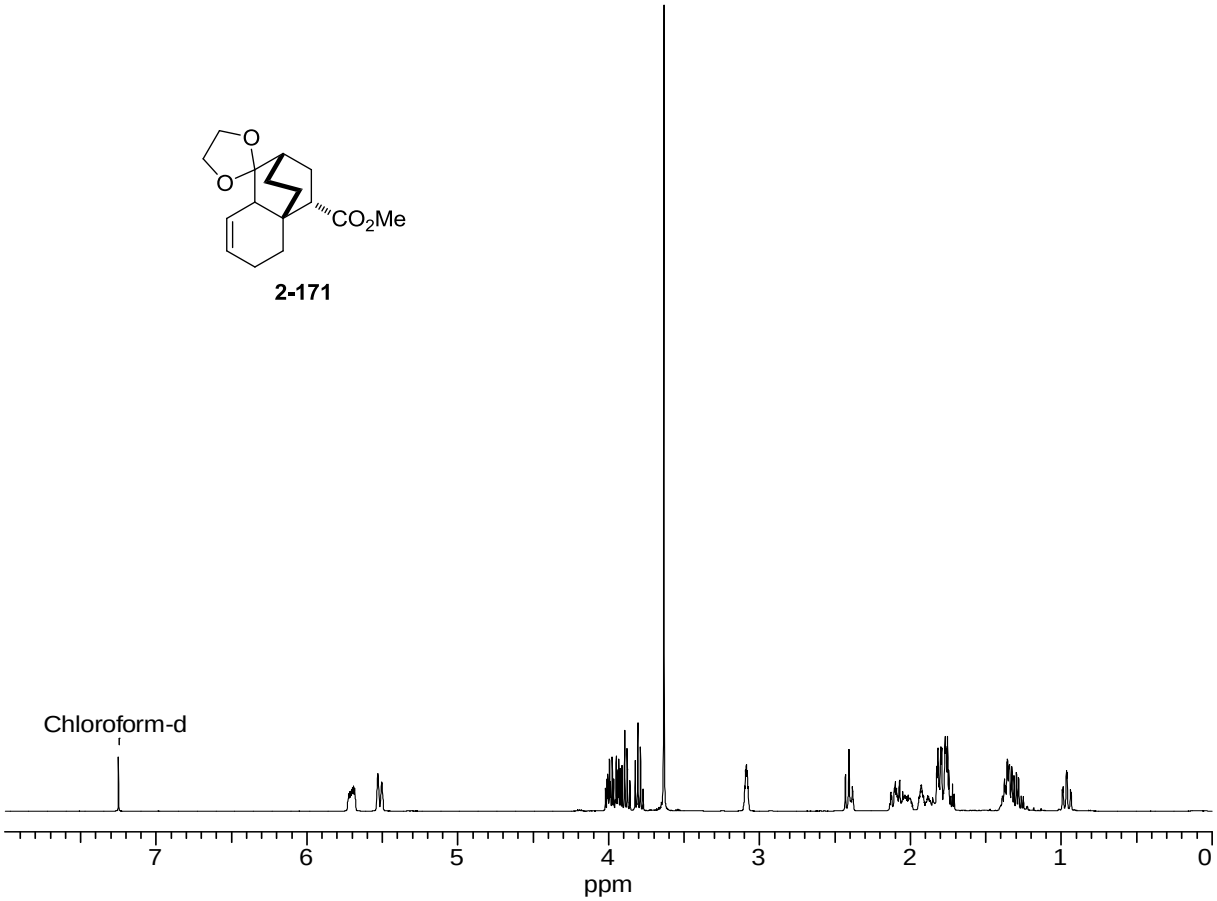

Chloroform-d
192.8
175.6
161.2
134.2
61.3
51.2
46.6
38.8
35.4
33.1
30.4
29.5
25.2
14.3


O
O
CO2Me
2-164
Chloroform-d
9
8
7
6
5
4
3
2
1
0
ppm
Chloroform-d
214.8
201.8
175.2
51.7
44.9
44.2
43.8
41.7
38.6
37.2
29.7
27.9
22.9
16.0

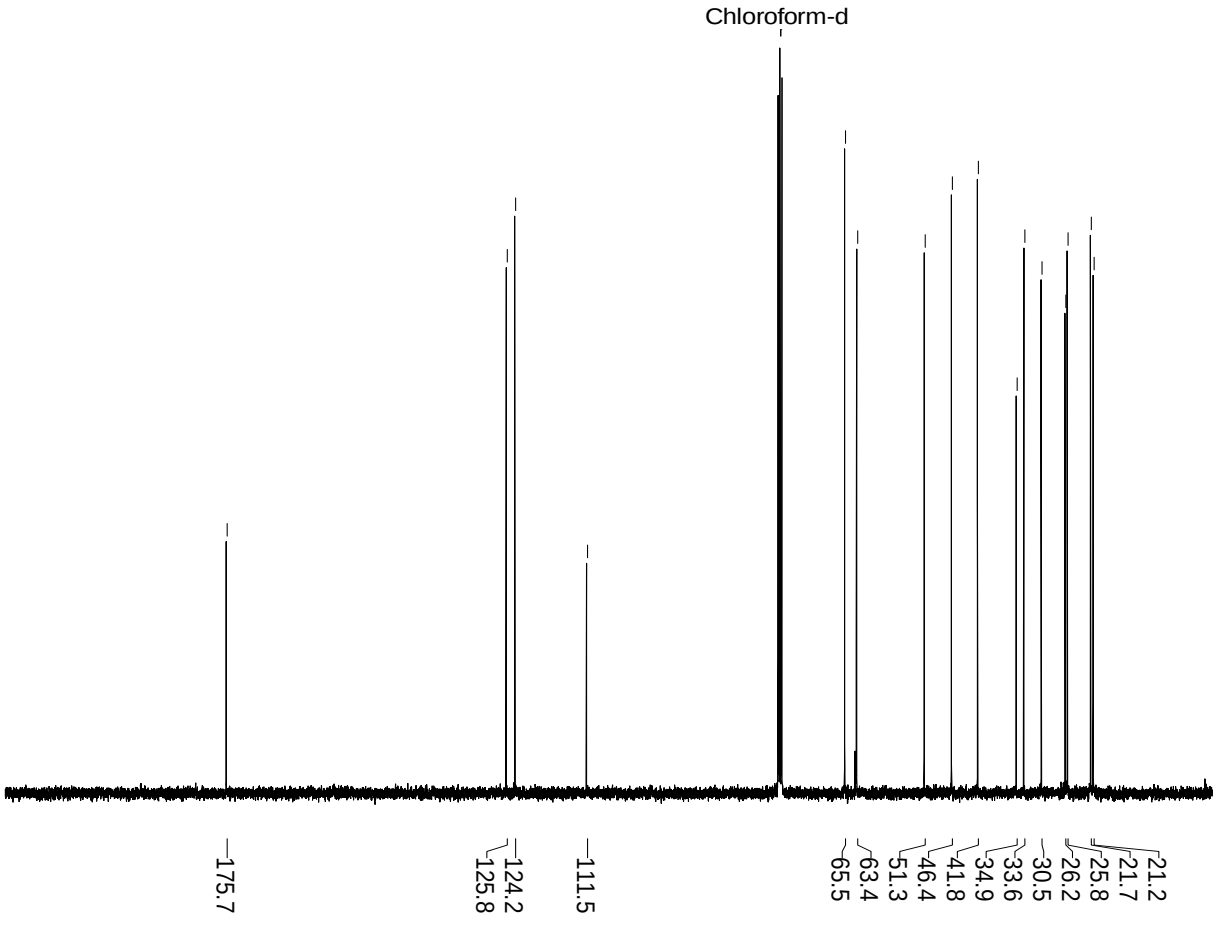

O
O
CO2Me
2-154
Chloroform-d
9
8
7
6
5
4
3
2
1
0
ppm
Chloroform-d
214.7
194.3
175.2
150.0
134.0
51.7
45.0
43.6
41.7
38.6
35.9
29.6
27.9
22.9
22.0

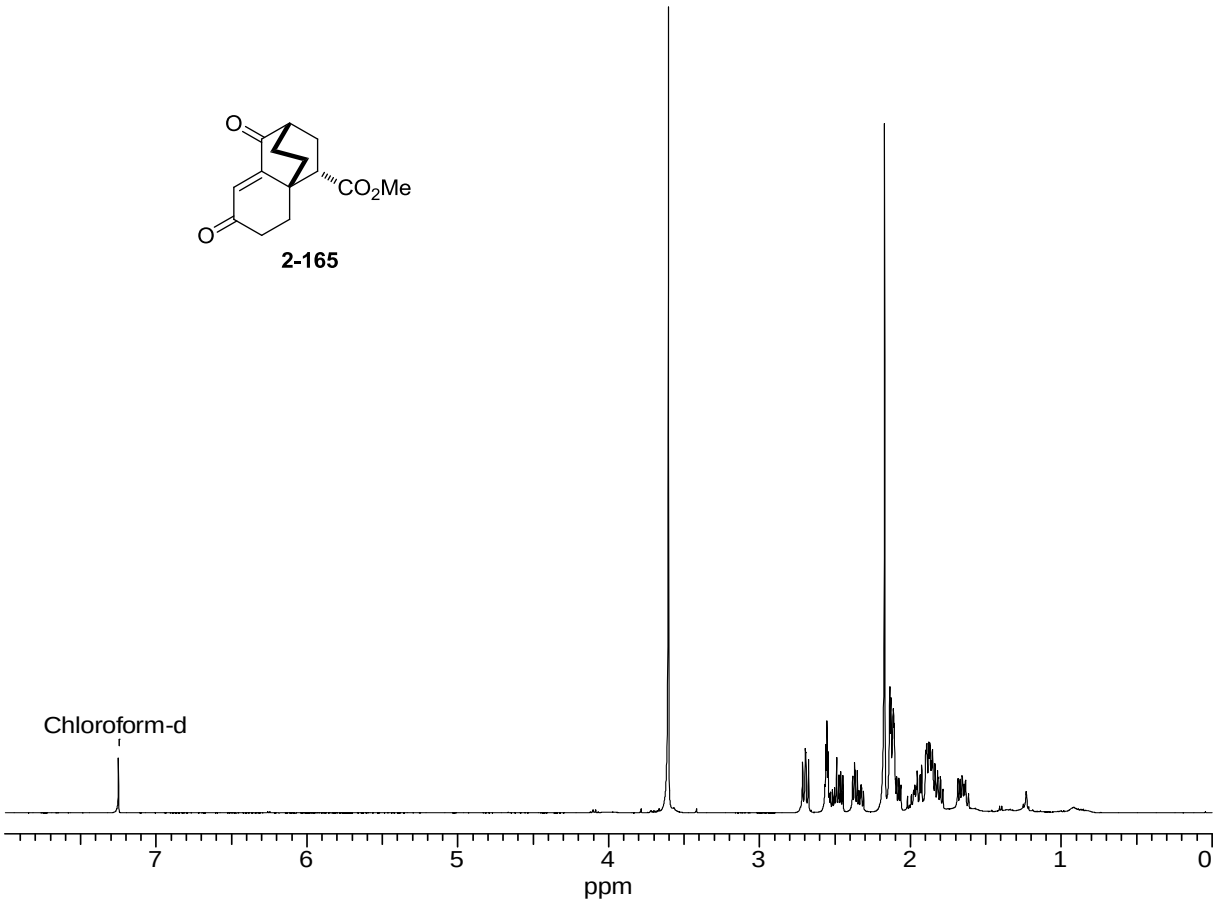

O
CO2Me
2-153
Chloroform-d
7
6
5
4
3
2
1
0
ppm


Chloroform-d
202.4
174.9
141.1
137.4
131.8
120.0
51.7
47.3
41.1
38.1
33.2
30.8
28.4
26.5
23.3

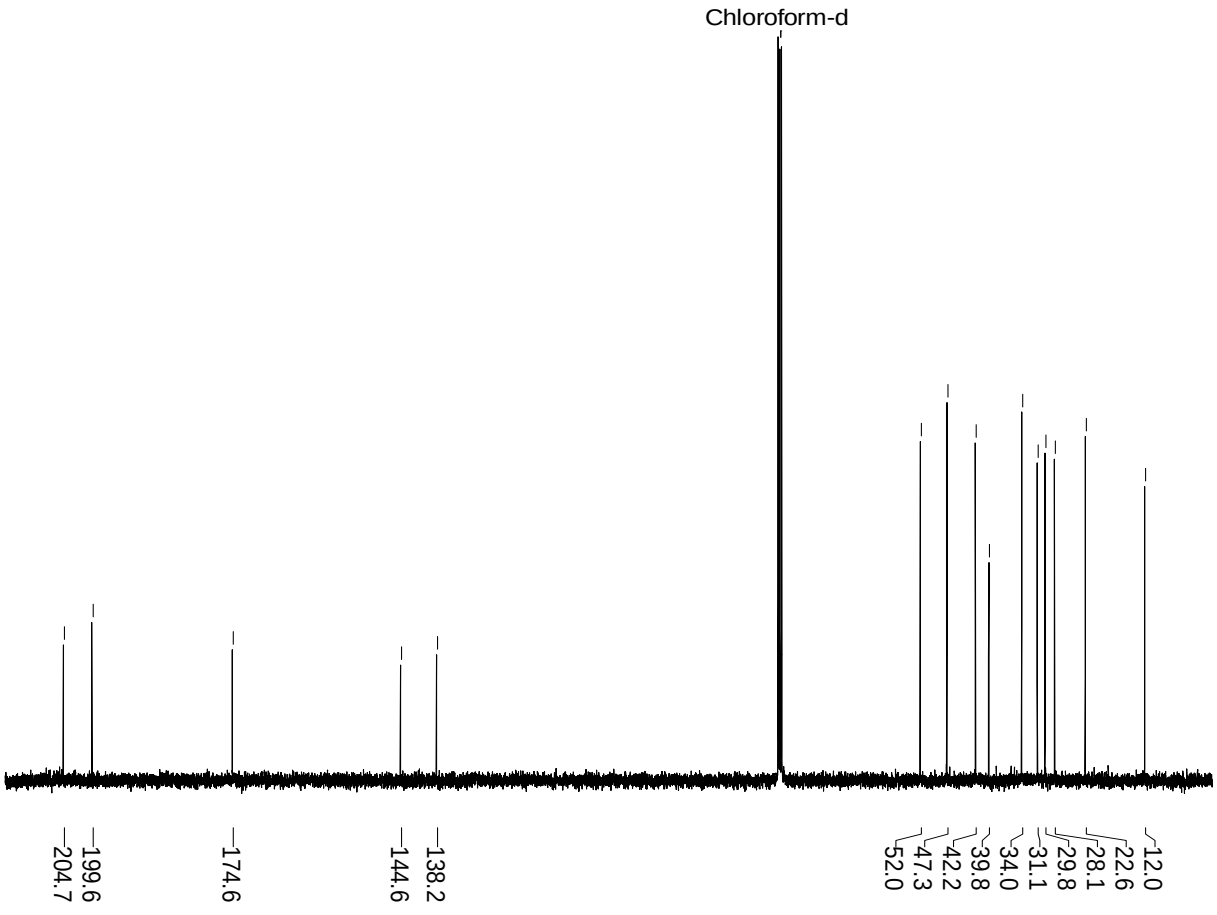

O
O
CO2Me
Chloroform-d
7
6
5
4
3
2
1
0
ppm

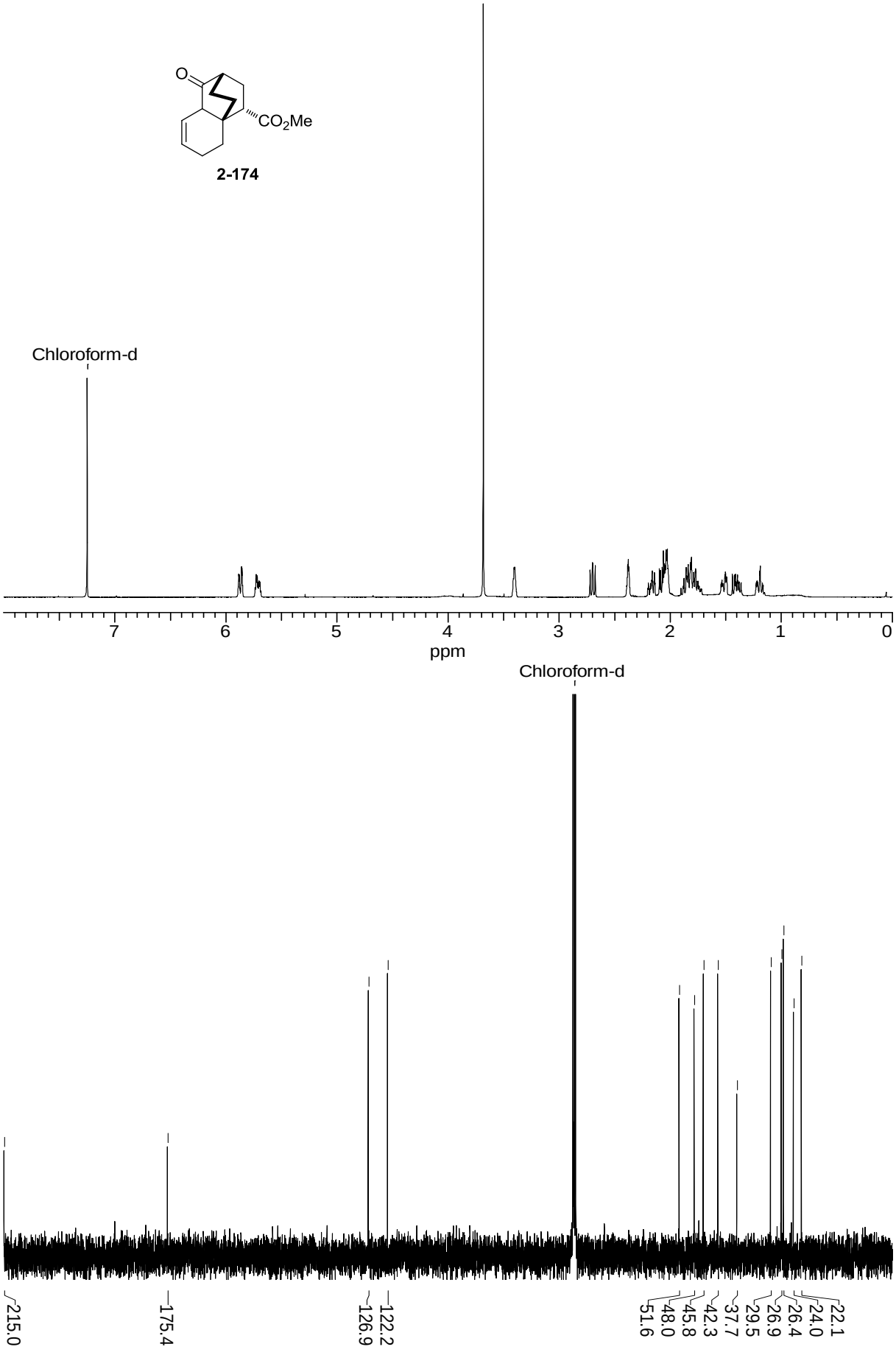
2-171

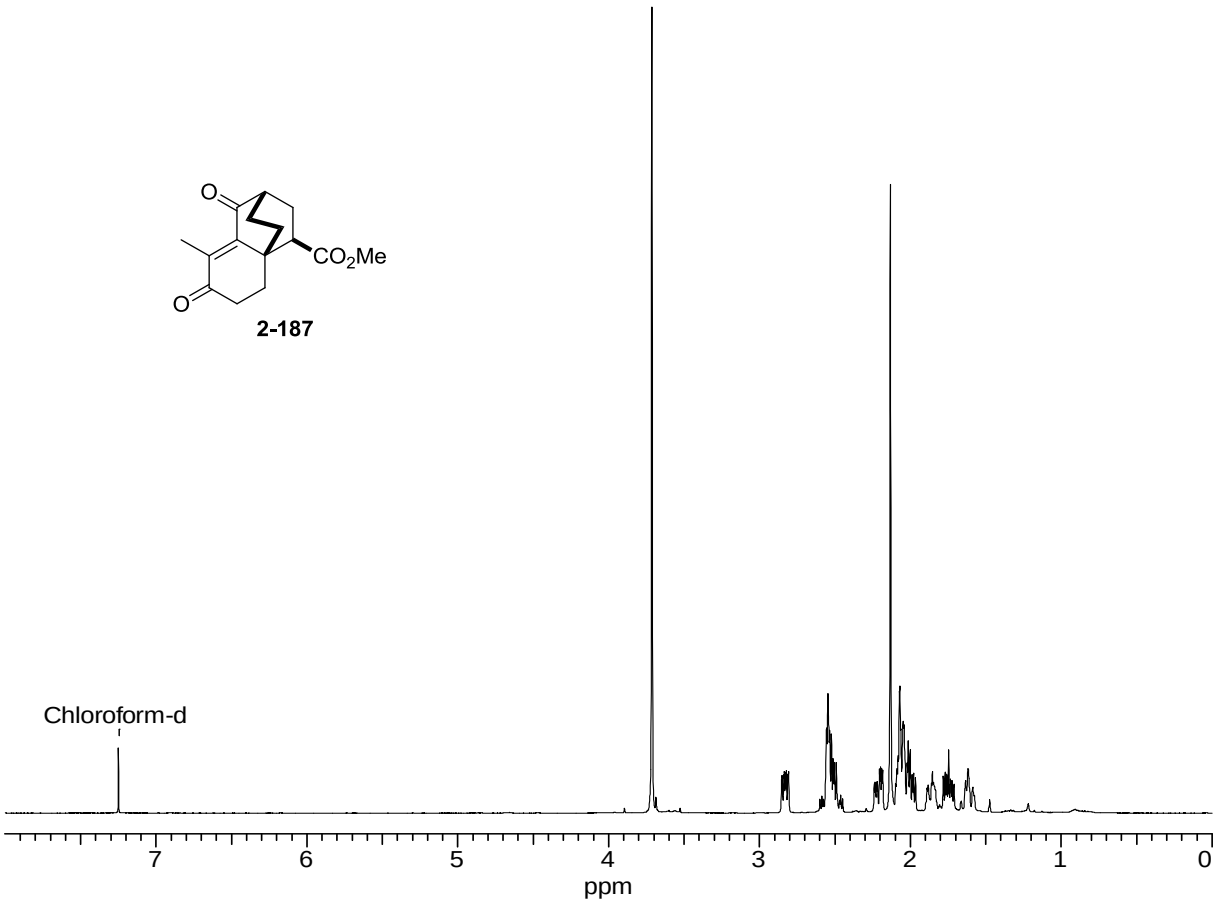

Chloroform-d
175.7
125.8
124.2
111.5
65.5
63.4
51.3
46.4
41.8
34.9
33.6
30.5
26.2
25.8
21.7
21.2

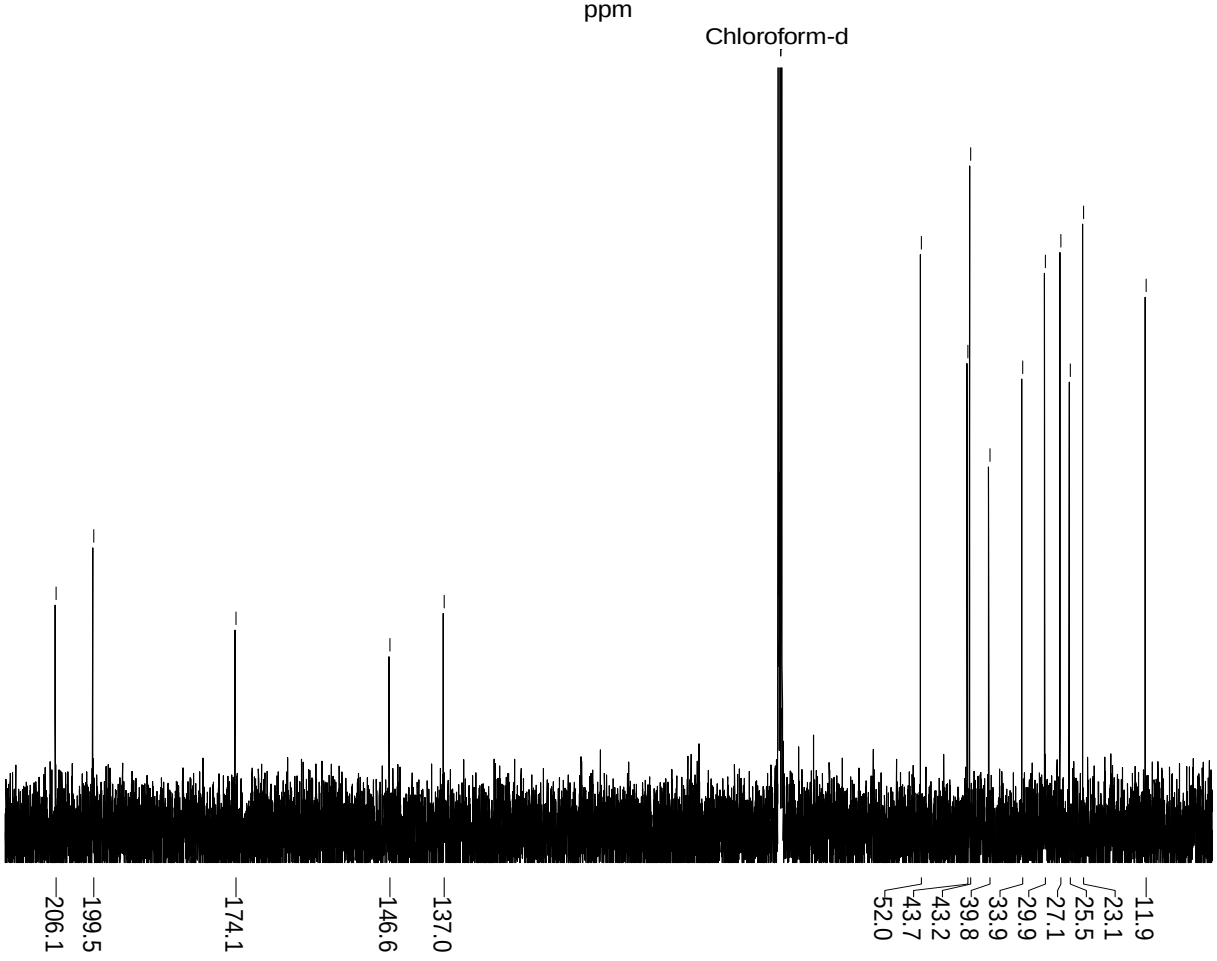

O
O
CO2Me
Chloroform-d
7
6
5
4
3
2
1
0
ppm

2-165


Chloroform-d
204.7
199.6
174.6
144.6
138.2
52.0
47.3
42.2
39.8
34.0
31.1
29.8
28.1
22.6
12.0


O
CO2Me
2-174
Chloroform-d
7
6
5
4
3
2
1
0
ppm
Chloroform-d
215.0
175.4
126.9
122.2
51.6
48.0
45.8
42.3
37.7
29.5
26.9
26.4
24.0
22.1


O
O
CO2Me
2-187
Chloroform-d
7
6
5
4
3
2
1
0
ppm


Chloroform-d
206.1
199.5
174.1
146.6
137.0
52.0
43.7
43.2
39.8
33.9
29.9
27.1
25.5
23.1
11.9

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