Syntheses of the left- and right-hand fragments of the anti-HIV schinortriterpenoid, pre-schisanartanin A

Ryotaro Yagita

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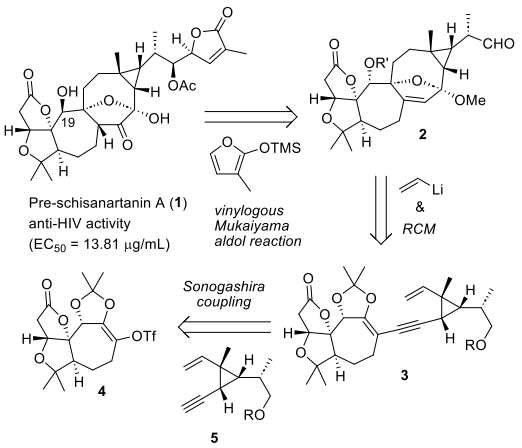
Summary

1. Introduction

Pre-schisanartanin A (**1**) is a schinortriterpenoid (SNT) isolated from *Schisandra chinensis* by the Sun group in 2007.[1] Its structural features include a unique pentacyclic framework comprising 5/5/7/8/3-membered rings and a highly oxygenated 7-membered ring and distorted all-*cis*-substituted cyclopropane, wherein the main chains on the cyclopropane ring are located on the same side of the ring. Notably, no studies regarding the total syntheses of SNTs with hydroxyl groups at their C19 positions are reported due to the challenge in forming the oxygen-functionalized framework. SNT **1** exhibits an anti-HIV activity, with an EC_{50} = 14 μg/mL, and we commenced the total synthesis of **1** because of its unique framework and critical biological activity.

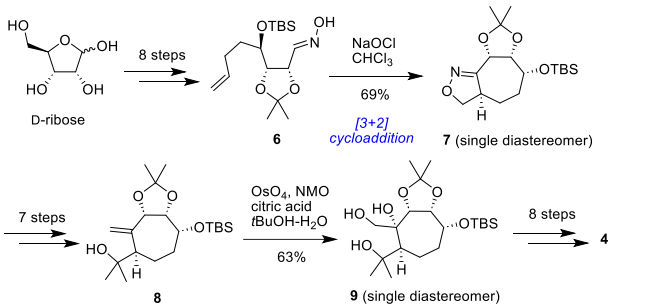


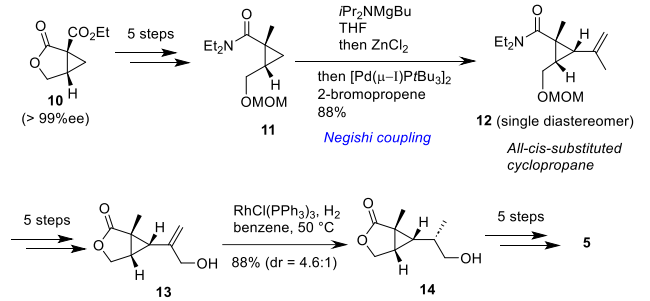
2. Plan

We designed a convergent route for the enantioselective total synthesis of **1**. SNT **1** should be synthesized using the triflate fragment **4** and alkyne fragment **5**. The highly oxygenated 7-membered ring structure of **4** should be accessed from D-ribose using [3+2] cycloaddition. Meanwhile, the all-*cis*-substituted cyclopropane structure of **5** should be generated from lactone **10** via Negishi coupling.[2]

3. Results

D-Ribose was converted to oxime **6** in 8 steps. Upon treatment of **6** with NaOCl, an intramolecular [3+2] cycloaddition proceeded to afford isoxazoline **7** as a single diastereomer. A computational study revealed that the transition state leading to the desired product **7** was 3.8 kcal/mol more favorable than that leading to the diastereomer. Dihydroxylation of **8**, which was synthesized from **7** in 7 steps, gave triol **9** as a single diastereomer because OsO_4 approached the face bearing the siloxy group and acetonide. Compound **4** was synthesized via an 8-step sequence.[3]





Compound **11**, which was obtained in five steps from **10**, was treated using iPr_2NMgBu, $ZnCl_2$, $[Pd(\mu\text{-}I)PtBu_3]_2$, and 2-bromopropene. The Negishi reaction proceeded smoothly, affording the all-*cis*-substituted cyclopropane **12** as a single diastereomer. This coupling reaction was susceptible to steric hindrance, and several substrates with different substitution patterns were examined, but only **11** enabled the introduction of the third substituent. After generating lactone **13**, hydrogenation in the presence of Wilkinson's catalyst produced **14** in an 88% yield with a good diastereoselectivity. Compound **5** was synthesized via a subsequent 5-step sequence.[4]

References

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3 Yagita R., Irie K., Tsukano C., *Eur. J. Org. Chem.*, **2021**, 4269 (2021).
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Abbreviations

Ac	acetyl
acac	acethylacetonate
ADMP	2-azido-1,3-dimethylimidazolinium hexafluorophosphate
AIBN	azobis(isobutyronitrile)
AIDS	aquired immunodeficiency syndrome
AZADO	azaadamantane *N*-oxyl
BAr_F	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	benzyl
Bu	butyl
cat.	catalyst
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
$Cu(tbs)_2$	bis(*N*-*tert*-butylsalicylaldiminato)copper (II)
CuTC	copper(I)-thiophene-2-carboxylate
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	dichloro ethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppm	bis(diphenylphosphino)methane
dr	diastereomeric ratio
DTBMP	2,6-di-*t*butyl-4-methylpyridine
EC_{50}	half maximal effective concentration
EDC	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide
ee	enantiomeric excess

ent	enantiomer
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropionicacid
Et	ethyl
eq	equivalent
gen.	generation
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
i	*iso*
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl
n	*normal*
NaHMDS	sodium bis(trimethylsilyl)amide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
o	*ortho*
p	*para*
PCy_3	tricyclohexylphosphine
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
Pr	propyl
py	pyridine
$pyHBr_3$	pyridinium bromide perbromide
quant.	quantitative yield

RCM	ring-closing metathesis
SDBBA	sodium diisobutyl(*t*butoxy)aluminium hydride
SM	starting material
SNT	*schisandra* nortriterpenoid
t	*tertiary*
TBAF	tetrabutylammonium fluoride
TBDPS	*t*butyldiphenylsilyl
TBHP	*t*butyl hydroperoxide
TBS	*t*butyldimethylsilyl
TES	triethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
thd	2,2,6,6-tetramethyl-3,5-heptanedionato
THF	tetrahydrofuran
TI	therapeutic index
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMTU	tetramethylthiourea
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1　Introduction

Section 1　HIV and AIDS

1.1.1　Pathological features of AIDS and its treatment

HIV is a retrovirus that infects human immune cells and causes immunodeficiency, and there are currently over 38 million patients worldwide, with 650,000 deaths annually.[1] Following infection, without appropriate treatment, individuals develop various opportunistic infections and malignancies that do not typically affect healthy individuals, and this condition is known as AIDS.

The current cornerstones of HIV treatment are antiretroviral drugs aimed at reducing the HIV levels in the blood below the detection threshold. Antiretroviral drugs are classified into four categories based on their anti-HIV actions: reverse transcriptase, protease, fusion, and integrase inhibitors. Using these drugs in monotherapy leads to the development of viral resistance within days to months, and thus, combination antiretroviral therapy, which combines multiple drugs, is commonly used. However, the virus has never been completely eradicated from the body, and the issue of patients requiring medication for their entire lives remains. Additionally, the long-term side effects associated with prolonged drug intake may not be ignored, rendering the development of new drugs with novel mechanisms of action an urgent challenge.

1.1.2　Triterpenoids with anti-HIV activities

To date, numerous compounds have been isolated from plants and structurally elucidated, with their diverse biological activities rendering them attractive targets in drug discovery. Among these, triterpenoids garner significant attention due to their multifaceted physiological functions, including anti-inflammatory and -tumor, cancer-preventive, and hypoglycemic properties.

One notable triterpenoid with an anti-HIV activity is betulinic acid (Fig. 1.1A, EC_{50} = 1.4 μM).[2] Since the discovery of its biological activity, structure-activity relationship studies aimed at pharmaceutical development have been undertaken, leading to the synthesis of 3-*O*-(3',3'-dimethylsuccinyl)betulinic acid (bevirimat, Fig. 1.1B, EC_{50} < 0.35 nM, TI = 20,000).[3, 4] Bevirimat represents the first class of HIV maturation inhibitors, specifically targeting the inhibition of HIV capsid proteins formation.[5] Due to its distinct mechanism of action, which differs from those of known anti-HIV drugs, bevirimat is effective against drug-resistant HIV. This has generated high expectations for its potential as a medicine, leading to its progression to Phase 2 clinical trials.

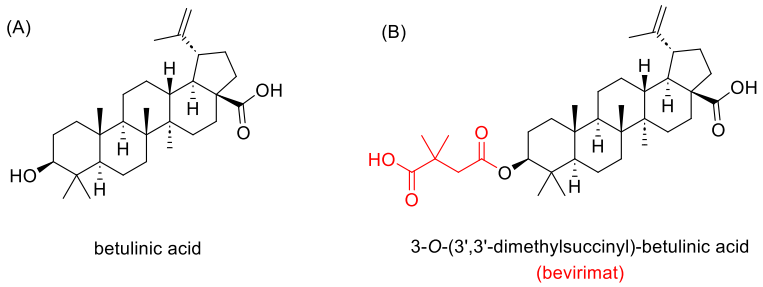


Fig. 1.1 Structures of betulinic acid and bevirimat
(A) Betulinic acid
(B) 3-*O*-(3',3'-Dimethylsuccinyl)betulinic acid (bevirimat)

Although its development is currently discontinued due to its significant dependence on the genetic polymorphisms of HIV-infected individuals, bevirimat serves as a critical example demonstrating the potential of triterpenes as novel anti-HIV drug candidates.

Additionally, various triterpenoids with anti-HIV activities have been reported. Colossolactone I (IC_{50} = 4.1 μM, Fig. 1.2A), which was isolated in 2008 from *Ganoderma colossum*, a mushroom native to Vietnam,[6] and lancilactone C (EC_{50} = 1.4 μM, Fig. 1.2B), which was isolated in 1999 from *Kadsura lancilimba*, a genus of medicinal plants traditionally used in Chinese herbal medicine,[7] are notable examples. Our research laboratory reported the total synthesis and proposed structural modification of lancilactone C.[8]

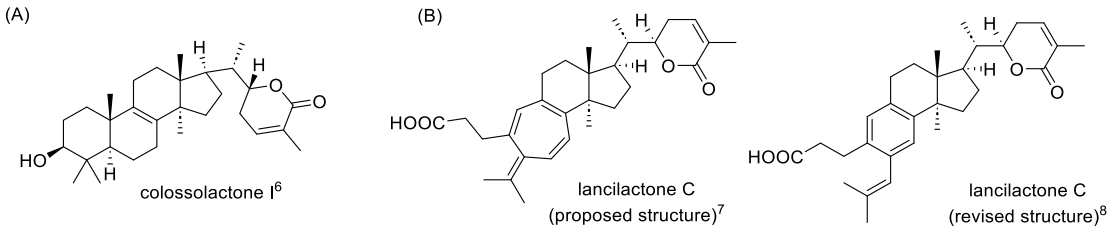


Fig. 1.2 Structures of triterpenoids with anti-HIV activities
(A) Colossolactone I
(B) Lancilactone C

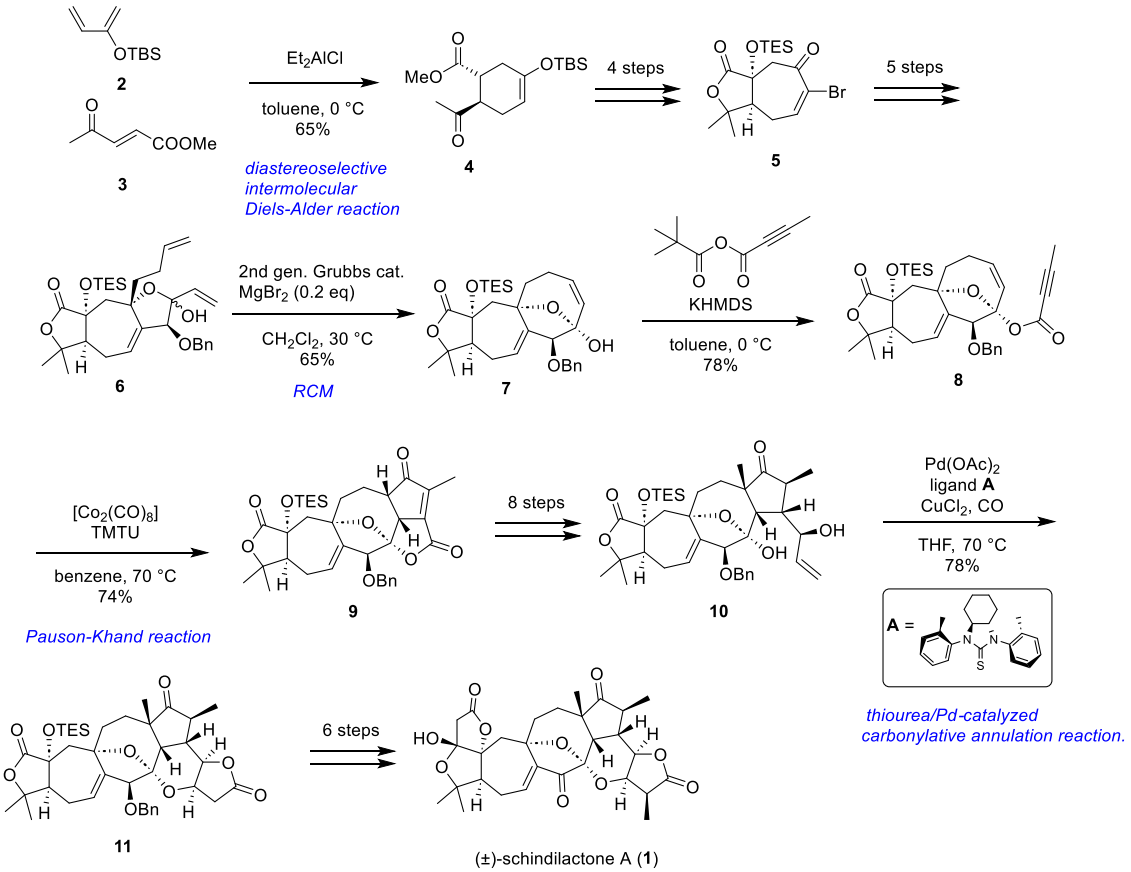
Section 2 Previous synthetic studies regarding SNTs

Schisandra chinensis, which is widely distributed in East Asia, is a plant belonging to the Schisandraceae family, and its fruits have been used as traditional herbal medicines. Triterpenoids derived from *Schisandra chinensis* (SNTs) attract significant interest among synthetic chemists due to their unique structures and crucial biological activities, including anti-hepatitis, -tumor, and -HIV activities.[9] In this section, the reported total syntheses of SNTs, along with their synthetic strategies, are summarized.

1.2.1 Schindilactone A

The total synthesis of schindilactone A (**1**) was reported by the Yang group at Peking University in 2011 (Scheme 1.1).[10] This was the first report of the total synthesis of a SNT. This compound was isolated and structurally elucidated in 2007, but it displayed no biological activity.[11]

The key synthetic steps involved a diastereoselective intermolecular Diels-Alder reaction between diene **2** and dienophile **3** to give **4**. Via a four-step sequence, including a ring expansion reaction, compound **5** was obtained, with the seven-membered ring framework successfully formed. With compound **6** in hand as a diastereomeric mixture, hemiacetal **7** was synthesized as a single diastereomer via a RCM, furnishing the eight-membered ring framework. Using a Pauson-Khand reaction with a thiourea/Co catalyst and ene-yne **8**, the hexacyclic compound **9** was synthesized. After a further eight steps, compound **10** was obtained, and heptacyclic compound **11** was successfully formed using a thiourea/Pd-catalyzed carbonylative annulation reaction. Finally, the total synthesis of (±)-**1** was realized via a six-step conversion.

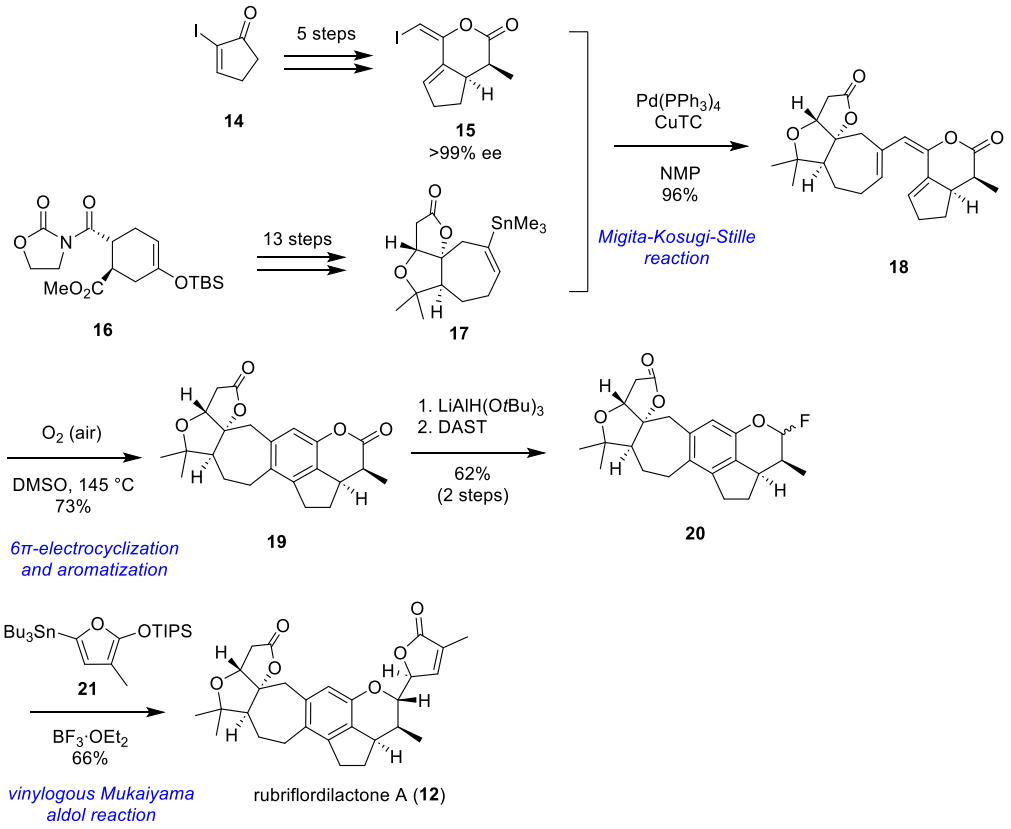


Scheme 1.1 Total synthesis of (±)-schindilactone A (Yang group)[10]

1.2.2 Rubriflordilactones A and B

Rubriflordilactones A (**12**) and B (**13**) were isolated and structurally elucidated in 2006.[12] Their structures are characterized by multisubstituted arene motifs in their heptacyclic frameworks distinct from those of the other SNTs. Compound **13** displays anti-HIV activity (EC_{50} = 9.8 μg/mL), but that of **12** is weak.

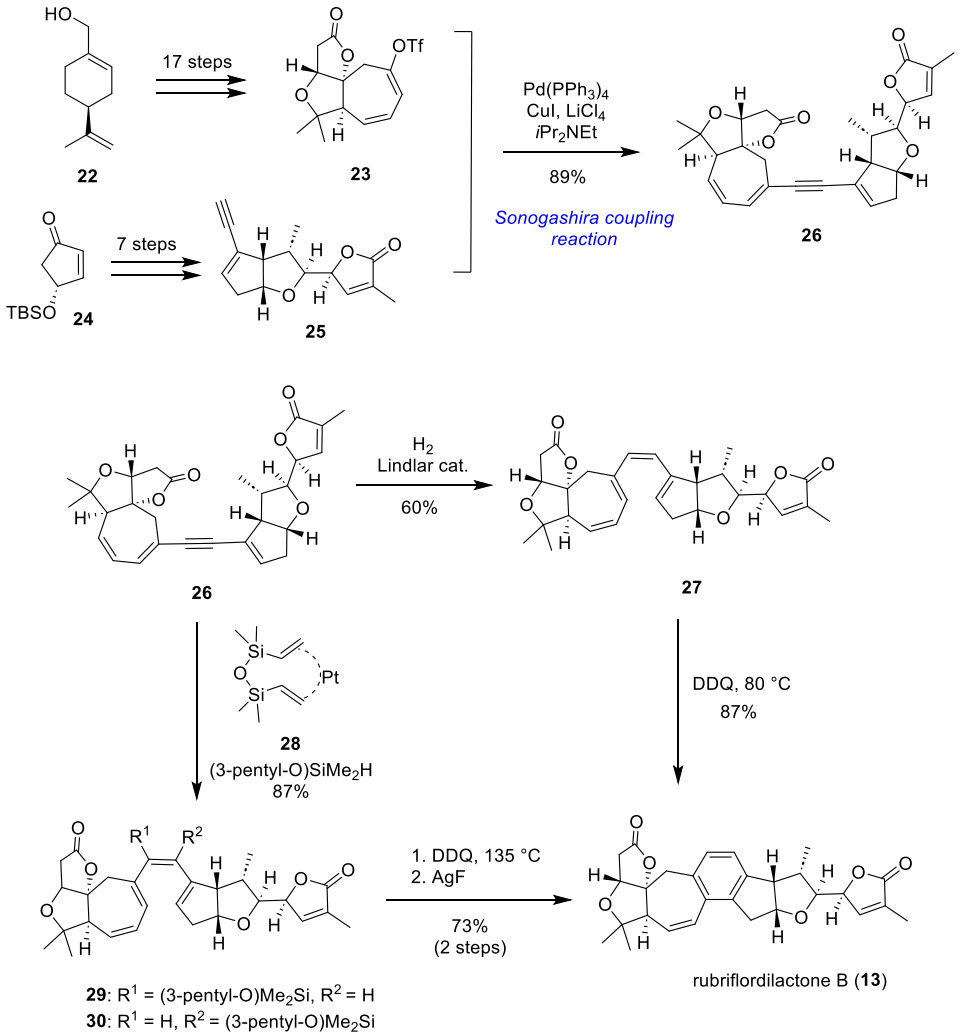
In 2014, the Li group reported the asymmetric total synthesis of **12** (Scheme 1.2).[13] Vinyl iodide **15** was synthesized using a five-step conversion starting with 2-iodocyclopent-2-en-1-one (**14**). A 13-step sequence starting with **16**, which was synthesized via a Diels-Alder reaction, gave the stannane **17**. The two synthesized fragments were connected via a Migita-Kosugi-Stille coupling reaction with a Pd catalyst to form **18**. Treating **18** with air at an elevated temperature facilitated an electrocyclization and aromatization to afford **19**. After conversion to fluoride **20**, a vinylogous Mukaiyama aldol reaction with siloxyfuran **21** resulted in the total synthesis of **12**.



Scheme 1.2 Total synthesis of rubriflordilactone A (Li group)[13]

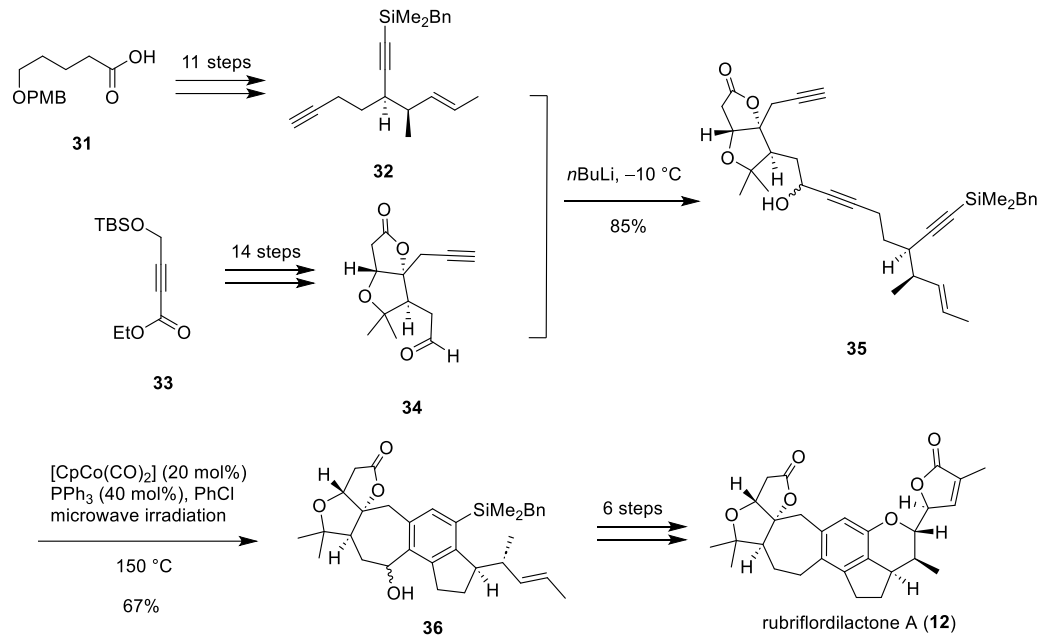
In 2016, the Li group also reported the asymmetric total synthesis of **13** (Scheme 1.3).[14] Triflate **23** was synthesized via a 17-step sequence starting with (−)-perillyl alcohol (**22**). Alkyne **25** was synthesized via a seven-step sequence using the known enone **24**, and the two synthesized fragments were connected via a Sonogashira coupling reaction to give **26**. Compound **26** was

converted to the *cis*-alkene using the Lindlar catalyst, followed by treatment with DDQ to realize the total synthesis of **13**. They also reported an alternative three-step synthesis due to the poor reproducibility of the conversion to the *cis*-alkene.



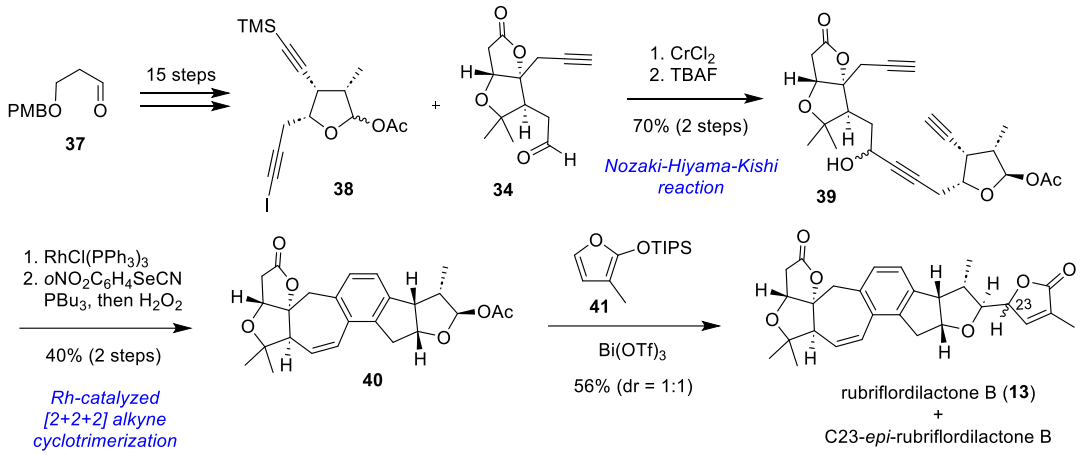
Scheme 1.3 Total synthesis of rubriflordilactone B (Li group)[14]

In 2015, the Anderson group reported the asymmetric total synthesis of **12** (Scheme 1.4).[15] Diyne **32** was synthesized via an 11-step sequence starting with the known carboxylic acid **31**, and furthermore, aldehyde **34** was synthesized via a 14-step sequence starting with the known ester **33**. The anion generated by base treatment of **32** reacted with aldehyde **34** to afford **35**. Treating **35** with a Co catalyst facilitated alkyne trimerization, producing **36**, with the simultaneous formation of three rings. The total synthesis of **12** was realized via a subsequent six-step sequence.



Scheme 1.4 Total synthesis of rubriflordilactone A (Anderson group)[15]

In 2019, the Anderson group also reported the asymmetric total synthesis of **13** (Scheme 1.5).[16]. Iodoalkyne **38** was synthesized via a 15-step sequence starting with the known aldehyde **37**, and the obtained **38** was then coupled with **34** via a Nozaki-Hiyama-Kishi reaction. Subsequently, the TMS group was removed to give the diyne **39**. Treating diyne **39** with Wilkinson's catalyst enabled alkyne cyclotrimerization, followed by dehydration to afford **40**. At this stage, the 5/5/7/6/5/5-fused ring system of **13** was successfully formed. The addition reaction of siloxyfran **41** using $Bi(OTf)_3$ as a Lewis acid gave **13** and C23-*epi*-rubriflordilactone B in a dr of 1:1. Additionally, they applied this synthetic strategy to successfully synthesize four other diastereomers.

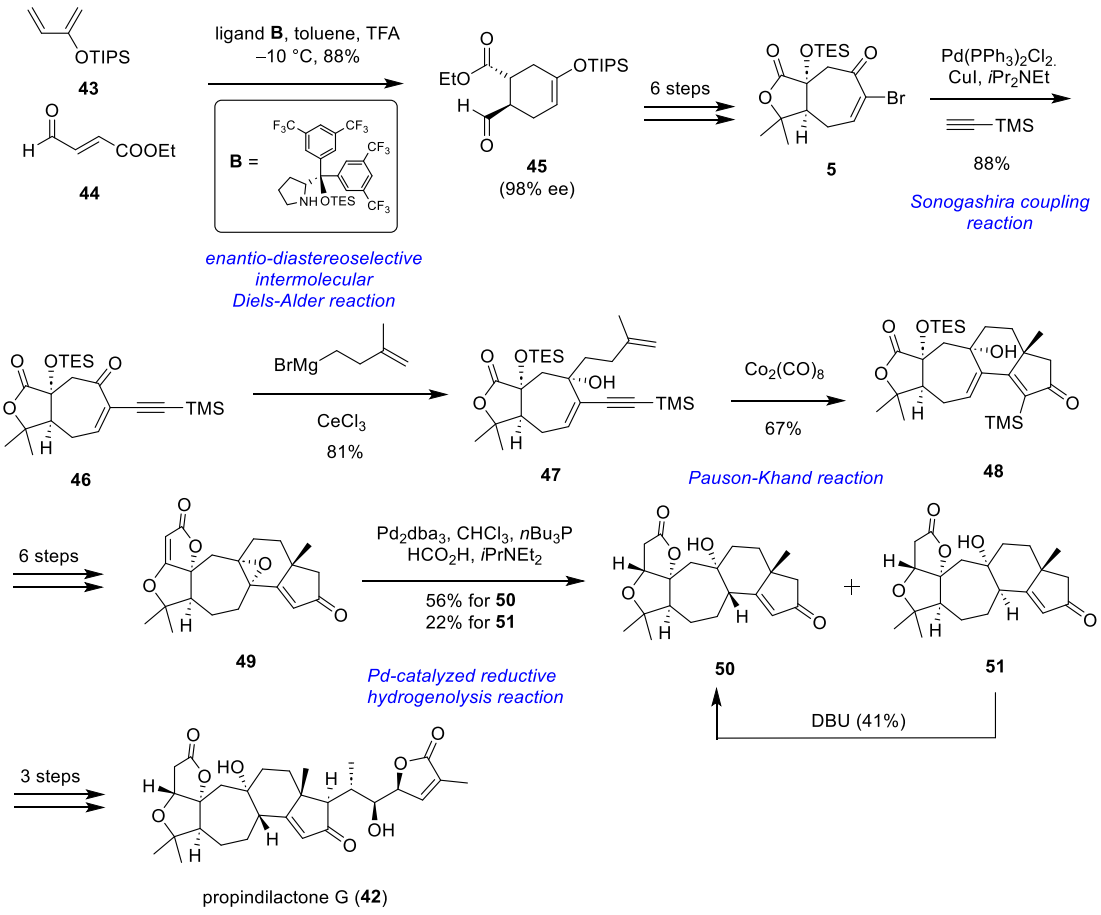


Scheme 1.5 Total synthesis of rubriflordilactone B (Anderson group)[16]

1.2.3 Propindilactone G

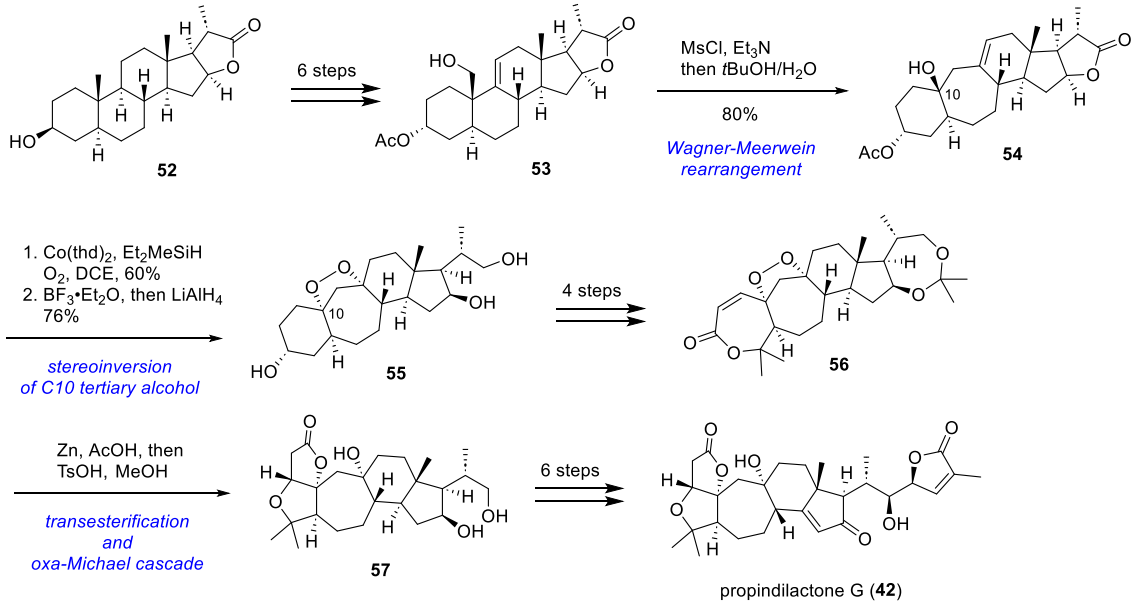
The asymmetric total synthesis of propindilactone G (**42**) was reported by the Yang group in 2015 (Scheme 1.6).[17] This SNT was isolated and structurally elucidated in 2008 although its biological activity was not described.[18] From a structural perspective, **42**, distinct from the other SNTs, contains a unique 5/5/7/6/5 pentacyclic core with seven stereocenters, three of which are quaternary centers.

Compound **45** was enantioselectively synthesized via an intermolecular Diels-Alder reaction using diene **43** and dienophile **44**. Via six steps, **5**, with a seven-membered ring, was obtained, followed by Sonogashira coupling, Grignard and Pauson-Khand reactions to afford tetracyclic compound **48**. After conversion to **49** via six additional steps, treating **49** with a Pd catalyst enabled reductive hydrogenolysis to give **50** and **51** in a combined yield of 78%. Additionally, treating **51**, which displayed the undesired stereochemistry, with DBU induced partial stereo inversion to access **50**. Finally, the total synthesis of (+)-**42** was realized via three additional transformations.



Scheme 1.6 Total synthesis of propindilactone G (Yang group)[17]

In 2020, the Gui group realized the enantioselective total synthesis of **42** (Scheme 1.7).[19] They employed **52**, with a steroid scaffold, as the starting material and established a synthetic route inspired by the biosynthetic pathway. Compound **52** was converted to **53** via a six-step sequence, and subsequent mesylation and treatment with *t*BuOH and H_2O facilitated the Wagner-Meerwein rearrangement to afford **54** with a seven-membered ring. Compound **54** was converted to a peroxysilyl alcohol via a hydroperoxylation using a Co catalyst, followed by treatment with $BF_3 \cdot Et_2O$ to generate endoperoxide **55**. Notably, stereoinversion of the tertiary alcohol at C10 was successfully achieved. Compound **55** was converted to **56** in four steps, and upon the reduction of the endoperoxide using Zn/acetic acid, the formation of a diol triggered a sequential transesterification followed by an oxa-Michael addition. Compound **57** was produced by removing the acetonide under the acidic conditions. At this stage, the 5/5/7/6/5-fused ring system of **42** was formed, and the total synthesis of **42** was realized via a further six-step sequence.

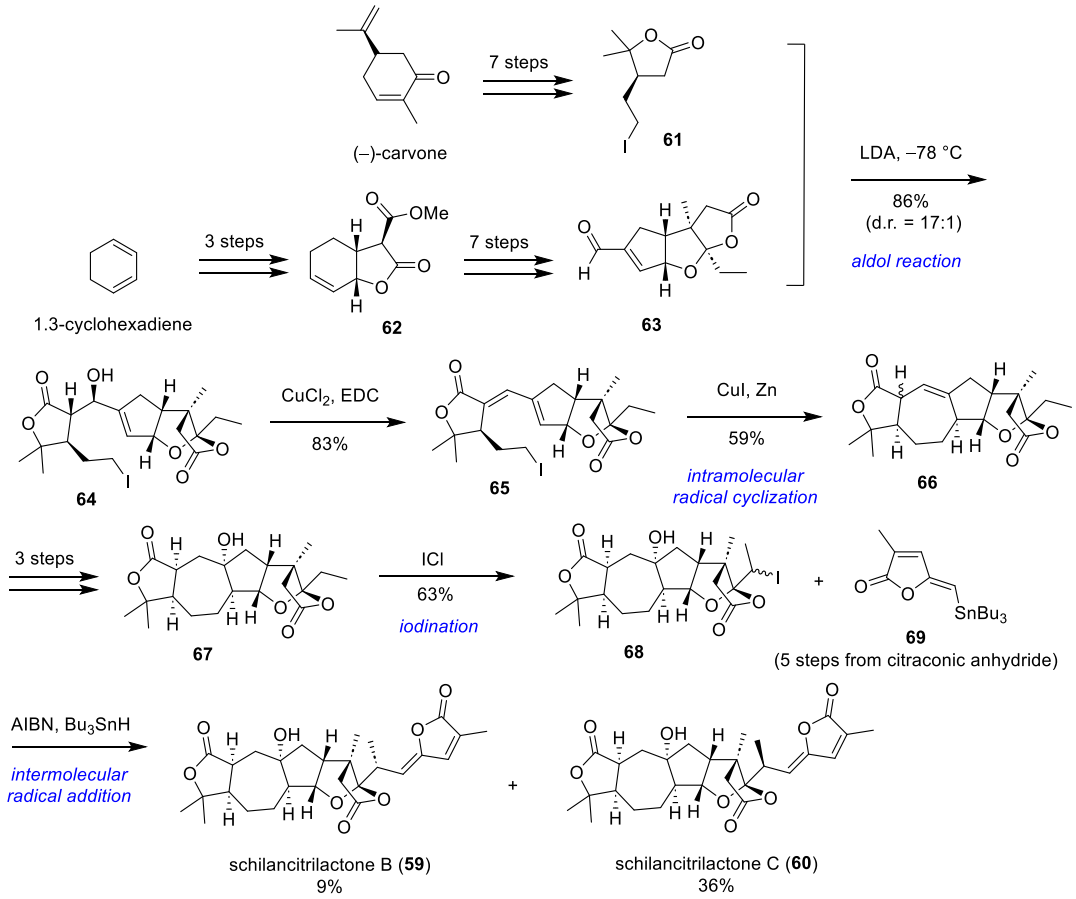


Scheme 1.7 Total synthesis of propindilactone G (Gui group)[19]

1.2.4 Schilancitrilactones A-C

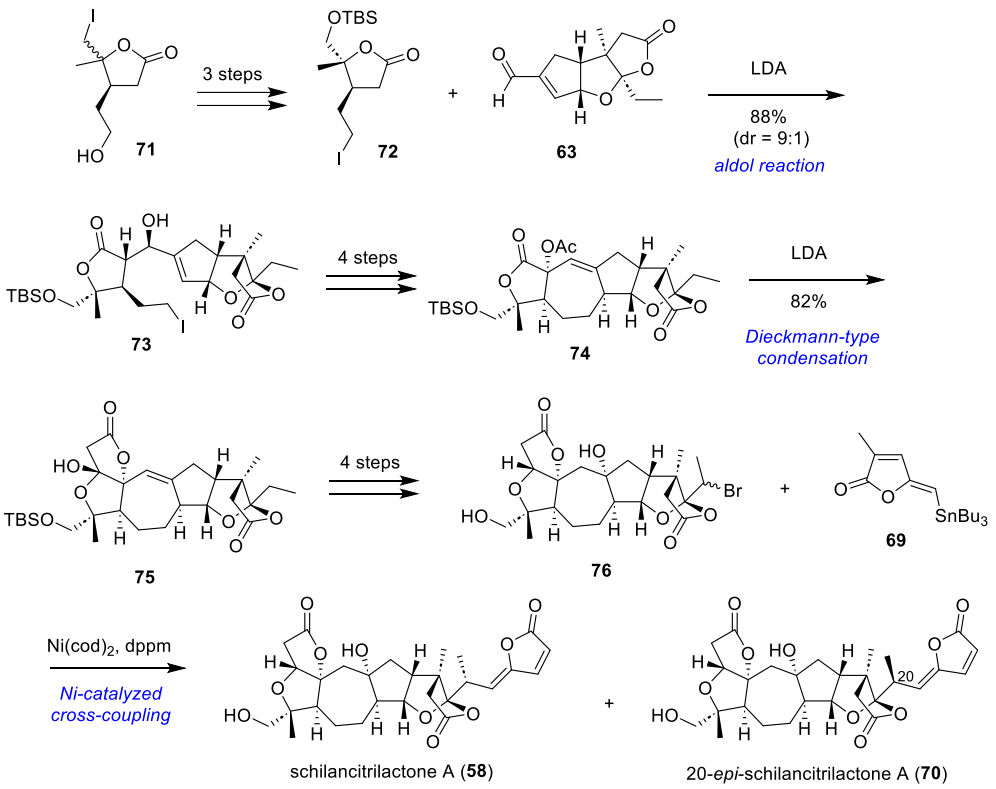
Schilancitrilactones A (**58**), B (**59**), and C (**60**) were isolated and structurally characterized in 2012.[20] The structures of these compounds are remarkable, featuring a 5/7/5/5/5-fused pentacyclic ring systems with nine stereocenters. Additionally, the three *cis*-fused five-membered rings, which adopt envelope conformations, along with seven contiguous stereocenters, contribute in forming a structurally rigid tricyclic ring system. Whereas no biological activity has been reported for SNT **59**, **58** and **60** display anti-feeding (EC_{50} = 16 μg/cm^2) and anti-HIV activities (EC_{50} = 28 μg/mL), respectively.

In 2015, the asymmetric total syntheses of **59** and **60** were reported by the Tang group (Scheme 1.8).[21] Initially, iodolactone **61** was synthesized from (−)-carvone, and optically active lactone **62**, which was produced using 1,3-cyclohexadiene, was transformed into aldehyde **63** in seven steps. Treating **61** with LDA was followed by the nucleophilic addition of the resulting lithium enolate to aldehyde **63** to form **64**, which was subsequently converted to **65** via dehydration. The intramolecular radical cyclization of **65** proceeded smoothly when treated with CuI and Zn to construct **66** with a seven-membered ring. After three additional transformations to give **67**, iodination followed by the coupling with the vinyl stannane **69** enabled the total syntheses of **59** and **60**.



Scheme 1.8 Total syntheses of schilancitrilactones B and C (Tang group)[21]

In addition, the enantioselective total syntheses of schilancitrilactone A (**58**) and 20-*epi*-schilancitrilactone A (**70**) were reported by the Tang group in 2017 (Scheme 1.9).[22] The known iodolactone **71** was converted in three steps to **72**, which was coupled with **63** to give **73**. Subsequent conversion in four steps gave **74**, which upon treatment with LDA resulted in Dieckmann-type condensation to afford **75** in an 82% yield. Further functionalization led to bromide **76**, and the total syntheses of **58** and **70** were realized via a cross-coupling reaction with **69** using a Ni catalyst.

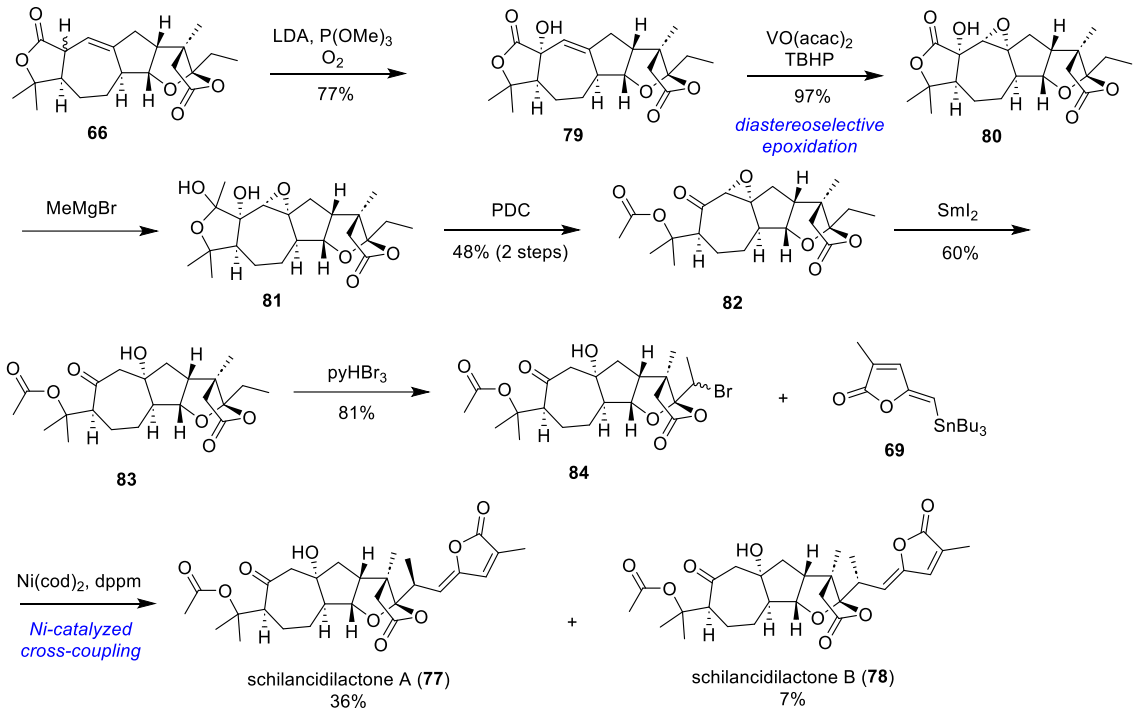


Scheme 1.9 Total synthesis of schilancitrilactones A (Tang group)[22]

1.2.5 Schilancidilactones A and B

Schilancidilactones A (**77**) and B (**78**) were isolated and structurally elucidated in 2009.[23] SNT **77** displays an anti-HIV activity (EC_{50} = 8.5 μg/mL), whereas no biological activity has been reported for **78**.

In 2017, the Tang group reported the enantioselective total syntheses of **77** and **78** (Scheme 1.10).[22] α-Hydroxylation of the known intermediate **66** gave **79**, which was converted to **82** via diastereoselective epoxidation, the addition of a methyl group, and oxidative cleavage of the diol using PDC. The reduction of the epoxide with SmI_2 and bromination led to the formation of **84**. Finally, the total syntheses of **77** and **78** were realized via a cross-coupling reaction with **69** using a Ni catalyst.



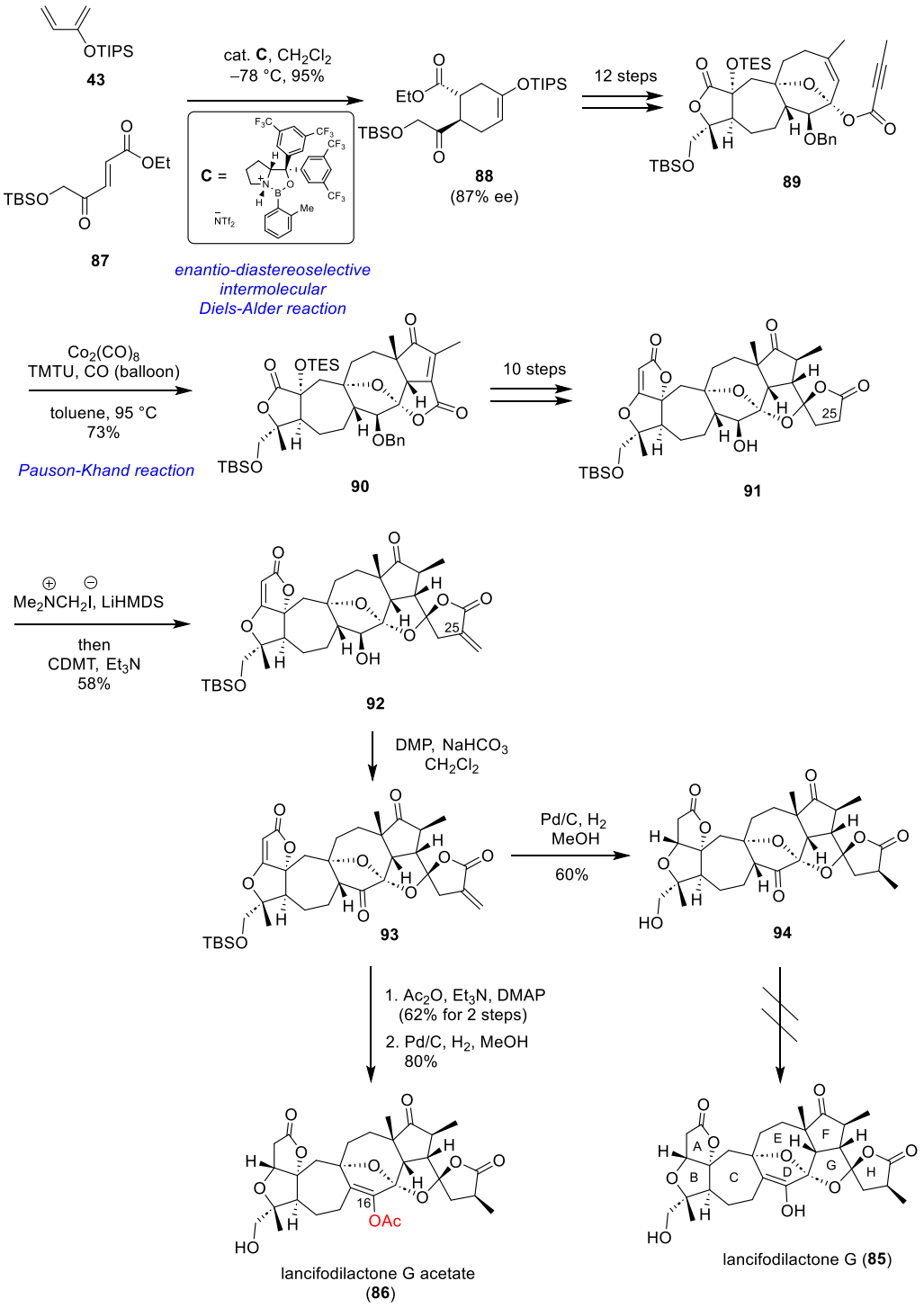
Scheme 1.10 Total syntheses of schilancidilactones A and B (Tang group)[22]

1.2.6 Lancifodilactone G

Lancifodilactone G (**85**) was isolated and structurally elucidated in 2005, with a reported anti-HIV activity (EC_{50} = 96 μg/mL).[24] Unlike the other members of the SNT family, **85** contains a CD ring that bears a rare nonresonance-stabilized aliphatic enol, and a highly congested FGH tricyclic ring system containing six contiguous stereocenters, and an unusual 2-fold anomerically stabilized bis-spiro system. Whereas the total synthesis of **85** has not yet been reported, the Yang group reported the enantioselective total synthesis of lancifodilactone G acetate (**86**) with the acetylation of the hydroxyl group at C16 in 2017.[25]

The intermolecular Diels-Alder reaction of diene **43** with dienophile **87** in the presence of organocatalyst **C** enantioselectively gave **88** (Scheme 1.11). Subsequently, **88** was converted to **89**, which was treated with $Co_2(CO)_8$ and TMTU under CO to form the hexacyclic framework **90**. Via a 10-step sequence, the octacyclic compound **91** was obtained, and a methylene group was introduced at C25 to give **92**. After oxidizing the secondary alcohol of **92** to obtain **93**, treating **93** with Pd/C under hydrogen atmosphere resulted in the simultaneous reduction of the olefin and removal of the TBS protecting group to give **94**, but enolization of **94** did not occur.

Therefore, **93** was acetylated to form the enol acetate, and the enantioselective total synthesis of **86** was realized via subsequent reduction and deprotection.



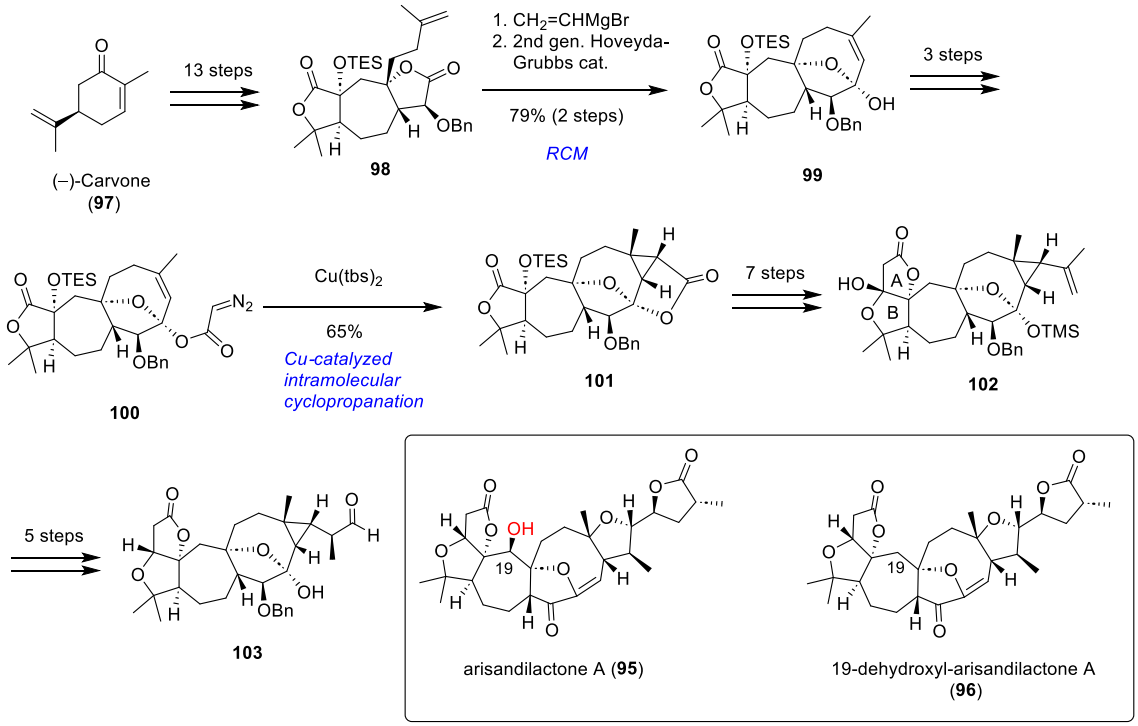
Scheme 1.11 Total synthesis of lancifodilactone G acetate (Yang group)[25]

1.2.7 Arisandilactone A

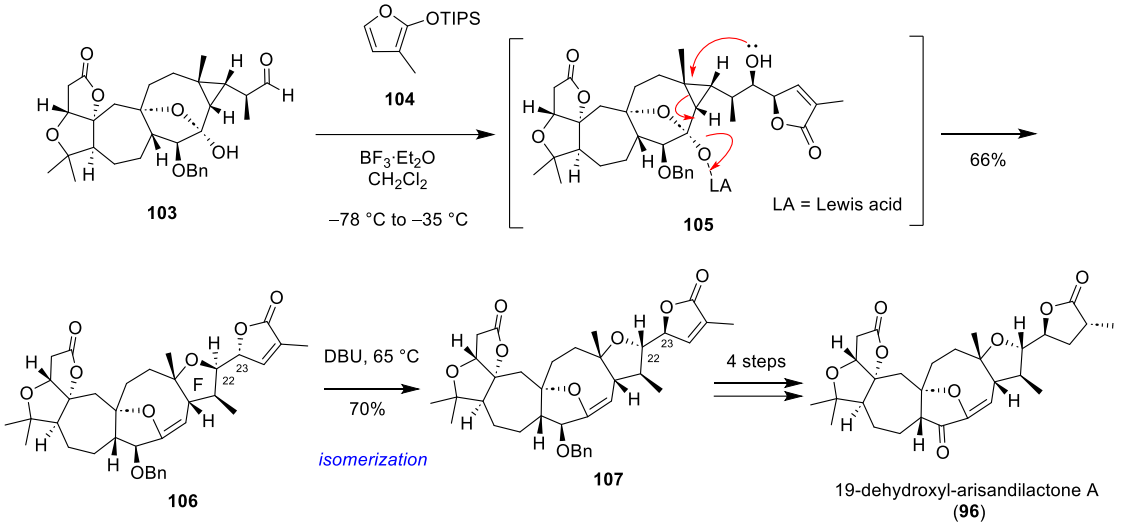
Arisandilactone A (**95**) was isolated and structurally elucidated in 2010, but its biological activity has not been reported.[26] Among the SNTs, **95** is unique in that it contains an oxa-bridged 7/9/5 tricyclic carbon core, which has not been previously observed in natural products. Although

the total synthesis of **95** has not yet been reported, the Yang group reported the enantioselective total synthesis of 19-dehydroxyl-arisandilactone A (**96**), which lacks the hydroxyl group at C19, in 2017.[27]

Compound **98** was obtained via a 13-step sequence from (–)-carvone (**97**, Scheme 1.12). After a Grignard reaction, treatment with a second generation Hoveyda-Grubbs catalyst produced **99** forming an eight-membered ring. Compound **99** was converted to the diazo compound **100**, which was treated over Cu catalyst to give **101** as a single diastereomer via intramolecular cyclopropanation. Compound **102** was obtained via a further seven-step transformation to construct ring A, and the subsequent five-step transformation generated aldehyde **103**. Subjecting **103** and silyloxyfuran **104** to the Mukaiyama aldol reaction conditions in the presence of $BF_3 \cdot Et_2O$ produced the aldol adduct **105**, which was followed by a cyclization involving the secondary alcohol, resulting in the formation of **106** containing ring F (Scheme 1.13). Treating **106** with DBU enabled the simultaneous isomerization of C22 and C23 to give the desired stereochemistry, and the enantioselective total synthesis of **96** was realized after four additional transformations.



Scheme 1.12 Synthesis of **103** and the structures of arisandilactone A and 19-dehydroxyl-arisandilactone A[27]

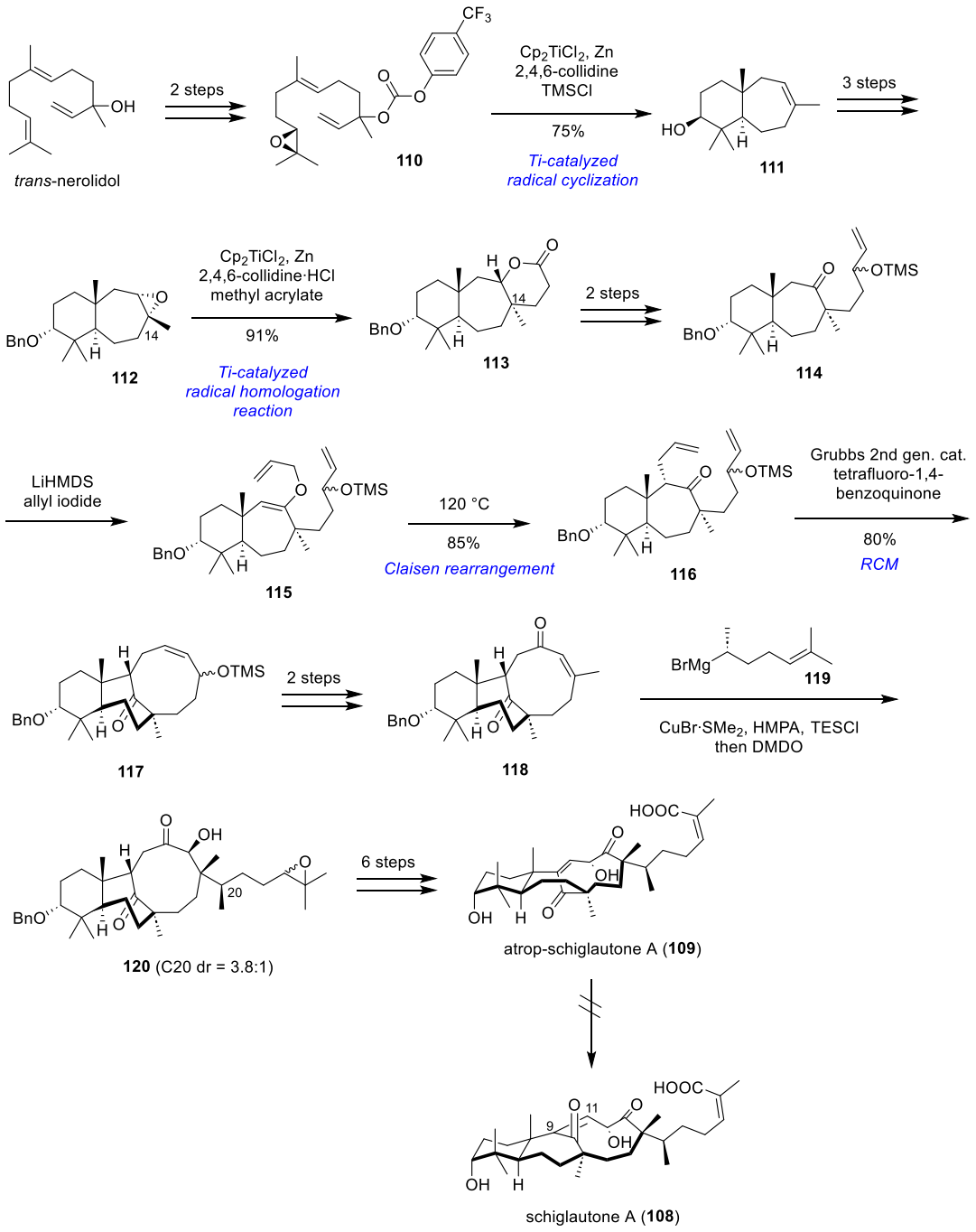


Scheme 1.13 Total synthesis of 19-dehydroxyl-arisandilactone A (Yang group)[27]

1.2.8 Schiglautone A

Schiglautone A (**108**) was isolated and structurally elucidated in 2011, but its biological activity has not been reported.[28] SNT **108** exhibits a cyclohexyl-fused bicyclo[6.4.1]tridecane carbon framework, featuring an uncommon bridgehead $\Delta^{9,11}$-alkene and six stereogenic centers, three of which are quaternary centers. Although the total synthesis of **108** has not yet been reported, the Ding group reported the total synthesis of the atropisomer **109** in 2018.[29]

Compound **110** was obtained in two steps from *trans*-nerolidol and subjected to a radical cyclization reaction using trivalent Ti to selectively synthesize **111**, forming the 6/7-membered fused-ring system (Scheme 1.14). Compound **111** was then converted in three steps to epoxide **112**, which was reacted with methyl acrylate to afford lactone **113**, successfully realizing homologation. The desired stereochemistry at C14 was inverted during this radical reaction. After two additional transformations to generate **114**, the Claisen rearrangement of the allylated compound **115** introduced an allyl group at the α-position of the ketone. Subsequently, using a second-generation Grubbs catalyst, RCM gave **117** to establish the strained nine-membered ring structure within the natural product. Compound **118** was furnished via two additional steps, and the Michael addition of Grignard reagent **119** to **118** provided **120** with a good diastereoselectivity. A similar scaffold to that of the natural product was then formed via six steps. However, the NMR spectrum of the synthetic product did not match that of the natural compound. X-ray crystallography revealed that the synthesized compound was not the natural product **108** but the atropisomer **109** and various attempts to convert atropisomer **109** to **108** were unsuccessful.

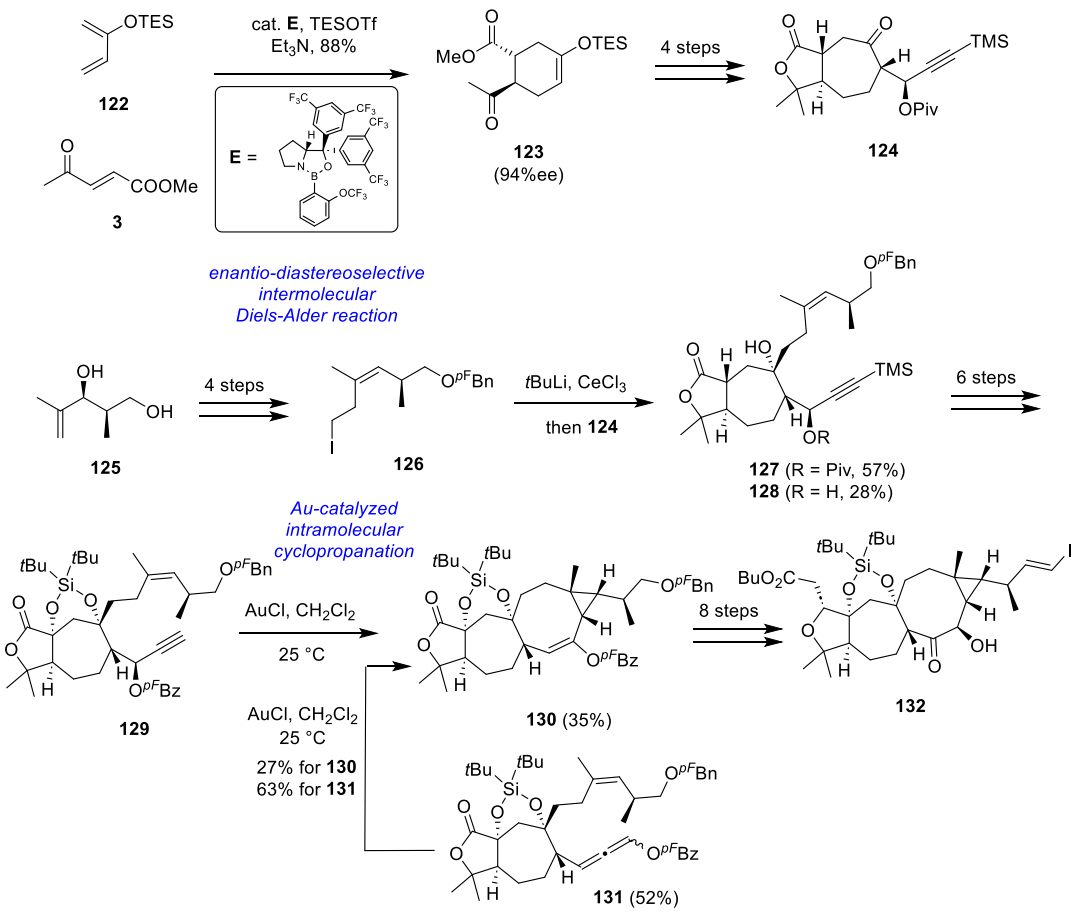


Scheme 1.14 Total synthesis of atrop-schiglautone A (Ding group)[29]

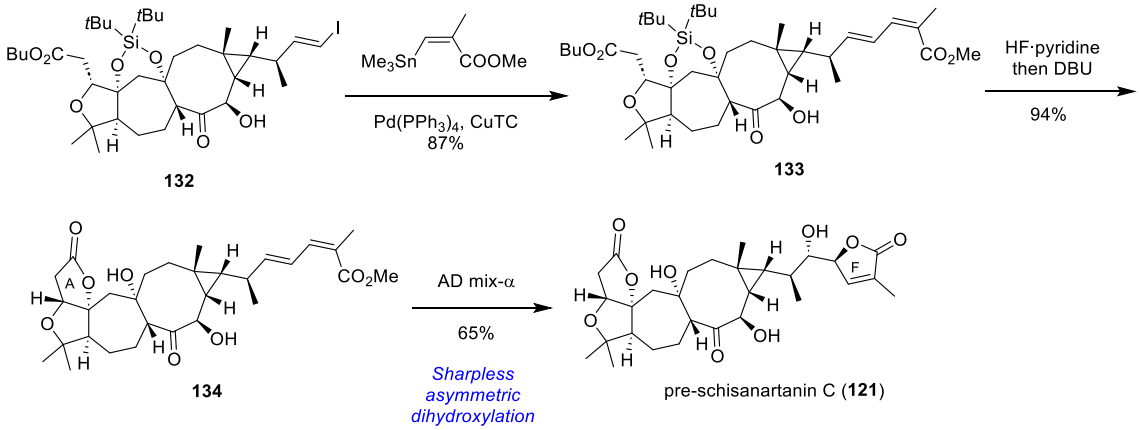
1.2.9 Pre-schisanartanin C

The total synthesis of pre-schisanartanin C (**121**) was reported by the Yang group in 2020.[30] This is the first total synthesis of a SNT with an all-*cis*-substituted cyclopropane. SNT **121** was isolated and structurally characterized in 2010, but its biological activity has not been described.[31]

Using diene **122** and dienophile **3**, compound **123** was enantioselectively synthesized via an intermolecular Diels-Alder reaction (Scheme 1.15), and it was then transformed into **124** via four steps. Compound **127** was obtained via the anion coupling of **124** with iodide **126**, which was generated in four steps from the known optically active diol **125**. Byproduct **128** was also produced in the anion coupling reaction via the removal of the pivaloyl group. Compound **129** was synthesized via a six-step sequence, followed by treatment with an Au catalyst to afford **130**, establishing the all-*cis*-substituted cyclopropane structure, albeit in a low yield. The allene byproduct **131** was also obtained, but it could be partially converted to the desired product **130** via treatment with an Au catalyst. Vinyl iodide **132** was synthesized from **130** in eight steps and then converted to **133** via Stille coupling with a vinylstannane compound (Scheme 1.16). The Yang group employed this route due to the undesired stereochemistry observed in intermediate **106** during the synthesis of **96** via the Mukaiyama aldol reaction (Scheme 1.13). After the removal of the silyl group of **133** and the formation of the A-ring lactone, Sharpless asymmetric dihydroxylation led to the formation of the F-ring lactone, realizing the enantioselective total synthesis of **121**.



Scheme 1.15 Synthesis of **132**[30]



Scheme 1.16 Total synthesis of pre-schisanartanin C (Yang group)[30]

Section 3 All-*cis*-substituted cyclopropane

1.3.1 Total syntheses of natural products containing an all-*cis*-substituted cyclopropane rings

The all-*cis*-substituted cyclopropane ring exhibits a configuration where all substituents on the cyclopropane ring are located on the same side of the ring, and its formation is considered challenging due to the distorted framework (Fig. 1.3). Several natural products with significant biological activities display this unique structure, which renders the establishment of synthetic strategies for use in its formation critical in the field of organic synthesis. This section presents an overview of the total syntheses of natural products with all-*cis*-substituted cyclopropane rings and their synthetic strategies. Notably, the total synthesis of **121** is analyzed above, and it is thus omitted from this section.

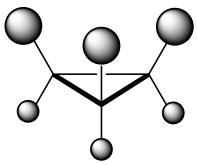


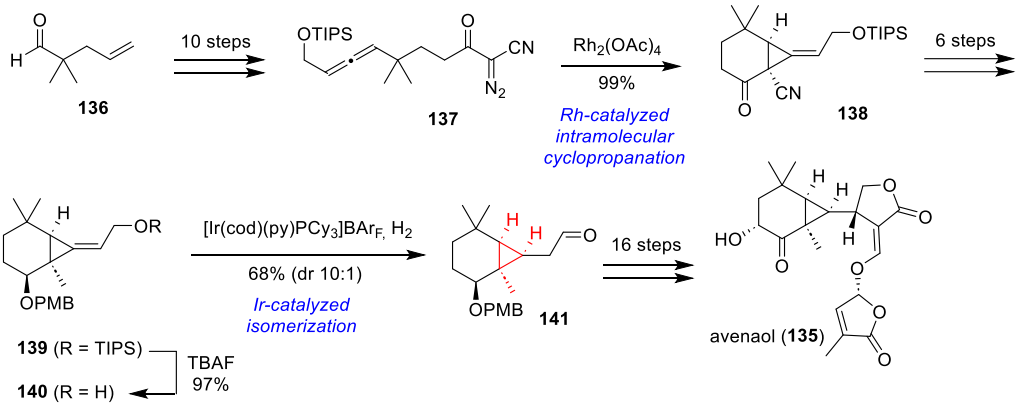
Fig. 1.3 Schematic diagram of an all-*cis*-substituted cyclopropane ring

1.3.1.1 Avenaol

Avenaol (**135**) is a strigolactone that was isolated and structurally elucidated in 2014, and it exhibits germination-stimulating activity toward the seeds of plants such as *Striga*.[32] In 2017, the total synthesis of avenaol was reported by the Takemoto group.[33,34] This is the first total synthesis of a natural product with an all-*cis*-substituted cyclopropane ring.

The synthesis commenced from the known aldehyde **136** to form diazoketone **137** in 10 steps (Scheme 1.17). Upon treatment with $Rh_2(OAc)_4$, intramolecular cyclopropanation afforded alkylidenecyclopropane **138**. After six additional transformations, compound **139** was obtained,

and it was then transformed into **140** by removing the TIPS group. Treating **140** with Crabtree's catalyst resulted in an isomerization to give **141** with the desired all-*cis*-substituted cyclopropane and an excellent diastereoselectivity. The total synthesis of **135** was realized by employing a series of 16 additional transformations without disrupting the all-*cis*-substituted cyclopropane moiety.



Scheme 1.17 Total synthesis of avenaol (Takemoto group)[33]

Yasui extensively investigated the isomerization of the alkylidenecyclopropane in the total synthesis of avenaol, (Scheme 1.18A, Table 1.1).[34] Treating nitrile **138** with Crabtree's catalyst under hydrogen atmosphere did not give any product (entry 1). Conversely, when the alcohol **142** was used as the substrate, the isomerization of the olefin proceeded smoothly, affording the enol ether **144** in an 89% yield as a single diastereomer (entry 2). However, the derivatization of **144** was challenging due to side reactions, such as cyclopropane ring-opening. Therefore, they further investigated the isomerization using deoxygenated compound **139**, which was converted to a methyl derivative. The isomerization product **145** was only obtained in trace amounts, and the selectivity was low (entry 3). When allylic alcohol **140**, with the TIPS group removed, was examined, the yield increased, but no significant improvement in selectivity was observed (entry 4). To enhance the yield and selectivity, the counteranion BAr_F,[35] which did not coordinate to the Ir catalyst, was employed, successfully realizing an improved selectivity of up to 10:1 *cis*/*trans* (entry 5).

Furthermore, Yasui analyzed the diastereoselectivity of this isomerization as follows. Crabtree's catalyst coordinates to functional groups such as hydroxyl groups and ether oxygen atoms to promote isomerization.[35] This was supported by the complete *cis* selectivity observed using alcohol **142** and the low reactivity observed using the deoxygenated compound **139** (Scheme 1.18A, Table 1.1, entries 2, 3). Similarly, the hydroxyl group might act as a directing group when the allylic alcohol **140** was used as the substrate, but the use of Crabtree's catalyst did not result in a sufficient selectivity (entry 4). Conversely, BAr_F enabled stronger coordination of the corresponding metal center, and thus, one reason for the improved selectivity was the stronger interaction with the directing group. When the allylic alcohol **140** was used as the substrate, two intermediates, **X1** or **X2** may be considered based on the direction of double bond

coordination (Scheme 1.18B). In intermediate **X2**, the bulky ligand of the Ir catalyst may undergo steric repulsion with the PMB group, rendering the pathway via **X1** more favorable.

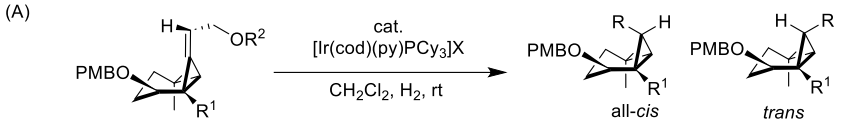
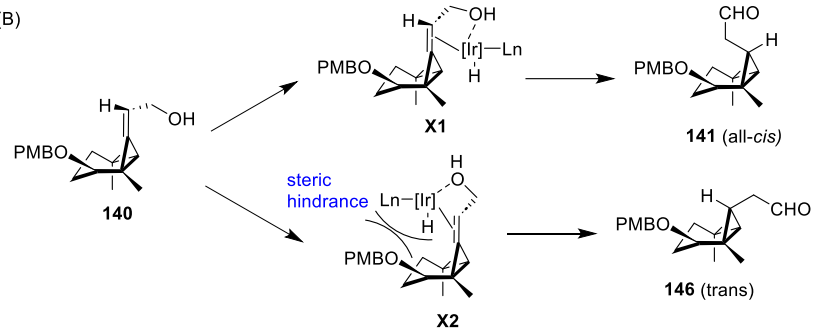


Table 1.1 Formation of the all-*cis*-substituted cyclopropane

Entry	SM	R^1	R^2	X	Product: R	Yield (all-*cis* : *trans*)[a]
1	**138**	CN	TIPS	PF_6	**143**: OTIPS	No reaction
2	**142**	CH_2OH	TIPS	PF_6	**144**: OTIPS	89% (all-*cis* only)
3	**139**	Me	TIPS	PF_6	**145**: OTIPS	6% (2.3 : 1)[b]
4	**140**	Me	H	PF_6	**141**: O	61% (2.7 : 1)
5	**140**	Me	H	BAr_F	**141**: O	68% (10 : 1)

[a] The ratio was estimated using ^{1}H NMR spectroscopy. [b] **139** (64%) was recovered.



Scheme 1.18 Formation of the all-*cis*-substituted cyclopropane structure of avenaol[34]
(A) Conditions of isomerization using the Ir catalyst
(B) Mechanism of diastereoselectivity

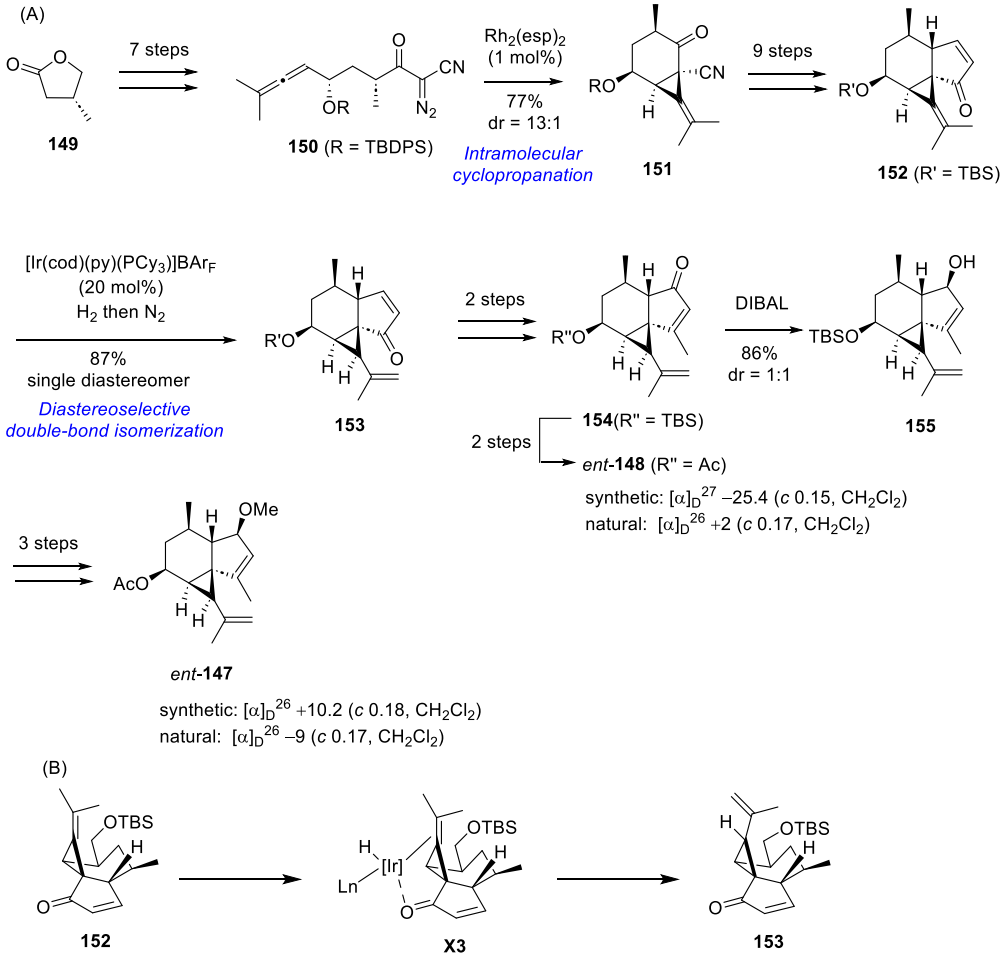
1.3.1.2 Shagenes A and B

Shagenes A (**147**) and B (**148**) are sesquiterpenes isolated from a soft coral in 2014.[36] Natural product **147** exhibits an antiparasitic activity against *Leishmania donovani*, which is the parasite responsible for leishmaniasis, with an IC_{50} of 5 μM. This activity is comparable to that of the currently used drug miltefosine (IC_{50} = 3 μM). Conversely, **147** displays no toxicity at 345 μM against J774.A1 mouse macrophage-like cells, indicating its high selectivity and potential as a novel lead compound. In 2021, the enantiomeric total syntheses of **147** and **148** were reported by the Takemoto group, revealing the absolute stereochemistries of the shagenes that had not been previously elucidated.[37]

Diazoketone **150** was synthesized in seven steps starting with the known lactone **149** (Scheme 1.19A). The intramolecular cyclopropanation of **150** proceeded, reselting in a good yield of the alkylidenecyclopropane **151**, with a good diastereoselectivity. After nine additional steps to

produce **152**, isomerization proceeded over an Ir catalyst, yielding the all-*cis*-substituted cyclopropane **153** with a high diastereoselectivity. After two steps to generate **154**, **148** was synthesized by replacing the TBS group with an acetyl group. Furthermore, **147** was synthesized via a three-step conversion from **155**, which was prepared via the reduction of **154**. Based on the optical rotations of the synthetic products compared to those of the natural compounds, the synthetic products were the enantiomers.

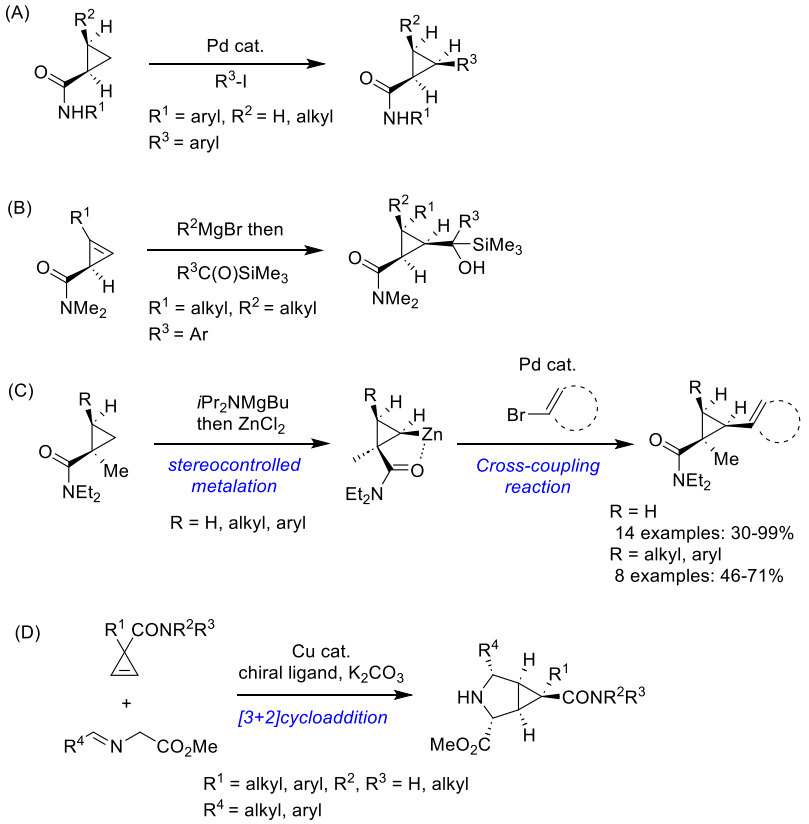
Additionally, isomerization starting with **152** may proceed stereoselectively to form the all-*cis*-substituted cyclopropane due to the coordination of the Ir catalyst to the carbonyl oxygen of the ketone (Scheme 1.19B). This is a unique aspect of this study, because no isomerization of tetrasubstituted olefins with a ketone as the directing group are reported.



Scheme 1.19 Total synthesis of shagenes A and B (Takemoto group)[37]
(A) Total syntheses
(B) Isomerization using an Ir catalyst

1.3.2 Synthetic strategies used in forming all-*cis*-substituted cyclopropane rings

Other strategies used in forming all-*cis*-substituted cyclopropane rings are briefly introduced here. Pd-catalyzed C-H functionalization of a cyclopropane ring to give a *cis*-substituted cyclopropane structure has been reported (Scheme 1.20A).[38-40] The Marek group reported the formation of an all-*cis*-substituted cyclopropane via carbometalation followed by the addition of acylsilane via carbometalation (Scheme 1.20B).[41,42] In 2018, the Takemoto group reported the formation of all-*cis*-substituted cyclopropanes via stereocontrolled metalation followed by Negishi coupling (Scheme 1.20C).[43] In this reaction, an intermediate with Zn coordinated to the carbonyl oxygen of the amide is formed to enable the reaction to proceed selectively on the same face as the amide. Using this strategy, they successfully synthesized 14 *cis*-substituted cyclopropanes and eight all-*cis*-substituted cyclopropane compounds. Additionally, Cu-catalyzed desymmetrization/cycloaddition of 1,1-disubstituted cyclopropenes to give aza bicyclo[3.1.0]hexane-based heterocycles containing cyclopropane and pyrrolidine motifs was reported by the Xu group (Scheme 1.20D).[44]



Scheme 1.20 Synthetic strategies used in forming all-*cis*-substituted cyclopropane rings
(A) C-H functionalization (B) Carbometalation and addition of acylsilane
(C) Negishi coupling (D) [3+2] Cycloaddition

Section 4　Purpose of this study

1.4.1　Pre-schisanartanin A

Pre-schisanartanin A is a triterpenoid isolated from *Schisandra chinensis* by the Sun group in 2007　(Fig. 1.4).[11] Structurally, it exhibits the following characteristics: 1) a unique pentacyclic framework formed by the fusion of 5/5/7/8/3-membered rings, 2) six or seven consecutive stereocenters, 3) a highly oxygenated seven-membered ring and 4) an all-*cis*-substituted cyclopropane structure. Although this compound displays an anti-HIV activity (EC_{50} = 14 μg/mL),[11] the mechanism remains unclear, and no studies regarding the total synthesis or structure-activity relationships have been reported.

1.4.2　Purpose of this study

As pre-schisanartanin A (Fig. 1.4) exhibits an anti-HIV activity, elucidating the mechanism of action and structure-activity relationships studies should contribute considerably in developing HIV drugs. In addition, as this SNT is isolated from *Schisandra chinensis*, which has been used as a herbal medicine for a long time, it should display low toxicities toward mammals, and pre-schisanartanin A exhibits a high potential as an anti-HIV drug lead. However, its complex structure renders the derivatization of the natural product challenging, and chemical synthesis is essential for structure-activity relationship studies using this SNT. In this study, we aimed to establish an asymmetric synthetic route toward pre-schisanartanin A. Although the total syntheses of several SNTs have been reported (Chapter 1, Section 2), the total synthesis of a highly oxygenated SNT with a hydroxyl group at C19 on its seven-membered ring has not yet been reported, and developing a novel synthetic strategy is essential.

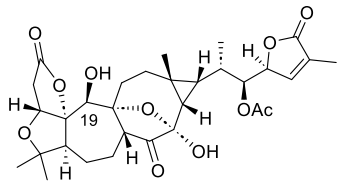
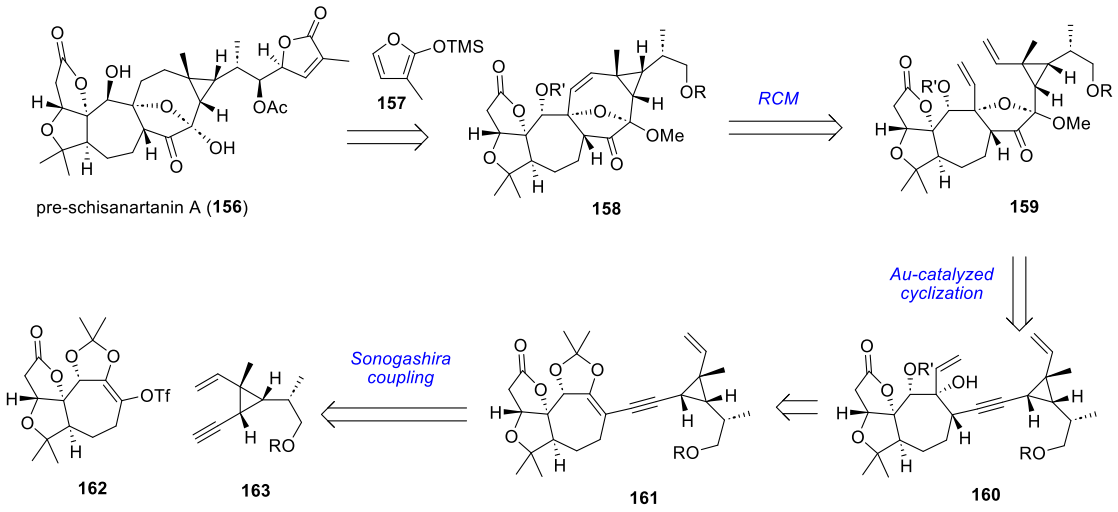


Fig. 1.4　Structure of pre-schisanartanin A

Chapter 2　Synthetic studies of pre-schisanartanin A

Section 1　Retrosynthetic analysis

We designed a convergent route for the enantioselective total synthesis of pre-schisanartanin A (**156**) utilizing triflate unit **162**, alkyne unit **163**, and butenolide unit **157** (Scheme 2.1). Natural product **156** should be accessed using **158**, and the eight-membered ring structure of **158** should be formed using **159** via RCM. Compound **159** should be derived from **160** via intramolecular cyclization catalyzed by an Au catalyst. Compound **160** should be synthesized in several steps from **161**, which is obtained via Sonogashira coupling involving **162** and **163**.



Scheme 2.1　Retrosynthesis of pre-schisanartanin A

Section 2　Synthesis of the left-hand fragment*

2.2.1　Retrosynthetic analysis of **162**

The retrosynthetic analysis of left-hand fragment **162** is presented below (Scheme 2.2). The highly oxygenated seven-membered ring structure of **162** should be accessed starting with D-ribose, and **162** should be directly derived from tetracyclic compound **164**. The synthesis of **164** was proposed to stem from isoxazoline **165**, which should be synthesized via the [3+2]

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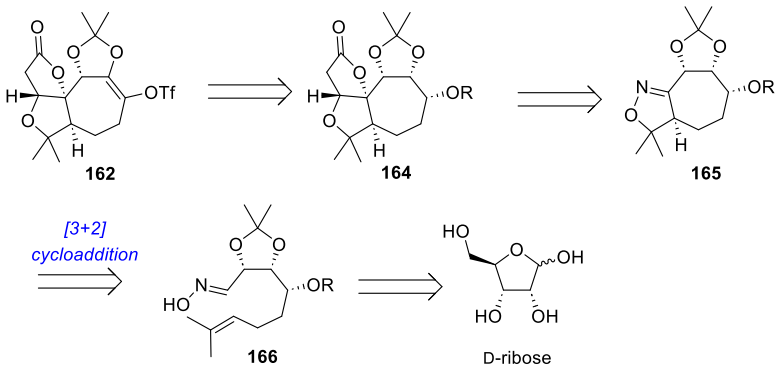
* The content described in this section was originally published in the *European Journal of Organic Chemistry*. Ryotaro Yagita, Kazuhiro Irie and Chihiro Tsukano, Studies Toward the Total Synthesis of Schinortriterpenoids: Diastereoselective Synthesis of the Left-Hand Fragment. *Eur. J. Org. Chem.* **2021**, *2021*, 4269–4272. © 2021 Wiley-VCH GmbH.

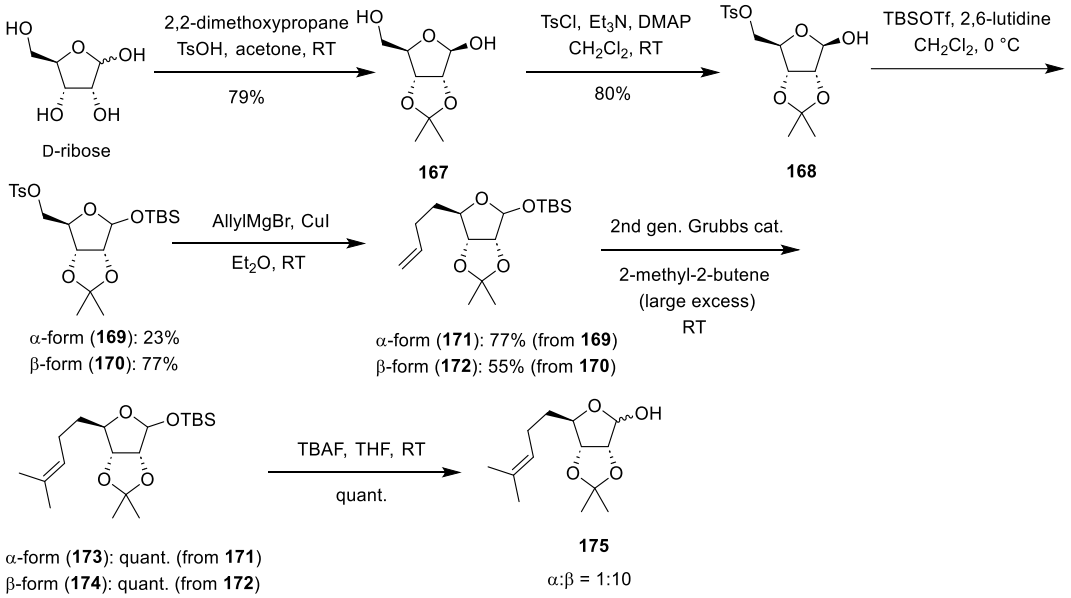
cycloaddition reaction of oxime-olefin **166**. Compound **166** should be prepared using D-ribose.



Scheme 2.2 Retrosynthetic analysis of left-hand fragment **162**

2.2.2 Synthesis of hemiacetal **175**

As shown in the retrosynthetic analysis (Scheme 2.2), we aimed to synthesize oxime **166**, which should be a precursor for use in intramolecular [3+2] cycloaddition. The known compound **168** was synthesized via a two-step sequence using D-ribose (Scheme 2.3).[45] The silylation of **168** proceeded quantitatively, affording the α- and β-isomer in 23% and 77% yields, respectively. Subsequent allylation and a cross-metathesis reaction using a second-generation Grubbs catalyst and 2-methyl-2-butene gave **173** and **174**.[46] Upon treatment of the obtained **173** and **174** with TBAF, desilylation of the α- and β-isomers proceeded quantitatively to give hemiacetal **175** as an anomeric mixture (α:β = 1:10).

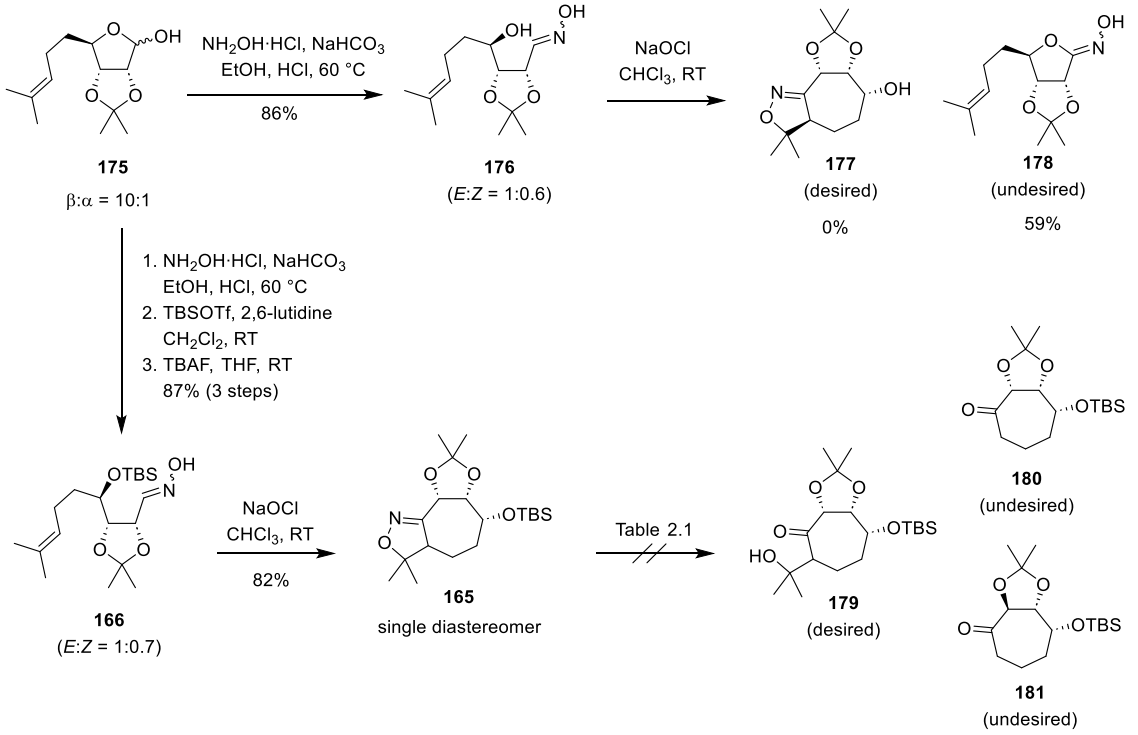


Scheme 2.3 Synthesis of hemiacetal **175**

2.2.3 [3+2] Cycloaddition of the trisubstituted olefin and reductive ring-opening

The conversion of **175** to oxime **176,** followed by treatment with NaOCl, afforded only **178**, with a five-membered ring, in a 59% yield, rather than the isoxazoline **177** expected from the [3+2] cycloaddition (Scheme 2.4). Therefore, **166** was synthesized with the secondary hydroxyl group protected as a TBS ether. Treating **166** with NaOCl led to the desired [3+2] cycloaddition, affording isoxazoline **165** as a single diastereomer.

Subsequently, we investigated the conditions for the transformation of the obtained isoxazoline **165** into the β-hydroxyketone **179** (Table 2.1). Treatment with Ti(O*i*Pr)$_4$ and ethylmagnesium bromide (entry 1),[47] and hydrogenation using Raney-Ni (W-2) (entry 2), resulted in the decomposition of the starting material. The reduction conditions with B(OH)$_3$ as a buffer did not give the desired product **179**, with Raney-Ni or Pd/C as the catalyst,[48] but instead only **180** with acetone released via a retro-aldol reaction (entries 3, 4). Treatment with Mo(CO)$_6$ led to the formation of **180** and the diastereomeric ketone **181** (entry 5).[49] Employment Fe in the reduction afforeded only **180** (entry 6),[50] and the use of B(OH)$_3$ or Al/CuCl$_2$ resulted in no reaction, with the starting material recovered (entries 7, 8).[51]

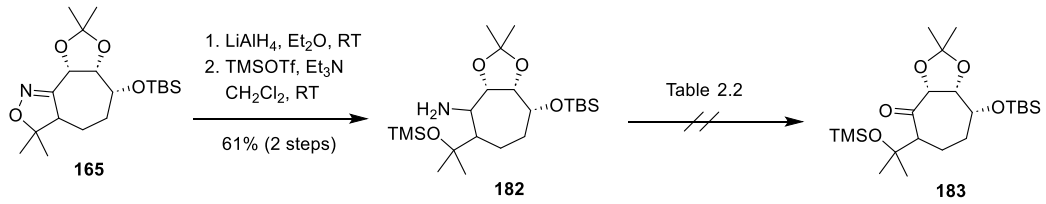


Scheme 2.4 Synthesis of oxime **166** and [3+2] cycloaddition

Table 2.1 Reduction of isoxazolin **165**

Entry	Conditions	Results
1	$Ti(OiPr)_4$, EtMgBr, RT	decomp.
2	Raney Ni (W-2), H_2, MeOH, RT	decomp.
3	Raney Ni (W-2), $B(OH)_3$, H_2 $MeOH:H_2O$ = 5:1, 45 °C	**165** (28%), **179** (0%), **180** (56%), **181** (0%)
4	Pd/C, $B(OH)_3$, H_2 $MeOH:H_2O$ = 5:1, 45 °C	**165** (54%), **179** (0%), **180** (19%), **181** (0%)
5	$Mo(CO)_6$ $MeCN:H_2O$ = 10:1, 90 °C	**165** (0%), **179** (0%), **180** (54%), **181** (16%)
6	Fe, NH_4Cl, $EtOH:H_2O$ = 1:1, 80 °C	**165** (66%), **179** (0%), **180** (23%), **181** (0%)
7	$B(OH)_3$, $MeOH:H_2O$ = 5:1, 50 °C	no reaction
8	Al, $CuCl_2{\cdot}2H_2O$, $EtOH:H_2O$ = 2:1, RT	no reaction

Due to the challenge of directly converting the isoxazoline to the β-hydroxyketone, we explored an alternative pathway involving reduction to the amino alcohol and subsequent oxidation of the amine to the ketone (Scheme 2.5). Isoxazoline **165** was treated with $LiAlH_4$, and the resulting amino alcohol was converted to **182** by treating it with TMSOTf and Et_3N. Subsequently, the oxidation of **182** to ketone **183** was investigated. Treatment with 3,5-di-*tert*-butyl-1,2-benzoquinone and oxalic acid led to the formation of a complex mixture (Table 2.2, entry 1).[52] Similar outcomes were observed using $(BzO)_2$ and Cs_2CO_3,[53] or ascorbic acid with a Cu catalyst (entries 2, 3).[54] Treatment with 4-formyl-1-methylpyridinium benzenesulfonate, DBU, and citric acid resulted in the recovery of the starting material (entry 4).[55]



Scheme 2.5 Synthesis of ketone **183**

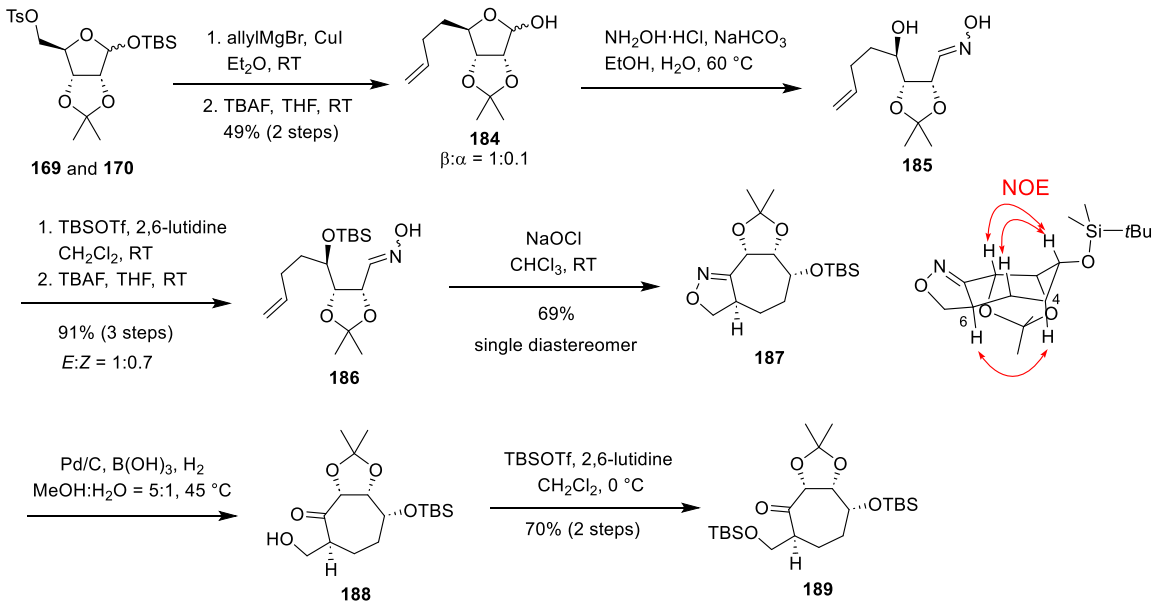
Table 2.2 Oxidation of the amine to the ketone

Entry	Conditions	Results
1	3,5-di-*t*Bu-1,2-benzoquinone $(COOH)_2$, $MeOH:H_2O$ = 1:1, RT	complex mixture
2	$(BzO)_2$, Cs_2CO_3, DMF, 50 °C	complex mixture
3	ascorbic acid, Cu(I) 3-methylsalicylate DMA, 80 °C	complex mixture
4	4-formyl-1-methylpyridinium benzenesulfonate $DMF:CH_2Cl_2$ = 1:1, RT then DBU, citric acid	no reaction

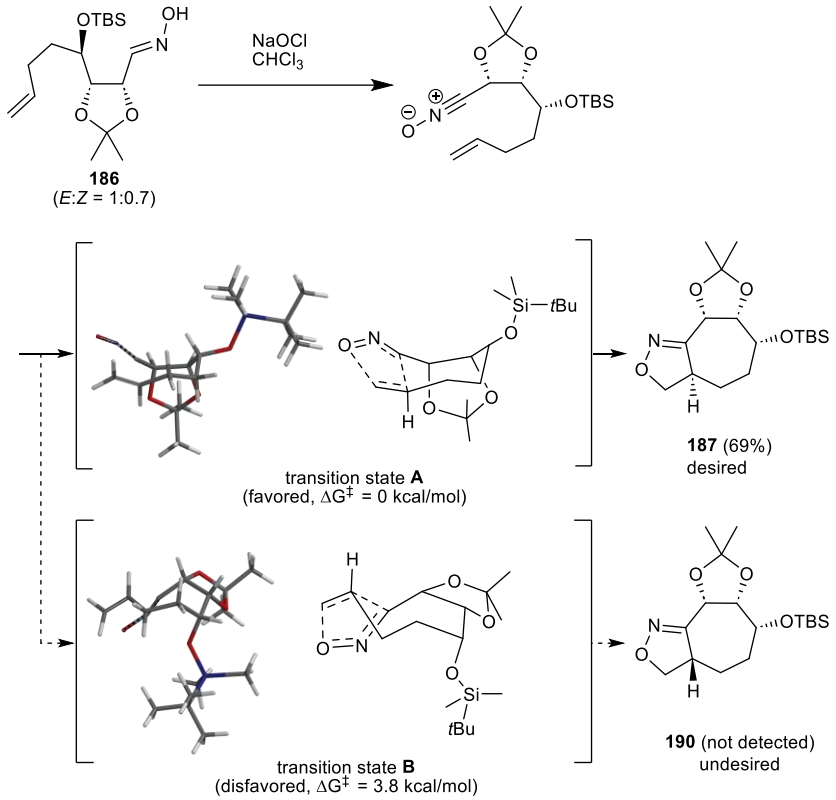
2.2.4 [3+2] Cycloaddition of the monosubstituted olefin and reductive ring-opening

When a framework beared a dimethyl moiety at the α-position of an isoxazoline oxygen atom, such as that in **165**, the retro-aldol reaction preferentially occurred, rendering conversion to a β-hydroxyketone challenging. Consequently, we attempted the reductive ring-opening of the isoxazoline derived from the monosubstituted olefin (Scheme 2.6). A mixture of **169** and **170** was converted to **184** via allylation and the removal of the TBS group, followed by a three-step sequence to give **186**. Treating **186** with NaOCl gave isoxazoline **187** as a single diastereomer. NOESY of **187** revealed a correlation between the newly formed stereocenter at C6 and the pseudo-axial proton at C4, suggesting the desired stereochemistry. Compound **187** was hydrogenated to give the target compound **188**, which was then protected with a TBS group to generate **189** in a 70% yield based on **187**.

To rationalize this selectivity, we evaluated the transition states of diastereomers **187** and **190** based on DFT calculations. (Scheme 2.7) The transition states of [3+2] cycloaddition were calculated based on the B3LYP/6-31G* level of theory (in a vacuum) using Spartan'18 (Wavefunction, Irvine, CA, USA). The calculations suggested that transition state **A** of **187** was more favorable than transition state **B** of **190**, which exhibited a boat-like conformation ($\Delta G^{\ddagger}$ = 3.8 kcal/mol).



Scheme 2.6 [3+2] Cycloaddition of monosubstituted olefin **186** and reductive ring-opening



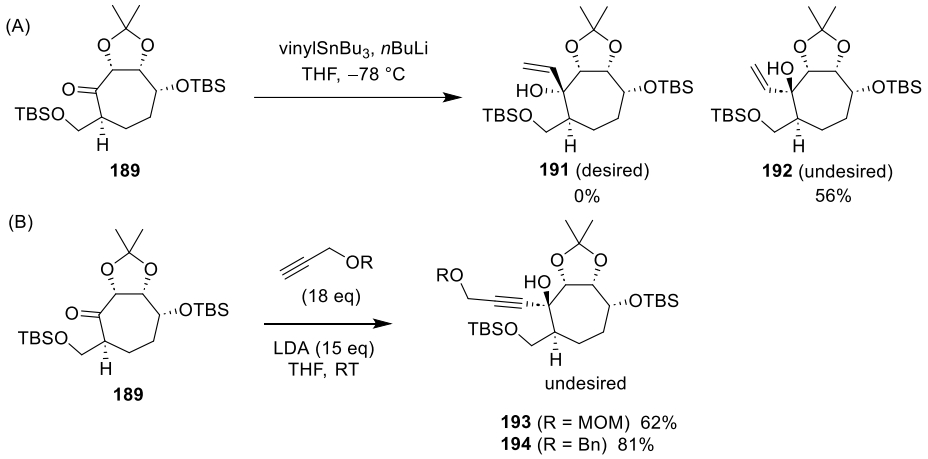
Scheme 2.7 Transition states of [3+2] cycloaddition based on the B3LYP/6-31G* level of theory (in a vacuum), as obtained using Spartan'18.

2.2.5 Diastereoselective alkyl chain introduction

Although the vinyl group should be introduced from the *Re*-face due to the steric hindrance of the acetonide, treating **189** in situ generated vinyl lithium using tributyl vinyltin and BuLi gave **192**. The stereochemistry of **192** was determined based on the NOE (Scheme 2.8A). The introduction of a terminal alkyne into **189** was also investigated (Scheme 2.8B). When a propargylic alcohol protected with a MOM group was used as a nucleophile, the adduct **193** was obtained in a 62% yield, and the adduct **194** was produced in an 81% yield when the propargylic alcohol was protected with a Bn group. The NOE correlations of the obtained compounds indicated that they displayed undesired stereochemistries, such as that of the vinyl group in **192**.

To explain this stereochemical selectivity, we investigated the thermodynamically stable conformations of a model compound wherein the two TBS groups of **189** were replaced with TMS groups (Fig. 2.1). The conformations were calculated using Spartan'18 at the ωB97X-D/6-31+G* level of theory. It is assumed that the model compound did not undergo nucleophilic addition in the most thermodynamically stable conformation, **A**, because the two silyl groups provided steric hindrance. Conversely, in the second most stable conformation, **B**, nucleophilic attack should not occur on the *Re*-face due to shielding by the silyl group, but attack on the *Si*-

face should proceed without steric hindrance.



Scheme 2.8 Introduction of a vinyl group or terminal alkyne into **189**

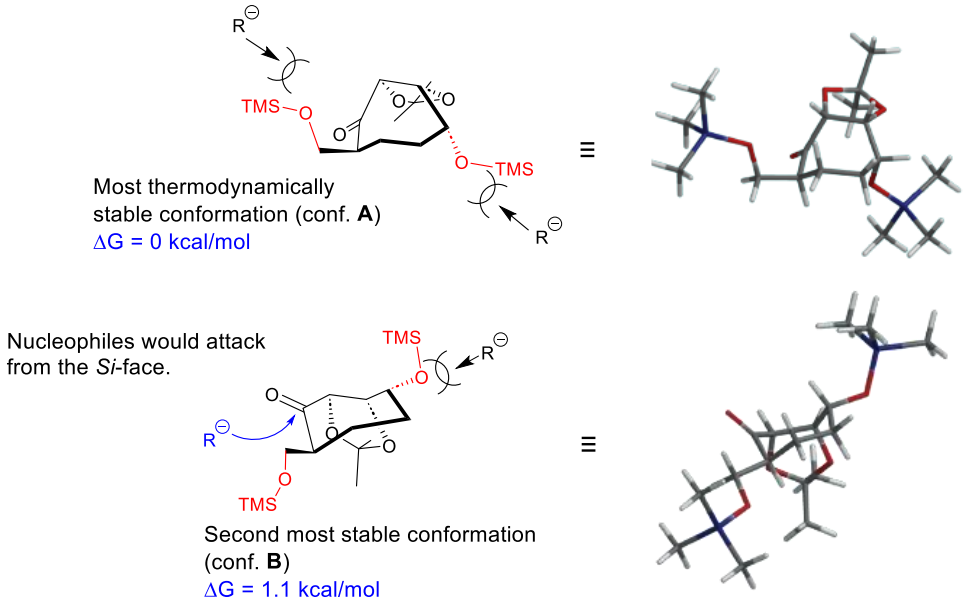
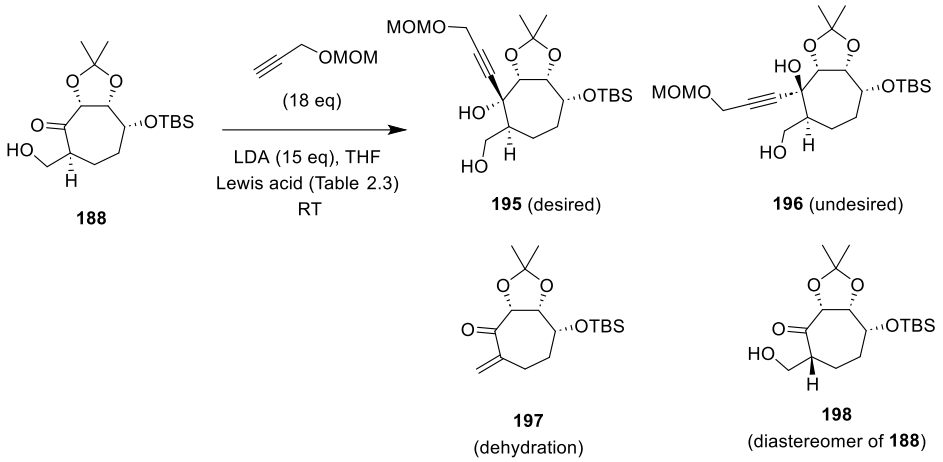


Fig. 2.1 Stereoselectivity of alkyl chain introduction, as calculated using spartan'18 at the ωB97X-D /6-31+G* level of theory.

Based on the insights gained by evaluating the conformation shown in Fig. 2.1, the steric hindrance caused by the TBS group of the primary alcohol could lead to the undesired stereochemistry during alkyne addition. Therefore, the introduction of terminal alkynes into ketone **188**, which did not bear a protecting group on the primary alcohol, was investigated (Scheme 2.9, Table 2.3). When using only the terminal alkyne and LDA as a base, 80% of the starting material was recovered (entry 1). The addition of a Lewis acid may activate the carbonyl group and increase the electrophilicity. When using $ZnCl_2$ or $TiCl_4$ as a Lewis acid, the starting material was recovered, and the desired product **195** was not obtained (entries 2, 3). In addition, byproducts, such as the dehydrated compound **197** and epimer **198**, were obtained.

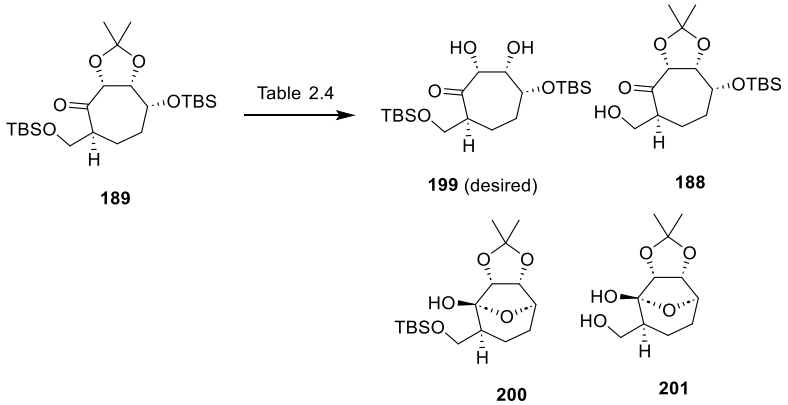


Scheme 2.9 Diastereoselective introduction of an alkyl chain into **188**

Table 2.3 Introducing of the MOM alkyne

Entry	Lewis acid	Results
1	none	**188**: 80%, **195**: 0%, **196**: 0%, **197**: 17%, **198**: 0%
2	$ZnCl_2$ (1.3 eq)	**188**: 76%, **195**: 0%, **196**: 0%, **197**: 0%, **198**: 10%
3	$TiCl_4$ (2.5 eq)	**188**: 86%, **195**: 0%, **196**: 0%, **197**: 17%, **198**: 0%

In **189**, two hydroxyl groups are protected as an acetal. This acetonide group restricted the conformation and would induce undesirable alkyne addition, and thus, the removal of the acetal moiety was investigated (Scheme 2.10, Table 2.4). Treatment with formic acid gave **188** and **200**, with the TBS groups removed instead of the acetonide (entry 1).[56] Removal of the TBS group of the secondary alcohol led to the formation of intramolecular hemiacetal structures, such as **200** and **201**, as confirmed using ^{13}C NMR spectroscopy. Although TFA was also employed, the target compound **199** was not obtained (entry 2).[57] Based on these results, introducing the alkyl chain from the *Re*-face was challenging.



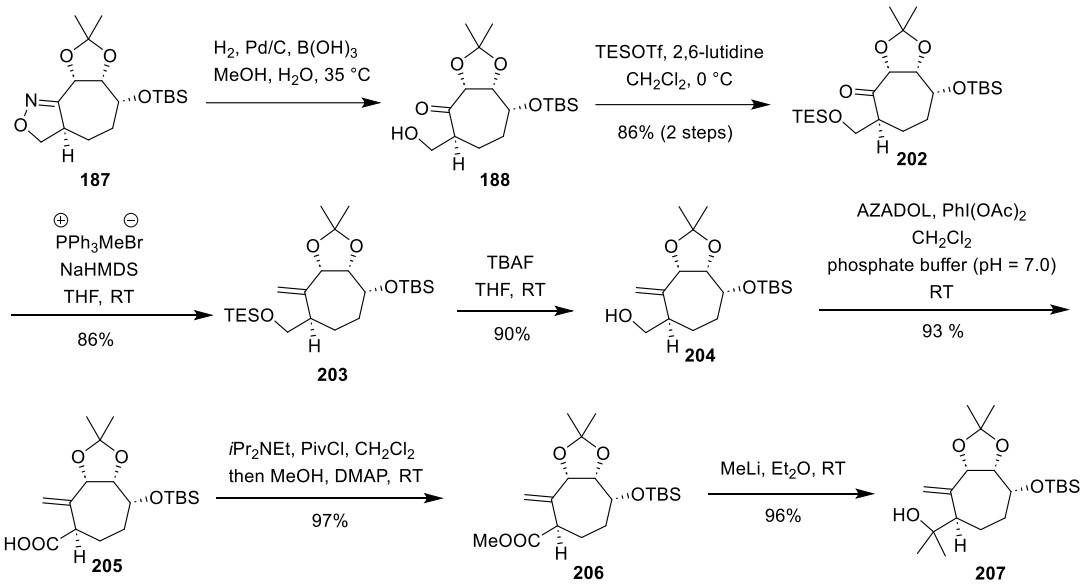
Scheme. 2.10 Removal of the acetonide group of **189**

Table 2.4 Removal of the acetonide group

Entry	Conditions	Results
1	HCOOH, EtOH	**199**: 0%, **188**: 28%, **200**: 21%, **201**: 0%
2	TFA, H_2O, CH_2Cl_2	**199**: 0%, **188**: 7%, **200**: 0%, **201**: 5%

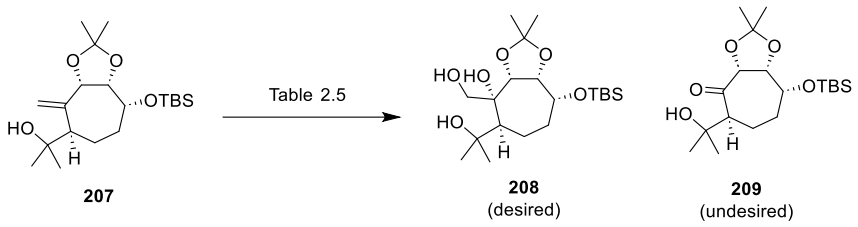
2.2.6 *exo*-Olefination and subsequent dihydroxylation

Considering the outcomes of nucleophilic addition from the *Si*-face, we focused on a synthetic strategy to introduce hydroxyl groups from the *Si*-face, too. Ketone **202** was synthesized using **187** via a two-step sequence, and **203** was produced in an 86% yield via a Wittig reaction (Scheme 2.11). Subsequently, the removal of the TES group, oxidation to the carboxylic acid, and methylesterification gave *exo*-methylene **206**. Treating **206** with MeLi gave tertiary alcohol **207**.



Scheme 2.11 Synthesis of tertiary alcohol **207**

We then investigated the dihydroxylation of **207** (Scheme 2.12, Table 2.5). Treatment with $NaIO_4$ and $RuCl_3$ did not generate the desired **208**, with only oxidative cleavage of the olefin to give **209** observed (entry 1),[58] and treatment with OsO_4 and NMO did not afford **208** (entry 2). As the dihydroxylation of electron-poor olefins occurred efficiently under acidic conditions, we added citric acid,[59] and the desired triol **208** was selectively obtained in a 63% yield as a single diastereomer (entry 3). As mentioned nucleophilic addition to the ketone (Scheme 2.8), OsO_4 may be added from the *Si*-face, thereby imparting the desired stereochemistry.



207 **208** (desired) **209** (undesired)

Scheme 2.12 Dihydroxylation of **207**

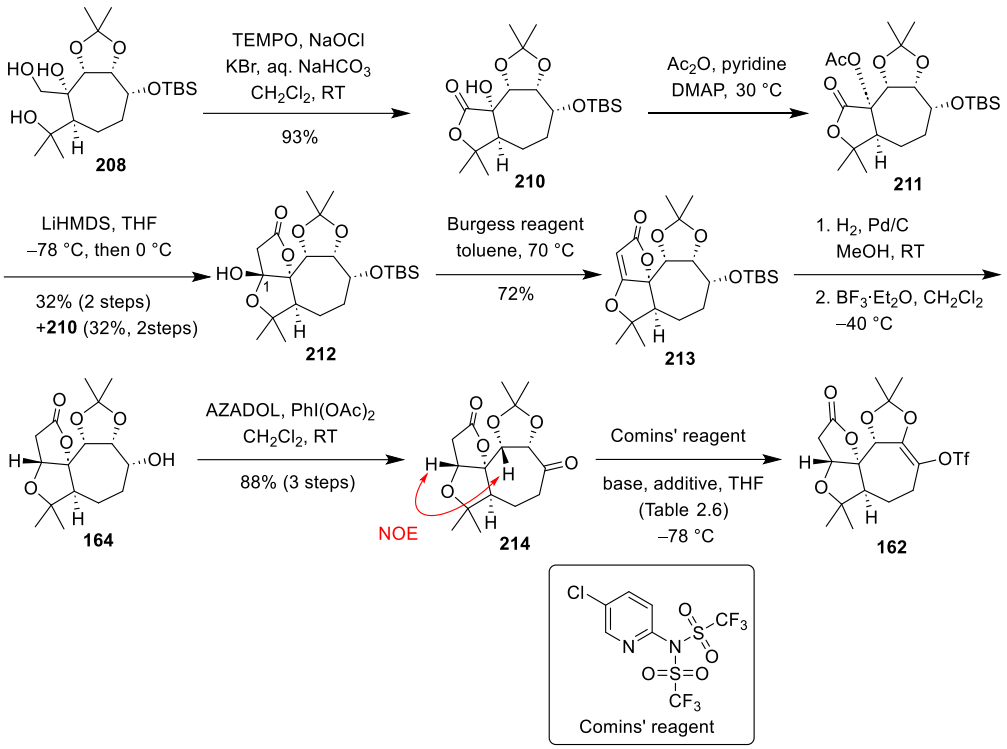
Table 2.5 Dihydroxylation

Entry	Conditions	Results
1	$NaIO_4$, $RuCl_3$ MeCN: EtOAc: H_2O = 1:1:1, RT	**207**: (0%), **208** (0%), **209** (22%)
2	OsO_4, NMO, *t*BuOH: H_2O = 1:1, 40 °C	**207**: (42%), **208** (0%), **209** (12%)
3	OsO_4, NMO, citric acid *t*BuOH: H_2O = 1:1, 40 °C	**207**: (0%), **208** (63%), **209** (trace)

2.2.7 Synthesis of left-hand fragment **162**

Treatment of **208** under TEMPO oxidation conditions gave lactone **210** without the cleavage of the diol (Scheme 2.13). upon TPAP oxidation and AZADO oxidation, ketone **209** was formed via diol cleavage. After acetylation of the tertiary alcohol and subsequent Dieckmann cyclization, **212** was obtained in a 32% yield based on **210**. The left-hand 5/5/7-membered fused-ring scaffold of pre-schisanartanin A was successfully formed. Due to the hydrolysis of the acetyl group by LiHMDS, lactone **210** was also recovered in a 32% yield. Dehydration using the Burgess reagent at 70 °C proceeded to afford **213** in a 72% yield,[60] and the obtained **213** was hydrogenated in the presence of Pd/C, followed by treatment with $BF_3 \cdot Et_2O$ to remove the TBS group, affording **164**. Ketone **214** was synthesized via AZADO oxidation in an 88% yield based on **213**. The observed NOE correlations shown in scheme 2.13 indicated the desired stereochemistry, and thus, we successfully synthesized the fragment with the oxygen functionality at C19.[61]

Subsequently, we investigated the formation of the enol triflate using ketone **214** (Table 2.6), with Comins' reagent employed at –78°C in triflation. When utilizing LiHMDS as a base, the starting material decomposed (entry 1), and changing the base to KHMDS also led to decomposition (entry 2). The addition of HMPA was effective, and left-hand fragment **162** was produced in a 32% yield (entry 3).



Scheme 2.13 Synthesis of left-hand fragment **162**

Table 2.6 Enol triflate formation

Entry	Base	Additive	Results
1	LiHMDS	none	decomp.
2	KHMDS	none	decomp.
3	KHMDS	HMPA	**162** (32%)

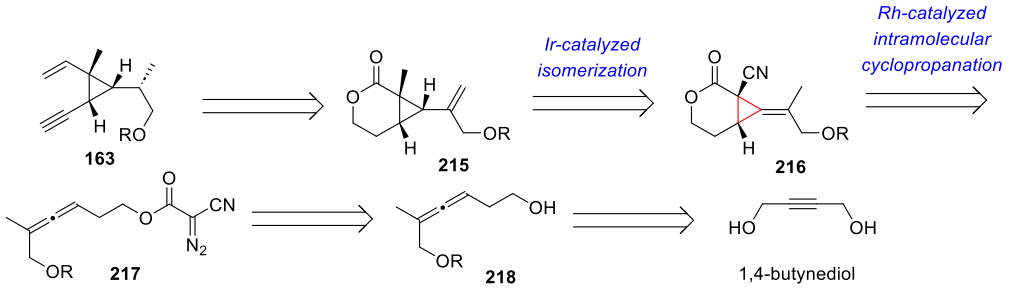
Section 3 Synthesis of the right-hand fragment**

2.3.1 Initial attempt involving Rh-catalyzed intramolecular cyclopropanation

A structural feature of the right-hand fragment **163** lies in the all-*cis*-substituted cyclopropane, where the main substituents on the cyclopropane ring are located on the same side of the ring. To synthesize this motif, we planned the stereoselective isomerization of an alkylidene cyclopropane, and the retrosynthetic analysis is presented below (Scheme 2.14). Fragment **163** should be synthesized using lactone **215**, which may be obtained via the reduction of the nitrile of **216** and isomerization of the olefin using an Ir catalyst. Alkylidenecyclopropane **216** should be obtained

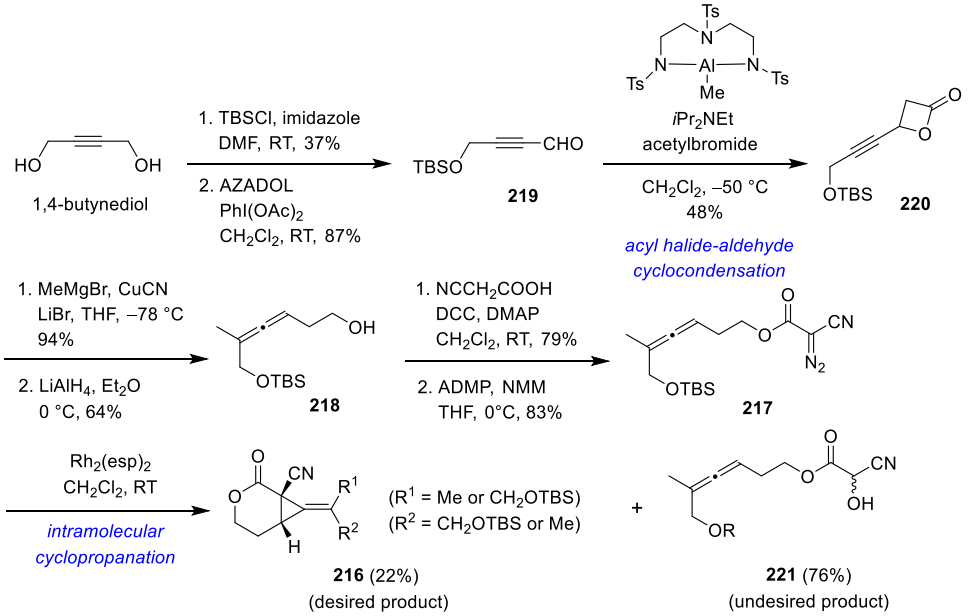
** The content described in this section was originally published in *Synlett*. Ryotaro Yagita, Kazuhiro Irie and Chihiro Tsukano, Toward the Total Synthesis of Schinortriterpenoids: Construction of the All-*cis*-Substituted Cyclopropane Unit. *Synlett* **2023**, *in press* (DOI: 10.1055/a-2102-8014). © 2023 Thieme.

via the Rh-catalyzed intramolecular cyclopropanation of diazoester **217**. Compound **217** should be accessed using alcohol **218**, which may be obtained using 1,4-butynediol.



Scheme 2.14 Retrosynthetic analysis of right-hand fragment **163**

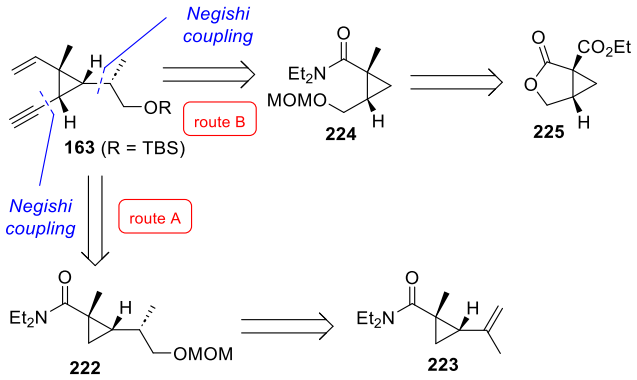
One of the hydroxyl groups of 1,4-butynediol was protected as a TBS ether, and the other was oxidized to afford **219** (Scheme 2.15). β-Lactone **220** was accessed via the halogenated acyl-aldehyde cyclocondensation using an aluminum triamine catalyst.[62] Treatment with an organocuprate reagent was followed by reduction to give alcohol **218** with an allene moiety. Compound **218** was subjected to a condensation with cyanoacetic acid, followed by diazotransfer using ADMP, affording diazonitrile **217**, which was a precursor for use in cyclization.[63] Upon treatment of **217** with $Rh_2(esp)_2$, the desired alkylidene cyclopropane **216** was obtained in a 22% yield, along with the byproduct **221**, where the diazo group was substituted with a hydroxyl group. Despite exploring several reaction conditions for this cyclopropanation, the yield did not improve, necessitating a change in the synthetic strategy.



Scheme 2.15 Synthesis of alkylidenecyclopropane **216**

2.3.2 Synthetic plan involving Negishi coupling

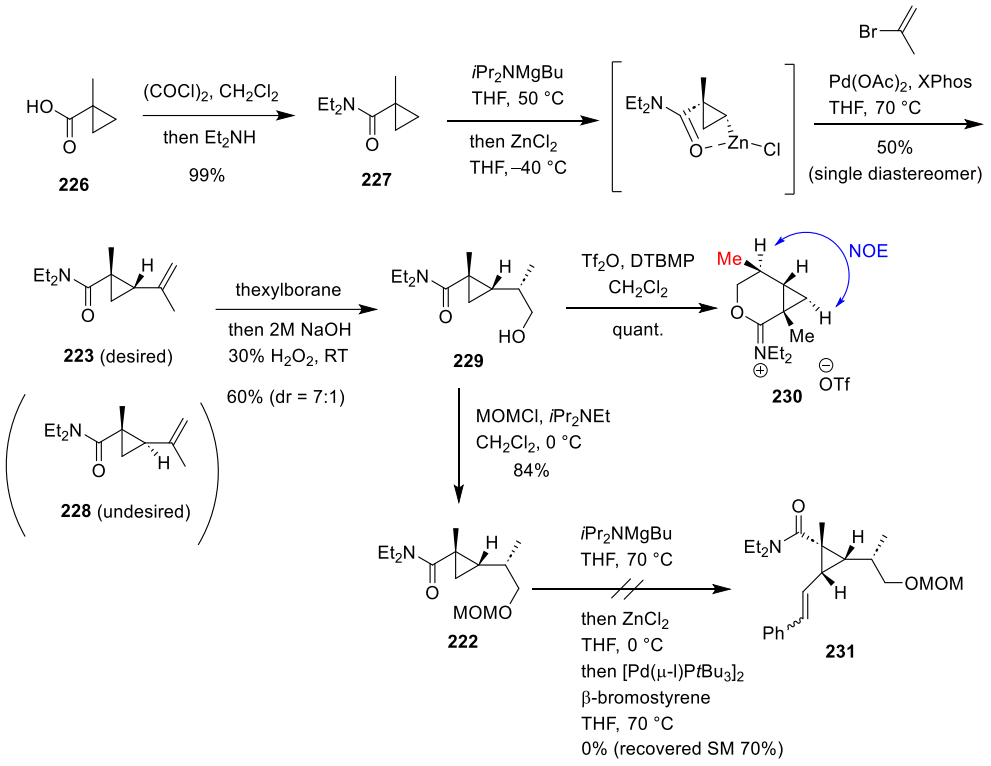
We focused on Negishi coupling,[43] and we planned two routes, route A and B, depending on which alkyl chain was introduced via Negishi coupling (Scheme 2.16). In route A, **163** could be synthesized using **222** via the Negishi coupling, and furthermore, **222** should be accessible using **223** via hydroboration. In route B, **163** could be synthesized using **224** via Negishi coupling, and **224** may be obtained using lactone **225**.



Scheme 2.16 Retrosynthesis of right-hand fragment **163** (based on Negishi coupling)

2.3.3 Synthesis of **163** via route A

We investigated the diastereoselective introduction of an isopropenyl moiety via Negishi coupling (Scheme 2.17). Commercially available carboxylic acid **226** was converted to the corresponding acid chloride using oxalyl chloride, and subsequent treatment with diethylamine gave amide **227** in a 99% yield. Amide **227** was transformed into **223** via a previously reported Negishi coupling.[43] In this reaction, introduction of the propenyl group into the cyclopropane ring was not selective, the obtained product was racemic. Hydroboration of **223** with thexylborane gave **229** in a 60% yield and with a diastereoselectivity of 7:1.[64] The stereochemistry of **229** was elucidated via its cyclization using DTBMP and Tf_2O, followed by NOESY of the obtained **230**. Alcohol **229** was protected as a MOM ether to give **222**, and Negishi coupling using **222** did not give **231**. The branched alkyl substituent on the cyclopropane ring may be too bulky to enable the approach of β-bromostyrene, and we thus focused on route B, which employed a less bulky substituent on the cyclopropane ring.



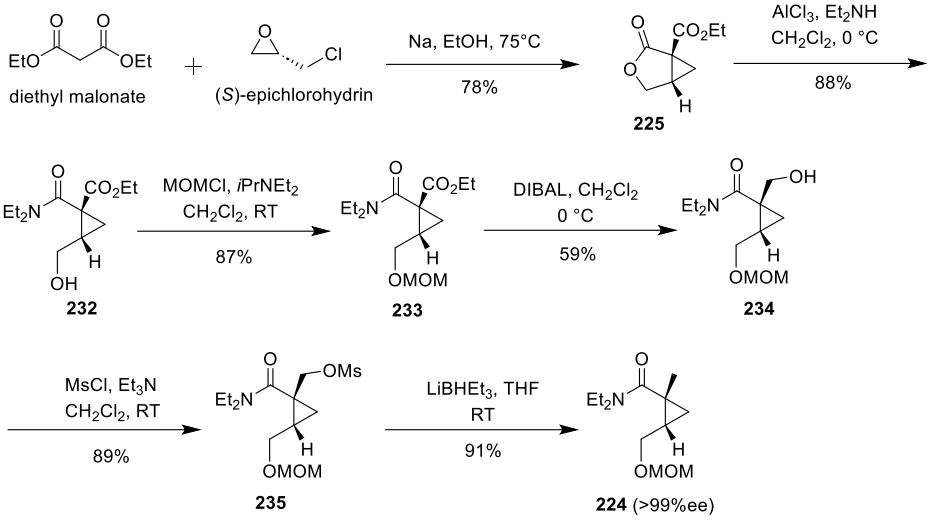
Scheme 2.17 Synthesis of all-*cis*-substituted cyclopropane **231** via route A

2.3.4 Synthesis of **163** via route B

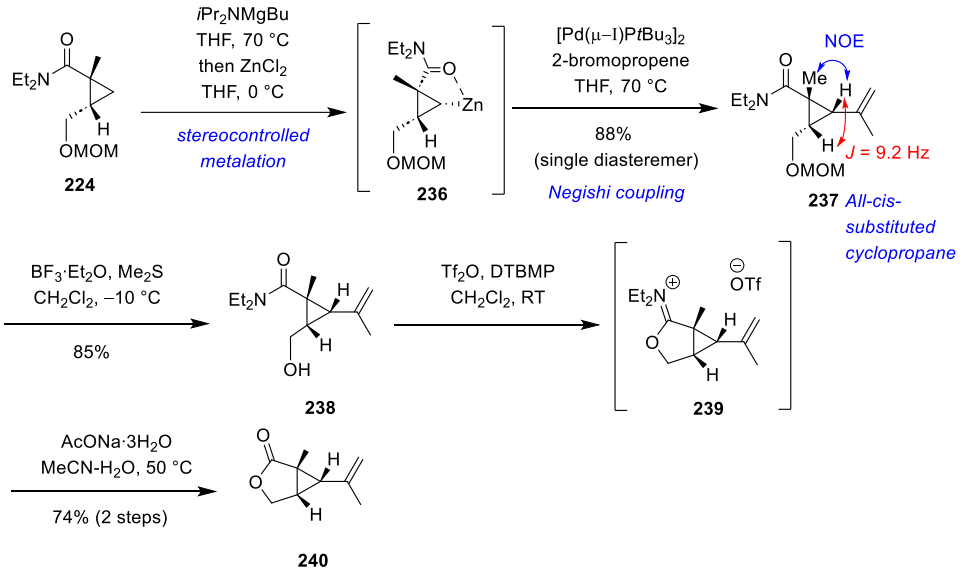
Synthesis via route B was then investigated. Whereas a racemic synthesis of **224** has been reported,[43] no asymmetric synthetic route has been established, and we initially aimed to asymmetrically synthesize **224**. Treating *S*-epichlorohydrin and diethyl malonate with sodium ethoxide gave the known lactone **225** (Scheme 2.18).[65] Lactone **225** was converted to amido **233** via treatment with $AlCl_3$ and diethylamine and a protection as a MOM ether. Subsequently, the selective reduction of the ester in **233** was optimally realized using DIBAL, affording the desired compound **234** in a moderate yield. After alcohol **234** was mesylated, **224** was successfully synthesized in a 91% yield via deoxygenation using Super-Hydride. HPLC analysis certified that the ee of **224** was over 99%.

The Negishi coupling of **224** with 2-bromopropene gave the all-*cis*-substituted cyclopropane **237** as a single diastereomer (Scheme 2.19). In this reaction, butylmagnesium diisopropylamide selectively metalated the cyclopropane ring from the lower face of **224**, with the diethylamide acting as a directing group. Addition of $ZnCl_2$ generated intermediate **236**, and subsequent treatment with $[Pd(\mu\text{-}I)PtBu_3]_2$ [66] and 2-bromopropene gave the coupling product. The all-*cis*-substituted structure of **237** was determined using NOE correlations and coupling constants. After removing the MOM group to give **238**, treating **238** with Tf_2O and DTBMP produced iminium

salt **239**. Hydrolysis of this compound under basic conditions gave lactone **240** in a 74% yield based on **238**.



Scheme 2.18 Asymmetric synthesis of **224**

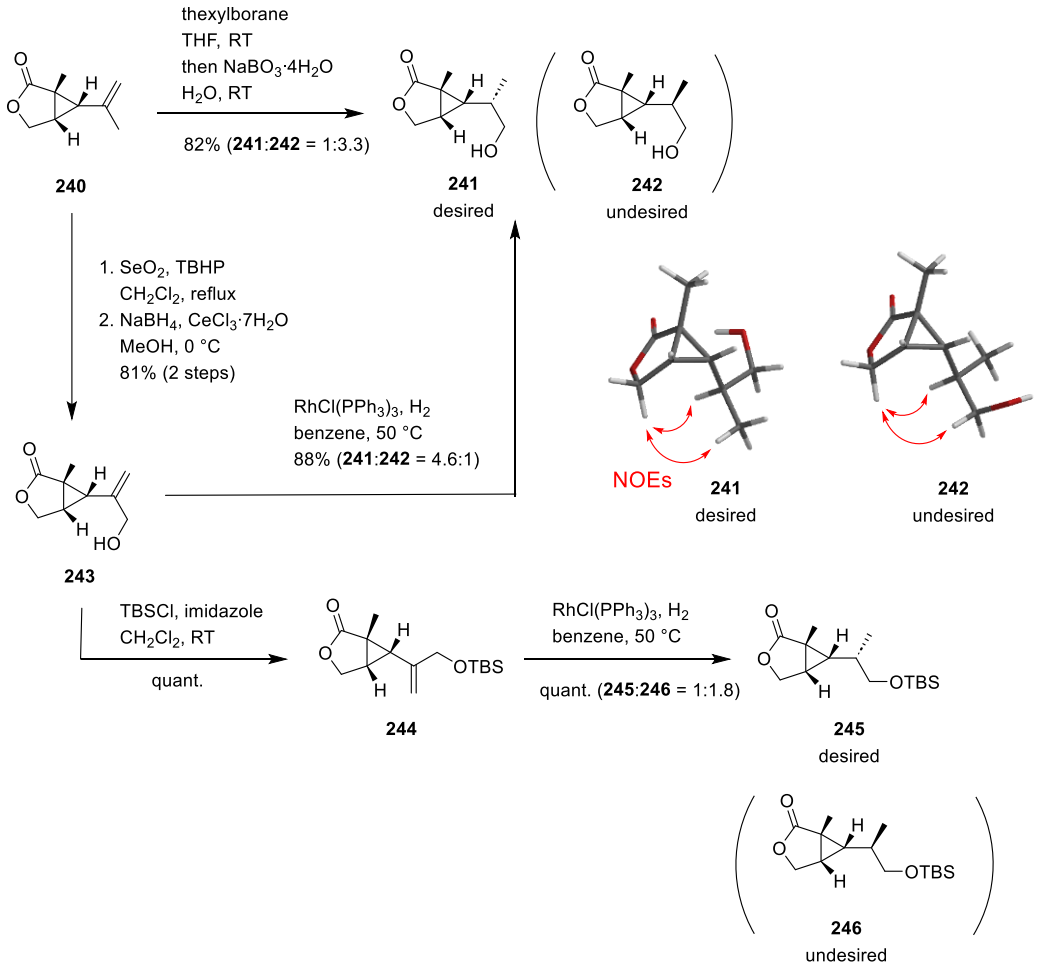


Scheme 2.19 Formation of the all-*cis*-substituted cyclopropane and the synthesis of **240**

2.3.5 Synthesis of right-hand fragment **163**

Hydroboration of **240** with thexylborane gave a mixture of primary alcohol in an 82% yield with a dr of 1:3.3 (Scheme 2.20). Each diastereomer was separated via silica gel column chromatography, and the NOE correlations of the diastereomers, **241** and **242**, enabled the determination of their relative stereochemistries, revealing that the major product was not the

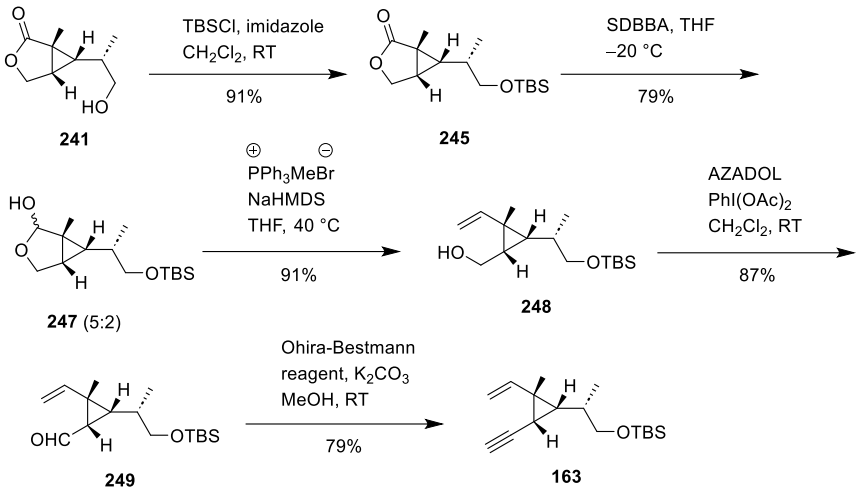
desired **241**, but its diastereomer **242**. Although other organoboron reagents were examined, none could reverse the stereoselectivity, and thus, an alternative synthetic route involving hydrogenation was pursued. Treating **240** with SeO_2 resulted in overoxidation of the allylic position to the aldehyde, in addition to the alcohol. Therefore, Luche reduction was performed, furnishing allylic alcohol **243** in an 81% yield based on **240**. Subsequent reduction of **243** using Wilkinson's catalyst successfully provided the desired stereochemistry of **241** as the major product in an 88% yield with a dr of 4.6:1.[67] In contrast, after converting **243** to TBS ether **244**, hydrogenation with Wilkinson's catalyst gave the undesired **246** as the major product with a low selectivity (**245**:**246** = 1:1.8).



Scheme 2.20 Synthesis of alcohol **241** with a good diastereoselectivity

After **241** was treated with TBSCl and imidazole to afford **245**, reduction using SDBBA gave lactol **247** (Scheme 2.21).[68] Aldehyde **249** was synthesized via a Wittig reaction, followed by AZADO oxidation. Aldehyde **249** was transformed into the right-hand fragment **163**[69] via treatment with the Ohira-Bestmann reagent [dimethyl(1-diazo-2-oxopropyl)phosphonate].[70-72]

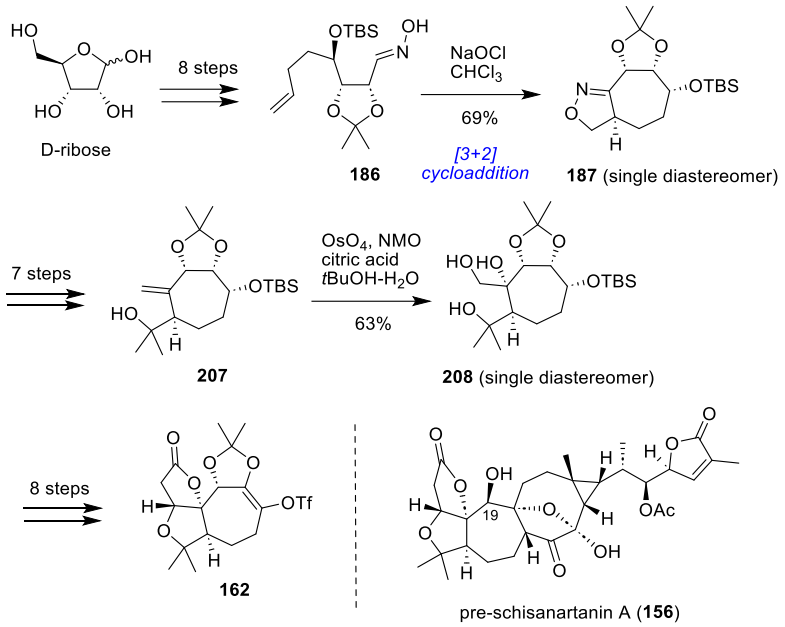
Alkyne **163** was unstable and decomposed within an hour when heated at 70 °C, and thus, it required a refrigerated storage.[73]



Scheme 2.21 Synthesis of right-hand fragment **163**

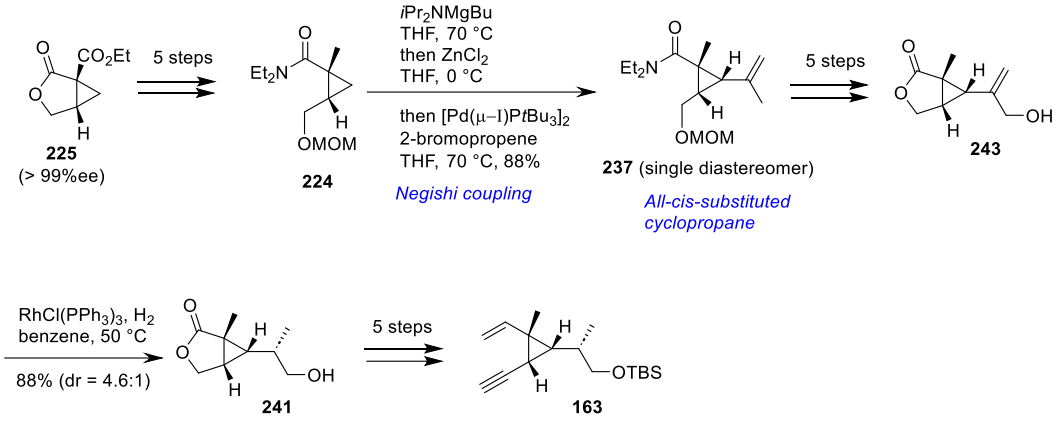
Section 4 Conclusion

In this study, we successfully synthesized left-hand fragment **162** in 25 steps from D-ribose, forming the characteristic 5/5/7-membered ring system of the target natural product, pre-schisanartanin A (Scheme 2.22). Starting with D-ribose, we synthesized oxime **186** in eight steps. Treating oxime **186** with NaOCl resulted in an intramolecular [3+2] cycloaddition, affording isoxazoline **187** as a single diastereomer. Using computational methods, we compared the transition states of this reaction and found that the transition state leading to the desired product **187** was 3.8 kcal/mol more favorable than that leading to its diastereomer. Dihydroxylation of **207**, which was obtained in the subsequent seven steps, gave triol **208** as a single diastereomer because OsO_4 approached from the face bearing the siloxy group and acetonide. After the subsequent eight steps, **162** was obtained.[61] To the best of our knowledge, no SNTs with hydroxyl groups at their C19 positions have been synthesizedreported (Chapter 1). Utilizing D-ribose as a starting material, we introduced a hydroxyl group at C19, highlighting the novelty of this synthetic route.



Scheme 2.22 Synthesis of left-hand fragment **162**

In synthesizing the right-hand fragment, which features an all-*cis*-substituted cyclopropane structure, we followed a 16-step sequence starting with optically active lactone **225** (Scheme 2.23). Compound **224**, which was obtained in five steps from **225**, was treated using iPr$_2$NMgBu, ZnCl$_2$, [Pd(μ-I)PtBu$_3$]$_2$ and 2-bromopropene. The Negishi reaction proceeded smoothly, affording the all-*cis*-substituted cyclopropane **237** as a single diastereomer. This coupling reaction was susceptible to steric hindrance, and several substrates with different substitution patterns were examined, but only **224** enabled the introduction of the third substituent. With lactone **243** in hand, hydrogenation in the presence of Wilkinson's catalyst produced **241** in an 88% yield with a good diastereoselectivity.[69] Compound **163** was synthesized via a subsequent five-step sequence. In a related study regarding the asymmetric total synthesis of pre-schisanartanin C reported by the Yang group, they utilized an enyne cyclization reaction over an Au catalyst, thereby forming the all-*cis*-substituted cyclopropane structure (Scheme 1.15).[30] Conversely, we generated this structure via Negishi coupling,[43] and this synthetic strategy has not been previously applied in natural product synthesis. In terms of synthetic organic chemistry, this study demonstrates a high degree of novelty.



225 (> 99%ee) 224 237 (single diastereomer) 243 241 163

All-cis-substituted cyclopropane

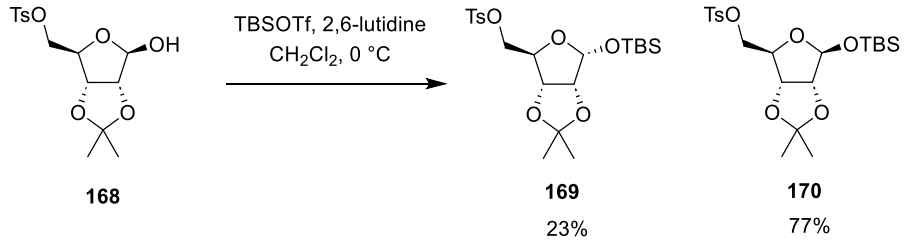
Scheme 2.23 Synthesis of right-hand fragment **163**

Chapter 3　Experimental section

1. General remarks

^{1}H and ^{13}C NMR were recorded on AVANCE III at 400 and 500 MHz. Chemical shifts of protons were reported relative to TMS (δ 0.00) in $CDCl_3$ or C_6D_6 (δ 7.15). Multiplicity in indicated by one or more of the following; s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Chemical shifts of carbon were reported relative to $CDCl_3$ (δ 77.0) or C_6D_6 (δ 127.7). Low and high resolution mass spectra were recorded on JEOL MS700 mass spectrometer for FAB-MS (matrix, *m*-nitrobenzyl alcohol) or Bruker timsTOF for ESI-MS and APCI-MS. Digital polarimeter were recorded on P-2000 (Jasco). IR were recorded on FT/IR-470 Plus (Jasco) and FT/IR-4X (Jasco). Analytical thin-layer chromatography was performed with Silica gel 60 (Merck). Silica gel column chromatography was performed with Wako-Gel C-200 and Fuji Silysia Chromatorex BW-300. All other chemicals and reagents were purchased from chemical companies and used without further purification.

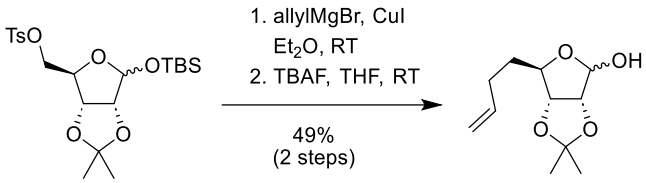
2. Experimental procedure



168　　**169** 23%　　**170** 77%

Compound 169, 170: To a solution of **168** (7.50 g, 21.8 mmol) in CH_2Cl_2 (90.0 mL) were added 2,6-lutidine (4.90 mL, 42.1 mmol) and TBSOTf (7.00 mL, 30.5 mmol) at 0 °C under N_2 atmosphere. The solution was stirred for 1 h at 0°C. After addition of water, the mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (8–12% EtOAc/hexane) to afford **169** (2.26 g, 23%) as a colorless oil and **170** (7.65 g, 77%) as a colorless oil. Compound **169**: $[\alpha]_D^{26}$ +20.3° (*c* 0.242, $CHCl_3$); IR (neat) 2952, 2931, 2858, 1599, 1463, 1369 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.3 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 5.16 (1H, d, *J* = 4.1 Hz), 4.55 (1H, dd, *J* = 7.1, 3.0 Hz), 4.49 (1H, dd, *J* = 7.1, 4.1 Hz), 4.24 (1H. dd, *J* = 6.5, 3.3 Hz), 4.18–4.10 (2H, m), 2.45 (3H, s), 1.51 (3H, s), 1.32 (3H, s), 0.89 (9H, s), 0.09 (3H, s), 0.08 (3H,s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 132.7, 129.9, 128.0, 115.6, 97.0, 81.3, 80.3, 78.4, 69.8, 26.2, 25.9, 25.8, 21.7, 18.2, –4.7, –4.9; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{20}H_{35}O_7SSi$, 459.1873; found, 459.1877; compound **170**: $[\alpha]_D^{26}$ –28.2° (*c* 0.608, $CHCl_3$); IR (neat) 2953, 2932, 2858, 1926, 1599, 1471,

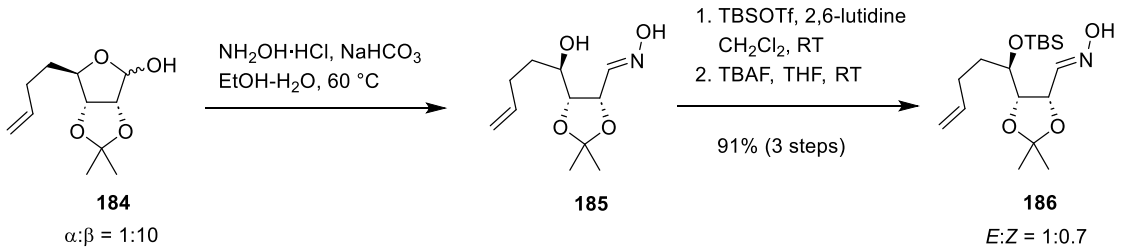
1371 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.3 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 5.33 (1H, s), 4.68 (1H, d, *J* = 5.9 Hz), 4.48 (1H, d, *J* = 5.8 Hz), 4.26 (1H. dd, *J* = 9.4, 5.4 Hz), 4.04 (1H, dd, *J* = 9.7, 9.7 Hz), 3.97 (1H, dd, *J* = 9.8, 5.4 Hz), 2.46 (3H, s), 1.44 (3H, s), 1.29 (3H, s), 0.84 (9H, s), 0.09 (3H, s), 0.04 (3H,s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 132.7, 129.9, 128.0, 112.6, 103.3, 86.9, 83.5, 82.0, 69.4, 26.4, 25.6, 24.9, 21.7, 17.8, –4.4, –5.5; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{20}H_{35}O_7SSi$, 459.1873; found, 459.1877.



169 + 170 **184** (α:β = 1:10)

Compound 184: To a solution of CuI (18.2 g, 95.6 mmol) in anhydrous Et_2O (80.0 mL) were added allylMgBr (1 M Et_2O solution, 180 mL, 180 mmol) at –20 °C under N_2 atmosphere. After the solution was stirred for 30 min at –20 °C, the solution of **169+170** (9.38g, 20.5 mmol) in anhydrous Et_2O (120 mL) was added at the same temperature. The solution was stirred for 30 min at 0 °C and for 19 h at room temperature. The reaction mixture was cooled to 0 °C and quenched with aqueous saturated NH_4Cl slowly. The mixture was filtered through a pad of celite and extracted with Et_2O twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was filtered through silica gel column to give crude allyl compound, which was used for the next reaction without further purification.

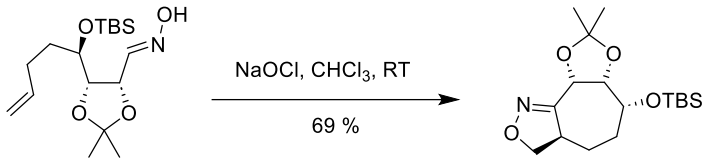
To a solution of the above crude allyl compound in THF (120 mL) was added TBAF (1 M THF solution, 13.0 mL, 13.0 mmol) at room temperature. The solution was stirred for 20 min. After addition of water, the mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10–25% EtOAc/hexane) to afford **184** (2.12g, 49%) as a colorless oil: $[\alpha]_D^{27}$ –8.52° (*c* 1.18, $CHCl_3$); IR (neat) 3435, 3078, 2982, 2940, 1641, 1442, 1375, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.85–5.77 (1H, m), 5.44 (1H, d, *J* = 2.8 Hz), 5.25 (0.1H, dd, *J* = 9.4, 4.1 Hz), 5.07–4.98 (1H, m), 5.07–4.98 (0.2H, m), 4.79 (0.1H, s, br), 4.64 (1H, d, *J* = 5.9 Hz), 4.65–4.62 (0.1H), 4.59 (1H, d, *J* = 5.3 Hz), 4.45 (0.1H, dd, *J* = 6.7, 2.9 Hz), 4.18 (1H. dd, *J* = 6.4, 6.4 Hz), 4.06 (0.1H, ddd, *J* = 8.6, 6.4, 2.9 Hz), 3.95 (0.1H, d, *J* = 9.3 Hz), 3.32(1H, s, br), 2.24–2.11 (2H, m), 2.24–2.11 (0.2H, m), 1.90–1.89 (0.1H, m), 1.83–1.75 (1H, m), 1.71–1.63 (1H, m), 1.61–1.55 (0.1H, m), 1.57 (0.3H, s), 1.48 (3H, s), 1.39(0.3H,s), 1.32 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 115.2, 112.4, 103.1, 86.7, 86.1, 84.4, 34.6, 30.2, 26.5, 25.0; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{11}H_{19}O_4$, 215.1283 found 215.1278.



Compound 186: To a solution of **184** (73.6 mg, 0.344 mmol) in EtOH (3.00 mL) and H_2O (3.00 mL) were added $NaHCO_3$ (121 mg, 1.44 mmol) and $NH_2OH{\cdot}HCl$ (69.3 mg, 0.997 mmol) at room temperature. The reaction solution was warmed to 60 °C and stirred for 13 h at 60 °C. The reaction was quenched with aqueous saturated NH_4Cl. The mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained crude oxime **185** was used for the next reaction without further purification.

To a solution of the above crude oxime **185** in CH_2Cl_2 (4.20 mL) were added 2,6-lutidine (0.200 mL, 1.72 mmol) and TBSOTf (0.250 mL, 1.09 mmol) at 0 °C under N_2 atmosphere. The solution was stirred for 1 h at room temperature. After addition of water, the mixture was extracted with $CHCl_3$ three times. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through silica gel column to give crude disilyl ether, which was used for the next reaction without further purification.

To a solution of the above crude disilyl ether in THF (5.00 mL) was added TBAF (1 M THF solution, 0.340 mL, 0.340 mmol) at room temperature. The solution was stirred for 6 min. After addition of water, the mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5–20% EtOAc/hexane) to afford **186** (108 mg, 91%,) as a colorless oil: $[\alpha]_D^{26}$ −6.06° (*c* 0.158, $CHCl_3$); IR (neat) 3088, 3079, 2985, 2953, 2931, 2896, 2858, 1642, 1472, 1382, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (0.7H, s, br), 7.70 (1H, s, br), 7.48 (1H, d, *J* = 8.3 Hz), 6.98 (0.7H, d, *J* = 6.1 Hz), 5.85–5.75 (1H, m), 5.85–5.75 (0.7H, m), 5.33 (1H, dd, *J* = 7.2, 6.1 Hz), 5.06–4.94 (2H, m), 5.06–4.94 (1.4H, m), 4.64 (1H, dd, *J* = 8.3, 6.1 Hz), 4.34 (1H, dd, *J* = 7.2, 3.1 Hz), 4.17 (1H, dd, *J* = 5.9, 5.9 Hz), 3.99 (1H, dd, *J* = 10.9, 5.4 Hz), 3.84 (1H, ddd, *J* = 7.5, 4.5, 3.2 Hz), 2.23-2.01 (2H, m), 2.23–2.01 (1.4H, m), 1.76–1.57 (2H, m), 1.76–1.57 (1.4H, m), 1.51 (2.1H, s), 1.48 (3H, s), 1.37 (3H, s), 1.37 (2.1H, s), 0.91 (6.3H, s), 0.90 (9H, s), 0.10 (2.1H, s), 0.08 (3H, s), 0.07 (3H, s), 0.06 (2.1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 149.5, 138.5, 138.3, 114.8, 114.7, 109.0, 108.9, 80.7, 79.5, 74.9, 70.9, 69.7, 69.3, 33.3, 32.7, 29.8, 28.6, 27.8, 26.9, 26.0, 26.0, 25.7, 25.3, 24.6, 18.1, 18.1, –3.6, –4.2, –4.3, –4.3, –4.4; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{17}H_{34}NO_4Si$, 344.2259 found 344.2257.

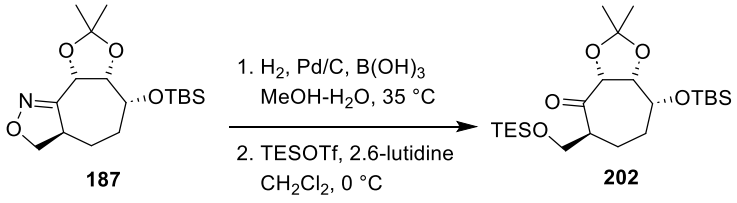


186

E:*Z* = 1:0.7

187

Compound 187: To a solution of **186** (1.30 g, 3.79 mmol) in $CHCl_3$ (340 mL) was added aqueous NaOCl (20.0 mL) at 0 °C. After the reaction solution was stirred at room temperature for 3 h, additional NaOCl (15.0 mL) was added. The solution was stirred for 2 h at room temperature. The solution was cooled to 0 °C and quenched with aqueous saturated $Na_2S_2O_3$. The mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*.The residue was purified by silica gel column chromatography (0–10% EtOAc/hexane) to afford **187** (890 mg, 69%) as a colorless oil: $[\alpha]_D^{27}$ –95.4° (*c* 0.375, $CHCl_3$); IR (neat) 2953, 2931, 1732, 1609, 1472, 1463, 1383, 1257, 1084 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (1H, d, *J* = 8.1 Hz), 4.54 (1H, d, *J* = 8.1 Hz), 4.26 (1H, dd, *J* = 8.5, 8.5 Hz), 4.17 (1H. dd, *J* = 8.2, 2.4 Hz), 3.62 (1H, ddd, *J* = 10.3, 2.8, 1.4 Hz), 3.15–3.09 (1H, m), 2.35–2.26 (1H, m), 1.84–1.79 (1H, m), 1.64–1.59 (1H, m), 1.57 (3H, s), 1.52–1.44 (1H, m), 1.42 (3H, s), 0.89 (9H, s), 0.08 (3H, s), 0.08 (3H,s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 109.7, 80.5, 76.5, 73.2, 70.8, 46.4, 30.5, 30.0, 26.5, 25.9, 24.1, 18.4, –4.5, –4.8; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{17}H_{32}NO_4Si$, 342.2103 found 342.2101.



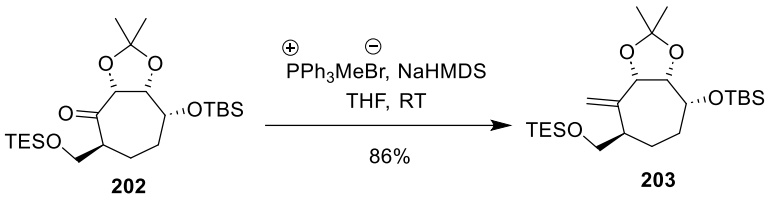
187

202

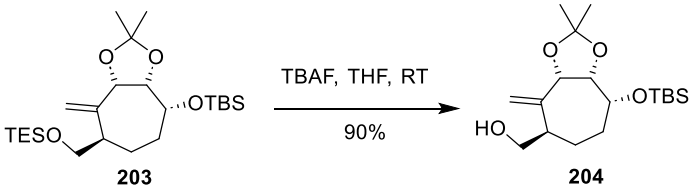
Compound 202: To a solution of **187** (334 mg, 0.919 mmol) in MeOH (20.0 mL) and H_2O (4.00 mL) was added $B(OH)_3$ (918 mg, 14.8 mmol) and 10% Pd/C (317 mg, 0.298 mmol) at room temperature. After replacement of hydrogen atmosphere, the reaction solution was stirred for 21 h at 35 °C. The solution was filtered through a pad of celite and evaporated. The residue was diluted with $CHCl_3$ and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The obtained crude alcohol was used for the next reaction without further purification.

To a solution of the above crude alcohol in CH_2Cl_2 (20.0 mL) were added 2,6-lutidine (0.320 mL, 2.75 mmol) and TESOTf (0.420 mL, 1.86 mmol) at 0 °C under N_2 atmosphere. The solution was stirred for 80 min at 0 °C. After addition of water, the mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (3–10% EtOAc/hexane) to afford **202** (360 mg, 86%,) as a colorless oil: $[\alpha]_D^{26}$ –38.1° (*c* 0.475, $CHCl_3$); IR (neat) 2953, 2935, 2878, 1731, 1463, 1381, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 (1H, d, *J* = 9.1 Hz), 4.52 (1H, dd, *J* = 9.1, 1.2 Hz), 4.16 (1H, s, br), 3.95 (1H, dd, *J* = 9.3, 4.4 Hz), 3.61

(1H, dd, J = 9.3, 3.2 Hz), 2.61 (1H, d, J = 10.1 Hz), 1.99–1.88 (2H, m), 1.79–1.71 (2H, m), 1.57 (3H, s), 1.35 (3H, s), 0.92 (9H, t, J = 7.9 Hz), 0.85 (9H, s), 0.57 (6H, q, J = 7.9 Hz), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 108.4, 81.3, 79.1, 70.7, 66.4, 51.3, 31.2, 25.9, 25.7, 23.4, 23.1, 18.0, 6.7, 4.2, 3.9, –4.9, –4.9; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{23}H_{46}O_5Si_2$, 459.2962 found 459.2964.

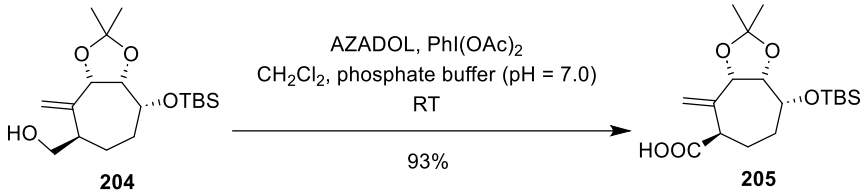


Compound 203: To a solution of methyltriphenylphophonium bromide (2.94 g, 8.24 mmol) in THF (11.0 mL) was added NaHMDS (0.89 M THF solution, 9.40 mL, 8.37 mmol) at 0 °C under N_2 atmosphere. After the solution was stirred for 30 min at 0 °C, the solution of **202** (1.26 g, 2.75 mmol) in THF (16.0 mL) was added at the same temperature. The solution was stirred for 2 h at room temperature. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with Et_2O twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (4% Et_2O/hexane) to afford **203** (1.08 g, 86%) as a colorless oil: $[\alpha]_D^{25}$ –195° (*c* 0.0333, $CHCl_3$); IR (neat) 3081, 2953, 2934, 2877, 1462, 1381, 1256, 1208, 1100, 1079, 992 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (1H, s), 4.84 (1H, s), 4.55 (1H, d, J = 8.6 Hz), 4.41 (1H, d, J = 8.6 Hz), 3.68–3.64 (2H, m), 3.56 (1H, dd, J = 9.6, 9.6 Hz), 2.39–2.24 (1H, m), 2.21–2.12 (2H, m), 1.63–1.56 (1H, m), 1.56 (3H, s), 1.38 (3H, s), 1.05–0.99 (1H, m), 0.95 (9H, t, J = 8.0 Hz), 0.89 (9H, s), 0.59 (6H, q, J = 8.0 Hz), 0.07 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 113.2, 108.7, 81.3, 81.0, 73.4, 65.9, 40.9, 31.7, 31.0, 26.0, 26.0, 23.9, 18.5, 6.8, 4.4, –4.5, –4.8; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{24}H_{49}O_4Si_2$, 457.3169 found 457.3174.

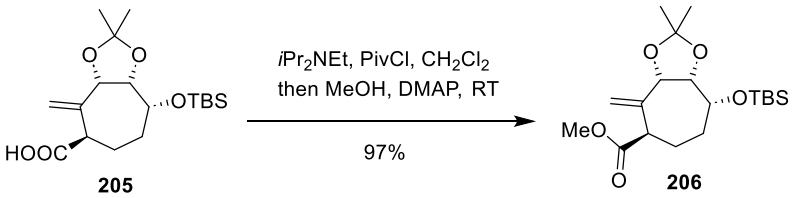


Compound 204: To a solution of **203** (9.7 mg, 0.021 mmol) in THF (1.00 mL) was added TBAF (1 M THF solution, 0.0230 mL, 0.0230 mmol) at room temperature. The solution was stirred for 40 min. After addition of water, the mixture was extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20–30% EtOAc/hexane) to afford **204** (6.5 mg, 90%) as a white solid: $[\alpha]_D^{26}$ –32.4° (*c* 0.525, $CHCl_3$); IR (neat) 3443, 2952, 2930, 2896, 2857, 1644, 1382, 1255, 1208, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (1H, s), 4.95 (1H, s), 4.61 (1H, d, J = 8.7 Hz), 4.43 (1H, ddd, J = 8.6, 2.5, 1.2 Hz), 3.74–3.59 (3H, m), 2.47 (1H, dddd, J = 14.6, 10.1, 7.4, 2.7 Hz), 2.21 (1H, dddd, J = 17.4, 14.1, 10.7, 3.7 Hz), 1.87 (1H, ddd, J = 10.7, 6.8, 3.8 Hz), 1.63–1.59 (1H, m), 1.58 (3H, s), 1.39 (3H, s), 1.03 (1H, ddd, J

= 16.8, 13.1, 3.7 Hz), 0.89 (3H, s), 0.07 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 113.5, 108.9, 81.2, 80.7, 73.1, 65.3, 41.3, 31.5, 30.8, 26.0, 23.9, 18.5, –4.5, –4.8; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{18}H_{35}O_4Si$, 343.2305 found 343.2303.

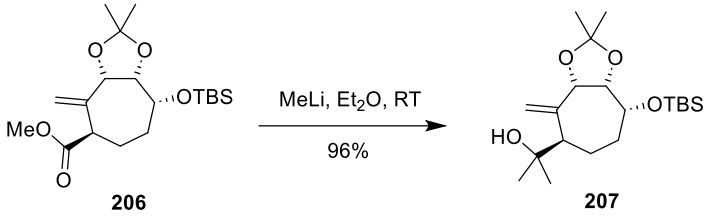


Compound 205: To a solution of **204** (35.6 mg, 0.104 mmol) in CH_2Cl_2 (1.00 mL) and phosphate buffer (pH = 7.0) (1.00 mL) was added AZADOL (5.0 mg, 0.033 mmol) and $PhI(OAc)_2$ (104 mg, 0.323 mmol) at room temperature. The reaction solution was stirred at room temperature for 6 h. After the solution was cooled to 0 °C, quenched with aqueous saturated $Na_2S_2O_3$ and stirred at room temperature for 1h. The mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7–30% EtOAc/hexane) to afford **205** (33.1 mg, 93%) as a white solid: $[\alpha]_D^{26}$ –60.2° (*c* 0.467, $CHCl_3$); IR (neat) 3089, 2953, 2929, 2857, 1707, 1383, 1256, 1207, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ5.18 (1H, s), 5.17 (1H, s), 4.68 (1H, d, *J* = 8.6 Hz), 4.42 (1H, d, *J* = 8.6 Hz), 3.69 (1H, d, *J* = 10.4 Hz), 3.32 (1H, dd, *J* = 12.0, 2.8 Hz), 2.17 (1H, dddd, *J* = 16.8, 13.9, 10.6, 3.6 Hz), 2.04 (1H, ddd, *J* = 10.9, 7.1, 3.7 Hz), 1.66–1.52 (2H, m), 1.60 (3H, s), 1.40 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 145.6, 115.8, 109.1, 81.1, 79.7, 72.6, 44.6, 30.5, 30.1, 26.1, 26.0, 23.8, 18.4, –4.5, –4.8; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{18}H_{33}O_5Si$, 357.2097 found 357.2102.



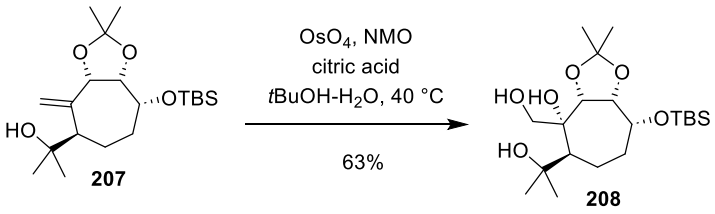
Compound 206: To a solution of **205** (408 mg, 1.14 mmol) in CH_2Cl_2 (18.5 mL) was added *i*Pr_2NEt (0.800 mL, 4.58 mmol) at room temperature. The reaction solution was stirred at room temperature for 3 min, cooled to 0 °C and added PivCl (0.300 mL, 2.44 mmol). After the solution was stirred for 25 min at 0 °C, added MeOH (0.490 mL, 12.1 mmol), DMAP (28.1 mg, 0.230 mmol) and stirred at 0 °C for 50 min. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ and extracted with $CHCl_3$ twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford **206** (409 mg, 97%) as a colorless oil: $[\alpha]_D^{25}$ –91.9° (*c* 0.175, $CHCl_3$); IR (neat) 2952, 2930, 1737, 1258, 1208, 1167, 1080 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (1H, s), 5.08 (1H, s), 4.66 (1H, d, *J* = 8.6 Hz), 4.42 (1H, d, *J* = 8.6 Hz),

3.69–3.67 (1H, m), 3.67 (3H, s), 3.30 (1H, dd, *J* = 12.3, 2.9 Hz), 2.17 (1H, dddd, *J* = 17.2, 13.9, 10.8, 3.6 Hz), 1.99 (1H, ddd, *J* = 11.0, 7.6, 4.0 Hz), 1.66–1.57 (2H, m), 1.60 (3H, s), 1.40 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 146.0, 115.4, 109.1, 81.1, 79.7, 72.7, 51.9, 44.7, 30.7, 30.1, 26.1, 26.0, 23.8, 18.4, –4.5, –4.8; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{19}H_{35}O_5Si$, 371.2254 found 371.2249.



206 **207**

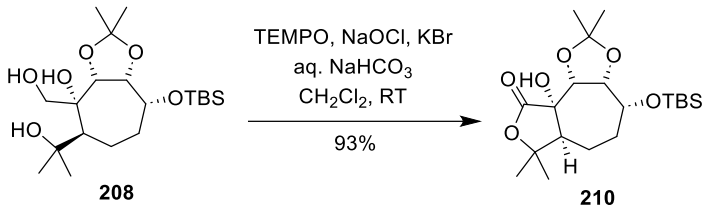
Compound 207: To a solution of **206** (409 mg, 1.10 mmol) in Et_2O (11.0 mL) was added MeLi (2.53 M Et_2O solution, 1.74 mL, 4.40 mmol) at 0 °C under N_2 atmosphere. The solution was stirred for 1 h at room temperature. The resulting mixture was quenched with aqueous saturated NH_4Cl, extracted with Et_2O twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10–25% EtOAc/hexane) to afford **207** (390 mg, 96%) as a colorless oil: $[\alpha]_D^{27}$ –25.8° (*c* 0.483, $CHCl_3$); IR (neat) 3503, 2952, 2931, 1381, 1258, 1208, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (1H, s), 5.08 (1H, s), 4.52 (1H, d, *J* = 8.5 Hz), 4.43 (1H, d, *J* = 8.5 Hz), 3.74 (1H, d, *J* = 10.3 Hz), 2.15-1.99 (1H, m), 1.70–1.67 (1H, m), 1.56 (3H, s), 1.39 (3H, s), 1.33–1.25 (1H, m), 1.29 (3H, s), 1.26 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 114.4, 108.9, 81.6, 81.4, 72.9, 72.7, 48.6, 31.5, 29.7, 29.6, 28.2, 26.2, 26.0, 24.1, 18.4, –4.5, –4.8; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{20}H_{39}O_4Si$, 371.2618 found 371.2613.



207 **208**

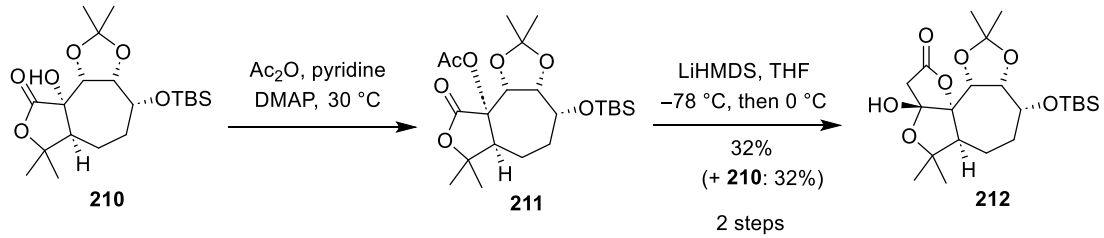
Compound 208: To a solution of **207** (65.0 mg, 0.175 mmol) in *t*BuOH (2.00 mL) and H_2O (1.00 mL) was added OsO_4 (1g / 100 mL *t*BuOH solution, 4.50 mL, 0.177 mmol) and NMO (308 mg, 2.63 mmol) and citric acid (343 mg, 1.79 mmol) at room temperature. The reaction solution was stirred at 40 °C for 17 h. After the solution was cooled to 0 °C, quenched with aqueous saturated $Na_2S_2O_3$ and stirred at room temperature for 40 min. The mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (40–60% EtOAc/hexane) to afford **208** (44.5 mg, 63%) as a colorless oil: $[\alpha]_D^{21}$ +2.00° (*c* 1.042, $CHCl_3$); IR (neat) 3375, 2955, 2930, 2897, 2858, 1471, 1381, 1258, 1210 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (1H, s, br), 4.46 (1H, s, br), 4.31 (1H, s, br), 4.07 (1H, s, br), 3.92 (1H, d, *J* = 11.4 Hz), 3.65

(1H, s, br), 2.80 (1H, s, br), 2.16 (1H, dd, J = 8.4, 2.4 Hz), 1.91 (1H, s, br), 1.78 (1H, s, br), 1.71 (1H, s, br), 1.57 (3H, s), 1.37 (3H, s), 1.35 (3H, s), 1.33 (3H, s), 0.92 (9H, s), 0.12 (3H, s), 0.10 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 107.6, 79.6, 78.5, 71.3, 60.4, 33.1, 26.5, 25.9, 25.8, 23.9, 18.3, –4.6, –4.7; HRMS (FAB, m/z): $[M+H]^+$ calcd for $C_{20}H_{41}O_6Si$, 405.2672 found 405.2674.



208 210

Compound 210: To a solution of **208** (1.26 g, 3.11 mmol) in CH_2Cl_2 (100 mL) was added 5% aqueous $NaHCO_3$ solution (40.0 mL) and KBr (45.0 mg, 0.378 mmol) and TEMPO (107 mg, 0.685 mmol) at room temperature. After the solution was cooled to 0 °C, added aqueous NaOCl (8.50 mL) and stirred at room temperature for 17 h. The solution was additional TEMPO (50.8 mg, 0.325) and aqueous NaOCl (4.00 mL) added and stirred at room temperature for 5 h. The reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$, extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (25–40% EtOAc/hexane) to afford **210** (1.16 g, 93%) as a white solid: $[\alpha]_D^{18}$ –26.8° (*c* 0.417, $CHCl_3$); IR (neat) 3276, 2928, 2854, 1768, 1469, 1380, 1265, 1206, 1170, 1022, 832 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.25 (1H, br), 4.21 (1H, d, J = 8.3 Hz), 4.01 (1H, ddd, J = 9.6, 6.2, 2.9 Hz), 3.86 (1H, dd, J = 8.3, 3.0 Hz), 2.40 (1H, dd, J = 11.7, 4.0 Hz), 1.60–1.51 (1H, m), 1.53 (3H, s), 1.49–1.42 (1H, m), 1.20 (3H, s), 1.20–1.15 (1H, m), 1.18 (3H, s), 0.96 (9H, s), 0.91 (3H, s), 0.86–0.78 (1H, m), 0.14 (3H, s), 0.03 (3H, s); ^{13}C NMR (126 MHz, C_6D_6) δ 173.0, 107.8, 81.5, 78.0, 77.6, 77.5, 68.7, 54.6, 30.9, 30.1, 25.9, 25.6, 24.3, 23.4, 21.1, 17.9, –4.9, –5.4; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{20}H_{37}O_6Si$, 401.2359 found 401.2362.

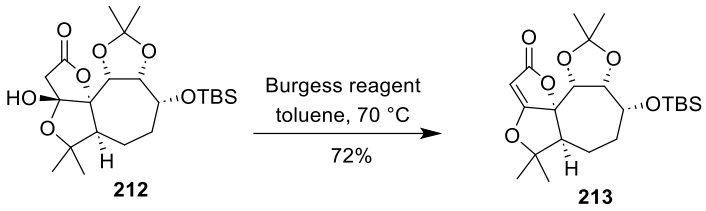


210 211 212

Compound 212: To a solution of **210** (29.3 mg, 0.0731 mmol) in Ac_2O (1.00 mL) and pyridine (1.00 mL) was added DMAP (12.0 mg, 0.0982 mmol) at room temperature under N_2 atmosphere. The reaction solution was stirred at 30 °C for 22 h. The resulting mixture was quenched with aqueous saturated $NaHCO_3$, extracted with EtOAc twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was filtered through silica gel column to give crude **211**, which was used for the next reaction without further purification.

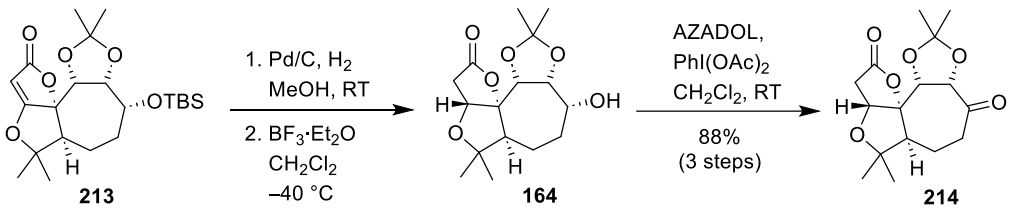
To a solution of the above crude **211** in THF (0.700 mL) was added LiHMDS (1 M THF solution, 0.200

mL, 0.200 mmol) at −78 °C under N_2 atmosphere. The reaction solution was stirred at 0 °C for 10 min. The resulting mixture was quenched with aqueous saturated $NaHCO_3$, extracted with EtOAc twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20–50% EtOAc/hexane) to afford **212** (10.7 mg, 32%) as a colorless oil and **210** (9.9 mg, 32%) as a white solid. Compound **212**: $[\alpha]_D^{22}$ −2.8° (*c* 0.375, $CHCl_3$); IR (neat) 3413, 2951, 2928, 2855, 1778, 1383, 1254, 1198, 1068, 1009 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ4.74 (1H, d, *J* = 8.1 Hz), 4.39 (1H, dd, *J* = 6.1, 3.6 Hz), 4.29 (1H, dd, *J* = 8.1, 3.2 Hz), 3.07 (1H, dd, *J* = 12.2, 3.9 Hz), 2.77 (2H, s), 2.61 (1H, br), 1.97–1.91 (1H, m), 1.87–1.80 (1H, m), 1.66–1.56 (2H, m), 1.46 (3H, s), 1.35 (3H, s), 1.29 (3H, s), 1.28 (3H, s), 0.94 (9H, s), 0.20 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 108.8, 108.6, 96.2, 87.1, 77.9, 74.0, 67.7, 51.6, 43.2, 31.2, 30.6, 26.0, 25.8, 25.5, 25.0, 22.0, 18.3, –3.9, –5.6; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{22}H_{39}O_7Si$, 443.2465 found 443.2458.



212 **213**

Compound 213: To a solution of **212** (2.6 mg, 5.9 μmol) in toluene (0.500 mL) was added Burgess reagent (10.0 mg, 0.0420 mmol) at room temperature under N_2 atmosphere. The reaction solution was stirred at 70 °C for 1.5 h. The resulting mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (15–50% EtOAc/hexane) to afford **213** (1.8 mg, 72%) as a white solid: $[\alpha]_D^{21}$ –34.5° (*c* 0. 208, $CHCl_3$); IR (neat) 2950, 2925, 2894, 2853, 1751, 1658, 1076, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ5.05 (1H, s), 4.39 (1H, dd, *J* = 8.2, 4.3 Hz), 4.32 (1H, d, *J* = 7.5 Hz), 4.26 (1H, dd, *J* = 7.5, 4.4 Hz), 2.50–2.39 (2H, m), 1.99–1.93 (1H, m), 1.65–1.58 (2H, m), 1.58 (3H, s), 1.52 (3H, s), 1.46 (3H, s), 1.33 (3H, s), 0.95 (9H, s), 0.21 (3H, s), 0.08 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.4, 175.0, 110.3, 99.7, 89.9, 88.3, 80.1, 74.8, 64.8, 49.8, 31.2, 27.9, 25.9, 25.8, 25.4, 25.1, 18.5, 18.1, –4.1, –5.4; HRMS (FAB, *m/z*): $[M+Na]^+$ calcd for $C_{22}H_{36}O_6SiNa$, 447.2179 found 447.2181.



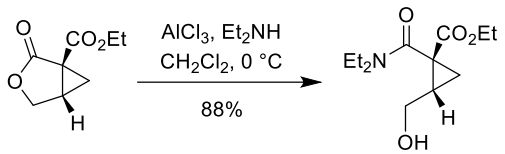
213 **164** **214**

Compound 214: To a solution of **213** (2.5 mg, 5.9 μmol) in MeOH (1.00 mL) was added 10% Pd/C (2.7 mg, 2.5 μmol) at room temperature. After replacement of hydrogen atmosphere, the reaction solution was stirred for 17 h at room temperature. The solution was filtered through a pad of celite and evaporated. The

obtained crude was used for the next reaction without further purification.

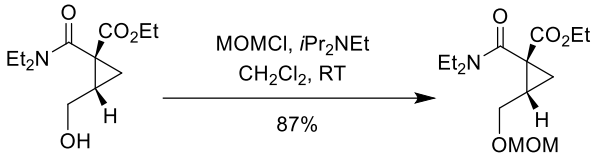
To a solution of the above crude in CH_2Cl_2 (0.500 mL) was added $BF_3{\cdot}Et_2O$ (10.0 μL, 0.0796 mmol) at –40 °C under N_2 atmosphere. The solution was stirred for 40 min at –40 °C. The resulting mixture was quenched with aqueous saturated $NaHCO_3$, extracted with EtOAc twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained crude alcohol **164** was used for the next reaction without further purification.

To a solution of the above crude alcohol **164** in CH_2Cl_2 (0.500 mL) added AZADOL (2.3 mg, 0.015 mmol) and $PhI(OAc)_2$ (8.0 mg, 0.025 mmol) at room temperature. The reaction solution was stirred at room temperature for 4 h. After the solution was cooled to 0 °C, quenched with aqueous saturated $Na_2S_2O_3$. The mixture was extracted with EtOAc twice. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (80–100% EtOAc/hexane) to afford **214** (1.6 mg, 88%) as a white solid: $[\alpha]_D^{25}$ –0.2° (*c* 0.133, $CHCl_3$); IR (neat) 2982, 2924, 2852, 1776, 1729, 1193, 1179, 933 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ4.94 (1H, d, *J* = 9.8 Hz), 4.73 (1H, d, *J* = 9.3 Hz), 4.54 (1H, dd, *J* = 6.9, 0.8 Hz), 2.81 (1H, dd, *J* = 18.5, 6.9 Hz), 2.75 (1H, ddd, *J* = 18.0, 7.2, 3.6 Hz), 2.62–2.53 (2H, m), 2.11 (1H, dd, *J* = 13.1, 3.4 Hz), 1.87–1.68 (2H, m), 1.50 (3H, s), 1.38 (3H, s), 1.35 (3H, s), 1.21 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 174.9, 110.3, 95.1, 83.6, 80.8, 78.6, 77.8, 57.4, 39.1, 36.4, 27.5, 25.8, 24.3, 20.9, 18.7; HRMS (FAB, *m/z*): $[M+Na]^+$ calcd for $C_{16}H_{22}O_6Na$, 333.1314 found 333.1309.



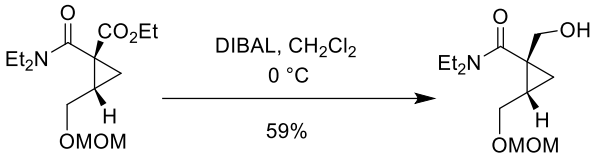
225 **232**

Compound 232: To a stirred suspension of $AlCl_3$ (11.5 g, 86.3 mmol) in anhydrous CH_2Cl_2 (250 mL) was added Et_2NH (17.5 mL, 170 mmol) at 0 °C under N_2 atmosphere. The reaction solution was warmed to room temperature and stirred for 30 min. After the solution was cooled to 0 °C, added the solution of **225** (5.65g, 33.2 mmol) in anhydrous CH_2Cl_2 (60.0 mL) and stirred for 1 h at the same temperature. After addition of ice water (300 mL), the reaction solution was warmed to room temperature and stirred for 2 h. The mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (60–90% EtOAc/hexane) to afford **232** (7.14 g, 88%) as a colorless oil: $[\alpha]_D^{27}$ +34.7° (*c* 0.890, $CHCl_3$); IR (neat) 3420, 2979, 2939, 2876, 1726, 1617, 1279 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.56 (1H, d, *J* = 9.6 Hz), 4.26–4.18 (1H, m), 4.16–4.09 (1H, m), 4.04 (1H, ddd, *J* = 12.3, 12.3, 4.5 Hz), 3.61–3.46 (2H, m), 3.43–3.33 (1H, m), 3.33–3.25 (1H, m), 3.06 (1H, ddd, *J* = 12.8, 12.8, 2.8 Hz), 2.13–2.06 (1H, m), 1.69 (1H, dd, *J* = 9.1, 4.5 Hz), 1.61 (1H, br), 1.26 (3H, t, *J* = 7.2 Hz), 1.21–1.14 (6H, m), 1.05 (1H, dd, *J* = 6.8, 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 167.5, 63.6, 61.7, 42.1, 39.3, 33.2, 31.4, 19.1, 14.1, 13.4, 11.9; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{12}H_{22}NO_4$, 244.1549 found 244.1544.



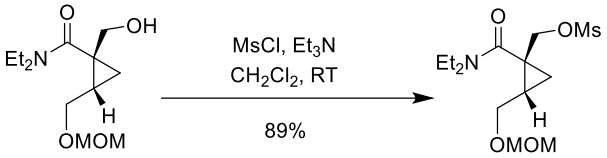
232 233

Compound 233: To a solution of **232** (7.14 g, 29.3 mmol) in anhydrous CH_2Cl_2 (190 mL) were added *i*Pr_2NEt (31.0 mL, 177 mmol) and MOMCl (9.00 mL, 120 mmol) at 0 °C under N_2 atmosphere. The solution was warmed to room temperature and stirred for 16 h. After addition of water, the mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (40–90% EtOAc/hexane) to afford **233** (7.34 g, 87%) as a colorless oil: $[\alpha]_D^{20}$ +73.9° (*c* 0.780, $CHCl_3$); IR (neat) 2979, 2937, 2883, 1725, 1643, 1463, 1445, 1432, 1281, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.59 (2H, dd, *J* = 17.3, 6.5 Hz), 4.23–4.10 (2H, m), 3.53–3.27 (6H, m), 3.34 (3H, s), 2.30–2.23 (1H, m), 1.49 (1H, dd, *J* = 7,1, 4.5 Hz), 1.44 (1H, dd, *J* = 9.3, 4,5 Hz), 1.26 (3H, t, *J* = 7.1 Hz), 1.17 (3H, t, *J* = 7.1 Hz), 1.13 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 165.5, 96.4, 66.8, 61.6, 55.3, 41.9, 38.8, 33.8, 26.7, 19.8, 14.0, 13.1, 12.1; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{14}H_{26}NO_5$, 288.1811 found 288.1814.



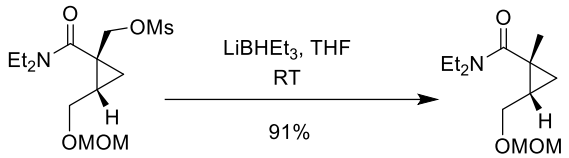
233 234

Compound 234: To a solution of **233** (7.34 g, 25.5 mmol) in anhydrous CH_2Cl_2 (250 mL) was added DIBAL (1 M toluene solution, 76.0 mL, 76.0 mmol) at −78 °C under N_2 atmosphere. The solution was warmed to 0 °C and stirred for 50 min. After addition of saturated aqueous potassium sodium tartrate, the reaction solution was warmed to room temperature and stirred for 18 h. The mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2% MeOH/$CHCl_3$) to afford **234** (3.67 g, 59%) as a colorless oil: $[\alpha]_D^{20}$ +87.4° (*c* 0.550, $CHCl_3$); IR (neat) 3370, 2946, 2885, 1604, 1465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.62 (2H, dd, *J* = 17.4, 6.5 Hz), 3.78 (1H, br), 3.78 (1H, dd, *J* = 11.2, 6.7 Hz), 3.67 (1H, dd, *J* = 10.7, 5.9 Hz), 3.47 (1H, dd, *J* = 11.2, 2.9 Hz), 3.44 (1H, br), 3.35 (3H, s), 3.33 (2H, br), 3.24 (1H, dd, *J* = 10.7, 6.7 Hz), 2.45 (1H, br), 1.44–1.38 (1H, m), 1.22 (3H, br), 1.10 (3H, br), 1.09 (1H, dd, *J* = 5.5, 5.5 Hz), 1.02 (1H, dd, *J* = 8.6, 5.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 96.4, 68.2, 68.0, 55.3, 41.7, 39.3, 32.5, 22.1, 15.3, 14.1, 12.6; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{12}H_{24}NO_4$, 246.1705 found 246.1709.



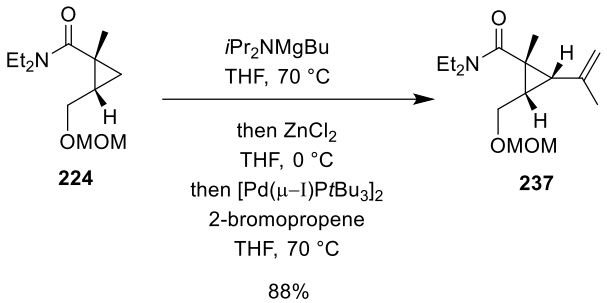
234 **235**

Compound 235: To a solution of **234** (3.67 g, 15.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was added Et_3N (6.00 mL, 43.3 mmol) at room temperature under N_2 atmosphere. The solution was cooled to 0 °C and added MsCl (2.30 mL, 29.7 mmol). The solution was warmed to room temperature and stirred for 1 h. The solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1% MeOH/$CHCl_3$) to afford **235** (4.30 g, 89%) as a colorless oil: $[\alpha]_D^{21}$ +63.9° (*c* 0.850, $CHCl_3$); IR (neat) 2973, 2937, 2885, 1629, 1353, 1175, 937 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.72 (1H, dd, *J* = 11.0, 1.2 Hz), 4.58 (2H, dd, *J* = 14.0, 6.5 Hz), 3.86 (1H, d, *J* = 11.0 Hz), 3.83–3.73 (1H, m), 3.58 (1H, dd, *J* = 10.9, 6.3 Hz), 3.34 (3H, s), 3.47–3.28 (4H, m), 3.05 (3H, s). 1.52–1.45 (1H, m), 1.28–1.19 (1H, m), 1.11 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 96.5, 74.9, 67.4, 55.3, 41.9, 39.5, 38.1, 29.6, 23.3, 15.8, 13.9, 12.5; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{13}H_{26}NO_6S$, 324.1481 found 324.1487.



235 **224**

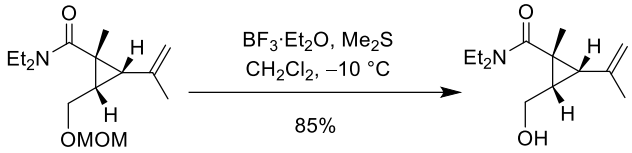
Compound 224: To a solution of **235** (9.76 g, 30.2 mmol) in anhydrous THF (200 mL) was added $LiBHEt_3$ (1 M THF solution, 66.0 mL, 66.0 mmol) at 0 °C under N_2 atmosphere. The solution was warmed to room temperature and stirred for 2 h. After addition of water, the mixture was extracted with EtOAc twice. The organic layer was washed with 1 M HCl and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50–100% EtOAc/hexane) to afford **224** (6.31 g, 91%) as a colorless oil: $[\alpha]_D^{20}$ +109° (*c* 0.400, $CHCl_3$); The ^1H NMR chart was consistent with the report (*Org. Lett.* **2018**, *20*, 7656).



224 **237**

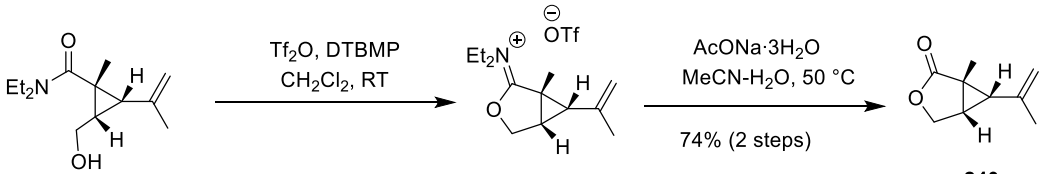
Compound 237: To a nBu_2Mg (1 M heptane solution, 4.53 mL, 4.53 mmol) was added iPr_2NH (0.600 mL, 4.27 mmol) at 0 °C under N_2 atmosphere. The solution was warmed to 50 °C and stirred for 10 min. The solution was cooled to room temperature, added the solution of **224** (281 mg, 1.23 mmol) in anhydrous

THF (4.00 mL). The solution was warmed to 70 °C and stirred for 3 h. The solution was cooled to 0 °C, added $ZnCl_2$ (1 M THF solution, 4.63 mL, 4.63 mmol) and stirred for 20 min at the same temperature. The solution were added the solution of $[Pd(\mu\text{-}I)P\textit{t}Bu_3]_2$ (117 mg, 0.134 mmol) in anhydrous toluene (4.00 mL) and 2-bromopropene (0.450 mL, 5.17 mmol). The solution was warmed to 70 °C and stirred for 19 h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20–50% EtOAc/hexane) to afford **237** (290 mg, 88%) as a brown oil: $[\alpha]_D^{17}$ −54.1° (*c* 0.480, $CHCl_3$); IR (neat) 2971, 2934, 2878, 1634, 1108, 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.82 (1H, s), 4.60 (2H, dd, *J* = 28.2, 6.4 Hz), 4.42 (1H, s), 4.11 (1H, dd, *J* = 11.2, 4.2 Hz), 3.71–3.61 (2H, m), 3.47–3.38 (1H, m), 3.32 (3H, s), 3.34–3.23 (2H, m), 1.88 (3H, s), 1.57 (1H, d, *J* = 9.2 Hz), 1.38 (1H, ddd, *J* = 13.6, 9.5, 4.2 Hz), 1.34 (3H, s), 1.21 (3H, t, *J* = 7.2 Hz), 1.10 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 140.9, 110.1, 96.6, 64.3, 55.1, 41.8, 38.5, 35.5, 31.0, 30.2, 26.0, 26.0, 13.9, 12.2; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{15}H_{28}NO_3$, 270.2069 found 270.2071.



237 **238**

Compound 238: To a solution of **237** (267 mg, 0.992 mmol) in anhydrous CH_2Cl_2 (10.0 mL) were added Me_2S (0.650 mL, 8.89 mmol) and $BF_3{\cdot}Et_2O$ (0.750 mL, 5.97 mmol) at −10 °C under N_2 atmosphere. The solution was stirred for 1h at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (60–80% EtOAc/hexane) to afford **238** (189 mg, 85%) as a yellow oil: $[\alpha]_D^{22}$ −156° (*c* 0.580, $CHCl_3$); IR (neat) 3403, 2973, 2937, 2878, 1611, 1466, 1427, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (3H, s), 4.67 (1H, dd, *J* = 11.1, 2.4 Hz), 4.44 (1H, s), 3.79–3.69 (2H, m), 3,61–3.48 (2H, m), 3.33–3.23 (2H, m), 1.78 (3H, s), 1.55 (1H, d, *J* = 9.8 Hz), 1.41 (1H, ddd, *J* = 15.9, 10.5, 5.5 Hz), 1.34 (3H, s), 1.24 (3H, t, *J* = 7.2 Hz), 1.14 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 140.5, 110.5, 59.2, 42.0, 38.8, 35.5, 32.6, 30.9, 26.3, 26.1, 13.8, 12.0; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{13}H_{24}NO_2$, 226.1807 found 226.1811.

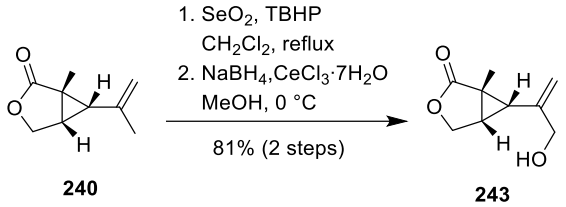


238 **239** **240**

Compound 240: To a solution of **238** (160 mg, 0.710 mmol) in anhydrous CH_2Cl_2 (8.00 mL) were added DTBMP (298 mg, 1.45 mmol) and Tf_2O (0.163 mL, 0.994 mmol) at 0 °C under N_2 atmosphere. The solution was warmed to room temperature and stirred for 50 min. The resulting mixture was concentrated *in vacuo*.

The obtained crude iminium salt **239** was used for the next reaction without further purification.

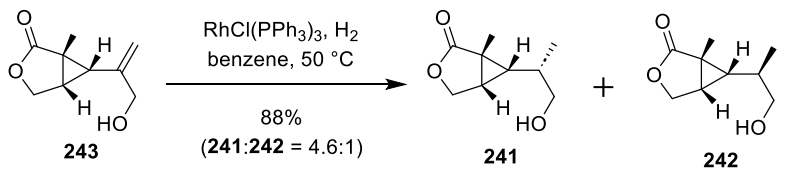
To a solution of the above iminium salt **239** in MeCN (7.20 mL) and H_2O (0.800 mL) was added AcONa ·$3H_2O$ (1.93g, 14.2 mmol) at room temperature. The solution was warmed to 50 °C and stirred for 15 h. The solution was cooled to room temperature and added water. The mixture was extracted with Et_2O twice. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% Et_2O/hexane) to afford **240** (80.3 mg, 74%) as a colorless oil: $[\alpha]_D^{23}$ −70.3° (*c* 0.500, $CHCl_3$); IR (neat) 3085, 2970, 2934, 1761, 1447, 1373, 1301, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, dd, *J* = 2.9, 1.5 Hz), 4.91 (1H, s), 4.32 (1H, dd, *J* = 9.7, 5.3 Hz), 4.06 (1H, d, *J* = 9.7 Hz), 2.19, (1H, dd, *J* = 7.9, 5.3 Hz), 1.90 (1H, d, *J* = 7.9 Hz), 1.80 (3H, s), 1.48 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 136.7, 115.1, 65.1, 34.8, 29.9, 29.3, 22.5, 15.9; HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_9H_{13}O_2$, 153.0910 found 153.0910.



240 **243**

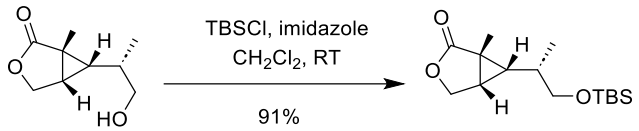
Compound 243: To a solution of **240** (751 mg, 4.93 mmol) in anhydrous CH_2Cl_2 (50.0 mL) were added SeO_2 (1.64 g, 14.8 mmol) and TBHP (5 M decane solution, 8.00 mL, 40.0 mmol) at room temperature under N_2 atmosphere. The solution was warmed to 50 °C and refluxed for 6 h. The solution was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ four times. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The obtained crude aldehyde was used for the next reaction without further purification.

To a solution of the above aldehyde in anhydrous MeOH (50.0 mL) were added $CeCl_3·7H_2O$ (3.79g, 10.2 mmol) and $NaBH_4$ (373 mg, 9.86 mmol) at room temperature under N_2 atmosphere. The solution was stirred for 20 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc seven times. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50–80% EtOAc/hexane) to afford **243** (671 mg, 81%) as a colorless oil: $[\alpha]_D^{27}$ −56.3° (*c* 0.290, $CHCl_3$); IR (neat) 3419, 2970, 2932, 2912, 2871, 1747,1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (1H, s), 5.12 (1H, s), 4.35 (1H, dd, *J* = 9.8, 5.3 Hz), 4.17–4.09 (3H, m), 2.25 (1H, dd, *J* = 7.5, 5.6 Hz), 1.97 (1H, d, *J* = 7.9 Hz), 1.50 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3, 140.3, 114.7, 65.6, 65.3, 31.0, 29.4, 29.3, 15.9; HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_9H_{13}O_3$, 169.0859 found 169.0859.



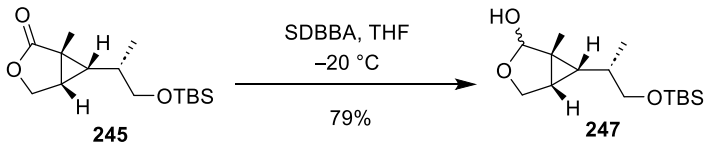
243 **241** **242**

Compound 241, 242: To a solution of **243** (671 mg, 3.99 mmol) in benzene (50.0 mL) was added $RhCl(PPh_3)_3$ (365 mg, 0.395 mmol) at room temperature. After replacement of hydrogen atmosphere, the reaction solution was stirred for 25 h at 50 °C. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50% EtOAc/hexane) to afford **241** (493 mg, 73%) as a brown oil and **242** (107 mg, 16%) as a brown oil. Compound **241**: $[\alpha]_D^{21}$ +18.5° (*c* 0.450, $CHCl_3$); IR (neat) 3461, 2963, 2931, 2872, 1758, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (1H, dd, *J* = 9.9, 5.4 Hz), 4.07 (1H, d, *J* = 9.9 Hz), 3.58 (1H, m), 2.11 (1H, dd, *J* = 7.6, 5.4 Hz), 1.44 (3H, s), 1.37 (1H, m), 1.12 (1H, dd, *J* = 11.0, 7.8 Hz), 1.08 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 67.4, 65.0, 32.7, 31.3, 29.2, 27.1, 16.5, 15.8; HRMS (FAB, *m/z*): $[M+Na]^+$ calcd for $C_9H_{14}O_3Na$, 193.0841 found 193.0839; compound **242**: $[\alpha]_D^{19}$ +36.5° (*c* 0.420, $CHCl_3$); IR (neat) 3420, 2963, 2931, 2873, 1749, 1458, 1382, 1303, 1089, 999 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.37 (1H, dd, *J* = 9.8, 5.4 Hz), 4.21 (1H, d, *J* = 9.8 Hz), 3.64-3.55 (2H, m), 2.13 (1H, dd, *J* = 7.4, 5.6 Hz), 1.49–1.41 (1H, m), 1.45 (3H, s), 1.11 (1H, dd, *J* = 10.9, 7.6 Hz), 1.03 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3, 67.9, 65.6, 33.3, 31.0, 28.7, 27.5, 16.5, 15.9; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_9H_{15}O_3$, 171.1021 found 171.1019.



241 **245**

Compound 245: To a solution of **241** (438 mg, 2.57 mmol) in anhydrous CH_2Cl_2 (30.0 mL) were added imidazole (360 mg, 5.29 mmol) and TBSCl (590 mg, 3.91 mmol) at 0 °C under N_2 atmosphere. The solution was warmed to room temperature and stirred for 1.5 h. After addition of water, the mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7–20% EtOAc/hexane) to afford **245** (667 mg, 91%) as a colorless oil: $[\alpha]_D^{23}$ +42.7° (*c* 0.760, $CHCl_3$); IR (neat) 2956, 2930, 2857, 1767, 1471, 1463, 1253, 1102, 1086, 838, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, dd, *J* = 9.8, 5.4 Hz), 4.05 (1H, d, *J* = 9.8 Hz), 3.58–3.47 (2H, m), 2.08 (1H, dd, *J* = 7.6, 5.4 Hz), 1.41 (3H, s), 1.37–1.28 (1H, m), 1.21 (1H, dd, *J* = 11.0, 7.8 Hz), 1.06 (3H, d, *J* = 6.7 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 67.1, 65.0, 32.5, 31.1, 28.9, 27.5, 25.9, 18.3, 16.7, 15.9, –5.5, –5.5; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{15}H_{29}O_3Si$, 285.1886 found 285.1884.

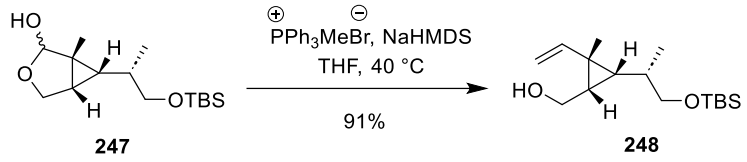


245 **247**

Preparation of SDBBA solution: To a solution of *t*BuONa (2 M THF solution, 1.00 mL, 2.00 mmol) was added DIBAL (1 M toluene solution, 2.00 mL, 2.00 mmol) at 0 °C under N_2 atmosphere. The solution was warmed to room temperature and stirred for 2 h to give SDBBA (0.67 M, 3.00 mL)

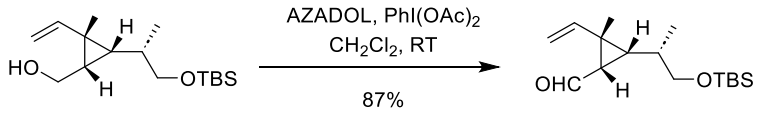
Compound 247: To a solution of **245** (135 mg, 0.475 mmol) in anhydrous THF (7.00 mL) was added

SDBBA (0.67 M toluene and THF solution, 1.50 mL, 1.00 mmol) at –20 °C under N_2 atmosphere. The solution was stirred for 2 h at the same temperature. After addition of Et_2O and saturated aqueous potassium sodium tartrate, the reaction solution was warmed to room temperature and stirred for 1 h. The mixture was extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (15–25% EtOAc/hexane) to afford **247** (107 mg, 79%) as a colorless oil: $[\alpha]_D^{20}$ –31.3° (*c* 0.700, $CHCl_3$); IR (neat) 3387, 2956, 2929, 2858, 1767, 1470, 1463, 1255, 1094, 1057, 837, 776 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.90 (0.4H, d, *J* = 11.6 Hz), 5.40 (0.4H, dd, *J* = 11.6, 0.9 Hz), 5.12 (1H, d, *J* = 4.3 Hz), 4.05 (1H, dd, *J* = 8.5, 3.7 Hz), 3.73 (0.4H, dd, *J* = 9.0, 3.6 Hz), 3.69 (0.4H, d, *J* = 9.0 Hz), 3.57 (1H, d, *J* = 8.5 Hz), 3.54 (0.4H, dd, *J* = 9.2, 3.7 Hz), 3.45–3.38 (2H, m), 3.10 (0.4H, dd, *J* = 10.7, 9.3 Hz), 2.61–2.52 (0.4H, m), 1.91–1.83 (2H, m), 1.28 (3H, s), 1.15 (1.2H, s), 1.03 (1H, dd, *J* = 8.0, 3.6 Hz), 0.99 (9H, s), 0.95 (3.6H, s), 0.93 (3H, d, *J* = 6.7 Hz), 0.87-0.84 (0.4H, m), 0.67 (1.2H, d, *J* = 6.8 Hz), 0.39 (1H, dd, *J* = 10.6, 8.0 Hz), 0.07 (4.2H, s), 0.07 (4.2H, s), 0.07–0.05 (0.4H); ^{13}C NMR (126 MHz, C_6D_6) δ 103.8, 99.2, 70.3, 68.8, 66.2, 63.9, 32.4, 31.9, 31.6, 31.4, 29.9, 29.9, 25.9, 25.1, 24.7, 18.4, 18.2, 17.8, 17.6, 17.4, 16.9, –5.5, –5.7, –5.8, –5.9; HRMS (FAB, *m/z*): $[M+Na]^+$ calcd for $C_{13}H_{30}O_3SiNa$, 309.1862 found 309.1858.



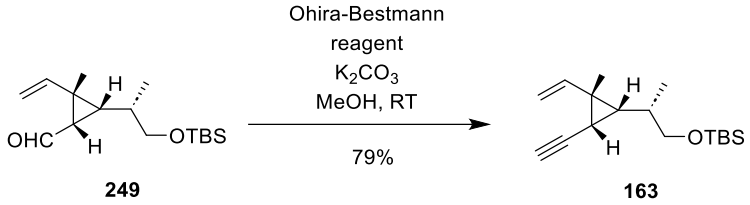
247 **248**

Compound 248: To a solution of methyltriphenylphophonium bromide (303 mg, 0.848 mmol) in anhydrous THF (1.00 mL) was added NaHMDS (1 M THF solution, 0.700 mL, 0.700 mmol) at 0 °C under N_2 atmosphere. After the solution was stirred for 30 min at 0 °C, added the solution of **247** (39.4 mg, 0.138 mmol) in THF (1.60 mL) at the same temperature. The solution was stirred for 2 h at 40 °C. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7–25% EtOAc/hexane) to afford **248** (35.8 mg, 91%) as a colorless oil: $[\alpha]_D^{21}$ +14.8° (*c* 0.680, $CHCl_3$); IR (neat) 3352, 3088, 2955, 2929, 2858, 1632, 1471, 1255, 1087, 1026, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, dd, *J* = 12.2, 10.9 Hz), 5.21 (1H, dd, *J* = 17.2, 1.5 Hz), 5.17 (1H, dd, *J* = 10.9, 1.5 Hz), 3.90–3.87 (1H, m), 3.71–3.66 (1H, m), 3.55 (1H, dd, *J* = 9.2, 4.0 Hz), 3.29 (1H, dd, *J* = 9.7, 7.8 Hz), 1.67–1.59 (1H, m), 1.29–1.23 (1H, m), 1.20 (3H, s), 1.00 (3H, d, *J* = 6.6 Hz), 0.88 (9H, s), 0.82 (1H, dd, *J* = 11.4, 9.2 Hz), 0.02 (3H, s), 0.02 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137,8, 114.6, 67.6, 59.9, 35.2, 32.4, 32.2, 26.0, 24.3, 24.3, 18.4, 17.9, –5.3, –5.4; HRMS (FAB, *m/z*): $[M+H]^+$ calcd for $C_{16}H_{33}O_2Si$, 285.2250 found 285.2252.



248 **249**

Compound 249: To a solution of **248** (21.4 mg, 0.0752 mmol) in CH_2Cl_2 (2.00 mL) were added AZADOL (1.5 mg, 9.8 μmol) and $PhI(OAc)_2$ (68.5 mg, 0.213 mmol) at room temperature. The reaction solution was stirred at room temperature for 2 h. After addition of water, the mixture was extracted with $CHCl_3$ twice. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0–10% EtOAc/hexane) to afford **249** (18.4 mg, 87%) as a colorless oil: $[\alpha]_D^{21}$ +56.3° (*c* 0.760, $CHCl_3$); IR (neat) 2956, 2930, 2858, 1703, 1471, 1254, 1096, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.53 (1H, d, *J* = 6.1 Hz), 6.26 (1H, dd, *J* = 17.6, 11.0 Hz), 5.26–5.21 (2H, m), 3.57 (1H, dd, *J* = 9.7, 4.6 Hz), 3.47 (1H, dd, *J* = 9.7, 6.3 Hz), 2.24–2.14 (1H, m), 1.91 (1H, dd, *J* = 7.8, 6.1 Hz), 1.45 (1H, dd, *J* = 11.4, 8.8 Hz), 1.30 (3H, s), 0.98 (3H, d, *J* = 6.7 Hz), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 135.4, 116.4, 67.3, 42.2, 40.7, 35.5, 31.5, 25.9, 24.7, 18.3, 17.3, –5.4, –5.5; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{16}H_{30}O_2SiNa$, 305.1907 found 305.1908.

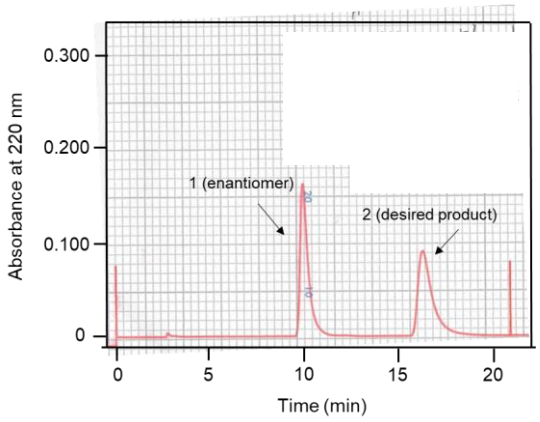


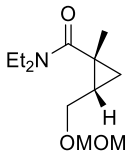
249 **163**

Compound 163: To a solution of **249** (38,1 mg, 0.135 mmol) in anhydrous MeOH (2.00 mL) was added K_2CO_3 (98.0 mg, 0.709 mmol) at room temperature under N_2 atmosphere. The solution was stirred at room temperature for 5 min. The solution was added Ohira-Bestmann reagent (81.0 μL, 0.541 mmol) and stirred for 3 h at the same temperature. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ and extracted with EtOAc twice. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2% Et_2O/hexane) to afford **163** (29.6 mg, 64%) as a colorless oil: $[\alpha]_D^{21}$ +83.4° (*c* 0.160, $CHCl_3$); IR (neat) 3316, 2957, 2930, 2858, 2111, 1471, 1257, 1092, 1039, 904, 837, 776 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.14 (1H, dd, *J* = 17.4, 11.0 Hz), 5.21–5.11 (2H, m), 3.59 (1H, dd, *J* = 9.5, 3.6 Hz), 3.41 (1H, dd, *J* = 9.5, 6.9 Hz), 1.94–1.83 (1H, m), 1.73 (1H, d, *J* = 2.2 Hz), 1.35 (1H, dd, *J* = 8.7, 2.2 Hz), 1.27 (3H, d, *J* = 6.6 Hz), 0.97 (9H, s), 0.92 (3H, s), 0.70 (1H, dd, *J* = 11.1, 8.7 Hz), 0.05 (3H, s), 0.05 (3H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 138.4, 114.1, 81.5, 69.0, 66.8, 35.3, 33.5, 27.2, 25.8, 22.3, 19.9, 18.2, 16.5, –5.5, –5.6; HRMS (APCI, *m/z*): $[M+H]^+$ calcd for $C_{17}H_{31}OSi$, 279.2139 found 279.2138.

3. HPLC analysis

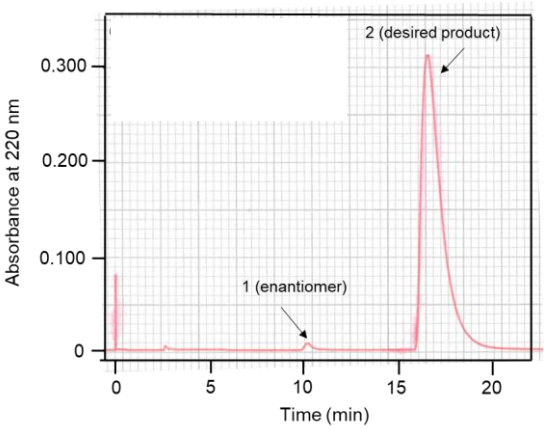
Enantiomeric excess (ee) was caluculated from the peak area of each enantiomers in HPLC (Daicel CHIRAL CEL OX-RH, λ = 220 nm, MeCN/H_2O = 1/4, 1.0 mL/min) by weighing each peak.

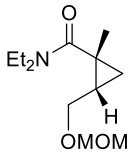




(±) **-224**

peak No.	ret. Time (min)	weight of Paper (mg)	weight of Paper (%)
1	10.0	16.5	48.8
2	16.4	17.3	51.2



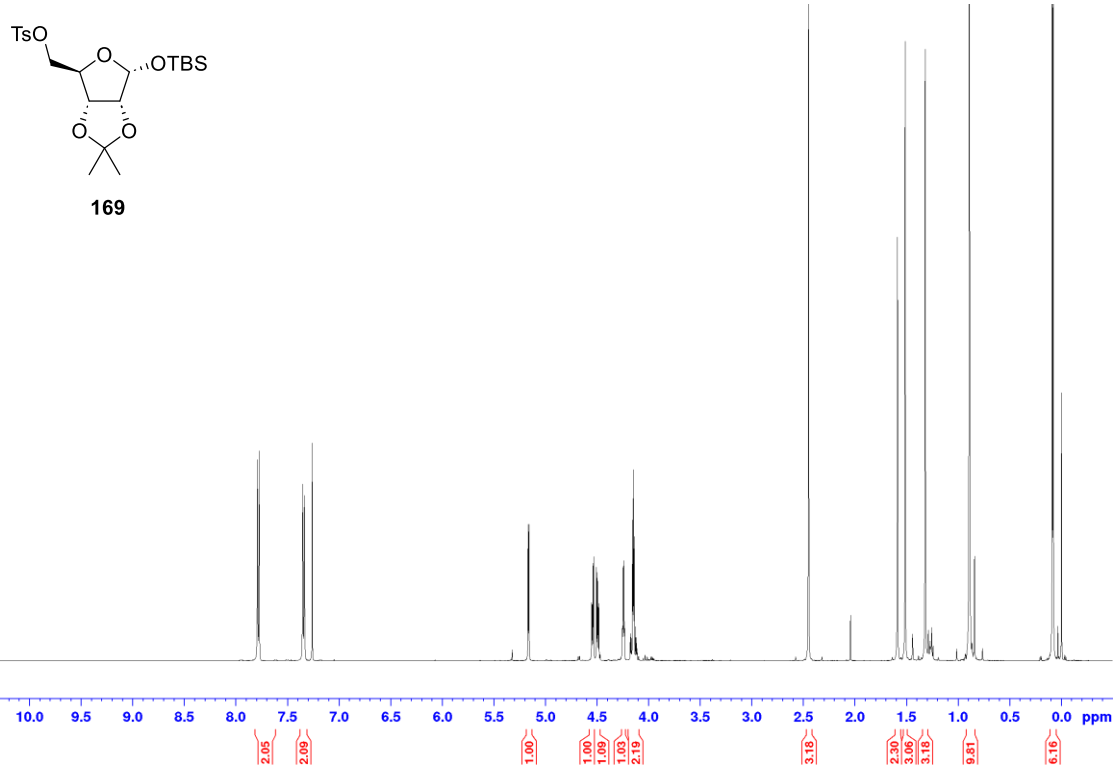


(–) **-224**

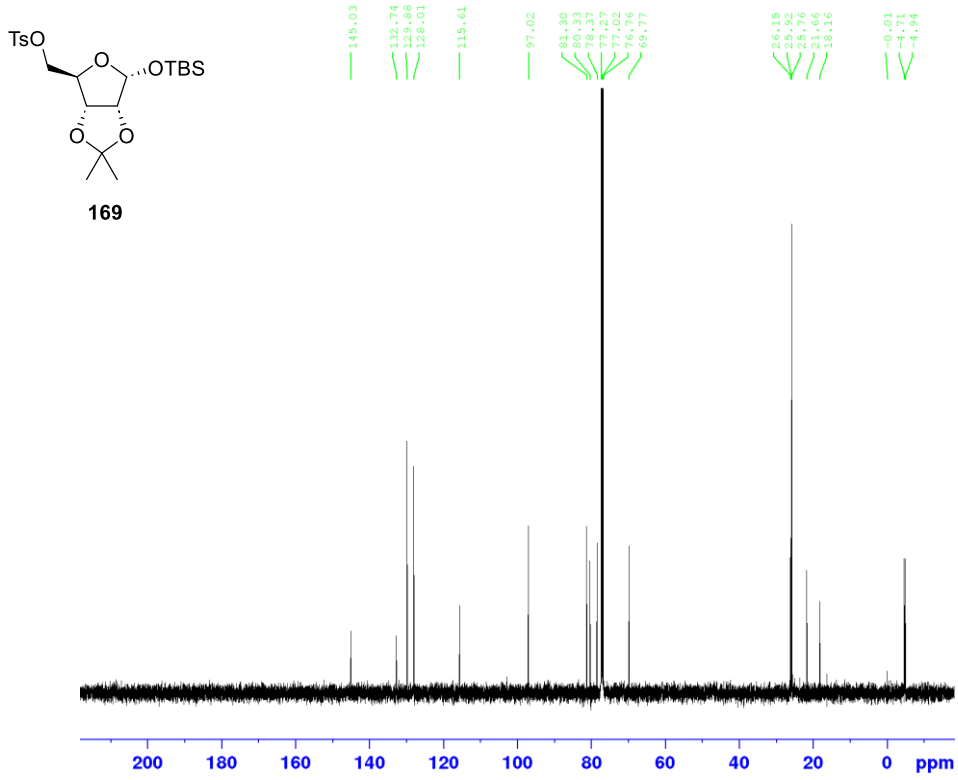
peak No.	ret. Time (min)	weight of Paper (mg)	weight of Paper (%)
1	10.1	0.1	
2	16.6	32.2	>99

4. NMR spectra

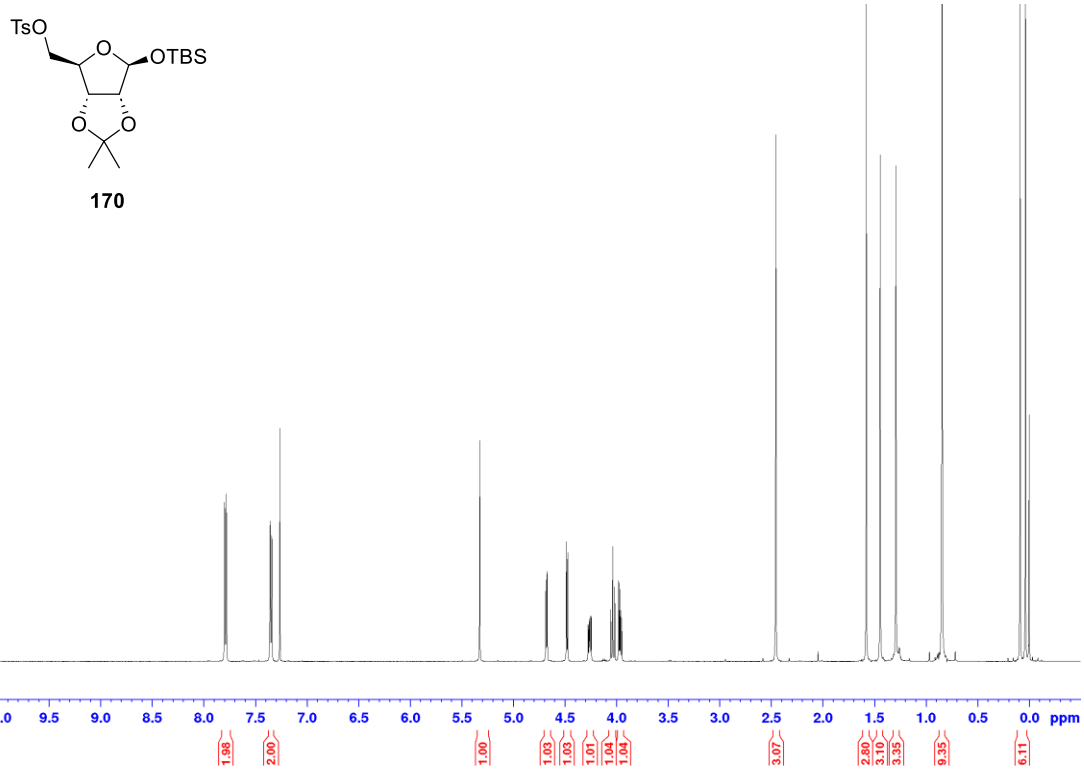
^{1}H NMR spectrum of **169** ($CDCl_3$, 500 MHz, 298 K)



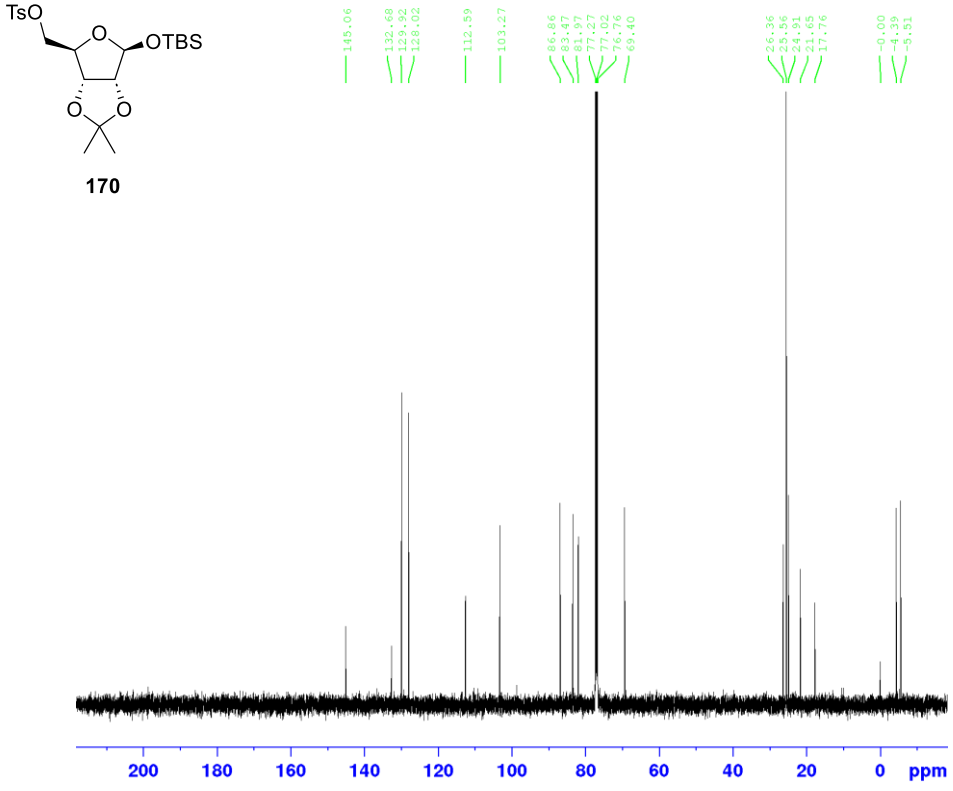
^{13}C NMR spectrum of **169** ($CDCl_3$, 126 MHz, 298 K)



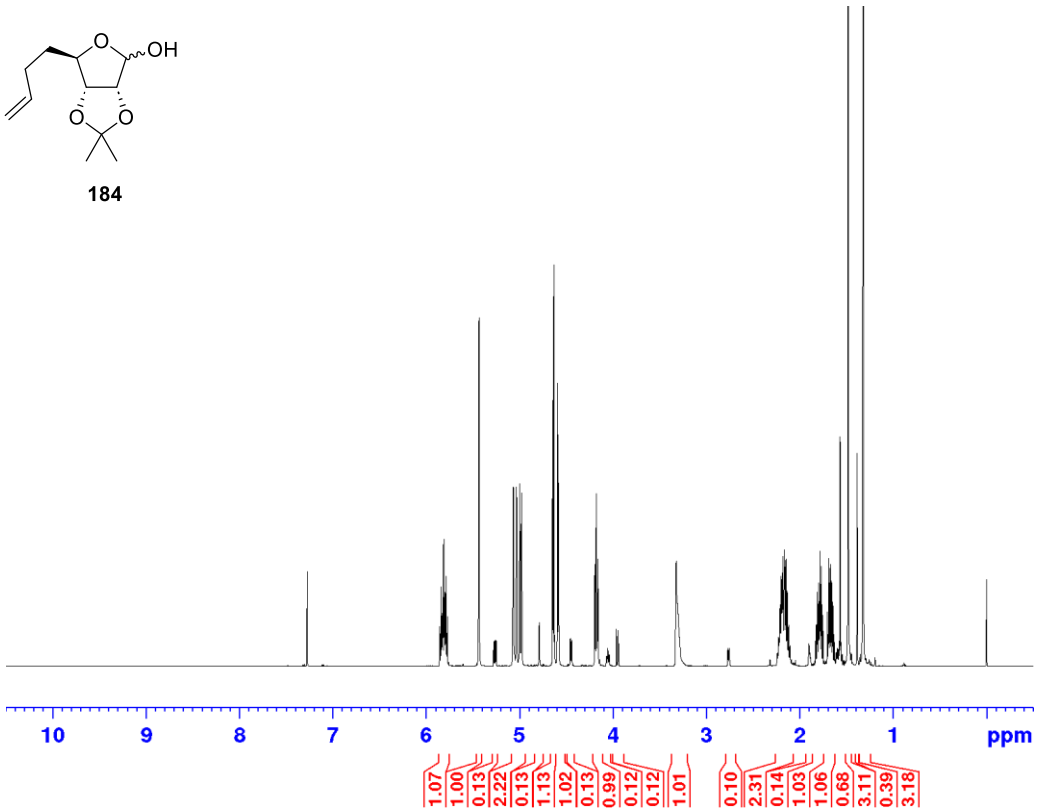
^{1}H NMR spectrum of **170** ($CDCl_3$, 500 MHz, 298 K)



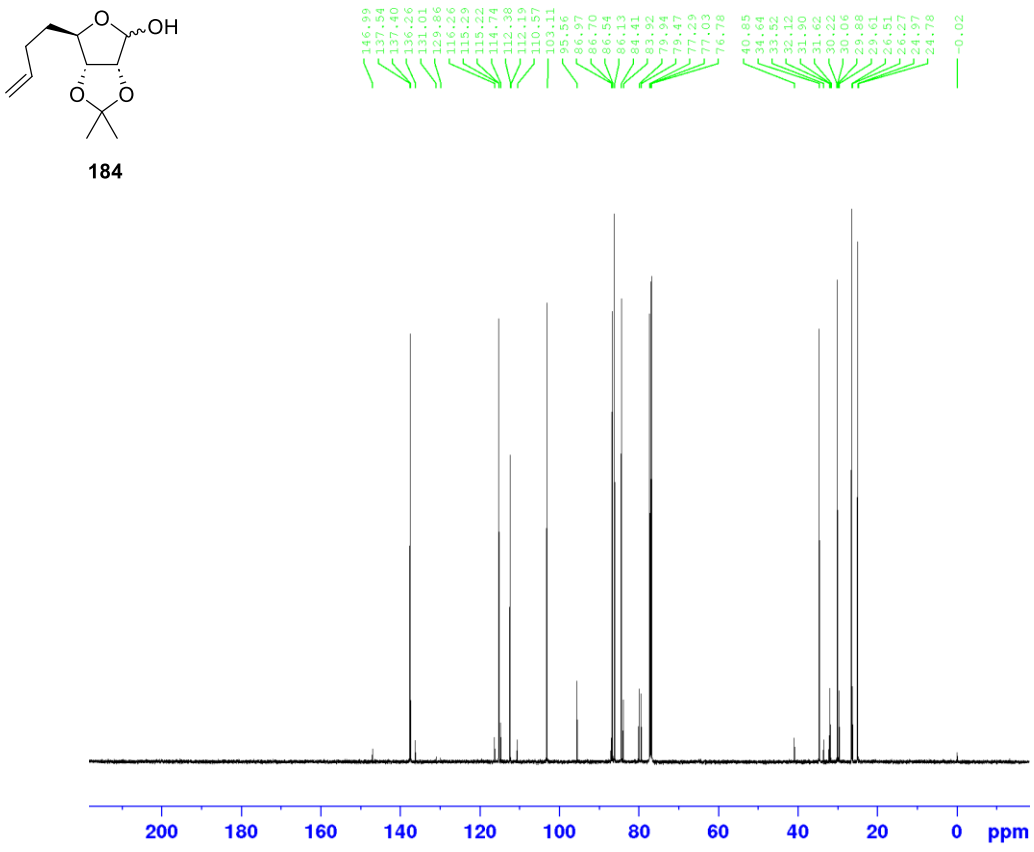
^{13}C NMR spectrum of **170** ($CDCl_3$, 126 MHz, 298 K)



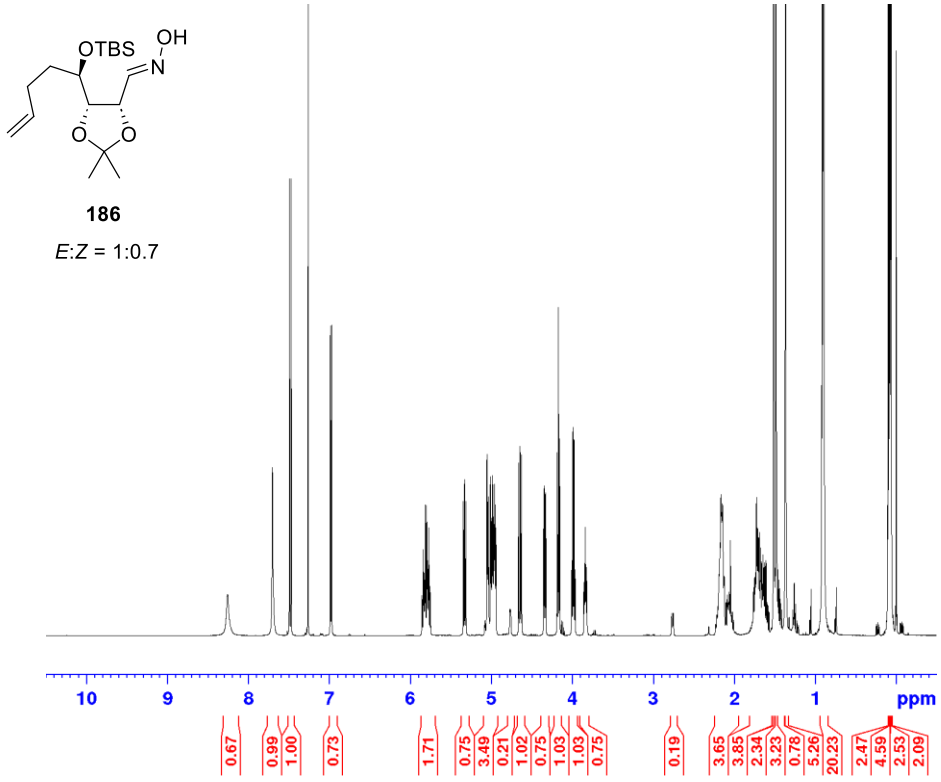
^{1}H NMR spectrum of **184** ($CDCl_3$, 500 MHz, 297 K)



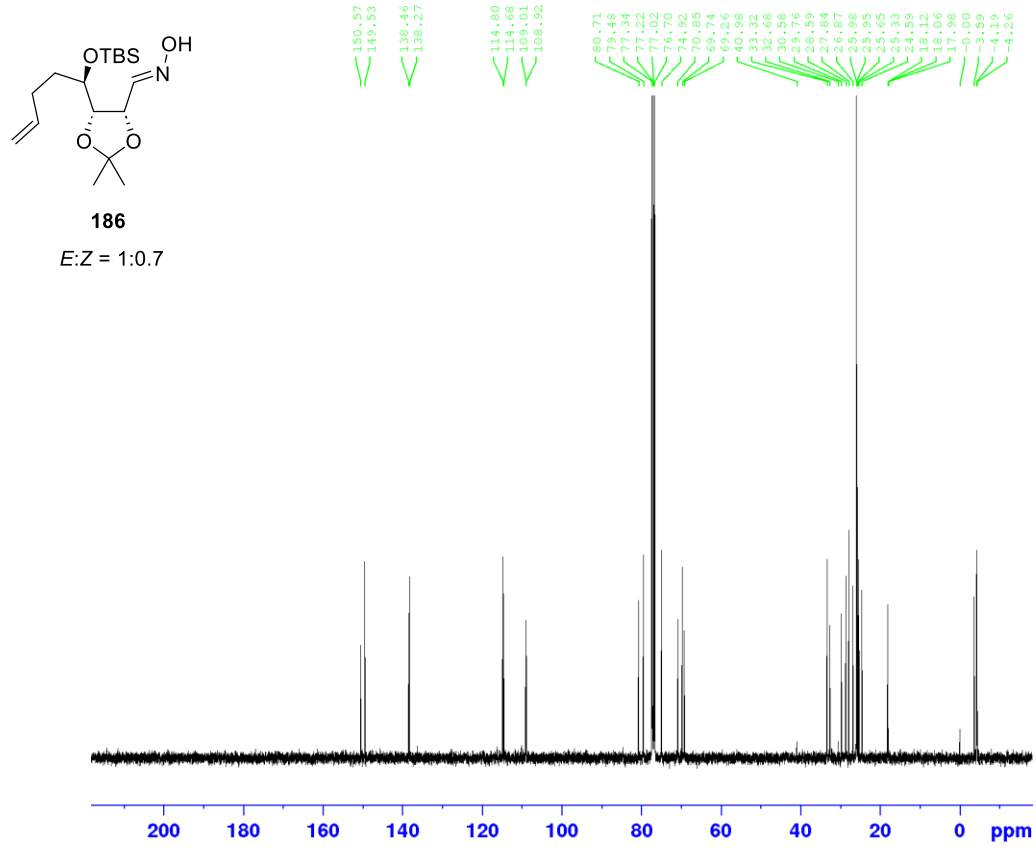
^{13}C NMR spectrum of **184** ($CDCl_3$, 126 MHz, 298 K)



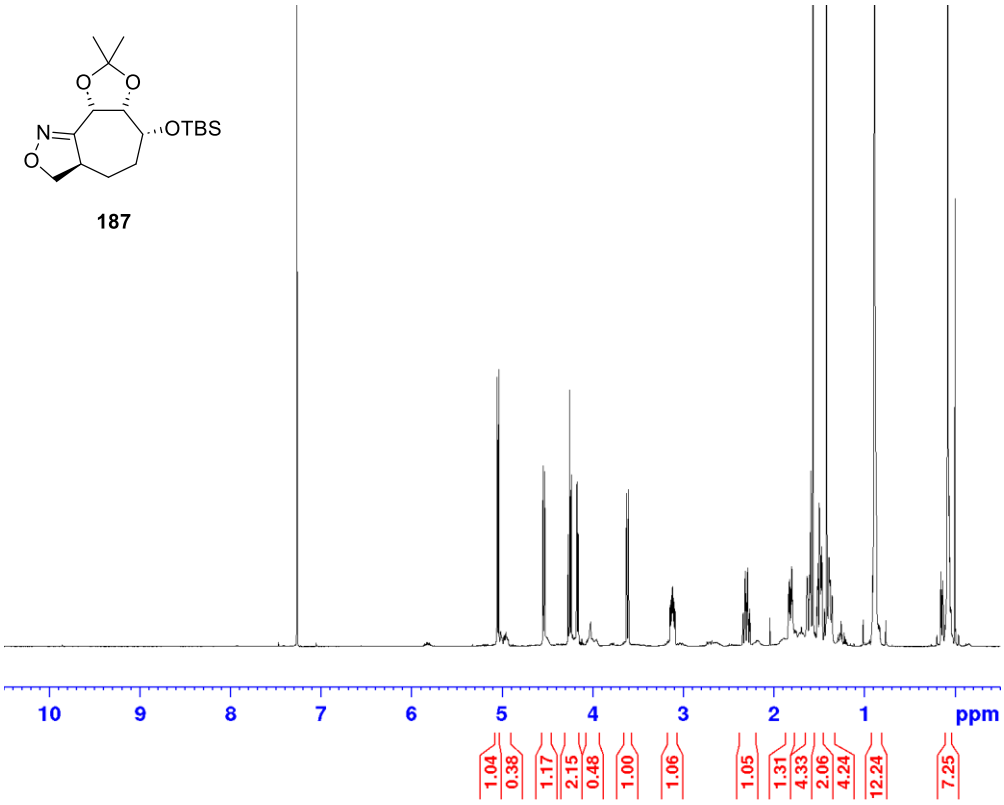
^{1}H NMR spectrum of **186** ($CDCl_3$, 400 MHz, 298 K)



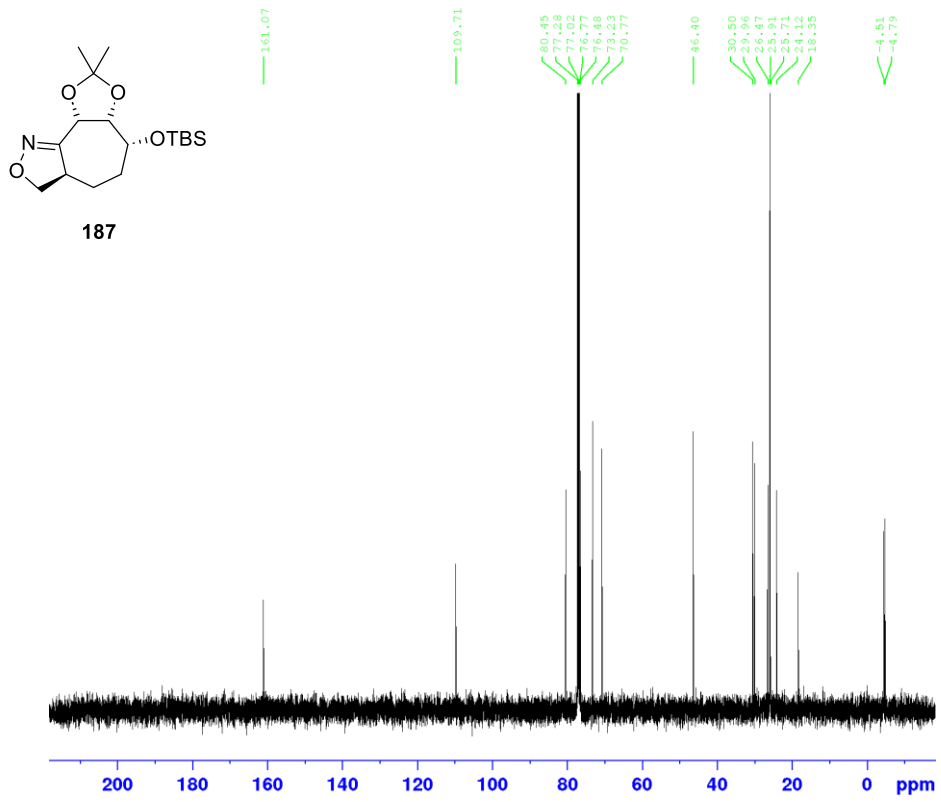
^{13}C NMR spectrum of **186** ($CDCl_3$, 100 MHz, 299 K)



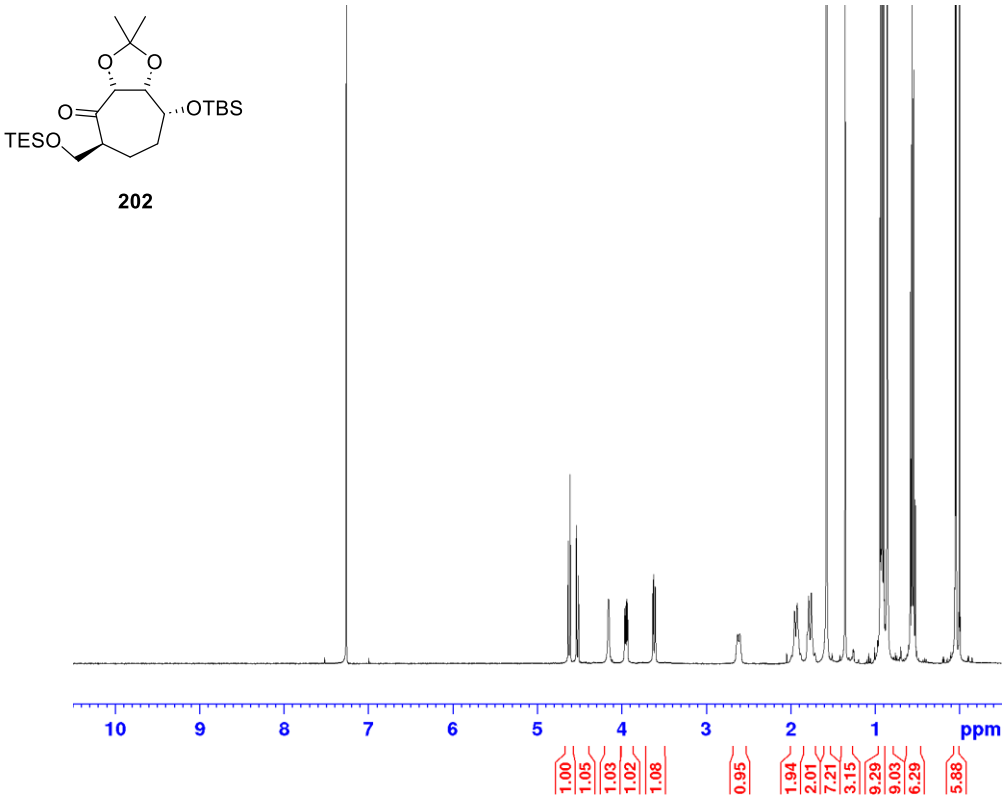
^{1}H NMR spectrum of **187** ($CDCl_3$, 500 MHz, 297 K)



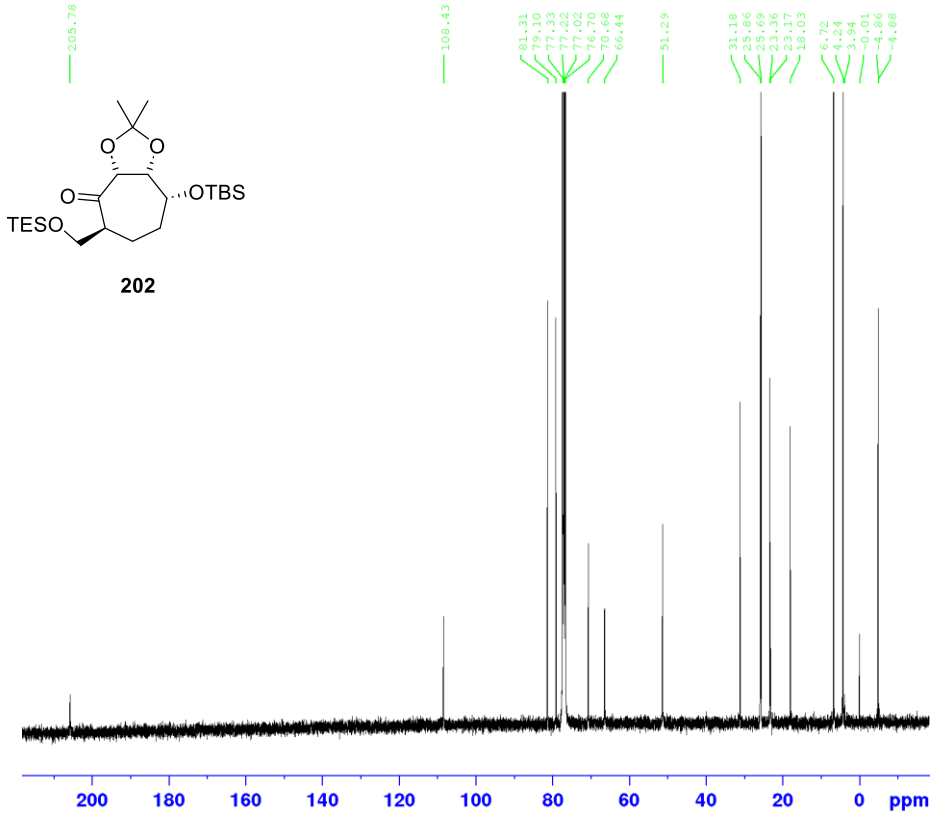
^{13}C NMR spectrum of **187** ($CDCl_3$, 126 MHz, 298 K)



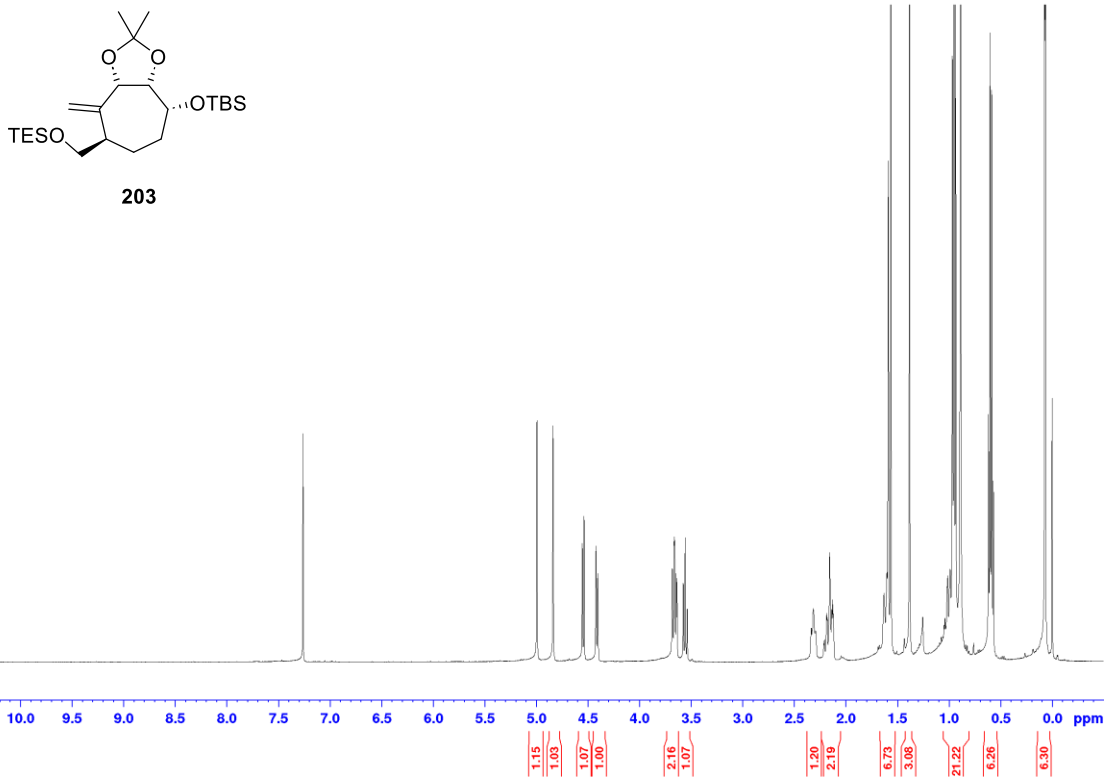
^{1}H NMR spectrum of **202** ($CDCl_3$, 400 MHz, 298 K)



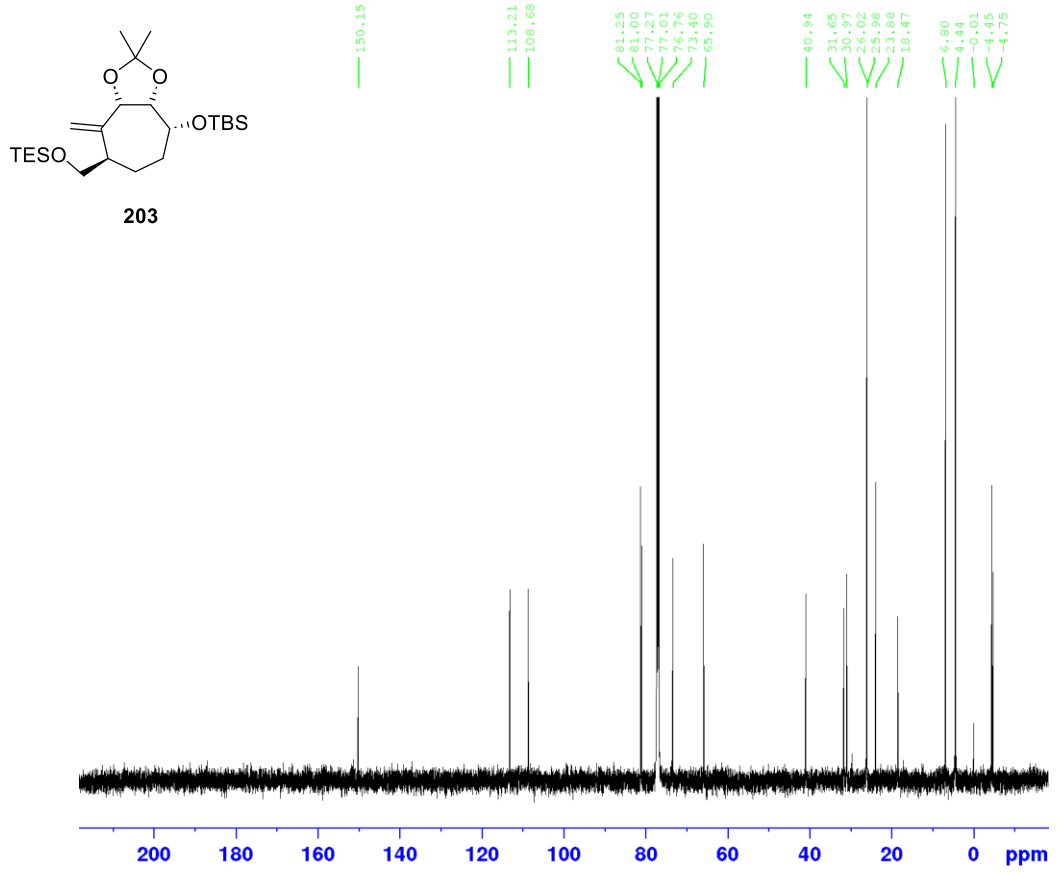
^{13}C NMR spectrum of **202** ($CDCl_3$, 100 MHz, 299 K)



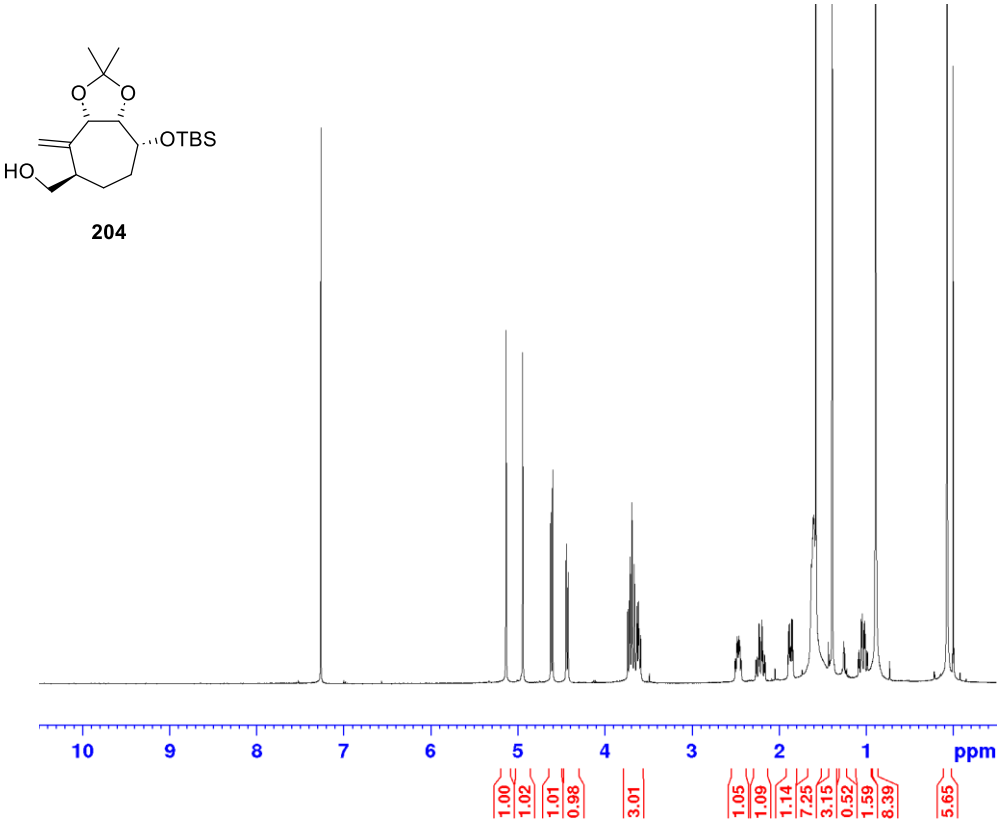
^{1}H NMR spectrum of **203** ($CDCl_3$, 500 MHz, 297 K)



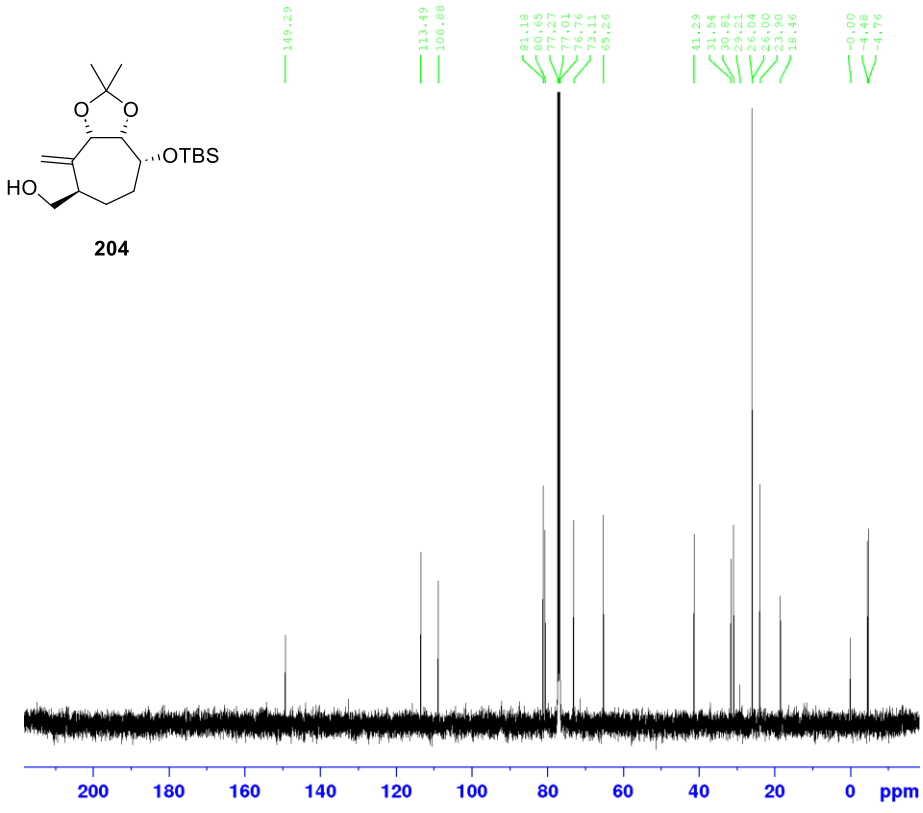
^{13}C NMR spectrum of **203** ($CDCl_3$, 126 MHz, 298 K)



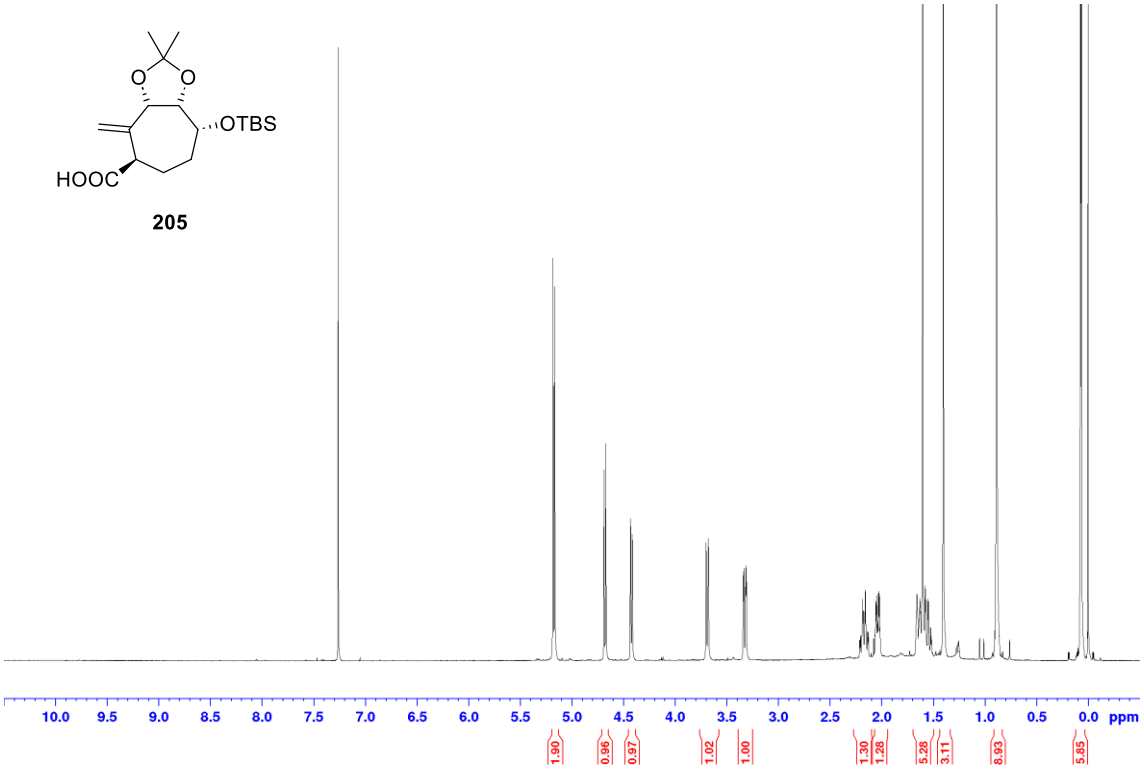
^{1}H NMR spectrum of **204** ($CDCl_3$, 400 MHz, 298 K)



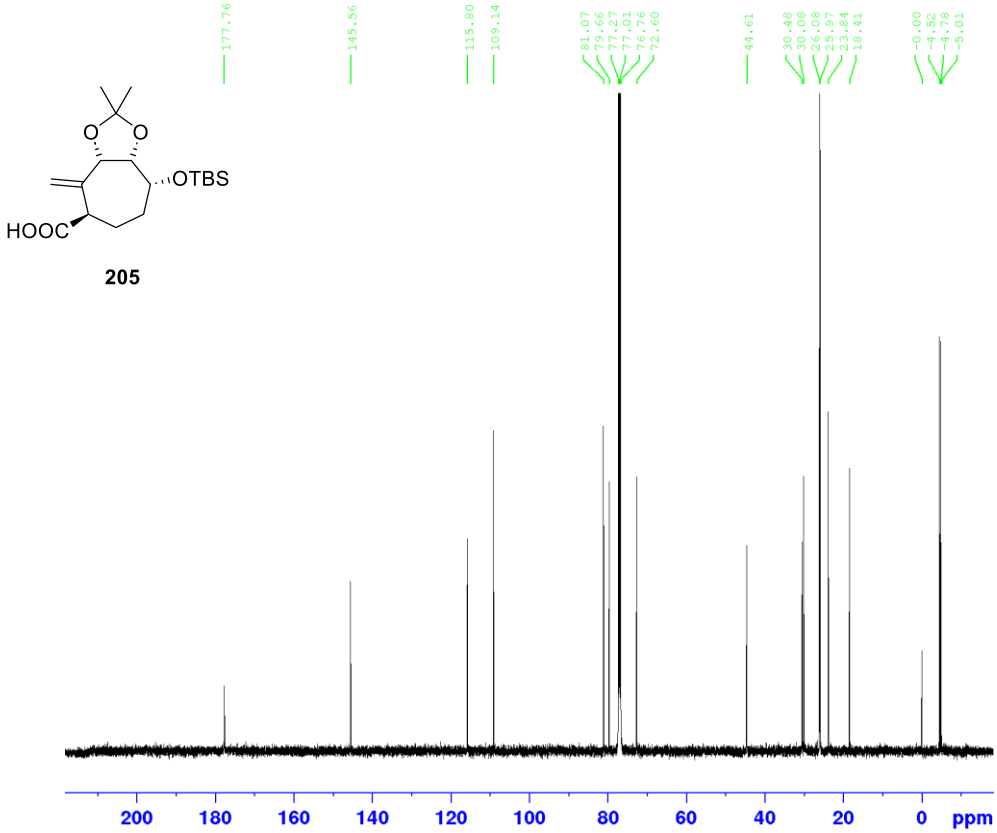
^{13}C NMR spectrum of **204** ($CDCl_3$, 126 MHz, 297 K)



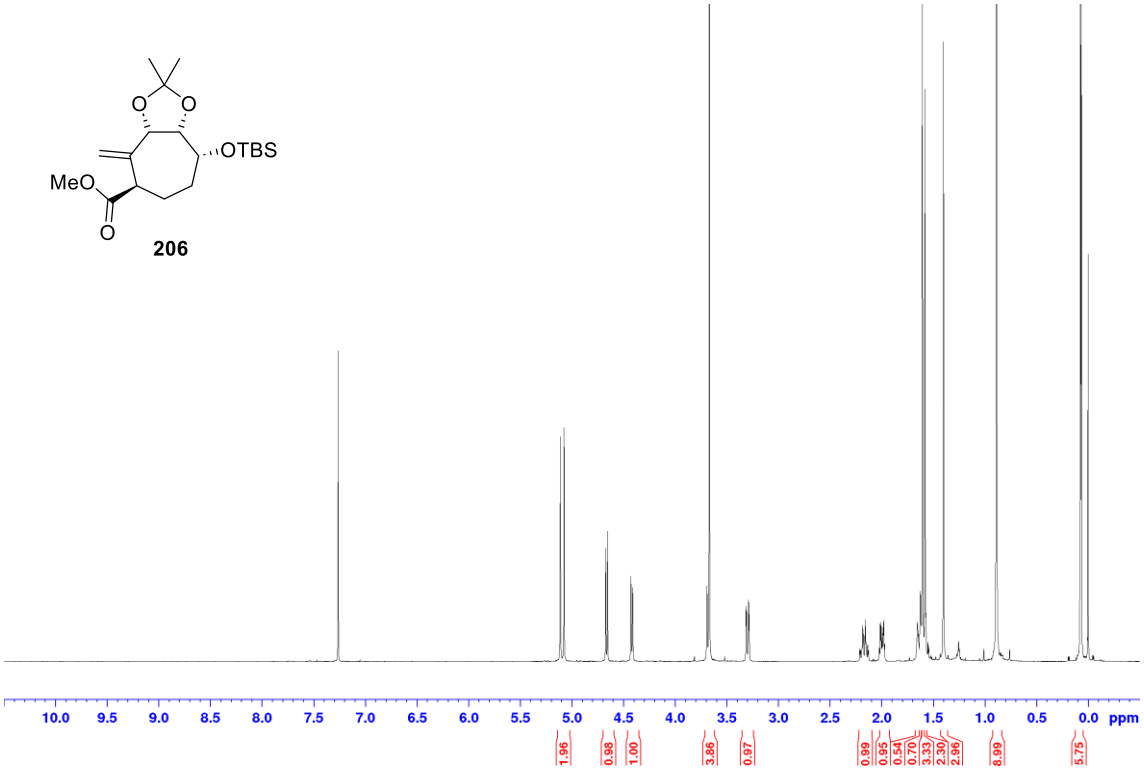
^{1}H NMR spectrum of **205** ($CDCl_3$, 500 MHz, 297 K)



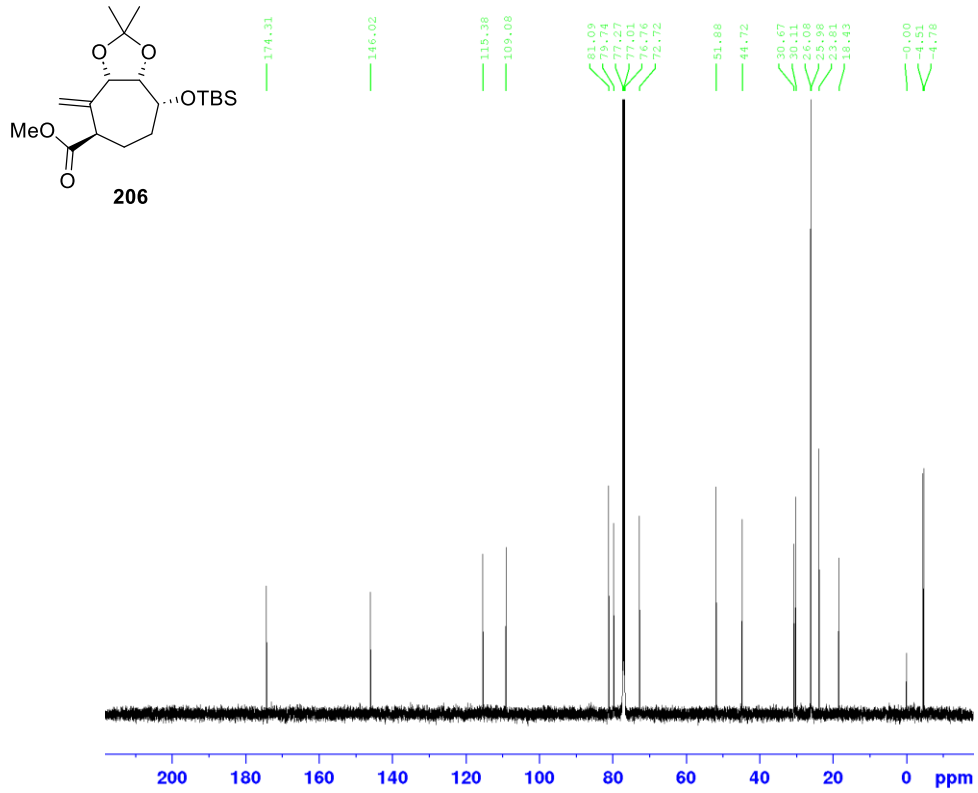
^{13}C NMR spectrum of **205** ($CDCl_3$, 126 MHz, 297 K)



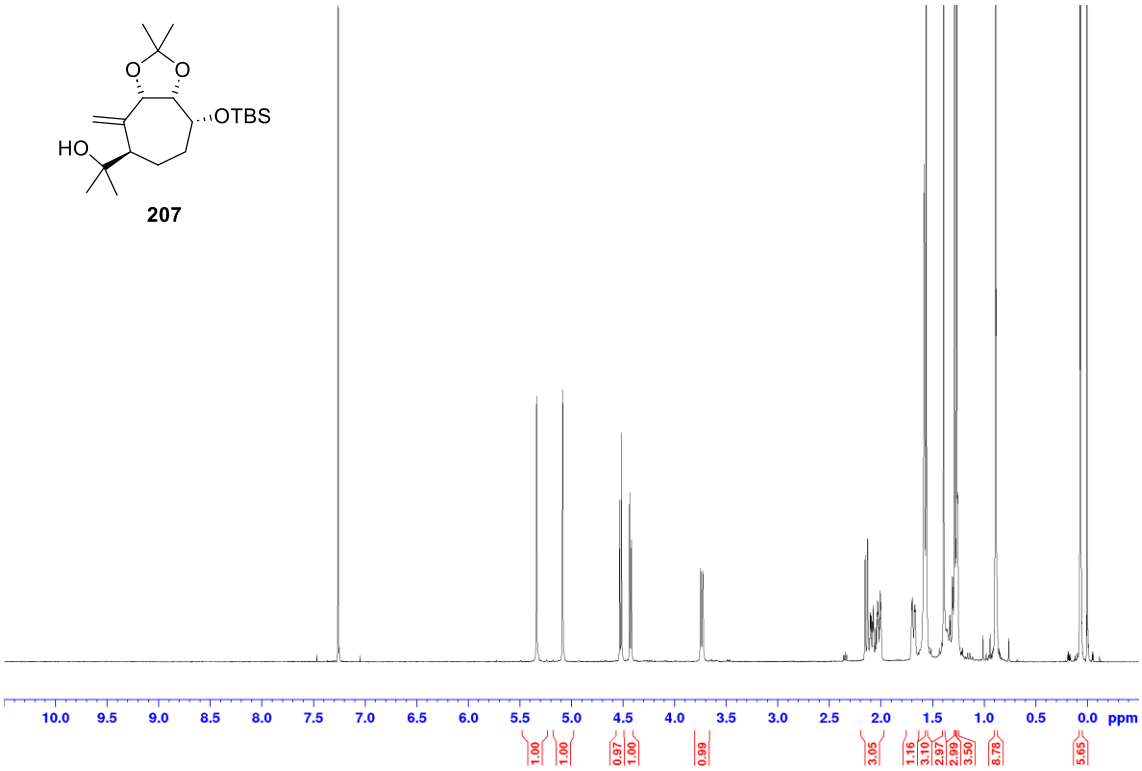
^{1}H NMR spectrum of **206** ($CDCl_3$, 500 MHz, 297 K)



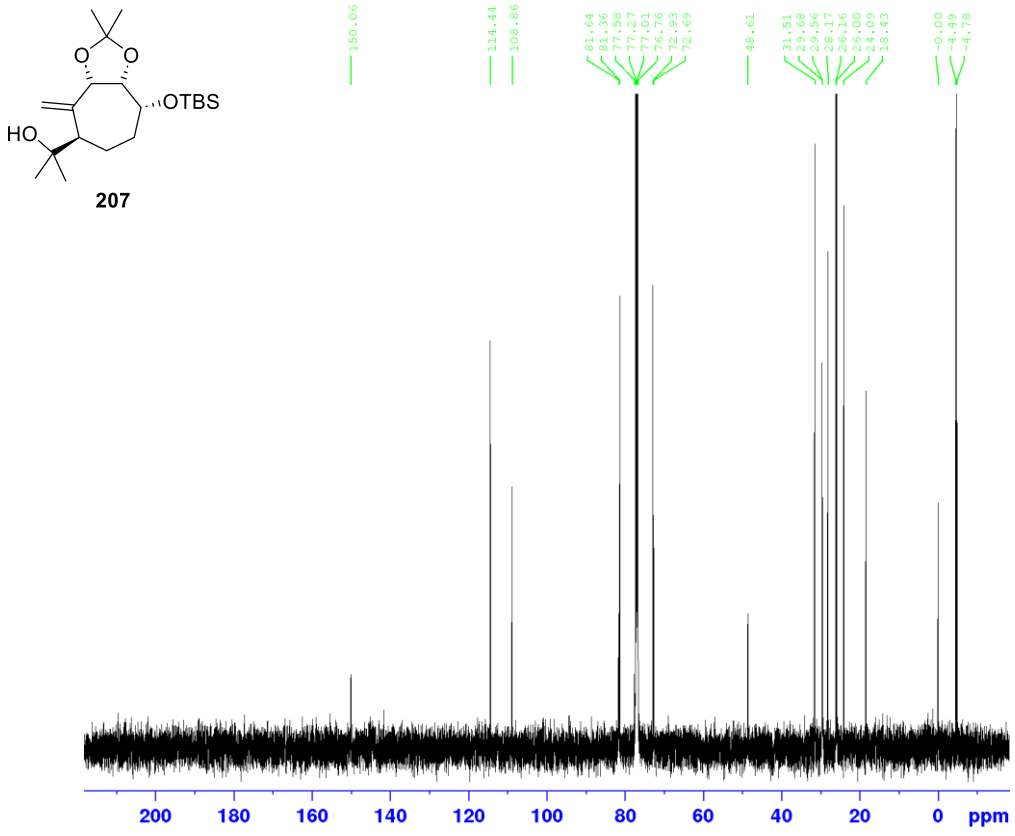
^{13}C NMR spectrum of **206** ($CDCl_3$, 126 MHz, 297 K)



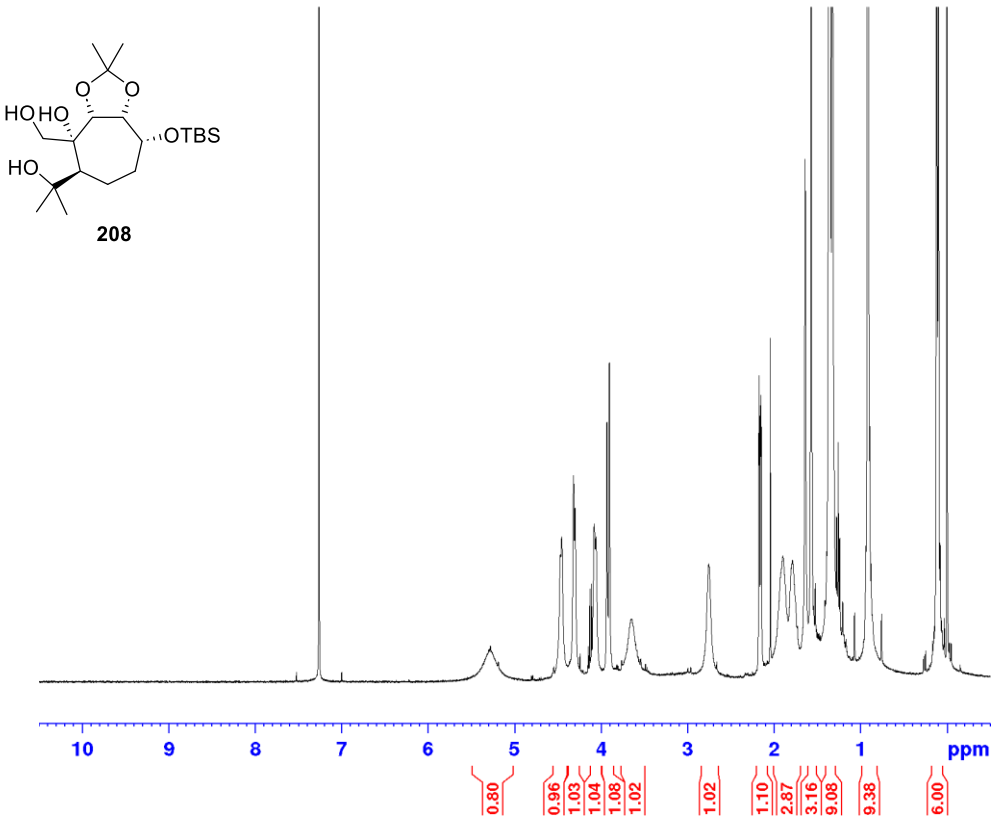
^{1}H NMR spectrum of **207** ($CDCl_3$, 500 MHz, 297 K)



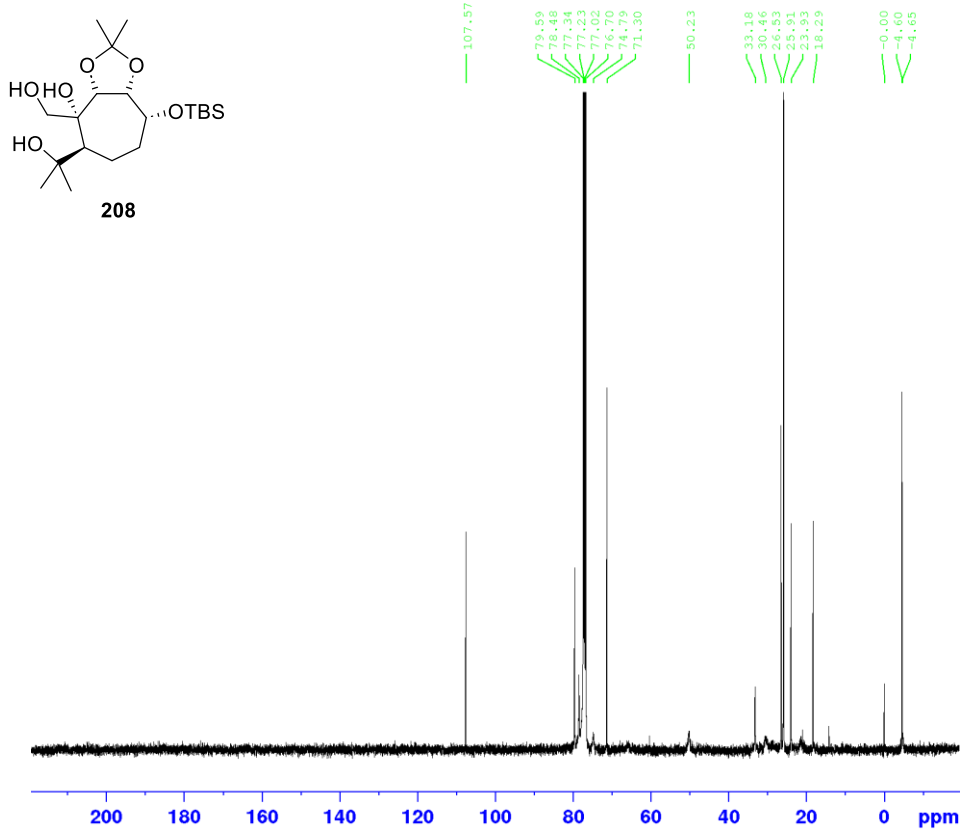
^{13}C NMR spectrum of **207** ($CDCl_3$, 126 MHz, 297 K)



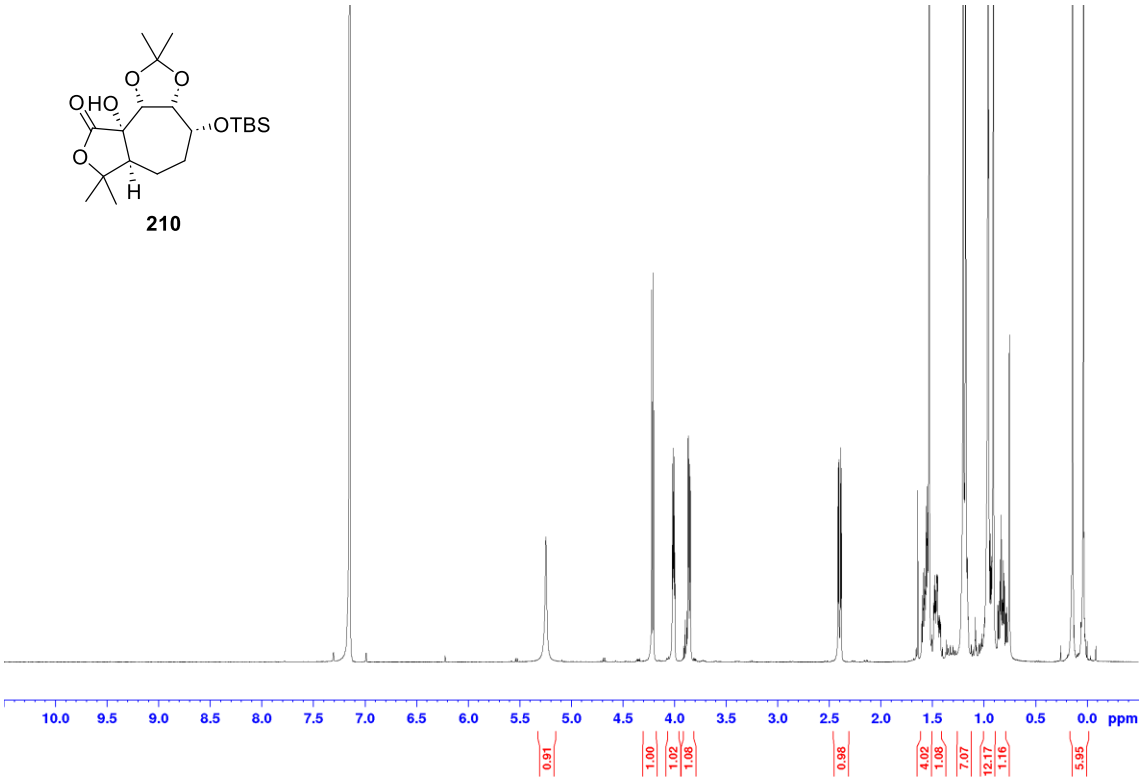
^{1}H NMR spectrum of **208** ($CDCl_3$, 500 MHz, 297 K)



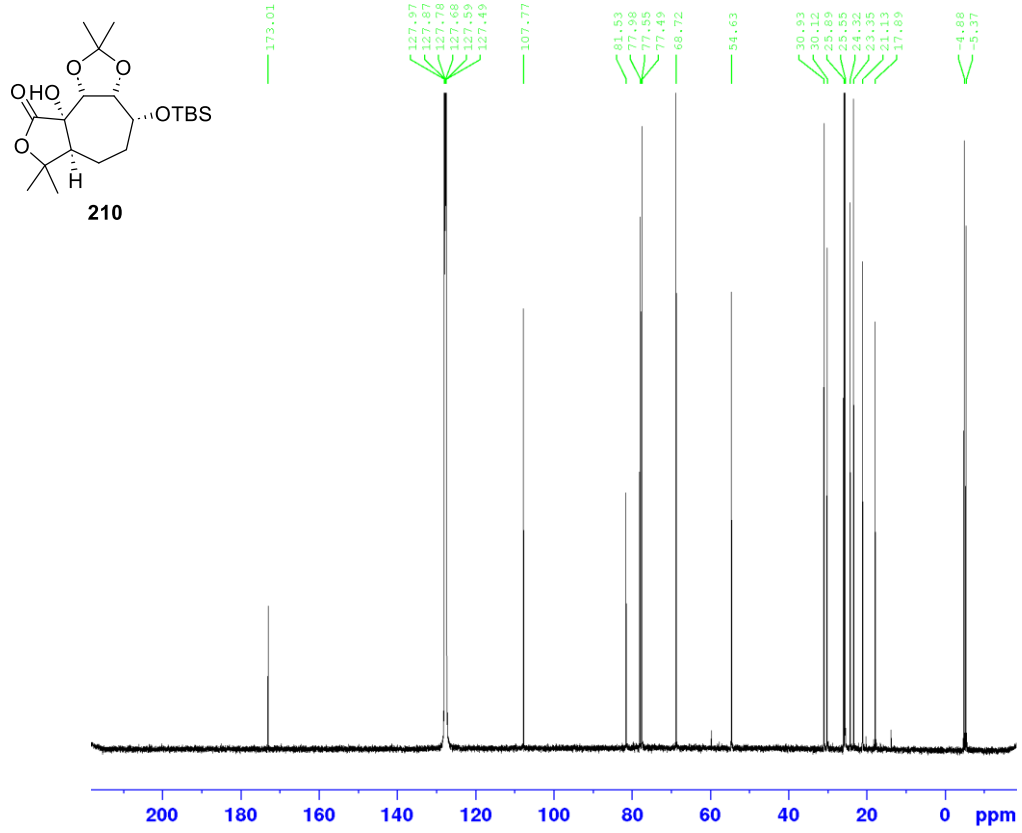
^{13}C NMR spectrum of **208** ($CDCl_3$, 126 MHz, 298 K)



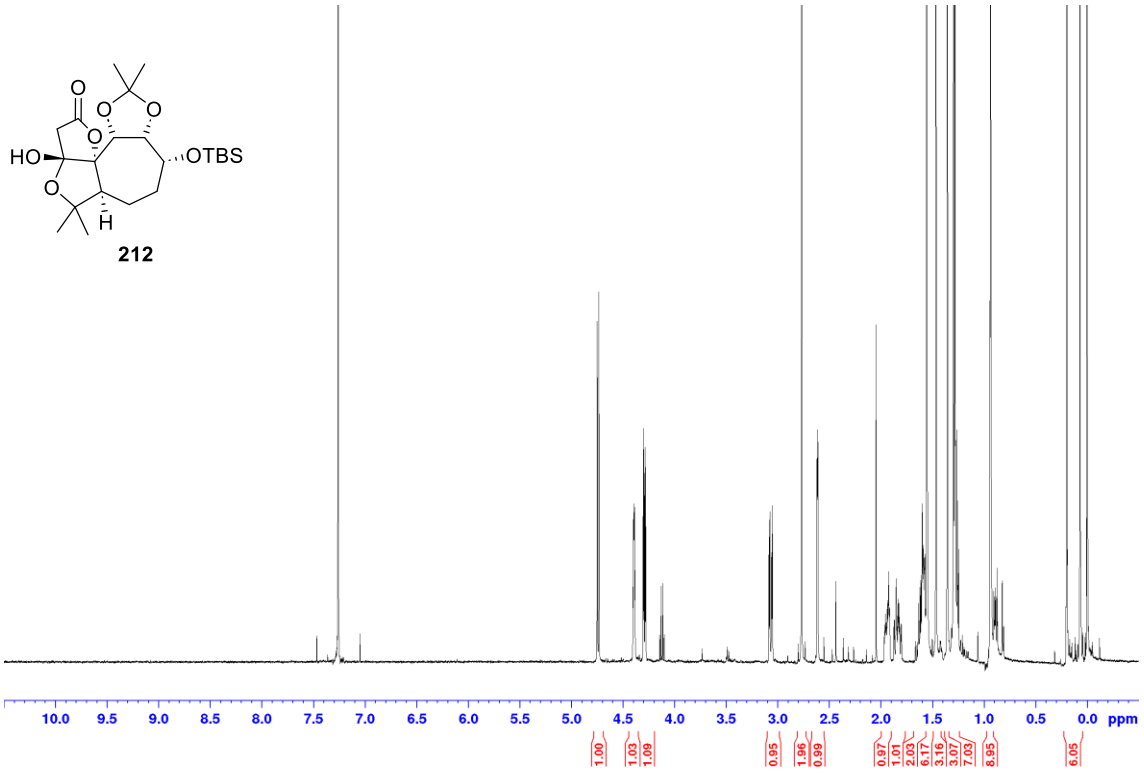
^{1}H NMR spectrum of **210** (C_6D_6, 500 MHz, 297 K)



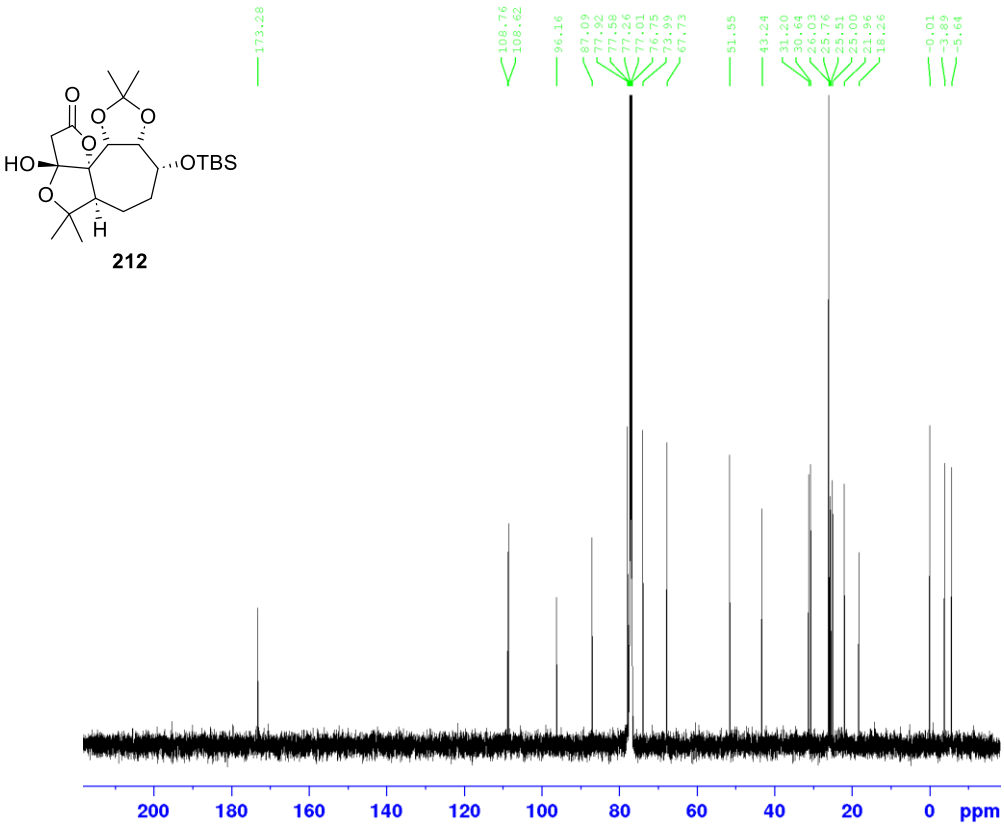
^{13}C NMR spectrum of **210** (C_6D_6, 500 MHz, 298 K)



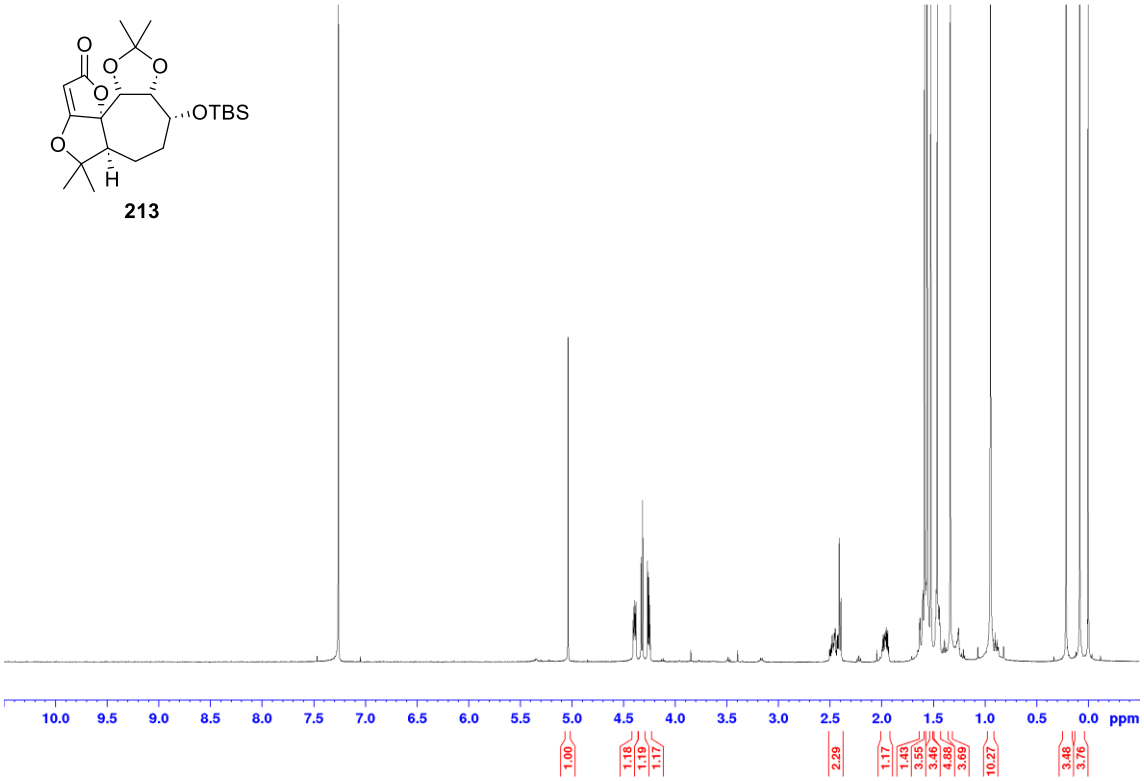
^{1}H NMR spectrum of **212** ($CDCl_3$, 500 MHz, 297 K)



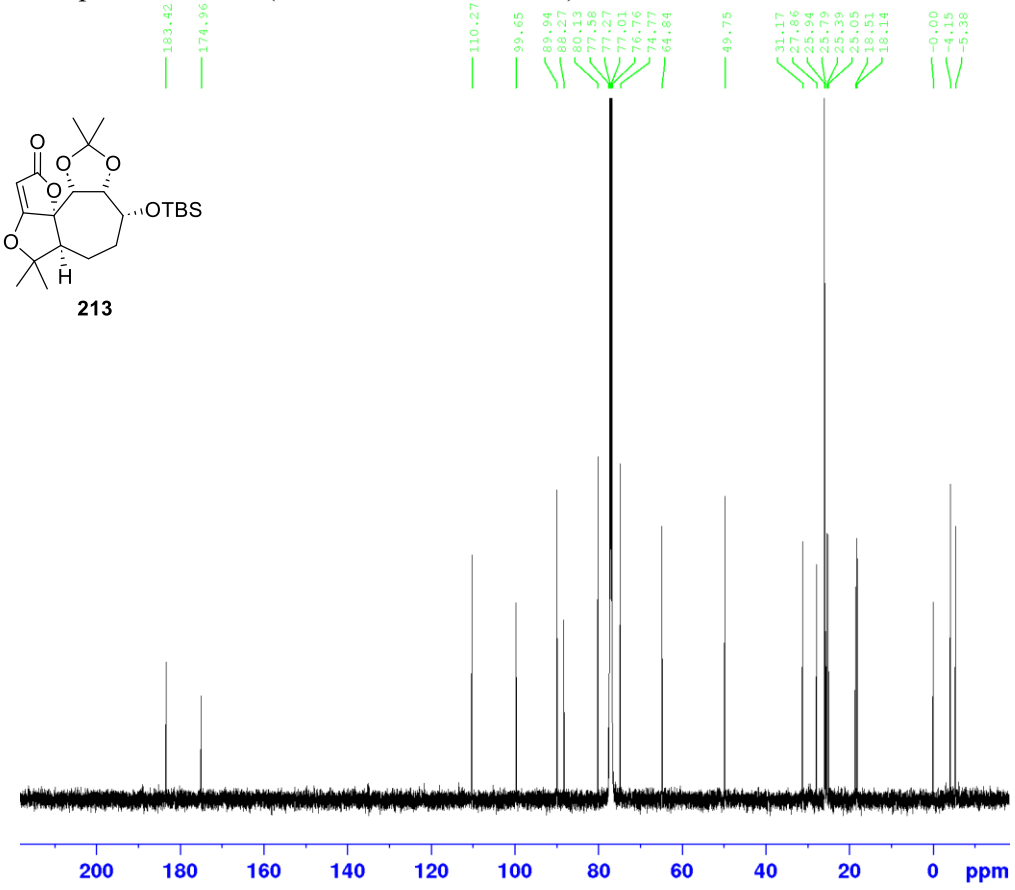
^{13}C NMR spectrum of **212** ($CDCl_3$, 126 MHz, 298 K)



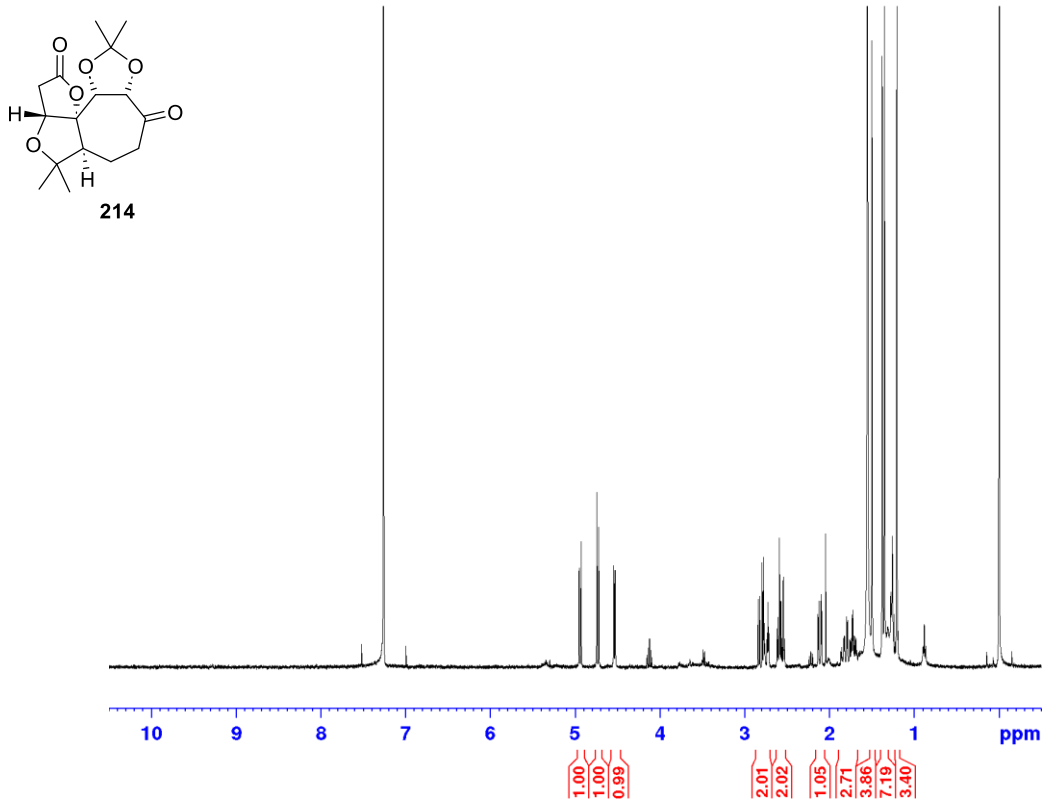
^{1}H NMR spectrum of **213** ($CDCl_3$, 500 MHz, 297 K)



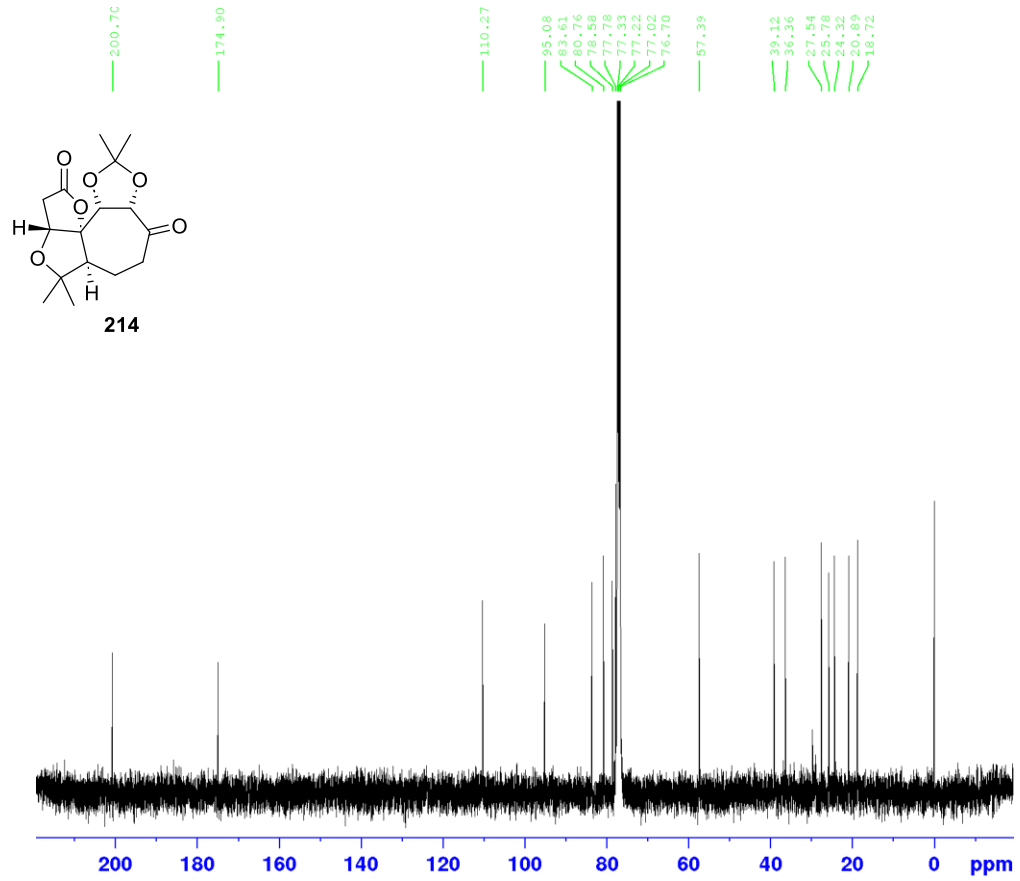
^{13}C NMR spectrum of **213** ($CDCl_3$, 126 MHz, 298 K)



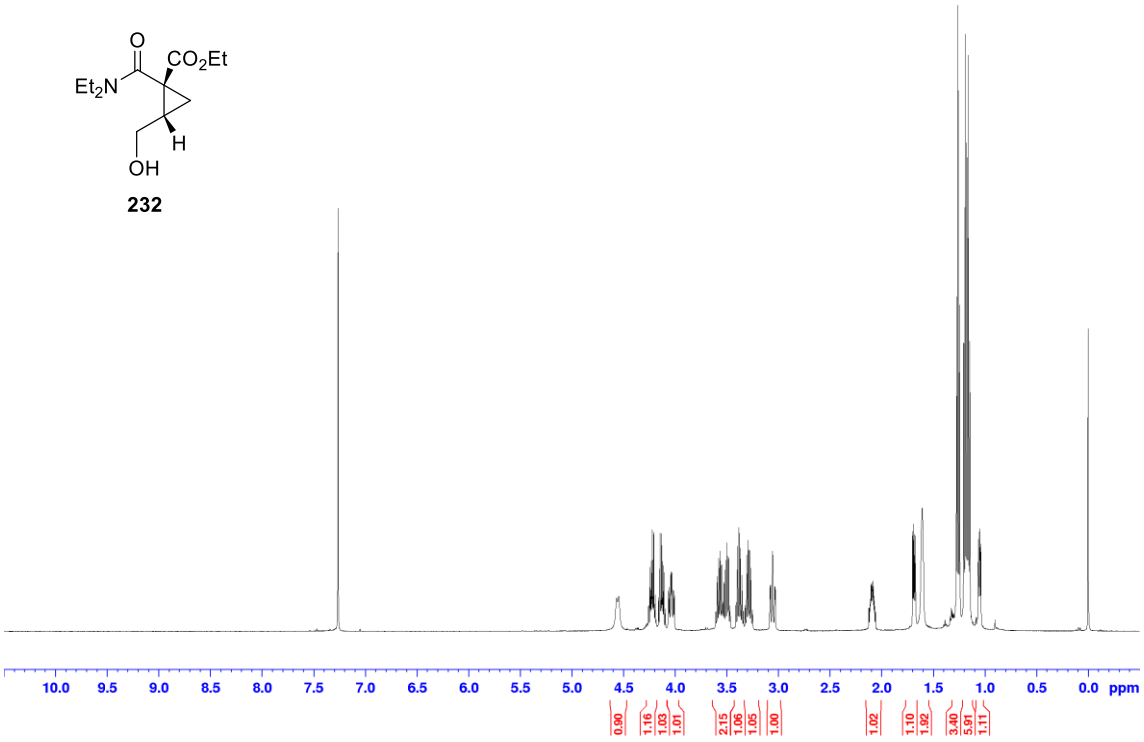
^{1}H NMR spectrum of **214** ($CDCl_3$, 400 MHz, 298 K)



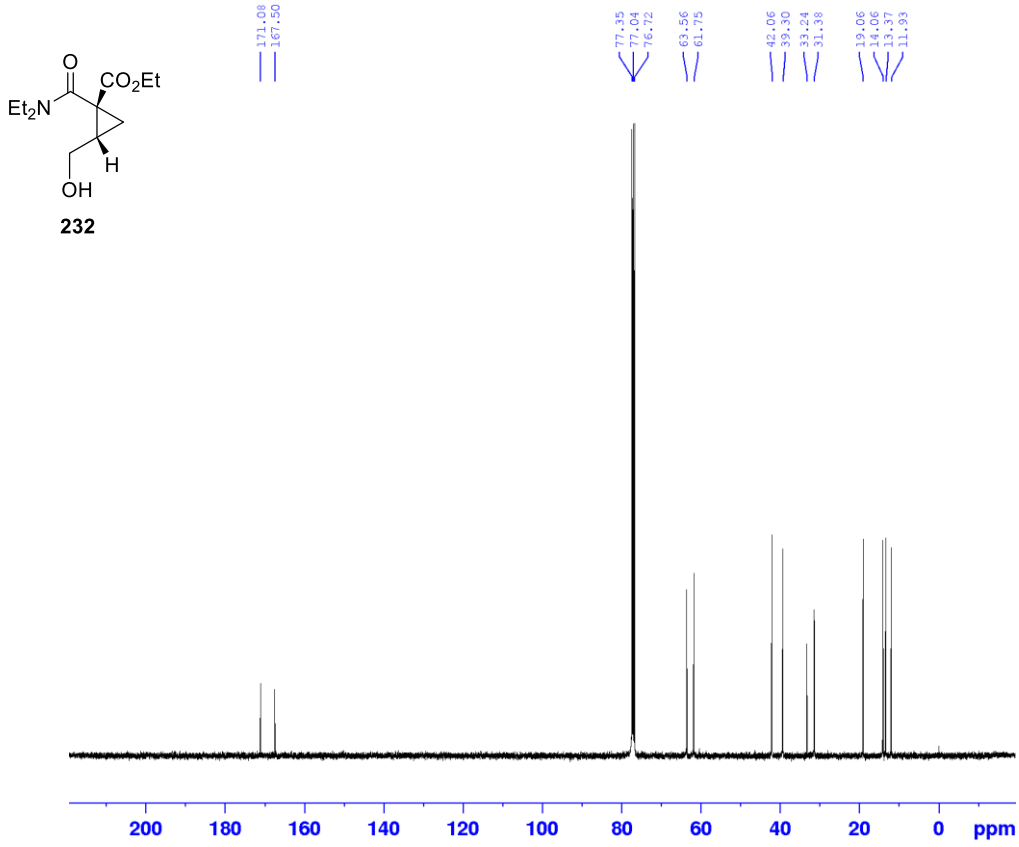
^{13}C NMR spectrum of **214** ($CDCl_3$, 100 MHz, 299 K)



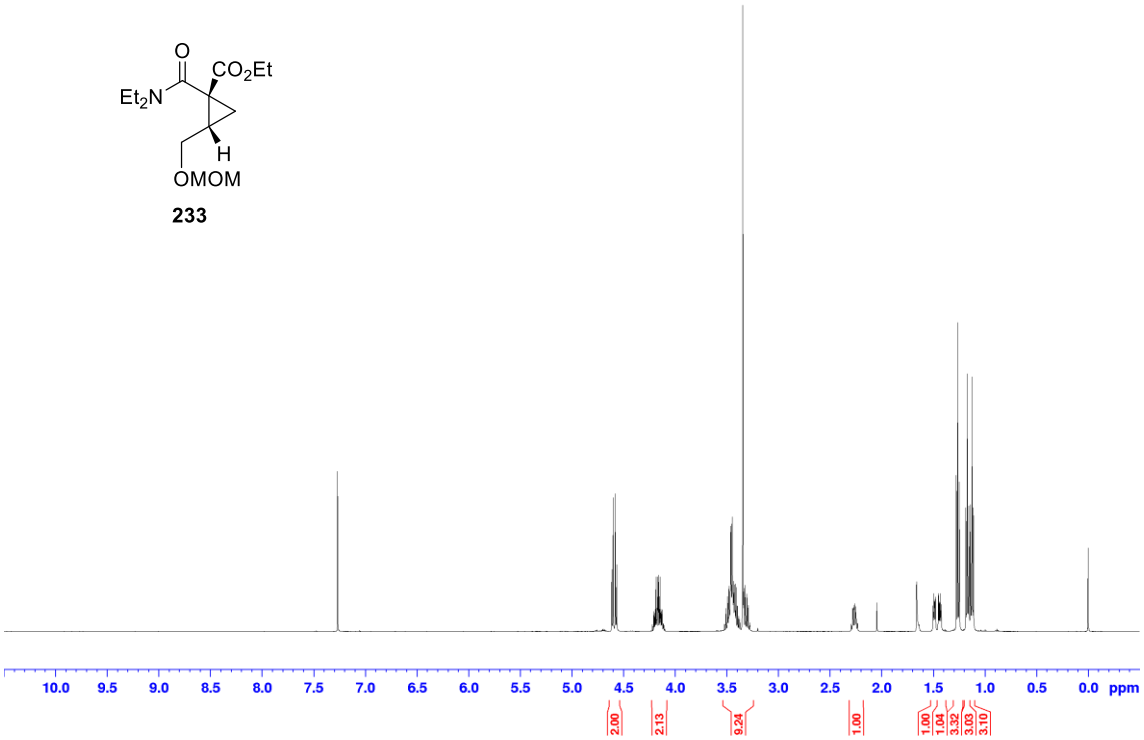
^{1}H NMR spectrum of **232** ($CDCl_3$, 500 MHz, 297 K)



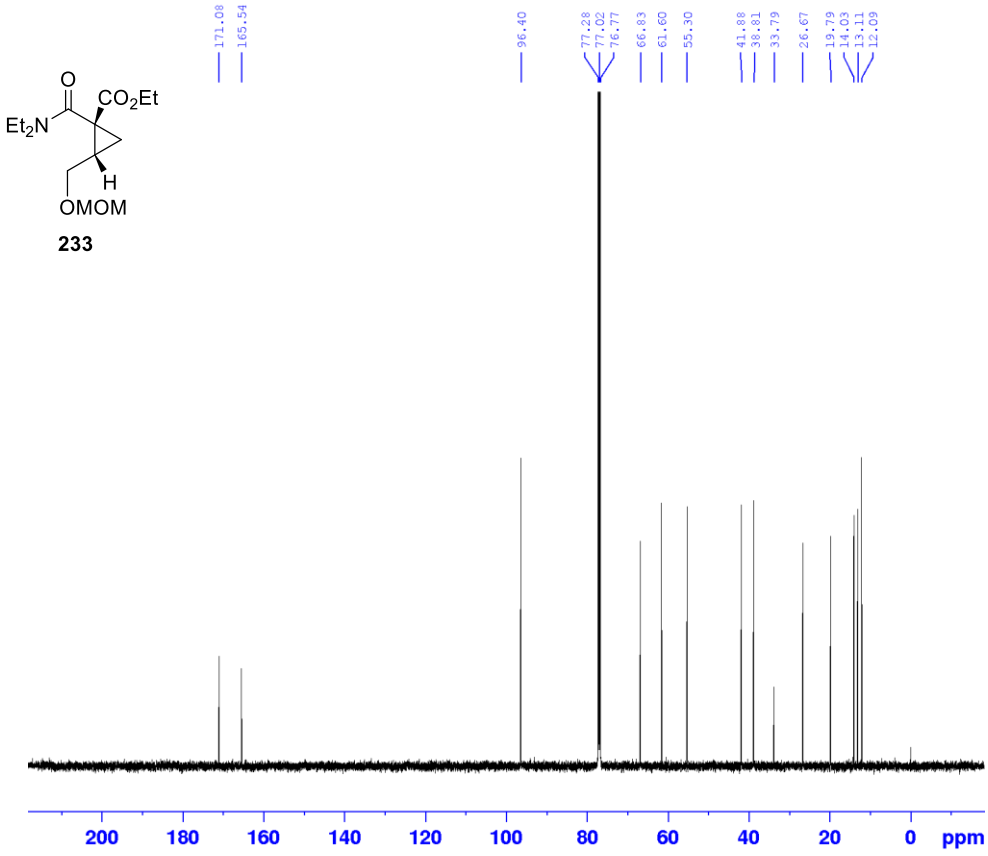
^{13}C NMR spectrum of **232** ($CDCl_3$, 100 MHz, 298 K)



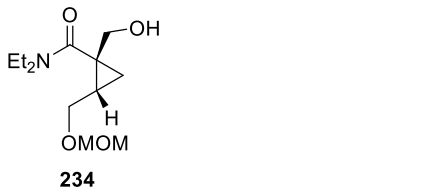
^{1}H NMR spectrum of **233** ($CDCl_3$, 500 MHz, 297 K)



^{13}C NMR spectrum of **233** ($CDCl_3$, 126 MHz, 298 K)

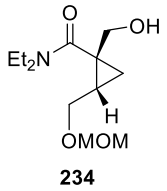


^{1}H NMR spectrum of **234** ($CDCl_3$, 500 MHz, 297 K)

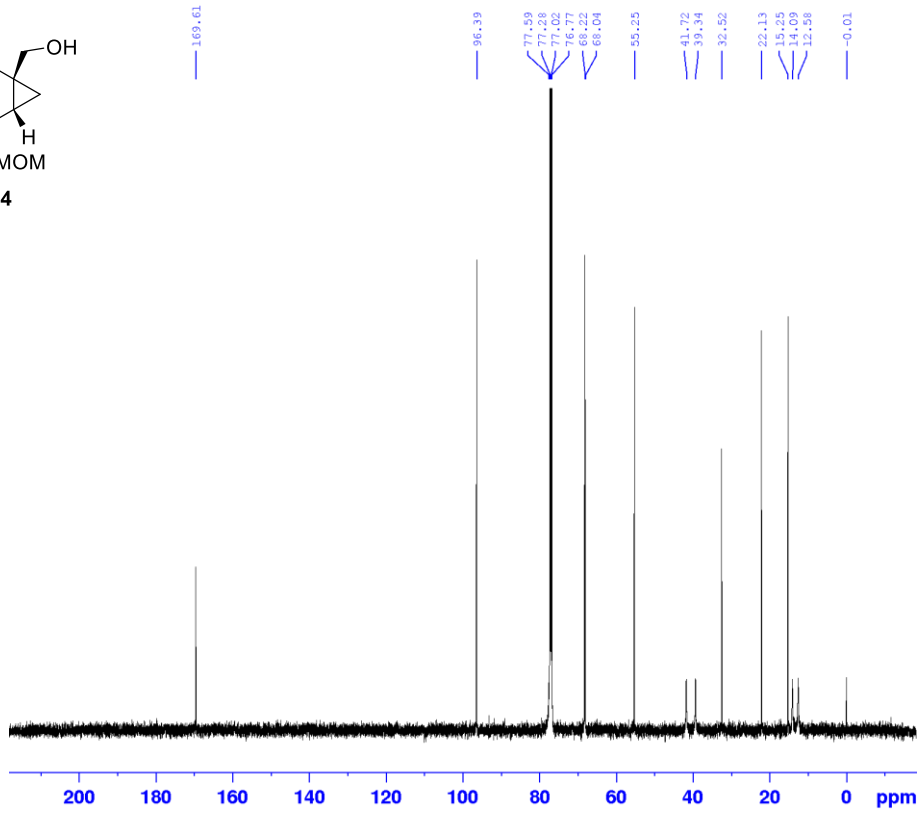


234

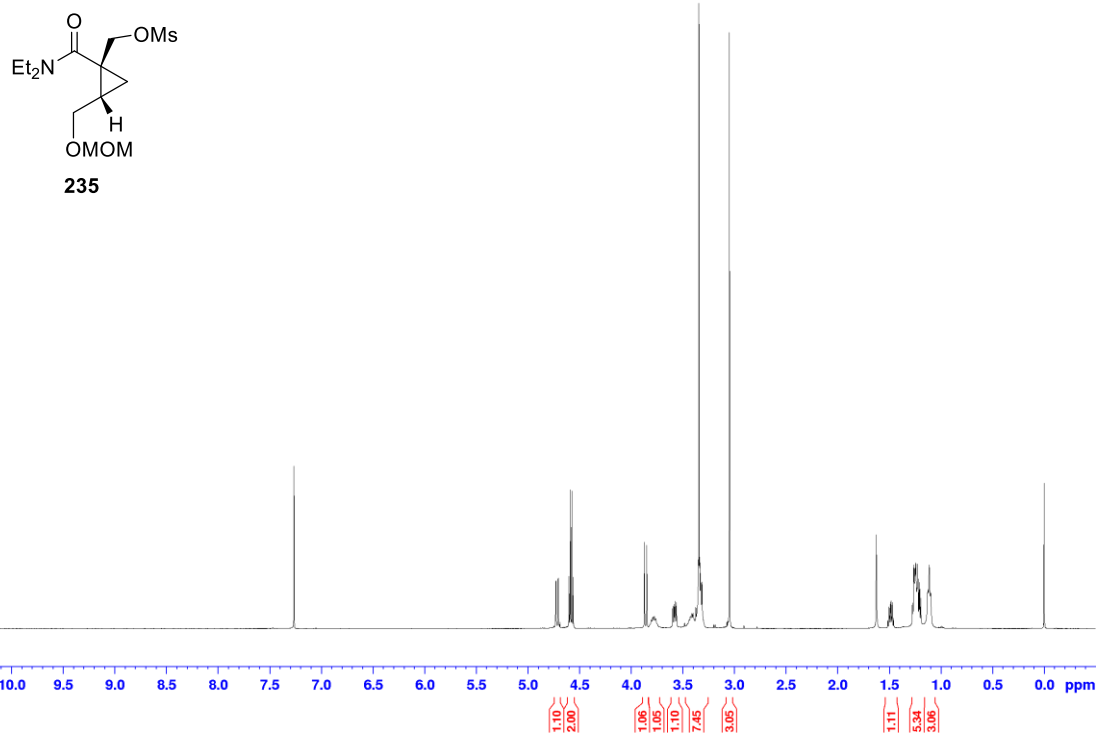
^{13}C NMR spectrum of **234** ($CDCl_3$, 126 MHz, 298 K)



234



^{1}H NMR spectrum of **235** ($CDCl_3$, 500 MHz, 297 K)



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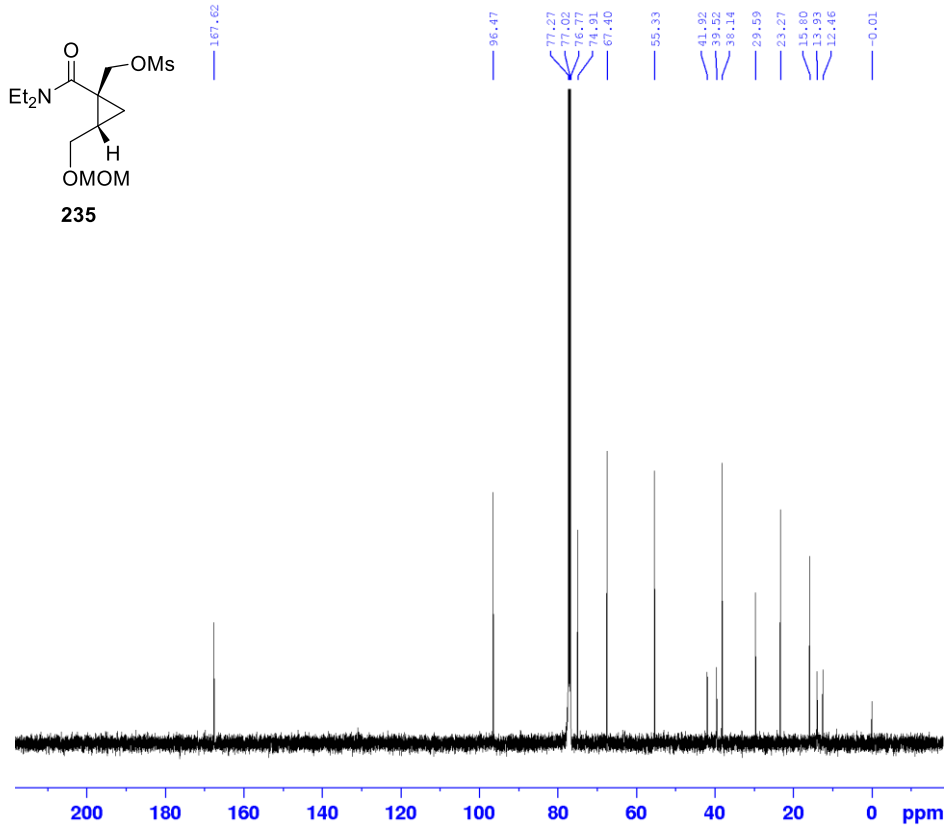

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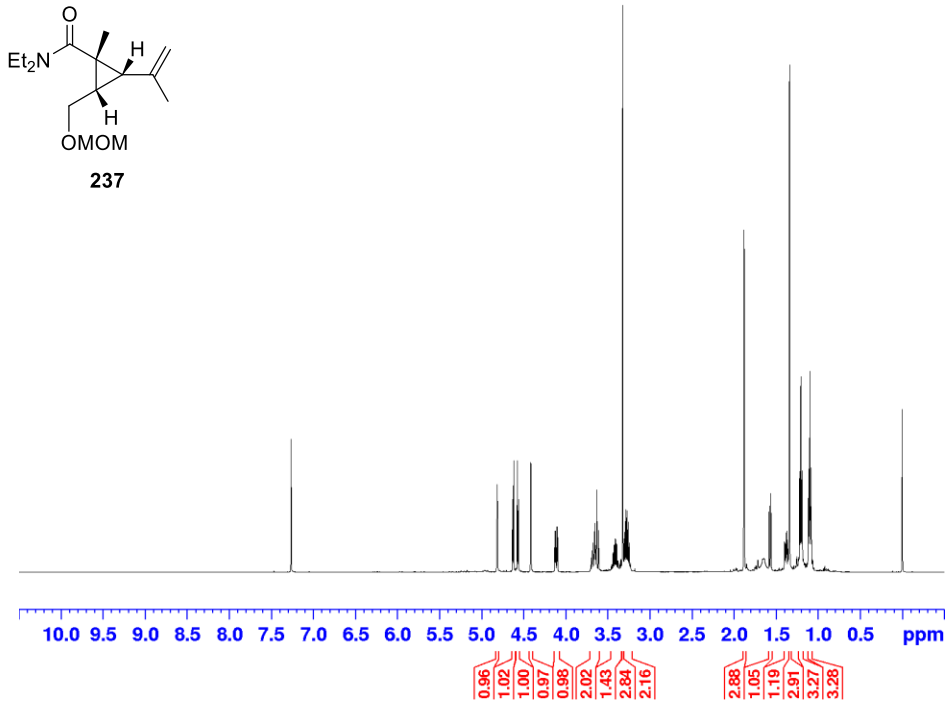

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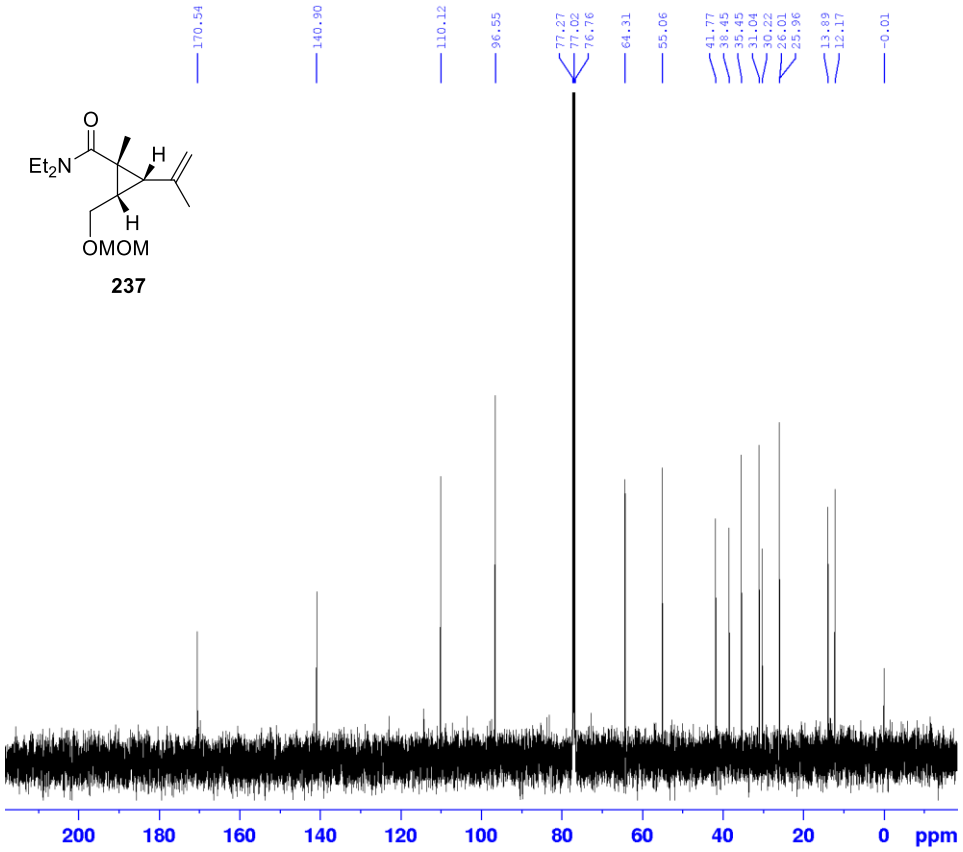

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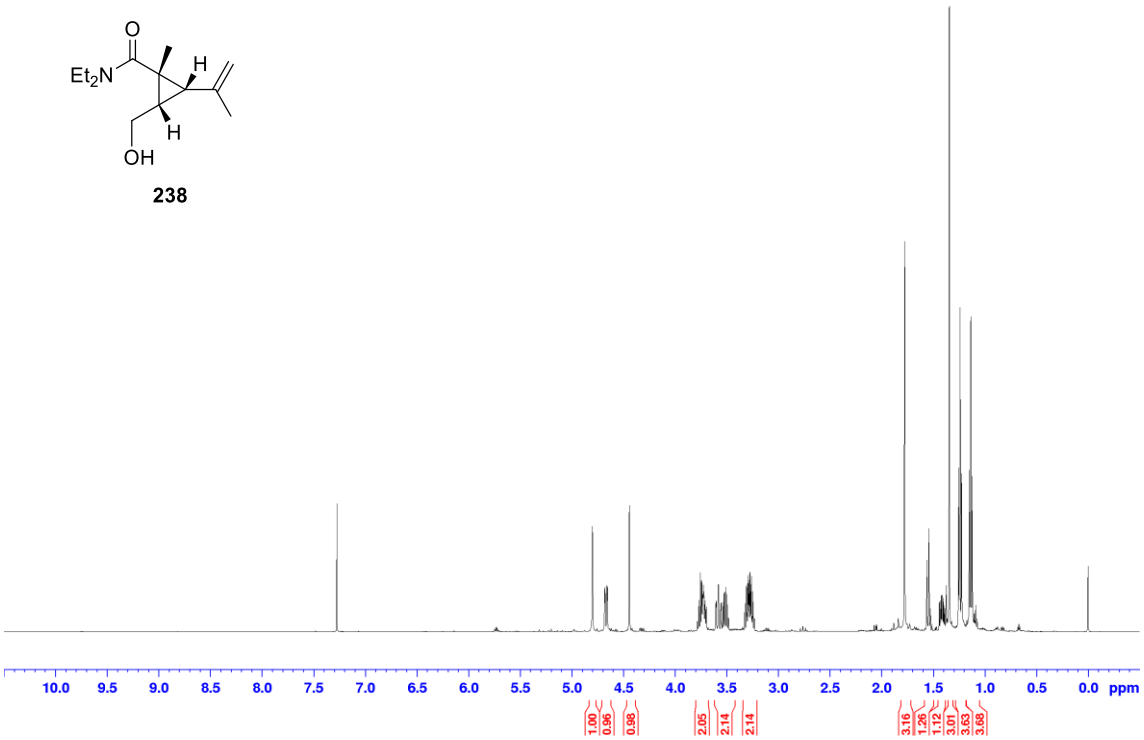
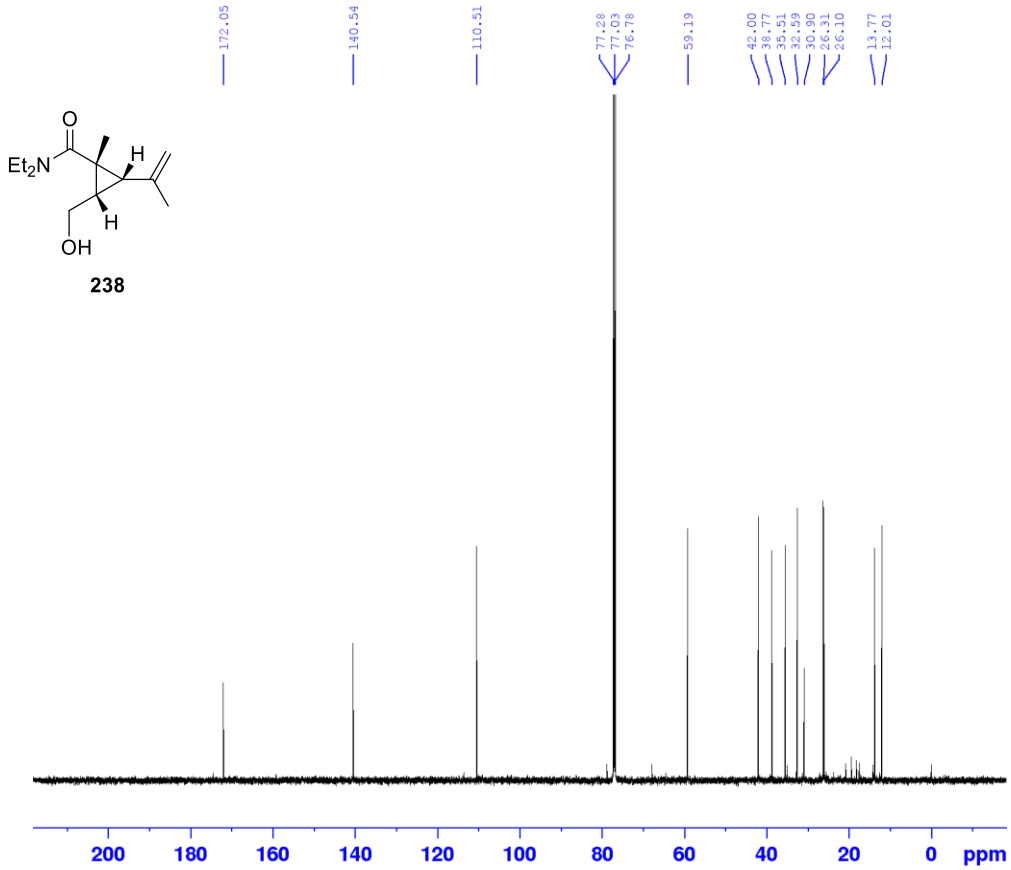
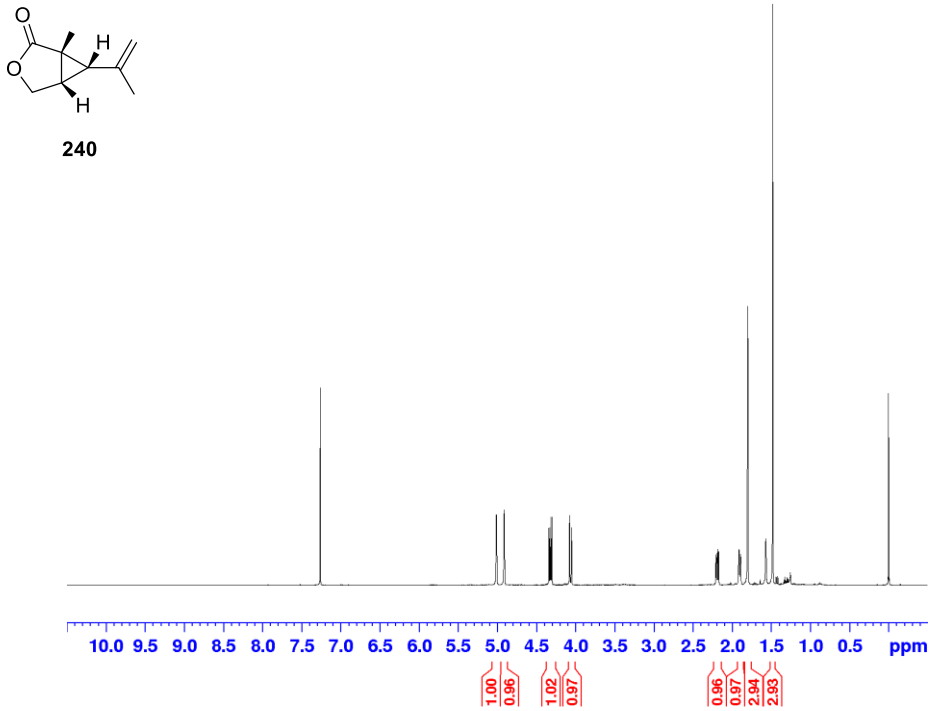


^{13}C NMR spectrum of **238** ($CDCl_3$, 126 MHz, 298 K)



^{1}H NMR spectrum of **240** ($CDCl_3$, 400 MHz, 297 K)



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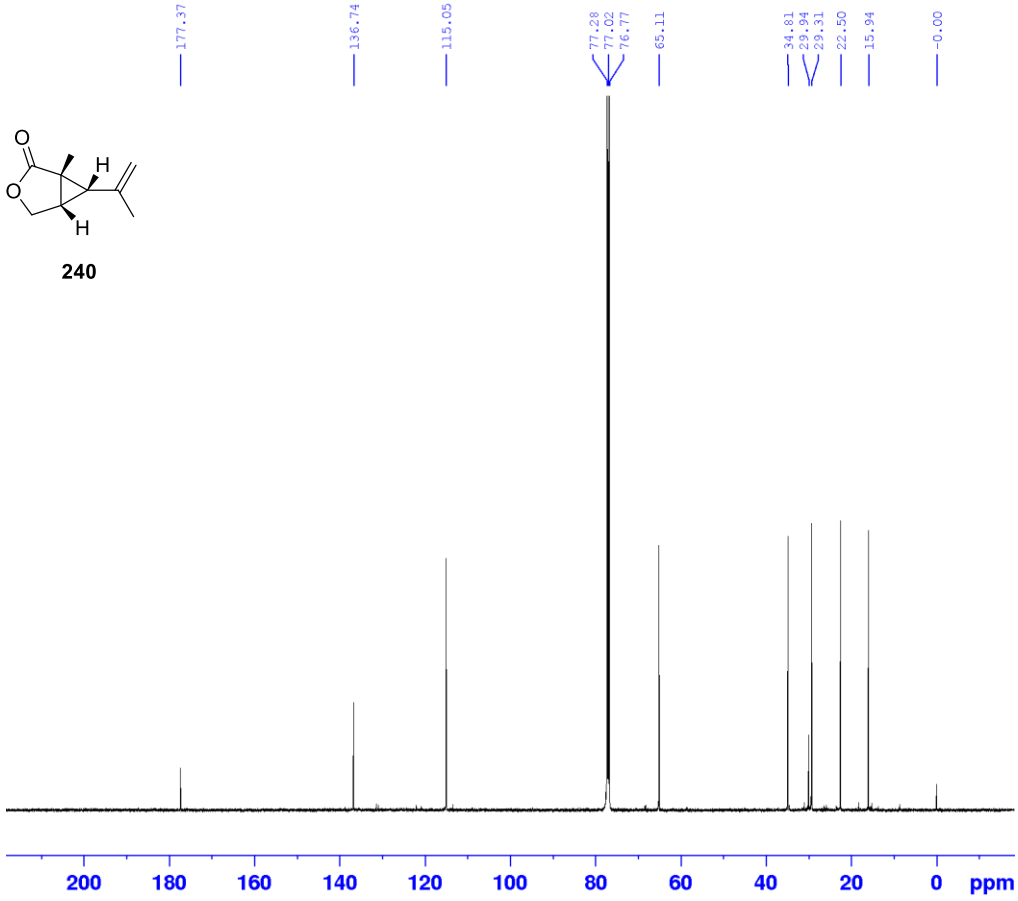
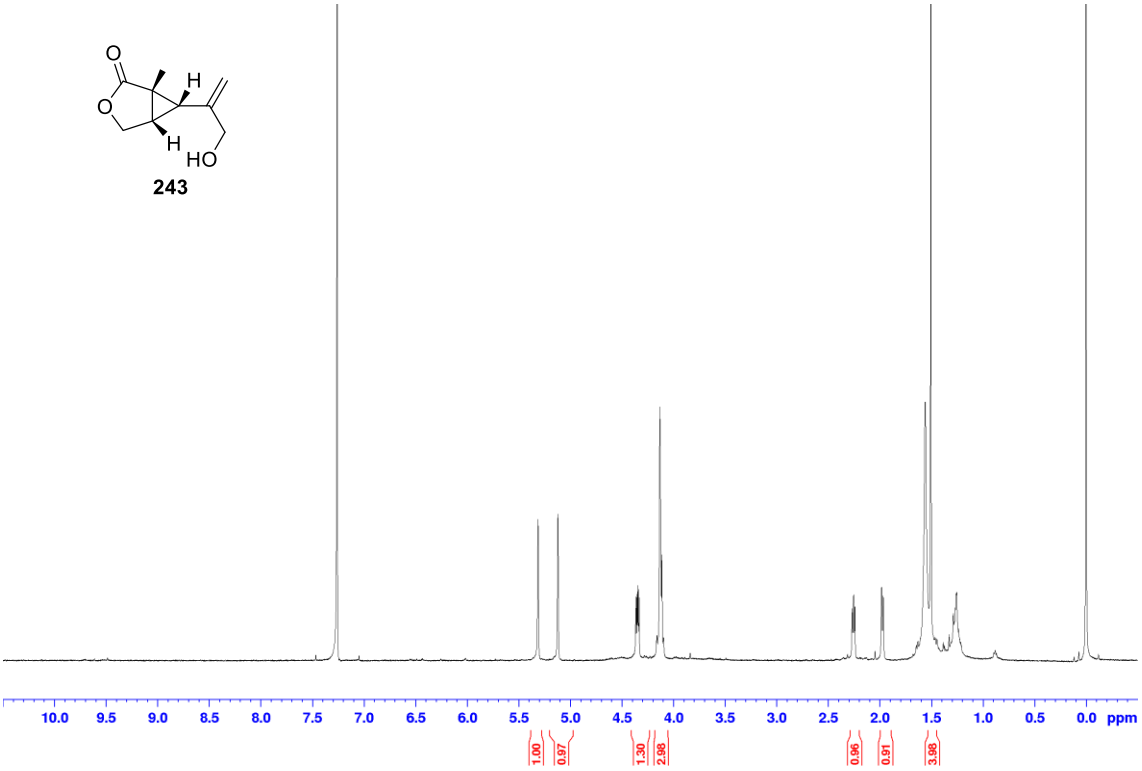


^{1}H NMR spectrum of **243** ($CDCl_3$, 500 MHz, 297 K)



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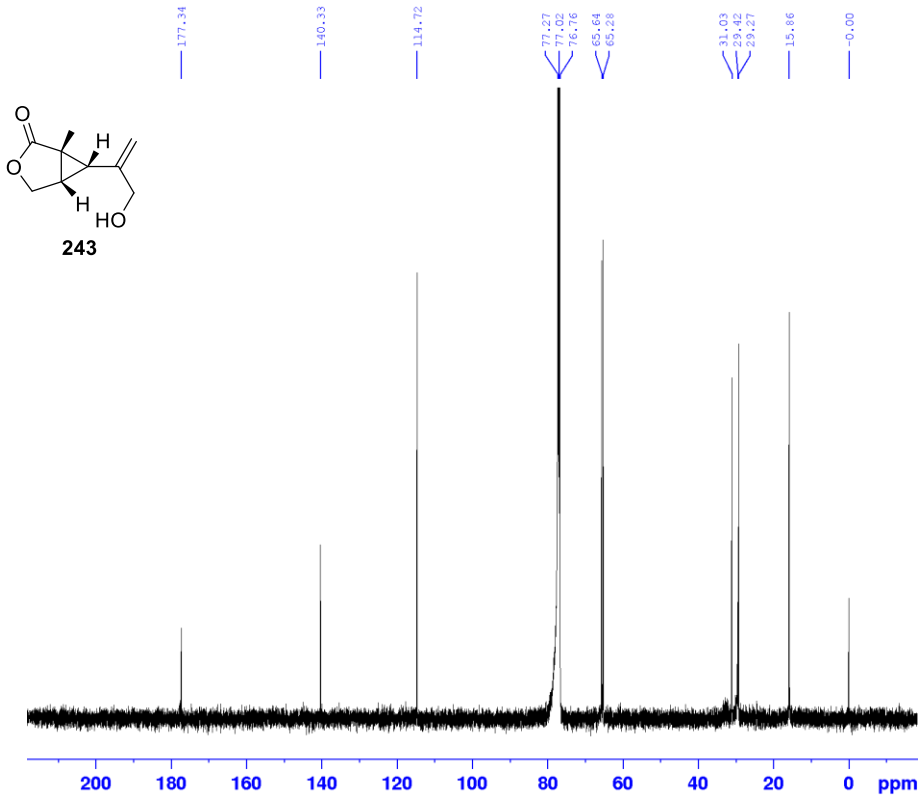
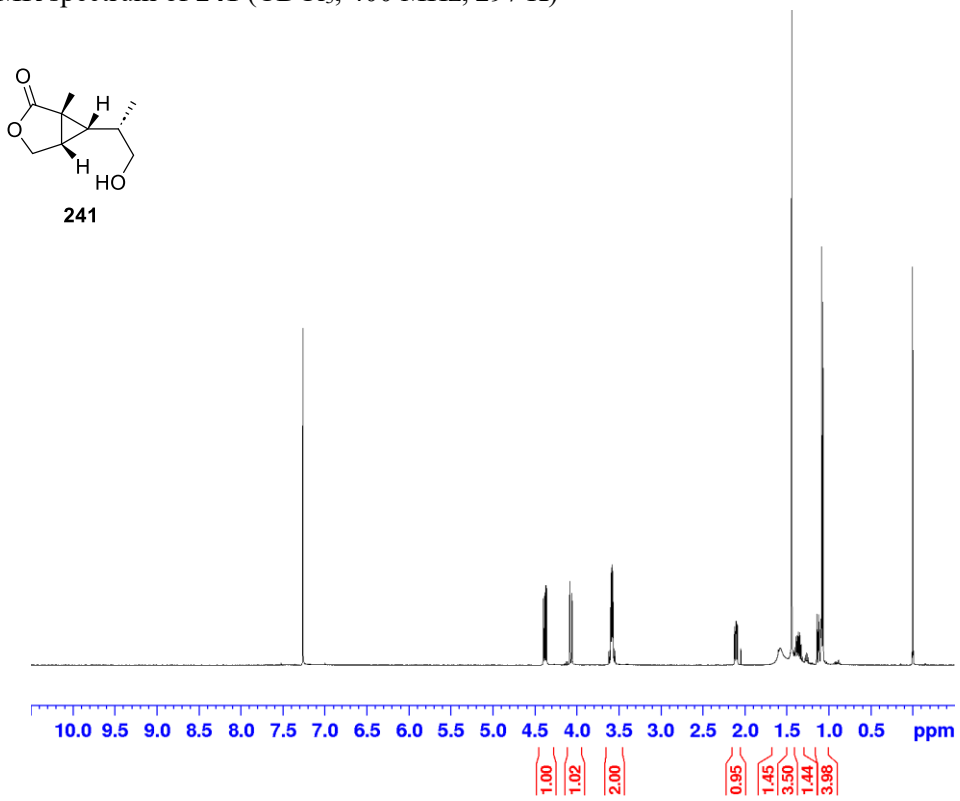
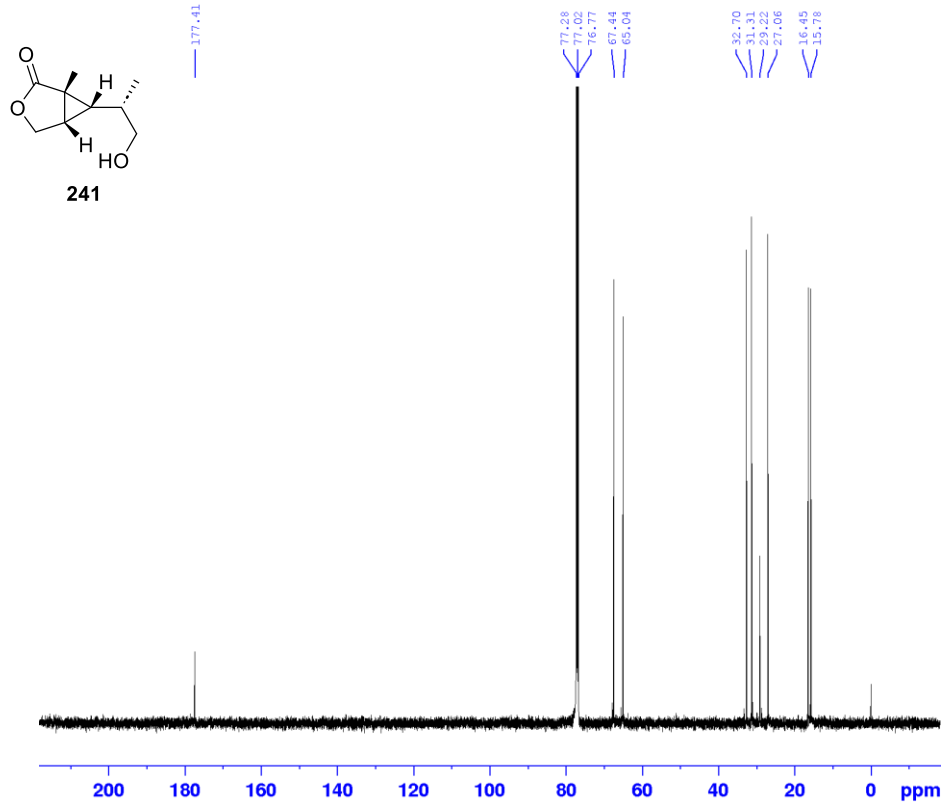


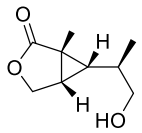
^{1}H NMR spectrum of **241** ($CDCl_3$, 400 MHz, 297 K)



^{13}C NMR spectrum of **241** ($CDCl_3$, 126 MHz, 298 K)

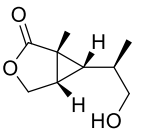


^{1}H NMR spectrum of **242** ($CDCl_3$, 500 MHz, 297 K)



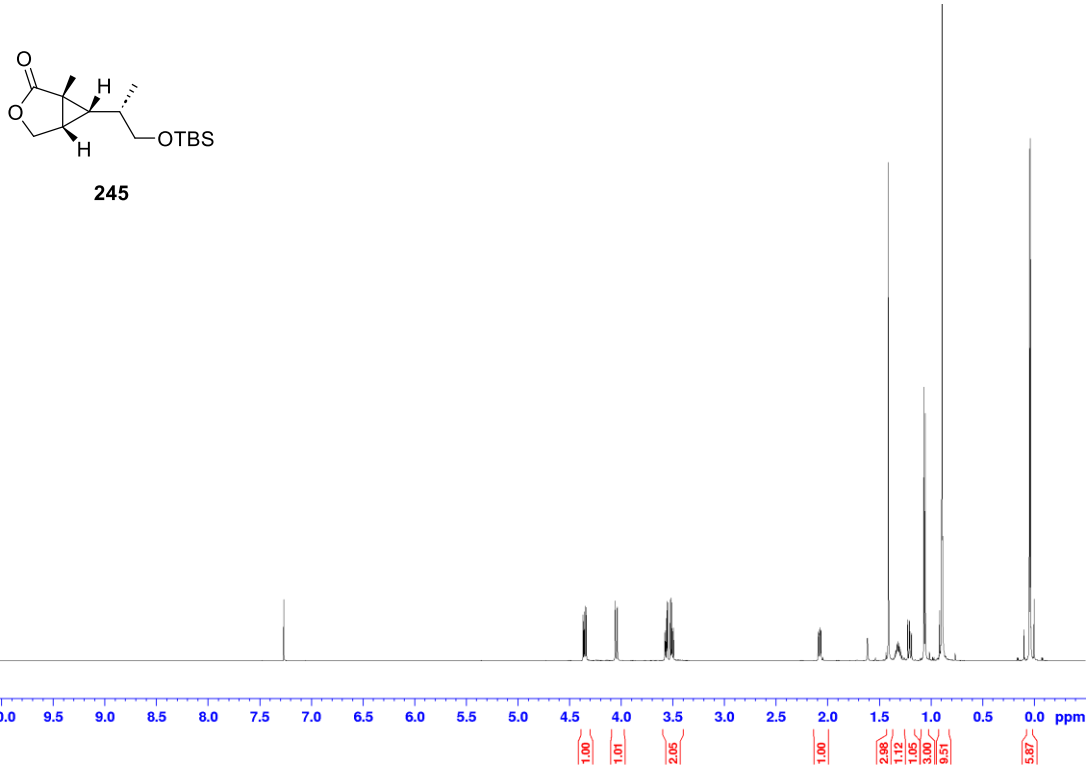
242

^{13}C NMR spectrum of **242** ($CDCl_3$, 126 MHz, 298 K)

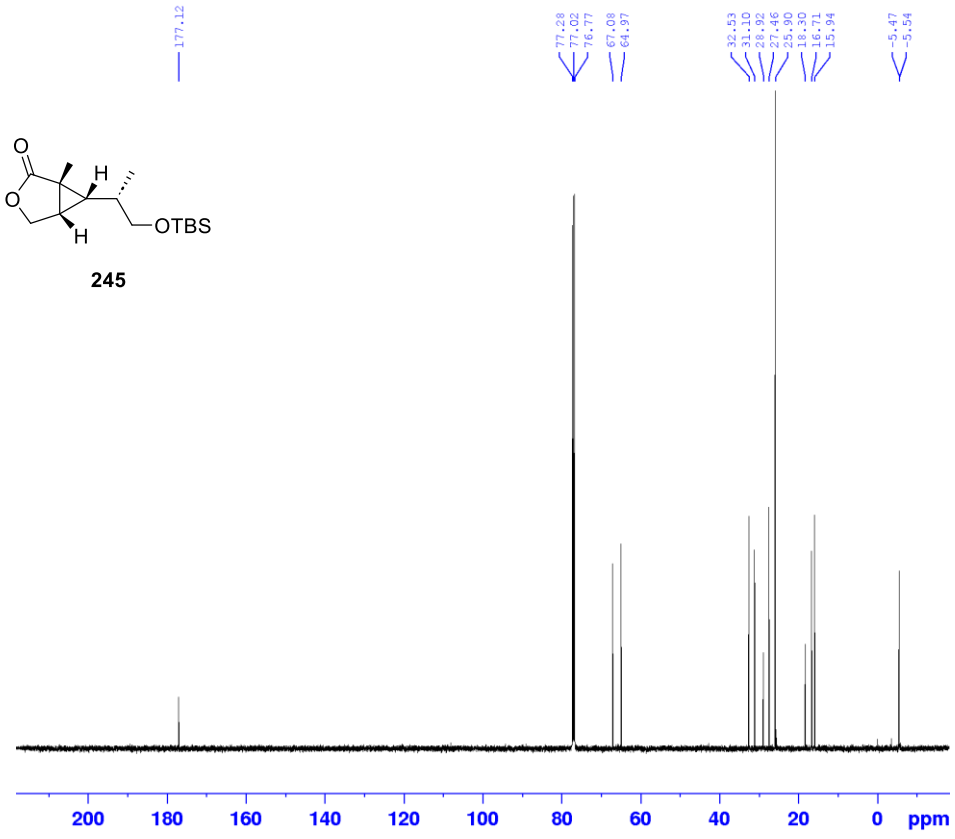


242

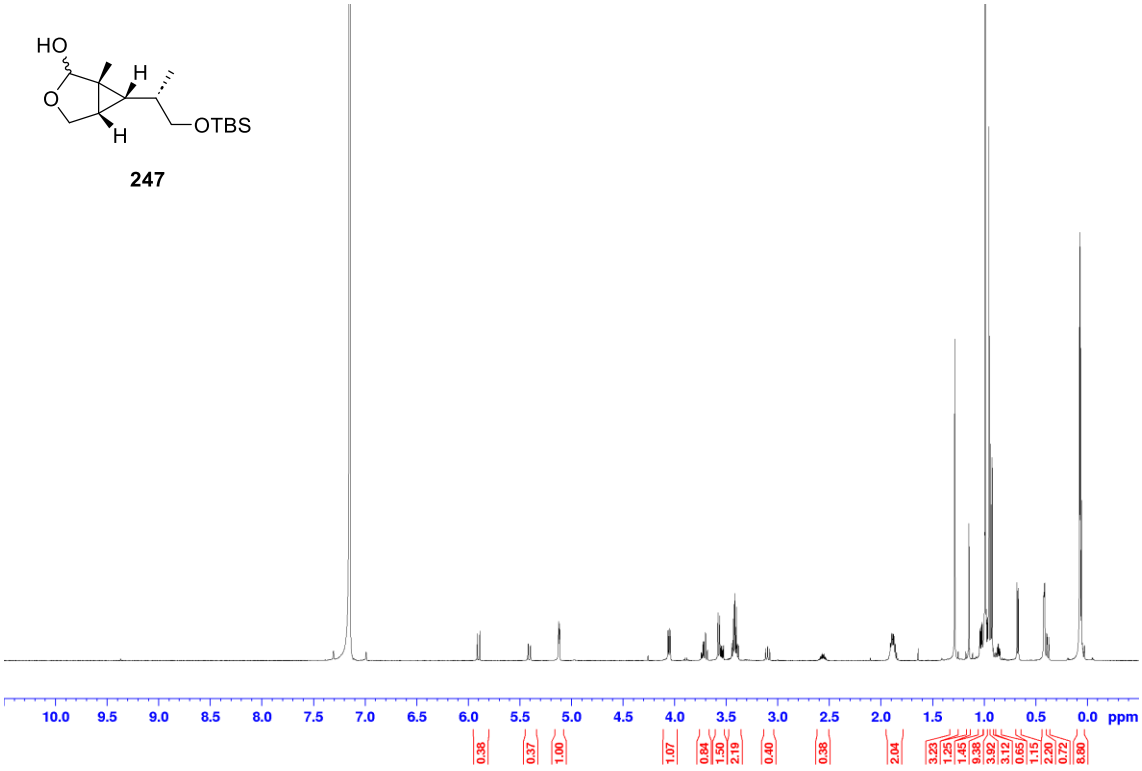
^{1}H NMR spectrum of **245** ($CDCl_3$, 500 MHz, 297 K)



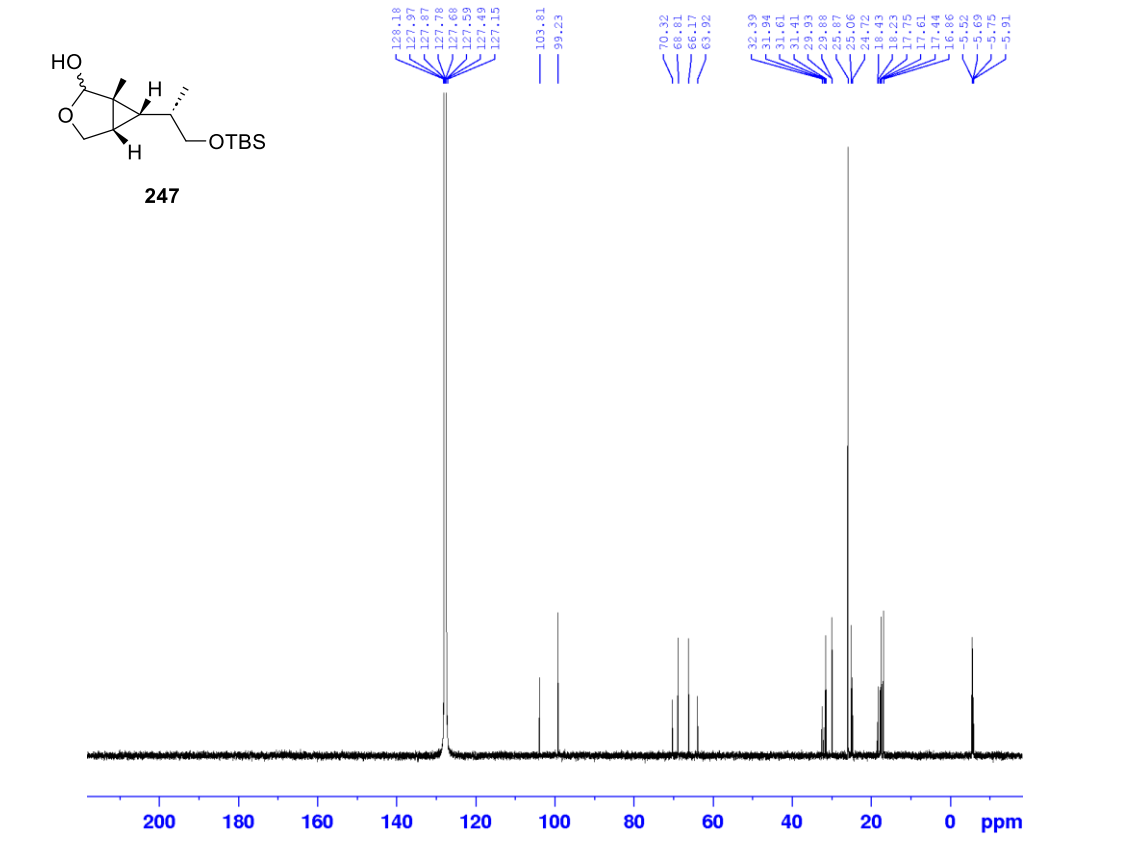
^{13}C NMR spectrum of **245** ($CDCl_3$, 126 MHz, 298 K)



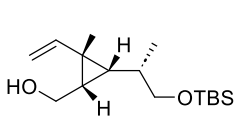
^{1}H NMR spectrum of **247** (C_6D_6, 500 MHz, 300 K)



^{13}C NMR spectrum of **247** (C_6D_6, 126 MHz, 300 K)

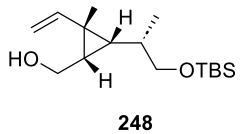


^{1}H NMR spectrum of **248** ($CDCl_3$, 500 MHz, 300 K)



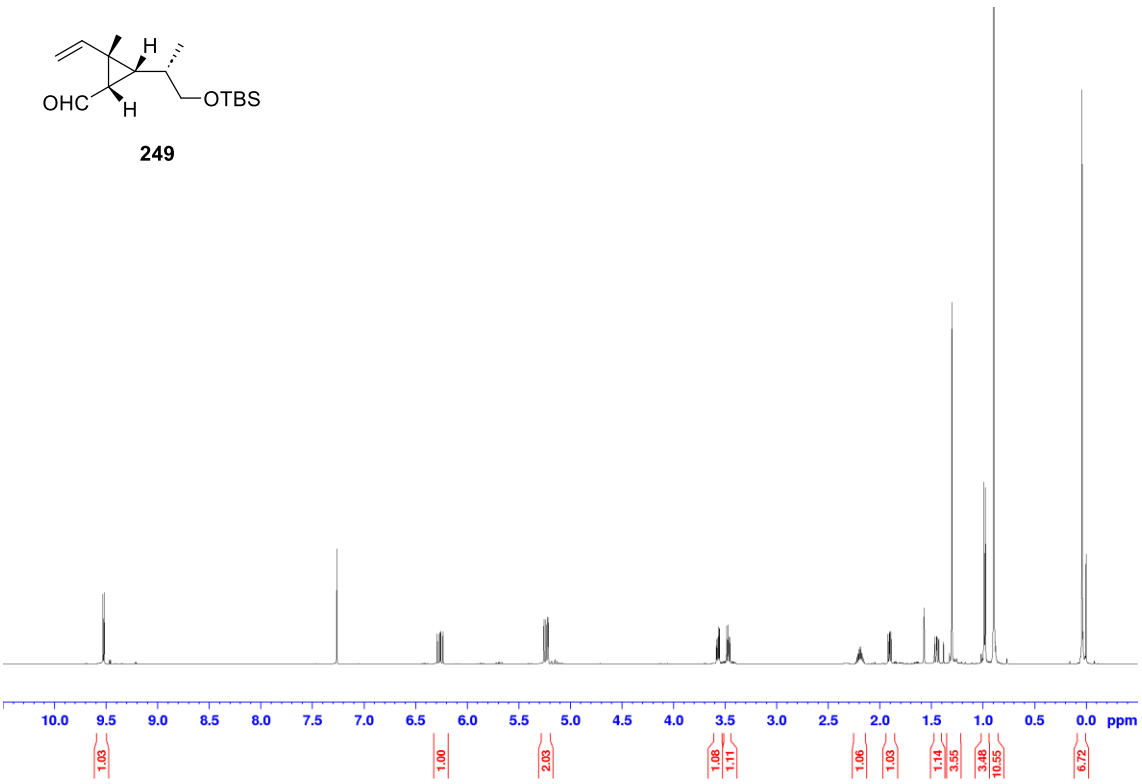
248

^{13}C NMR spectrum of **248** ($CDCl_3$, 126 MHz, 297 K)

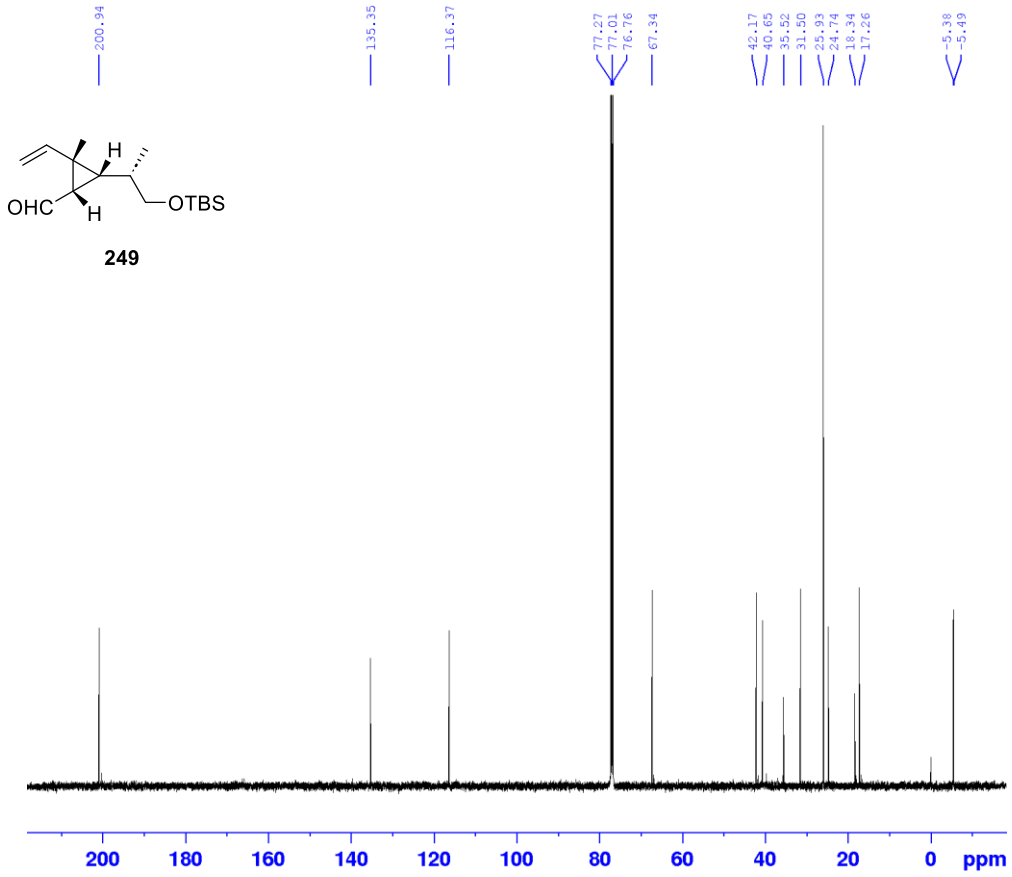


248

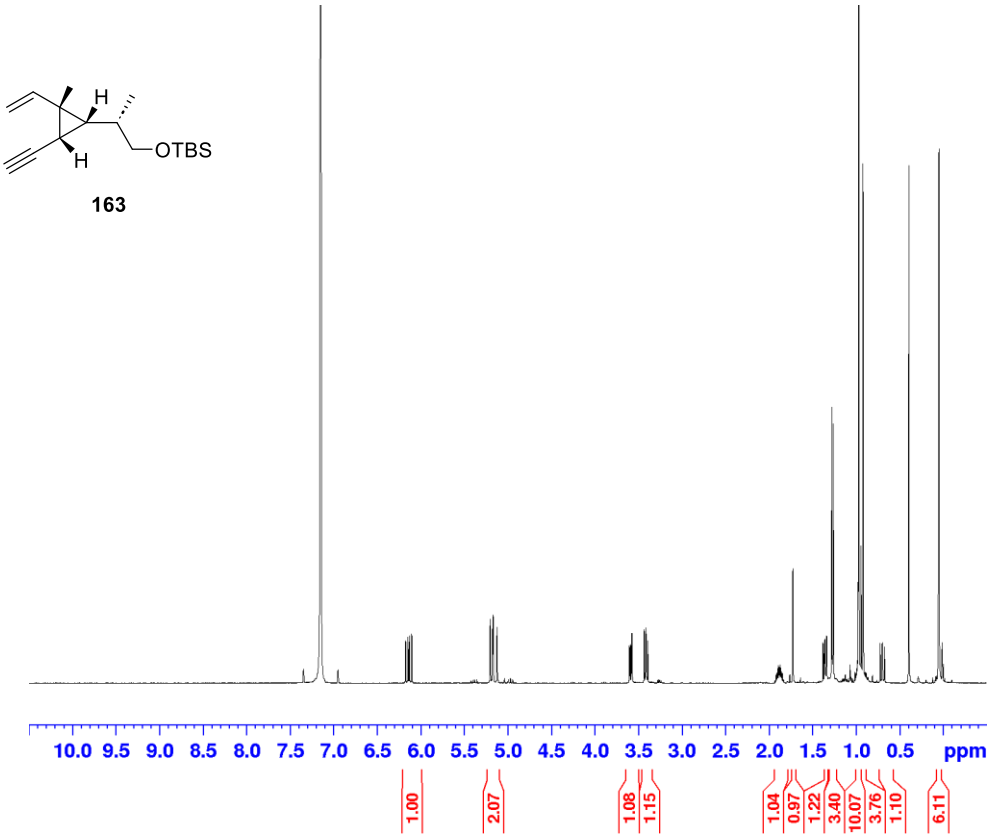
^{1}H NMR spectrum of **249** ($CDCl_3$, 500 MHz, 300 K)



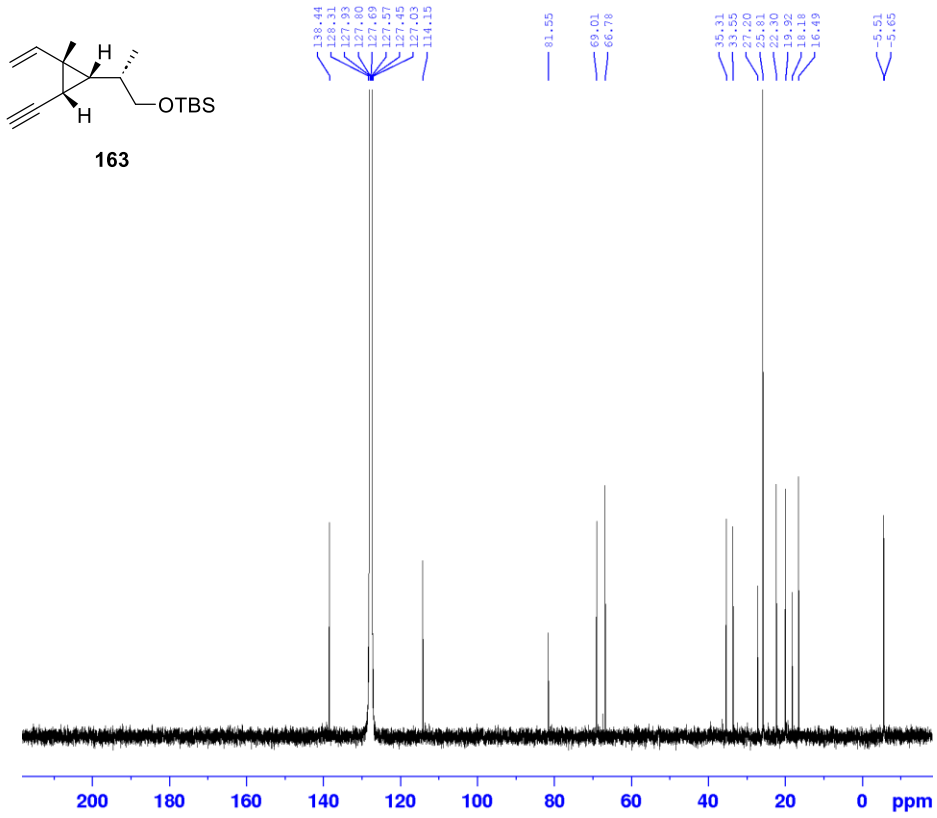
^{13}C NMR spectrum of **249** ($CDCl_3$, 126 MHz, 300 K)



^{1}H NMR spectrum of **163** (C_6D_6, 400 MHz, 297 K)



^{13}C NMR spectrum of **163** (C_6D_6, 100 MHz, 297 K)



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List of publications

Original papers for doctorate thesis

(1) Ryotaro Yagita, Kazuhiro Irie and Chihiro Tsukano, Studies toward the total synthesis of schinortriterpenoids: diastereoselective synthesis of the left-hand fragment. *Eur. J. Org. Chem*. **2021**, *2021*, 4269–4272.

(2) Ryotaro Yagita, Kazuhiro Irie and Chihiro Tsukano, Toward the total synthesis of schinortriterpenoids: construction of the all-*cis*-substituted cyclopropane unit. *Synlett* **2023**, *in press* (DOI: 10.1055/a-2102-8014).

Other original papers

(3) Chihiro Tsukano, Ryotaro Yagita, Takayoshi Heike, Tagwa A. Mohammed, Kazuya Nishibayashi, Kazuhiro Irie and Yoshiji Takemoto, Asymmetric total synthesis of shagenes A and B. *Angew. Chem. Int. Ed.* **2021**, *60*, 23106-23111.

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