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**Catalytic Enantioselective Total Synthesis of Picrotoxane
Alkaloids and Guaiane Sesquiterpene Englerins A and B**

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genehmigte Abhandlung

vorgelegt von

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Die vorliegende Arbeit entstand auf Anregung und unter Anleitung von Herrn Prof. Dr. Bernd Plietker am Institut für Organische Chemie der Universität Stuttgart im Zeitraum von Oktober 2015 bis Januar 2019.

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Declaration of Independence on Dissertation

Hereby I declare that I have completed the dissertation "Catalytic Enantioselective Total Synthesis of Picrotoxane Alkaloids and Guaiane Sesquiterpene Englerins A and B" independently and have not used sources other than those mentioned in this dissertation.

Erklärung über die Eigenständigkeit der Dissertation

Hiermit erkläre ich, dass ich die vorliegende Dissertation „Catalytic Enantioselective Total Synthesis of Picrotoxane Alkaloids and Englerins A and B“ selbstständig verfasst und keine anderen als die genannten Quellen und Hilfsmittel verwendet habe. Die aus fremden Quellen entnommenen Passagen und Gedanken sind als solche kenntlich gemacht.

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Lei Guo

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“Life is like a journey,

I too am on the way”

—Su Shi

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List of Abbreviations

Ac	Acetyl
AIBN	2,2'-Azo- <i>bis</i> (2-methylpropionitrile)
Ar	Aryl
AQN	Anthraquinone
9-BBN	9-Borabicyclo-nonane
BINOL	1,1'-Bi-2-naphthol
BINAMIDE	2,2'-Bisamide-1,1'-binaphthalene
BINUREA	2,2'-Bisurea-1,1'-binaphthalene
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
BOM	Benzyloxymethyl
BOX	Bisoxazoline
<i>n</i> Bu	<i>n</i> -Butyl (<i>normal</i> -Butyl)
<i>t</i> -Bu	<i>tert</i> -Butyl
Bz	Benzoyl
CBS catalyst	Corey-Bakshi-Shibata catalyst
cat.	catalyst
CoA	Coenzyme A
conc.	concentration
Cp	Cyclopentadienyl
<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic acid
DBU	1,8-Diazabicyclo[5. 4. 0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEMS	Diethoxymethylsilane
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DIBAL-H	Di- <i>iso</i> -butylaluminum hydride
DMA	<i>N,N'</i> -Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMAPP	Dimethylallyl pyrophosphate

DME	Dimethoxyethane
DMF	<i>N,N'</i> -Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DTBHN	Di- <i>tert</i> -butyl hyponitrite
<i>ee</i>	enantiomeric excess
EI	Electron ionization
eq (equiv)	equivalent
ESI	Electrospray ionization
Et	Ethyl
EVK	Ethyl vinyl ketone
EWG	Electron withdrawing group
FPP	Farnesyl pyrophosphate
GC	Gas chromatography
GC-MS	Gas chromatography – mass spectrometry
GPP	Geranyl pyrophosphate
h	hour
HFIP	Hexafluoro- <i>iso</i> -propanol
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
Hz	Hertz
IBX	2-Iodoxybenzoic acid
Im	Imidazole
IPP	Isopentenyl pyrophosphate
IR	Infrared spectroscopy
<i>J</i>	Coupling constant
KS	Ketosynthase
LA	Lewis acid
LDA	Lithium di- <i>iso</i> -propylamine
LLS	Longest linear sequence

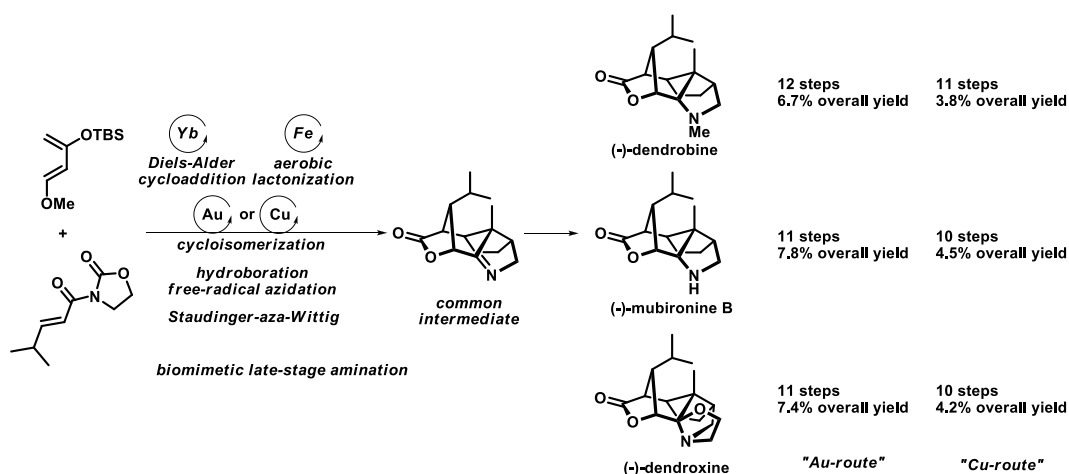
M	Molarity
MAHT	Malonic acid half thioester
Me	Methyl
min.	minute
m.p.	melting point
MP	Mevalonate pathway
4Å MS	4Å Molecular sieves
MS	Mass spectrometry
Ms	Methanesulfonyl
MTBE	Methyl <i>tert</i> -butyl ether
N.D.	Not detected
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
N.R.	No reaction
PFS	Progression-free survival
PG	Protecting group
Ph	Phenyl
PHAL	1,4-Phthalazine
PHT	Pyrrolidone hydrotribromide
PKS	Polyketide synthase
PMB	<i>para</i> -Methoxybenzyl
ppm	parts per million
<i>n</i> Pr	<i>n</i> -Propyl (<i>normal</i> -Propyl)
<i>i</i> Pr	<i>iso</i> -Propyl
PTSA	<i>para</i> -Toluenesulfonic acid
RCM	Ring-closing metathesis
R_f	Retention factor
rt	room temperature
Salen	Salicylaldehyde + ethylenediamine ligand
sat.	saturated
SEGPHOS	5,5'- <i>Bis</i> (diphenylphosphino)-4,4'- <i>bi</i> -1,3-benzodioxole
<i>t</i>	<i>tert</i>

TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBACl	Tetra- <i>n</i> -butylammonium chloride
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS (TBDMS)	<i>tert</i> -Butyldimethylsilyl
Tce	2,2,2-Trichloroethyl
TES	Triethylsilyl
Tf	Triflate (Trifluoromethanesulfonate)
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIPS	Triisopropylsilane chloride
TMS	Trimethylsilyl
TosMIC	Toluenesulfonylmethyl isocyanide
TPAP	Tetra- <i>n</i> -propylammonium perruthenate
TRPC	Transit receptor potential cation channels
Trifimide	Trifluoromethanesulfonimide
Ts	Tosyl (Toluenesulfonate)
VAZO	2,2'-Azo- <i>bis</i> -(2,4-dimethylvaleronitrile)
Vol.	Volume

Abstract (English)

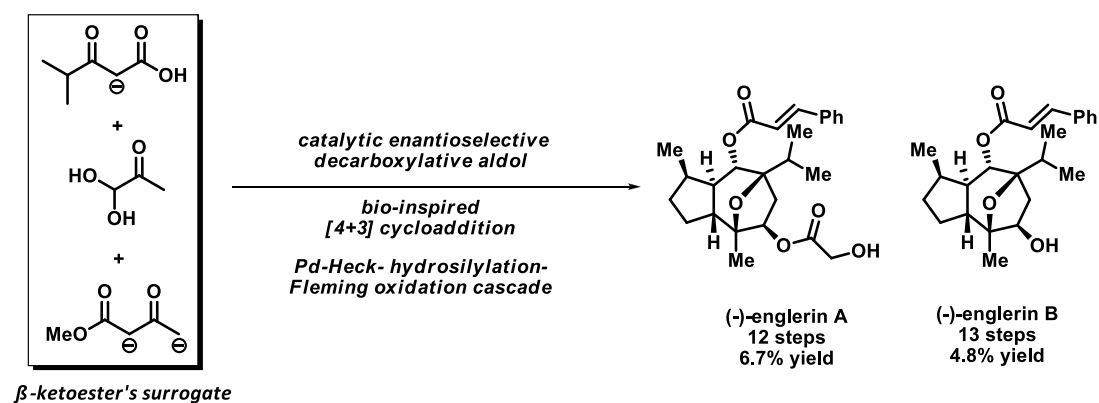
Molecular chirality plays an important role in discovery and manufacture of pharmaceutical candidates, products as well as their biological activities *in vivo*. The tragedy of thalidomide in the 1960s is still reminding us to synthesize bioactive molecules in enantioselective way. Asymmetric catalysis has changed the procedures of chemical development dramatically and provides a state-of-the-art, environmentally sustainable strategy to reach this goal. The research contained in this thesis is focusing on the total synthesis of two series of bioactive, structurally complex natural products utilizing enantioselective catalysis, which can be divided into the following parts:

Part I:



Alkaloids from the picrotoxane family are biologically potent natural products that show hypertensive, antipyretic, analgesic and anti-influenza A virus activities. Herein a concise catalytic, enantioselective total synthesis of (-)-dendrobine, (-)-mubironine B and (-)-dendroxine is described with an overall yield of 6.7%, 7.8% and 7.4%, respectively. This represents a significantly improved yield as compared to synthetic approaches reported in the past, and it is the first report on the total synthesis of (-)-dendroxine. Importantly, the asymmetric Yb-catalyzed Diels-Alder reaction between Danishefsky's diene and an oxazolidinone moiety allowed for an enantioselective synthesis of the natural products in the enantioselective way, while the Fe-catalyzed aerobic oxidation, Cu- or Au-catalyzed cycloisomerization and hydroazidation underlined the strength of modern synthetic sequences in total synthesis.

Part II:

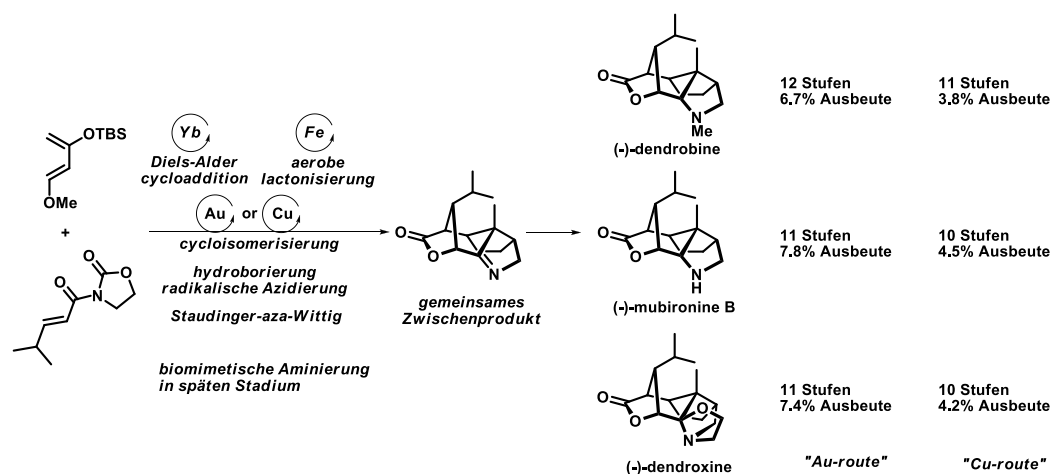


Englerin A is a guaianes sesquiterpene natural product that shows antitumor activity when binding to the TRPC4/5 target (a new target for antitumor compounds) *in vitro*. In this part a bio-inspired, catalytic enantioselective strategy towards the total synthesis of (-)-englerins A and B in 12 or 13 steps with 6.7% or 4.8% yield, respectively, is described. The success was initialized by a biomimetic catalytic enantioselective decarboxylative aldol reaction for chirality introduction. A [4+3] cycloaddition with neighboring group participation was used for the construction of the central core structure, which was inspired by the biogenesis of tropinone. A late stage one-pot Heck coupling-regioselective hydrosilylation-Fleming oxidation cascade sequence afforded the cyclopentane core while a kinetic CBS reduction enriched enantiopurity and eventually delivered the natural products.

Abstract (German)

Die molekulare Chiralität spielt eine wichtige Rolle bei der Entdeckung und Herstellung von Arzneimitteln sowie bei deren biologischen Aktivitäten *in vivo*. Die Tragödie von Thalidomid in den 1960er Jahren erinnert uns immer noch daran, bioaktive Moleküle in enantiomerenreiner Form zu synthetisieren. Die asymmetrische Katalyse hat die Verfahren der chemischen Entwicklung grundlegend verändert und bietet eine hochmoderne, ökologisch nachhaltige Strategie um dieses Ziel zu erreichen. Die Forschung dieser Arbeit befasst sich mit der Totalsynthese von zwei bioaktiven, strukturell komplexen Naturstoffgruppen unter Verwendung der enantioselektiven Katalyse. Die Arbeit ist in die folgenden Teile aufgeteilt:

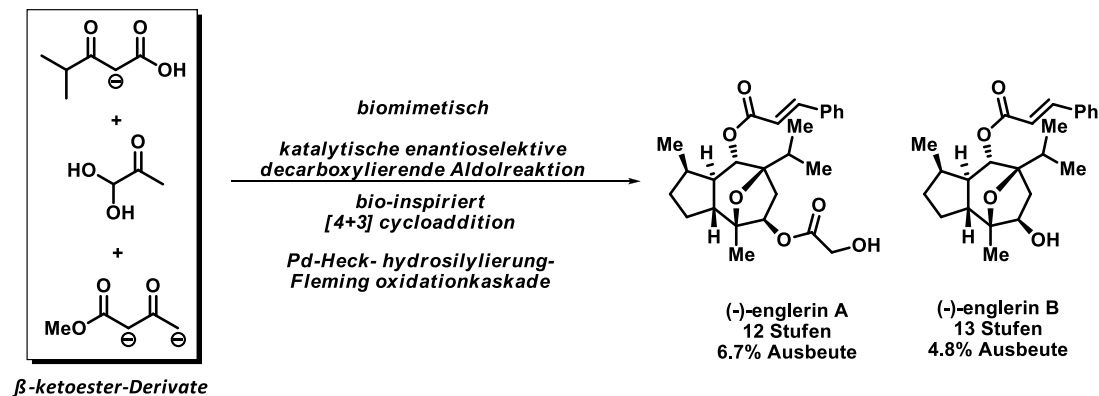
Teil I:



Alkaloide aus der PicROTOXAN-Familie sind bioaktive Naturstoffe, die blutdrucksteigernde, fiebersenkende, schmerzlindernde und Anti-Influenza-A-Virus Aktivität zeigen. In diesem Teil wird eine kurze katalytische enantioselektive Totalsynthese von (-)-Dendrobine, (-)-Mubironin B und (-)-Dendroxin mit Gesamtausbeuten von 6,7%, 7,8% bzw. 7,4% beschrieben. Diese stellen deutlich verbesserte Ausbeuten im Vergleich zu bisher bekannten Syntheseansätzen dar und es ist zudem die erste berichtete Totalsynthese von (-)-Dendroxin. Hierbei ist wichtig, dass die asymmetrische Yb-katalysierte Diels-Alder-Reaktion zwischen Danishefskys Diene und einem Oxazolidinon eine enantioselektive Synthese der Naturstoffe in enantiomerenreiner Form ermöglicht, während die eisenkatalysierte, aerobe Oxidation, kupfer- oder gold-katalysierte Cycloisomerisierung und

Hydroazidierung die Stärke moderner Synthesesequenzen in der Totalsynthese unterstrichen haben.

Teil II:



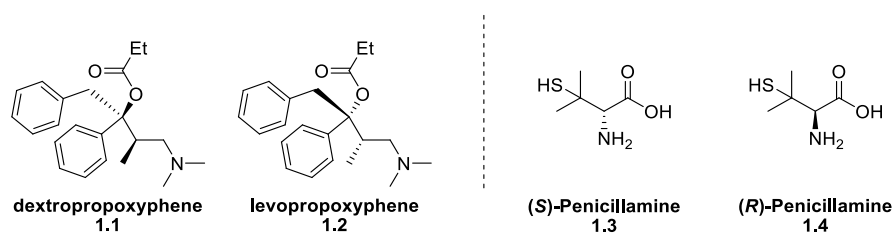
Englerin A ist ein Guaian-Sesquiterpen-Naturstoff, das auf den TRPC4 / 5-Rezeptor (ein neues Ziel für Antitumorverbindungen) *in vitro* abzielt und Antitumoraktivität zeigt. In diesem Teil der Arbeit wird eine biologisch inspirierte, katalytische enantioselektive Strategie zur Totalsynthese von (-) - Englerinen A und B in 12 oder 13 Stufen mit Ausbeuten von 6,7% bzw. 4,8% beschrieben. Der Erfolg wurde durch eine biomimetische katalytische enantioselektive decarboxylierende Aldol reaktion zur Einführung der Chiralität initialisiert. Für die Konstruktion des zentralen Gerüsts wurde eine [4 + 3] -Cycloaddition mit Nachbarbeteiligung verwendet, die von der Biogenese des Tropinons inspiriert wurde. Eine Eintopf Heckkupplung-regioselektive Hydrosilylierungs-Fleming-Oxidationskaskadensequenz gegen Ende der Synthese lieferte den Cyclopentan-Kern, während eine kinetische CBS-Reduktion die Enantiomerenreinheit erholt auf 95% *ee* angereichert und schließlich den Naturstoff geliefert.

I. Theoretical Section

1. Introduction

1.1. Chirality and Asymmetric Catalysis

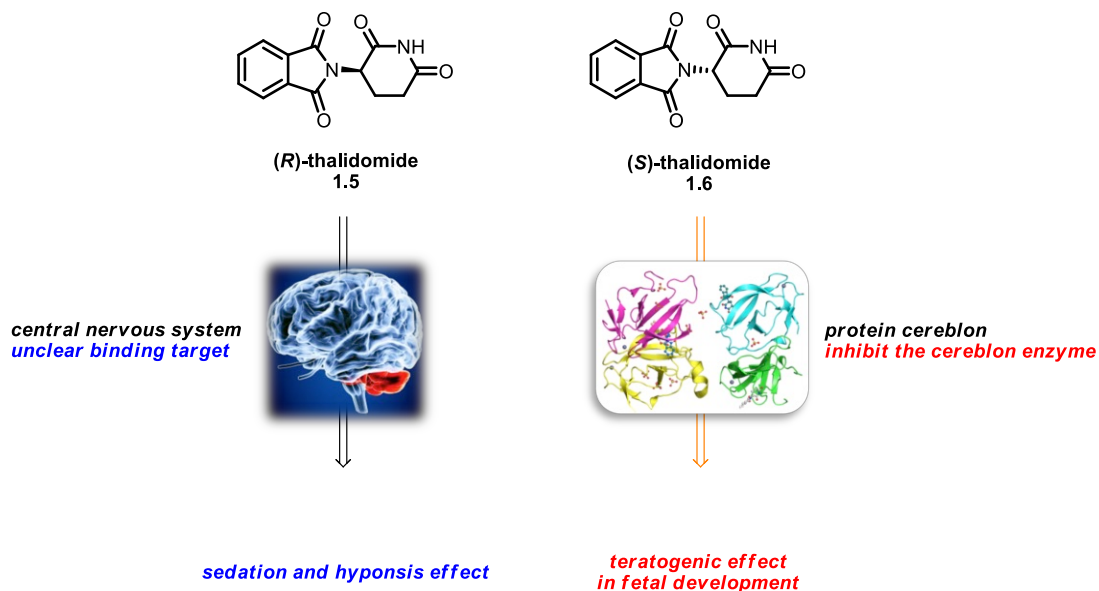
Chirality is the property of asymmetry which is a fundamental feature in chemical structure, macroscopic anatomy as well as living organisms' behavior.^[1] Organisms usually show highly rigid stereospecificity in their metabolism process, in which one chiral molecule recognizes two different enantiomeric molecules in different ways. Particularly in drug discovery, manufacture and biological activities *in vivo*, bio-receptors interact with drugs that having the proper stereochemical properties, while the inappropriate binding between receptors and the other enantiomers might result in remarkable differences in the pharmacological activities.^[2] For instance, Darvon (dextropropoxyphene) **1.1** is a μ -opioid receptor agonist which acts as analgesic, whereas its enantiomer, Novrad (levopropoxyphene) **1.2** is an antitussive (Scheme 1-1).^[3]



Scheme 1-1. Examples of enantiomers with different biological actions

However, in some cases the non-therapeutic enantiomer can cause serious side effects. In cases of penicillamine, the *S*-enantiomer **1.3** is used for treatment of primary chronic arthritis, while its *R*-enantiomer **1.4** is proven to be highly toxic (Scheme 1-1).^[4] In the 1960s, insufficient research on the enantiomers' pharmacological actions *in vivo* led to the tragedy of thalidomide, which is still vivid in mind after several decades. Thalidomide was first marketed in 1957 in the racemic form to act against nausea and morning sickness of pregnant women. However, shortly after thalidomide was approved throughout the world, about 10,000 infants were born with phocomelia and only 50% of the 10,000 survived. It was unknown in the 1960s that only *R*-thalidomide **1.5** is pharmacologically useful while *S*-thalidomide **1.6** causes the inhibition of the cereblon enzyme and further leads to severe teratogenicity in fetal development (Scheme 1-2).^[5] Even though extensive research on thalidomide showed that the *R*-enantiomer is metabolized to its racemic mixture *in vivo*,^[6]

this is a tragic lesson invoking more research on the adverse drug reaction of chiral drugs,^[7] and urging synthetic chemists to synthesize the potentially bioactive compounds in their enantiomerically pure form.



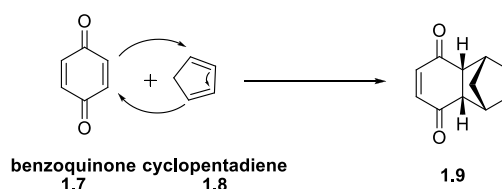
Scheme 1-2. Enantiomers of thalidomide with different pharmacological actions

In 1992, the US FDA (Food and Drug Administration) approved the “racemic switches” guideline to initialize the commercialization of enantiomerically pure drugs.^[1, 8] This guideline, together with the tremendous accomplishment in organic synthesis over the past decades, has dramatically improved the development of the synthesis of enantiomerically pure bioactive compounds. Traditional methods in stereoselective synthesis included using stoichiometric amounts of ex-chiral-pool substances for kinetic resolution, as building blocks or auxiliaries, which limited the scope of the variation of products and increased the cost-efficiency ratio. The 2001 Nobel Prize in chemistry has witnessed the dramatic growth of asymmetric catalysis, which provides an alternative shortcut to the enantiomerically enriched products from prochiral compounds using catalytic amounts of chiral compounds as catalysts or ligands. Thanks to its extensive products scope, low cost-efficiency ratio as well as low energy consumption, asymmetric catalysis is nowadays widely used in academia as well as in industry.^[1]

This part of introduction will focus on two types of enantioselective catalytic transformations: the catalytic asymmetric Diels-Alder cycloaddition and the catalytic asymmetric aldol reaction, which are relevant to the topics described in this thesis.

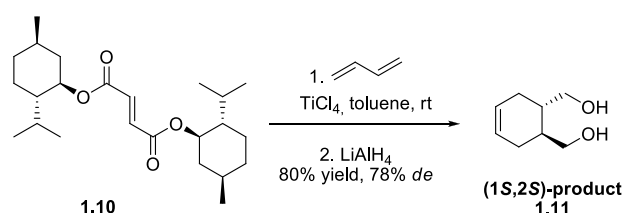
1.1.1. Catalytic Enantioselective Diels-Alder Cycloaddition

In 1950, the Nobel Prize in chemistry was awarded to Otto Paul Hermann Diels and Kurt Alder for their contribution in the discovery and development of diene synthesis methodology, which is today known as the Diels-Alder (DA) cycloaddition. Studies towards this cycloaddition were commenced with the reaction between benzoquinone **1.7** and cyclopentadiene **1.8** (Scheme 1-3),^[9] and were focused on mechanistic investigations as well as non-enantiomeric research before 1950s. However, since the landmark Nobel Prize, great progress in this area has been achieved in exploration and application of the enantioselective version of the DA cycloaddition due to its capacity to afford complex enantioenriched structures rapidly from very simple substrates.



Scheme. 1-3. The first reported DA cycloaddition

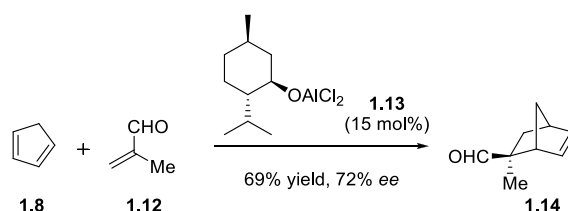
Initially, the enantioselective Diels-Alder reaction was investigated with a chiral auxiliary on the dienophile to favor the formation of one enantiomer over the other. In 1963, Walborsky's group published the first enantioselective DA cycloaddition with chiral auxiliaries to achieve high enantioselectivity (Scheme 1-4).^[10] However, the drawbacks of auxiliary assisted stereoselective DA are evident: the substrate scope is limited and stoichiometric amounts of ex-chiral compound are necessary (though the chiral auxiliary can be recycled, in this case a further separation step is required).



Scheme. 1-4. Walborsky's chiral auxiliaries assisted enantioselective DA cycloaddition

Hence, it was found that Lewis acids could catalyze the DA cycloaddition, and the activation process involves the coordination of the Lewis acid to an electron deficient dienophile.^[11] If the corresponding chiral Lewis acid for this process could be synthesized,

its coordination to the dienophile might further lead to the catalysis in an enantioselective fashion. With this concept, Koga reported the first catalytic enantioselective DA cycloaddition with catalyst **1.13** prepared *in situ* from (-)-menthol and ethylaluminum dichloride, which promoted the stereoselective cycloaddition of cyclopentadiene **1.8** and 2-ethyl-2-propenal **1.12** to afford the *exo*-adduct **1.14** in 69% yield and 72% *ee* (Scheme 1-5).^[12]



Scheme 1-5. Koga's first catalytic enantioselective DA cycloaddition

Accordingly, it is possible to develop effective chiral catalysts for the stereoselective DA cycloaddition, and to design chiral catalysts with high asymmetric induction is crucial to achieve high stereoselectivity. Over the past decades, several types of chiral Lewis acid-based complexes have dominated the field of asymmetric catalysis, which have been extensively explored and applied to the asymmetric DA cycloaddition, while the organocatalyzed DA cycloaddition is still an ongoing major research topic in organocatalysis since 2000.^[13]

In this chapter, examples of the Diels-Alder reactions with simple substrates will be the main focus, and hetero-Diels-Alder cycloadditions (*oxa*-DA and *aza*-DA) will not be covered.

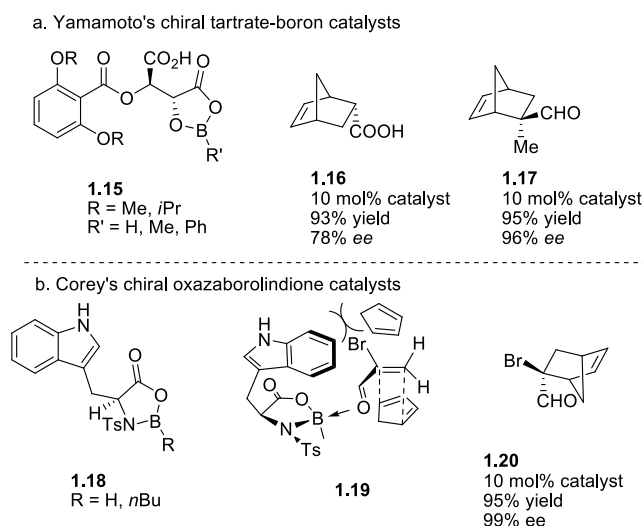
1.1.1.1. Lewis acid Catalyzed Asymmetric Diels-Alder Cycloaddition

Chiral Lewis acid catalyzed asymmetric reactions represent a powerful method to afford enantioenriched compounds. For DA cycloadditions, many excellent results have been achieved by applying various chiral Lewis acids.

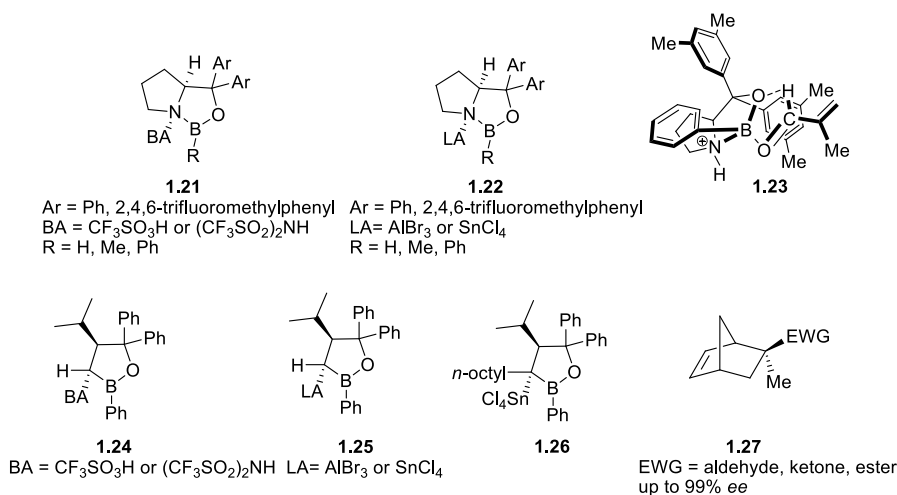
A. Chiral Boron Complex Catalyzed Asymmetric DA Cycloaddition

Traditionally, chiral boron complexes were synthesized *via* dehydration of boronic acid derivatives (such as phenylboronic acid or methylboronic acid) and chiral ligands (usually tartrate or amino acid derivatives) (Scheme 1-6). Yamamoto's group reported the first

series of practical chiral boron catalysts **1.15** derived from tartrates for the DA cycloadditions between α,β -unsaturated dienophiles and cyclic dienes (Scheme 1-6a).^[14] Corey's group found that chiral oxazaborolidinones **1.18** facilitated the DA cycloaddition with up to 95% yield and 99% *ee* before they were investigated for stereoselective ketone reduction (Scheme 1-6b). The steric repulsion between catalyst and diene led to high stereodifferentiation and resulted in high enantioselectivity (Scheme 1-6, **1.19**).^[15]



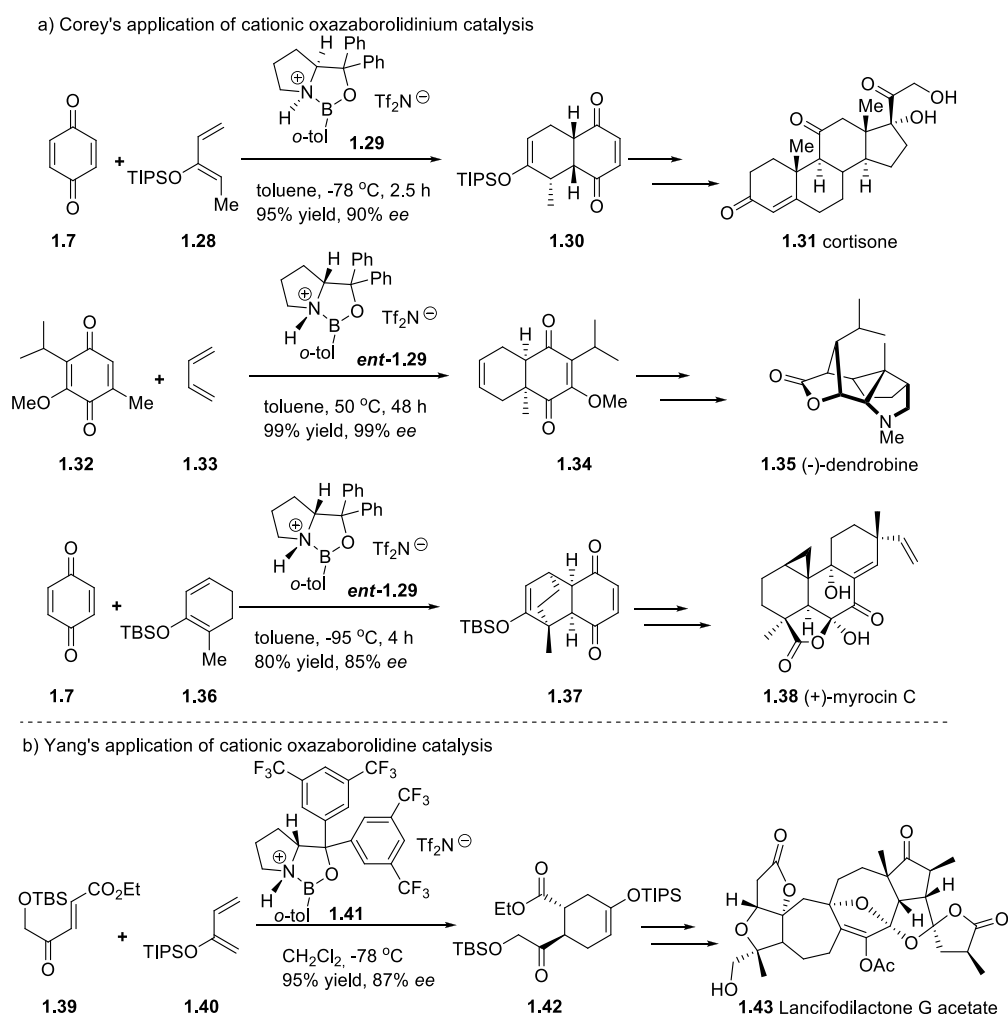
Scheme 1-6. Boron complexes catalyzed asymmetric DA cycloadditions



Scheme. 1-7. Cationic chiral oxazaborolidinones as asymmetric DA cycloaddition catalysts

Cationic chiral oxazaborolidinones are a series of versatile and electron-deficient catalysts (Scheme 1-7), which were obtained easily from the corresponding optically pure amino alcohols by dehydration with boronic acid derivatives to afford oxazaborolidinones, followed

by subsequent activation with Brønsted acids or strong Lewis acids (usually triflic acid, triflimide or AlBr_3).^[16] The intramolecular acid was found to be essential in accelerating the rate of the DA cycloaddition and in obtaining a high level of enantioselectivity due to intramolecular hydrogen bonding effect (Brønsted acid) or π - π donor-acceptor interaction (Lewis acid) (Scheme 1-7, **1.23**).^[16] Trifimide complexes were proven to be more stable than the triflic acid complexes. In the work of Corey's group, these catalysts were tested with the DA cycloadditions between a wide range of dienophiles including acrylates, quinones, enones, fumarates and cyclic or acyclic dienes to give the corresponding products in high yields and *ee*.^[17]

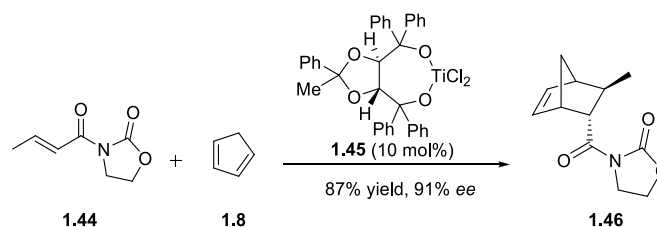


Scheme 1-8. Synthesis of natural products *via* cationic oxazaborolidines catalyzed asymmetric DA cycloadditions

However, this series of catalysts are highly moisture-sensitive and have to be handled carefully in moisture-free conditions.^[18] In 2005, Yamamoto's report demonstrated that a slight modification of the oxazaborolidine backbone afforded the moisture- and oxygen-stable cationic chiral oxazaborolidine **1.26** (Scheme 1-7), which had wide implications for versatile catalysts design.^[18]

The cationic oxazaborolidines catalyzed asymmetric DA cycloadditions have been applied to the total synthesis of several natural products by Corey's group at the time of its initial investigation (Scheme 1-8a)^[19] and very recently by Yang's group (Scheme 1-8b)^[20].

B. Chiral Metal Complex Catalyzed Asymmetric DA Cycloaddition



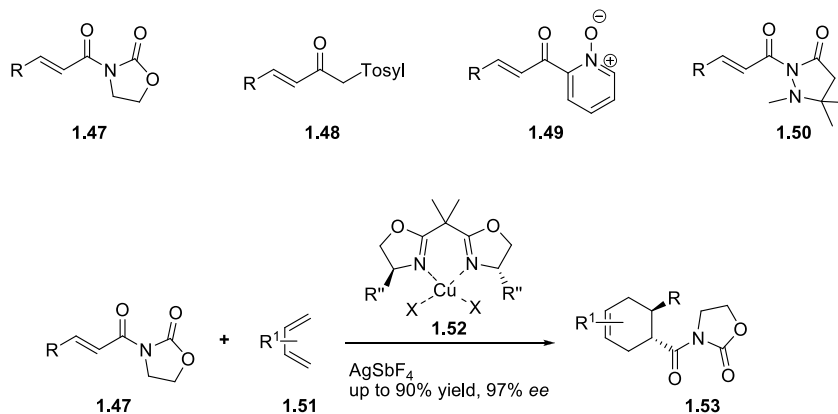
Scheme. 1-9. Narasaka's catalytic enantioselective DA cycloaddition with a bidentate dienophile

As previously mentioned, the dienophiles involved in boron complex catalyzed DA cycloadditions are acrylates, quinones, enones and fumarates, which are monodentate dienophiles. However, the implement of a coordinating chiral ligand to the Lewis acidic center usually reduces its Lewis acidity, since the electron density is shifted from the chiral ligand to the active center, which results in weaker coordination to the dienophile. In chiral boron complex catalysis, this issue is successfully solved by introducing an external acid for the generation of a reactive chiral complex.^[16-20] In the case of chiral metal complex, the general strategies are to replace the monodentate dienophile with its bidentate equivalent or to use a strongly coordinating diene (i.e. Rawal's diene).^[21] Selected examples for chiral metal complexes catalyzed enantioselective DA cycloadditions will be discussed below.

N-acryloyl oxazolidinone is the bidentate substrate and is widely used in asymmetric catalysis.^[16] The bidentate substrate provides additional coordination site to the chiral center, and can be conveniently converted into multiple functional groups such as esters, amides and alcohols.^[16] The first stereoselective DA cycloaddition using *N*-acryloxazolidinone was reported by Narasaka's group in 1989 (Scheme 1-9).^[22] The strongly

coordinating property of *N*-acryloyloxazolidinone allowed sufficient compensation to the weak Lewis acidity of titanium complex **1.45**, which resulted in the DA cycloaddition product **1.46** in high yield and enantiomeric excess.

dienophiles:

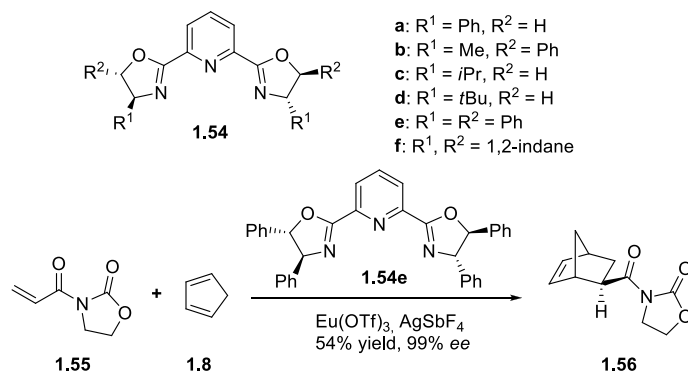


Scheme 1-10. Copper-BOX complexes catalyzed DA cycloadditions

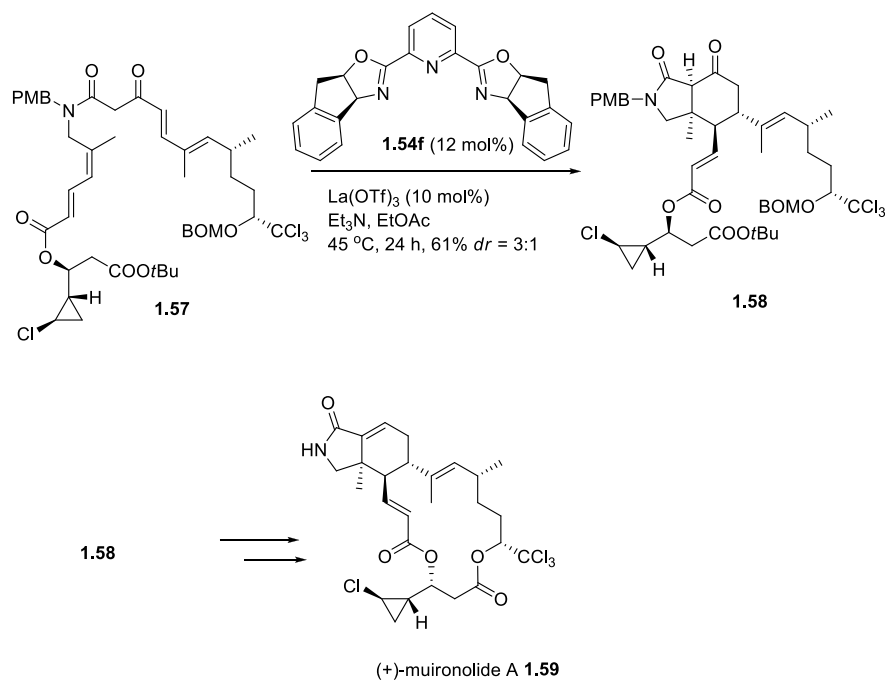
Evans' group showed that *bis*(oxazoline) compounds (Scheme 1-10) were a series of highly coordinating bidentate ligands to metal centers.^[23] Systematical research indicated that *bis*(oxazoline) compounds have broad compatibility with different metals (including copper, iron, magnesium and zinc), and the complexes are effective catalysts for DA cycloadditions between bidentate dienophiles (including acryloylpyridine-oxides, *N*-acryloyl pyrazolidinones and α -tosyl-enones) and different dienes with good yields and excellent enantioselectivities.^[23] Dienes like 1,3-butadiene or cyclopentadiene are highly compatible with this series of catalysts, while Danishefsky's diene is too labile towards Lewis acid to be used, as the strong Lewis acidity might lead to decomposition of Danishefsky's diene. AgSbF_6 is usually used as an additive because counterions like SbF_6^- are critically essential for this reaction.^[23]

Based on Evans' BOX ligands, Fukuzawa's group disclosed that chiral pyBOX complexes (**1.54**, Scheme 1-11) have a wide range of application in the rare-earth metal catalyzed enantioselective DA cycloadditions.^[24] With *isopropyl*-pyBOX-Sc complex (**1.54**, Scheme 1-11), the reaction between *N*-acryloyl oxazolidinone bidentate dienophiles and cyclic or acyclic dienes yielded the corresponding DA products in moderate yields and good enantioselectivities (up to 90% ee). In the report of Desimoni's group, with diphenyl-pyBOX-Eu(OTf)₃ (**1.54e**, Scheme 1-11) as catalytic complex, diastereoselective DA product **1.56** was obtained from the reaction between *N*-acryloyl oxazolidinone bidentate dienophile **1.55**

with cyclopentadiene **1.8** in 99% *ee* (Scheme 1-11).^[25] The additional phenyl group at the R² position of **1.54e** was believed to induce the high enantioselectivity. Further studies also showed that the substituents on the pyBOX backbone and the lanthanide cations significantly affect the reactivity as well as the enantioselectivity of the reaction due to variations in electronic and steric properties.^[25]



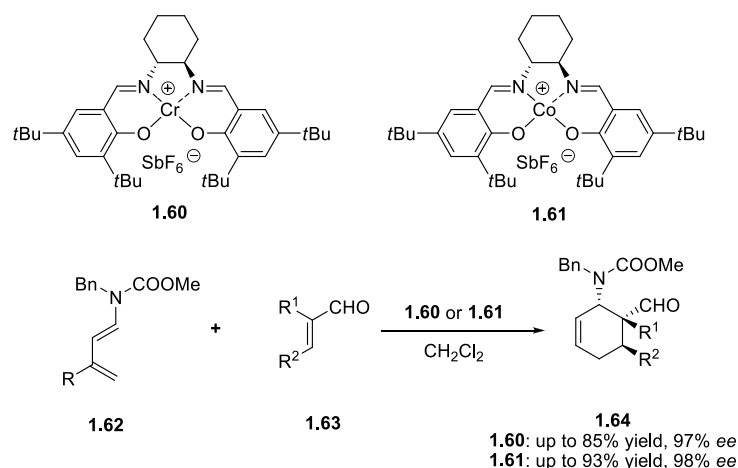
Scheme 1-11. Enantioselective DA cycloadditions catalyzed by pyBOX-rare-earth metal complexes



Scheme 1-12. Total synthesis of (+)-muironolide A *via* intramolecular DA cycloaddition

Meanwhile, chiral rare-earth metal complexes are more stable towards moisture than the corresponding chiral transition metal complexes,^[16] they can be handled more easily

and are more practical for application in total synthesis. In 2015, Zakarian's group reported the enantioselective total synthesis of the exceedingly rare natural product (+)-muironolide A **1.59** (Scheme 1-12), in which a diastereoselective intramolecular Diels-Alder cycloaddition catalyzed by a $\text{La}(\text{OTf})_3$ -pyBOX complex was used to construct the backbone structure **1.58** of the macrolide (Scheme 1-12).^[26]

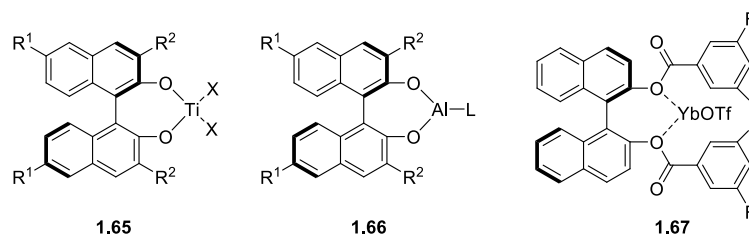


Scheme 1-13. Salen-metal complexes catalyzed DA cycloadditions

Additionally, a highly enantioselective DA cycloaddition with salen-Cr(III) **1.60** or salen-Co(III) complexes **1.61** was reported by Rawal's group (Scheme 1-13).^[27] Importantly, monodentate dienophiles (acrolein for example) **1.63** can be used in the catalysis, as the bidentate Rawal's dienes **1.62** might provide additional coordination to the chiral complexes. Furthermore, the catalysis was conducted at room temperature under air atmosphere conveniently, which is highly desirable for total synthesis and industrial applications.^[27]

Other progresses in DA cycloadditions catalyzed by chiral metal complexes include the development of BINOL-titanium complex **1.65**^[28], BINOL-aluminum complex **1.66**^[29] and BINAMIDE-rare-earth complex **1.67**^[30] (Scheme 1-14). The BINOL-titanium and BINOL-aluminum complexes can be used for the reaction of monodentate dienophiles with different dienes, as titanium and aluminum exhibit a relatively higher Lewis acidity. Nishida's group's recent investigation of BINAMIDE-rare-earth metal catalysis represented the first highly enantioselective DA cycloaddition of electron-rich Danishefsky's diene with electron-deficient bidentate dienophiles, as the electron-rich Danishefsky's diene is stable with this less Lewis acidic complex **1.67** (Scheme 1-14).^[30] The DA cycloaddition catalyzed by the

BINAMIDE derived BINUREA-Yb(OTf)₃ has been successfully applied to the catalytic enantioselective total synthesis of picrotoxane alkaloids by our group.^[31]



Scheme 1-14. Chiral biaryl-metal complexes

1.1.1.2. Organocatalyzed Asymmetric Diels-Alder Cycloaddition

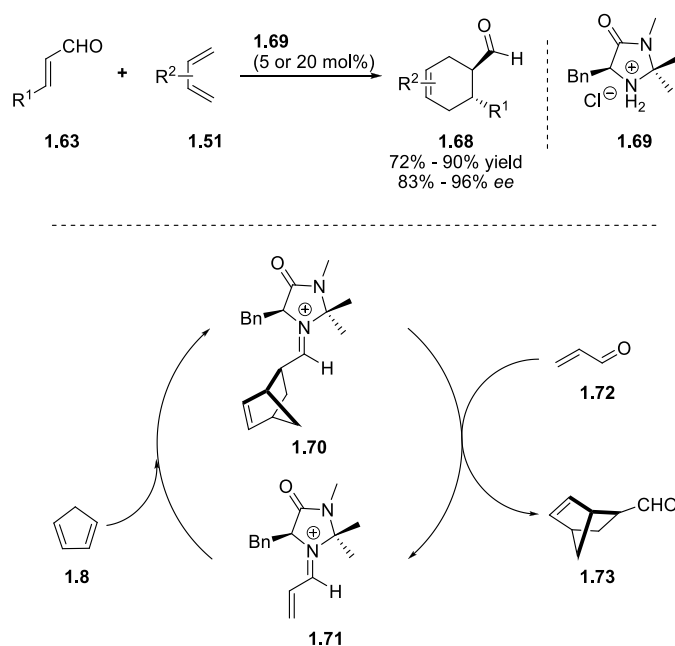
In nature, enzymes are the biocatalysts for DA cycloaddition, however in the laboratory the reactions are too complex and too specific to be used.^[32] Small organic molecules used as organocatalysts emerged as good surrogates for enzymes during the past decades because they are environmentally friendly, can be synthesized in large scale and show broad tolerance towards different substrates.^[32]

Organocatalyzed DA cycloaddition can be divided into three categories according to the general catalytic mechanisms:^[33] chiral base catalysis, hydrogen-bond catalysis and heterocyclic carbene catalysis. Typically, chiral base catalysts contain secondary or primary amines; they can condense with the carbonyl group-containing dienophiles to give iminium ions or imines as the reactive intermediates for the cyclization with dienes. Small molecules capable of forming hydrogen-bond interactions with the substrates are hydrogen-bond catalysts. By activating the dienophiles through hydrogen-bond interactions, cyclization can be promoted stereo- and diastereoselectively. Heterocyclic carbenes are powerful organocatalysts in multi-bond formation reactions and domino reactions. They can catalyze (mainly) asymmetric hetero-DA reactions in a similar way as chiral base catalysts by nucleophilic addition to the dienophiles.^[34]

A. Chiral Base Catalyzed DA Cycloaddition

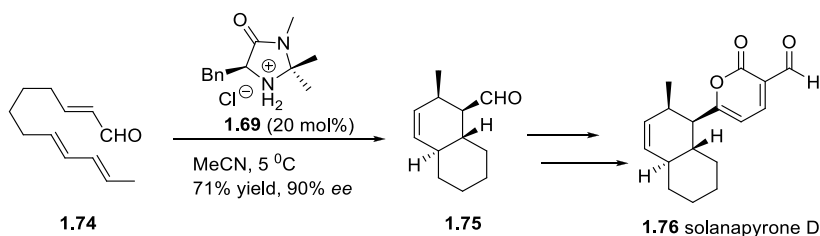
MacMillan pioneered the first chiral base catalyzed DA cycloaddition by using imidazolidinone **1.69** as organocatalyst to provide the DA adducts in very good yields and excellent enantioselectivities (Scheme 1-15).^[13b] Accordingly, the activation of acrolein **1.72**

by amine-containing catalyst **1.69** leads to the formation of iminium ion intermediate **1.71** with a lower LUMO energy, which can facilitate the reaction. DA cycloaddition then takes place to give the iminium ion-containing product **1.70**, which upon hydrolysis provides the final product **1.73** with high enantiomeric excess and regenerates the catalyst **1.69**. The activation of corresponding α,β -unsaturated ketone was proven to be more difficult than acrolein. However, by modifying the organocatalyst, the organocatalyzed DA cycloadditions between different α,β -unsaturated ketones and dienes were achieved by MacMillan's group with high yields and enantioselectivities.^[35]



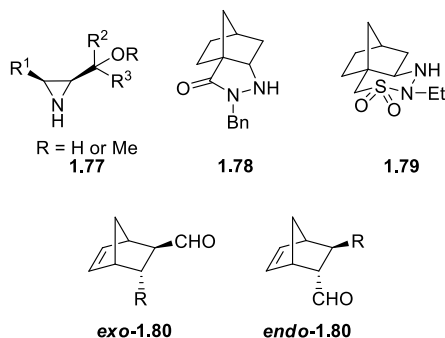
Scheme 1-15. MacMillan's imidazolidinone catalysis in DA cycloaddition

MacMillan's group then applied this protocol to the enantioselective total synthesis of marine metabolite solanapyrone D (Scheme 1-16), which is a phytotoxic polyketide isolated from the fungus *Altenaria solani*.^[36]



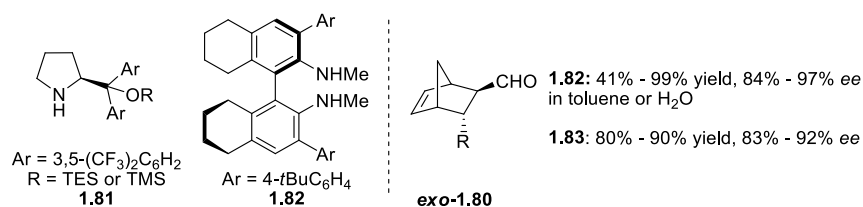
Scheme 1-16. Total synthesis of solanapyrone D *via* organocatalyzed DA cycloaddition

Besides imidazolidinone, the chiral aziridines **1.77** were employed to catalyze the DA cycloadditions by Bonini's group albeit with moderate diastereoselectivity (mixture of *exo*- and *endo*- products).^[37] Similar results were obtained by Lemay and Ogilvie's report^[38] as well as Lee's^[39] camphor-based hydrazine catalysis (**1.78** and **1.79**, Scheme 1-17).



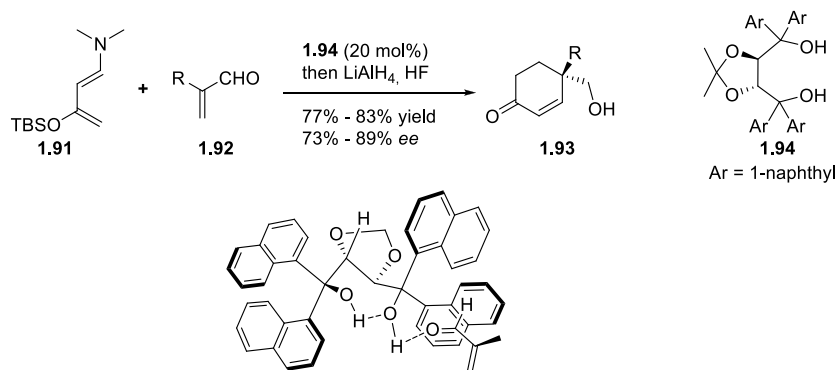
Scheme 1-17. Organocatalyzed DA cycloadditions *via* chiral aziridines or hydrazines

According to the *Alder rule*, *endo*-selectivity is generally considered the attribute of the DA cycloaddition due to the favorable interaction between the π -systems of the diene and the dienophile substituent.^[16] However, stereoselective DA cycloaddition with exclusive *exo*-selectivity can be achieved by modifying the catalyst and the reaction system. Hayashi's group developed the diarylprolinol catalysts **1.81** that afforded the *exo*-DA adducts with good diastereo- and enantioselectivities in acidic conditions (Scheme 1-18).^[40] A practical procedure was successfully investigated to allow the reaction to be carried out in water (hydrogen-bond atmosphere) and an improvement of enantioselectivity was observed.^[41] Maruoka investigated the binaphthyl-based diamine catalyst **1.82** to synthesize the *exo*-DA cycloaddition products with high diastereo- and enantioselectivities. The reaction was usually carried out in trifluoromethylbenzene and in the presence of catalytic amount of TsOH, which were believed to induce the reversed diastereoselectivity.^[42]



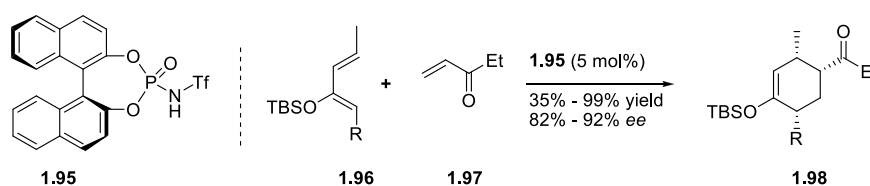
Scheme 1-18. *Exo*-selective asymmetric DA cycloaddition

B. Hydrogen-bond Catalyzed DA Cycloaddition



Scheme 1-21. Rawal's TADDOL catalyzed DA cycloaddition

Hydrogen-bond catalysts are Brønsted or Lewis acid containing chiral compounds such as chiral thioureas, amidinium ions, diols as well as chiral phosphoric acids that can be used as hydrogen-bond donors.^[34] They are more widely used in catalytic enantioselective hetero-Diels-Alder (*oxa*-DA or *aza*-DA) cycloadditions because the corresponding aldehydes and imines tend to be activated easily by hydrogen-bond donors.^[16] Rawal's group reported the first highly enantioselective (all-carbon) DA cycloaddition catalyzed by TADDOL **1.94** as hydrogen-bond donor (Scheme 1-21).^[47] Rawal's diene **1.91** and different bulky dienophiles **1.92** were used to afford the cyclohexenone products **1.93** with up to 92% *ee*. The proposed transition state of the catalysis is shown in Scheme 1-21, in which the dienophile is activated by intermolecular hydrogen-bond interaction, and the intramolecular hydrogen-bond interaction of the catalyst allows the formation of a stable seven-membered ring, which is a rigid catalytic transition state that lead to the high enantioselectivity.^[47]

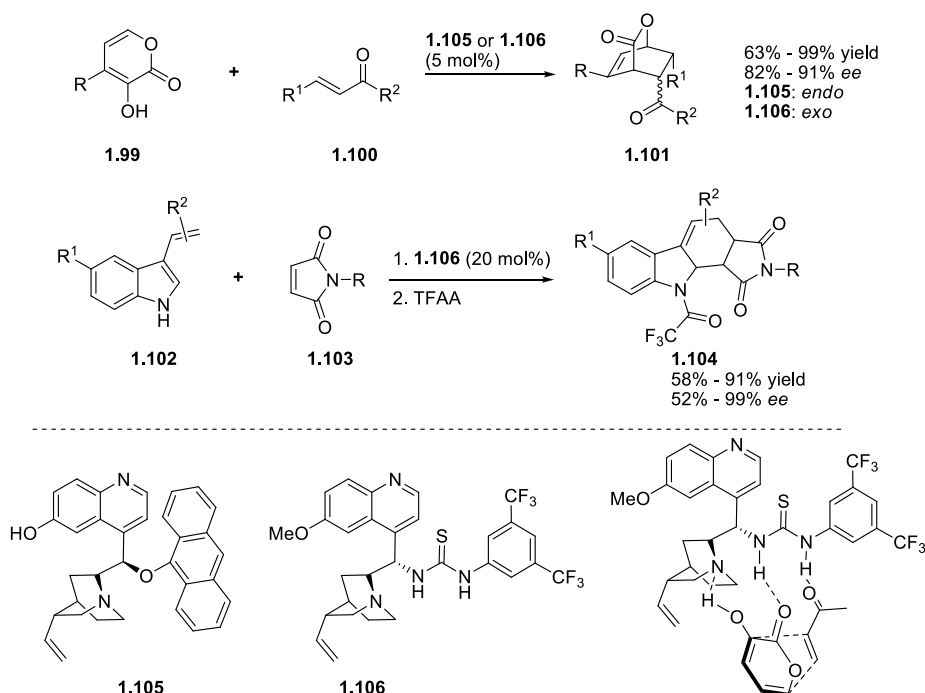


Scheme 1-22. DA cycloaddition catalyzed by chiral phosphoramidate

Due to the weak hydrogen-bond interaction between chiral phosphoric acid and dienophile, only a few reports are available on chiral phosphoric acid catalyzed enantioselective (all-carbon) DA cycloaddition. However, by converting the chiral phosphoric acid into the stronger hydrogen-bond donor biaryl-*N*-triflyl phosphoramidate **1.95**,

Yamamoto's group developed the enantioselective DA cycloaddition between EVK **1.97** and Danishefsky's diene **1.96** to yield the enantioenriched silyl-enol ether **1.98** (Scheme 1-22)^[48]. Additionally, the less acidic phosphoramidate **1.95** (compared to the corresponding phosphoric acid) avoids the decomposition of Danishefsky's diene **1.96**, which is the key for the success of this protocol.^[48]

C. Bifunctional Organocatalyst for DA Cycloaddition

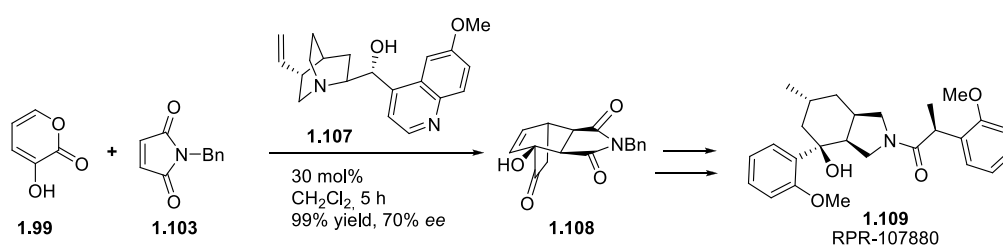


Scheme 1-23. Cinchona-based bifunctional organocatalysts for asymmetric DA cycloadditions

Catalysts activating dienophiles through ion pair and hydrogen-bond can be regarded as bifunctional catalysts, which usually contain tertiary amines as basic moieties as well as amides or alcohols as hydrogen-donors. Cinchona alkaloids and their derivatives have been widely used as bifunctional organocatalysts because of their abundance in nature.^[16] Meanwhile, the presence of cinchona alkaloids as pseudoenantiomeric pairs (i.e. quinine and quinidine) allows for stereoselective synthesis with both enantiomers.

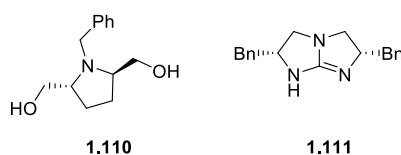
With bifunctional catalysts derived from different cinchona alkaloids, Deng's group investigated the enantioselective DA cycloadditions of 2-pyrones **1.99** with different dienophiles **1.100** to afford the products **1.101** in high yields and ee (Scheme 1-23). As seen

in the transition state, the cinchona catalyst activates both diene and dienophile *via* the ion pair and hydrogen-bond interactions, and the rigid structure of the cinchona backbone further induces the high enantioselectivity.^[49] Meanwhile, controlling the *endo/exo* selectivity can be achieved by modification of the cinchona catalyst (**1.105** or **1.106**, Scheme 1-23).^[49a] When 3-vinylindoles **1.102** and maleimides **1.103** were used as substrates, the cycloadditions were promoted by ionic pair interactions between the basic moiety of **1.106** and the acidic indole N-H bonds as well as the hydrogen-bond interactions between thiourea motif of **1.106** and the maleimides **1.103**.^[50] The resulting heterocycles **1.104** are potentially important for the synthesis of interesting biologically alkaloids.



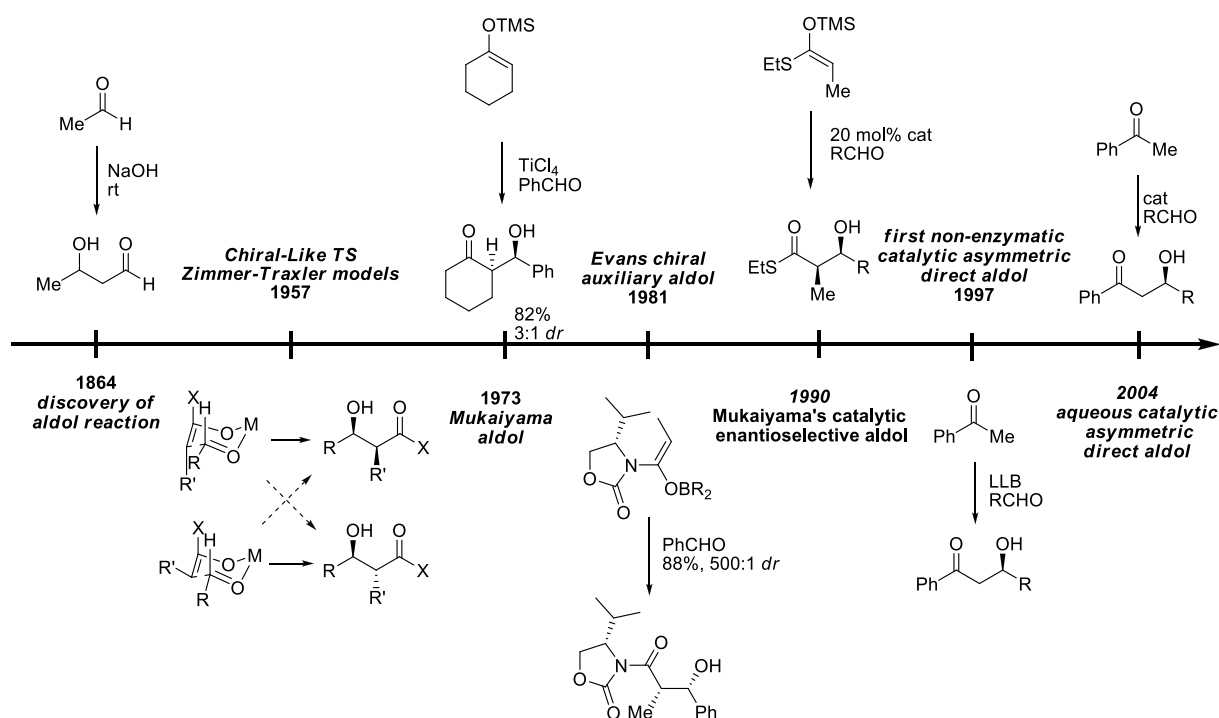
Scheme 1-24. Key intermediate of RPR-107880 synthesis *via* cinchona catalysis

Accordingly, the enantio- and diastereoselective cycloaddition between pyrone **1.99** and maleimide **1.103** was achieved to afford tricyclic scaffold **1.108**, which is a key intermediate in the synthesis of RPR 107880, which is a neurotransmitter that act as a substance-P antagonist^[51] (Scheme 1-24).^[52] Other bifunctional organocatalysts include the tertiary amine-containing binol **1.110**^[53] and the bicyclic guanidine **1.111**^[54] (Scheme 1-25), which promote the asymmetric DA cycloaddition effectively as well.

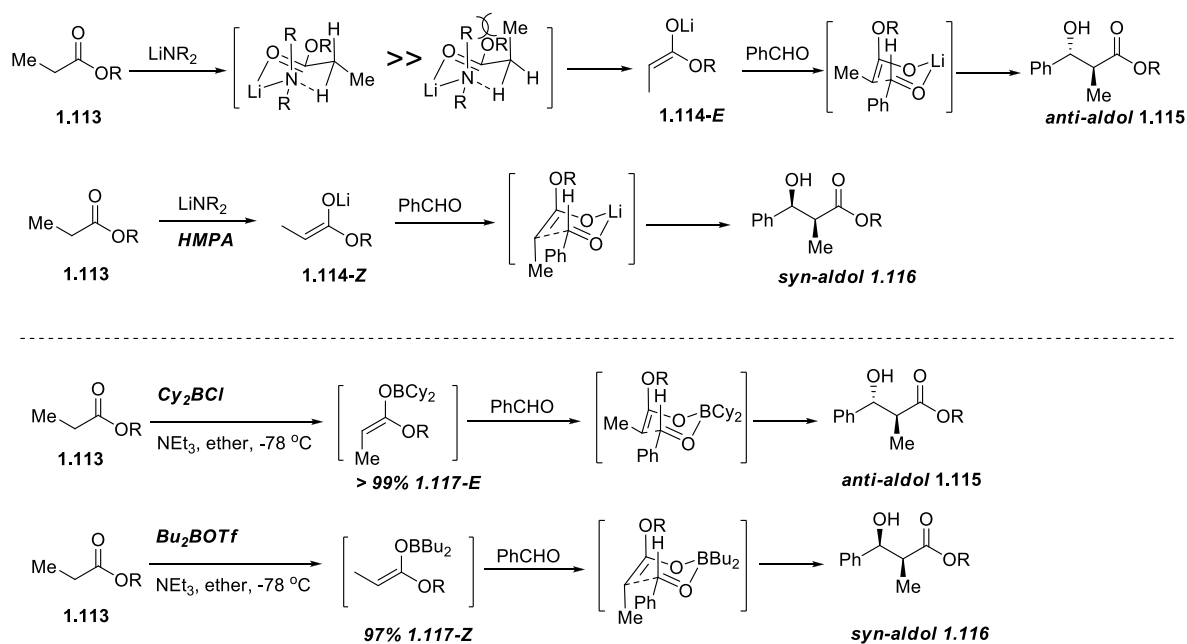
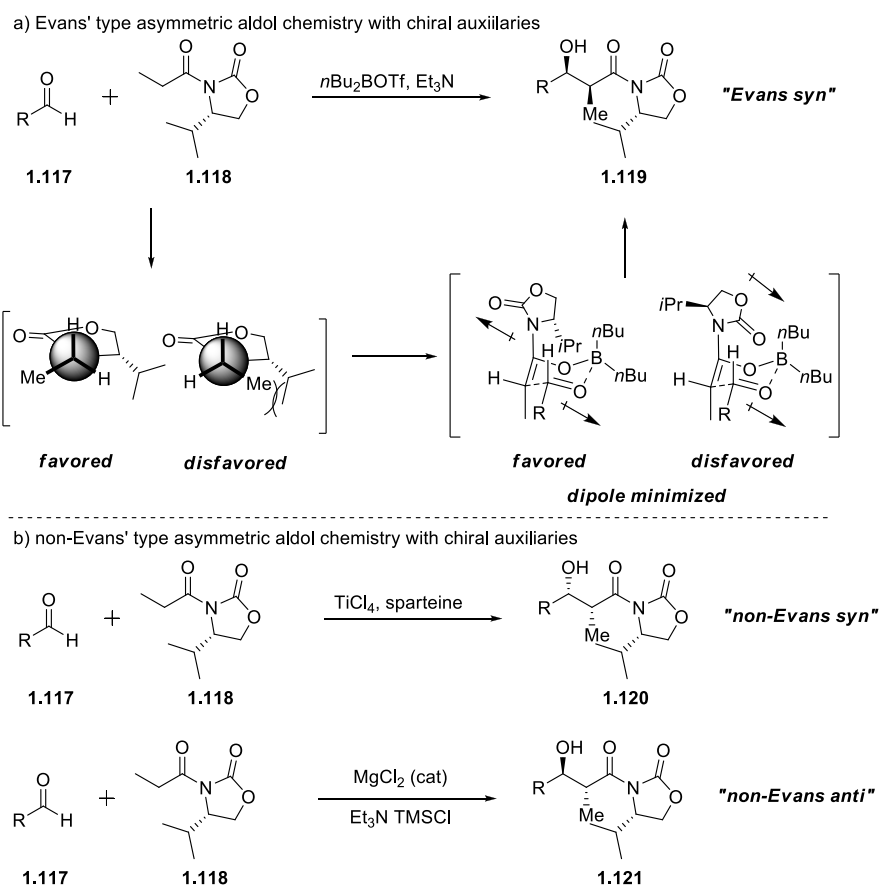


Scheme 1-25. Examples of other bifunctional organocatalysts

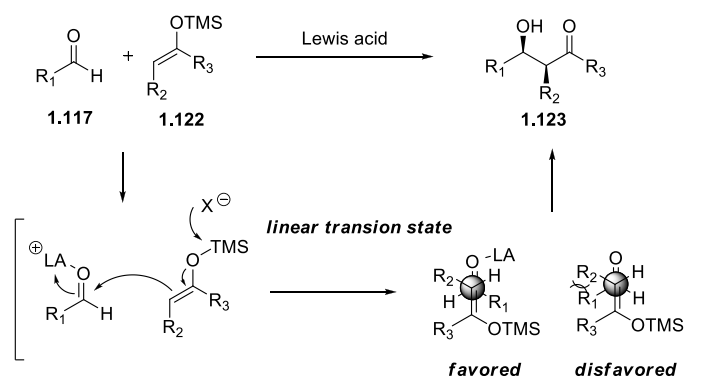
1.1.2. Catalytic Enantioselective Aldol Reaction

Scheme 1-26. Timeline of the aldol reaction^[57]

The aldol reaction, discovered independently by Borodin (1869)^[55] and Wurtz (1872)^[56], represents a significantly powerful transformations in organic chemistry. In aldol reaction, β -hydroxylketones with up to two new stereocenters are formed when it comes with two carbonyl-containing substrates as reactant.^[57] The aldol reaction encountered various challenges and difficulties since its discovery, including issues of chemo-, regio-, diastereo- and enantioselectivity, which have promoted the development of many elegant protocols to solve these difficulties (Scheme 1-26).^[57] Though with the problems of chemo-, regio- and diastereoselectivities initially, they were gradually solved in the 1950s with preformed metal-enolate^[58] or boron-enolate^[59] to increase the aforementioned selectivities. With the Zimmermann-Traxler model, the prediction or explanation of the formation of *syn*- and *anti*-aldol products became possible (Scheme 1-27).^[60]

Scheme 1-27. Aldol reactions with preformed enolates^[57]Scheme 1-28. Evans' and non-Evans' asymmetric aldol reactions with chiral auxiliaries^[57]

Preformation of boron-enolates is a powerful method to approach highly diastereoselective aldol chemistry due to the relatively short and stable boron-oxygen bond, which leads to a relatively tight six-membered transition state.^[61] Accordingly, by introducing a chiral oxazolidinone auxiliary, a non-catalytic asymmetric aldol reaction with high enantio- and diastereoselectivities was successfully developed by Evans' group (Scheme 1-28a).^[62] Since enolization of the *N*-acyl oxazolidinone **1.118** leads to the (*Z*)-boron-enolate, the *syn*-aldol product **1.119** always predominates, and the high enantioselectivity can be explained by the dipole minimized transition state.^[62] *N*-acyl oxazolidinone can be further functionalized to the corresponding alcohol, aldehyde, acid, ester or Weinreb amide, which renders Evans' aldol reaction synthetically useful.^[63] Apart from Evans'-type aldol reaction, the groups of Heathcock^[64] and Crimmins^[65] developed the non-Evans'-type asymmetric aldol reaction by the introduction of a Lewis acid as additive to expand the scope of chiral auxiliary-assisted aldol chemistry (Scheme 1-28b).^{[66][67]}

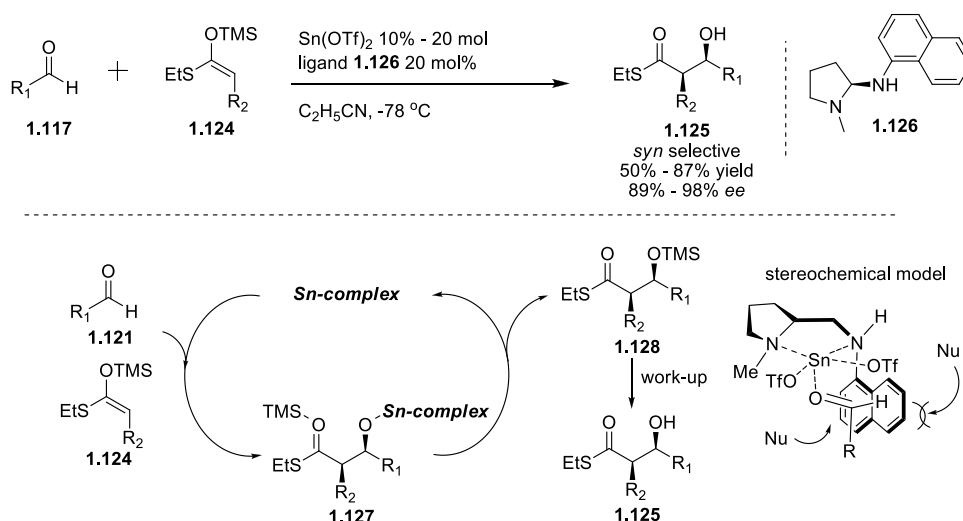


Scheme 1-29. Mukaiyama aldol reaction

In the course of catalysis, metal-enolates and boron-enolates are too labile towards moisture, hard to purify, and their reactivities in asymmetric catalysis are difficult to control. However, the silyl-enolate as an alternative surrogate in aldol chemistry was first introduced by Mukaiyama's group in 1973 and overcame the aforementioned problems.^[68] The aldehyde **1.117** is activated with Lewis acid (such as TiCl_4 , SnCl_4 or TMSOTf), followed by a nucleophilic addition of silyl-enolates **1.122** to afford the aldol products **1.123**.^[68] The transition state of the Mukaiyama reaction should be explained with a linear model instead of the Zimmermann-Traxler model, because the formation of a six-membered transition state is very difficult in the case of silyl-enolates due to the weak Lewis acidity of silicon.^[57,68] Consequently, the diastereoselectivity of the Mukaiyama aldol reaction could be poor and

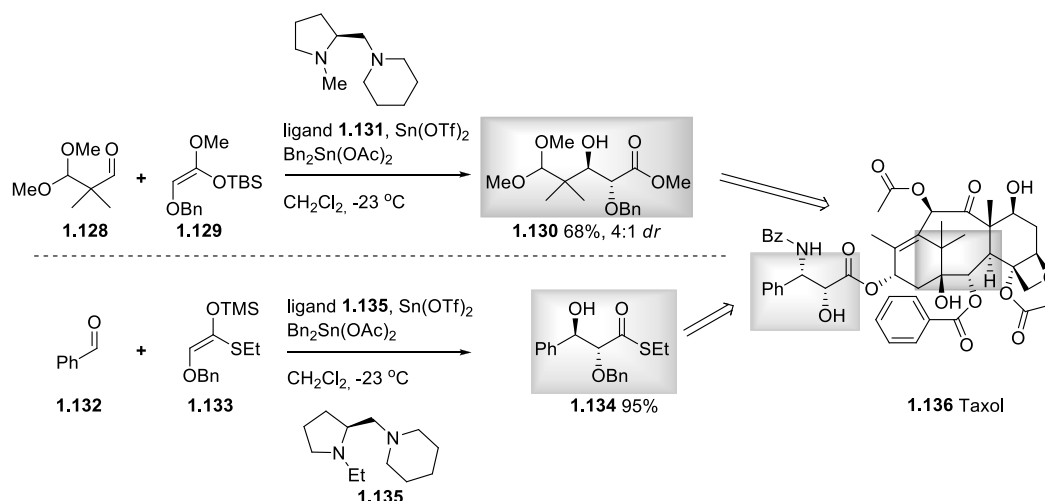
is greatly influenced by the substrates, catalysts, solvents and additives (Scheme 1-29). However, the less reactive silyl-enolates are more amenable for a controlled reaction since the use of an additional activating reagent can modulate the reactivity of the aldol reaction. This means that an enantioselective fashion of the Mukaiyama aldol reaction can be performed when a chiral activating reagent is introduced.^[68-69]

1.1.2.1. Catalytic Asymmetric Mukaiyama Aldol Reaction



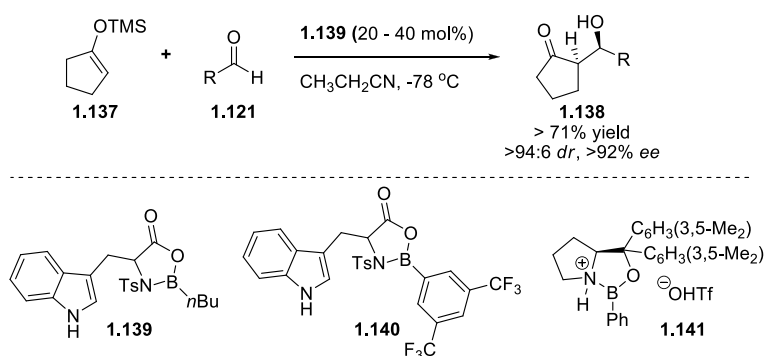
Scheme 1-30. Mukaiyama's catalytic asymmetric aldol reaction

In Mukaiyama aldol chemistry, a silicon transfer to the hydroxyl group on the formed product was observed (Scheme 1-30). This is an important observation which explained the regeneration of the catalyst when a catalytic amount of a chiral Lewis acid complex is used.^[57,68] In 1990, the first catalytic asymmetric Mukaiyama aldol reaction was reported.^[70] With a chiral tin complex derived from $Sn(OTf)_2$ and the proline-derived chiral diamine **1.126**, Mukaiyama demonstrated that high enantio- and diastereoselectivities can be achieved with preformed silyl-enolates **1.124** to obtain the *syn*-aldol products **1.125** (Scheme 1-30).^[70] This well-developed protocol was successfully applied to the total synthesis of Taxol **1.136** (Scheme 1-31).^[71]



Scheme 1-31. Mukaiyama's total synthesis of Taxol

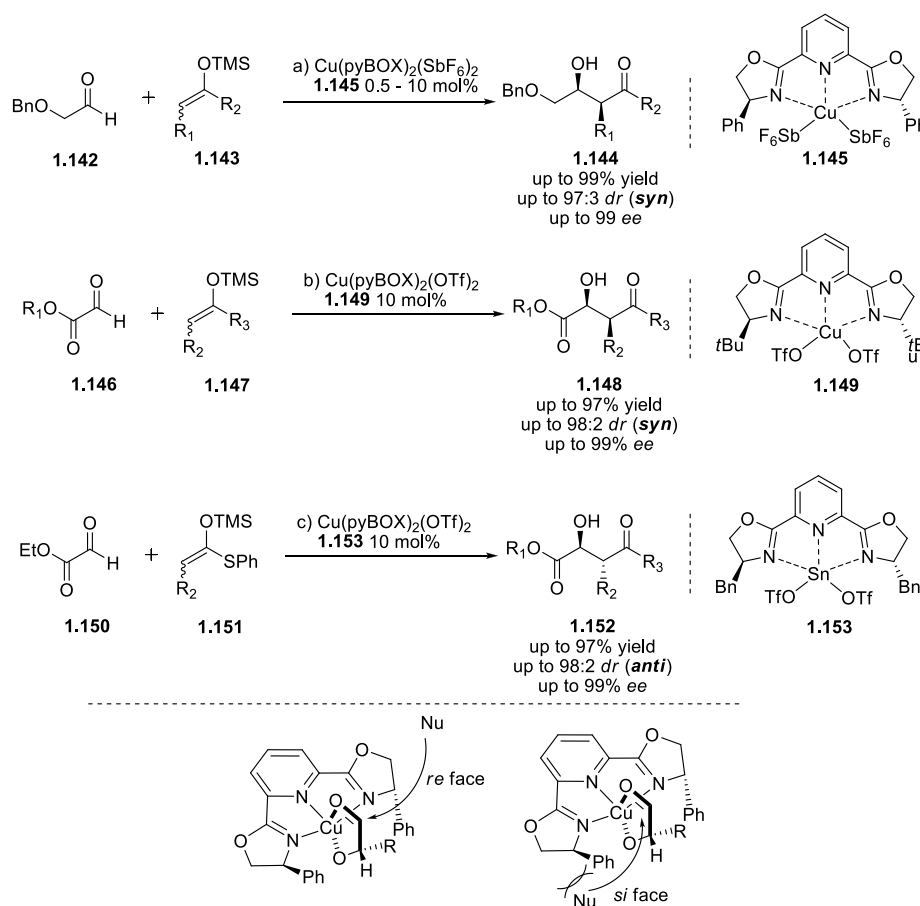
As in DA cycloaddition, boron-complex catalysis is also applicable in asymmetric Mukaiyama aldol chemistry. Corey's group developed the chiral tryptophan-derived oxazaborolidinone **1.139** as catalyst for enantioselective Mukaiyama aldol reactions (Scheme 1-32).^[72] The reaction of different aldehydes **1.121** with the cyclic silyl-enolate **1.137** led to the desired products **1.138** in good yields with high *syn*- and enantioselectivities. Introduction of a 3,5-*bis*(trifluoromethyl)phenyl group on the boron center in **1.140** enhanced the stability of the catalyst, which led to the reduction of the catalyst loading to 5 mol%.^[73] Meanwhile, asymmetric Mukaiyama aldol reaction catalyzed by the chiral oxazaborolidinium complex **1.141** has also been reported.^[74]



Scheme 1-32. Mukaiyama enantioselective aldol reactions catalyzed by chiral boron-complexes

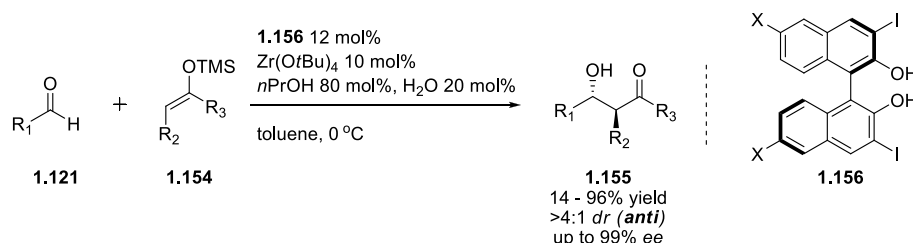
Chiral *bis*oxazoline compounds are privileged multidentate ligands to metal centers that have been widely used in asymmetric catalysis.^[57] With the chiral copper-pyBOX complex

1.145 as catalyst, Evans' group developed the enantioselective Mukaiyama aldol reactions with α -benzyloxyacetaldehyde **1.142** as the electrophile (Scheme 1-33a).^[75] Research in Evans' group indicated that the bidentate coordination of the aldehyde to the copper center was crucial, and aldehydes without the α -benzyloxy group didn't afford any products.^[76] In addition, the diastereoselectivity was found to be independent of the Z/E of silyl-enolates (**1.143** and **1.147**, Scheme 1-33).^[76] Meanwhile, 1,2-diketone compounds like pyruvates **1.146** were found to be compatible with the above-mentioned catalytic complex to afford products in high regio-, diastereo- and enantioselectivities, which further confirmed the importance of the bidentate coordination role in catalysis (Scheme 1-33b).^[77] Interestingly, Evans' group also reported that the catalysis of the chiral pyBOX ligand-Sn(OTf)₂ complex **1.153** afforded products **1.152** in the *anti*-selective fashion (Scheme 1-33c), which represented the first highly enantio-, *anti*-selective Mukaiyama aldol reaction and served to complement the *syn*-selective Mukaiyama aldol chemistry.^[78]



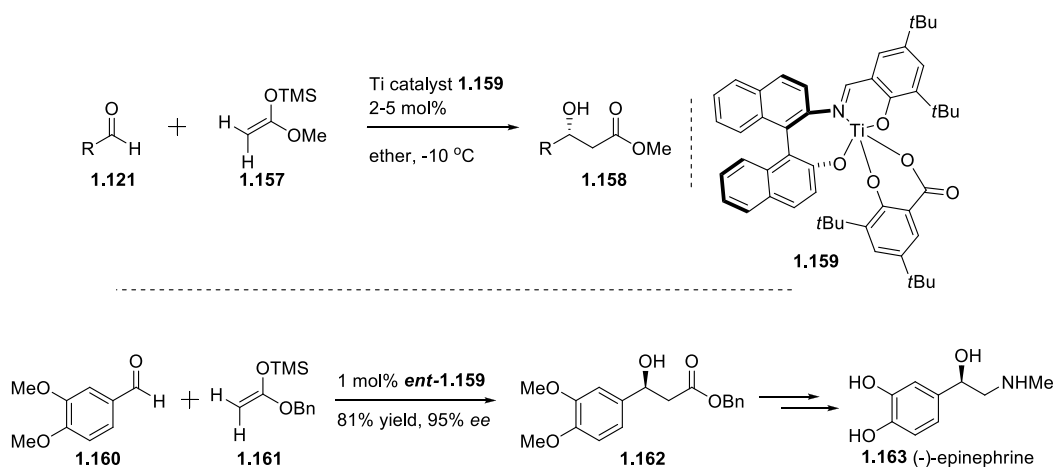
Scheme 1-33. Asymmetric Mukaiyama aldol reactions catalyzed by chiral metal-pyBOX complexes

In 2000, Kobayashi reported *anti*-selective Mukaiyama aldol reaction catalyzed by the chiral zirconium-BINOL complex **1.156** (Scheme 1-34).^[79] The presence of propanol and H₂O was found to be necessary for the silicon transfer, which is essential to promote the catalytic cycle.^[57,68]



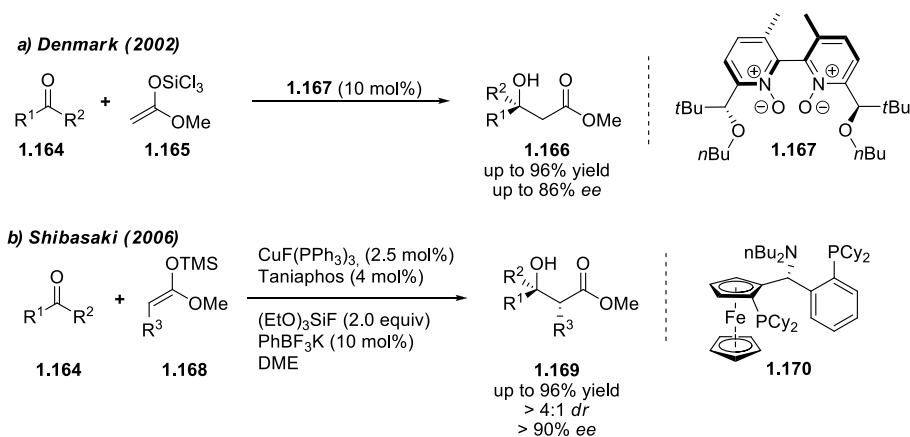
Scheme 1-34. Chiral zirconium complex catalyzed Mukaiyama aldol reaction

It can be seen above that the substituted silyl-enolates were predominantly used as nucleophiles, which resulted in high enantioselectivity in the catalysis. Nevertheless a highly enantioselective Mukaiyama aldol reaction with non-substituted silyl-enolates such as **1.157** was still troublesome due to lack of effective enantiocontrol.^[80]



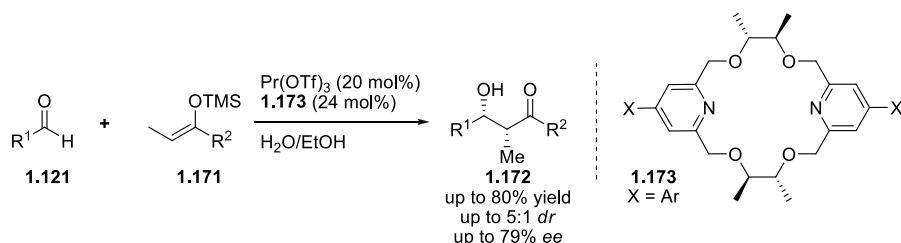
Scheme 1-35. Mukaiyama aldol reactions with non-substituted substrates

This long-standing puzzle was solved by Carreira's group in 1994 (Scheme 1-35).^[80] By introducing the bulky chiral titanium catalyst **1.159**, the less hindered silyl-enolate **1.157** became suitable for highly enantioselective aldol reactions. The salicylic acid moiety in complex **1.159** was significantly important as it promotes the intramolecular silicon transfer process, which improved the reaction rate and enantioselectivity.^[80] This protocol has been used to synthesize (*R*)-epinephrine **1.163** with 95% *ee*.^[81]



Scheme 1-36. Asymmetric Mukaiyama aldol reactions with ketones as electrophiles

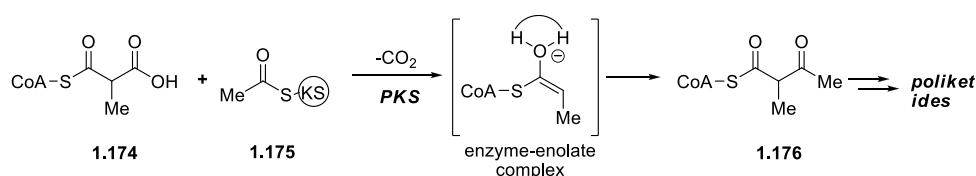
Another long-standing issue in Mukaiyama aldol chemistry was the low reactivity and selectivity of ketones when they were used as electrophiles.^[82] In 2002, Denmark's group took the first step to report the chiral *bis-N,N'*-dioxide complex **1.67** to catalyze the Mukaiyama aldol reaction in an enantioselective fashion (Scheme 1-36a). The more reactive trichlorosilyl-enolate **1.165** was reported to be essential albeit with limited substrate scope.^[82] Later in 2006, Shibasaki's group expanded the scope to more hindered trimethyl silyl-enolates **1.168** using the chiral copper(I) complex **1.170** as catalyst (Scheme 1-36b).^[83]



Scheme 1-37. Asymmetric Mukaiyama aldol reactions catalyzed by chiral metal complex in water

It is commonly accepted that Lewis acids are rapidly deactivated in water due to their high affinity towards oxygen.^[84] However Kobayashi's group developed the first Mukaiyama aldol reaction catalyzed by a chiral praseodymium complex and performed in an aqueous solution (Scheme 1-37), which provided the first concept for the design of chiral catalysts functioning effectively in aqueous media.^[84]

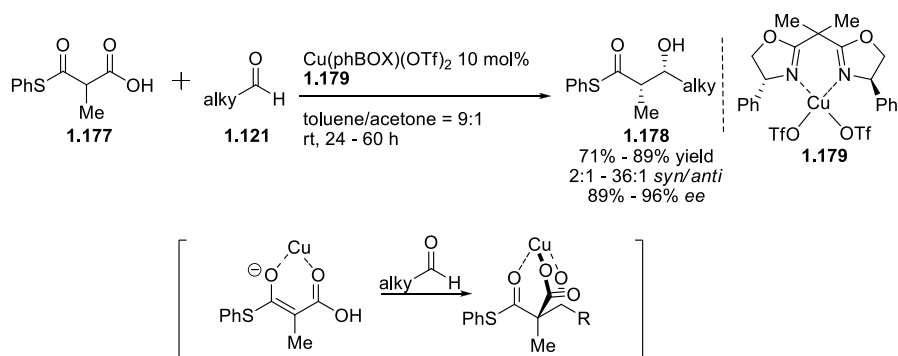
1.1.2.2. Catalytic Asymmetric Decarboxylative Aldol Reaction



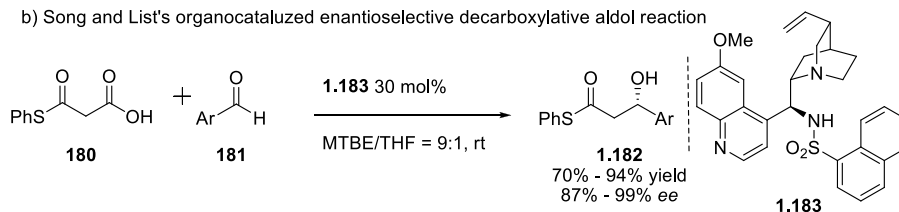
Scheme 1-38. Polyketides biosynthesis

In nature, polyketides are biosynthesized *via* decarboxylative processes from malonic acid half thioesters (MAHTs) with polyketide synthases (Scheme 1-38).^[85] Similar to MAHTs, β -carbonyl carboxylic acids are a series of reactive acids that can be regarded as enolate surrogates after decarboxylation and might be used in aldol chemistry. Inspired by nature, the catalytic enantioselective decarboxylative aldol chemistry was investigated over the past decade.^[57]

a) Shair's Cu-phBOX catalyzed enantioselective decarboxylative aldol reaction



b) Song and List's organocatalyzed enantioselective decarboxylative aldol reaction

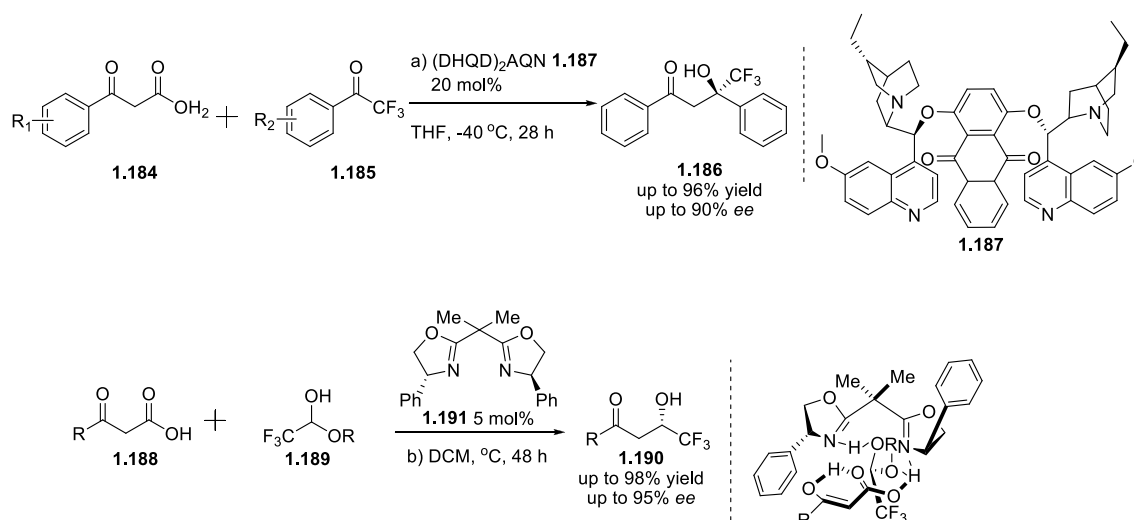


Scheme 1-39. Enantioselective decarboxylative aldol reaction with MAHTs

Shair's group extensively developed the Cu(II)-BOX complex catalyzed enantioselective, decarboxylative aldol reaction between methyl-MAHT **1.177** and aldehydes **1.121**, yielding the aldol products in high yields as well as high diastereo- and enantioselectivities (Scheme 1-39a).^[86] Unlike nature's decarboxylation-C-C bond formation mechanism, this biomimetic transformation was confirmed to be a deprotonation-aldol-decarboxylation process.^[86] The

reaction proceeded smoothly with aliphatic aldehydes at room temperature without base. Recently, the group of List and Song reported a similar process with cinchona base-derived catalyst **1.183** (Scheme 1-39b), which allowed the reactions to proceed with non-substituted MAHTs **1.180** and aromatic aldehydes **1.181** as substrates.^[87]

Compared to MAHTs, application of β -ketone carboxylic acids in this transformation is relatively difficult due to a lack of effective stereocontrol and unimolecular decomposition of β -ketone carboxylic acids.^[88] Ma disclosed the first asymmetric decarboxylative aldol reaction involving β -ketone carboxylic acids **1.184** (Scheme 1-40a) employing cinchona base-derived (DHQD)₂AQN **1.187** as organocatalyst.^[88] However, the scope of the electrophiles was limited to trifluoromethylaryl ketones **1.185**. Very recently a similar process with phBOX **1.191** as organocatalyst was reported by the same group (Scheme 1-40b), with the electrophiles being limited to α -trifluoromethylaldehyde hemiacetals **1.189**.^[89]



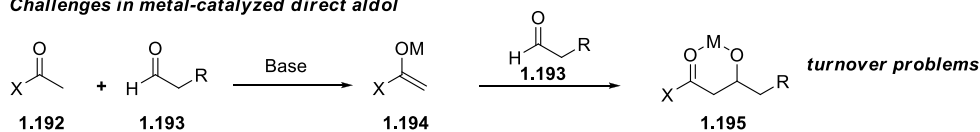
Scheme 1-40. Enantioselective decarboxylative aldol reaction with β -ketone acids

1.1.2.3. Catalytic Asymmetric Direct Aldol Reaction

The use of preformed silyl-enolate in catalytic enantioselective aldol chemistry is extensively investigated, however the preformation of silyl-enolate requires stoichiometric amounts of base and organosilane compound, which is less atom economic compared to the direct aldol reaction.^[57] The direct aldol reactions can be regarded as a proton

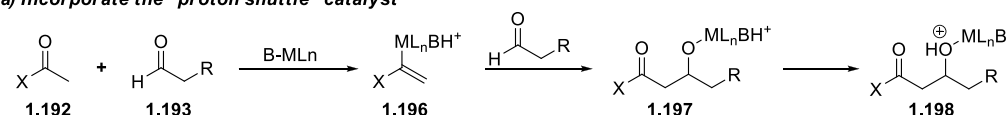
migration process with the whole atom utilization and no side product. This represents the ideal organic transformation in view of atom economy and green chemistry.^[90]

Challenges in metal-catalyzed direct aldol

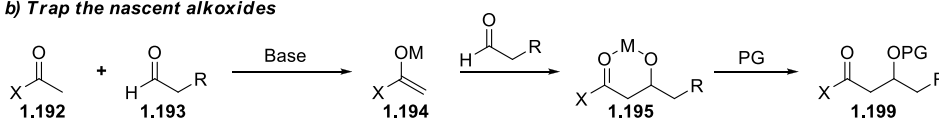


Solutions

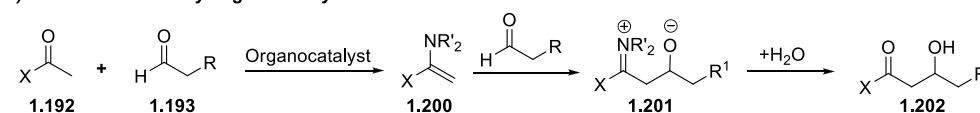
a) Incorporate the "proton shuttle" catalyst



b) Trap the nascent alkoxides

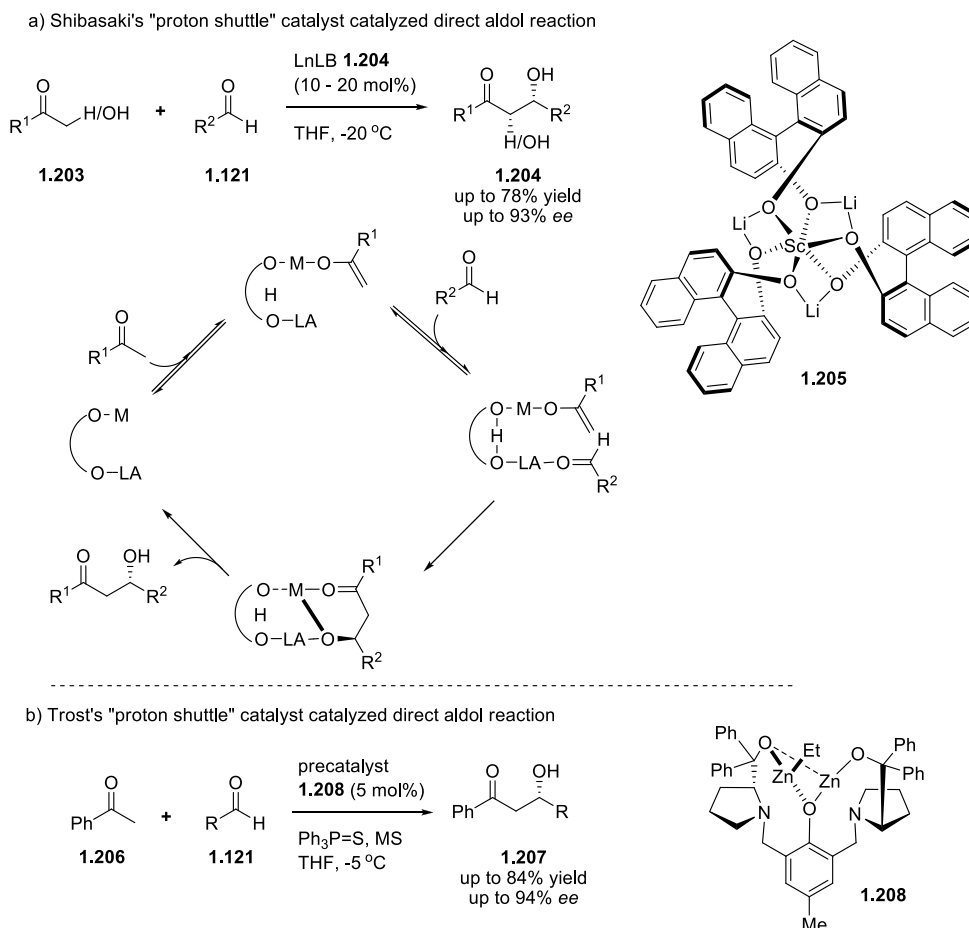


c) Avoid alkoxides by organocatalysis



Scheme 1-41. Challenges and solutions in metal-catalyzed direct aldol reactions^[57]

The employment of metal complex for the direct aldol reaction is inspired by type-II aldolase, which possesses a zinc ion cofactor to facilitate the deprotonation process.^[91] Besides issues of chemo- and regioselectivities in direct aldol chemistry, the turnover problem has to be addressed.^[57] As shown in Scheme 1-41, the direct aldol process includes the formation of metal-enolate intermediate **1.194**, followed by a nucleophilic addition to the aldehyde **1.193** to give the bidentate alkoxide intermediate **1.195**, which undergoes metal-proton exchange to afford the aldol product and to recycle the metal catalyst. However, due to the stability of the metal-alkoxide intermediate **1.195**, the quenching of this intermediate to achieve the turnover of the metal catalyst was a puzzle to be solved.^[57] Approaches to this issue include the incorporation of a proton shuttle in the catalyst that can transfer the proton from the catalyst to the alkoxide (Scheme 1-41a), and the trapping of the nascent alkoxide^[57] with a protecting group (Scheme 1-41b).^[57] Additionally, the use of an organocatalyst can avoid the formation of the alkoxide directly, which initializes the development of organocatalyzed direct aldol chemistry (Scheme 1-41c).^[57]

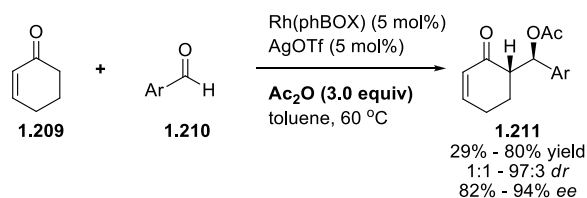


Scheme 1-42. Asymmetric direct aldol reactions catalyzed by proton shuttle catalysts^[57]

The first breakthrough was accomplished by the group of Shibasaki in 1999 with a lanthanum-lithium-*bis*(binaphthoxide) complex as proton shuttle (**1.204**, Scheme 1-42a).^[92] The Brønsted basic lithium alkoxide moiety deprotonates the substrates **1.202** to give the enolates, then the Lewis acidic lanthanum center activates the aldehydes **1.121** to promote the C-C bond formation. The proton can be transferred back to the alkoxide afterwards to release the products and recycle the catalyst. The moderate diastereoselectivity and high enantioselectivity is controlled by the rigid backbone structure of catalyst. According to the same inspiration, Trost's group designed a similar proton shuttle catalyst (**1.207**, Scheme 1-42b) that consists of a dinuclear Zinc-alkoxide center and a chiral ligand, which afforded the products in high enantioselective fashion.^[93] These two pioneering works influenced the following design of metal catalysts in asymmetric direct aldol chemistry.

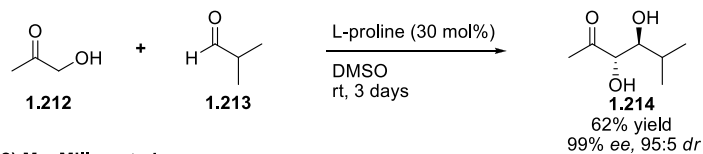
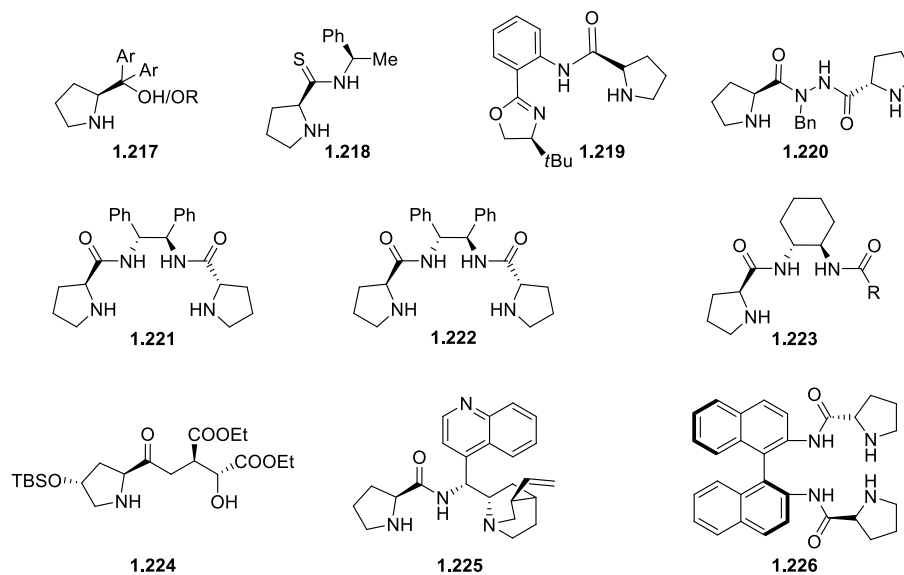
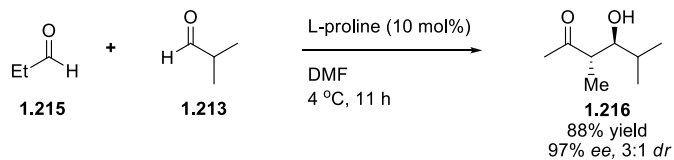
In 2009, Nishiyama's group reported that the chiral rhodium-BOX complex catalyzed the enantioselective direct aldol reactions between cyclic enone **1.209** and aldehydes **1.210**

(Scheme 1-43). Meanwhile, stoichiometric amounts of acetic anhydride were necessary to quench the alkoxide, which represents another strategy to solve the catalyst turnover problem.^[94]



Scheme 1-43. Catalytic asymmetric direct aldol reaction by incorporation of an acetyl group

As discussed above, the formation of metal-alkoxide intermediates can be avoided when an organocatalyst is used. However, the power of this type of catalysis was not fully appreciated until the report by the group of List and Barbas in 2000 employing proline as the organocatalyst.^[13a] As shown in Scheme 1-44, the organocatalyzed direct aldol reactions are compatible with ketones or aldehydes and lead to the corresponding products in highly regio-, chemo-, diastereo- and enantioselective fashion. No additives or protecting groups are required in the reaction systems. Organocatalysts are easily available and non-toxic compared to metal complexes, which provide an ideal alternative for direct aldol chemistry.^[95] Over the past decades, numerous improved proline-type organocatalysts (Scheme 1-44) have been developed and their potency has been fully demonstrated. Research on the organocatalyzed direct aldol reaction is still an ongoing topic especially in the development of new types of catalysts and substrate scope expansion.

1) List *et al.*2) MacMillan *et al.*

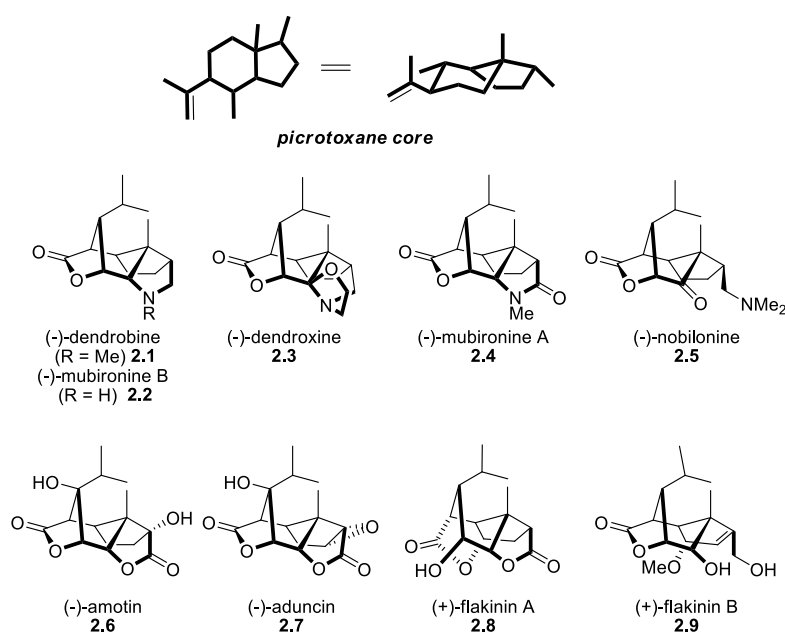
Scheme 1-44. Organocatalyzed direct aldol reactions and representative

proline-type catalysts

2. Catalytic Enantioselective Total Synthesis of Picrotoxane Alkaloids

2.1. Introduction to the Picrotoxane Alkaloids

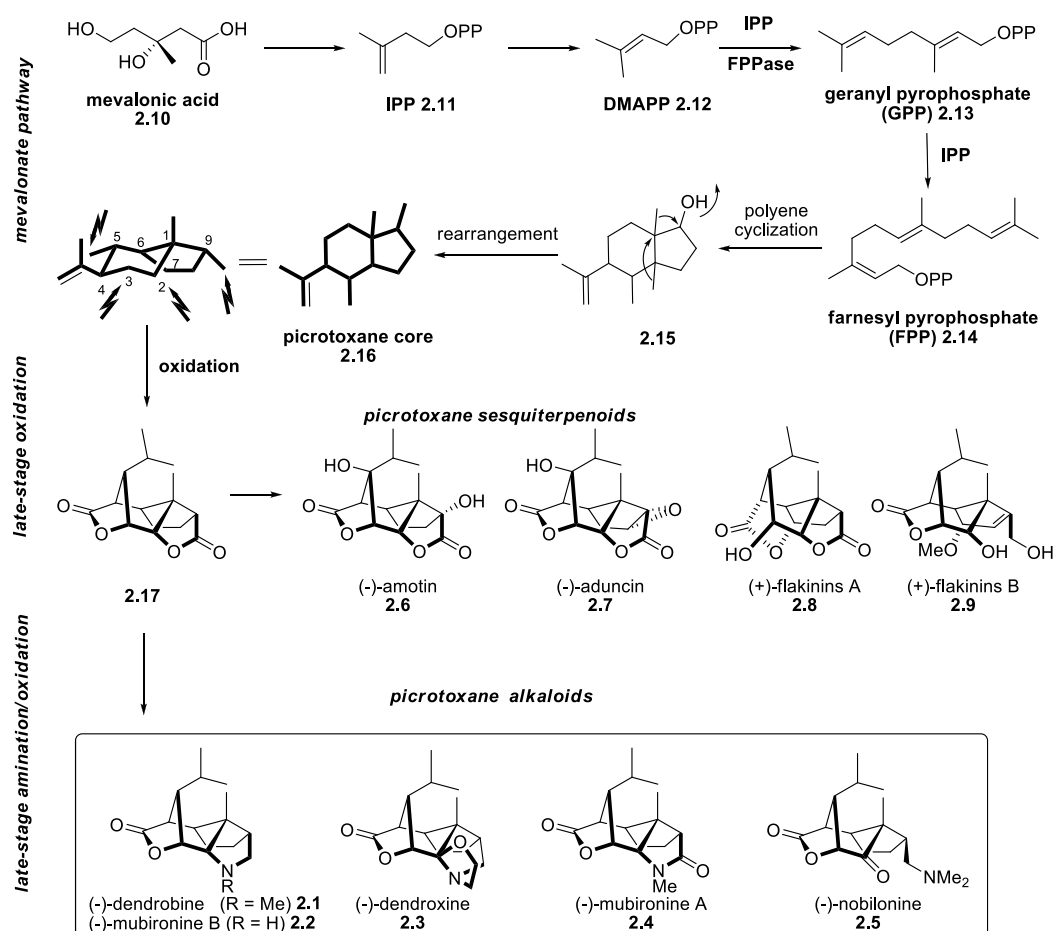
Chinese medicine has a 2000 year-old tradition, its medical treatment relies on the use of crude extracts mostly from plants. The plant *Dendrobium nobile* belongs to the family of Orchidaceae, named “Shi Hu” in Chinese, which has been used as a tonic and antipyretic for a long time. In the Chinese pharmacopoeia, the fresh or dried stem of *Dendrobium nobile* was recorded as the traditional herb with hypotensive, antipyretic, analgesic effect,^[96] and it was recently found to possess anti-influenza A virus activity.^[97]



Scheme 2-1. Natural products belonging to the picrotoxane family

Dendrobium nobile possesses diverse pharmacological activities as it contains multiple chemical components including alkaloids and sesquiterpenoids. As the most abundant one and the main component for *Dendrobium nobile*'s biological activities, (-)-dendrobine (Scheme 2-1, **2.1**) was first isolated in 1932^[98]. Structurally speaking, it bears a picrotoxane-type skeleton, which consists of a highly condensed 5,5,6,5-tetracyclic-ring system with a nitrogen atom, a lactone bridge and seven continuous stereocenters. The structural complexity renders (-)-dendrobine a challenging synthetic target. Since the identification of (-)-dendrobine, the structurally related alkaloids and sesquiterpenoids were continuously isolated,^[99] among which (-)-dendroxine (**2.3**, Scheme 2-1) owning an additional and more

congested *aza*-hemiketal moiety. The eight naturally occurring compounds can be divided into two families according to their structure: (-)-dendrobine **2.1**, (-)-mubirone A **2.2**, (-)-mubironine B **2.4**, (-)-dendroxine **2.3**, and (-)-nobilonine **2.5** belong to the picrotoxane alkaloid family whereas the others (**2.6** – **2.9**) are picrotoxane sesquiterpenoids with different oxidation states. Their structural similarities imply that they arise from the same biogenetic pathway.



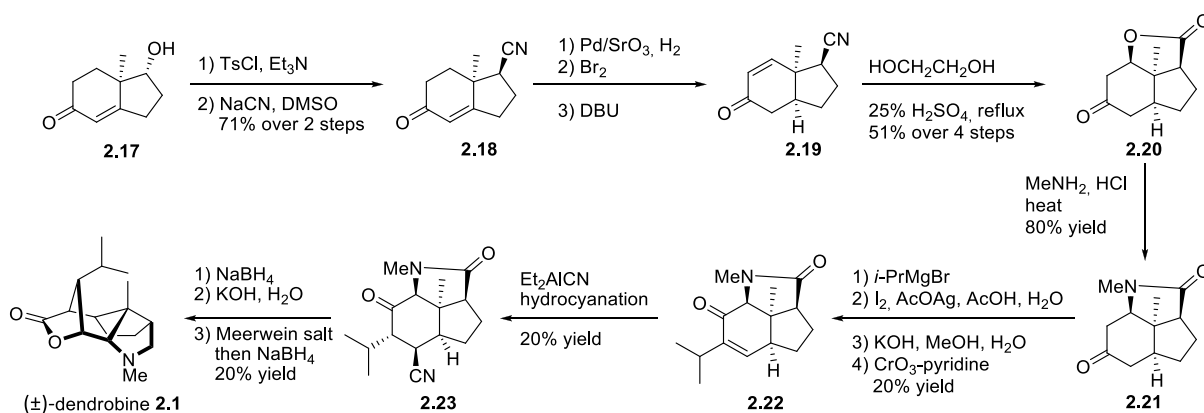
Scheme 2-2. Biosynthesis of picrotoxane alkaloids

Terpenoids are a large class of naturally occurring organic molecules that represent 60% of the known organic natural products. Though structurally diverse and complicated, they all derive biogenetically from very simple precursors such as isopentenyl pyrophosphate and its isomer dimethylallyl pyrophosphate.^[100] As illustrated in Scheme 2-2, farnesyl pyrophosphate synthase catalyzes the condensation between DMAPP and IPP to afford geranyl pyrophosphate **2.13**, followed by condensation with another molecule of IPP to form farnesyl pyrophosphate **2.14** via the mevalonate pathway. Farnesyl pyrophosphate

2.14 undergoes a sequence of polyene cyclization and subsequent ring rearrangement to the bicyclo[4.3.0] core **2.16** that is common to all picrotoxane natural products. Site-selective oxidations of the C-5/C-9 methyl groups and the adjacent C-2/C-3 methylene groups afford the tricyclic skeleton **2.17** found in the aforementioned subfamilies. Further site-selective late-stage oxidations lead to picrotoxane sesquiterpenoids like (-)-amotin **2.6**, (-)-aduncin **2.7**, (+)-flakinin A **2.8** and (+)-flakinin B **2.9**, while late-stage amination-oxidation sequence affords the corresponding alkaloids (-)-dendrobine **2.1**, (-)-mubironine A **2.4**, (-)-mubironine B **2.2**, (-)-dendroxine **2.3**, or (-)-nobilonine **2.5**.^[101] The proposed biogenetic pathway was confirmed by Yamazaki's experimental results.^[102]

2.2. Prior Synthetic Strategies towards Picrotoxane Alkaloids

Dendrobine received considerable attention over the past decades due to its promising biological activities. Meanwhile, it is a challenging synthetic target owing to the presence of seven continuous stereocenters on a congested carbon skeleton. The promising bioactivities plus the intriguing structure render dendrobine the ideal target to verify the practicality of novel synthetic methodologies.

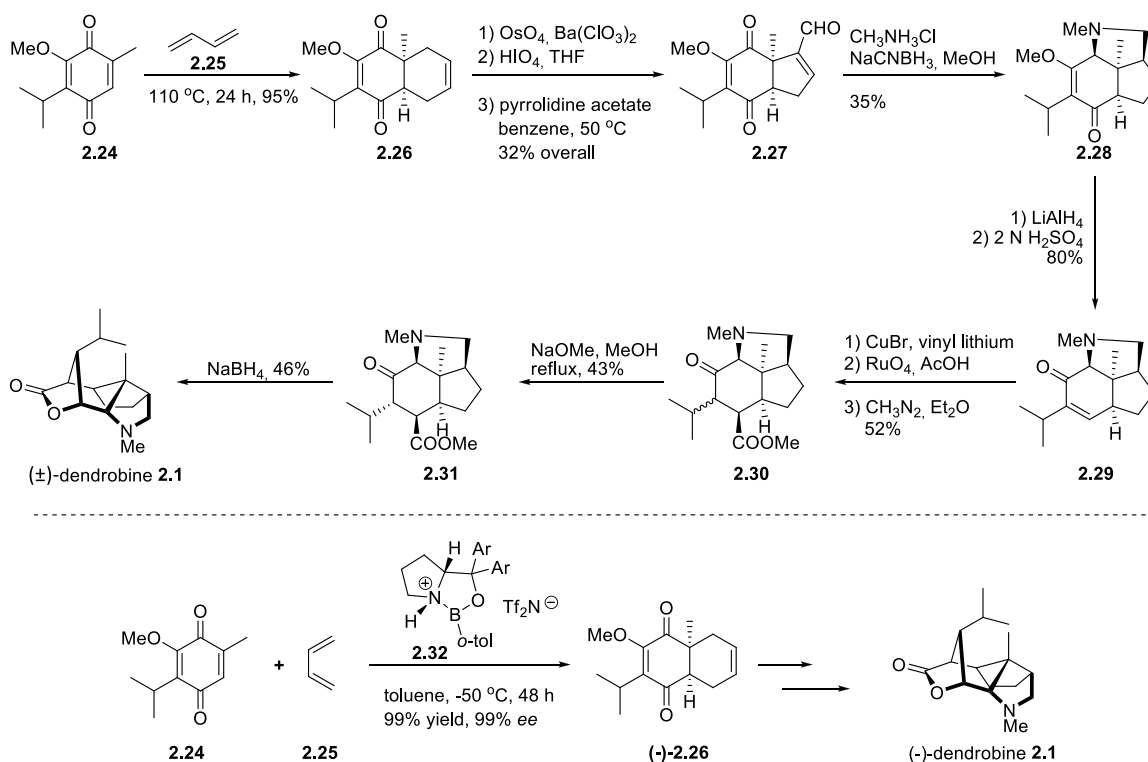


Scheme 2-3. Inubushi's first total synthesis of (±)-dendrobine

Inubushi reported the first total synthesis of (±)-dendrobine employing a hydrocyanation reaction to introduce the lactone moiety.^[103] As illustrated in Scheme 2-3, the lactam moiety in **2.21** was first constructed *via* a sequence of nucleophilic substitution, an enone isomerization and a conjugate addition. The introduction of the isopropyl group and the lactone moiety lacked regio- and diastereocontrol, though the cyanide compound **2.23** was synthesized *via* a novel hydrocyanation reaction. After reductive lactonization and lactam

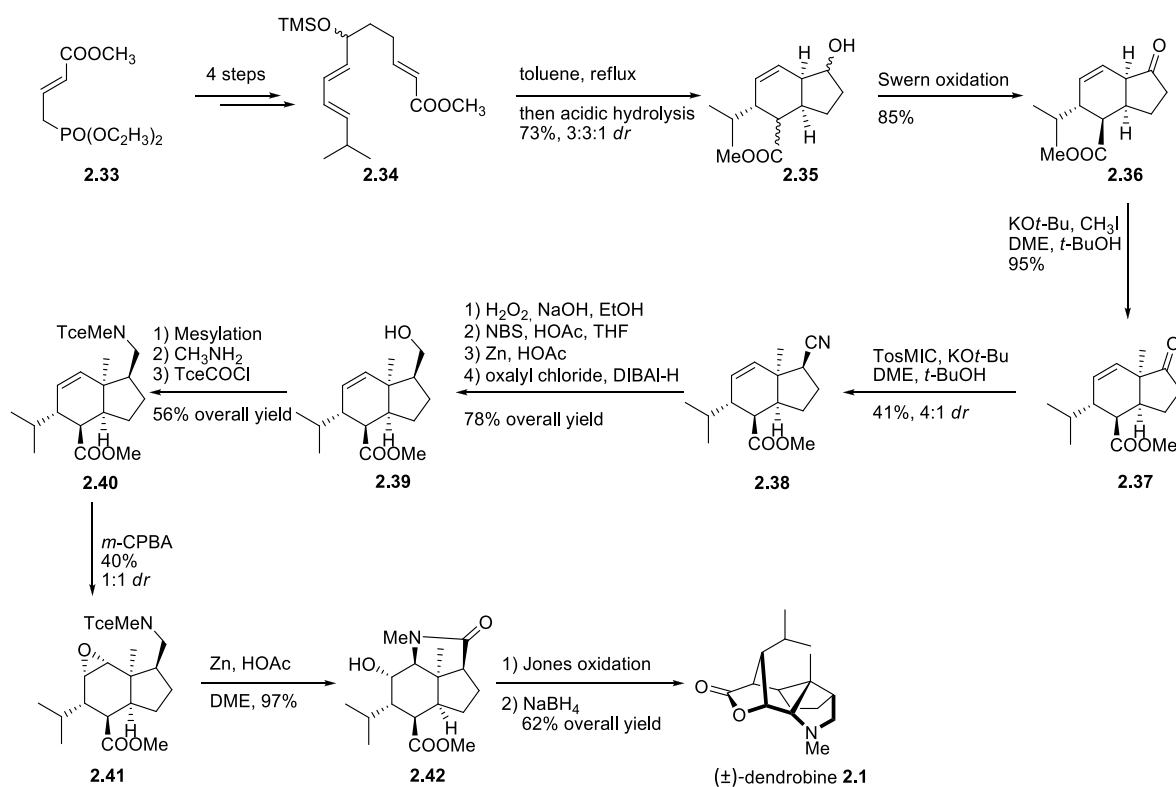
reduction, (\pm)-dendrobine was synthetically obtained for the first time. However, the regio- and diastereoselective introduction of functional groups was still an issue to be further investigated.

A Diels-Alder cycloaddition was first used in the total synthesis of dendrobine by Kende in 1974.^[104] As shown in Scheme 2-4, a sequence of Diels-Alder cycloaddition, oxidative C=C bond cleavage and aldol reaction afforded **2.26** with the cyclopentane moiety of dendrobine, and the pyrrolidine ring in **2.28** was installed with a reductive amination strategy. After enone isomerization and conjugate addition to access the lactone moiety, the total synthesis of dendrobine was achieved within 13 steps. It is noteworthy that Corey reported the catalytic asymmetric Diels-Alder cycloaddition between **2.24** and 1,3-pentadiene **2.25** in 2004, with the cationic chiral oxazaborolidinium **2.32** as catalyst. With this reaction, Kende's intermediate **2.26** was obtained in 95% yield and 99% *ee*, which represented the first catalytic enantioselective formal synthesis of (-)-dendrobine.^[19]



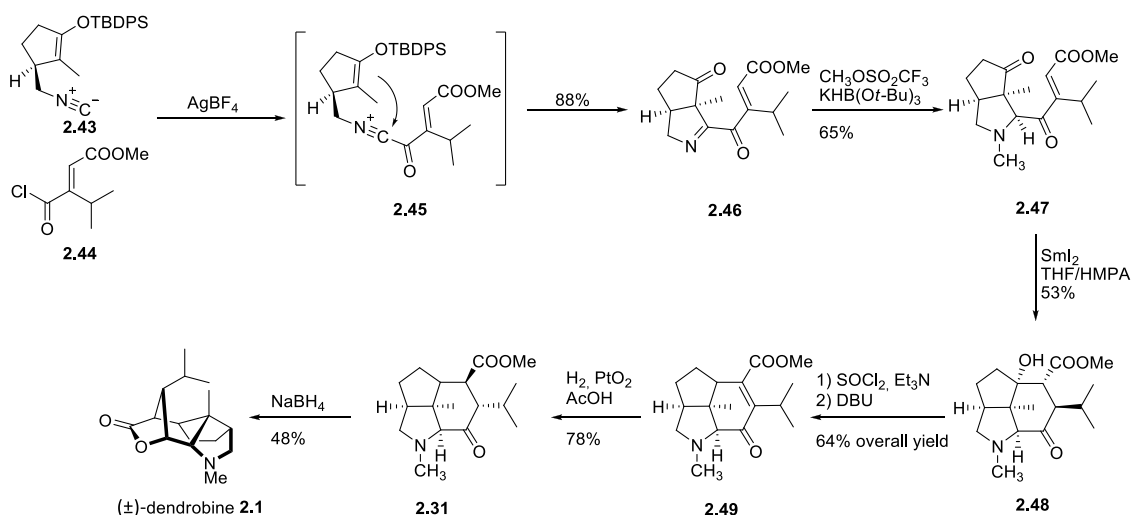
Scheme 2-4. Kende's total synthesis of (\pm)-dendrobine and Corey's catalytic asymmetric formal synthesis

The Diels-Alder cycloaddition was further utilized for the total synthesis of (\pm)-dendrobine by Roush in 1978 (Scheme 2-5).^[105] A series of Wittig reactions were carried out to afford the Diels-Alder precursor **2.34**, which annulated into the bicyclic product **2.33** in refluxing toluene with 3:3:1 *dr*. The isomers epimerized to the desired **2.36** as a single isomer during Swern oxidation. Similar to Kende's end-up strategy, the total synthesis of (\pm)-dendrobine was finished in 19 steps.



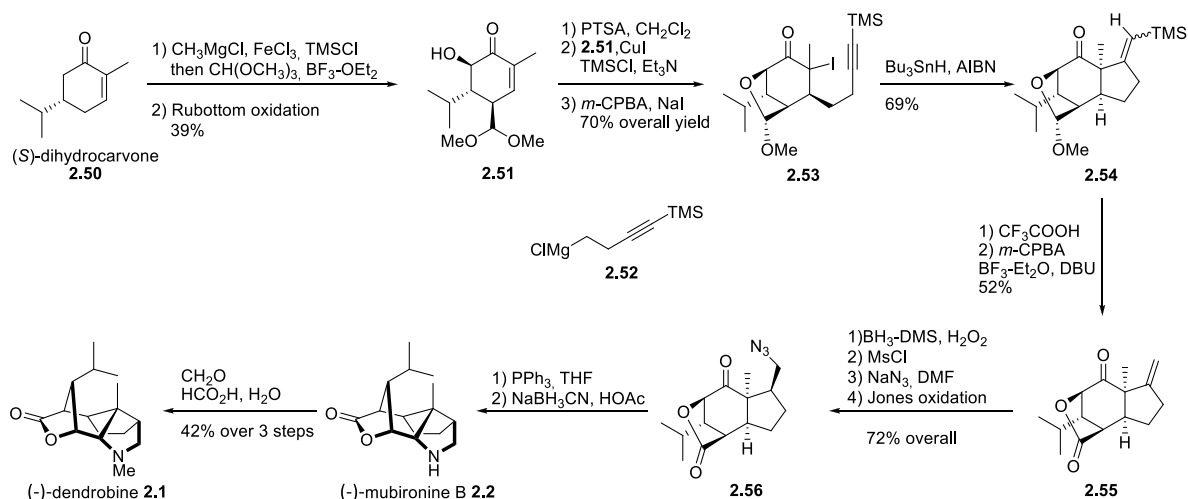
Scheme 2-5. Roush's total synthesis of (\pm)-dendrobine

A completely novel approach towards (\pm)-dendrobine was described by Livinghouse's group *via* an acylnitrilium ion-initiated cyclization, which afforded the bicyclic scaffold **2.46** (Scheme 2-6).^[106] Construction of the central six-membered ring in **2.48** was first attempted *via* an intramolecular reductive-aldol reaction sequence but failed to give any products, as the substrate was inactive towards conjugate reductive reactions. Eventually a samarium iodide-mediated reductive coupling was applied to afford the densely fused tricyclic scaffold **2.48**, with which the total synthesis of (\pm)-dendrobine was accomplished after an additional isomerization and lactone construction sequence.

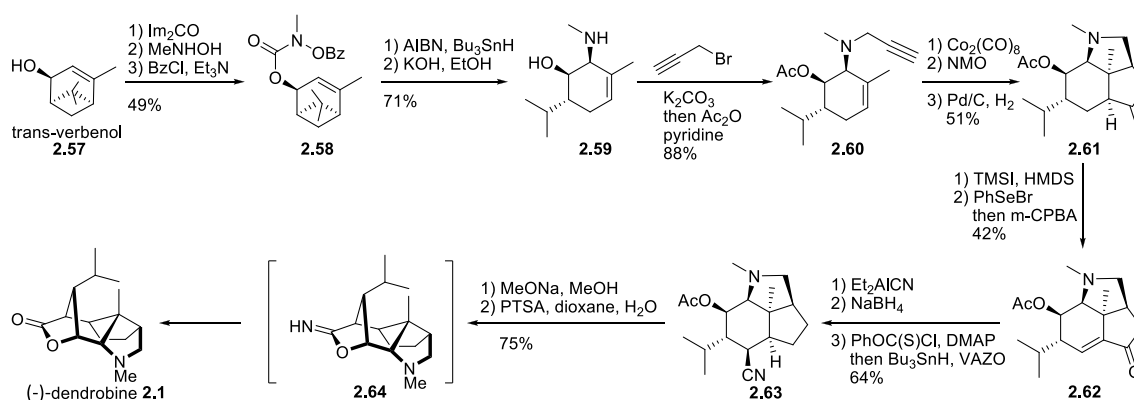


Scheme 2-6. Livinghouse's total synthesis of (±)-dendrobine

As discussed before, synthesizing bioactive compounds in their enantiomerically pure form is still an ongoing research topic in organic chemistry. Sha's group communicated the first enantioselective total synthesis of (-)-dendrobine in 1997 (Scheme 2-7) starting from the ex-chiral-pool compound (*S*)-dihydrocarvone **2.50**^[107]. The hemiketal moiety in **2.51** was constructed by a FeCl₃-mediated Mukaiyama-type aldol reaction-cyclization sequence, while the cyclopentane scaffold **2.54** containing an all-carbon quaternary center was obtained through a free-radical mediated cycloaddition. The nitrogen atom was introduced in the form of the azido compound **2.56**, which was then elaborated into (-)-mubironine B and (-)-dendrobine *via* a Staudinger-*aza*-Wittig reaction followed by reductive work-up.

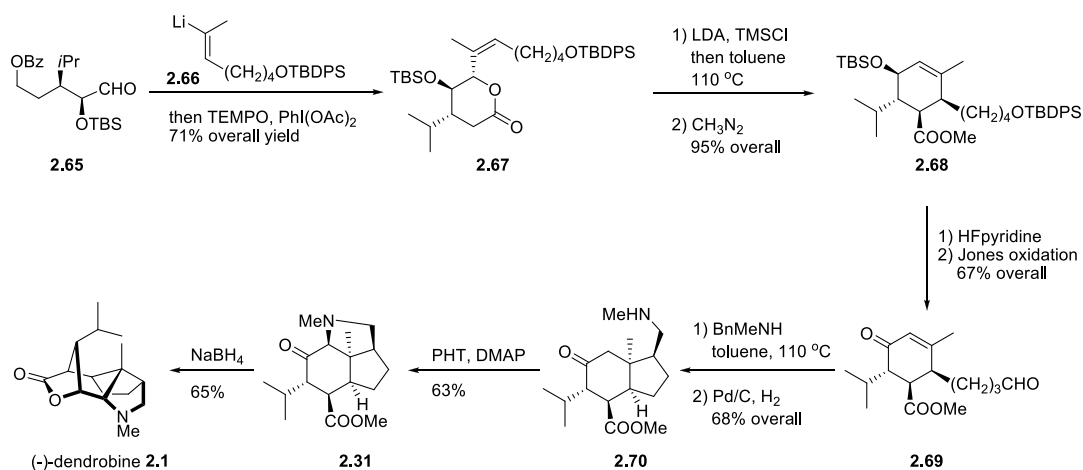


Scheme 2-7. Sha's first asymmetric total synthesis of (-)-dendrobine



Scheme 2-8. Zard's asymmetric total synthesis of (-)-dendrobine

Verbenols, another series of naturally occurring monoterpene alcohols that contain the desired stereocenters of dendrobine, have been used by Zard's group as the ex-chiral material for the total synthesis of (-)-dendrobine (Scheme 2-8).^[108] As illustrated in Scheme 2-8, *trans*-verbenol **2.57** was converted into the protected *N*-hydroxyl amide **2.58**, followed by amine introduction *via* a novel nitrogen-centered free radical cyclization reaction. Simple alkylation and protection of **2.59** delivered enyne **2.60**, which was cyclized to the densely fused tricyclic moiety **2.61** through a cobalt-Pauson Khand reaction. This synthesis featured the first use of enyne-cycloisomerization in picrotoxane type natural products' syntheses although stoichiometric amounts of cobalt complex were used. The subsequent lactone construction was similar to Inubushi's strategy, which allowed the synthesis of (-)-dendrobine within 17 steps.



Scheme 2-9. Carreira's asymmetric total synthesis of (-)-dendrobine

Recently, Carreira reported another novel total synthesis of (-)-dendrobine (Scheme 2-9), which highlighted the 3,3-rearrangement to afford the poly-substituted cyclohexene **2.68**.^[109] A conjugate addition-hydrogenation sequence was used to install the cyclopentane with an all-carbon quaternary center in **2.70**, and a regioselective ketone bromination-pyrrolidine formation reaction afforded the pyrrolidine core in **2.31**.

It can be seen above that each work represents its particular excellent methodologies in the total synthesis, however synthetic efficiency has become more important in modern chemistry. By comparing these representative synthetic strategies with their synthetic efficiencies, Christmann's color-coded flowchart-method is utilized to visualize the differences in efficiency and help us to evaluate our own project.

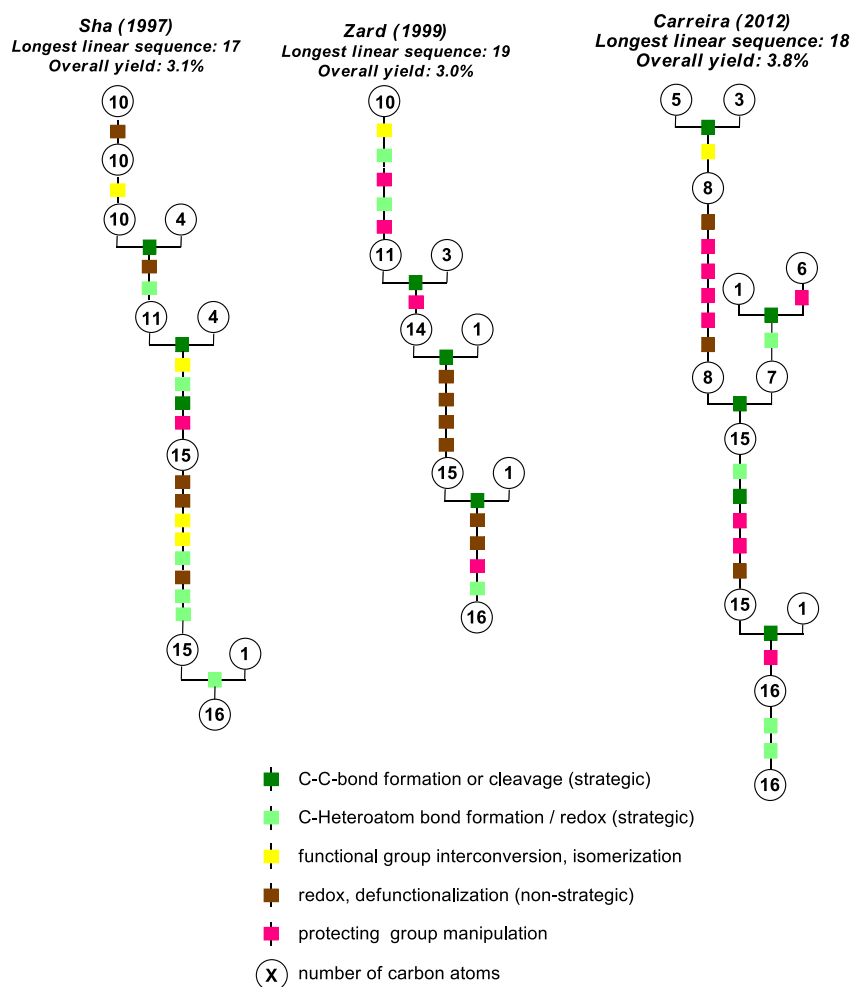
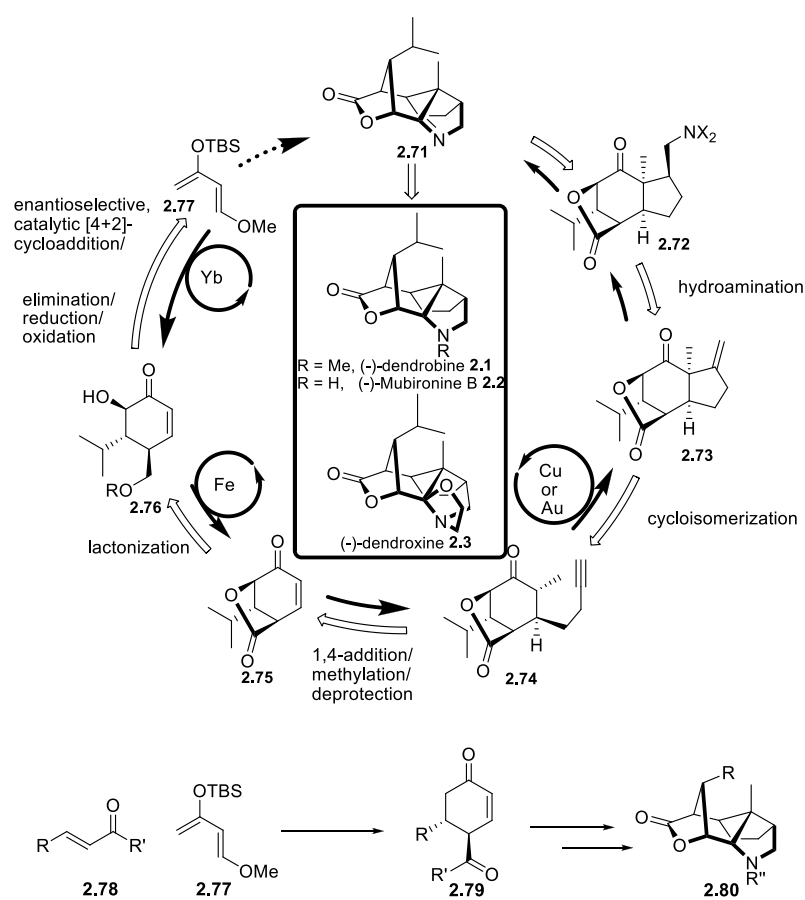


Figure 2-1. Step-efficiency analysis according to Christmann's method

If we compare the three available enantioselective total syntheses with Christmann's method, Sha's synthesis represents the shortest LLS (18 steps) with the least non-strategic manipulations. In Carreira's work, the natural product was obtained in the highest yield though trivial functional group manipulations and protecting-group chemistry were employed. However, despite its relatively high yield, the amounts of waste and atom-redox-efficiencies in the synthesis are more inflected by the number of steps. Thus, a efficient synthesis inherently requires less protecting group manipulations and less non-strategic redox or functional group interconversions.^[110]

2.3. Project Design and Retrosynthetic Analysis



Scheme 2-10. Retrosynthetic analysis

As previously discussed, all the available total syntheses of dendrobine are either racemic or ex-chiral-pool oriented enantioselective versions, and no reports on catalytic, enantioselective total synthesis of dendrobine or other picrotoxane alkaloids are available. Ex-chiral-pool compounds are cheap, however the defined structures limit their variability

compared to asymmetric catalysis, which can create multiple compounds with the similar core scaffold. In the view of medicinal chemistry, structural proliferation is the essential part for structure-activity relationship assessment and might lead to identification of new leading compounds. Meanwhile, traditional methods are less efficiency, which require multiple steps for a simple transformation as well as stoichiometric amounts of metal catalysts that might be replaced by modern synthetic methods. For the sake of developing a “state-of-the-art” catalytic strategy towards the picrotoxane alkaloids as well as their derivatives, we disclosed our synthetic analysis as shown in Scheme 2-10.

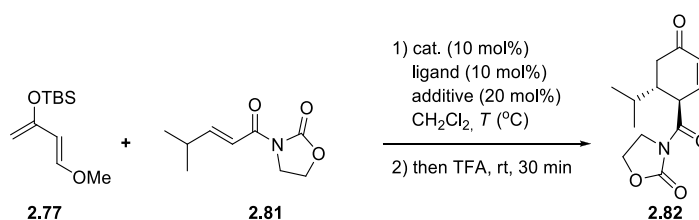
Retrosynthetically, we envisioned that dehydropyrrolidine **2.71** might serve as a common intermediate for picrotoxane alkaloids. With this dehydropyrrolidine intermediate, the alkaloids could be obtained with either reductive or redox-neutral conditions. Imine disconnection in **2.71** led to the nitrogen-containing compound **2.72**, which was planned to be synthesized from olefin **2.73** via a direct *anti*-Markovnikov hydroamination, a very challenging and seldomly used transformation in total synthesis. The olefin in **2.73** with an adjacent all-carbon quaternary center might be accessed from lactone **2.75** via a conjugate addition followed by a metal-catalyzed cycloisomerization. Before lactonization to lactone **2.75**, the central structure of cyclohexenone **2.76** was envisioned to originate from Danishefsky’s diene by diastereo- and enantioselective catalytic [4+2]-cycloaddition. Significantly, Diels-Alder cycloadditions using different dienophiles **2.78** might lead to different 5-substituted cyclohexenones **2.79**, which could proliferate the library-pool of picrotoxane alkaloids **2.80** for further structure-activity relationship assessment.

2.4. Synthesis of Three Picrotoxane Alkaloids

The synthesis commenced with the investigation of asymmetric Diels-Alder cycloaddition between Danishefsky’s diene **2.77** and the bidentate dienophile **2.81** catalyzed by chiral metal complexes (Table 2-1). However, the initial attempt with Evans’ cationic Cu²⁺-*bis*(oxazoline) complex (Cu²⁺-ligand **L2.1**) led to decomposition of Danishefsky’s diene **2.77** (Table 2-1, entry 1).^[23a, 23b, 111] Extensive literature research showed that no literature precedence of DA cycloaddition between Danishefsky’s diene and oxazolidinone dienophile catalyzed by a Cu²⁺-*bis*(oxazoline) complex has been reported due to the lability of Danishefsky’s diene towards Lewis acidic conditions. Shibasaki’s recent report on the cationic Fe³⁺-*bis*(oxazoline) complex (Fe³⁺- ligand **L2.2**) catalysis was then tested and to our delight the product was produced diastereoselectively with moderate yield although the

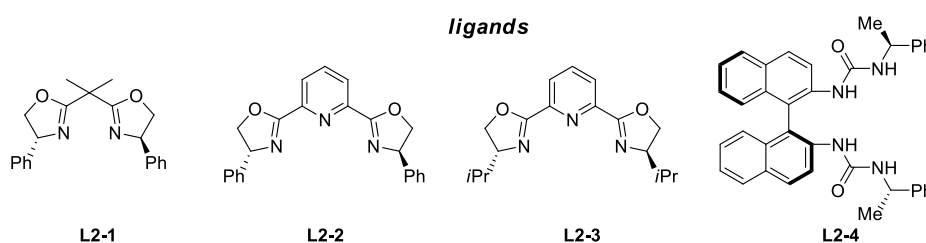
enantioselectivity was underprivileged (Table 2-1, entry 2).^[112] Slightly decreasing the temperature to -50 °C did increase the enantioselectivity however at the cost of more decomposition of Danishefsky's diene (Table 2-1, entry 3), which indicated that the catalyst was partially deactivated over time. It was noteworthy that compared to ligand **L2.1**, ligand **L2.2** gave the product with opposite enantioselectivity (Table 2-1, entry 4), even though ligand screening was proven to be unfruitful to increase enantioselectivity (Table 2-1, entry 1-5). Meanwhile, low to moderate yield for Fe³⁺ complex catalysis further demonstrated that non-acidic catalytic systems might allow the transformation to be more feasible in this case.

Table 2-1. Asymmetric catalytic Diels-Alder cycloaddition



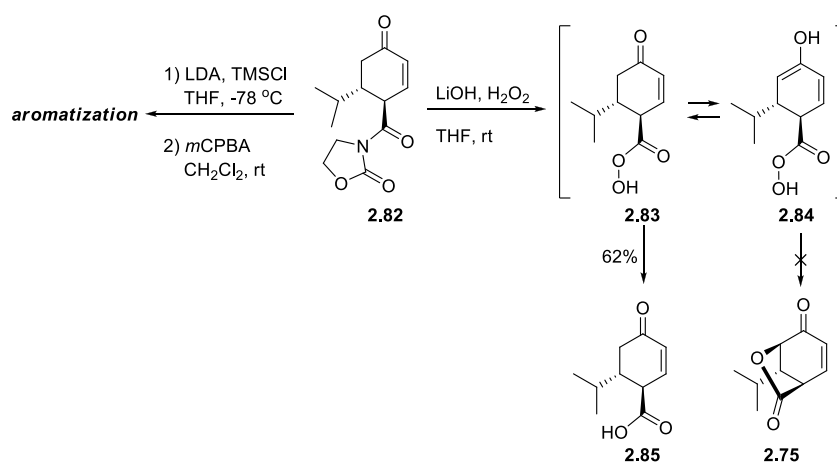
Entry ^a	Catalyst	Ligand	Additive	Temperature (°C)	Yield (%) ^b	ee ^c (%)
1	Cu(OTf) ₂	L2-1	AgBF ₄	-40	-	-
2	FeBr ₃	L2-2	AgBF ₄	-40	47	0
3	FeBr ₃	L2-2	AgBF ₄	-50	25	17
4	FeBr ₃	L2-1	AgBF ₄	-40	33	-25
5	FeBr ₃	L2-3	AgBF ₄	-40	44	11
6	Yb(OTf) ₃	L2-4	DBU	0	78	91

^a The reaction was stirred at indicated temperature for 7 h; ^b Isolated yield; ^c Enantiomeric excess was determined by chiral HPLC; ^d The reaction was stirred at 0 °C for 3 h.



To overcome this problem, rare-earth metal salts were found to be the key to avoid the decomposition of Danishefsky's diene, as they are not as Lewis acidic as transition metal

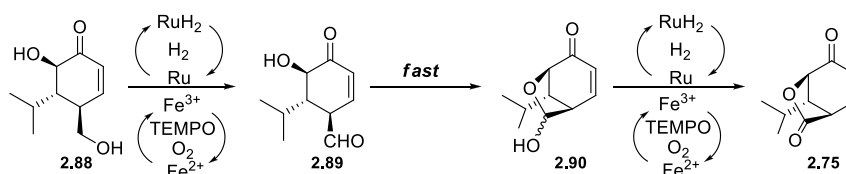
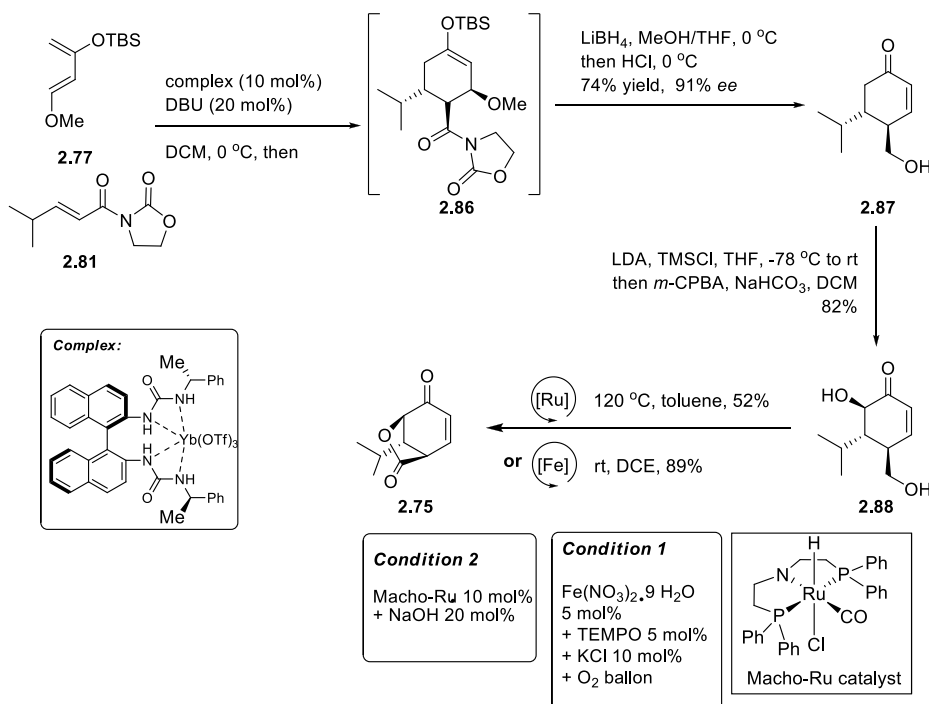
salts.^[30] Finally, with Nishida's recently reported Yb-(S)-BINUREA complex (Yb³⁺-ligand **L2-4**), the desired product was isolated in a highly diastereoselective fashion in 78% yield (Table 2-1, entry 6).^[113] The labile silyl-enolate product could not be further purified and was treated with acid to give the rearranged enone **2.82**. The enantiomeric excess was determined by chiral HPLC to be 91%, which might be further improved by late-stage recrystallization. The reaction was scaled up to 5 mmol without erosion of enantiomeric excess. The catalytic complex is sensitive towards moisture, and *in situ* formation of active catalyst should be carefully handled under absolutely moisture-free conditions (see experimental part). With the optimized conditions in hand, oxazolidinone **2.78** with different substituent patterns could be employed to produce different oxazolidinones **2.79**, hence enriching the library-pool of picROTOXANE alkaloids (Scheme 2-10).



Scheme 2-11. Attempts on direct lactonization

With the Diels-Alder cycloaddition product in hand, we attempted to start from the oxazolidinone motif in **2.82** for a direct lactone formation (Scheme 2-11). Direct treatment of the enone **2.82** with LDA at -78 °C led to a fast decomposition. Crude NMR analysis revealed the formation of aromatic side-products, which was the result of competitive deprotonation at the more acidic γ -enone- α -oxazolidinone position, followed with fast aromatization. We then speculated that the oxazolidinone auxiliary in **2.82** could be hydrolyzed under oxidative and moderately basic conditions (LiOH, H₂O₂ or *t*-BuOOH) to afford the peracid **2.83** *in situ*, which might in turn be able to undergo an intramolecular RuBottom-oxidation-lactonization sequence without competitive deprotonation. Unfortunately, under all tested conditions no lactone product was detected by GC-MS while the carboxylic

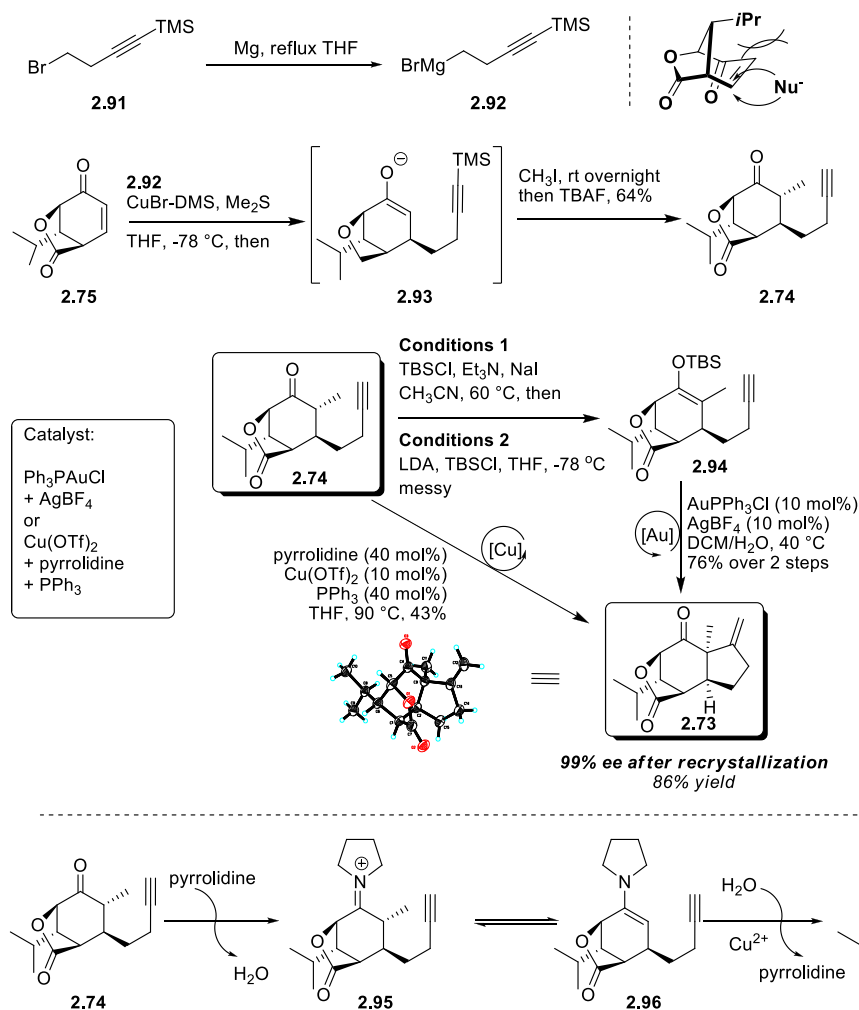
acid **2.85** was isolated as the only product in 62% yield because the preacid **2.83** tends to decompose to the corresponding carboxylic acid in basic conditions.



Scheme 2-12. Effective lactone construction protocols

Considering that the presence of the oxazolidinone auxiliary is problematic under oxidative lactonization conditions, we turned back to reduce the oxazolidinone immediately after the Diels-Alder cycloaddition. As shown in Scheme 2-12, the Diels-Alder cycloaddition was performed under the optimized conditions, and the labile silyl-enolate product was reduced with lithium borohydride followed by acidic work-up to the rearranged enone **2.87** with 74% overall yield and 91% *ee*.^[114] Gratifyingly, deprotonation of the alcohol **2.87** with two equivalents of LDA at -78 °C gave the corresponding enolate smoothly, which was oxidized with Davis' oxaziridine to the diol **2.88** in 68% yield. The oxidation was diastereoselectively controlled by the adjacent *i*Pr-group, probably due to the directing effect of the primary alcohol. Employing Rubottom oxidation conditions after further optimization allowed us to

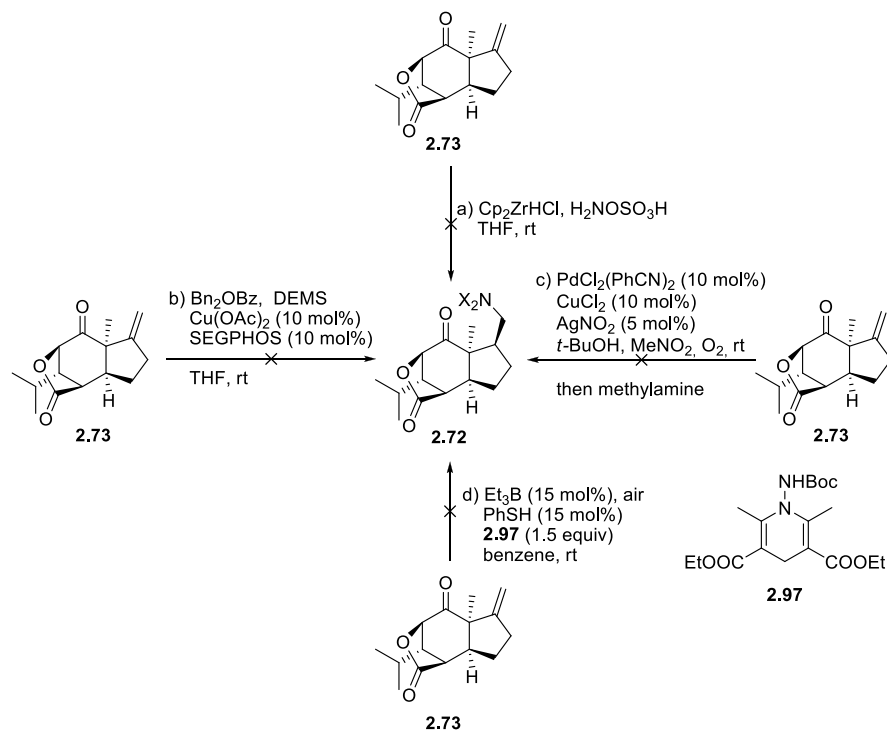
isolate the diol **2.88** in 82% overall yield. The oxidative lactonization was first tested with the Macho-ruthenium catalyzed hydrogen-transfer strategy. To our delight, the desired lactone **2.75** was isolated with 76% yield under hydrogen acceptor-free conditions (Scheme 2-12, conditions 1). Literature research indicated that a catalytic dehydrogenative coupling occurred with evolution of H₂ gas, which can be expelled in refluxing toluene.^[115] However, the harsh conditions (refluxing toluene) undoubtedly led to the moderate yield, which pushed us to explore milder catalytic conditions. Finally, Ma's recently reported iron nitrate-catalyzed aerobic oxidation (Scheme 2-12, conditions 2) provided the alternative option to afford the lactone product **2.75** with 89% yield with water as the only byproduct.^[116] In both cases, the primary alcohol in **2.88** was chemoselectively oxidized to the corresponding aldehyde **2.89** that condensed with the secondary alcohol at C-6 to hemiacetal **2.90**, which was further oxidized to the lactone **2.75**. Compared to the traditional oxidative strategies in which stoichiometric amounts of oxidants are necessary, the two catalytic lactonization protocols are highly eco-friendly, while the latter, more energy-effective iron-catalyzed approach is more applicable in total synthesis. With lactone **2.75** in hand, we set out to install the cyclopentane scaffold **2.73** containing the all-carbon quaternary center (Scheme 2-13). Diastereoselective conjugate addition of **2.92**-derived cuprate *trans* to the *i*Pr-group led to the formation of enolate **2.93**, which was quenched by methyl iodide followed with deprotection, affording the diastereomerically pure ketone **2.74** in 64% yield. The use of terminal protected alkyne **2.91** was necessary to avoid homocoupling byproducts during the organocuprate reagent synthesis. Transformation of **2.74** into the corresponding TBS-enol ether **2.94** was performed under thermal conditions (Scheme 2-13, conditions 1), as the kinetic conditions with strong bases like LDA led to competitive deprotonation of the terminal alkyne (Scheme 2-13, conditions 2). Stoichiometric amounts of sodium iodide were used as an additive to form the stronger enolating reagent TBSI *in situ*. Without further purification, the TBS-enoether **2.94** was treated with 10 mol% of Au catalyst Ph₃PAuCl/AgBF₄ in a mixture of CH₂Cl₂/H₂O and resulted in cycloisomerization to **2.73** in 76% overall yield with the quaternary center installed.^[117] The structure of compound **2.73** was unambiguously confirmed by X-ray crystallography (Scheme 2-13).



Scheme 2-13. Cycloisomerization strategies

Due to its weak nucleophilicity, the ketone **2.74** usually requires pre-activation as a silyl-enol ether in cycloisomerization chemistry. However, if the activated enolate is formed *in situ*, the additional synthesis of silyl-enol ether **2.94** can be omitted. Indeed, with Dixon's recently reported $\text{Cu}(\text{OTf})_2$ -pyrrolidine co-catalyzed cycloisomerization conditions, a direct conversion of **2.74** to **2.73** without labile silyl-enol ether **2.94** synthesis was possible though in a lower overall yield compared to the two-step Au-catalyzed sequence (Scheme 2-13).^[118] Initially, the condensation of the pyrrolidine with ketone **2.74** affords the iminium ion **2.95**, which tautomerizes into the enamine species **2.96** as a well-activated nucleophilic reagent. Activation of the alkyne in **2.96** by the copper catalyst leads to simultaneous cycloisomerization to afford the product **2.73**, concomitant with catalyst regeneration. Considering the availability of the copper catalyst, this provided an alternative for an intramolecular

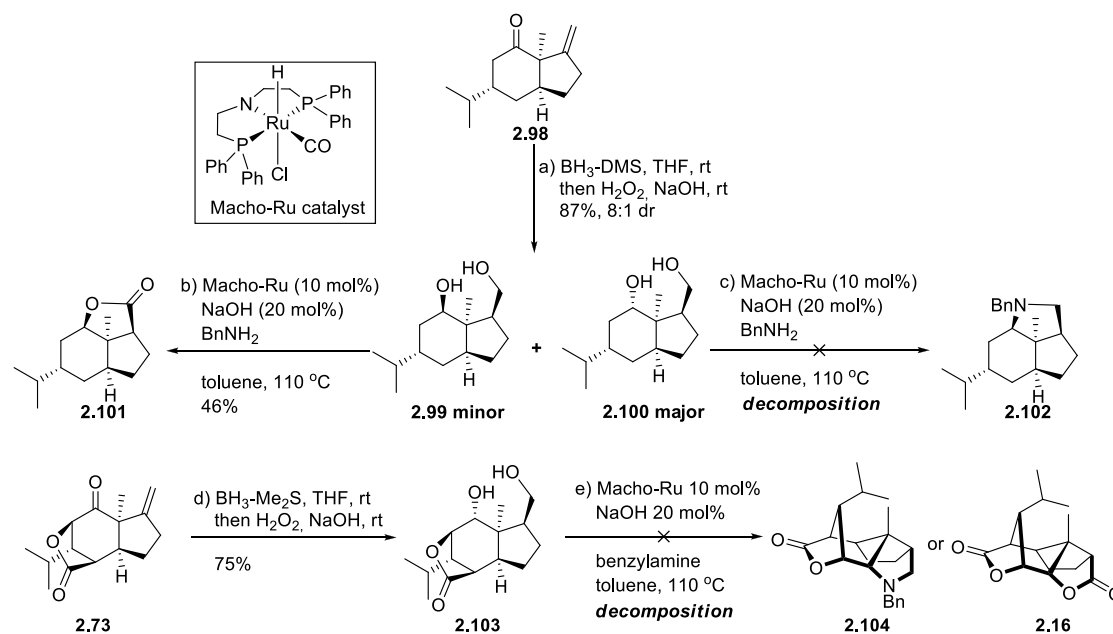
cycloisomerization approach for natural products synthesis. At this stage, the enantiomeric excess of **2.73** was improved after recrystallization to 99% with 86% yield.



Scheme 2-14. Direct *anti*-Markovnikov hydroamination attempts

With the optically pure olefin **2.73** being efficiently synthesized, introduction of the nitrogen atom was first investigated with the envisioned regio- and diastereoselective direct *anti*-Markovnikov hydroamination strategy. In 2013, Hartwig's group reported a one-pot hydrozirconation/amination sequence to introduce the C-N bond in an *anti*-Markovnikov fashion,^[119] and Stoltz's group first utilized this protocol in the total synthesis of (-)-goniomitine in 2016 by late-stage functionalization of a terminal mono-substituted olefin.^[120] However, in our case only starting material was recovered with olefin **2.73** (Scheme 2-14a). We reasoned that the direct hydroamination might be troublesome due to the steric hindrance of the 1,1'-disubstituted exocyclic olefin and the adjacent vicinal all-carbon quaternary center. The hypothesis was further confirmed by the fact that the olefin **2.73** was inactive under CuH-catalyzed hydroamination conditions (Scheme 2-14b)^[121] as well as palladium-catalyzed Wacker oxidation conditions (Scheme 2-14c)^[122]. Based on these results, we envisioned that less sterically-demanding free-radical approaches

might be more feasible. However, Studer's free radical hydroamination conditions^[123] were still unfruitful and resulted in starting material recovery only (Scheme 2-14d).

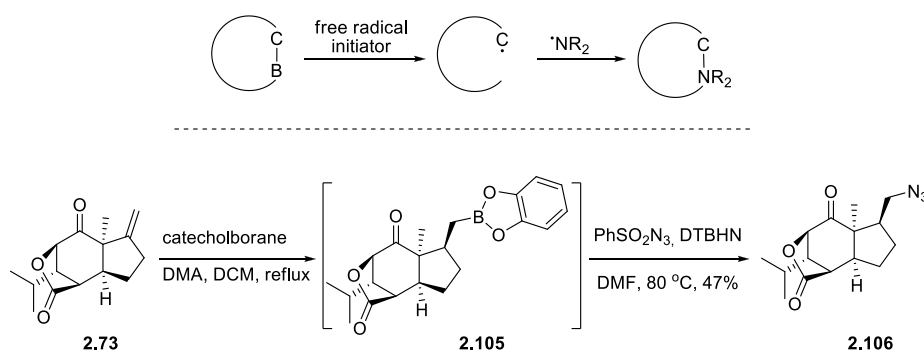


Scheme 2-15. Investigations of hydrogen auto-transfer catalysis

We then turned to the catalytic hydrogen auto-transfer strategy for the amine synthesis from the corresponding alcohol with water as the only by-product. To the best of our knowledge, this strategy has never been used in total synthesis.^[124] In the model case studies, olefin **2.98** was treated with borane-dimethyl sulfide complex followed by an oxidative work-up to give the diols **2.99** and **2.100** as a pair of diastereomers (Scheme 2-15a). The minor *cis*-diol **2.99** was first tested in the ruthenium-catalyzed hydrogen auto-transfer catalysis with benzylamine as the amine source. Surprisingly, the lactone compound **2.101** was isolated in 46% yield (Scheme 2-15b), which represented a pathway that analogous to the Ru-catalyzed lactone synthesis shown in Scheme 2-12. It was reasoned that the intramolecular hemiacetal formation was faster than the desired, intermolecular imine formation. Nevertheless, we assumed that this might not be an issue for the major *trans*-diol **2.100** as the corresponding *trans*-hemiacetal formation is really difficult. However, applying the same conditions to *trans*-diol **2.100** only led to decomposition instead of formation of the desired amine **2.102** (Scheme 2-15c). This is due to the instability of the aldehyde intermediate at high temperatures. Same results were obtained

when the less basic *tert*-butanesulfinamides (*R*, *S* or racemic) or other catalytic systems were used.

On the other hand, the isolation of lactone **2.101** offered us a novel, biomimetic total synthesis of picrotoxane sesquiterpenoids **2.6** – **2.9** by carefully investigating the selective oxidation conditions. Therefore we turned our attention to the olefin **2.73** to test the feasibility of additional lactone formation. To our disappointment, the hydroboration-oxidation sequence led to *trans*-diol **2.103** diastereoselectively (Scheme 2-15d) which then decomposed under the catalytic conditions instead of giving the desired intermediate **2.16** or amine **2.104** (Scheme 2-15e). Further investigation into *cis*-diol synthesis from olefin **2.73** with more sterically hindered borane complexes such as 9-BBN or catecholborane were fruitless.

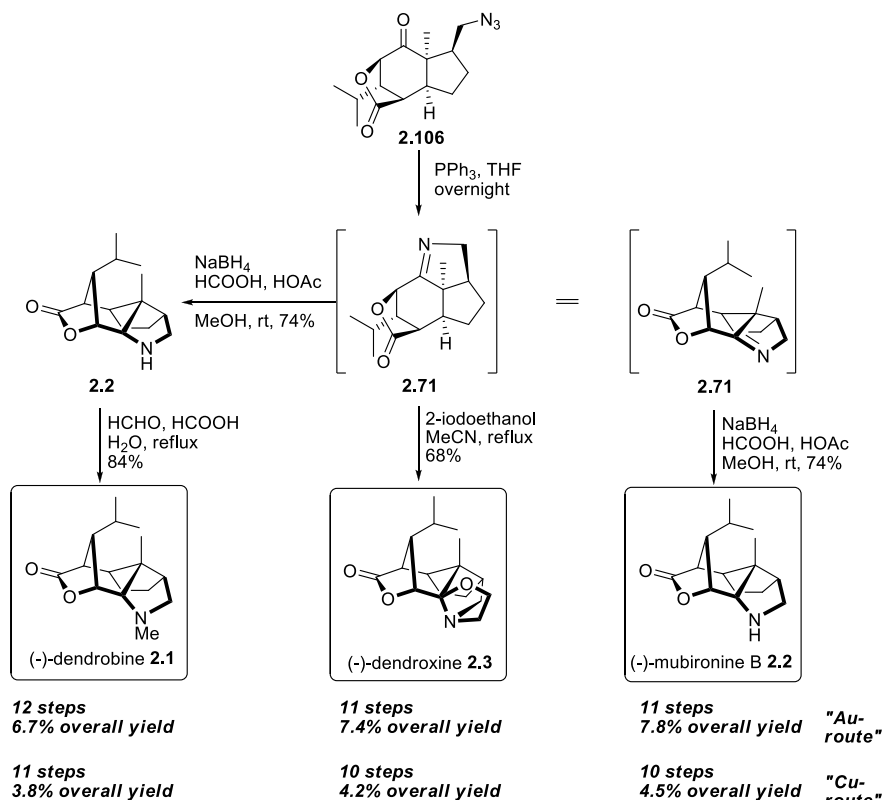


Scheme 2-16. Hydroboration-azidation strategy for C-N bond formation

However, the fact that the olefin could be hydroborated inspired us to trigger C-B bond disconnection in the boron-intermediate with a free radical initiator to give the corresponding carbon-radical, which might collapse with another nitrogen-radical species to implement the C-N bond (Scheme 2-16). After careful evaluation of available strategies, a sequence of hydroboration with catecholborane to **2.105** followed by subsequent free radical-initiated azidation of the C-B bond under Renaud's conditions^[125] was successful and constructed the desired C-N bond in **2.106** in exclusively diastereo- and regioselective fashion, and azide **2.106** was isolated in 47% overall yield. The uncommon free radical initiator di-*tert*-butyl hyponitrite was used because the oxygen radical has a stronger affinity to boron compounds according to Renaud's investigations.^[125a]

Gratifyingly, azide **2.106** underwent an intramolecular *aza*-Wittig reaction smoothly affording the dehydropyrrolidine **2.71** as a common intermediate, which was used directly

in the following steps due to the lability of the imine moiety towards moisture (Scheme 2-17). Starting from the common intermediate **2.71**, (-)-dendrobine **2.1** and (-)-mubironine B **2.2** were synthesized under reductive work-up with 74% and 62% yield, respectively.



Scheme 2-17. Collective synthesis of three picrotoxane alkaloids

(-)-Dendroxine **2.3** was obtained upon treatment of dehydropyrrolidine intermediate **2.71** with 2-iodoethanol under thermal conditions, through an iminium ion formation followed by a very fast intramolecular nucleophilic *O*-addition.^[126] In summary, the asymmetric total synthesis of **2.1**, **2.2** and **2.3** was accomplished in 12 or 11 steps in 6.7%, 7.8% and 7.4% yield, respectively (Scheme 2-17). The spectroscopic data of the synthesized alkaloids are identical to the data reported in the literature (a comparison of spectroscopic data can be seen in experimental part). As can be seen from the flowchart (Figure 2-2), this synthesis represents optimized synthetic efficiency which minimized non-strategic manipulations and the highest overall yield so far.

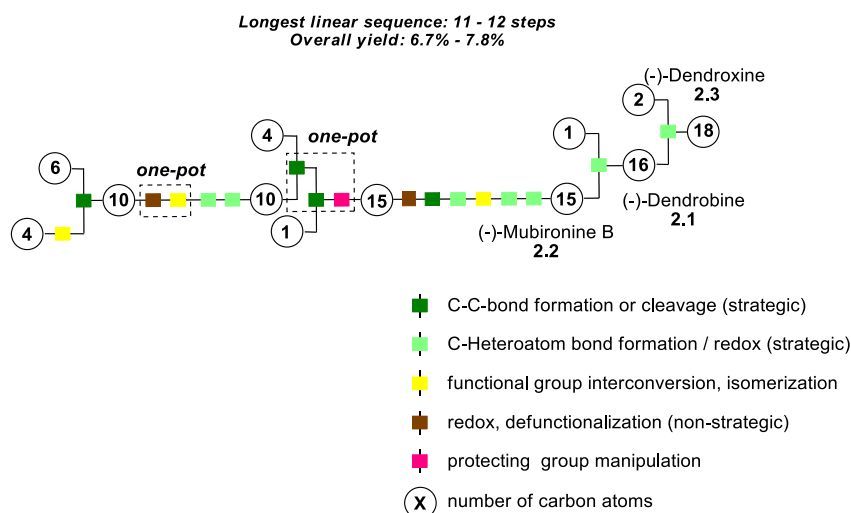


Figure 2-2. Step-efficiency analysis according to Christmann's method^[110]

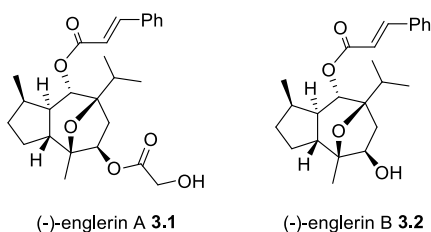
In the meantime, the enantioselectivity in our approach is a direct consequence of the stereoselective intermolecular Diels-Alder cycloaddition between Danishefsky's diene **2.77** and dienophile **2.81**. As far as we know, all the other available enantioselective total syntheses started from chiral pool material. To underline the strength of our approach, we turned to synthesize the corresponding enantiomeric alkaloids and to characterize these non-natural antipodes. As illustrated in Scheme 2-18, starting with the (*R*)-catalyst, the corresponding cyclohexenone (+)-**2.87** was accessible in 71% yield and 91% enantiomeric excess. With this cyclohexenone (+)-**2.87** in hand, (+)-dendrobine **2.1**, (+)-mubironine B **2.2** and (+)-dendroxine **2.3** could be synthesized within 10 or 11 steps respectively. The absolute configuration of the natural products and their optical antipodes were confirmed by X-ray crystallography of the intermediate **2.73** and *ent*-**2.73**. Combined with the possibility of the natural products' analogues can be synthesized by introducing different substitution patterns in oxazolidinone moiety, this approach is highly useful for expanding the library pool of picrotoxane alkaloids for further investigation into their structure-activity relationships.

catalyzed aerobic oxidation, the copper-catalyzed cycloisomerization and the hydroazidation underline the strength of modern synthetic sequences compared to the conventional counterparts. Further work will concentrate on the construction of additional picrotoxane alkaloids and sesquiterpenoids in order to explore their biological activities.

3. Catalytic Enantioselective Total Synthesis of Englerins A and B

3.1. Introduction to the Guaiane Sesquiterpene Englerins A and B

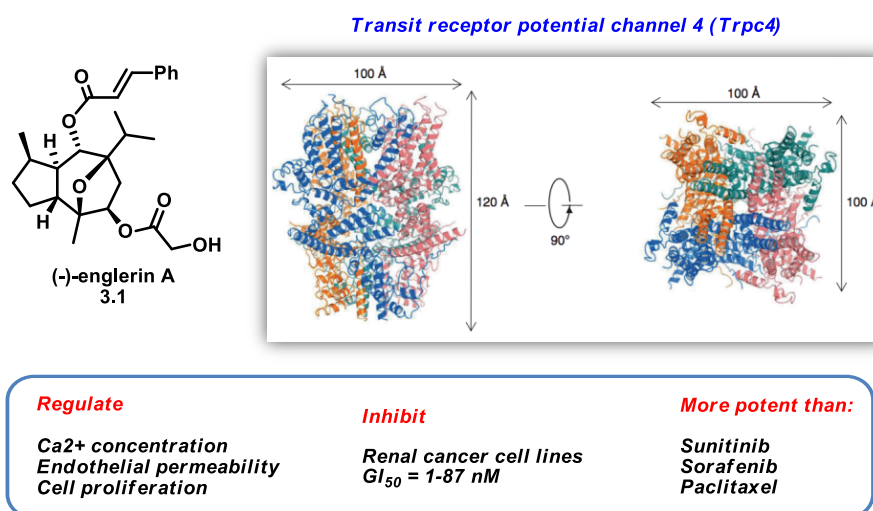
Renal cancer is the eighth most common adult cancer in the world, and the newest epidemiological research indicates that there are around 65,340 new renal cancer cases in the United States and 73,400 cases in Europe every year, which account for more than 50% of yearly new cases all around the world.^[127-129] Surgery serves as the most common treatment as renal cancer cells often do not respond to radiotherapy or chemotherapy. However when surgery is not possible, chemotherapy is necessary to prolong the progression-free survival.^[130] Nevertheless, the current standard of care does not prolong the PFS significantly. For example, sorafenib and sunitinib are currently used as the anti-renal cancer drugs in market, however the median PFS was 5.5 months in the sorafenib group^[131] and 11 months in the sunitinib group^[132]. Pharmacologically speaking, sorafenib^[131] and sunitinib^[132] are inhibitors to the renal cancer cellular signaling pathway that inhibit multiple receptor tyrosine kinases. In other words, identification of small molecules targeting on novel renal cancer receptors might be significantly helpful in renal cancer chemotherapy investigations.



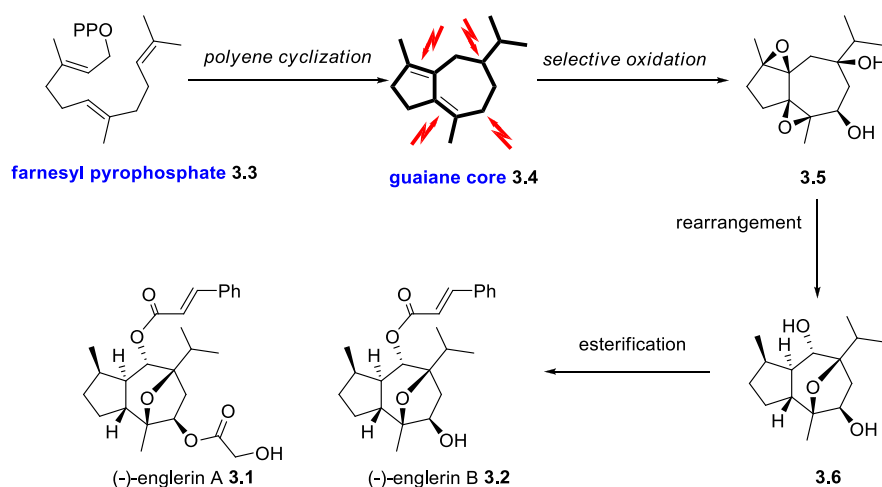
Scheme 3-1. Guaiane sesquiterpene englerins A and B

(-)-Englerins A and B (**3.1** and **3.2** Scheme 3-1) are guaiane sesquiterpenes that were isolated from the East Africa shrub tree *Phyllanthus engleri's* extracts by Beutler's group in 2009.^[133] Biological evaluation revealed that (-)-englerin A **3.1** inhibits renal cancer cell line's growth with GI₅₀ ranges between 1-87 nM, which is 2-3 fold more potent than the current standard of care sunitinib and sorafenib.^[134] Consequently, (-)-englerin A **3.1** might be a promising new lead compound to the treatment of renal cancer. Pharmacologically speaking, (-)-englerin A **3.1** targets an unprecedented anti-tumor target TRPC4/5, which is known as the transit receptor potential cation channels that regulate the Ca²⁺

concentration within cells, further more control endothelial permeability, and finally influence the cell's proliferation (Scheme 3-2).^[135] This unusual working targets renders englerin A to be a potent anti-cancer drug candidate and an interesting part in potential novel antitumor target research.



Scheme 3-2. Englerin A's inhibition of renal cancer cells



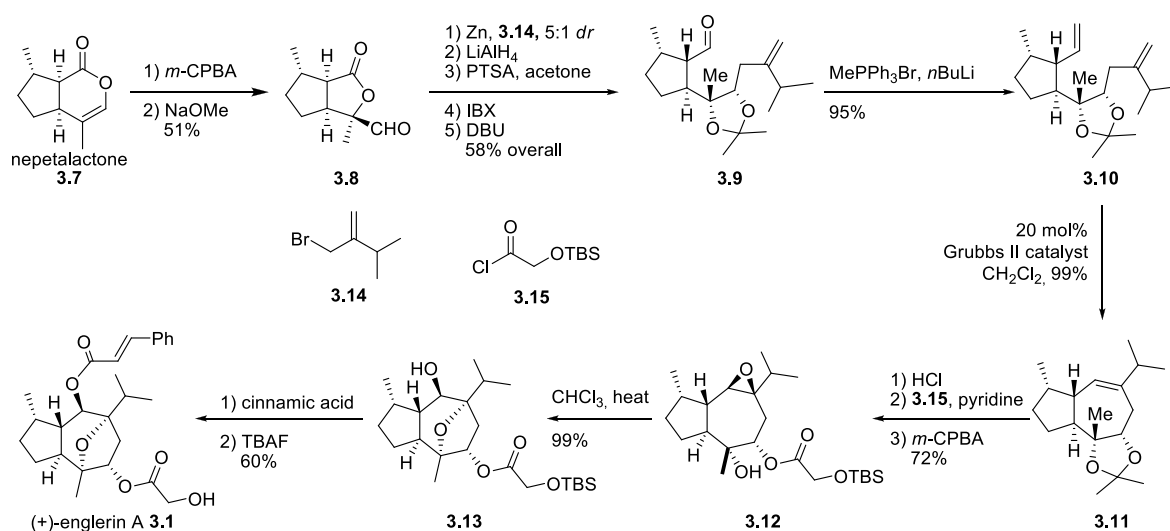
Scheme 3-3. Biosynthesis of guaiane sesquiterpene englerins

Structurally speaking, the englerins belong to guaiane sesquiterpene natural products, featuring a challenging *trans*-fused bicyclo[5.3.0] core structure, an oxygen bridge and a seven-membered ring that in an oxabicyclo[3.2.1] heptane system. The central framework is highly oxidized and bears seven contiguous stereocenters. Similar to the picrotoxane sesquiterpenoids, englerins biogenetically arise from the mevalonate pathway (Scheme 3-

3). The guaiene core structure **3.4** is synthesized *via* FPP polyene cyclization, and a subsequent late-stage selective oxidation-rearrangement gives the central structure **3.6** bearing an oxygen bridge, which is eventually esterificated to give the englerins A and B.^[136]

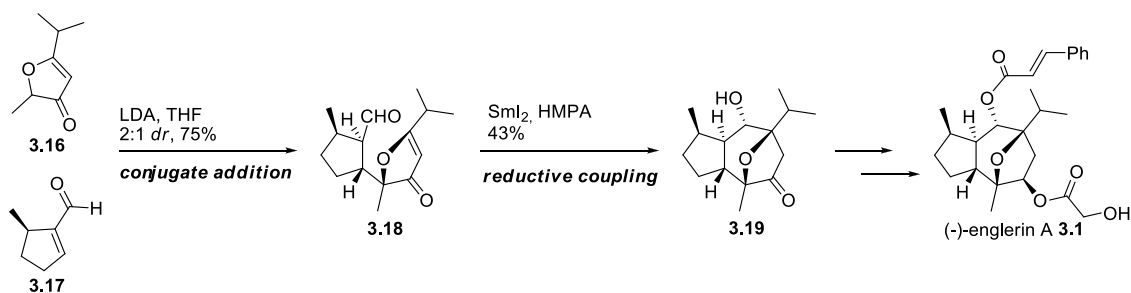
3.2. Prior Synthetic Approaches towards Englerins A and B

The interesting molecular structure of the englerins plus its bio-potential reactivities have spurred interest in synthetic chemists to develop efficient synthetic protocols. However, the complex tricyclic core represents a severe synthetic challenge that needs to be addressed.



Scheme 3-4. Christmann's first total synthesis of (+)-englerin A *via* RCM strategy

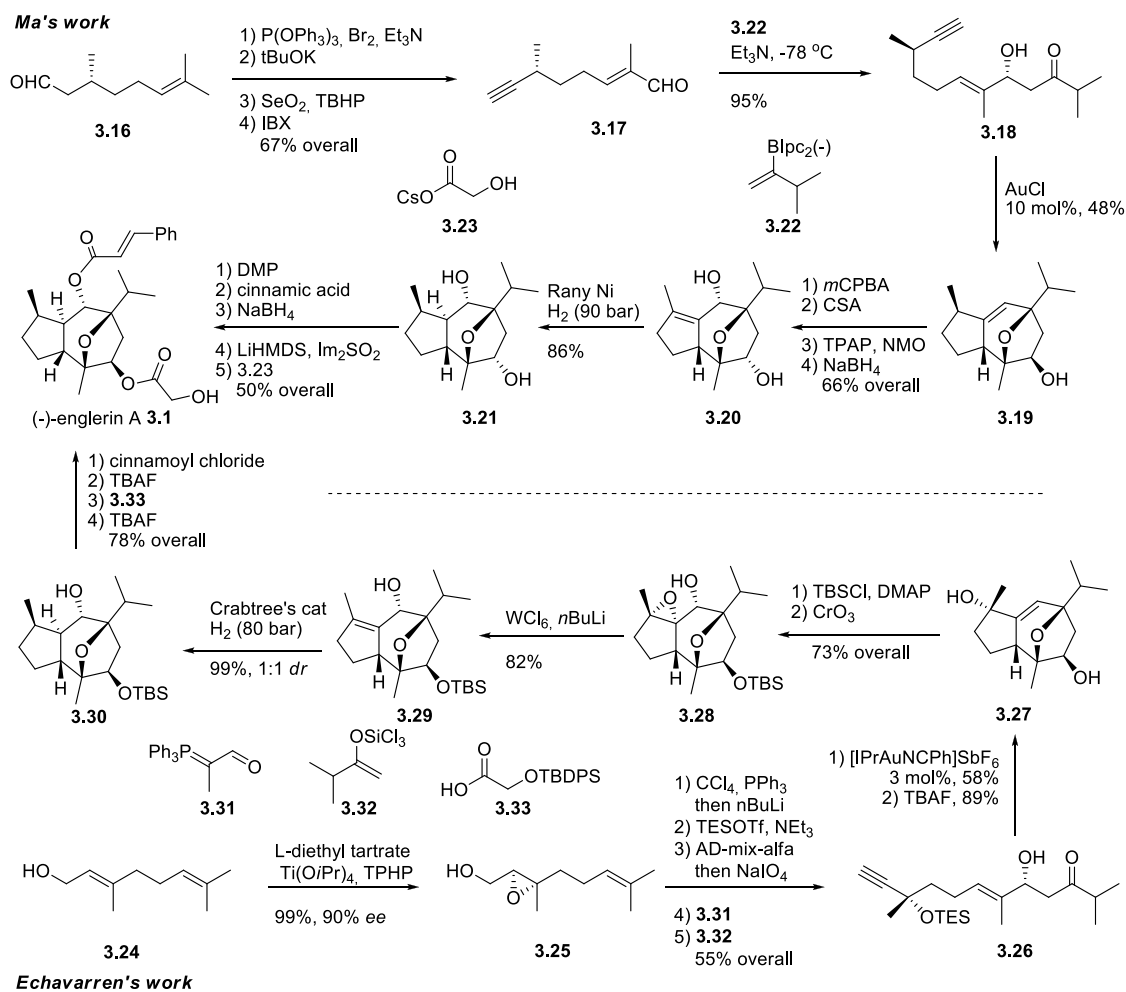
Ring-closing olefin metathesis was proven to be a powerful strategy and was widely used towards the construction of macro ring system. In 2009, Christmann's group reported the first total synthesis of (+)-englerin A **3.1** starting from bicyclic nepetalactone **3.7**, which bears the desired cyclopentane moiety and the chiral stereocenters. As illustrated in Scheme 3-4, a ring closing metathesis approach followed by a biomimetic oxidation-transannular epoxide-opening strategy afforded the central scaffold. After additional esterification, *ent*-englerin A **3.1** was synthesized for the first time together with its absolute configuration determination.^[137] Meanwhile, a similar RCM-biomimetic oxidation-transannular epoxide opening sequence was utilized by Metz's group in their synthesis of (-)-englerin A.^[138]



Scheme 3-5. Chain's efficient total synthesis of (-)-englerin A

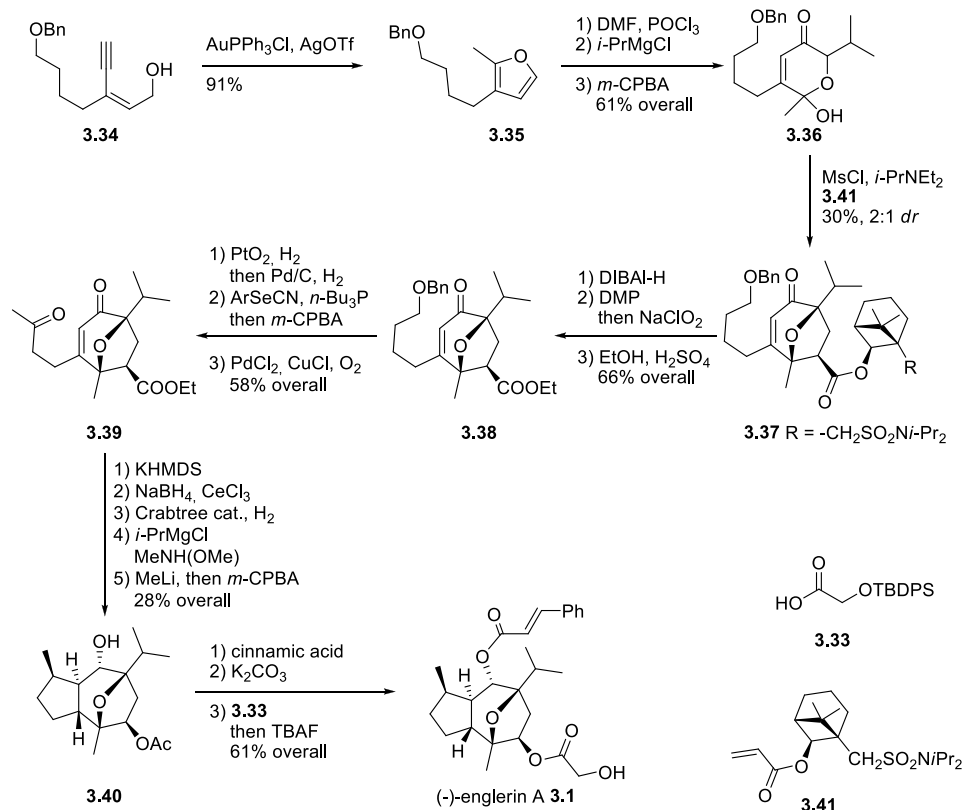
Meanwhile, Chain's group developed a conjugate addition-reductive coupling sequence to access the tricyclic core efficiently (Scheme 3-5).^[139] Starting from the 3-furanone **3.16** and the enantiomerically pure α,β -unsaturated aldehyde **3.17**, the conjugate addition occurred smoothly to give the adduct **3.18** in 75% yield with moderate diastereoselectivity. Subsequent umpolung coupling was problematic due to the low reactivity of the bulky furanone **3.18**, and only a combination of samarium iodide and HMPA afforded the reductive coupling product **3.19** with moderate yield. With the central scaffold being constructed, the total synthesis of (-)-englerin A **2.1** was finished in 6 steps very concisely.

Aside from the elegant RCM-epoxide-opening and conjugate addition-reductive coupling strategies, the majority of available strategies are based on the cycloadditions as the key steps, such as Ma's^[140] and Echavarren's^[141] independent syntheses of (-)-englerin A **2.1** via Au(I)-catalyzed enyne-carbonyl [2+2+2] cycloaddition (Scheme 3-6). The enantioselective synthesis of enyne-carbonyl compound **3.18** in Ma's work was achieved from ex-chiral-pool (*R*)-citronellal **3.16**, while the corresponding cycloaddition precursor **3.26** in Echavarren's work was synthesized via Sharpless' catalytic asymmetric epoxidation. Ma used the relatively simpler and commercially available AuCl (10 mol%) as catalyst to afford the cyclized product **3.19** with 48% yield, while Echavarren reported the use of only 3 mol% of $[\text{IPrAuNCPH}]\text{SbF}_6$ that delivered the product in 58% yield.



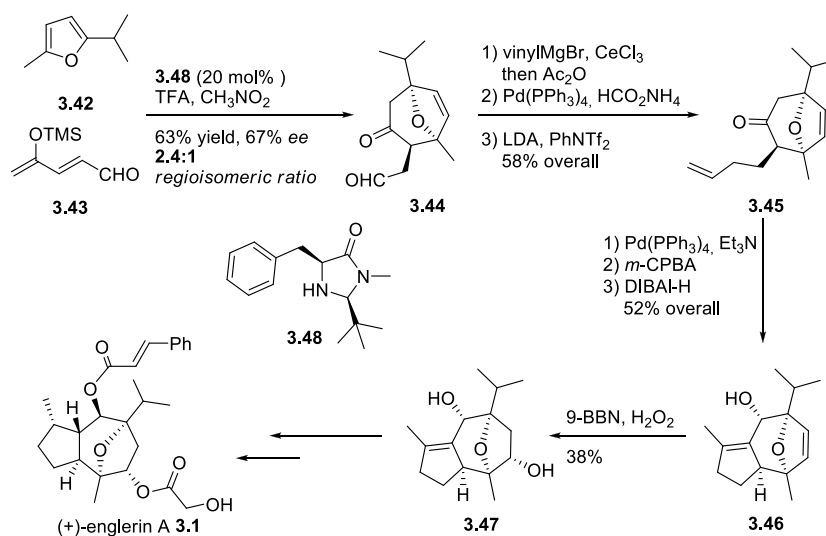
Scheme 3-6. Ma's and Echavarren's independent total syntheses of (-)-englerin A

Contemporaneously, Nicolaou's group reported a total synthesis of (-)-englerin A based on a [5+2] cycloaddition between oxidopyrylium species **3.36** and the camphorsulfonamide-derived acrylate **3.41** (Scheme 3-7).^[142] The enantioselectivity was induced by the use of camphorsulfonamide moiety in **3.41** as chiral auxiliary. Though trivial functional group transformations were necessary in this work, the use of an Achmatowicz rearrangement- [5+2] cycloaddition provided a novel strategy towards oxabicyclo[3.2.1] heptane core which is still vivid today.^[143]



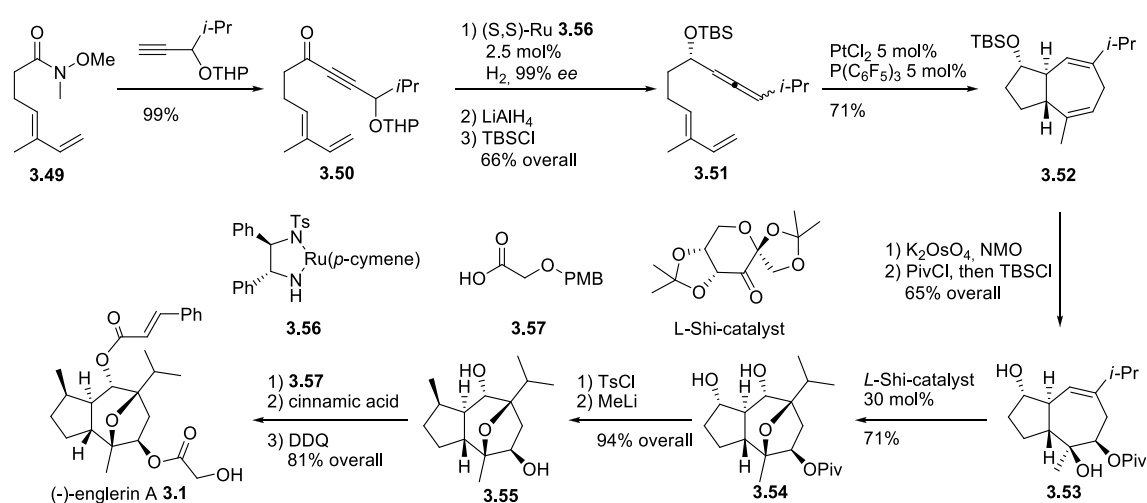
Scheme 3-7. Nicolaou's total synthesis of (-)-englerin A via [5+2] cycloaddition

Lin's group finished the total synthesis of (+)-englerin A 3.1 by approaching Ma's intermediate **3.47** with an organocatalyzed [4+3] cycloaddition (Scheme 3-8).^[144] However, the moderate regioselectivity and enantioselectivity in the organocatalysis limited its further application compared to the other cycloaddition strategies.



Scheme 3-8. Lin's total synthesis of (+)-englerin A via [4+3] cycloaddition

Very recently, Mascareñas' group reported a total synthesis of (-)-englerin A based on platinum catalyzed [4+3] cycloaddition (Scheme 3-9).^[145] Similar to the englerin biogenesis pathway, the synthesis can be divided into a polycyclization process affording the guaiane moiety and a selective oxidation process. As shown in Scheme 3-9, enantioselective catalytic hydrogenation of the ynone **3.50** with Noyori's ruthenium catalyst **3.56** afforded the enantiomerically pure propargylic alcohol, which was cyclized into the guaiane core **3.52** with platinum catalysis in 71% yield. Late-stage sequential selective oxidation was achieved with potassium osmate and *L*-Shi-catalyst to afford the englerin scaffold **3.54** in 46% overall yield. With the central skeleton being effectively constructed, total synthesis of (-)-englerin A was completed after conventional transformations.



Scheme 3-9. Mascareñas' total synthesis of (-)-englerin A *via* [4+3] cycloaddition

Flowcharts of a selected examples of the syntheses are listed below, and Chain's synthesis represents the optimal that the majority of the transformations are the strategic C-C bonds or C-Hetero bonds formation, with the shortest LLS (8 steps) and the highest overall yield so far. Biomimetic approaches usually allow relatively shorter syntheses and higher efficiency due to nature itself adopt the most optimized strategy in biosynthesis. Inspired by nature's high efficiency, Christmann's and Mascareñas' syntheses were finished with more than 10% overall yields.

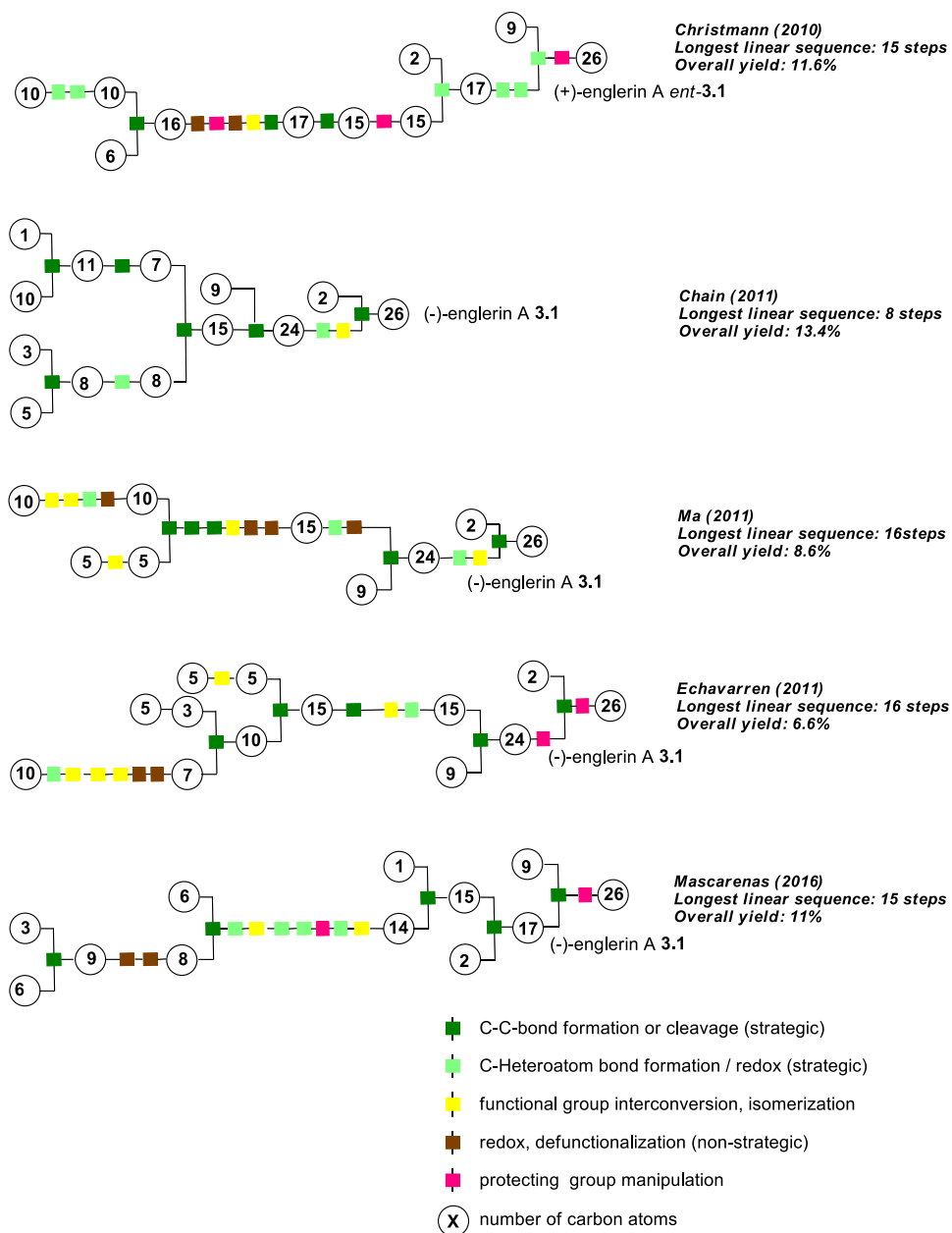
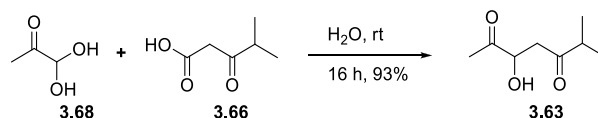


Figure 3-1. Step-efficiency analysis according to Christmann's method^[110]

compounds would allow for a short, straightforward modular total synthesis of englerins A and B.^[147]

The corresponding retrosynthetic analysis is illustrated in Scheme 3-10. Accordingly, simple later-stage transformations of **3.71** would provide the englerins, and alcohol **3.71** might be synthesized through a diastereoselective oxidation of **3.70**, which was envisaged to derive from a diastereoselective reductive Heck coupling reaction. Coupling precursor **3.69** could be prepared in a straightforward way from the β -ketone ester **3.62**. The oxabicyclo[3.2.1] heptane core-containing **3.62** might be furnished by an annulation between the 1,4-diketone **3.63** and methyl acetoacetate **3.64** (surrogate to 1,3-dianion **3.65**), which was inspired by tropinone's biogenesis. Obviously the α -hydroxyl-1,4-diketone **3.63** could be synthesized from methylglyoxal **3.68** and the enolate **3.67** *via* aldol reaction. Meanwhile, according to the biomimetic decarboxylative aldol chemistry utilizing MAHTs as enolate equivalents for stereoselective transformations, enantioselective synthesis of **3.63** should be possible between enolate **3.67**'s surrogate β -ketone acid **3.66** and methylglyoxal **3.68** if a polyketide synthase-type catalyst is applied.^[86a, 87]

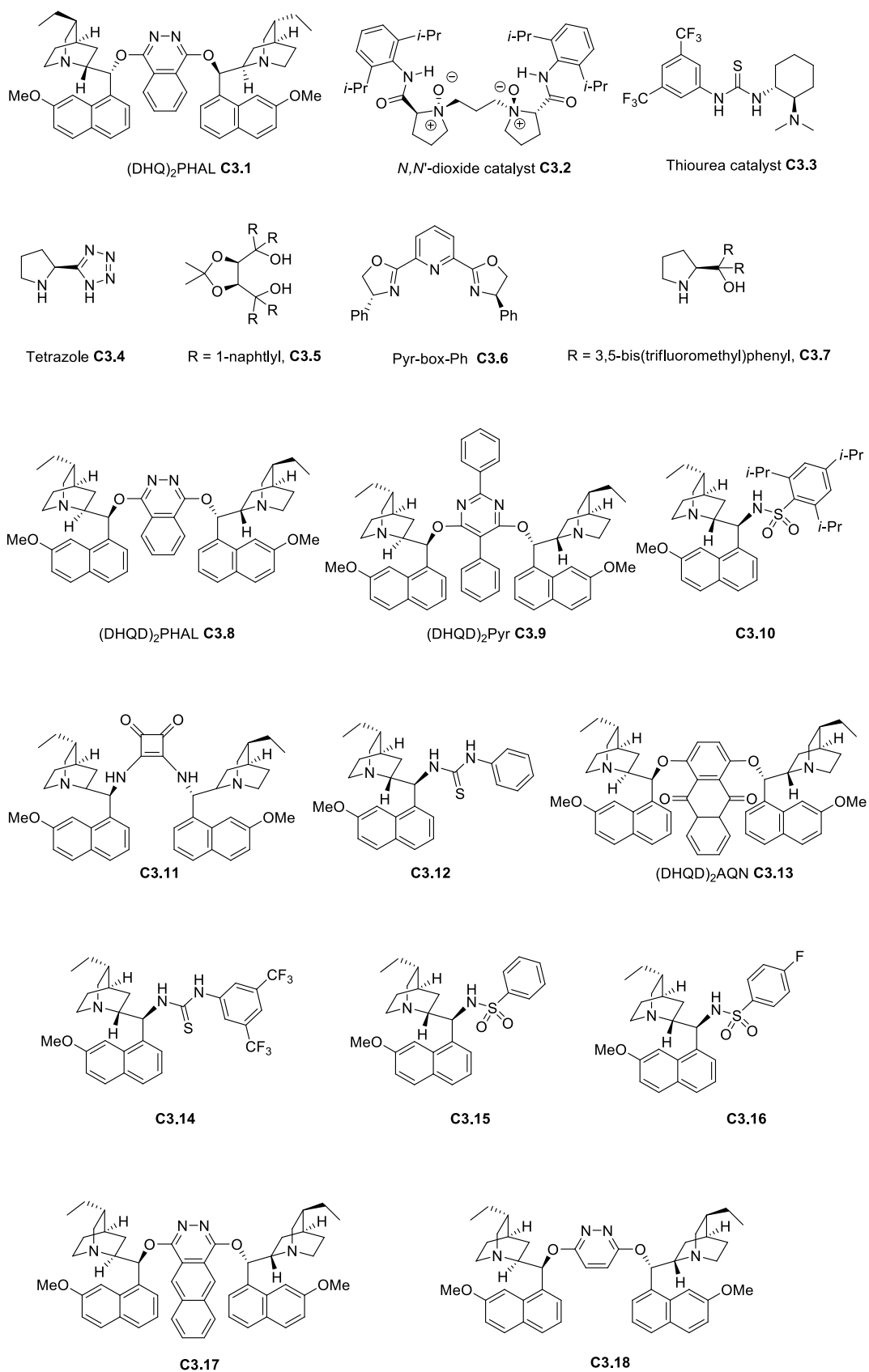
3.4. Bio-inspired Synthesis of Englerins A and B



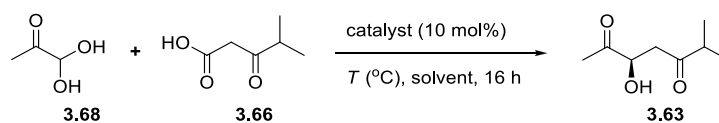
Scheme 3-11. Racemic decarboxylative aldol reaction

As discussed in the previous part, the project started with an aldol reaction between the β -ketone acid **3.66** and methylglyoxal **3.68**, and it was found that the reaction proceeded smoothly non-enantioselectively in water without any catalysts (base, acid, metal *etc.*) in 93% yield.^[148] For the enantioselective counterpart, a biomimetic, PKS-type catalyst is highly desired. However, as far as we know the substrate scope of this chemistry is rather limited^[149], and no protocol for stereoselective decarboxylative aldol reactions between the two desired substrates were reported. Therefore, we initiated to investigate the enantioselective transformation with chiral organocatalysts since methylglyoxal is only available in aqueous solution.

The catalysis was performed initially at -20 °C according to the control experiments (Table 3-1, entries 1-2), a primary catalysts screening (Table 3-1, Scheme 3-12) showed that the cinchona-type catalysts promoted this reaction at low temperature in organic solvents while other types of organocatalysts were inactive (Table 3-1, entries 3-10). Cinchona dimers, used for ligands as Os-catalyzed asymmetric dihydroxylations, were more effective than their corresponding monomers in improving the enantioselectivity (Table 3-1, entries 11-16). Cinchona monomers that provide additional hydrogen-bond interactions did not improve the enantioselectivity (Table 3-1, entries 15 and 17-19). Hence, it was postulated that the Brønsted-basic tertiary amines are the main catalytic reactive sites. Nevertheless, the linkers of cinchona dimers had a strong effect. A phthalazine linker was found to be superior to both anthraquinone and pyrimidine linkers (Table 3-1, entries 11, 12, 14 and 16), and yielded the aldol product in 79% yield and 51% *ee*. Considering the enolizable β -ketone acid and methylglyoxal hydrate are decent multiple hydrogen-bond donors, the two concurrent nitrogen atoms on the phthalazine linker might provide as additional hydrogen-bond acceptors. Therefore, a six-membered transition state was proposed with multiple hydrogen-bond interactions. When the phthalazine linker was combined with different cinchona alkaloids, a reversal in enantioselectivity was observed (Table 3-1, entries 3 and 11), which suggested the enantioselectivity was determined by the benzyl stereocenter. Similar to phthalazine, catalysts with “concurrent nitrogen atoms” linkers were tested and were found to have minor effects on the enantioselectivity (Table 3-1, entries 20 and 21). Furthermore, the reactivity of the catalyst was inhibited at lower temperatures and longer reaction times were required to reach a full conversion of β -ketone acid **3.66**. However, no significant improvement of enantioselectivity was possible (Table 3-1, entries 22-24). Nevertheless, a strong solvent effect was observed (Table 3-1, entries 28-32) after extensive solvent screening, and trifluoroethanol as co-solvent was found to increase of the enantiomeric excess slightly to 60% in 81% yield. Further attempts to increase the *ee* by increasing the catalyst loading did not provide encouraging results (Table 3-1, entries 34 and 35).

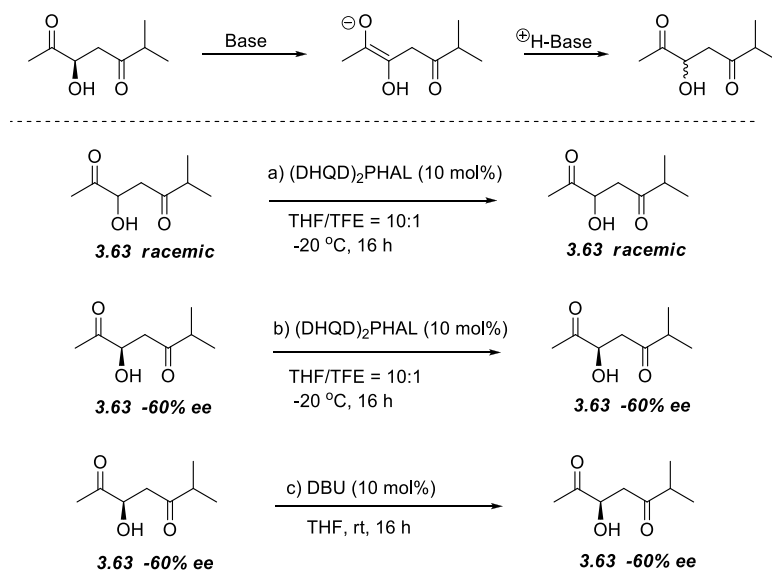


Scheme 3-12. Organocatalysts investigation for the aldol reaction

Table 3-1. Condition optimization and postulated transition state

Entry	Catalyst (10 mol%)	Temperature ($^\circ\text{C}$)	Solvent (0.1 M)	Yield (%) ^a	ee (%) ^b
1	---	0	THF	92	n.d.
2	---	-20	THF	0	n.d.
3	C3.1	-20	THF	79	51
4	C3.2	-20	THF	62	2
5	C3.3	-20	THF	18	0
6	C3.4	-20	THF	0	n.d.
8	C3.5	-20	THF	0	n.d.
9	C3.6	-20	THF	0	n.d.
10	C3.7	-20	THF	0	n.d.
11	C3.8	-20	THF	76	-52
12	C3.9	-20	THF	83	-24
13	C3.10	-20	THF	76	-20
14	C3.11	-20	THF	81	-19
15	C3.12	-20	THF	76	-27
16	C3.13	-20	THF	67	-28
17	C3.14	-20	THF	71	-18
18	C3.15	-20	THF	76	-27
19	C3.16	-20	THF	83	0
20	C3.17	-20	THF	68	-50
21	C3.18	-20	THF	72	-51
22 ^c	C3.8	-40	THF	76	-52
23 ^c	C3.8	-60	THF	66	-52
24 ^c	C3.8	-80	THF	71	-52
25	C3.8	-20	CH ₂ Cl ₂	56	-40
26	C3.8	-20	MeCN	56	-43
27	C3.8	-20	Toluene	0	n.d.
28	C3.8	-20	DME/MTBE = 3:1	71	-52
29	C3.8	-20	THF/TFE = 3:1	75	-60
30	C3.8	-20	THF/TFE = 10:1	81	-60
31	C3.8	-20	THF/TFE = 1:1	19	-60
32	C3.8	-20	THF/HFIP = 10:1	66	-47
33 ^c	C3.8	-40	THF/TFE = 10:1	82	-60
34 ^d	C3.8	-20	THF/TFE = 10:1	83	-60
35 ^e	C3.8	-20	THF/TFE = 10:1	85	-60

^a Isolated yield; ^b Enantiomeric excess was analyzed by chiral GC; ^c The reaction was stirred at the indicated temperature for 72 h. ^d Catalyst loading 20 mol%. ^e Catalyst loading 50 mol%.

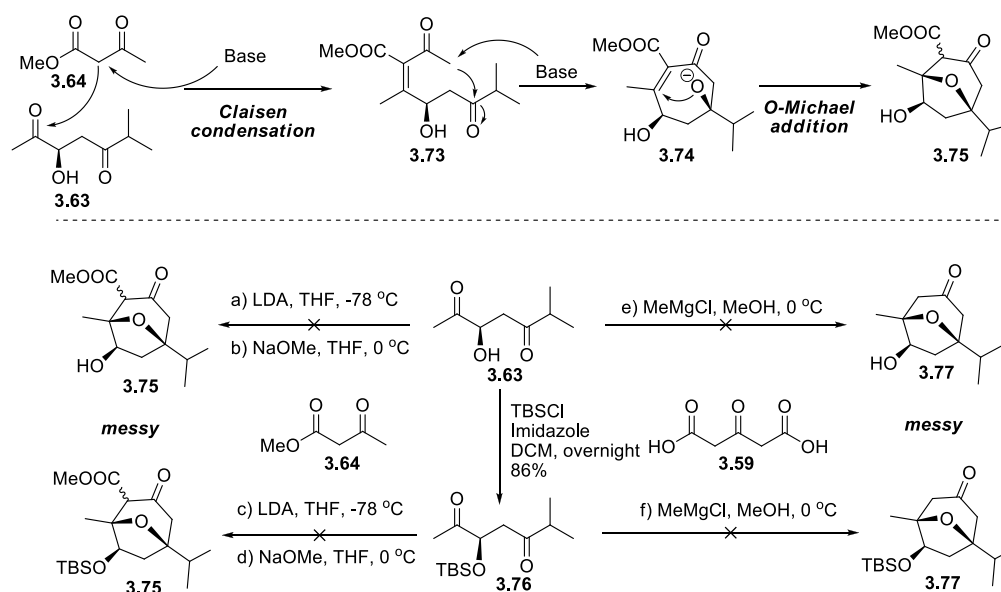


Scheme 3-13. Control experiments to investigate the basic stability of product

It is known that chiral α -hydroxyl ketones tend to racemize under basic conditions. Therefore control experiments were performed to test the enantiomeric stability of the product in the presence of catalytic amount of base (Scheme 3-13), and the results showed the aldol product is enantiomerically stable towards Brønsted base. Considering the fact that the facial discrimination imposed by the non-substituted β -ketone acid is not sufficient to achieve high enantiomeric excess and the asymmetric aldol chemistry of sterically non-demanding substrates is still an on going difficulty, we decided at this point to continue the synthesis with the enantiomerically enriched aldol product **3.63** (81% yield, -60% ee, 2.0 mmol scale) and to increase the enantiomeric purity in a late-stage transformation.

The bio-inspired annulation was then investigated to approach the oxabicyclo[3.2.1] heptane core. In Robinson's example, methylamine was used as an internal base while in our case an additional base was required for the dianion formation. Initial tests between **3.63** and methyl acetoacetate **3.64** with LDA or sodium methoxide as bases led to non-identified messy mixtures (Scheme 3-14, a and b), which implied the necessity to simplify the reaction system. However, same results were obtained when the free alcohol was protected with a TBS group **3.76** (Scheme 3-14, c and d). It was reasoned that the regio- and chemoselectivity could not be effectively controlled in the presence of multi-ketone components and the flexibility of both substrates led to a poor diastereoselectivity. The symmetric dianion-surrogate acetonedicarboxylic acid **3.59** was then considered as the

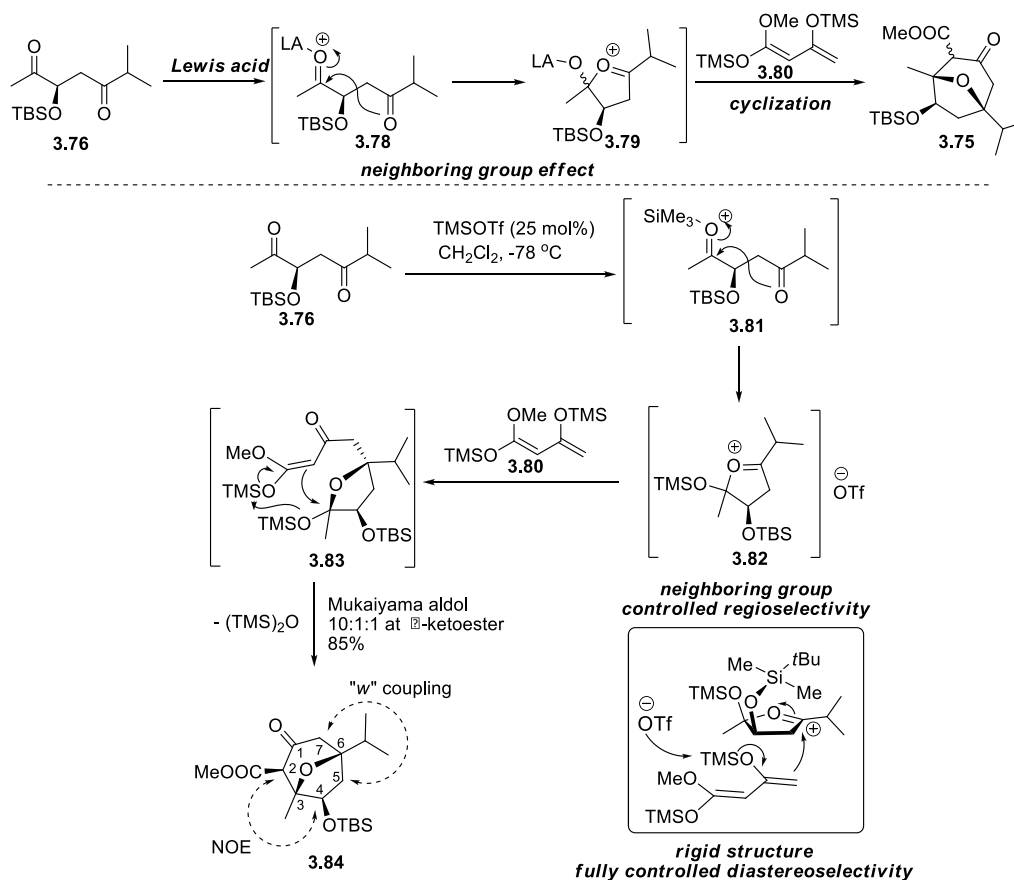
optimal substrate to avoid the non-productive regio- and chemoisomers. Actually, a similar transformation has been done in our lab for the syntheses of polyprenylated polycyclic acylphloroglucines.^[147, 150] The *in situ* formed magnesium might be utilized as a coordinating Lewis acid and to enable the diastereoselectivity control. Nevertheless, only decomposition occurred as the alcohol is sensitive towards acidic magnesium salts (Scheme 3-14, e and f).^[151]



Scheme 3-14. Bio-inspired annulation under basic conditions

The unproductive results above suggested that Lewis acid catalysis with pre-activated acetoacetate might be superior to base promoted dianion chemistry, as Lewis acid forces the 1,4-diketone to form a more rigid hemiketal intermediate **3.79** due to the neighboring group effect (Scheme 3-15). Hemiketal intermediate **3.79** may undergo highly regio- and diastereoselective cycloaddition with the pre-activated acetoacetate. Indeed, by following Molander's TMSOTf catalyzed [4+3] cycloaddition with 1,4-diketone **3.76** as electrophile towards *bis*-silylenolether **3.80**, the oxabicyclo[3.2.1] heptane core was obtained in an exclusively regioselective and diastereoselective fashion of the C-O bonds at C-3 and C-4 in 85% yield.^[152] Accordingly, the sterically less hindered ketone was silylated, which led to oxonium **3.81**. This oxonium species **3.81** was stabilized by the neighboring group stabilization of the adjacent ketone to afford hemiketal **3.82**. The bulky TBS silyl-ether thus shielded the top face of **3.82**, forcing the diene **3.80** to nucleophilic attack from the opposite side of the TBS silyl-ether to give the first C-C bond in **3.83** with desired relative configuration. Intramolecular Mukaiyama aldol reaction afforded **3.84** and its

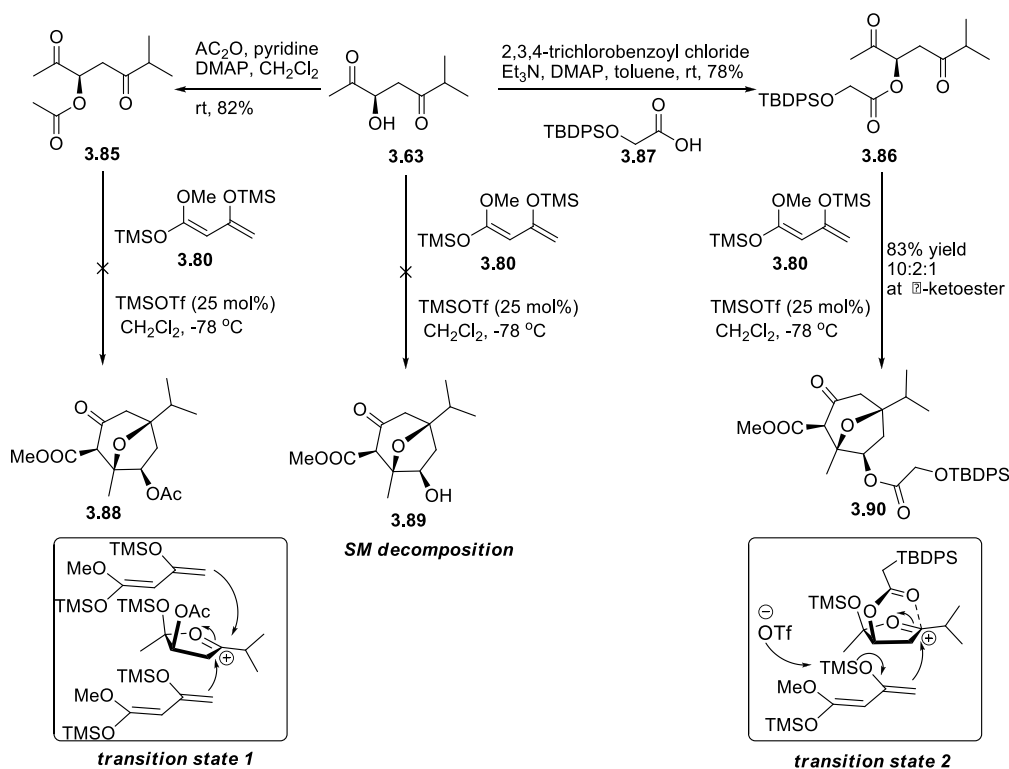
diastereomers at the β -ketoester position with 10:1:1 ratio. The structure of the major product **3.84** was fully characterized by NMR analyses.



Scheme 3-15. Lewis acid catalyzed cyclization under neighboring group effect control

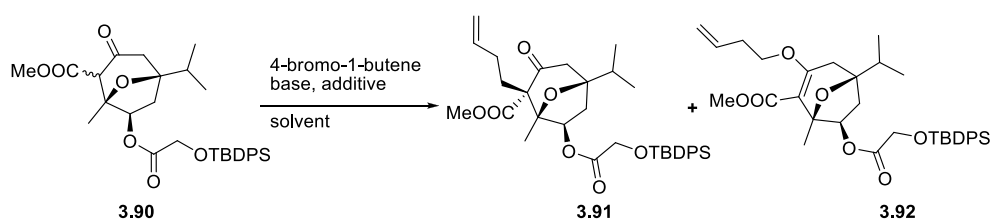
With regards to efficiency in total synthesis, the free alcohol **3.89**, acetate and glycolate protected oxabicyclo[3.2.1] heptane compounds **3.88** and **3.90** are better intermediates compared to the TBS-ether **3.84**, which needs trivial protecting group manipulations to afford the natural products. Therefore, acetate and glycolate compounds **3.85** and **3.86** were synthesized *via* esterification affording the product with 82% and 78% yield, respectively (Scheme 3-16). When the three available 1,4-diketones were subjected to the optimized [4+3] cycloaddition with *bis*-silylenolether **3.80**, the free alcohol **3.63** underwent decomposition due to its lability towards Lewis acids. Acetate **3.85** led to a non-identified messy mixture. Crude NMR analysis showed the acetate carbonyl group was involved in the reaction, as the singlet around 2.0 ppm was missing. Additionally, we postulated that the acetate group might not be bulky enough to shield the top face of the hemiketal, which led to poor diastereoselective control. Gratifyingly, glycolate **3.86** led to a clean reaction to the

desired products in 83% yield, which contains 3 diastereomers at the β -ketoester position with 10:2:1 ratio. The structure of **3.90** was fully characterized by NMR analysis. Additional transition state analysis indicated that except for the shielding effect of bulky TBDPS, the adjacent carbonyl group of glycolate further stabilizes the cyclic oxonium species to improve diastereoselective control (Scheme 3-16).



Scheme 3-16. Protecting group screening in TMSOTf catalyzed [4+3] cycloaddition

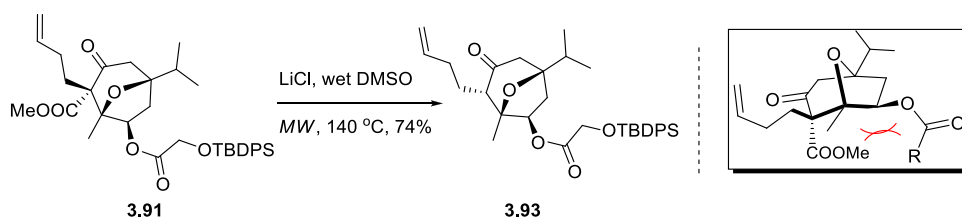
With the fully characterized bicyclic heptane **3.90** in hand, we turned to explore the feasibility of the cyclopentane structure construction. Metal bases and the additive were found to influence the *C*- or *O*-alkylation of β -ketoester **3.90** dramatically (Table 3-2). Among different metal bases, sodium or potassium carbonate led to *O*-alkylation exclusively (Table 3-2, entry 1-2), while cesium carbonate was found to give a mixture of *C*- and *O*-alkylated products in 1:1 ratio (Table 3-2, entry 3). Even though lithium-HMDS gave *O*-alkylated product initially (Table 3-2, entry 4), the addition of 2 equivalents of DMPU was found to reverse the selectivity towards the *C*-alkylated product **3.91** in 86% yield, with *O*-alkylated product **3.92** obtained as a minor product in 5% yield (Table 3-2, entry 5).

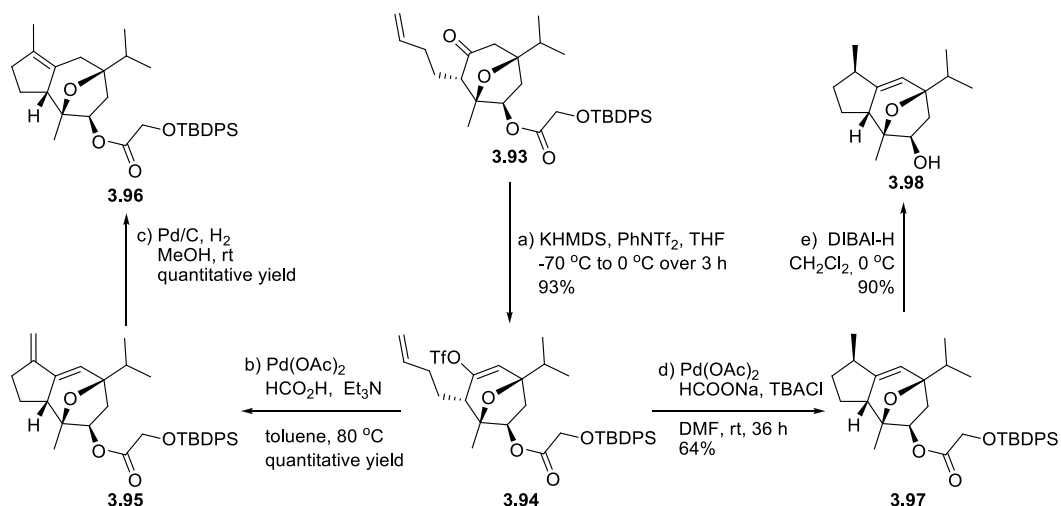
Table 3-2. Alkylation investigations

Entry	Base	Additive	Solvent ^a	C-yield ^b /%	O-yield ^b /%
1 ^c	NaH	---	THF	n.d.	74
2 ^d	K ₂ CO ₃	---	CH ₃ CN	n.d.	96
3 ^d	Cs ₂ CO ₃	---	CH ₃ CN	42	46
4 ^e	LiHMDS	---	THF	10	81
5 ^e	LiHMDS	DMPU (2.0 eq.)	THF	86	5

^a c = 0.3 M; ^b Isolated yield; ^c temperature: 25 °C; ^d refluxing in CH₃CN; ^e temperature: -78 °C.

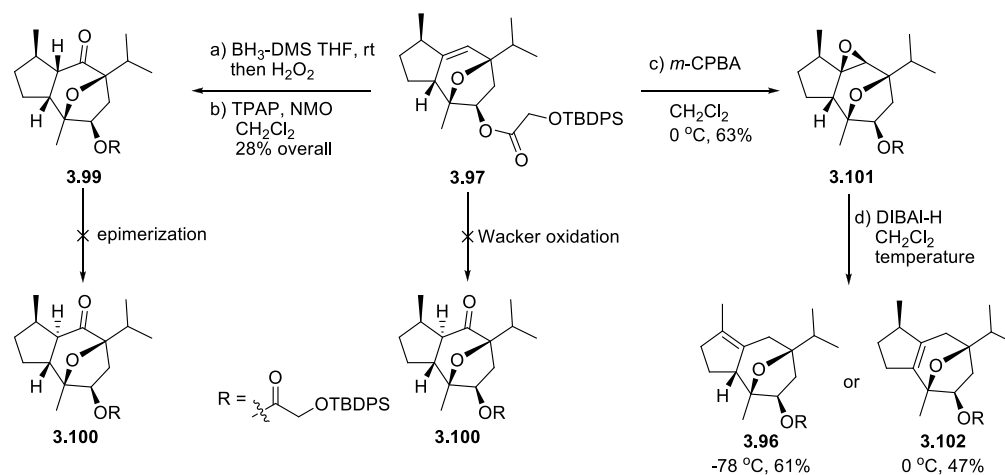
The following decarboxylation was attempted by ester hydrolysis with lithium hydroxide in refluxing THF/H₂O, however the hydrolysis was fruitless with 100% starting material recovered. The 3D structure of **3.91** indicated that the methyl ester was pushed into the “concave face” of the bicyclic system after alkylation, and the approach of this methyl ester was difficult in gentle hydrolysis conditions (Scheme 3-17). Consequently, Krapcho decarboxylation was performed at 150 °C and trace amounts of decarboxylated **3.93** were detected. As the starting material or product might not be thermally stable, microwave irradiation was thought to accelerate the decarboxylation.^[153] To our delight irradiation of the reaction mixture in the microwave for 1 h led to the formation of the decarboxylated product **3.93** with reversed C-2 configuration during the quenching process.

**Scheme 3-17.** Decarboxylation investigations



Scheme 3-18. Cyclopentane moiety construction

The formation of compound **3.93** set the stage for the synthesis of the coupling precursor, which was performed *via* regioselective deprotonation at $-78\text{ }^\circ\text{C}$ with KHMDs , followed by quenching of the resulting enolate with trifluoromethanesulfonimide to give the enol-triflate **3.94** in 93% yield (Scheme 3-18a). The temperature had to be strictly held at $-78\text{ }^\circ\text{C}$ for one hour and then warmed up to $0\text{ }^\circ\text{C}$ over three hours to avoid enolate exchange to its thermally stable regioisomer. The subsequently desired diastereoselective reductive Heck reaction was performed under standard conditions with formic acid as hydride donor, but a clean formation of Heck product **3.95** in quantitative yield was observed (Scheme 3-18b). Attempts to hydrogenate the 1,3-diene chemo- and diastereoselectively at the 1,2-position resulted in a 1,4-reduced *tetra*-substituted olefin **3.96** due to its thermal stability (Scheme 3-18c). Finally, Cook's gentle reductive Heck condition at room temperature (to inhibit the competitive intramolecular β -hydride elimination) afforded the reductive Heck product **3.97** in 64% yield (3-18d),^[154] and the configuration of the newly formed stereocenter was confirmed as the desired one since the structurally similar alcohol **3.98** is literature-known.^[140]

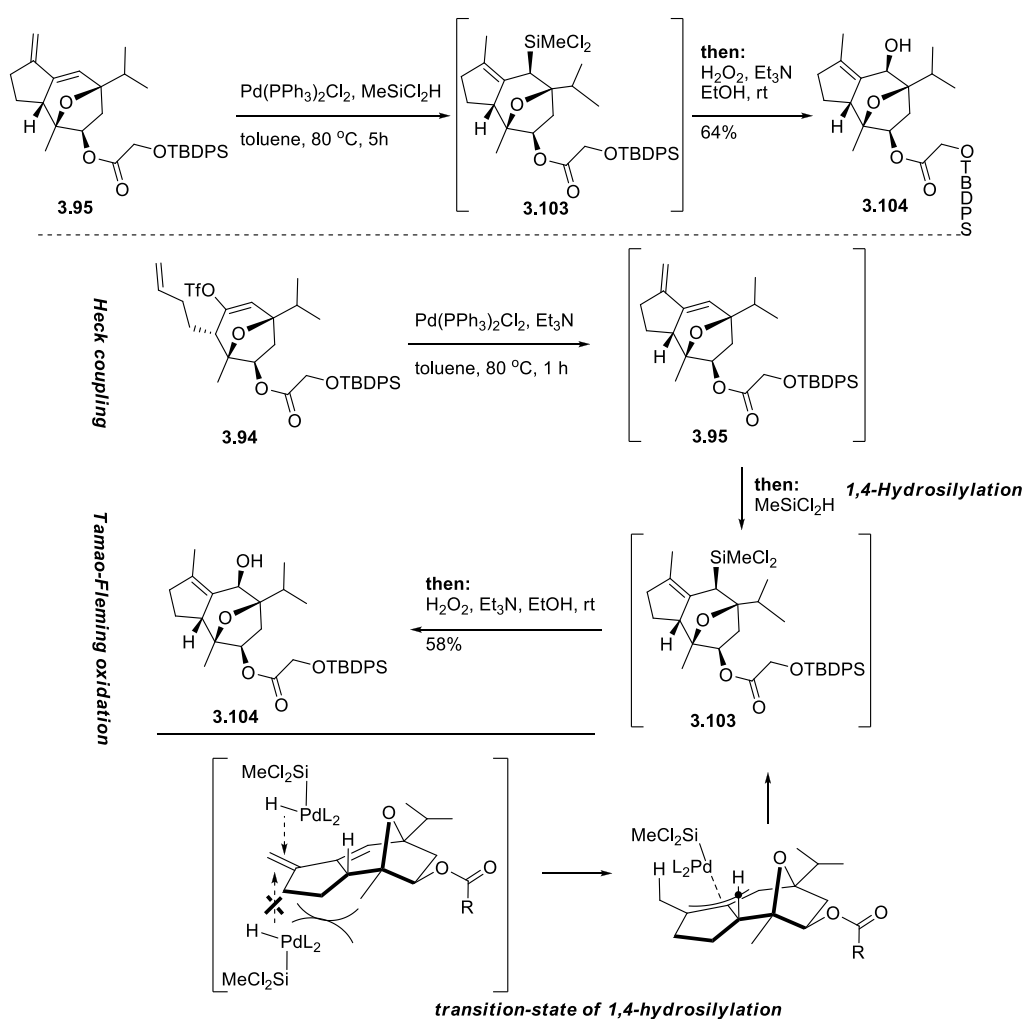


Scheme 3-19. Attempts on olefin diastereoselective oxidation

The reductive Heck product **3.97** was then subjected to a diastereoselective olefin oxidation to construct the *trans*-fused core. Wacker oxidation led to starting material recovery only, while hydroboration-oxidation sequence was exclusively convex face selective (Scheme 3-19a). When a bulky, soft Lewis acid (TBSOTf) was used to coordinate to the oxygen bridge to shield the convex face in the hydroboration, only decomposition occurred due to oxygen bridge disconnection. The hydroboration-oxidation product was further oxidized *via* Ley oxidation (Scheme 3-19b) and the *cis*-fused compound **3.99** was isolated as the only product in 28% combined yield. Attempts to epimerize the α -ketone proton with bases (DBU, LDA TMSOTf+Et₃N) did not afford any promising results due to the thermal stability of the *cis*-fused scaffold. Further epoxidation of **3.97** was convex face selective to give the epoxide **3.101** in moderate yield (Scheme 3-19c). The following epoxide opening with hydride (Scheme 3-19d) was temperature sensitive, reduction at -78 °C led to epoxide opening and simultaneous *trans*-elimination to the *tetra*-substituted olefin **3.96** in 81% yield. Epoxide opening with *cis*-elimination to **3.102** was observed when DIBAL-H was added at 0 °C, which indicated the existence of a carbon cation intermediate during the latter elimination process.

Inspired by the tendency of *tetra*-substituted olefin formation (Scheme 3-18c, Scheme 3-19d), we envisioned a similar 1,4-functionalization of diene **3.95** might introduce the hydroxyl group in **3.104**, and the *tetra*-substituted double bond could be reduced by diastereoselective hydrogenation (Scheme 3-20). Selective 1,4-hydroboration-oxidation sequence with simple borane BH_3 or 9-BBN led to messy mixtures due to their high reactivity, while palladium catalyzed hydrosilylation with dichloromethylsilane as hydride

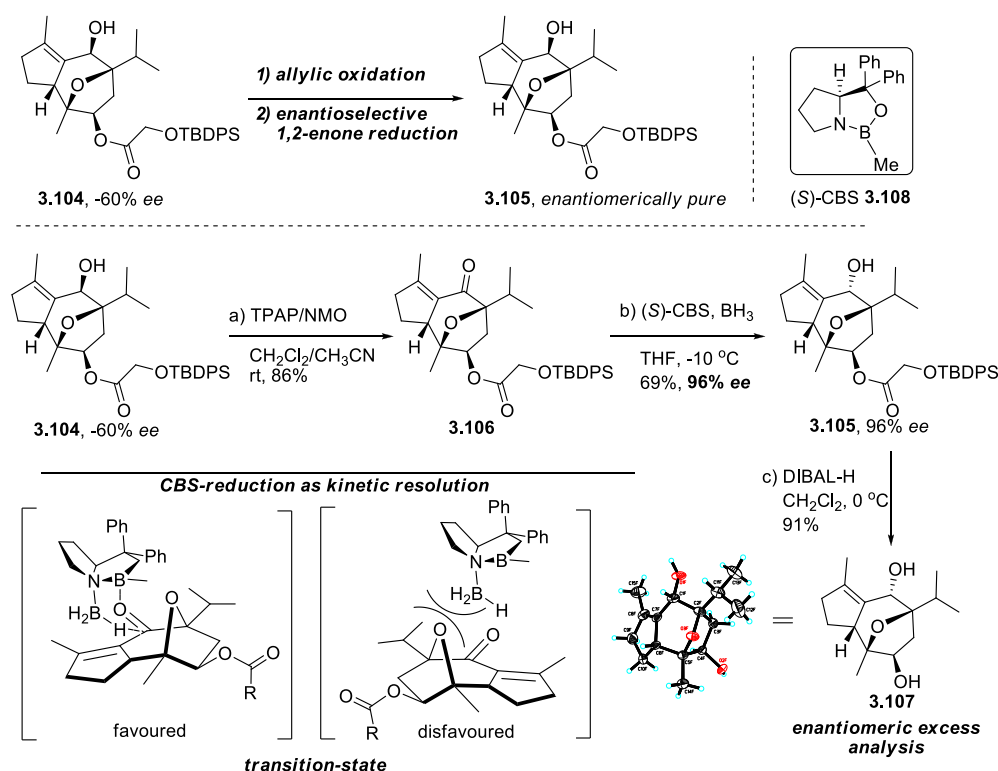
donor provided the desired allylsilane **3.103**, which was converted to the alcohol **3.104** in 64% yield after oxidative work-up (Scheme 3-20).^[155] The highly regio- and diastereoselective control can be explained through the palladium species approach the diene **3.95** from the less hindered convex face, while the hydride being transferred to the least hindered exocyclic olefin (Scheme 3-20). Oxidative work-up *via* Tamao-Fleming oxidation resulted in clean oxidation of the allylic silane **3.103** to give the corresponding allylic alcohol **3.104** with retention of the configuration. Additionally, it was found that the two palladium catalyzed transformations could be done one-pot with Pd(PPh₃)₂Cl₂ as catalyst by adding the reagents sequentially. After oxidative work-up the allylic alcohol **3.104** could be isolated with 58% overall yield from enol-triflate **3.94**.



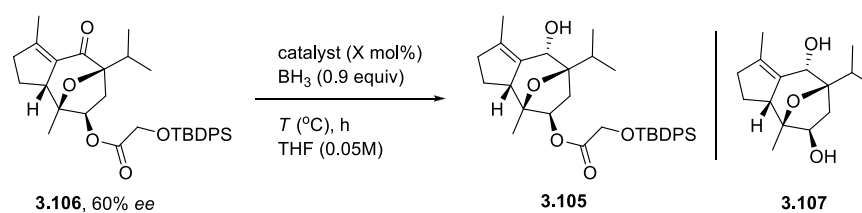
Scheme 3-20. Palladium-catalyzed Heck-1,4-hydrosilylation sequence

In order to obtain alcohol **3.105** with the correct relative configuration, the oxidation-reduction sequence was envisioned as a suitable strategy (Scheme 3-21). Considering that

until this point the synthesis was done using material with 60% enantiomeric excess, we were hoping to increase the enantiopurity through the use of enantioselective transformation. Allylic alcohol **3.104** was inactive with freshly made MnO_2 or DMP as well as iron-catalyzed aerobic oxidation. Following to Ma's report^[140], Ley oxidation was used to give the enone **3.106** with 86% yield. Corey-Bakshi-Shibata reduction with catalytic amounts of chiral oxazaborolidine **3.108** is widely known for its enantioselective ketone reduction and could be used for kinetic resolution in our case.^[156] Indeed, we were delighted to find that when (*S*)-CBS catalyst **3.108** was used under the optimized conditions, the reaction proceeded very fast at $-10\text{ }^\circ\text{C}$ in 69% yield and 96% enantiomeric excess (*ee*) with the desired concave face alcohol installed. Detailed conditions optimization can be found in Table 3-3. The unfavorable steric repulsions between the catalyst and the undesired enantiomer's oxygen bridge and isopropyl group might lead to the kinetic resolution. The enantiomeric excess was analyzed on **3.107** (Scheme 3-21c), and its absolute configuration was unambiguously confirmed by X-ray analysis. Interestingly, 6 independent conformers were detected in each unit cell (see experimental section). Meanwhile, the enantiomeric excess of **3.107** directly derived from **3.106** was analyzed as 60%, which indicated that no enantiomeric excess erosion occurred before this step.



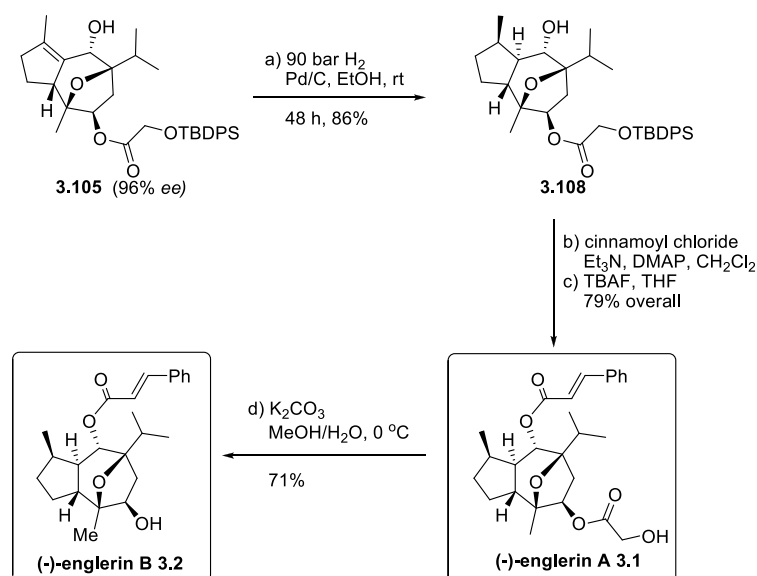
Scheme 3-21. Alcohol configuration inversion and enantiomeric purity improvement

Table 3-3. Optimization of enantioselective CBS reduction

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%) ^a	<i>ee</i> (%) ^b
1	(<i>R</i>)-CBS (20)	0	3	66	43
2	(<i>S</i>)-CBS (20)	0	3	83	76
3	(<i>S</i>)-CBS (20)	0	1	81	84
4	(<i>S</i>)-CBS (20)	-10	1	69	91
5	(<i>S</i>)-CBS (30)	-10	1	69	96
6	(<i>S</i>)-CBS (30)	-20	1	29	96
7	(<i>S</i>)-CBS (40)	-10	1	70	96

^a Isolated yield; ^b Enantiomeric excess was analyzed on compound **3.107** via chiral GC.

By effective discrimination of two enantiomers' reactivity as well as by installing the desired stereocenter with excellent diastereoselectivity, we set out for the diastereoselective hydrogenation of the *tetra*-substituted double bond under high pressure (Scheme 3-22). Allylic alcohols are known as good directing groups for diastereoselective hydrogenation from the sterically less favored face, therefore homogeneous catalysts were chosen for this selective hydrogenation. However, neither Wilkinson's catalyst nor Crabtree's catalyst led to the detectable amounts of reduced product under high pressure. The heterogeneous catalysts PtO₂, Pd/C were tested and Pd/C was found to give the hydrogenated product **3.108** with the desired diastereoselectivity in 86% yield. This result further proved that alcohols can be used as directing group for heterogeneous catalysts as well. Esterification and deprotection sequence eventually provided englerin A **3.1** in 79% yield over two steps. Optical rotation analysis as well as X-ray crystallographic structure of **3.107** confirmed our sample to be identical to natural (-)-englerin A. Selective hydrolysis of the more reactive glycolic ester moiety gave (-)-englerin B **3.2** in 71% yield.



Scheme 3-22. Synthesis of (-)-englerins A and B

In summary, a novel synthesis of the anti-tumor active compound (-)-englerins was developed. This protocol featuring an organocatalyzed enantioselective decarboxylative aldol reaction, a bio-inspired, Lewis acid catalyzed [4+3] cycloaddition of β -ketoester-derived *bis*-silylenolether to a 1,4-diketone and a sequential Pd-catalyzed Heck-reaction-1,4-hydrosilylation-Tamao-Fleming-oxidation. The state-of-the-art catalytic methodologies allowed a highly efficient and enantioselective synthesis, which can also be used as the starting point for the synthesis of various englerin analogues for further structure-activity relationship research.

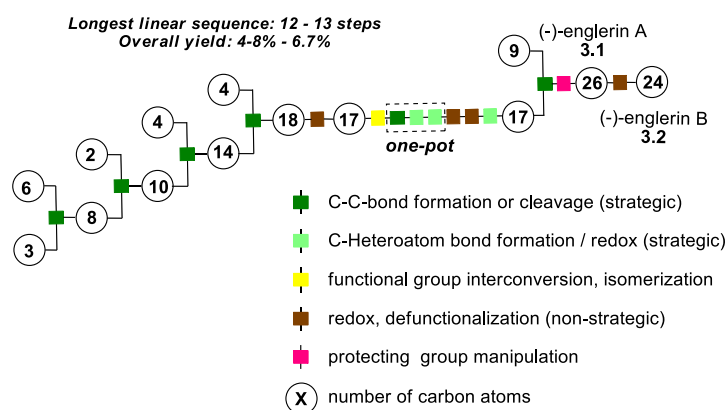


Figure 3-2. Step-efficiency analysis according to Christmann's method^[110]

3.5. Conclusion and Outlook

In this part, we highlighted the state-of-the-art chemical transformations that are inspired from classical chemistry, which allowed the conceptually novel 12-step total synthesis of the anti-tumor active natural products (-)-englerin A and (-)-englerin B. The synthesis featured an organocatalyzed enantioselective decarboxylative aldol reaction which was inspired by the polyketide biogenesis. A [4+3] cycloaddition of β -ketoester-derived *bis*-silylenoether to a 1,4-diketone was employed for the construction of the bicyclic[3.2.1] heptane core. A sequential Pd-catalyzed Heck-reaction-1,4-hydrosilylation-Tamao-Fleming-oxidation afforded the cyclopentane moiety, while kinetic resolution with a CBS reduction step allowed us to obtain the desired product with 96% enantiomeric excess. The synthesis based on the initial catalytic aldol reaction sets the stage to enrich englerin A library and to study the structure-activity relationships, which is significantly important for further anti-tumor entities as well as potential target investigation.

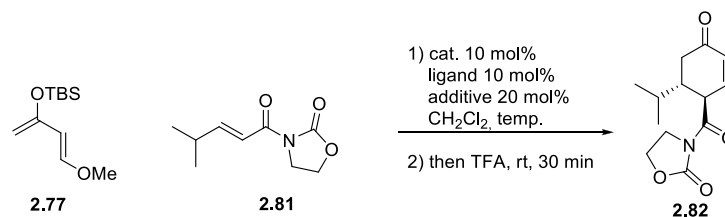
II. Experimental Section

1. General Remarks

All the reactions, which were sensitive to air or moisture were performed under dry nitrogen using standard Schlenk techniques. All solvents were purified prior to use. All chemicals were purchased from Acros Organics, Sigma Aldrich, TCI or Alfa Aesar. NMR spectra were recorded on a Bruker AV 300 spectrometer at 300 MHz (^1H -NMR), 75 MHz (^{13}C -NMR), a Bruker AV 400 spectrometer at 400 MHz (^1H NMR), 100 MHz (^{13}C -NMR), a Bruker AV 500 spectrometer at 500 MHz (^1H NMR), 125 MHz (^{13}C -NMR), or a Bruker AV 700 spectrometer at 700 MHz (^1H NMR), 175 MHz (^{13}C NMR). Chemical shifts were reported in ppm down field using tetramethylsilane as internal standards. IR spectra were measured on a Bruker Vector 22 FT-IR spectrometer in an ART mode. Mass spectra were measured using electrospray ionization on a Bruker Micro-TOF-Q. High performance liquid chromatography (HPLC) was performed using a Knauer K-501 pump, Knauer RI-detector K 2400 and a Macherey-Nagel VP250/21 Nucleodur 100-5 column. Analytical chiral HPLC was performed using a HP series 1050 HPLC module and a Daciel Chiralpak AD-H 250*4.6 mm column. ECD measurements were performed using a JASCO J-815 Circular Dichroism Spectrometer.

2. Experimental Details in Picrotoxane Alkaloids Synthesis

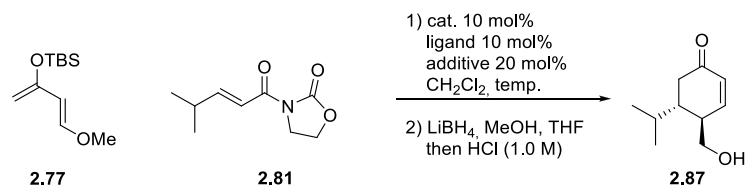
Enantioselective Diels-Alder reaction



To a flame dried schlenk flask with a stirring bar, Yb(OTf)₃ (55.8 mg, 0.09 mmol, 0.1 equiv) and (*R*)-BINUERA **L2-4** (52.2 mg, 0.09 mmol, 0.1 equiv) ligand were charged, then the schlenk flask was heated at 120 °C under reduced pressure (<0.1 mbar) for 2 h, and then cooled down to room temperature under nitrogen. 3 mL DCM was added followed with DBU (0.027 mL, 0.18 mmol, 0.2 equiv), and the resulting solution was stirred at room temperature for 2 h. At this time, the clear colorless solution turned to a faint yellow solution, and the mixture was cooled down to 0 °C and a solution of the dienophile **2.81** (164.7 mg, 0.9 mmol, 1.0 equiv) in 1.5 mL DCM was added followed with freshly prepared diene **2.77** (385.2 mg, 1.8 mmol, 2.0 equiv) drop wise. The schlenk flask was sealed, stirred for 3 h at 0 °C. After the starting dienophile **2.81** was consumed completely, the mixture was quenched with TFA (0.5 mL) at 0 °C. After stirring for additional 30 min at room temperature, the reaction was diluted by 10 mL saturated NaHCO₃ aqueous solution. The aqueous layer was extracted three times with DCM (3*20 mL). The combined organic layers were washed with brine (3*10 mL), dried over Na₂SO₄, concentrated under reduced pressure gave the crude product as faint yellow oil. The crude product was purified by column chromatography (PE/EtOAc = 2:1) gave the oxazolidinone **2.82** as faint yellow solid (176 mg, 0.69 mmol, 78% yield).

Compound (-)-2.82: ¹H NMR (400 MHz, CDCl₃): δ 6.70 (dd, *J* = 10.12, 2.99 Hz, 1 *H*), 6.10 (dd, *J* = 10.12, 2.62 Hz, 1 *H*), 4.83 – 4.86 (m, 1 *H*), 4.48 (t, *J* = 7.97 Hz, 2 *H*), 4.01 (t, *J* = 8.08 Hz, 2 *H*), 2.60 (dd, *J* = 15.61, 4.20 Hz, 1 *H*), 2.52 – 2.57 (m, 1 *H*), 2.26 - 2.33 (m, 1 *H*), 1.67 – 1.73 (m, 1 *H*), 0.95 (d, *J* = 6.85 Hz, 3 *H*), 0.88 (d, *J* = 6.85 Hz, 3 *H*) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 198.9, 172.1, 153.2, 145.0, 130.6, 62.1, 44.5, 42.9, 42.5, 37.1, 29.7, 20.7, 17.7 ppm; IR (film): ν 2960 (s), 2929 (w), 1770 (s), 1674 (s), 1385 (s), 1370 (s), 1219 (s), 1112 (s), 1039 (s),

758 (s), 705 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{13}\text{H}_{17}\text{NO}_4\text{Na}^+$: 274.1050, found: 274.1031; **M.p.** 92 °C; $[\alpha]_{\text{D}}^{25}$ -29.0 (c 1.3, CHCl_3 , 91% *ee*).

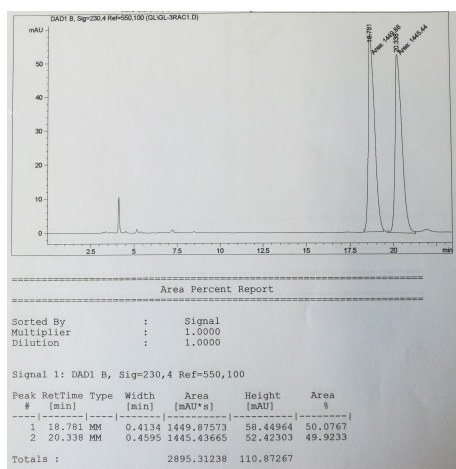
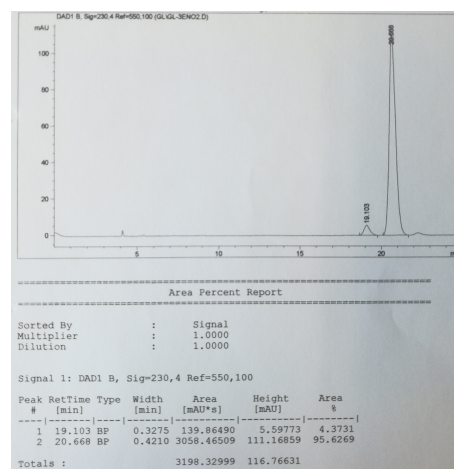


The Diels-Alder reaction was performed according to the same procedure above. The reaction was quenched with 5 mL water when the dienophile **2.81** was consumed completely. The aqueous layer was extracted three times with DCM (3*20 mL). The combined organic layers were washed with brine (3*10 mL), dried over Na_2SO_4 , concentrated under reduced pressure gave the crude product **2.86** as faint yellow oil. The crude product **2.86** was labile and used directly without further purification.

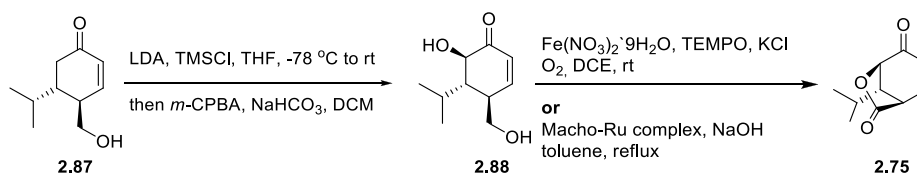
To a solution of the crude product **2.86** in THF (9 mL) was added MeOH (0.1 mL, 2.7 mmol, 3.0 equiv) and LiBH_4 solution (2.0 M, 1.35 mL, 2.7 mmol, 3.0 equiv) drop wise at 0 °C. The mixture was stirred for 1 h at room temperature, then the reaction was cooled down to 0 °C, quenched by addition of 10 mL 1N HCl drop wise. The mixture was stirred for additional 30 min at this temperature, and the aqueous layer was extracted three times with DCM (3*20 mL). The combined organic layers were washed with brine (3*10 mL), dried over Na_2SO_4 , concentrated under reduced pressure gave the crude product as faint yellow oil. The crude product was purified by column chromatography (PE/EtOAc = 3:1) gave the alcohol **2.87** as faint yellow oil (112 mg, 0.67 mmol, 74% yield). The enantio excess was determined by chiral HPLC as 91% *ee*.

Compound (-)-28.6: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.99 (dd, $J = 10.17, 2.87$ Hz, 1 *H*), 6.05 (dd, $J = 10.13, 1.87$ Hz, 1 *H*), 3.89 (dd, $J = 10.64, 4.52$ Hz, 1 *H*), 3.71 (dd, $J = 10.62, 6.13$ Hz, 1 *H*), 2.54 – 2.49 (m, 1 *H*), 2.47 (dd, $J = 16.28, 4.05$ Hz, 1 *H*), 2.23 (dd, $J = 16.20, 11.23$ Hz, 1 *H*), 2.04 – 1.91 (m, 3 *H*), 0.93 (d, $J = 6.80$ Hz, 3 *H*), 0.86 (d, $J = 6.76$ Hz, 3 *H*) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 200.5, 152.3, 130.0, 63.0, 41.6, 41.4, 36.8, 27.8, 20.8, 16.9 ppm; **IR** (film): ν 3422 (w), 2959 (s), 1666 (s), 1391 (s), 1261 (s), 1081 (s), 840 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{10}\text{H}_{16}\text{O}_2\text{Na}^+$: 191.1043, found: 191.1041; $[\alpha]_{\text{D}}^{25}$ -76.8 (c 1.6, CHCl_3 , 91% *ee*); **Daicel Chiralcel AD-H**, hexane/*i*-PrOH = 95/5, $f = 1.0$ mL/min, 230.4 nm, retention time: 19.1 min (minor) and 20.6 min (major).

HPLC Spectrums:

(±)-compound 28.6**(-)-compound 28.6**

Lactone core synthesis



To a flame dried flask with a stirring bar, a solution of the substrate **2.87** (168 mg, 1.0 mmol, 1.0 equiv) in THF (2 ml) was charged under nitrogen. The flask was cooled down to -78 °C, then a solution of LDA in THF [freshly prepared by treating a solution of *i*Pr₂NH (0.32 mL, 2.3 mmol, 2.3 equiv) in THF (8 mL) with *n*BuLi (1.6M in THF, 1.4 mL, 2.2 mmol, 2.2 equiv) under -78 °C and then stirred at 0 °C for 15 min] was added drop wise at this temperature. The faint yellow mixture was stirred at -78 °C for 30 min followed by addition of TMSCl (0.3 mL, 2.4 mmol, 2.4 equiv) drop wise. This mixture was warmed to room temperature and stirred for 2 h, and then quenched with saturated NaHCO₃ aqueous solution. The aqueous layer was extracted with diethyl ether (3*20 mL), the combined organic layers were washed with brine (3*10 mL), dried over Na₂SO₄, concentrated under reduced pressure gave the crude enolate product as faint yellow oil. The crude enolate product was dissolved in 5 mL DCM, and then NaHCO₃ (117.6 mg, 1.4 mmol, 1.4 equiv) was added at 0 °C followed by *m*-CPBA (75%, 276 mg, 1.2 mmol, 1.2 equiv) in one portion. The mixture was stirred for 30 min at room temperature, and then quenched with saturated Na₂S₂O₃ solution. The aqueous

layer was extracted with DCM (3*20 mL), the combined organic layers were washed with HCl (2*N*, 3*20 mL) and brine (3*10 mL), dried over Na₂SO₄, concentrated under reduced pressure gave the crude product as faint yellow oil. The crude product was purified by column chromatography (PE/EtOAc = 2:1) gave the diol product **2.88** as faint yellow oil (150.9 mg, 0.82 mmol, 82% yield).

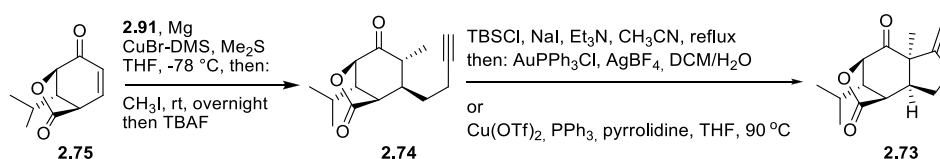
Compound (+)-2.88: ¹H NMR (400 MHz, CDCl₃): δ 7.03 (dd, *J* = 10.12, 2.41 Hz, 1 *H*), 6.18 (dd, *J* = 10.12, 2.76 Hz, 1 *H*), 4.15 (d, *J* = 12.14 Hz, 1 *H*), 3.95 (dd, *J* = 10.73, 3.49 Hz, 1 *H*), 3.72 (dd, *J* = 10.66, 6.23 Hz, 1 *H*), 2.59 – 2.54 (m, 1 *H*), 2.17 – 2.10 (m, 1 *H*), 1.93 (ddd, *J* = 11.97, 9.88, 1.55, 1 *H*), 1.55 (br s, 2 *H*), 1.14 (d, *J* = 7.13 Hz, 3 *H*), 1.10 (d, *J* = 7.04 Hz, 3 *H*) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 153.4, 126.5, 73.7, 63.8, 48.3, 42.2, 27.9, 21.5, 18.2 ppm; IR (film): ν 3422 (w), 2957 (s), 2875 (s), 1680 (s), 1247 (s), 1031 (s), 786 (s) cm⁻¹; MS (ESI) calculated for C₁₀H₁₆O₃Na⁺: 207.0992, found: 207.0987; [α]_D²⁵ +11.6 (c 2.3, CHCl₃, 91% *ee*).

Lactonization method I with Fe-catalysis: to a flask charged with stirring bar were added Fe(NO₃)₃·9H₂O (20.2 mg, 0.05 mmol, 5 mol% equiv), TEMPO (7.8 mg, 0.05 mmol, 5 mol% equiv), KCl (7.5 mg, 0.1 mmol, 10 mol% equiv), the diol substrate **2.88** (184 mg, 1.0 mmol, 1.0 equiv) and 10 mL 1,2-dichloroethane successively, then the mixture was bubbled with a balloon of oxygen for 5 min. The mixture was stirred under this balloon of oxygen at room temperature overnight, and with TLC monitored the reaction progress. After the substrate was consumed completely, the mixture was loaded to a pad of Celite to remove insoluble materials (eluted with EtOAc). The organic layer was concentrated gave a brown yellow residue, which was purified by column chromatography (PE/EtOAc = 15:1) gave the lactone product **2.75** as faint yellow oil (160.2 mg, 0.89 mmol, 89% yield).

Lactonization method II with Ru-catalysis: to a flask charged with stirring bar were added Macho-Ru complex (60.7 mg, 0.1 mmol, 10 mol% equiv), NaOH (8.0 mg, 0.2 mmol, 20 mol% equiv), the diol substrate **2.88** (184 mg, 1.0 mmol, 1.0 equiv) and 10 mL anhydrous toluene successively. The mixture was stirred under reflux for 6 h until the substrate was consumed completely. The mixture was loaded to a pad of Celite to remove insoluble materials (eluted with EtOAc). The organic layer was concentrated gave a brown yellow residue, which was purified by column chromatography (PE/EtOAc = 15:1) gave the lactone product **2.75** as faint yellow oil (93.6 mg, 0.52 mmol, 52% yield).

Compound (-)-2.75: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.10 (ddd, $J = 9.19, 7.15, 1.81$ Hz, 1 H), 6.20 (dd, $J = 9.66, 1.54$ Hz, 1 H), 4.67 (d, $J = 5.16$ Hz, 1 H), 3.31 (dd, $J = 7.02, 4.03$ Hz, 1 H), 2.74 – 2.69 (m, 1 H), 1.88 – 1.79 (m, 1 H), 0.97 (d, $J = 6.62$ Hz, 3 H), 0.93 (d, $J = 6.58$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 190.3, 173.2, 142.7, 130.2, 84.4, 60.0, 43.9, 23.9, 21.3, 19.6 ppm; IR (film): ν 2962(s), 2875 (w), 1790 (s), 1699 (s), 1124 (s), 989 (s), 953 (s), 881 (d) cm^{-1} ; MS (ESI) calculated for $\text{C}_{10}\text{H}_{12}\text{O}_3^+$: 180.0786, found: 180.0783; $[\alpha]_D^{25}$ -248.6 (c 2.6, CHCl_3 , 91% ee).

Cyclopentane moiety construction



To a flame-dried flask charged with stirring bar and reflux condenser, magnesium (48 mg, 2.0 mmol, 2.0 equiv) was added followed by 2 mL THF under nitrogen, then catalytic amount of I₂ was added in one portion. A solution of 4-bromo-1-(trimethylsilyl)-1-butyne **2.91** (304.5 mg, 1.5 mmol, 1.5 equiv) in 5 mL THF was added via syringe pump over a period of 1 h under refluxing condition. The reaction mixture was refluxed for additional 30 min and then cooled down to -78 °C. CuBr-DMS (154.2 mg, 0.75 mmol, 0.75 equiv) was added in one portion followed by Me₂S (0.073 mL, 1.0 mmol, 1.0 equiv). The resulting mixture was stirred at this temperature for 30 min for the cuprate complex formation. After 30 min, a solution of the lactone **2.75** (180 mg, 1.0 mmol, 1.0 equiv) in 2 mL THF was added drop wise, and the reaction progress was detected with TLC until the substrate was consumed completely (less than 5 min), then CH₃I (0.18 mL, 3.0 mmol, 3.0 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stirred overnight, after which TBAF trihydrate was added in one portion. The mixture was stirred for additional 1 h, quenched with 5 mL saturated NH₄Cl solution. The mixture was filtrated through a pad of Celite to remove the black solid (eluted with diethyl ether), the aqueous layer was extracted with diethyl ether (3*20 mL), the combined organic layers were washed with aqueous NH₄Cl (3*20 mL) solution and brine (3*10 mL), dried over Na₂SO₄, concentrated under reduced pressure gave a residue. The residue was purified by column chromatography (PE/EtOAc = 30:1) gave the product **2.74** as faint yellow liquid (158.7 mg, 0.64 mmol, 64% overall yield).

Compound (-)-2.74: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.57 (d, $J = 5.77$ Hz, 1 H), 2.82 (dd, $J = 4.43, 2.83$ Hz, 1 H), 2.49 – 2.45 (m, 1 H), 2.44 – 2.36 (m, 3 H), 2.05 (tt, $J = 10.52, 2.95$, 1 H), 1.97 (t, $J = 2.68$ Hz, 1 H), 1.88 – 1.80 (m, 1 H), 1.78 – 1.69 (m, 1 H), 1.45 – 1.35 (m, 1 H), 1.15 (d, $J = 6.57$ Hz, 3 H), 0.97 (d, $J = 6.52$ Hz, 3 H), 0.92 (d, $J = 6.41$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 205.8, 175.6, 83.7, 82.5, 69.9, 53.2, 45.1, 41.7, 37.6, 28.6, 24.2, 20.3, 19.5, 16.1, 11.2 ppm; **IR** (film): ν 3285 (w), 2964 (w), 1785 (s), 1725 (s), 1320 (s), 1062 (s), 1009 (s), 925 (s), 757 (s), 660 (w) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{Na}^+$: 271.1305, found: 271.1308; $[\alpha]_{\text{D}}^{25}$ -163.6 (c 1.9, CHCl_3 , 91% ee).

Cycloisomerization method I with Au-catalysis: to a flame-dried flask charged with stirring bar, a solution of the substrate **2.74** (248 mg, 1.0 mmol, 1.0 equiv) in acetonitrile (10 mL) was added via syringe followed by triethylamine (0.21 mL, 1.5 mmol, 1.5 equiv), tert-butyldimethylsilyl chloride (225.8 mg, 1.5 mmol, 1.5 equiv) and NaI (225 mg, 1.5 mmol, 1.5 equiv) in this order subsequently. The reaction mixture was warmed to 60 °C, stirred overnight, and with TLC monitored the reaction progress. After the substrate was consumed completely, the reaction was cooled down to room temperature, then 10 mL petroleum ether and 5 mL saturated NaHCO_3 aqueous solution were added. The aqueous layer was extracted with petroleum ether (3*20 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated under reduced pressure gave the crude product **2.94**, which was labile and was used directly in the catalytic reaction without further purification. To a nitrogen protected schlenk flask charged with stirring bar, a solution of the crude silyl enolate ether **2.94** in 10 mL DCM was added via syringe followed by 1 mL distilled H_2O under nitrogen. Then chloro(triphenylphosphine)gold(I) (49.5 mg, 0.1 mmol, 10 mol% equiv) and silver tetrafluoroborate (19.5 mg, 0.1 mol, 10 mol% equiv) were added subsequently. The flask was sealed, heated at 40 °C for 30 min. Then the mixture was diluted with 50 mL DCM, dried over Na_2SO_4 , concentrated under reduced pressure gave a residue, which was purified by column chromatography (PE/EtOAc = 20:1) gave the product **2.73** as white solid (188.5 mg, 0.76 mmol, 76% yield over two steps). Then the product **2.73** was recrystallized in a mixture of PE/EtOAc = 5:1 gave white crystals; upon recrystallization the ee was improved from 91% to 99%.

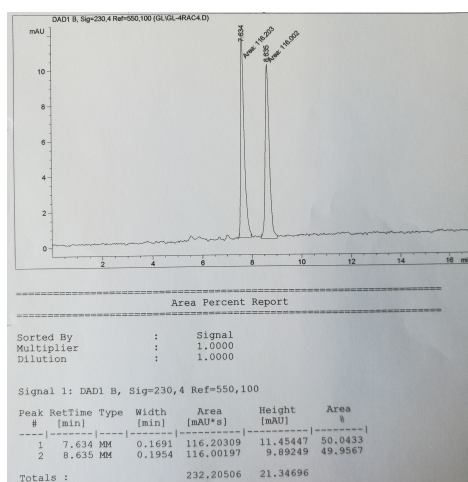
Cycloisomerization method II with Cu-catalysis: To a flame dried schlenk flask charged with stirring bar, a solution of the substrate **2.74** (124 mg, 0.5 mmol, 1.0 equiv) in 5 mL THF was added via syringe followed by catalytic amount of copper(II) triflate (18.1 mg, 0.05

mmol, 10 mol% equiv), triphenylphosphine (52.5 mg, 0.2 mmol, 40 mol% equiv) and pyrrolidine (0.016 mL, 0.2 mmol, 40 mol% equiv) under nitrogen. The schlenk flask was sealed, warmed to 90 °C and stirred for 72 h, and with TLC monitored the progress of the reaction. After 72 h, the solution was allowed to cool down to room temperature, diluted with 5 mL EtOAc and then filtered through Celite (eluted with EtOAc). The filtrate was concentrated in vacuum and loaded to silica gel, purified by column chromatography (PE/EtOAc = 20:1) gave the product **2.73** as white solid (53.3 mg, 0.22 mmol, 43% yield with 26% of starting material recovered).

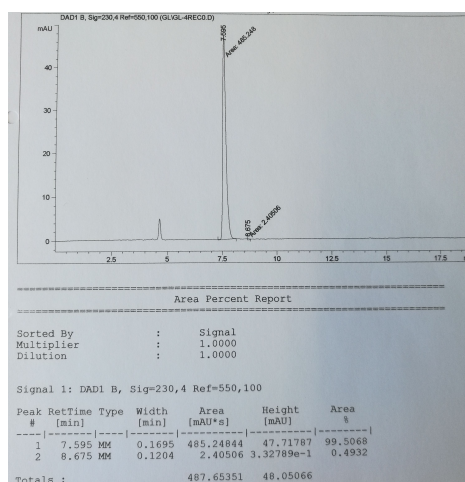
Compound (+)-2.73: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.93 (t, $J = 2.07$ Hz, 1 H), 4.76 (t, $J = 2.54$ Hz, 1 H), 4.57 (d, $J = 5.53$ Hz, 1 H), 2.73 – 2.54 (m, 3 H), 2.45 – 2.40 (m, 2 H), 2.23 – 2.15 (m, 1 H), 2.13 – 2.04 (m, 1 H), 1.53 – 1.44 (m, 1 H), 1.30 (s, 3 H), 0.99 (d, $J = 6.48$ Hz, 3 H), 0.95 (d, $J = 6.44$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 204.7, 177.5, 152.8, 108.3, 83.9, 58.2, 54.4, 46.4, 44.8, 30.6, 26.6, 25.7, 24.7, 20.7, 19.5 ppm; **IR** (film): ν 2966 (s), 1796 (s), 1713 (s), 1124 (s), 1006 (s), 911 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{Na}^+$: 271.1305, found : 271.1318; **M.p.** 163 °C; $[\alpha]_{\text{D}}^{25}$ +60.3 (c 1.8, CHCl_3 , 99% ee). **Daicel Chiralcel AD-H**, hexane/*i*-PrOH = 98/2, $f = 1.0$ mL/min, 230.4 nm, retention time: 7.6 min (major) and 8.7 min (minor).

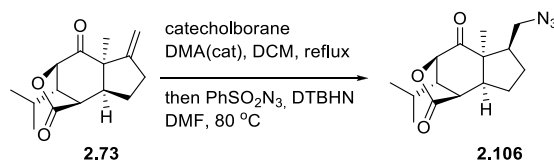
HPLC Spectrums

(±)-compound 2.73



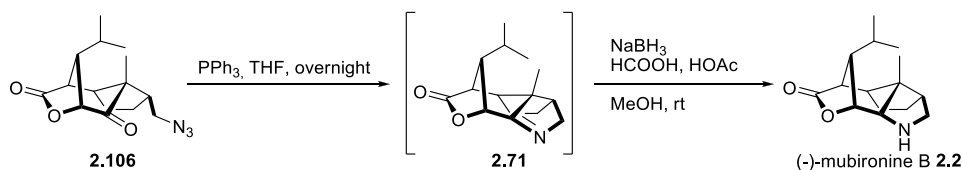
(+)-compound 2.73 (after recrystallization)



Free radical-mediated hydroazidation

To a flame dried flask charged with stirring bar, catecholborane (1.0 M in THF, 0.6 mL, 0.6 mmol, 3.0 equiv) was added drop wise at 0 °C to a solution of the olefin **2.73** (49.6 mg, 0.2 mmol, 1.0 equiv) and *N,N*-dimethylamide (0.002 mL, 0.02 mmol, 0.1 equiv) in 2 mL DCM under nitrogen. The mixture was heated under reflux for 5 h, after the substrate was consumed completely (monitored by TLC), the reaction mixture was cooled down to 0 °C, 0.2 mL *t*-BuOH was added drop wise to consume the rest of catecholborane. After evaporation of the solvent under reduced pressure, 2 mL *N,N*-dimethylformamide, PhSO₂N₃ (109.8 mg, 0.6 mmol, 3.0 equiv) and DTBHN (di-*tert*-butylhyponitrite) (3.5 mg, 0.02 mol, 0.1 equiv) were added and the solution was stirred at 80 °C. After 3 h, the reaction mixture was cooled down to room temperature, diluted with Et₂O, filtered through a pad of Celite to remove insoluble solid (eluted with Et₂O). The filtrate was washed with brine, dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 10:1) gave the azide **2.106** as white solid (27.4 mg, 0.09 mmol, 47% yield).

Compound (+)-2.106: ¹H NMR (400 MHz, CDCl₃): δ 4.47 (d, *J* = 5.47 Hz, 1 *H*), 3.33 (dd, *J* = 11.95, 4.69 Hz, 1 *H*), 3.02 (dd, *J* = 11.78, 10.16 Hz, 1 *H*), 2.63 (t, *J* = 4.67 Hz, 1 *H*), 2.43 – 2.38 (m, 1 *H*), 2.36 – 2.32 (m, 1 *H*), 2.10 – 2.02 (m, 4 *H*), 1.72 – 1.62 (m, 1 *H*), 1.60 – 1.53 (m, 1 *H*), 1.38 (s, 3 *H*), 0.99 (d, *J* = 6.48 Hz, 3 *H*), 0.92 (d, *J* = 6.46 Hz, 3 *H*) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 207.7, 177.2, 83.3, 55.6, 53.9, 53.3, 53.1, 45.8, 44.8, 30.9, 29.6, 28.7, 24.5, 20.9, 19.5 ppm; IR (film): ν 2965 (s), 2096 (s), 1789 (s), 1741 (s), 1461 (s), 1115 (s), 998 (s) cm⁻¹; MS (ESI) calculated for C₁₅H₂₁N₃O₃Na⁺: 314.1475, found : 314.1478; **M.p.** 106 °C; [α]_D²⁵ +46.7 (c 1.7, CHCl₃, 99% *ee*).

Synthesis of (-)-mubironine B 2.2

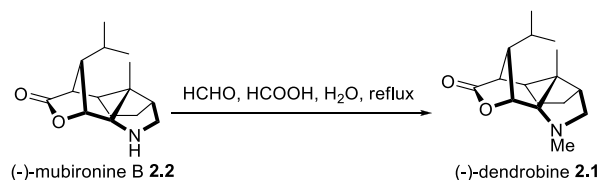
To a flame dried flask charged with stirring bar, a solution of the azide substrate **2.106** (14.6 mg, 0.05 mmol, 1.0 equiv) in 2 mL THF was added followed by PPh_3 (15.7 mg, 0.06 mmol, 1.2 equiv) in one portion. The reaction mixture was stirred at room temperature for 12 h, and the reaction progress was detected by TLC until the substrate was consumed completely. To this mixture, 3 mL MeOH, HOAc (0.029 mL, 0.5 mmol, 10 equiv) and HCOOH (0.019 mL, 0.5 mmol, 10 equiv) were added subsequently, and then NaBH_3CN (63 mg, 1 mmol, 20 equiv) was added in one portion. The mixture was stirred at room temperature for additional 12 h, after which 10 mL 1N HCl was added drop wise. The mixture was stirred for 1 h, and then washed with 5 mL Et_2O . The aqueous layer was basified with 10 mL 3N NaOH solution, then extracted with DCM (4*30 mL), and the combined organic layers were dried over Na_2SO_4 , concentrated under reduced pressure gave a residue. The residue was purified by column chromatography (EtOAc/MeOH/TEA = 100:4:1) gave (-)-mubironine B **2.2** as colorless oil (9.7 mg, 0.038 mmol, 78% yield).

(-)-Mubironine B 2.1: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.68 (dd, $J = 5.24, 3.48$ Hz, 1 H), 3.95 (br s, 1 H), 3.24 (dd, $J = 11.33, 8.61$ Hz, 1 H), 2.95 (d, $J = 3.36$ Hz, 1 H), 2.88 (dd, $J = 11.37, 7.12$ Hz, 1 H), 2.46 (dd, $J = 5.45, 4.64$ Hz, 1 H), 2.37 – 2.28 (m, 1 H), 2.21 – 2.02 (m, 4 H), 1.85 – 1.75 (m, 2 H), 1.53 – 1.44 (m, 1 H), 1.37 (s, 3 H), 0.98 (d, $J = 4.68$ Hz, 3 H), 0.96 (d, $J = 4.68$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 178.9, 82.4, 63.2, 56.6, 53.7, 53.3, 51.6, 43.8, 42.4, 33.3, 32.2, 30.2, 24.5, 21.1, 20.4 ppm; IR (film): ν 2957 (s), 2924 (s), 1775 (s), 1465 (w), 1119(s), 969 (s) cm^{-1} ; MS (ESI) calculated for $\text{C}_{15}\text{H}_{24}\text{NO}_2^+$: 250.1802, found: 250.1804; $[\alpha]_D^{25}$ -16.5 (c 1.4, CHCl_3 , 99% ee).

NMR data for reported and our synthetic (-)-mubironine B:

δ_{H} (m, <i>J</i> (Hz), xH)	
Reported (CDCl ₃ , 300 MHz)	Ours' (CDCl ₃ , 400 MHz)
4.61 (dd, <i>J</i> = 5.3, 3.5 Hz, 1 <i>H</i>)	4.68 (dd, <i>J</i> = 5.24, 3.48 Hz, 1 <i>H</i>)
3.18 (dd, <i>J</i> = 11.4, 8.5 Hz, 1 <i>H</i>)	3.24 (dd, <i>J</i> = 11.33, 8.61 Hz, 1 <i>H</i>)
2.86 (d, <i>J</i> = 3.5 Hz, 1 <i>H</i>)	2.95 (d, <i>J</i> = 3.36 Hz, 1 <i>H</i>)
2.83 (dd, <i>J</i> = 11.4, 6.9 Hz, 1 <i>H</i>)	2.88 (dd, <i>J</i> = 11.37, 7.12 Hz, 1 <i>H</i>)
2.47 – 2.43 (m, 1 <i>H</i>)	2.46 (dd, <i>J</i> = 5.45, 4.64 Hz, 1 <i>H</i>)
2.35 – 2.20 (m, 1 <i>H</i>)	2.37 – 2.28 (m, 1 <i>H</i>)
2.20 – 2.00 (m, 5 <i>H</i>),	2.21 – 2.02 (m, 4 <i>H</i>), 3.95 (br s, 1 <i>H</i>)
1.89 – 1.71 (m, 1 <i>H</i>)	1.85 – 1.75 (m, 1 <i>H</i>)
1.55 – 1.39 (m, 1 <i>H</i>)	1.53 – 1.44 (m, 1 <i>H</i>)
1.34 (s, 3 <i>H</i>)	1.37 (s, 3 <i>H</i>)
0.96 (d, <i>J</i> = 6.4 Hz, 3 <i>H</i>)	0.98 (d, <i>J</i> = 4.68 Hz, 3 <i>H</i>)
0.95 (d, <i>J</i> = 6.4 Hz, 3 <i>H</i>)	0.96 (d, <i>J</i> = 4.68 Hz, 3 <i>H</i>)

Synthesis of (-)-dendrobine **2.1**

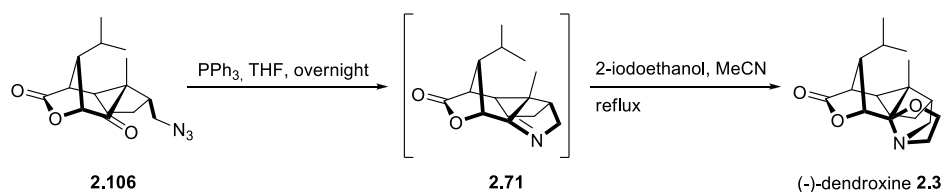


To a flask charged with stirring bar and (-)-mubironine B **2.2** (7.5 mg, 0.03 mmol, 1.0 equiv) was added 5 mL water followed with HCOOH (0.11 mL, 3 mmol, 100 equiv) and paraformaldehyde (22.5 mg, 0.75 mmol, 25 equiv). The suspension mixture was heated under reflux and stirred for 12 h. After cooling down to room temperature, the reaction mixture was basified with 10 mL 3*N* NaOH solution. The aqueous layer was extracted with DCM (4*30 mL), and the combined organic layers were dried over Na₂SO₄, concentrated under reduced pressure gave a residue. The residue was purified by column chromatography (PE/EtOAc/MeOH/TEA = 250:250:10:1) gave (-)-dendrobine **2.1** as white crystals (6.6 mg, 0.025 mmol, 84% yield).

(-)-Dendrobine (-)-2.1: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.84 (dd, $J = 5.53, 2.99$ Hz, 1 H), 3.16 (t, $J = 8.70$ Hz, 1 H), 2.71 – 2.67 (m, 2 H), 2.50 (s, 3 H), 2.45 (dd, $J = 5.32, 4.56$ Hz, 1 H), 2.41 – 2.32 (m, 1 H), 2.16 – 2.04 (m, 3 H), 2.02 – 1.99 (m, 1 H), 1.89 – 1.75 (m, 2 H), 1.60 – 1.49 (m, 1 H), 1.38 (s, 3 H), 0.97 (d, $J = 6.44$ Hz, 3 H), 0.96 (d, $J = 6.44$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 179.0, 79.3, 66.8, 62.0, 53.7, 52.5, 51.6, 44.0, 43.1, 36.5, 32.8, 32.7, 30.8, 24.5, 21.1, 20.4 ppm; **IR** (film): ν 2956 (s), 2921 (s), 1774 (s), 1464 (s), 1118 (s), 794 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{16}\text{H}_{26}\text{NO}_2^+$: 264.1958, found: 264.1961; **M.p.** 132 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25}$ -52.6 (c 1.6, CHCl_3).

NMR data for Carreira's and our synthetic (-)-dendrobine:

δ_{H} (m, J (Hz), xH)		δ_{C} (x C)	
Carreira's (CDCl_3 , 600 MHz)	Our's (CDCl_3 , 400 MHz)	Carreira's (CDCl_3 , 150 MHz)	Our's (CDCl_3 , 100 MHz)
4.87 (dd, $J = 5.3, 3.0$ Hz, 1 H)	4.84 (dd, $J = 5.53, 2.99$ Hz, 1 H)	179.1	179.0
3.18 (app. t, $J = 8.7$ Hz, 1 H)	3.16 (t, $J = 8.70$ Hz, 1 H)	79.3	79.3
2.74 – 2.69 (m, 2 H)	2.71 – 2.67 (m, 2 H)	66.9	66.8
2.53 (s, 3 H)	2.50 (s, 3 H)	62.0	62.0
2.48 (dd, $J = 5.7, 4.4$ Hz, 1 H)	2.45 (dd, $J = 5.32, 4.56$ Hz, 1 H)	53.8	53.7
2.39 (app. pentet, $J = 8.8$ Hz, 1 H)	2.45 (dd, $J = 5.32, 4.56$ Hz, 1 H)	52.5	52.5
2.18 – 2.06 (m, 3 H),	2.16 – 2.04 (m, 3 H),	51.6	51.6
2.4 (dd, $J = 7.9, 5.9$ Hz, 1 H)	2.02 – 1.99 (m, 1 H)	44.0	44.0
1.91 – 1.79 (m, 2 H)	1.89 – 1.75 (m, 2 H)	43.1	43.1
1.62 – 1.54 (m, 1 H)	1.60 – 1.49 (m, 1 H)	36.6	36.5
1.41 (s, 3 H)	1.38 (s, 3 H)	32.8	32.8
1.00 (app. dd, $J = 6.5, 4.0$ Hz, 6 H)	0.97 (d, $J = 6.44$ Hz, 3 H), 0.96 (d, $J = 6.44$ Hz, 3 H)	32.8	32.7
		30.8	30.8
		24.5	24.5
		21.1	21.1
		20.5	20.4

Late stage redox-neutral elaboration to dendroxine

To a flame dried flask charged with stirring bar, a solution of the azide substrate **2.106** (7.3 mg, 0.025 mmol, 1.0 equiv) in 1 mL THF was added followed by PPh_3 (6.6 mg, 0.03 mmol, 1.2 equiv) in one portion. The reaction mixture was stirred at room temperature for 12 h until the substrate was consumed completely. Then the solvent was evaporated under vacuum, and the residue was dissolved in 1 mL CH_3CN . 2-iodoethanol (0.01 mL, 0.13 mmol, 5.0 equiv) was added in one portion to this solution, and the solution was warmed to reflux under nitrogen and stirred at this temperature for 24 h. Meanwhile the system was covered with aluminum foil due to the light-sensitivity of 2-iodoethanol. After 24 h the mixture was cooled down to room temperature, the reaction mixture was basified with 5 mL 3*N* NaOH solution and stirring was continued for additional 15 min. Then the aqueous layer was extracted with EtOAc (3*10 mL), and the combined organic layers were dried over Na_2SO_4 , concentrated under reduced pressure gave a residue. The residue was purified by column chromatography (PE/EtOAc/TEA = 100:200:3) gave (-)-dendroxine **2.3** as colorless oil (4.9 mg, 0.017 mmol, 68% yield).

(-)-Dendroxine (-)-2.3: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.35 (d, $J = 4.67$ Hz, 1 *H*), 3.93 – 3.98 (m, 1 *H*), 3.85 (dd, $J = 14.07, 7.81$ Hz, 1 *H*), 3.25 – 3.31 (m, 1 *H*), 3.00 – 3.08 (m, 2 *H*), 2.86 (dd, $J = 10.07, 7.48$ Hz, 1 *H*), 2.48 (dd, $J = 6.57, 4.11$ Hz, 1 *H*), 2.24 – 2.32 (m, 1 *H*), 2.07 – 2.15 (m, 2 *H*), 1.98 – 2.04 (m, 2 *H*), 1.89 – 1.96 (m, 1 *H*), 1.73 – 1.80 (m, 1 *H*), 1.50 – 1.62 (m, 1 *H*), 1.26 (s, 3 *H*), 1.02 (d, $J = 6.14$ Hz, 3 *H*), 0.93 (d, $J = 6.54$ Hz, 3 *H*) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 178.0, 103.5, 80.5, 65.2, 55.7, 54.0, 53.6, 51.8, 51.6, 43.3, 42.4, 31.7, 30.8, 27.9, 24.3, 21.2, 21.0 ppm; IR (film): ν 2958 (s), 2925 (s), 2868 (s), 1774 (s), 1469 (s), 1351 (s), 1111 (s), 1005 (s), 928 (s), 773 (s) cm^{-1} ; MS (ESI) calculated for $\text{C}_{17}\text{H}_{25}\text{NO}_3\text{Na}^+$: 314.1727, found: 314.1723; $[\alpha]_{\text{D}}^{25}$ -17.3 (c 0.97, EtOH).

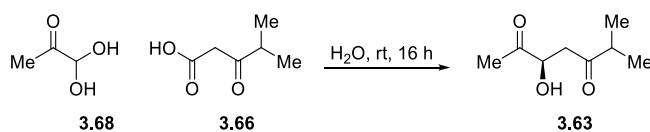
A selected ^1H NMR data for natural¹⁹ and synthetic (-)-dendroxine:

δ_{H} (m, J (Hz), x H)	
Natural	Synthetic (CDCl_3 , 400 MHz)
0.95 (q, 6 H)	1.02 (d, $J = 6.14$ Hz, 3 H), 0.93 (d, $J = 6.54$ Hz, 3 H)
1.20 (s, 3 H)	1.26 (s, 3 H)
2.7 – 3.2 (m, 4 H)	3.25 – 3.31 (m, 1 H), 3.00 – 3.08 (m, 2 H), 2.86 (dd, $J = 10.07, 7.48$ Hz, 1 H)
3.8 (t, 2 H)	3.93 – 3.98 (m, 1 H), 3.85 (dd, $J = 14.07, 7.81$ Hz, 1 H)
4.10 (d, 1 H)	4.35 (d, $J = 4.67$ Hz, 1 H)

Note: A detailed ^1H NMR data for natural (-)-dendroxine cannot be extracted due to the low resolution of original spectra.

3. Experimental Details in Guaiane Sesquiterpene Englerins Synthesis

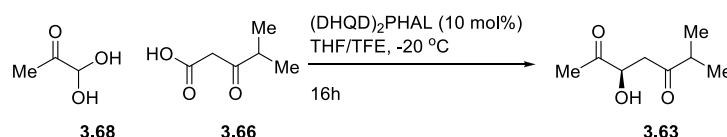
I. Racemic decarboxylative aldol reaction



To a solution of the β -ketone carboxylic acid **3.66** (1.3 g, 10 mmol, 1.0 equiv) in H₂O (50 mL, 0.2 M) was added methyl glyoxal **3.68** solution (2.2 mL, 12 mmol, 1.2 equiv) in water (commercially available, ~40%) at room temperature. The reaction was stirred at room temperature for 12 h until the β -ketone carboxylic acid **3.66** was consumed completely. The mixture was diluted with additional 50 mL H₂O, extracted with CH₂Cl₂ (50 mL*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give the crude aldol product. The product was slightly sensitive to acid and has to be purified by column chromatography fast on silica (PE/EA = 3:1) to give the pure product **3.63** (1.47 mg, 9.3 mmol, 93% yield) as light yellow liquid.

Compound (\pm)-3.63: ¹H NMR (300 MHz, CDCl₃), δ 4.32 (dd, J = 6.08, 3.88 Hz, 1 H), 3.67 (br s, 1 H), 2.99 (dd, J = 17.37, 3.91 Hz, 1 H), 2.87 (dd, J = 17.37, 6.12 Hz, 1 H), 2.65 – 2.56 (m, 1 H), 2.25 (s, 3 H), 1.11 (d, J = 1.0 Hz, 3 H), 1.08 (d, J = 1.0 Hz, 3 H) ppm; ¹³C NMR (75 MHz, CDCl₃), δ 213.1, 209.5, 73.8, 43.0, 41.4, 25.4, 17.7, 17.6 ppm; IR (film): ν 3465 (br s), 2971 (s), 1706 (s), 1356 (s), 1103 (s), 1081 (s) cm⁻¹; MS (ESI) calculated for C₈H₁₅O₃⁺: 159.0977, found: 159.0979.

Organocatalyzed asymmetric decarboxylative aldol reaction under optimized condition

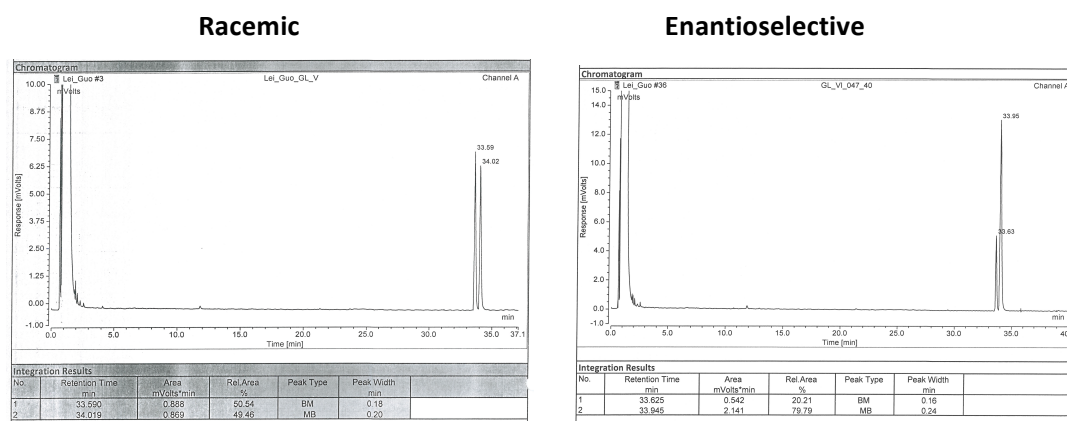


In a flask charged with stirring bar, 1.8 mL trifluoroethanol was added to a solution of β -ketone carboxylic acid **9** (260 mg, 2.0 mmol, 1.0 equiv) in 18.2 mL THF under stirring. The solution was cooled to -20 °C, and then methyl glyoxal **10** solution (0.43 mL, 2.4 mmol, 1.2 equiv) in water (commercially available, ~40%) was added in once followed by

organocatalyst (DHQD)₂PHAL (155.8 mg, 0.2 mmol, 0.1 equiv). The mixture was stirred at -20 °C for 16 h until the β-ketone carboxylic acid **9** was consumed completely. Then the reaction was quenched by addition of 5 mL water, allowed to warm to room temperature, extracted with CH₂Cl₂ (20 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give the crude enantioselective aldol product. The product was slightly sensitive to acid and has to be purified by column chromatography fast on silica (PE/EA = 3:1) to give the pure product **8** (262 mg, 1.66 mmol, 83% yield) as light yellow liquid.

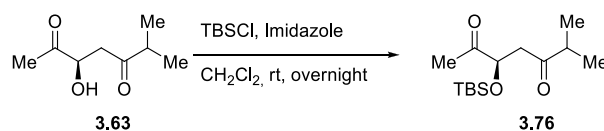
Compound (-)-3.63: ¹H NMR, ¹³C NMR, IR, MS spectrums are identical as the racemic product. [α]_D²⁵ -8.8 (c 0.54, CHCl₃, -60% ee); Enantiomeric excess was analyzed by chiral GC analysis: **Column: Amidex_C, Temperature program: initial temperature at 40 °C, hold for 1 min, then ramping in a rate of 2 °C/min to 200 °C;** Retention Time: 33.6 min (minor), 34.0 min (major).

Chiral GC spectrums



Free alcohol protection

TBS-protection:

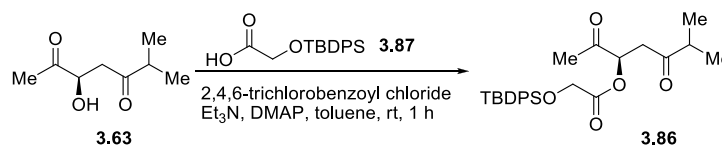


In an oven-dried flask, a solution of enantioselective aldol product **3.63** (158.0 mg, 1.0 mmol, 1.0 equiv) in anhydrous CH₂Cl₂ (10 mL, 0.1 M) was charged under nitrogen followed

by TBSCl (158.3 mg, 1.05 mmol, 1.05 equiv) at room temperature. Then imidazole (81.6 mg, 1.2 mmol, 1.2 equiv) was added in one portion. The mixture turned cloudy and was stirred at room temperature for overnight until the substrate **3.63** was consumed completely. The reaction was quenched by addition of 5 mL water, extracted with CH₂Cl₂ (20 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to the crude liquid, which was purified by column chromatography on silica (PE/EA = 30:1) to give the pure product **3.76** (234 mg, 0.86 mmol, 86% yield) as light yellow liquid.

Compound (-)-3.76: ¹H NMR (400 MHz, CDCl₃), δ 4.44 (dd, *J* = 5.61, 5.615 Hz, 1 *H*), 2.84 (dd, *J* = 16.66, 5.78 Hz, 1 *H*), 2.77 (dd, *J* = 16.53, 4.84 Hz, 1 *H*), 2.61 – 2.54 (m, 1 *H*), 2.25 (s, 3 *H*), 1.10 (d, *J* = 3.43 Hz, 3 *H*), 1.08 (d, *J* = 3.43 Hz, 3 *H*) 0.89 (s, 9 *H*), 0.10 (s, 3 *H*), 0.05 (s, 3 *H*) ppm; ¹³C NMR (100 MHz, CDCl₃), δ 211.3 210.7, 74.7, 45.0, 41.4, 26.1, 25.7, 17.9, 17.8, 17.7, -4.9, -5.1; IR (film): ν 3481 (br s), 2956 (s), 1716 (s), 1362 (s), 1122 (s) cm⁻¹; MS (ESI) calculated for C₁₄H₂₉O₃Si⁺: 273.1880, found: 273.1874; [α]_D²⁵ -5.9 (c 0.82, CHCl₃, -60% *ee*).

Glycolate-protection (Yamaguchi's esterification):



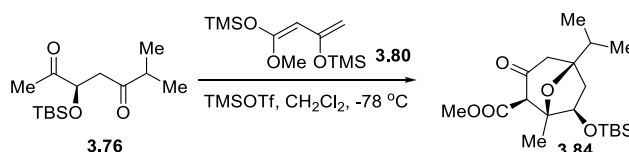
In an oven-dried flask, a solution of enantioselective aldol product **3.63** (158.0 mg, 1.0 mmol, 1.0 equiv) in anhydrous toluene (10 mL, 0.1 M) was charged under nitrogen followed by TBDPDS protected glycolic acid **3.87** (330 mg, 1.05 mmol, 1.05 equiv) at room temperature. Then Et₃N (166 μL, 1.2 mmol, 1.2 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), 2,4,6-trichlorobenzoyl chloride (164 μL, 1.05 mmol, 1.05 equiv) were added in sequence. The mixture turned cloudy and was stirred at room temperature for 1 h until the substrate **3.63** was consumed completely. The reaction was quenched by addition of 5 mL water, extracted with Et₂O (20 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to the crude liquid, which was purified by column chromatography on silica (PE/EA = 20:1) to give the pure product **3.86** (354 mg, 0.78 mmol, 78% yield) as light yellow liquid.

Compound (-)-3.86: ¹H NMR (300 MHz, CDCl₃), δ 7.70 – 7.66 (m, 4 *H*), 7.44 – 7.36 (m, 6 *H*), 5.39 (dd, *J* = 5.64, 4.93 Hz, 1 *H*), 4.30 (d, *J* = 1.02 Hz, 2 *H*), 3.00 (dd, *J* = 17.77, 5.76 Hz, 1

H), 2.92 (dd, $J = 17.77, 4.86$ Hz, 1 *H*), 2.58 – 2.49 (m, 1 *H*), 2.15 (s, 3 *H*), 1.08 (s, 9 *H*), 1.07 (s, 3 *H*), 1.05 (s, 3 *H*) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3), δ 209.6, 205.4, 170.5, 135.5, 132.6, 130.0, 127.8, 74.3, 62.0, 41.2, 40.8, 26.6, 26.5, 19.2, 17.8, 17.7 ppm; **IR** (film): ν 2931 (s), 1768 (s), 1717 (s), 1140 (s), 1113 (s), 704 (s), 505 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{26}\text{H}_{34}\text{O}_5\text{SiNa}^+$: 477.2608, found : 477.2608; $[\alpha]_{\text{D}}^{25}$ -4.3 (c 0.82, CHCl_3 , -60% *ee*).

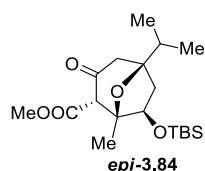
TMSOTf catalyzed, regio- and diastereoselective [4+3] cycloaddition

With TBS protected substrate **3.76**



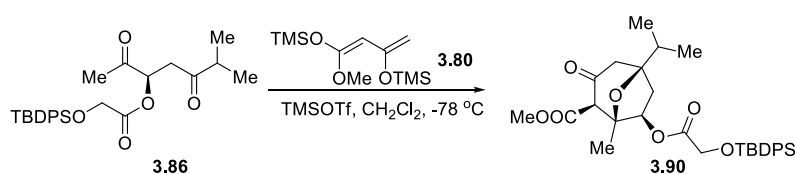
In an oven-dried flask, a solution of the substrate **3.76** (272 mg, 1.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 mL, 0.1 M) was charged under nitrogen at room temperature. The flask was then cooled to $-78\text{ }^\circ\text{C}$, followed by addition of the *bis*-silylenolether **3.80** (390 mg, 1.5 mmol, 1.5 equiv) at this temperature. Then a catalytic amount of TMSOTf (36 μL , 0.2 mmol, 0.2 equiv) was added, and the mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min until the substrate **3.76** was consumed completely. The reaction was quenched by addition of 5 mL saturated NaHCO_3 aqueous solution, allowed to warm to room temperature, extracted with CH_2Cl_2 (20 mL*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to the crude liquid, which was purified by column chromatography on silica (PE/EA = 40:1) to give the product (314 mg, 0.85 mmol, 85% overall yield) as light yellow liquid, which contained the three isomers (8:1:2) at the β -ketone ester position.

Compound (+)-3.84: $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 3.88 (dd, $J = 7.26, 3.19$ Hz, 1 *H*), 3.71 (s, 3 *H*), 3.12 (s, 1 *H*), 2.86 (dd, $J = 14.64, 1.93$ Hz, 1 *H*), 2.30 (dd, $J = 14.50, 0.81$ Hz, 1 *H*), 2.09 – 1.99 (m, 2 *H*), 1.68 – 1.62 (m, 1 *H*), 1.31 (s, 3 *H*), 0.97 (d, $J = 6.95$, 1 *H*), 0.93 (d, $J = 6.85$ Hz, 3 *H*), 0.86 (s, 9 *H*), 0.01 (s, 6 *H*) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3), δ 204.7, 167.3, 86.0, 85.8, 77.2, 65.7, 55.2, 47.6, 44.7, 35.9, 25.7, 18.1, 18.0, 17.5, 17.0, -4.5, -5.1; **IR** (film): ν 2971 (s), 1763 (s), 1121 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{19}\text{H}_{34}\text{O}_5\text{SiNa}^+$: 393.2068, found : 393.2071; $[\alpha]_{\text{D}}^{25}$ +35.0 (c 0.91, CHCl_3 , -60% *ee*).



Compound (+)-epi-3.84: $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 4.72 (dd, $J = 7.30, 2.74$ Hz, 1 H), 3.75 (s, 3 H), 3.48 (s, 1 H), 2.34 (s, 2 H), 2.15 – 2.10 (m, 1 H), 2.02 – 1.95 (m, 1 H), 1.72 – 1.68 (m, 1 H), 1.34 (s, 3 H), 0.96 (d, $J = 6.92$, 1 H), 0.93 (d, $J = 6.92$ Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3), δ 203.3, 168.4, 87.1, 85.8, 73.6, 66.9, 52.0, 48.1, 45.4, 35.9, 25.8, 25.7, 19.7, 19.1, 17.5, 17.1, -4.8, -5.0; **IR** (film): ν 2983 (s), 1773 (s), 1121 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{19}\text{H}_{34}\text{O}_5\text{SiNa}^+$: 393.2068, found : 393.2064; $[\alpha]_D^{25} +47.1$ (c 0.53, CHCl_3 , -60% ee).

With glycolate protected substrate 3.86



In an oven-dried flask, a solution of the substrate **3.86** (454 mg, 1.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 mL, 0.1 M) was charged under nitrogen at room temperature. The flask was then cooled to -78 °C, followed by addition of the *bis*-silylenolether **3.80** (390 mg, 1.5 mmol, 1.5 equiv) at this temperature. Then a catalytic amount of TMSOTf (36 μL , 0.2 mmol, 0.2 equiv) was added, and the mixture was stirred at -78 °C for 30 min until the substrate **3.86** was consumed completely. The reaction was quenched by addition of 5 mL saturated NaHCO_3 aqueous solution, allowed to warm to room temperature, extracted with CH_2Cl_2 (20 mL*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to the crude liquid, which was purified by column chromatography on silica (PE/EA = 40:1) to give the product (458 mg, 0.83 mmol, 83% overall yield) as light yellow liquid, which contained the three isomers (8:1:2) at the β -ketone ester position.

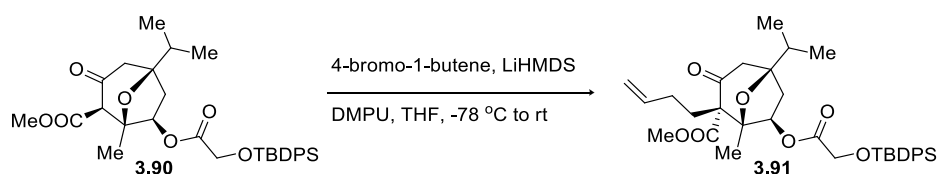
Compound (+)-3.90: $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 7.68 – 7.66 (m, 4 H), 7.46 – 7.38 (m, 6 H), 4.83 (dd, $J = 10.60, 4.33$ Hz, 1 H), 4.22 (s, 2 H), 3.71 (s, 3 H), 3.38 (s, 1 H), 2.83 (d, $J = 15.80$ Hz, 1 H), 2.42 – 2.35 (m, 2 H), 1.97 – 1.90 (m, 1 H), 1.37 (s, 3 H), 1.32 (dd, $J = 14.30, 4.50$, 1 H), 1.10 (s, 9 H), 0.96 (d, $J = 6.84$ Hz, 3 H), 0.91 (d, $J = 6.84$ Hz, 3 H) ppm; $^{13}\text{C NMR}$

(100 MHz, CDCl₃), δ 202.7, 170.5, 167.8, 135.6, 132.6, 130.0, 127.8, 85.0, 82.1, 79.6, 62.0, 60.4, 52.3, 47.6, 39.5, 35.8, 26.7, 22.8, 19.2, 17.0, 16.8 ppm; **IR** (film): ν 2959 (s), 2933 (s), 1767 (s), 1738 (s), 1720 (s), 1138 (s), 703 (s) cm⁻¹; **MS** (ESI) calculated for C₃₁H₄₀O₇SiNa⁺: 575.2436, found : 575.2444; [α]_D²⁵ +35.0 (c 0.62, CHCl₃, -60% ee).



Compounds (+)-epi-3.90: ¹H NMR (400 MHz, CDCl₃), δ 12.28 (s, 0.6 H), 7.71 – 7.67 (m, 4 H), 7.44 – 7.37 (m, 6 H), 5.79 (dd, J = 7.55, 2.55 Hz, 0.33 H), 5.18 (d, J = 6.26 Hz, 0.6 H), 4.30 – 4.19 (m, 2 H), 3.80 – 3.78 (m, 3 H), 3.46 (s, 0.33 H), 2.56 (d, J = 17.67 Hz, 0.6 H), 2.39 (s, 0.6 H), 2.78 (dd, J = 14.73, 7.66 Hz, 0.33 H), 2.15 – 2.04 (m, 1.33 H), 1.96 – 1.83 (m, 1.33 H), 1.74 – 1.67 (m, 1 H), 1.44 (s, 2 H), 1.33 (s, 1.2 H), 1.28 – 1.24 (m, 0.6 H), 1.10 (s, 9 H), 0.96 – 0.84 (m, 6 H) ppm; ¹³C NMR (100 MHz, CDCl₃), δ 201.9, 172.6, 171.2, 170.7, 170.0, 167.8, 135.7, 135.6, 132.8, 129.9, 127.8, 103.9, 86.0, 85.4, 82.5, 81.0, 80.1, 68.0, 66.7, 62.3, 62.2, 52.3, 51.6, 47.8, 42.3, 40.8, 39.0, 35.9, 35.8, 26.7, 19.6, 19.2, 19.7, 17.4, 17.3, 17.0, 16.5 ppm; **IR** (film): ν 2933 (s), 2954 (s), 1767 (s), 1745 (s), 1738 (s), 1720 (s), 1701 (s), 1144 (s), 711 (s) cm⁻¹; **MS** (ESI) calculated for C₃₁H₄₀O₇SiNa⁺: 575.2436, found : 575.2439; [α]_D²⁵ +28.5 (c 0.82, CHCl₃, -60% ee).

Alkylation reaction

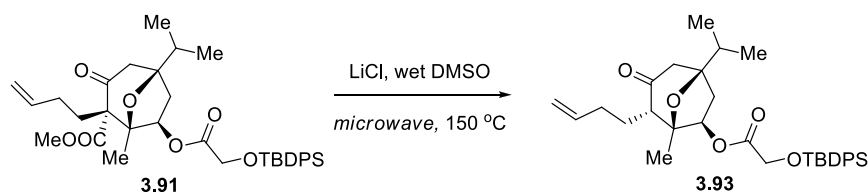


In an oven-dried flask, a solution of the cycloaddition product **3.90** (552 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (10 mL, 0.1 M) was charged under nitrogen at room temperature. The flask was then cooled to -78 °C, followed by dropwise addition of LiHMDS (1.0 M, 1.1 mL, 1.1 equiv) over 10 min at this temperature. The solution was stirred at -78 °C for 30 min, followed by addition of DMPU (240 μ L, 2.0 mmol, 2.0 equiv) and 4-bromo-1-butene (152 μ L, 1.5 mmol, 1.5 equiv). The mixture was warmed to room temperature over 2 h, and stirred at room temperature until the substrate was consumed completely. The

reaction was quenched by addition of 5 mL saturated NaHCO₃ aqueous solution, extracted with Et₂O (20 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 40:1) to yield the product **3.91** (521 mg, 0.83 mmol, 86% yield) as light yellow liquid.

Compound (+)-3.91: ¹H NMR (400 MHz, CDCl₃), δ 7.68 – 7.66 (m, 4 H), 7.45 – 7.36 (m, 6 H), 5.98 (dd, *J* = 7.77, 3.21 Hz, 1 H), 5.82 – 5.72 (m, 1 H), 5.01 (d, *J* = 17.14 Hz, 1 H), 4.96 (d, *J* = 10.18 Hz, 1 H), 4.23 (s, 2 H), 3.80 (s, 3 H), 2.37 – 2.24 (m, 4 H), 2.11 – 2.02 (m, 2 H), 1.97 – 1.90 (m, 1 H), 1.58 – 1.68 (m, 2 H), 1.13 (s, 3 H), 1.08 (s, 9 H), 0.95 (d, *J* = 6.74 Hz, 3 H), 0.89 (d, *J* = 6.99 Hz, 3 H) ppm; ¹³C NMR (100 MHz, CDCl₃), δ 204.4, 170.0, 169.6, 137.6, 135.6, 132.7, 130.0, 127.8, 115.1, 87.5, 85.7, 76.5, 68.6, 62.2, 52.5, 46.0, 41.9, 35.8, 29.6, 28.9, 26.6, 19.2, 17.4, 16.9, 15.2 ppm; IR (film): ν 2958 (s), 2857(s), 1764 (s), 1731 (s), 1136 (s), 1113 (s), 703 (s), 505 (s) cm⁻¹; MS (ESI) calculated for C₃₅H₄₆O₇SiNa⁺: 629.2905, found : 629.2918; [α]_D²⁵ +82.3 (c 0.31, CHCl₃, -60% ee).

Microwave-assisted Krapcho decarboxylation

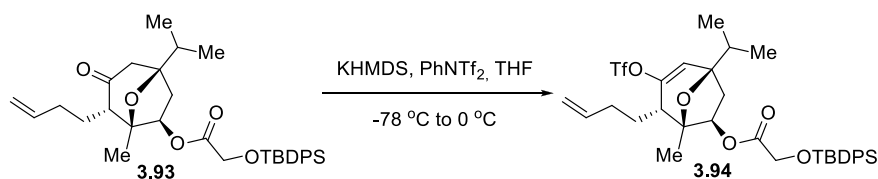


A solution of the alkylated product **3.91** (181.8 mg, 0.3 mmol, 1.0 equiv) in wet DMSO (6 mL, 0.05 M) was charged to a microwave vial under nitrogen at room temperature, followed by addition of LiCl (19.1 mg, 0.45 mmol, 1.5 equiv) in one portion. The vial was loaded onto the microwave reactor, irradiated at 150 °C for 1 h. It was then cooled down to room temperature, and the decarboxylation reaction was quenched by addition of 20 mL water, extracted with Et₂O (20 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 40:1) to yield the product **3.93** (129.9 mg, 0.22 mmol, 74% yield) as light yellow liquid.

Compound (+)-3.93: ¹H NMR (400 MHz, CDCl₃), δ 7.68 – 7.66 (m, 4 H), 7.43 – 7.36 (m, 6 H), 5.81 – 5.71 (m, 1 H), 5.03 – 4.98 (m, 3 H), 4.23 (s, 1 H), 2.42 (d, *J* = 13.91 Hz, 1 H), 2.31 (d, *J* = 14.13 Hz, 1 H), 2.28 – 2.25 (m, 2 H), 2.15 – 2.10 (m, 1 H), 2.08 – 2.00 (m, 2 H), 1.94 – 1.88

(m, 1 H), 1.67 (d, $J = 14.6$ Hz, 1 H), 1.29 – 1.25 (m, 1 H), 1.24 (s, 3 H), 1.09 (s, 9 H), 0.94 (d, $J = 6.73$ Hz, 3 H), 0.87 (d, $J = 6.82$ Hz, 3 H) ppm; ^{13}C NMR (100 MHz, CDCl_3), δ 208.3, 170.4, 138.0, 135.6, 132.7, 129.9, 127.8, 115.5, 87.5, 85.5, 75.9, 62.1, 59.5, 48.7, 41.9, 36.0, 33.4, 26.6, 23.2, 19.4, 19.2, 17.5, 17.0 ppm; IR (film): ν 2960 (s), 2932 (s), 1763 (s), 1735 (s), 1711 (s), 1137 (s), 1112 (s), 702 (s), 505 (s) cm^{-1} ; MS (ESI) calculated for $\text{C}_{33}\text{H}_{44}\text{O}_5\text{SiNa}^+$: 571.2850, found : 571.2827; $[\alpha]_{\text{D}}^{25} +77.8$ (c 0.27, CHCl_3 , -60% ee).

Enol-triflate synthesis



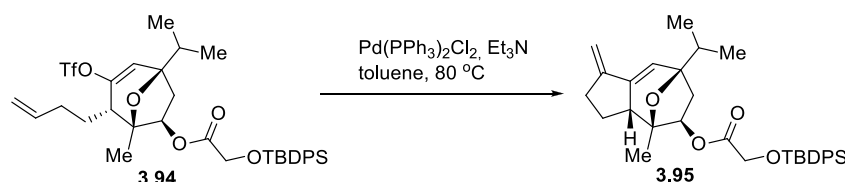
In an oven-dried flask, a solution of the decarboxylated product **3.93** (164.4 mg, 0.3 mmol, 1.0 equiv) in anhydrous THF (3 mL, 0.1 M) was charged under nitrogen at room temperature, followed by *N*-phenyl-*bis*(trifluoromethanesulfonimide) (128.5 mg, 0.36 mmol, 1.2 equiv). The flask was then cooled to -78 °C, followed by dropwise addition of KHMDS (0.5 M, 0.72 ml, 1.2 equiv) at this temperature. The solution was stirred at -78 °C for 30 min, warmed to 0 °C over 3 h (the reaction has to be warmed to 0 °C slowly to avoid side products) until the substrate was consumed completely. The reaction was quenched by addition of 5 mL saturated NaHCO_3 aqueous solution, warmed to room temperature, extracted with Et_2O (10 ml*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 80:1) to yield the product **3.94** (189.7 mg, 0.28 mmol, 93% yield) as light yellow liquid.

Compound (+)-3.94: ^1H NMR (700 MHz, CDCl_3), δ 7.69 – 7.67 (m, 4 H), 7.45 – 7.43 (m, 2 H), 7.40 – 7.38 (m, 4 H), 5.89 (s, 1 H), 5.79 – 5.73 (m, 1 H), 5.33 (dd, $J = 7.70, 5.13$ Hz, 1 H), 5.09 (d, $J = 17.14$ Hz, 1 H), 5.05 (d, $J = 10.09$ Hz, 1 H), 4.26 (d, $J = 3.64$ Hz, 2 H), 2.65 (d, $J = 7.26$ Hz, 1 H), 2.54 (dd, $J = 12.86, 7.91$ Hz, 1 H), 2.37 – 2.32 (m, 1 H), 2.17 – 2.11 (m, 1 H), 1.91 – 1.87 (m, 1 H), 1.72 – 1.66 (m, 2 H), 1.63 (dd, $J = 12.92, 5.16$ Hz, 1 H), 1.19 (s, 3 H), 1.10 (s, 9 H), 0.93 (d, $J = 5.91$ Hz, 3 H), 0.92 (d, $J = 6.51$ Hz, 3 H) ppm; ^{13}C NMR (175 MHz, CDCl_3), δ 170.5, 150.4, 137.1, 135.6, 135.5, 132.7, 132.6, 130.0, 129.9, 127.8, 127.7, 120.1, 118.4 (q, $J_{\text{C-F}} = 320.8$ Hz), 116.3, 85.9, 82.8, 75.9, 62.1, 48.1, 46.3, 34.2, 33.8, 26.7, 25.9, 19.5,

19.2, 17.2, 17.1 ppm; **R** (film): ν 2961 (s), 2934 (s), 1763 (s), 1736 (s), 1420 (s), 1139 (s), 702 (s), 608 (s), 504 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{34}\text{H}_{43}\text{F}_3\text{O}_7\text{SiNa}^+$: 703.2343, found : 703.2308; $[\alpha]_{\text{D}}^{25}$ +61.3 (c 0.47, CHCl_3 , -60% *ee*).

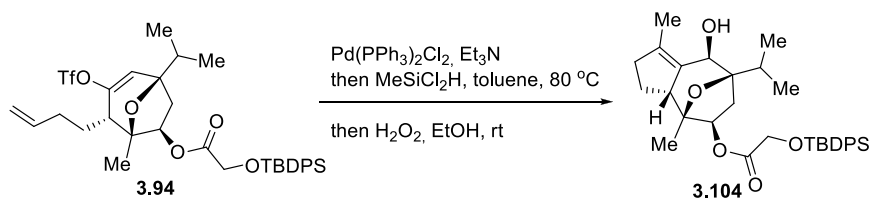
Heck-coupling-hydrosilylation-Tamao-Fleming-oxidation sequence

Step-wise Heck reaction:



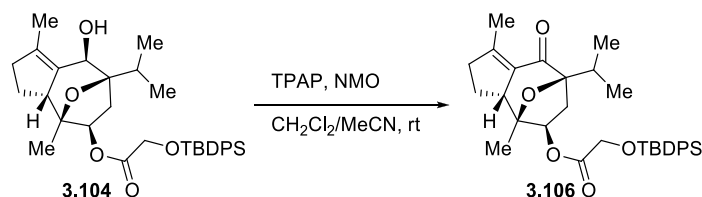
In an oven-dried flask, a solution of the enol-triflate compound **3.94** (136 mg, 0.2 mmol, 1.0 equiv) in anhydrous toluene (10 mL, 0.02 M) was charged under nitrogen at room temperature, followed by Et_3N (41.5 μL , 0.3 mmol, 1.5 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (14.0 mg, 0.02 mmol, 0.1 equiv) in one portion. The flask was then heated at $80\text{ }^\circ\text{C}$ for 30 min until the substrate was consumed completely. The reaction was quenched by addition of 5 mL H_2O , cooled down to room temperature, extracted with Et_2O (10 ml*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 80:1) to yield the product **3.95** (189.7 mg, 0.28 mmol, quantitative yield) as light yellow liquid.

Compound (-)-3.95: $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 7.69 – 7.67 (m, 4 H), 7.45 – 7.36 (m, 6 H), 5.94 (d, $J = 2.72$ Hz, 1 H), 5.28 (s, 1 H), 5.22 (dd, $J = 6.90, 6.74$ Hz, 1 H), 4.90 (s, 1 H), 4.24 (s, 2 H), 2.79 – 2.74 (m, 1 H), 2.49 (dd, $J = 16.12, 7.98$ Hz, 1 H), 2.41 (dd, $J = 12.05, 7.82$ Hz, 1 H), 2.38 – 2.31 (m, 1 H), 1.95 – 1.90 (m, 1 H), 1.88 – 1.80 (m, 1 H), 1.64 (dd, $J = 11.94, 5.97$ Hz, 1 H), 1.54 – 1.43 (m, 1 H), 1.17 (s, 3 H), 1.09 (s, 9 H), 0.98 (d, $J = 7.23$ Hz, 3 H), 0.96 (d, $J = 6.96$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3), δ 170.7, 146.6, 139.9, 135.6, 132.8, 129.9, 127.8, 119.1, 103.9, 84.0, 83.8, 75.6, 62.2, 52.5, 47.1, 33.8, 32.1, 26.7, 25.2, 20.1, 19.2, 17.7, 17.6 ppm; **R** (film): ν 2959 (s), 2932 (s), 1760 (s), 1733 (s), 1140 (s), 702 (s), 504 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{33}\text{H}_{46}\text{NO}_4\text{Si}^+$: 548.3191, found : 548.3181; $[\alpha]_{\text{D}}^{25}$ -2.5 (c 0.12, CHCl_3 , -60% *ee*).

One-pot transformation:

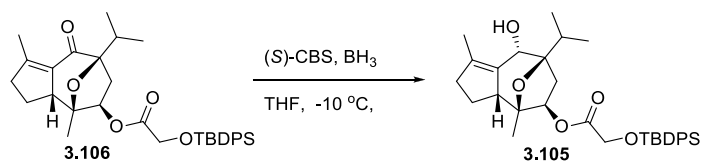
In an oven-dried flask, a solution of the triflate compound **3.94** (68 mg, 0.1 mmol, 1.0 equiv) in anhydrous toluene (5 mL, 0.02 M) was charged under nitrogen at room temperature, followed by Et₃N (41.5 μ L, 0.3 mmol, 3.0 equiv) and Pd(PPh₃)₂Cl₂ (7.0 mg, 0.01 mmol, 0.1 equiv) in one portion. The flask was then heated at 80 °C for 30 min until the substrate was consumed completely. Then dichloromethylsilane (28.5 μ L, 0.25 mmol, 2.5 equiv) was added via syringe in one portion. The reaction was stirred at 80 °C for additional 5 h until the Heck coupling intermediate was consumed completely. The reaction was then cooled down to room temperature, quenched by addition of ethanol (5 mL), followed by H₂O₂ (0.5 mL) in one portion. The resulting suspension was stirred vigorously at room temperature for 2 h, extracted with Et₂O (10 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 20:1) to yield the product **3.104** (31.8 mg, 0.06 mmol, 58%) as light yellow liquid.

Compound (-)-3.104: ¹H NMR (400 MHz, CDCl₃), δ 7.69 – 7.67 (m, 4 H), 7.45 – 7.36 (m, 6 H), 5.02 (dd, *J* = 7.11, 2.75 Hz, 1 H), 4.24 (s, 2 H), 4.07 (s, 1 H), 2.95 (m, 1 H), 2.44 – 2.28 (m, 3 H), 1.99 – 1.95 (m, 1 H), 1.73 (s, 3 H), 1.64 – 1.61 (m, 2 H), 1.58 – 1.52 (m, 2 H), 1.09 (s, 12 H), 0.89 (d, *J* = 6.29 Hz, 3 H), 0.88 (d, *J* = 6.33 Hz, 3 H) ppm; ¹³C NMR (100 MHz, CDCl₃), δ 171.0, 137.5, 135.6, 132.8, 132.0, 129.9, 127.8, 87.5, 75.0, 66.7, 62.2, 52.3, 37.5, 36.1, 28.2, 26.6, 23.0, 19.2, 18.7, 17.7, 15.9, 13.5 ppm; **R** (film): ν 2957 (s), 2932 (s), 1758 (s), 1731 (s), 1138 (s), 1113 (s), 702 (s), 504 (s) cm⁻¹; **MS** (ESI) calculated for C₃₃H₄₄O₅SiNa⁺: 571.2850, found : 571.2843; [α]_D²⁵ -17.9 (c 0.14, CHCl₃, -60% ee).

Ley oxidation

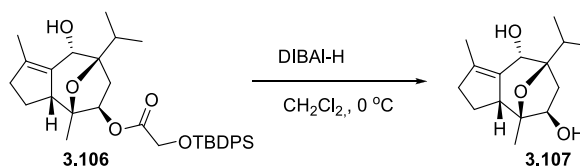
In an oven-dried flask, a solution of the alcohol **3.104** (27.4 mg, 0.05 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2 mL) was charged under nitrogen at room temperature, followed by anhydrous MeCN (0.2 mL), *N*-methylmorpholine-*N*-oxide (7.0 mg, 0.06 mmol, 1.2 equiv), and TPAP (1.8 mg, 0.005 mmol, 0.1 equiv) in one portion. The flask was then stirred at room temperature for 2 h until the substrate was consumed completely. The reaction was quenched by addition of 5 mL H_2O , extracted with CH_2Cl_2 (10 mL*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 40:1) to yield the oxidation product **3.106** (23.5 mg, 0.043 mmol, 86%) as light yellow liquid, which has to stored under 0 °C.

Compound (-)-3.106: $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 7.70 – 7.66 (m, 4 *H*), 7.44 – 7.37 (m, 6 *H*), 5.36 (dd, $J = 4.41, 8.13$ Hz, 1 *H*), 4.27 (s, 2 *H*), 3.27 – 3.22 (m, 1 *H*), 2.57 – 2.45 (m, 1 *H*), 2.37 (dd, $J = 17.78, 9.57$ Hz, 1 *H*), 2.24 – 2.14 (m, 2 *H*), 2.07 (s, 3 *H*), 1.98 – 1.88 (m, 2 *H*), 1.77 – 1.66 (m, 1 *H*), 1.14 (s, 3 *H*), 1.09 (s, 9 *H*), 1.01 (d, $J = 1.46$ Hz, 3 *H*), 0.99 (d, $J = 1.32$ Hz, 3 *H*) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3), δ 198.6, 170.9, 155.8, 135.6, 135.3, 132.7, 129.9, 127.8, 89.7, 86.1, 74.6, 62.2, 56.7, 41.5, 38.7, 30.0, 26.7, 25.2, 19.2, 18.9, 18.0, 17.2, 15.9 ppm; **R** (film): ν 2932 (s), 1759 (s), 1734 (s), 1691 (s), 1625 (s), 1428 (s), 1139 (s), 702 (s), 504 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{33}\text{H}_{42}\text{O}_5\text{SiNa}^+$: 569.2694, found : 569.2666; $[\alpha]_{\text{D}}^{25}$ -58.3 (c 0.24, CHCl_3 , -60% *ee*).

Kinetic CBS reduction under optimized condition

In an oven-dried flask, a solution of the enone **3.106** (27.3 mg, 0.05 mmol, 1.0 equiv) in anhydrous THF (2 mL) was charged under nitrogen at room temperature. The flask was cooled to -10 °C, and then (S)-CBS catalyst (4.2 mg, 0.015, 0.3 mmol) was added in one portion followed by borane tetrahydrofuran complex solution (1.0 M in THF, 45 μL, 0.9 equiv) dropwise. The flask was then stirred at -10 °C for 2 h, it was then quenched by addition of 1.0 mL methanol (the reaction has to be quenched before the enone was consumed completely to ensure higher *ee*). After it was brought to room temperature, the mixture was diluted with 10 mL saturated NH₄Cl aqueous solution, extracted with Et₂O (10 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 20:1) to yield the reduced product **3.105** (18.9 mg, 0.035 mmol, 69%) as light yellow liquid.

Compound (-)-3.105: ¹H NMR (400 MHz, CDCl₃), δ 7.70 – 7.68 (m, 4 H), 7.43 – 7.36 (m, 6 H), 5.09 (dd, *J* = 7.91, 1.95 Hz, 1 H), 4.39 (s, 1 H), 4.24 (s, 2 H), 2.68 (m, 1 H), 2.33 (br s, 1 H), 2.27 (dd, *J* = 14.27, 8.27 Hz, 1 H), 1.98 – 1.91 (m, 1 H), 1.88 (s, 3 H), 1.86 – 1.82 (m, 1 H), 1.58 – 1.49 (m, 3 H), 1.09 (s, 9 H), 1.04 (s, 3 H), 1.03 (d, *J* = 6.16, 3 H), 0.98 (d, *J* = 6.72 Hz, 3 H) ppm; ¹³C NMR (100 MHz, CDCl₃), δ 170.9, 135.6, 134.4, 132.8, 131.5, 129.9, 127.8, 86.1, 75.9, 73.3, 62.3, 56.4, 39.1, 37.5, 31.2, 26.7, 23.1, 19.2, 18.4, 17.9, 17.2, 14.6 ppm; **R** (film): ν 3500 (s), 2958 (s), 2932 (s), 1757 (s), 11139 (s), 1113 (s), 702 (s), 504 (s) cm⁻¹; **MS** (ESI) calculated for C₃₃H₄₄O₅SiNa⁺: 571.2850, found : 571.2842; [**α**]_D²⁵ -35.7 (c 0.21, CHCl₃, 96% *ee*).

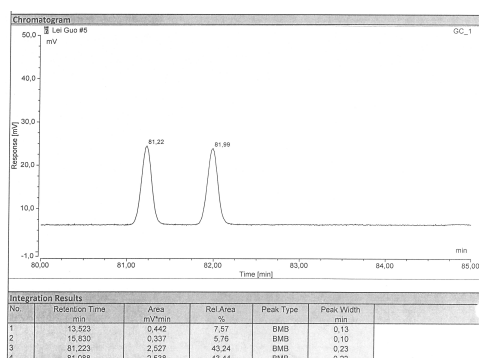
Enantiomeric excess determination

In an oven-dried flask, a solution of the reduced product **3.106** (16.5 mg, 0.03 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (3 mL) was charged under nitrogen at room temperature. The flask was cooled to $0\text{ }^\circ\text{C}$, and then DIBAL-H solution (1.0 M in hexanes, 0.15 mL, 5 equiv) was added in one portion. The flask was stirred at $0\text{ }^\circ\text{C}$ for 30 min until the substrate was consumed completely. Then the reaction was quenched by dropwise addition of 1 mL saturated sodium potassium tartrate aqueous solution. The resulting suspension was stirred vigorously until it became homogeneous, then it was diluted with 10 mL H_2O , extracted with CH_2Cl_2 (10 mL*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 4:1) to yield the *trans*-diol **3.107** (6.9 mg, 0.028 mmol, 92%) as colorless solid.

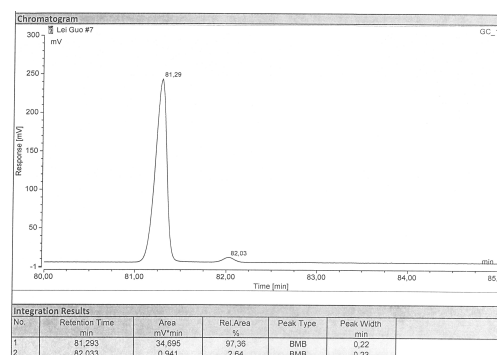
Compound (-)-3.107: $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 4.39 (s, 1 H), 3.94 (dd, $J = 7.31, 1.51$ Hz, 1 H), 2.75 – 2.68 (m, 1 H), 2.37 – 2.23 (m, 2 H), 2.27 (dd, $J = 14.34, 7.44$ Hz, 1 H), 2.03 – 1.94 (m, 1 H), 1.89 – 1.82 (m, 1 H), 1.88 (s, 3 H), 1.56 (dt, $J = 14.30, 1.73$ Hz, 1 H), 1.53 (br s, 2 H), 1.36 – 1.25 (m, 2 H), 1.20 (s, 3 H), 1.07 (d, $J = 3.43$ Hz, 3 H), 1.05 (d, $J = 3.26$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3), δ 133.6, 132.2, 86.8, 85.7, 73.5, 56.1, 40.5, 38.9, 30.9, 23.6, 18.8, 17.8, 17.2, 14.6 ppm; **R** (film): ν 3445 (s), 3356 (s), 1455 (s), 1038 (s), 973 (s), 893 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{15}\text{H}_{24}\text{O}_3\text{Na}^+$: 275.1618, found : 275.1617; $[\alpha]_{\text{D}}^{25}$ -40.2 (c 0.13, CHCl_3 , 96% ee); enantiomeric excess was measured by chiral GC: **Colum:** BetaDex_120, **Temperature program:** initial temperature at $40\text{ }^\circ\text{C}$, hold for 1 min, then ramping in the rate of $2.5\text{ }^\circ\text{C}/\text{min}$ to $200\text{ }^\circ\text{C}$, then hold at $200\text{ }^\circ\text{C}$; Retention Time: 81.29 min (major), 82.03 min (minor).

Chiral GC spectrums

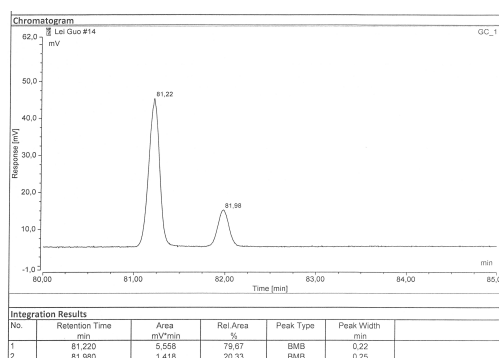
Racemic



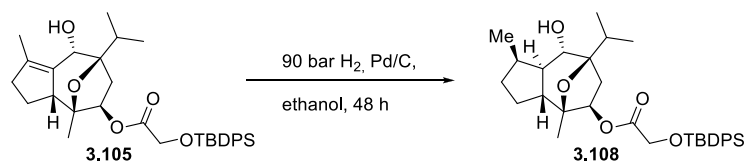
Kinetic (S)-CBS



Non-chiral reduction



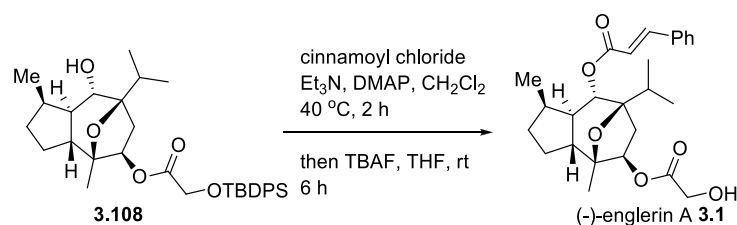
Hydrogenation of the tetra-substituted olefin



To a solution of the substrate **3.105** (16.5 mg, 0.03 mmol, 1.0 equiv) in anhydrous ethanol (10 mL) in a vial was added palladium on charcoal (Pd 10%, 16.5 mg, 10% w/w) in one portion. The vial was loaded into autoclave, pressurized under H₂ atmosphere at 90 bar for 48 h at room temperature. The suspension was then loaded onto a pad of Celite, flushed with EA. The filtrate was concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 20:1) to yield the product **3.108** (14.2 mg, 0.026 mmol, 86%) as colorless liquid.

Compound (-)-3.105: $^1\text{H NMR}$ (75 MHz, CDCl_3), δ 7.70 – 7.67 (m, 4 H), 7.46 – 7.34 (m, 6 H), 5.07 (dd, $J = 7.91, 2.89$ Hz, 1 H), 4.25 (s, 2 H), 3.63 (d, $J = 10.09$ Hz, 1 H), 2.40 (dd, $J = 14.58, 8.00$ Hz, 1 H), 2.33 – 2.29 (m, 1 H), 2.05 – 1.91 (m, 2 H), 1.69 – 1.62 (m, 2 H), 1.35 – 1.17 (m, 5 H), 1.09 (s, 9 H), 1.07 (s, 3 H), 1.03 (d, $J = 7.17$ Hz, 3 H), 1.01 (d, $J = 7.03$, 3 H), 0.88 (d, $J = 7.17$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3), δ 170.90, 135.59, 132.79, 129.90, 127.79, 85.82, 84.40, 75.44, 70.69, 62.24, 47.91, 38.41, 31.97, 31.27, 30.51, 26.65, 25.52, 19.23, 18.89, 18.22, 17.36, 16.84 ppm; **R** (film): ν 2956 (s), 2933 (s), 1758 (s), 1139 (s), 702 (s), 504 (s) cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{33}\text{H}_{46}\text{O}_5\text{SiNa}^+$: 573.3007, found : 573.3005; $[\alpha]_{\text{D}}^{25}$ -16.1 (c 0.21, CHCl_3 , 96% *ee*).

Esterification with cinnamoyl chloride and synthesis of (-)-englerin A



In an oven-dried flask, a solution of the substrate **3.108** (11.0 mg, 0.02 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2 mL) was charged under nitrogen at room temperature. Then DMAP (0.5 mg, 0.004, 0.2 equiv), Et_3N (0.2 mL), cinnamoyl chloride (3.7 mg, 0.022 mmol, 1.1 equiv) was added in this order. The flask was warmed to $40\text{ }^\circ\text{C}$ for 2 h until the substrate was consumed completely. Then the reaction was cooled to room temperature, quenched by addition of 1 mL saturated NaHCO_3 aqueous solution. The resulting mixture was diluted with 10 mL H_2O , extracted with CH_2Cl_2 (10 mL*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to give the crude liquid **3.109**, which was used directly in the next step without further purification.

Compound (-)-3.109: $^1\text{H NMR}$ (400 MHz, CDCl_3), δ 7.72 – 7.68 (m, 4 H), 7.66 (d, $J = 15.92$, 1 H), 7.55 – 7.51 (m, 2 H), 7.45 – 7.36 (m, 9 H), 6.39 (d, $J = 15.92$, 1 H), 5.16 – 5.09 (m, 2 H), 4.27 (s, 2 H), 2.61 (dd, $J = 14.50, 7.96$ Hz, 1 H), 2.17 – 2.10 (m, 1 H), 1.99 – 1.90 (m, 1 H), 1.87 – 1.81 (m, 1 H), 1.78 – 1.69 (m, 3 H), 1.53 – 1.49 (m, 1 H), 1.12 (s, 3 H), 1.10 (s, 9 H), 0.97 (d, $J = 6.87$ Hz, 3 H), 0.95 (d, $J = 2.99$ Hz, 3 H), 0.93 (d, $J = 2.93$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3), δ 171.0, 165.6, 145.1, 135.6, 134.3, 132.7, 130.4, 129.9, 128.9, 128.1, 127.8, 128.1, 85.4, 84.5, 75.4, 71.3, 62.3, 47.5, 46.9, 39.8, 32.9, 31.2, 30.9, 26.7, 24.6, 19.2, 18.9, 18.2, 17.5, 16.9 ppm; **R** (film): ν 2948 (s), 1731 (s), 1345 (s),

1316 (s), 898 (s), 706 (s), cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{42}\text{H}_{52}\text{O}_6\text{Na}^+$: 703.9334, found : 703.9341; $[\alpha]_{\text{D}}^{25}$ -18.7 (c 0.14, CHCl_3 , 96% *ee*).

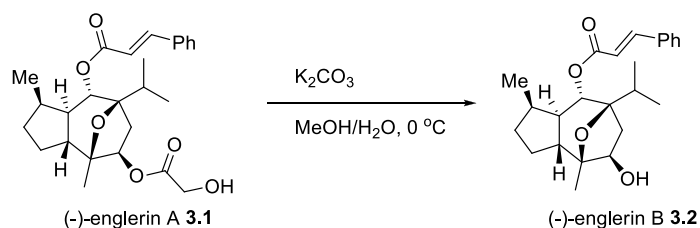
To a solution of the substrate **3.109** in THF was added a solution of TBAF (1.0 M in THF, 0.1 mL, 5.0 equiv) at room temperature. The mixture was stirred at room temperature for 6 h until the substrate was consumed completely. The reaction was quenched by addition of 1 mL saturated NH_4Cl aqueous solution, extracted with EA (10 ml*3), dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 3:1) to yield (-)-englerin A **3.1** (7.0 mg, 0.016 mmol, 79% over 2 steps) as colorless solid.

(-)-Englerin A 3.1: $^1\text{H NMR}$ (400 MHz, CD_3OD), δ 7.69 (d, $J = 16.0$ Hz, 1 H), 7.60 – 7.62 (m, 2 H), 7.40 – 7.42 (m, 3 H), 6.50 (d, $J = 16.1$ Hz, 1 H), 5.27 (dd, $J = 7.9, 2.8$ Hz, 1 H), 5.12 (d, $J = 9.9$ Hz, 1 H), 4.15 (s, 2 H), 2.70 (dd, $J = 14.6, 8.0$ Hz, 1 H), 2.11 – 2.16 (m, 1 H), 1.96 – 2.04 (m, 1 H), 1.84 – 1.90 (m, 2 H), 1.73 – 1.81 (m, 2 H), 1.64 – 1.71 (m, 1 H), 1.26 – 1.36 (m, 2 H), 1.19 (s, 3 H), 1.02 (d, $J = 6.8$ Hz, 3 H), 0.97 (d, $J = 7.1$ Hz, 3 H), 0.93 (d, $J = 7.1$ Hz, 3 H) ppm; $^{13}\text{C NMR}$ (100 MHz, CD_3OD), δ 174.0, 167.3, 146.8, 135.7, 131.6, 130.1, 129.3, 118.8, 86.7, 86.1, 76.7, 72.5, 61.1, 48.9, 48.0, 40.7, 34.1, 32.5, 32.0, 25.5, 19.2, 18.6, 17.7, 17.2 ppm; **R** (film): ν 3373 (br s), 2957 (s), 2489 (br s), 1709 (s), 1336 (s), 1118 (s), 971 (s), cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{26}\text{H}_{34}\text{O}_6\text{Na}^+$: 465.2248, found : 465.2248; $[\alpha]_{\text{D}}^{25}$ -27.9 (c 0.11, MeOH, 96% *ee*).

δ_{H} (synthetic)	δ_{H} (natural)	δ_{C} (synthetic)	δ_{C} (natural)
CD_3OD , 400 MHz	CD_3OD , 500 MHz	CD_3OD 100 MHz	CD_3OD 125 MHz
7.69 (d, $J = 16.0$ Hz, 1 H)	7.68 (d, $J = 16.0$ Hz, 1 H)	174.0	173.9
7.60 – 7.62 (m, 2 H)	7.61 (m, 2 H)	167.3	167.3
7.40 – 7.42 (m, 3 H)	7.40 (m, 3 H)	146.8	146.8
6.50 (d, $J = 16.1$ Hz, 1 H)	6.50 (d, $J = 16.0$ Hz, 1 H)	135.7	135.6
5.27 (dd, $J = 7.9, 2.8$ Hz, 1 H)	5.26 (dd, $J = 8.1, 2.9$ Hz, 1 H)	131.6	131.6
5.12 (d, $J = 9.9$ Hz, 1 H)	5.11 (d, $J = 9.6$ Hz, 1 H)	130.1	130.1
4.15 (s, 2 H)	4.15 (s, 2 H)	129.3	129.3
2.70 (dd, $J = 14.6, 8.0$ Hz, 1 H)	2.69 (dd, $J = 14.5, 7.9$ Hz, 1 H)	118.8	118.8
	H)		
2.11 – 2.16 (m, 1 H)	2.14 (m, 1 H)	86.7	86.4
1.96 – 2.04 (m, 1 H)	1.99 (m, 1 H)	86.1	86.0

1.84 – 1.90 (m, 2 H)	1.86 (m, 2 H)	76.7	76.6
1.73 – 1.81 (m, 2 H)	1.71 (m, 1 H)	72.5	72.4
	1.75 (m, 1 H)	61.1	61.0
1.64 – 1.71 (m, 1 H)	1.67 (m, 1 H)	48.9	48.9
1.26 – 1.36 (m, 2 H)	1.30 (m, 2 H)	48.0	48.0
1.19 (s, 3 H)	1.18 (s, 3 H)	40.7	40.7
1.02 (d, $J = 6.8$ Hz, 3 H)	1.01 (d, $J = 6.8$ Hz, 3 H)	34.1	34.0
0.97 (d, $J = 7.1$ Hz, 3 H)	0.96 (d, $J = 7.0$ Hz, 3 H)	32.5	32.4
0.93 (d, $J = 7.1$ Hz, 3 H)	0.92 (d, $J = 7.0$ Hz, 3 H)	32.0	32.0
		25.5	25.5
		19.2	19.3
		18.6	18.6
		17.7	17.8
		17.2	17.3

Synthesis of (-)-englerin B 3.1



To a solution of (-)-englerin A (8.8 mg, 0.02 mmol, 1.0 equiv) in a mixture of methanol and H₂O (3 mL, 2:1) was added K₂CO₃ (8.3 mg, 0.06 mmol, 3.0 equiv) at 0 °C. The mixture was stirred at this temperature for 4 h until englerin A was consumed completely. The reaction was diluted with 5 mL H₂O, extracted with EA (10 ml*3), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give the crude liquid, which was purified by column chromatography on silica (PE/EA = 1:1) to yield (-)-englerin B (5.5 mg, 0.014 mmol, 71%) as colorless liquid.

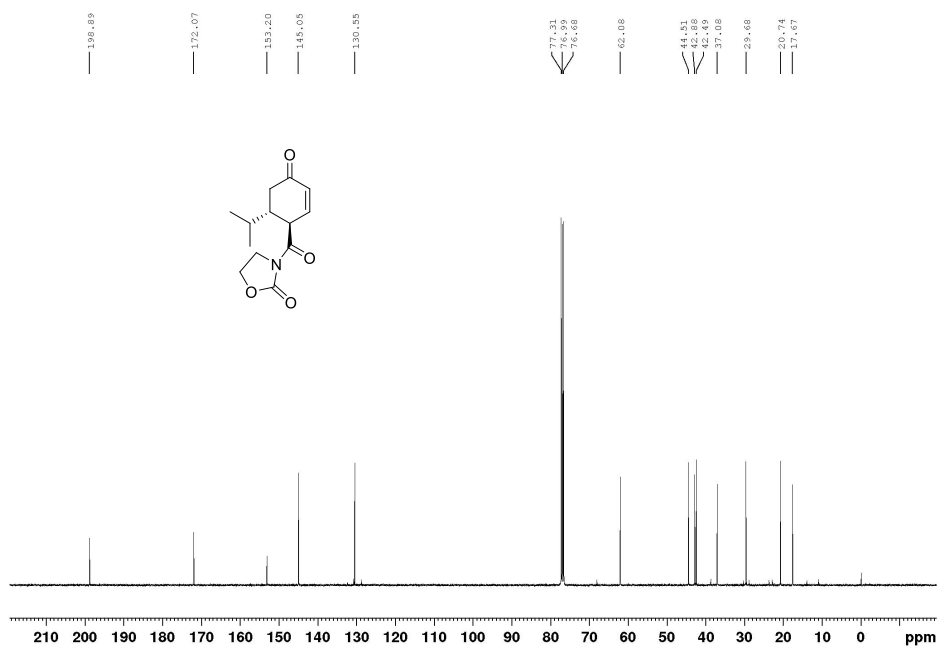
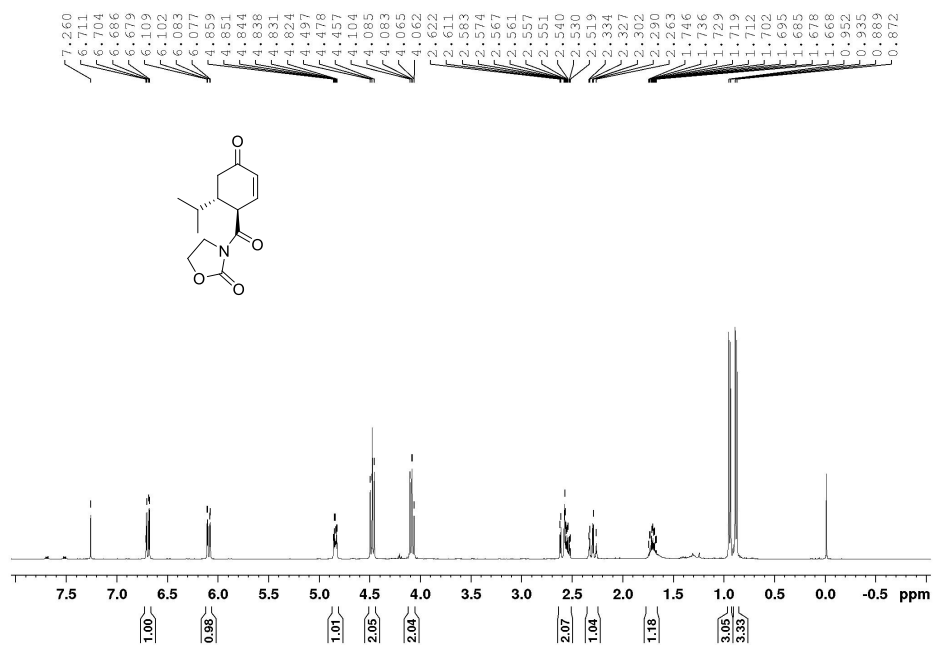
(-)-Englerin B 3.2: ¹H NMR (400 MHz, CD₃OD), δ 7.69 (d, $J = 16.1$ Hz, 1 H), 7.60 (m, 2 H), 7.39 – 7.41 (m, 3 H), 6.49 (d, $J = 16.0$ Hz, 1 H), 5.07 (d, $J = 10.1$ Hz, 1 H), 4.04 (dd, $J = 7.8, 2.7$ Hz, 1 H), 2.63 (dd, $J = 14.1, 7.8$ Hz, 1 H), 2.06 – 2.11 (m, 1 H), 1.90 – 2.00 (m, 1 H), 1.83 – 1.88 (m, 1 H), 1.68 – 1.75 (m, 3 H), 1.54 – 1.61 (m, 1 H), 1.26 – 1.31 (m, 1 H), 1.22 (s, 3 H), 1.16 – 1.18 (m, 1 H), 1.02 (d, $J = 6.8$ Hz, 3 H), 0.95 (d, $J = 7.1$ Hz, 3 H), 0.91 (d, $J = 7.1$ Hz, 3 H)

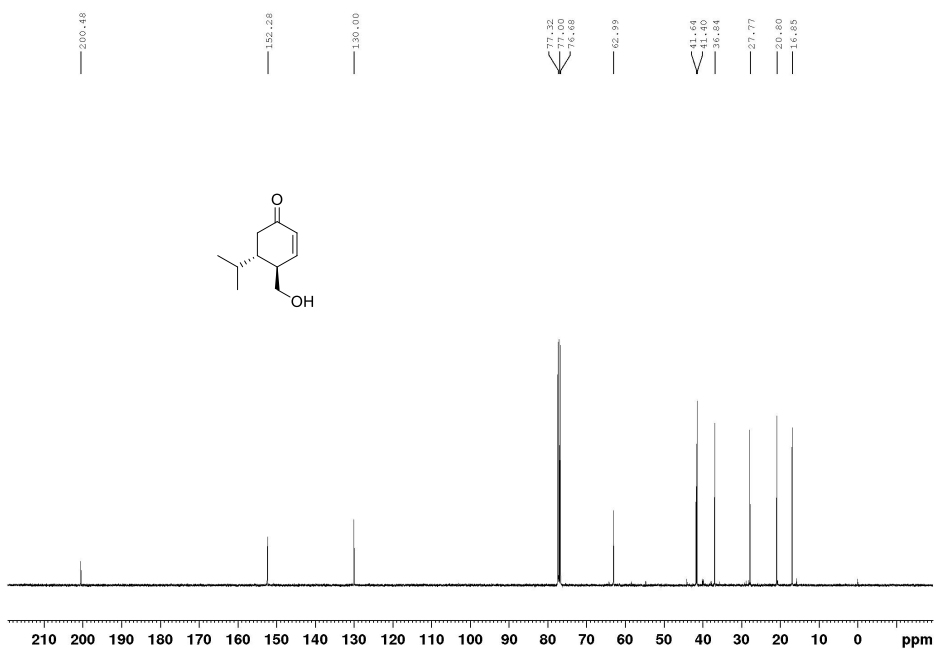
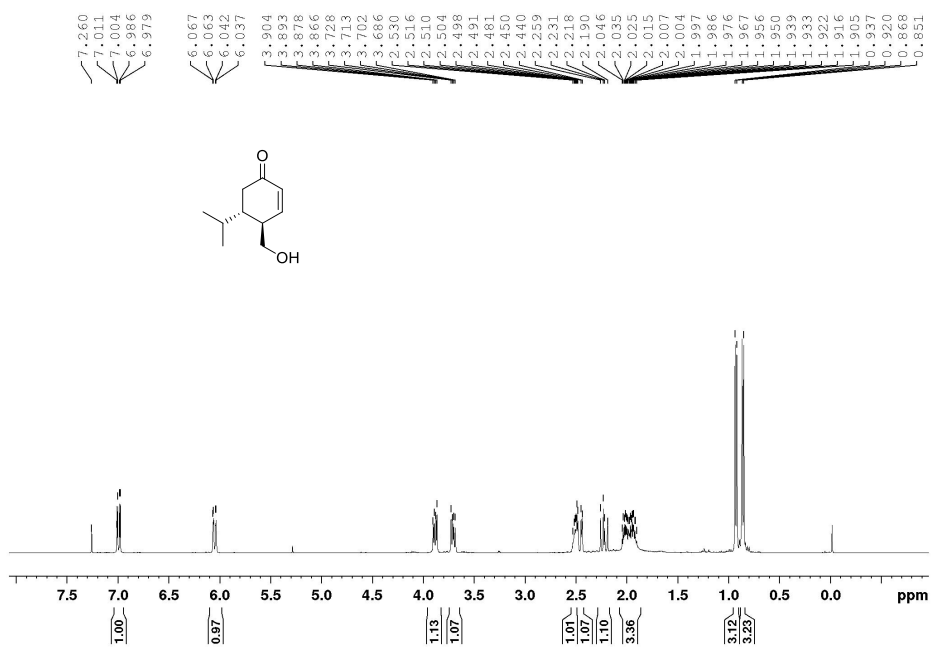
ppm; ^{13}C NMR (100 MHz, CD_3OD), δ 167.5, 146.7, 135.7, 131.6, 130.1, 129.3, 119.0, 86.8, 86.3, 73.2, 48.9, 47.8, 43.5, 34.6, 32.4, 32.1, 25.7, 19.5, 18.8, 17.9, 17.3 ppm; **R** (film): ν 3453 (br s), 2956 (s), 1708 (s), 1636 (s), 1171 (s), 766 (s), cm^{-1} ; **MS** (ESI) calculated for $\text{C}_{24}\text{H}_{32}\text{O}_4\text{Na}^+$: 407.2193, found : 407.2168; $[\alpha]_D^{25}$ -12.4 (c 0.1, MeOH, 96% ee).

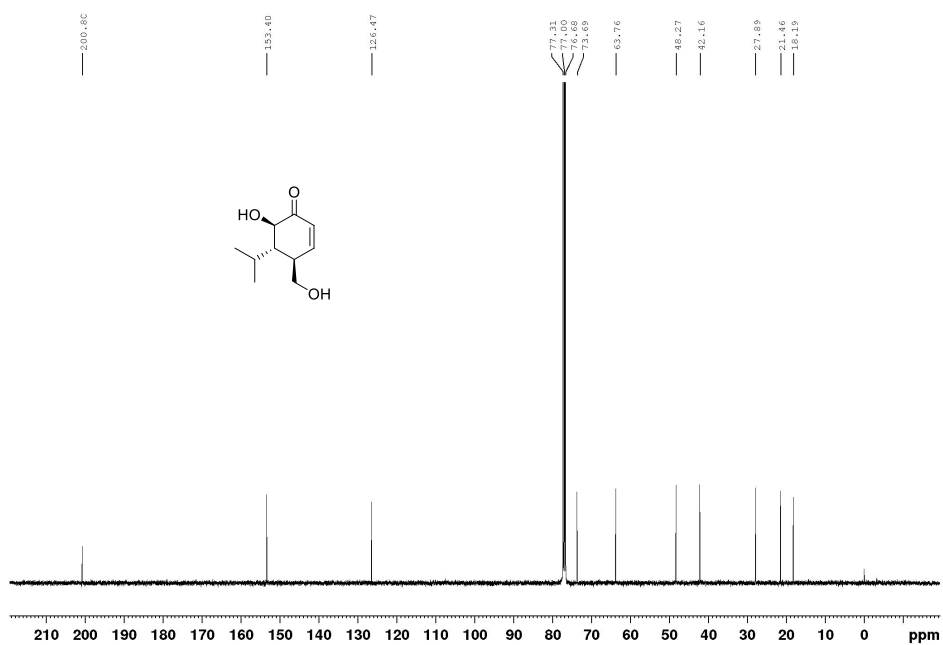
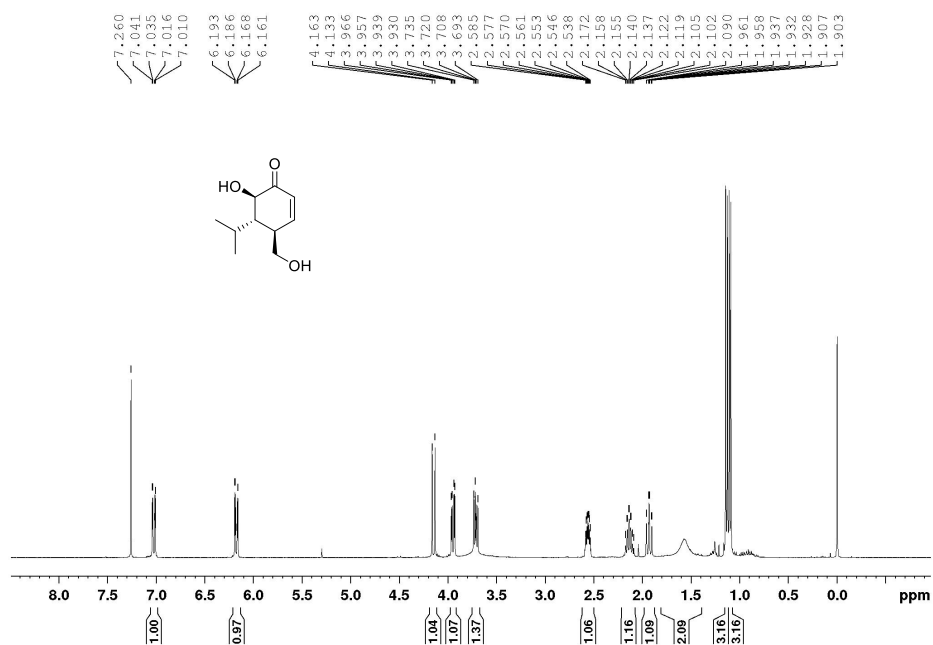
δ_{H} (synthetic) CD_3OD , 400 MHz	δ_{H} (natural) CD_3OD , 500 MHz	δ_{C} (synthetic) CD_3OD , 100 MHz	δ_{C} (natural) CD_3OD , 125 MHz
7.69 (d, $J = 16.1$ Hz, 1 H)	7.67 (d, $J = 16.0$ Hz, 1 H)	167.5	168.4
7.60 (m, 2 H)	7.60 (m, 2 H)	146.7	146.6
7.39 – 7.41 (m, 3 H)	7.39 (m, 3 H)	135.7	135.7
6.49 (d, $J = 16.0$ Hz, 1 H)	6.48 (d, $J = 16.0$ Hz, 1 H)	131.6	131.6
5.07 (d, $J = 10.1$ Hz, 1 H)	5.06 (d, $J = 10.0$ Hz, 1 H)	130.1	130.0
4.04 (dd, $J = 7.8, 2.7$ Hz, 1 H)	4.02 (dd, $J = 8.0, 2.5$ Hz, 1 H)	129.3	129.3
2.63 (dd, $J = 14.1, 7.8$ Hz, 1 H)	2.60 (dd, $J = 14.0, 8.0$ Hz, 1 H)	119.0	118.9
2.06 – 2.11 (m, 1 H)	2.7 (m, 1 H)	86.8	86.7
1.90 – 2.00 (m, 1 H)	1.94 (m, 1 H)	86.3	86.2
1.83 – 1.88 (m, 1 H)	1.86 (m, 1 H)	73.2	73.2
1.68 – 1.75 (m, 3 H)	1.73 (dd, $J = 14.0, 2.5$ Hz, 2 H)	48.9	48.9
	1.70 (m, 2 H)	47.8	47.8
1.54 – 1.61 (m, 1 H)	1.57 (m, 1 H)	43.5	43.4
1.26 – 1.31 (m, 1 H)	1.24 (m, 1 H)	34.6	34.6
1.22 (s, 3 H)	1.22 (s, 3 H)	32.4	32.4
1.16 – 1.18 (m, 1 H)	1.18 (m, 1 H)	32.1	32.1
1.02 (d, $J = 6.8$ Hz, 3 H)	1.02 (d, $J = 7.0$ Hz, 3 H)	25.7	25.7
0.95 (d, $J = 7.1$ Hz, 3 H)	0.95 (d, $J = 7.0$ Hz, 3 H)	19.5	19.5
0.91 (d, $J = 7.1$ Hz, 3 H)	0.90 (d, $J = 7.0$ Hz, 3 H)	18.8	18.8
		17.9	17.9
		17.3	17.3

Attachment: NMR Spectrums

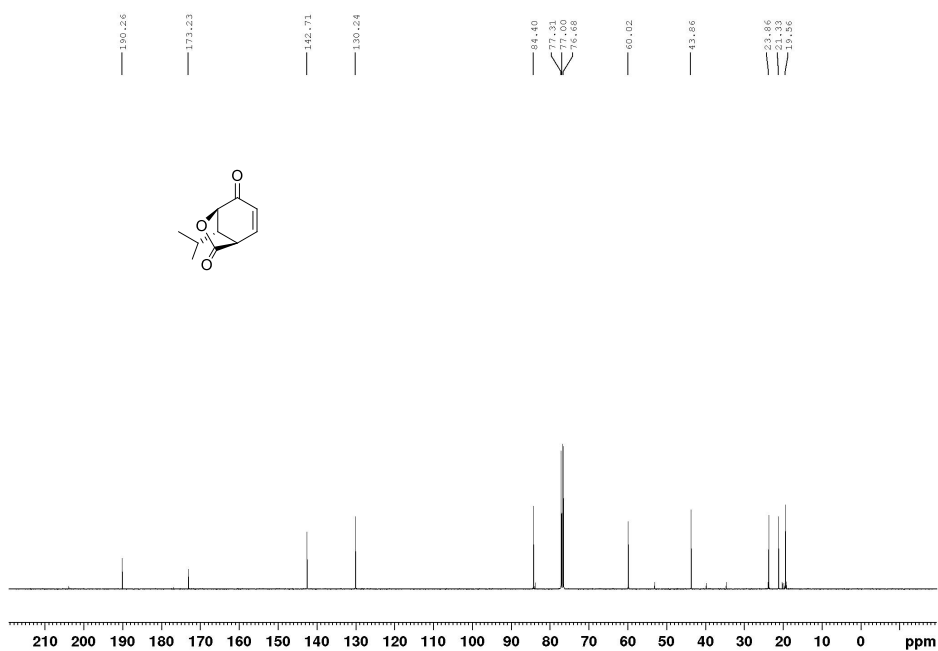
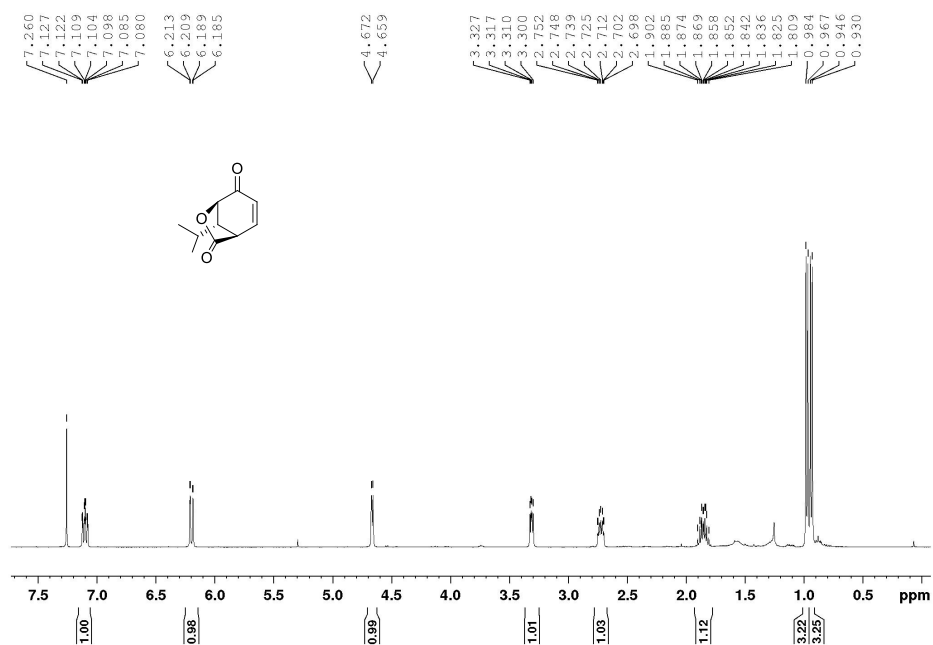
Compound 2.82



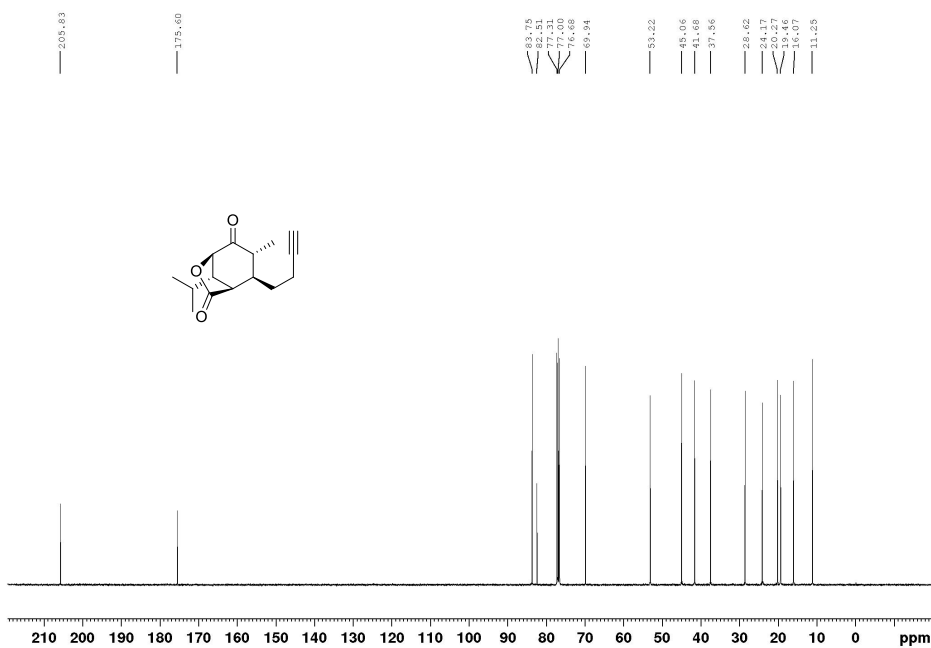
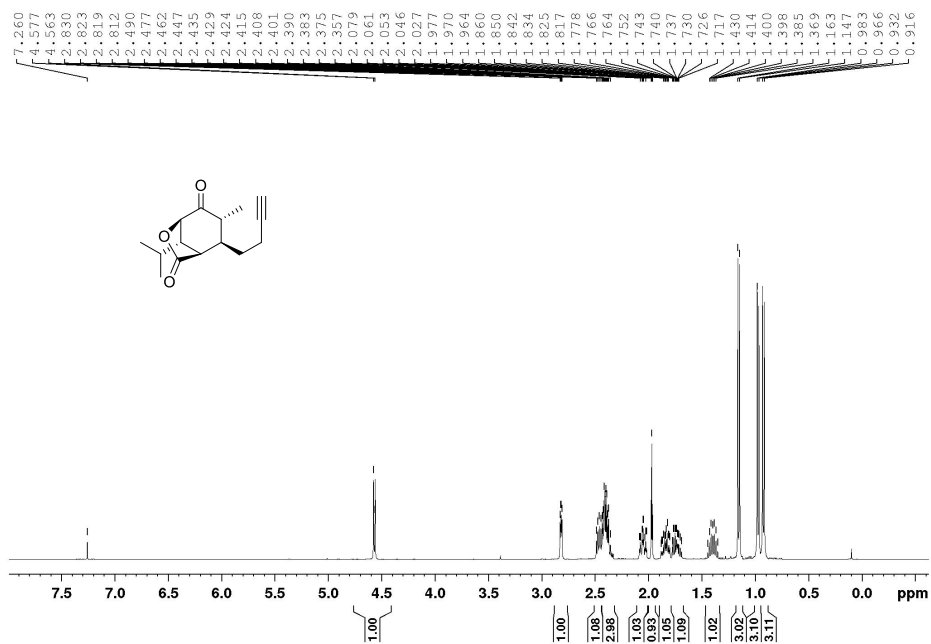
Compound **2.87**

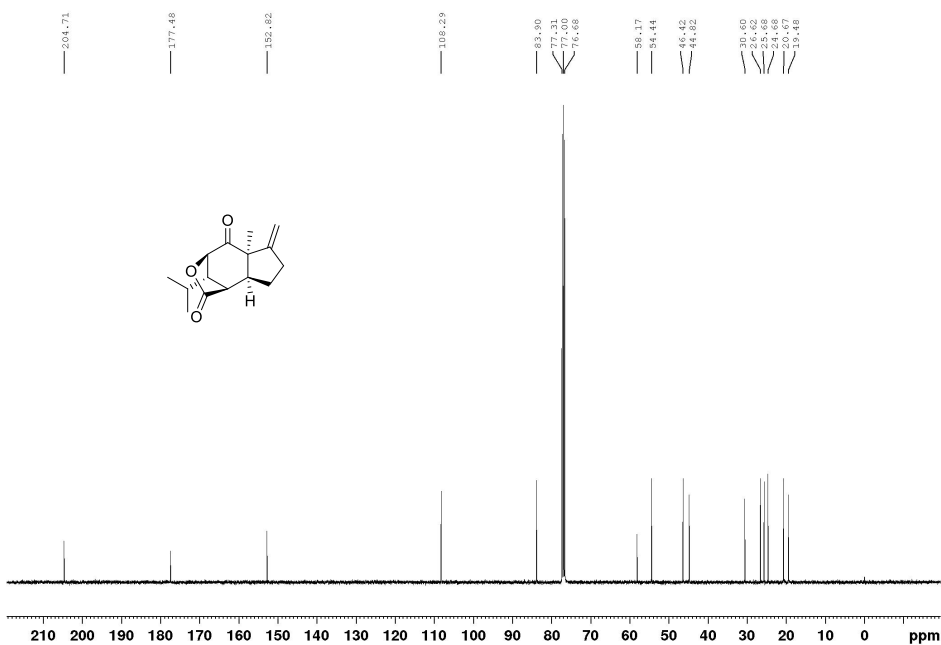
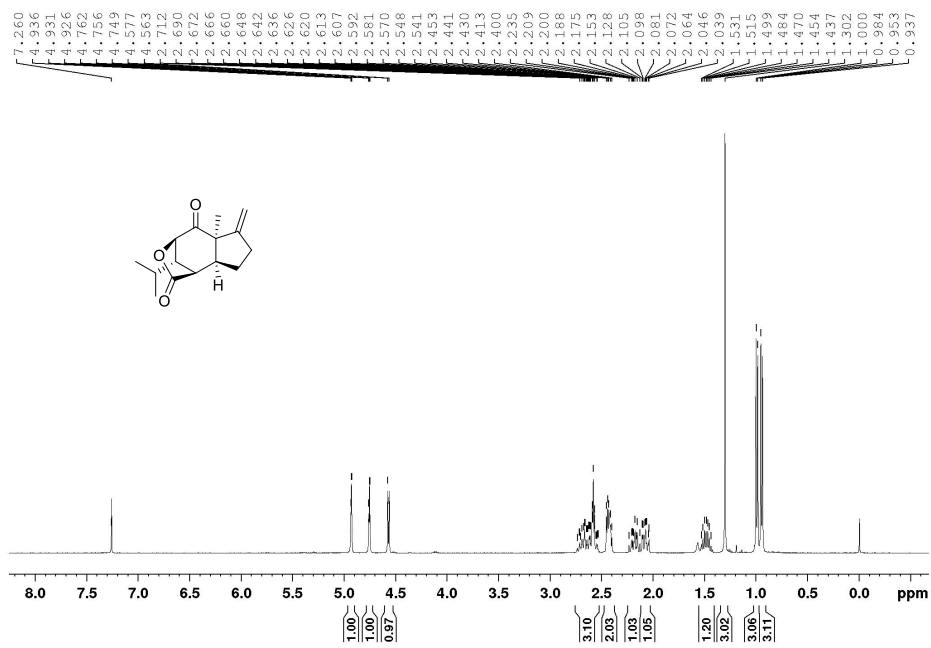
Compound **2.88**

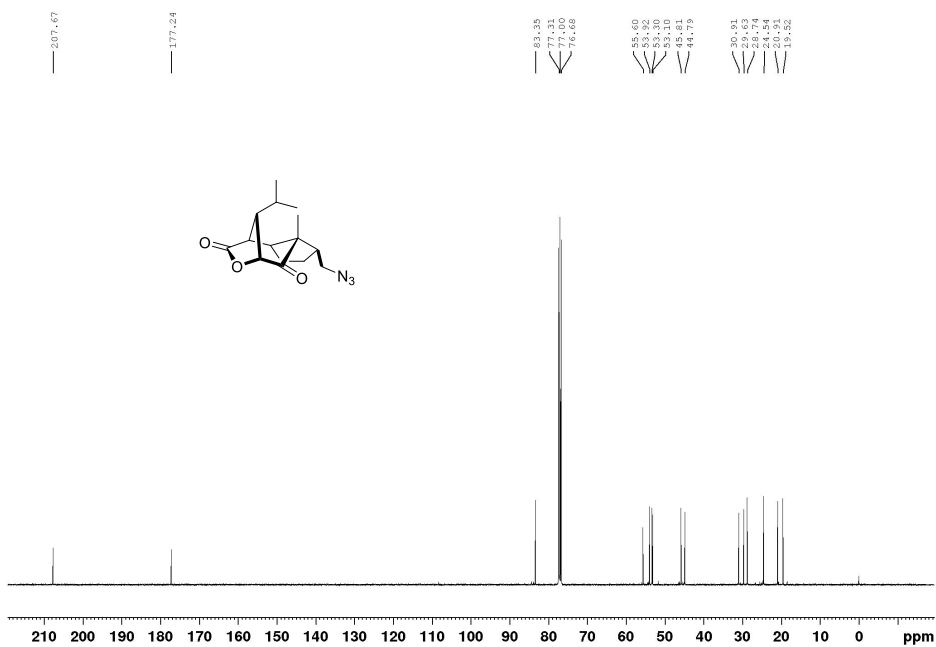
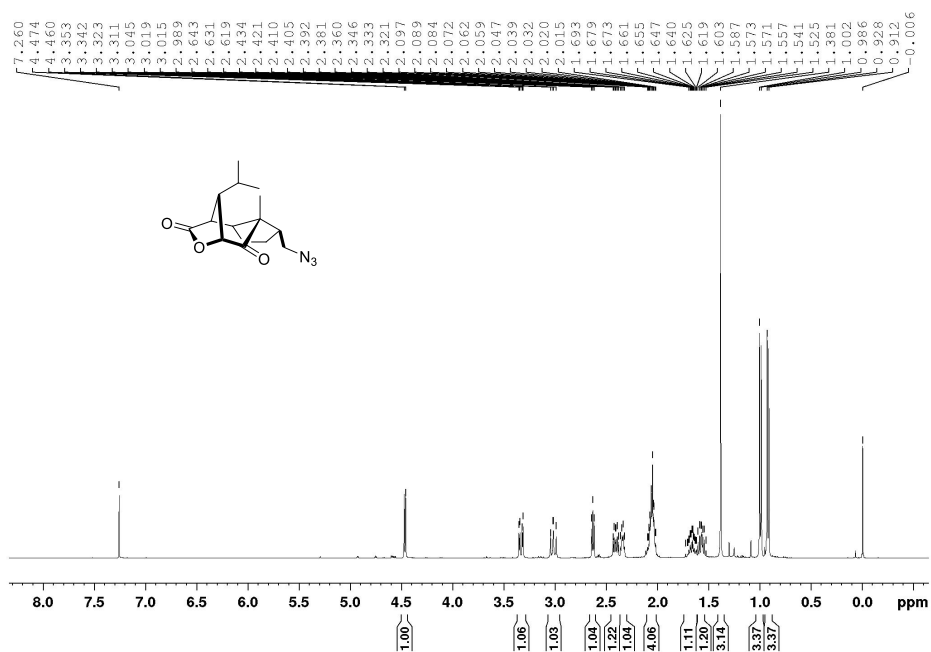
Compound 2.75



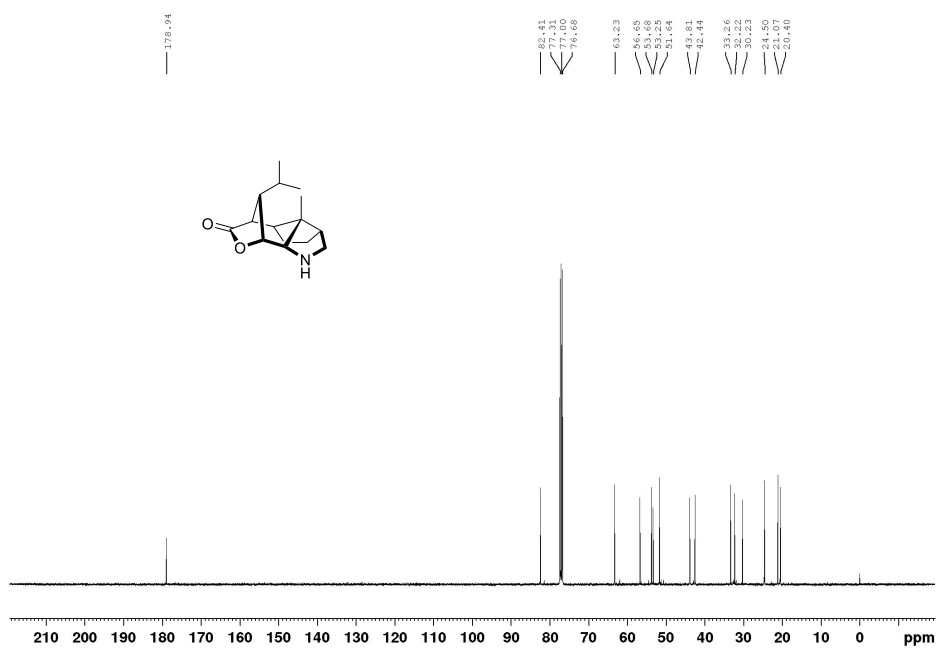
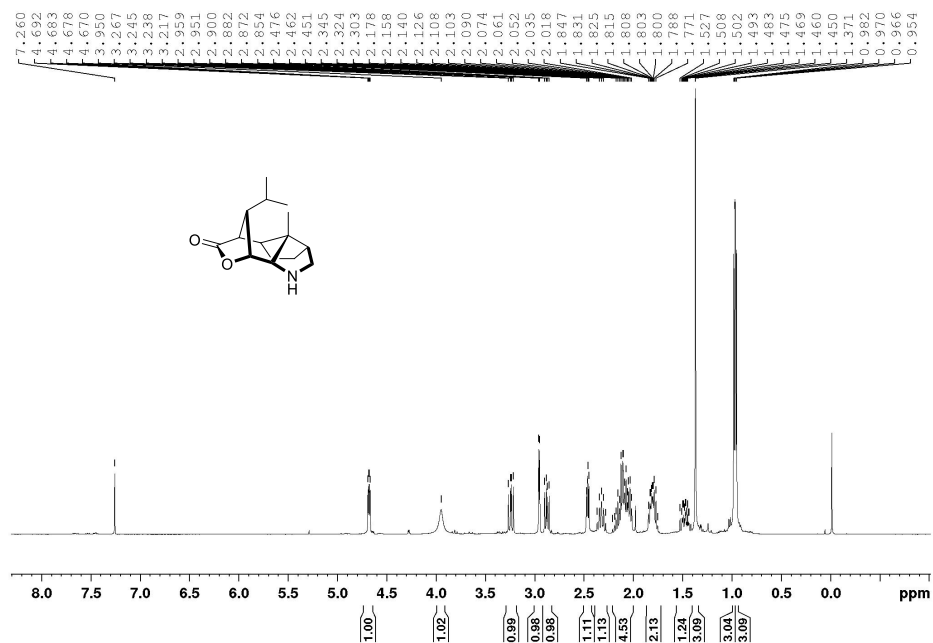
Compound 2.74

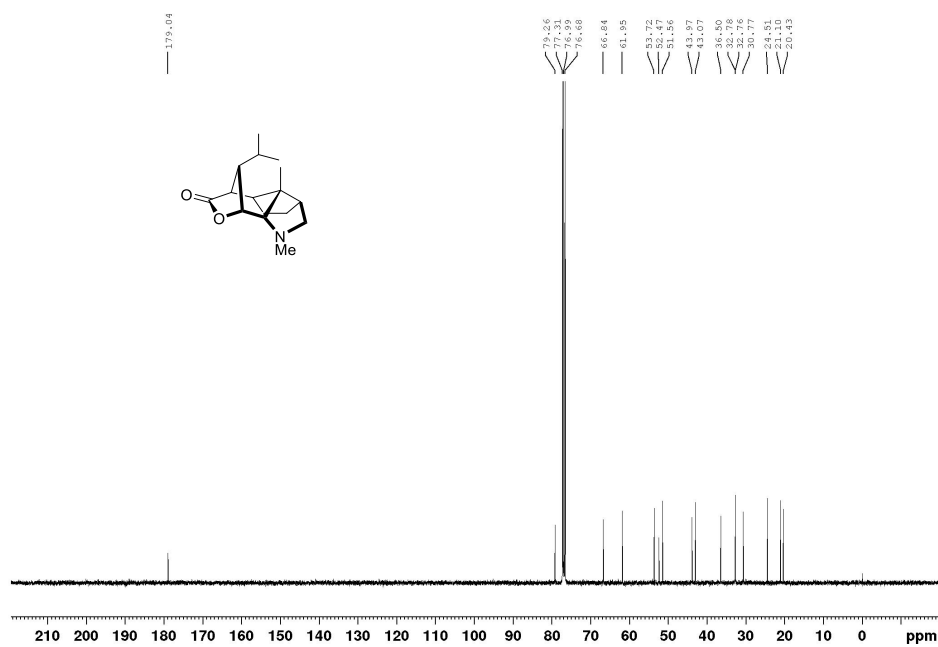
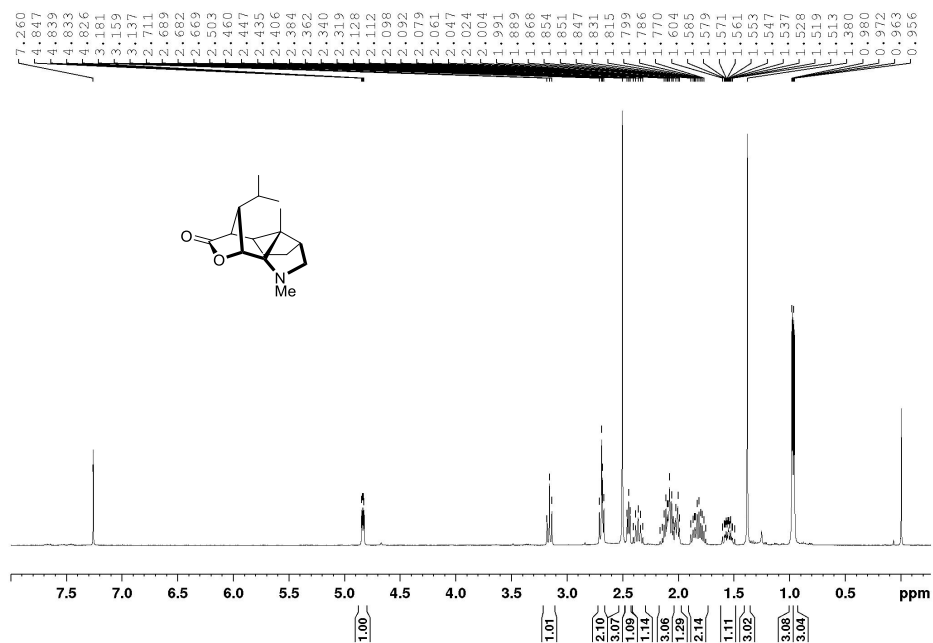


Compound **2.73**

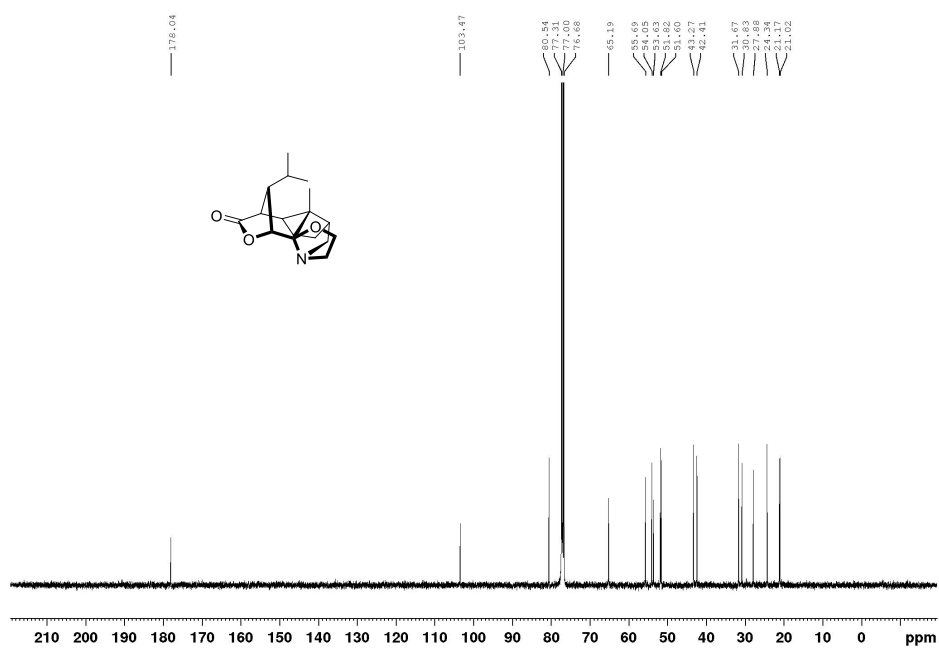
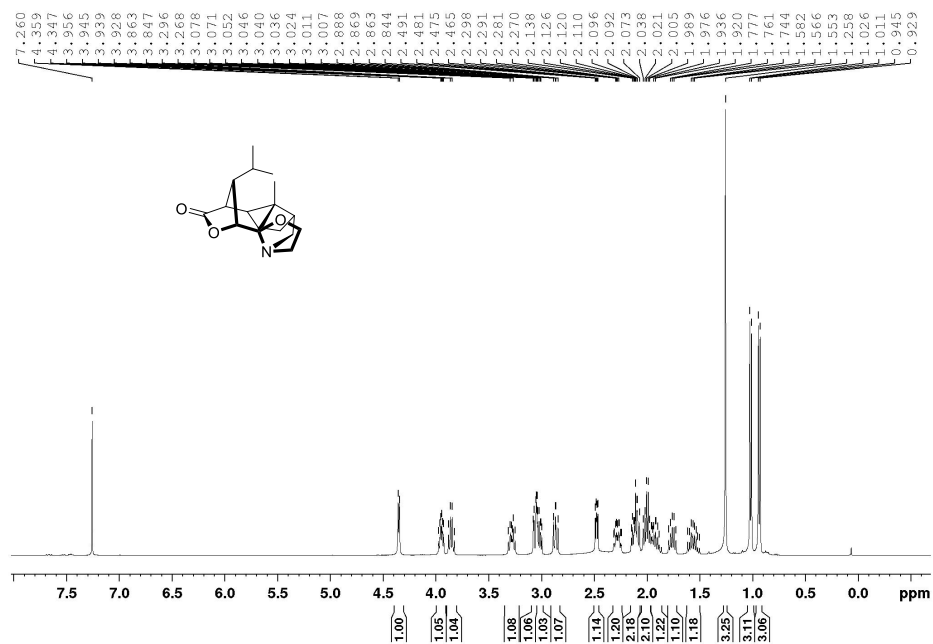
Compound **2.106**

(-)-Mubironine B 2.2

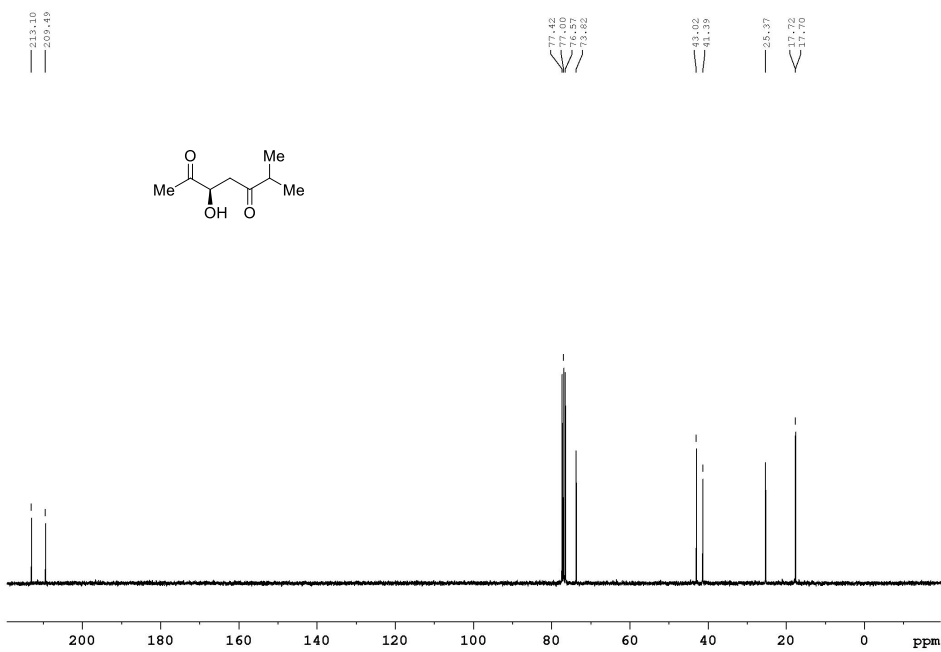
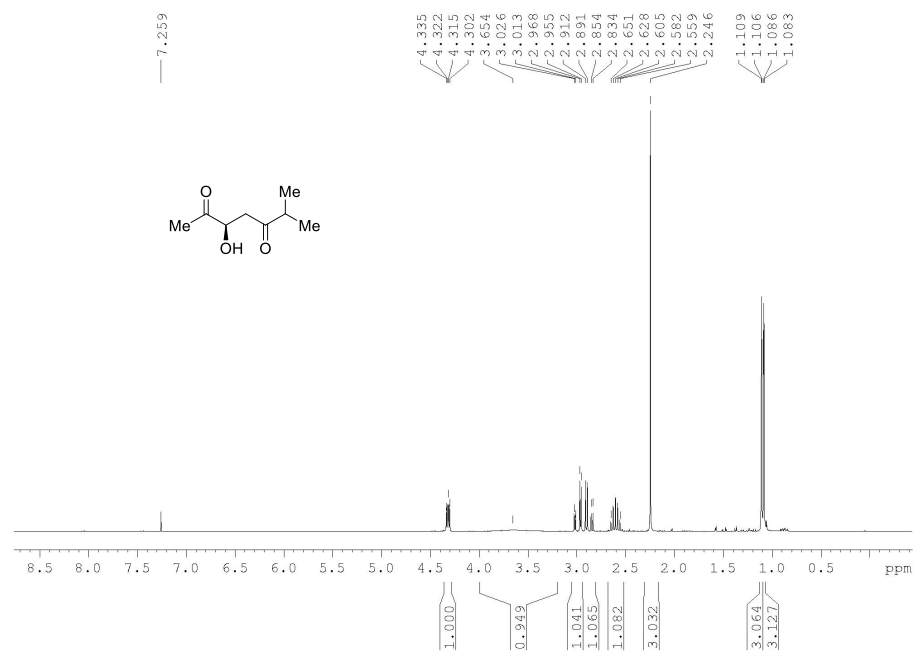


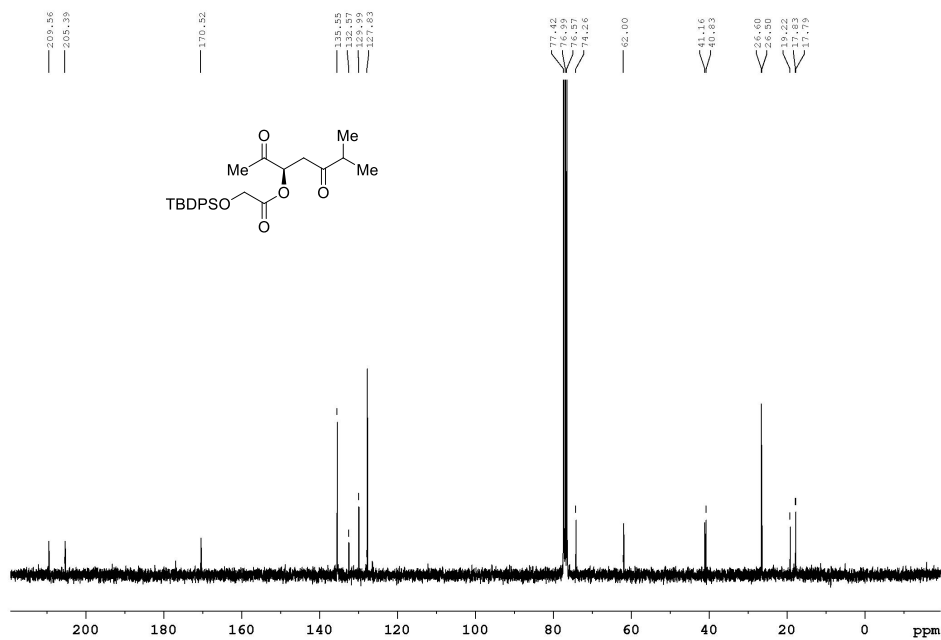
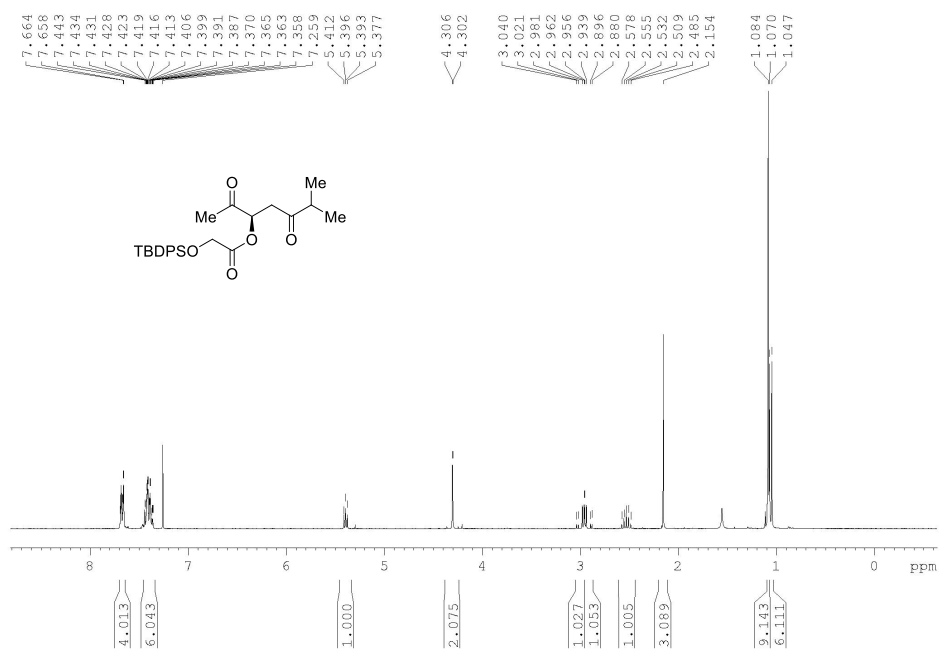
(-)-Dendribine **2.1**

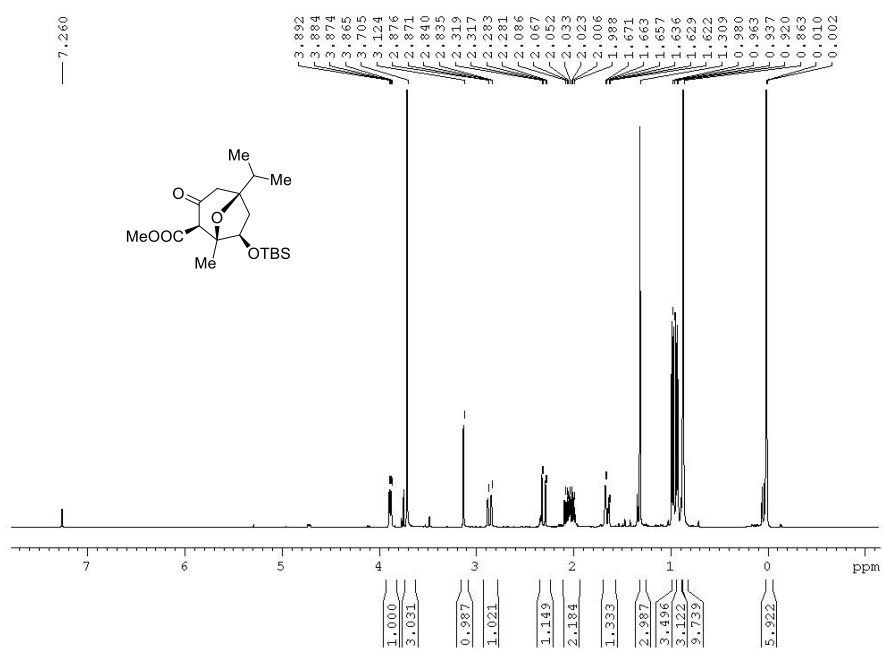
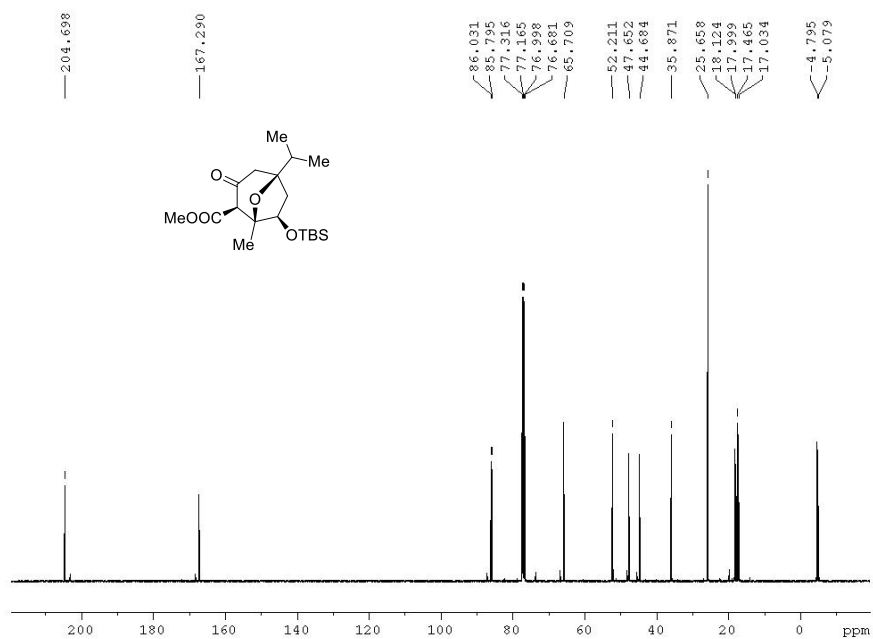
(-)-Dndroxine 2.3

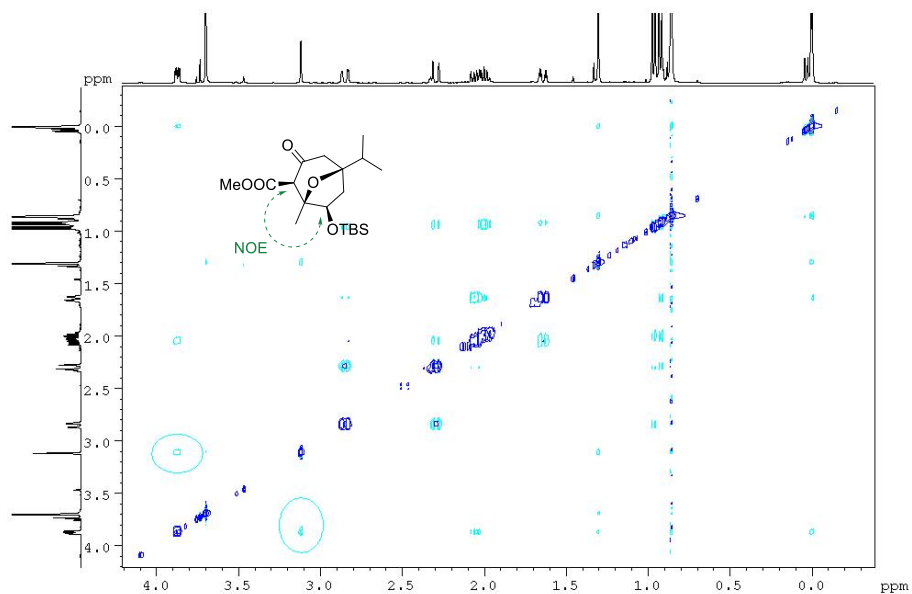
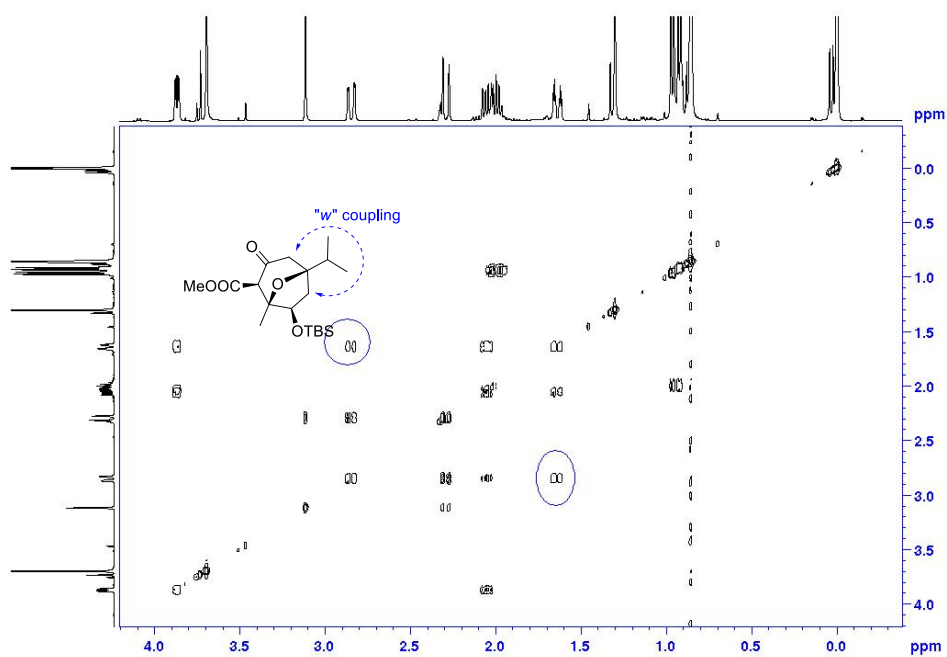


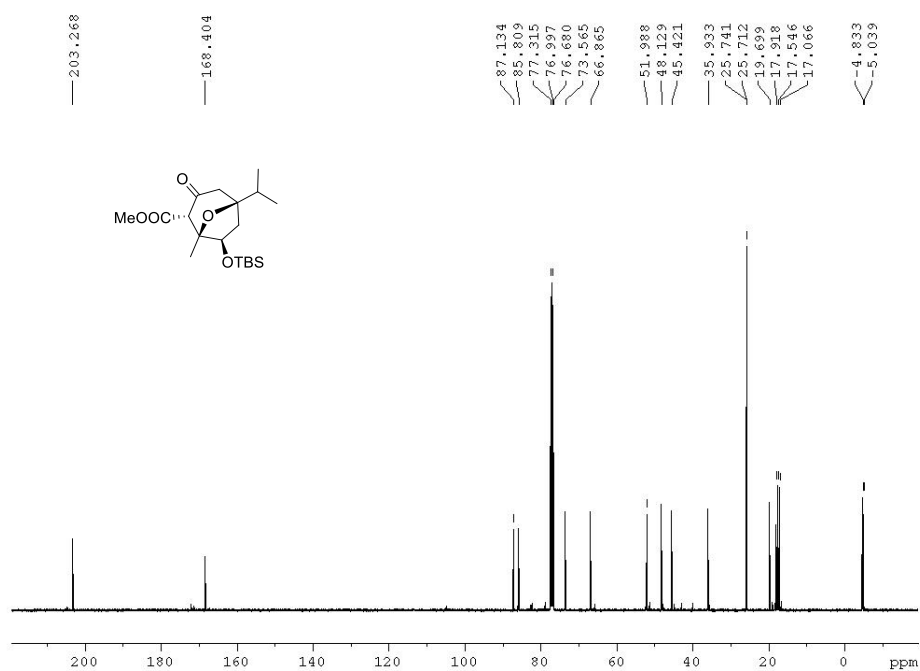
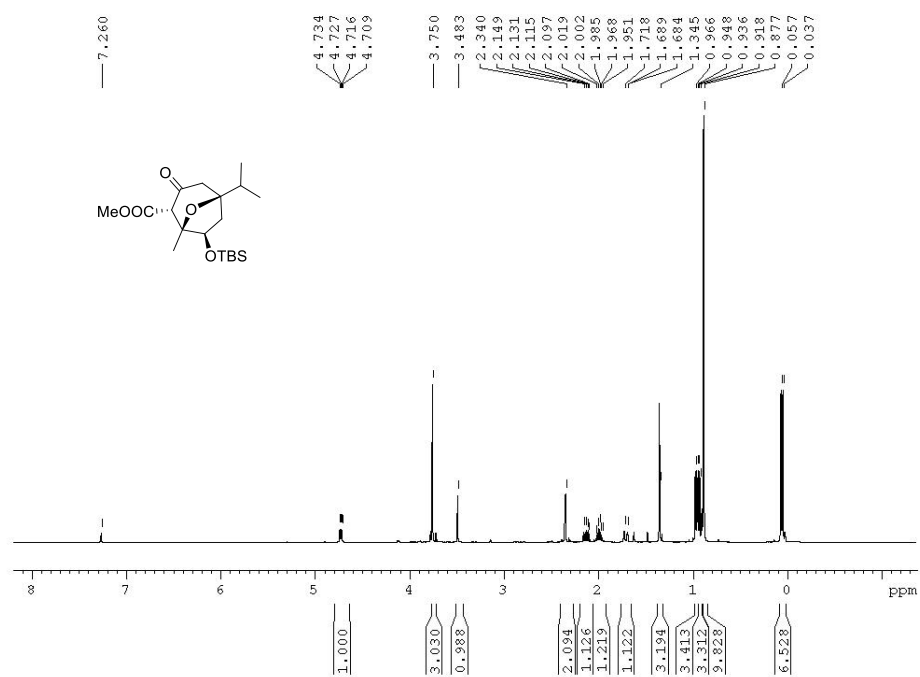
Compound 3.63



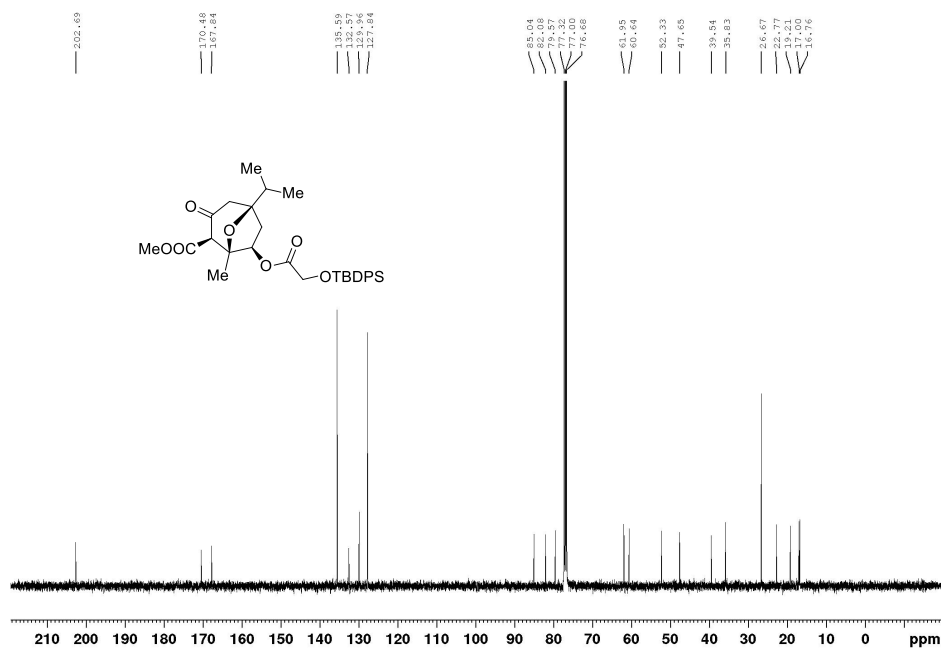
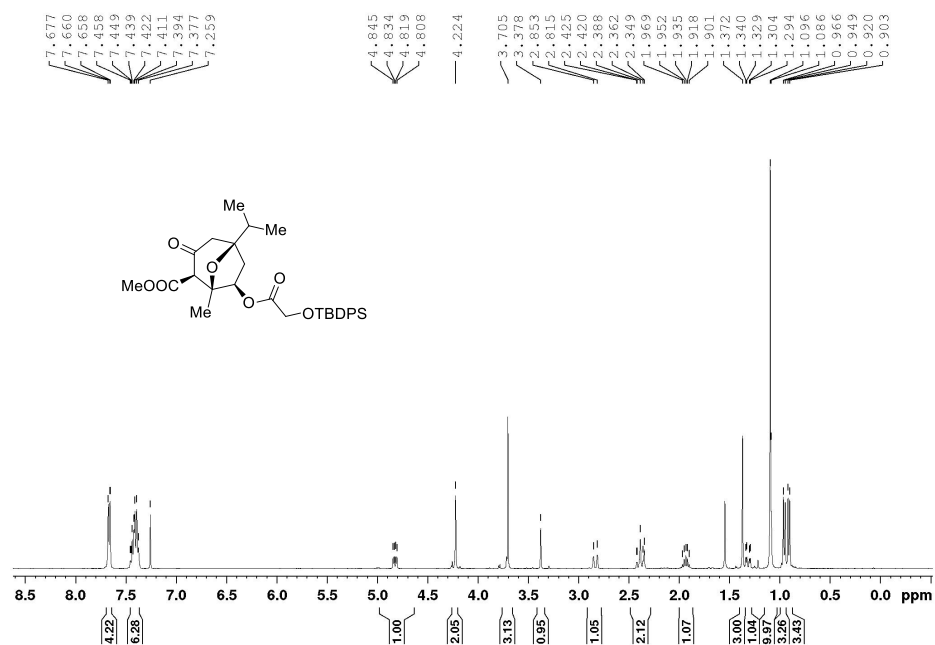
Compound **3.86**

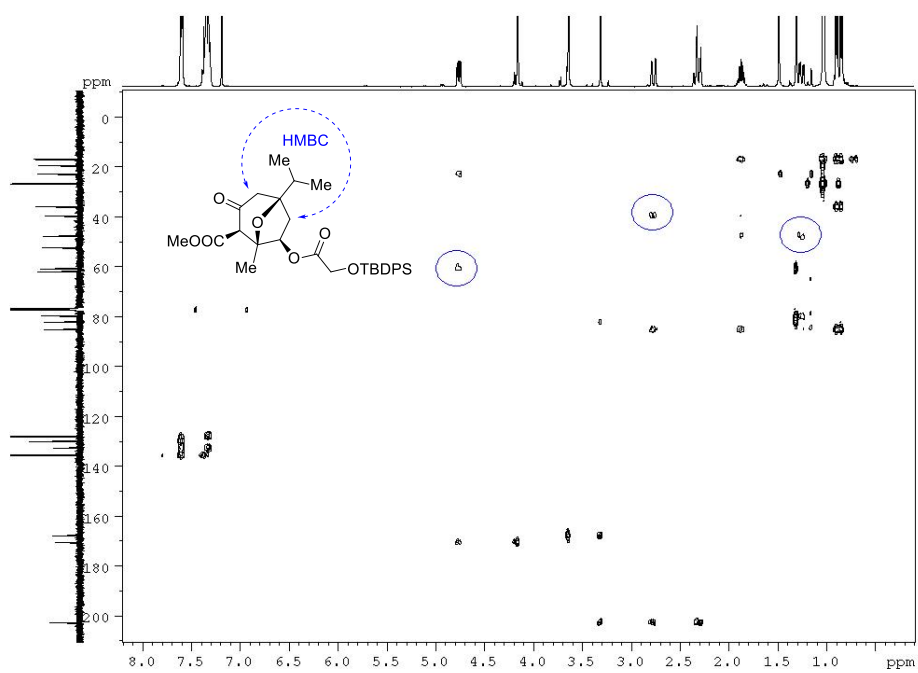
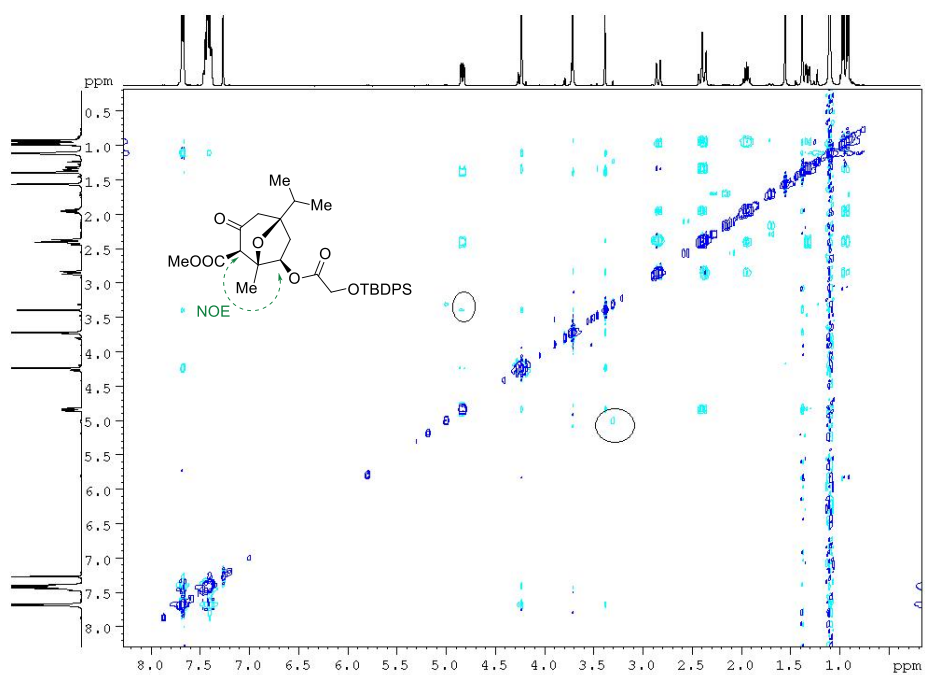
Compound **3.84**

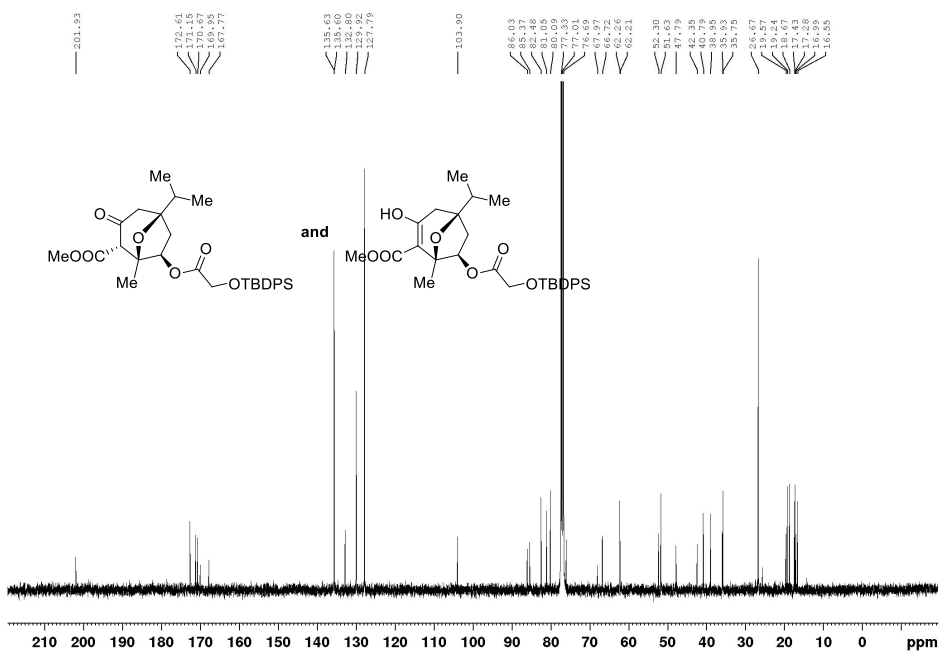
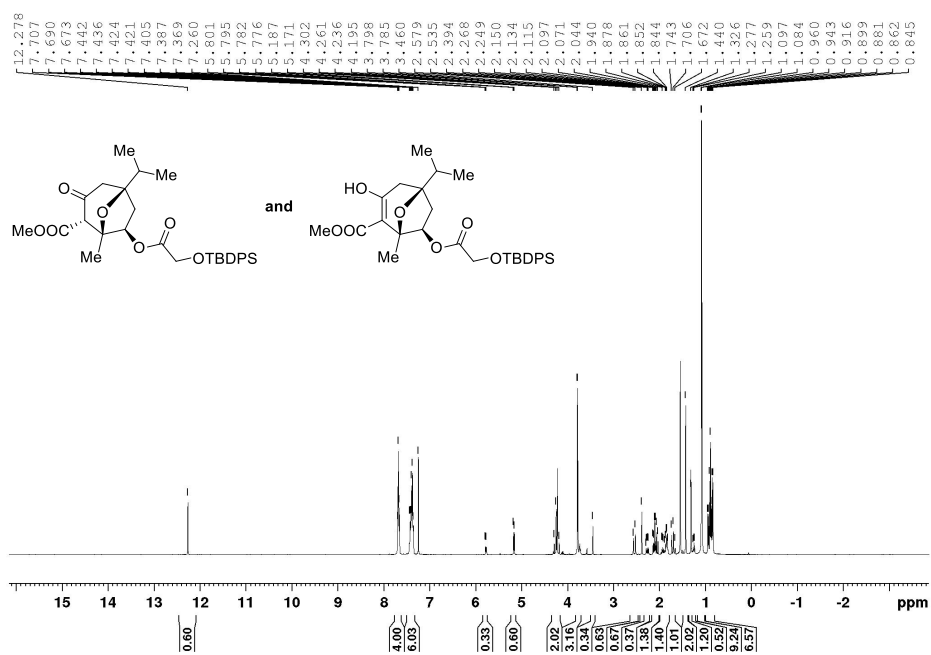


Compound **3.84**

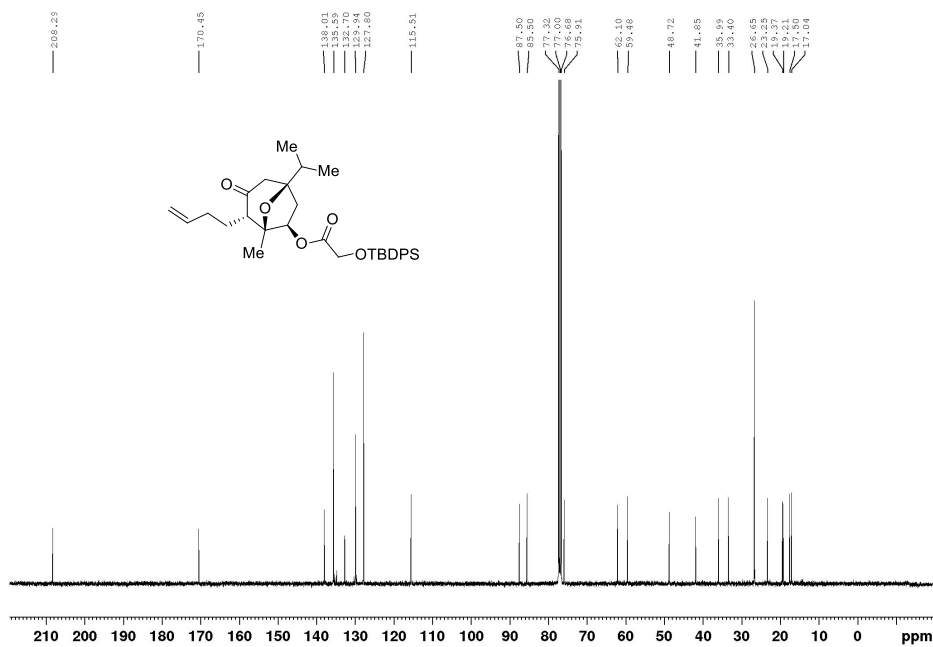
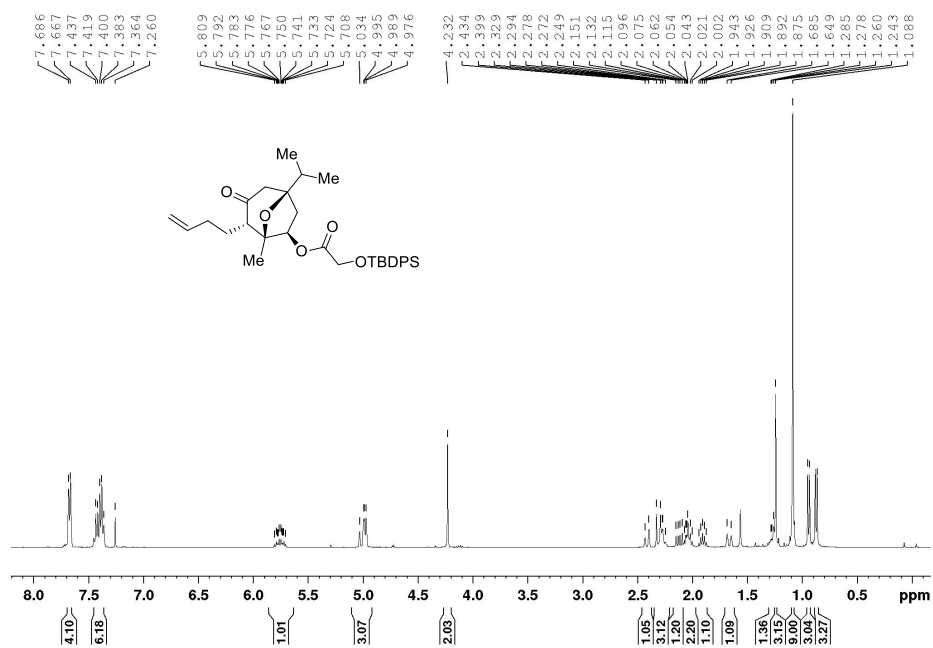
Compound 3.90

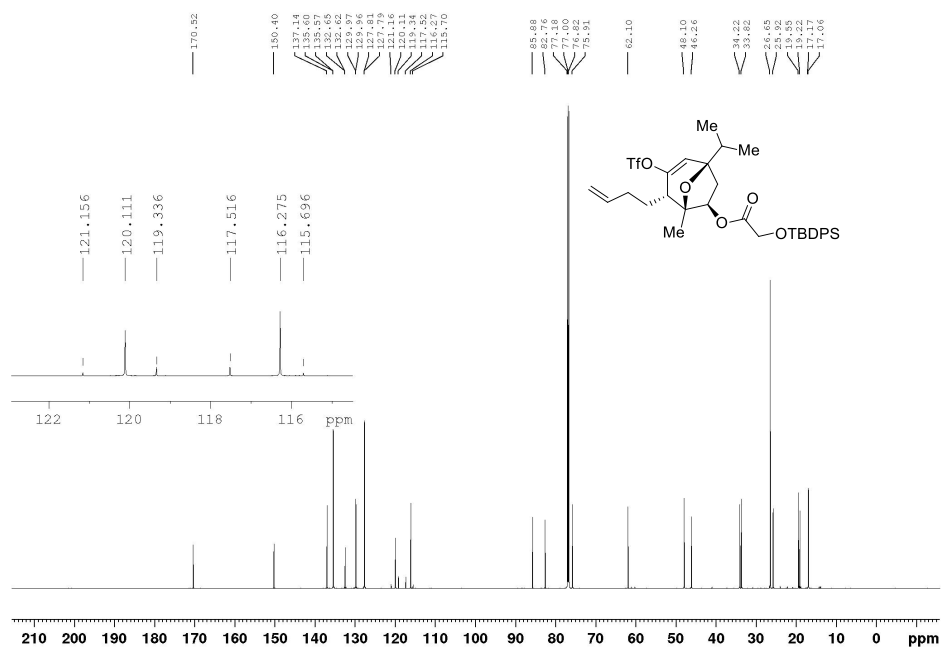
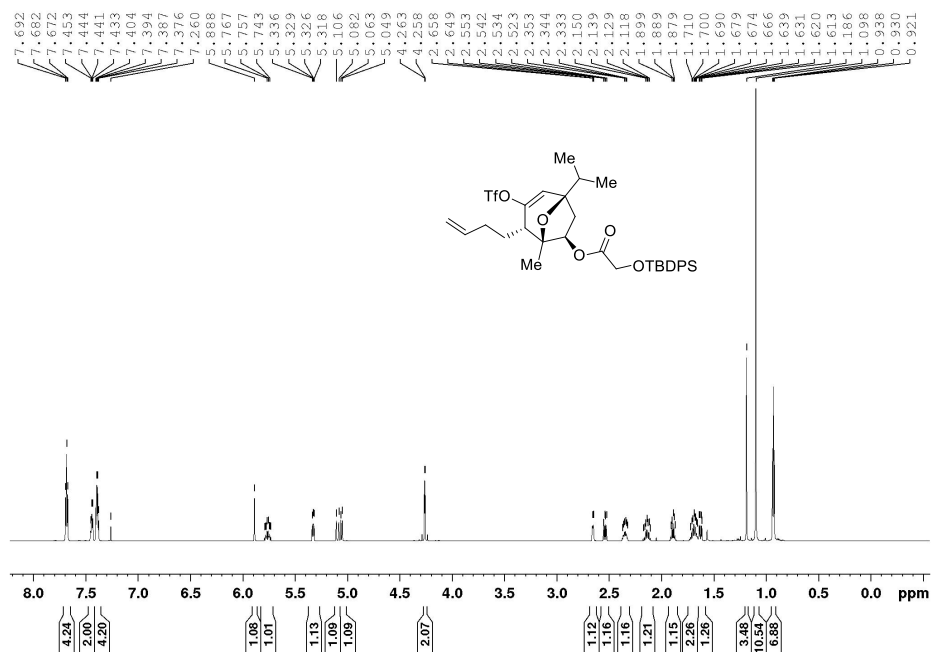




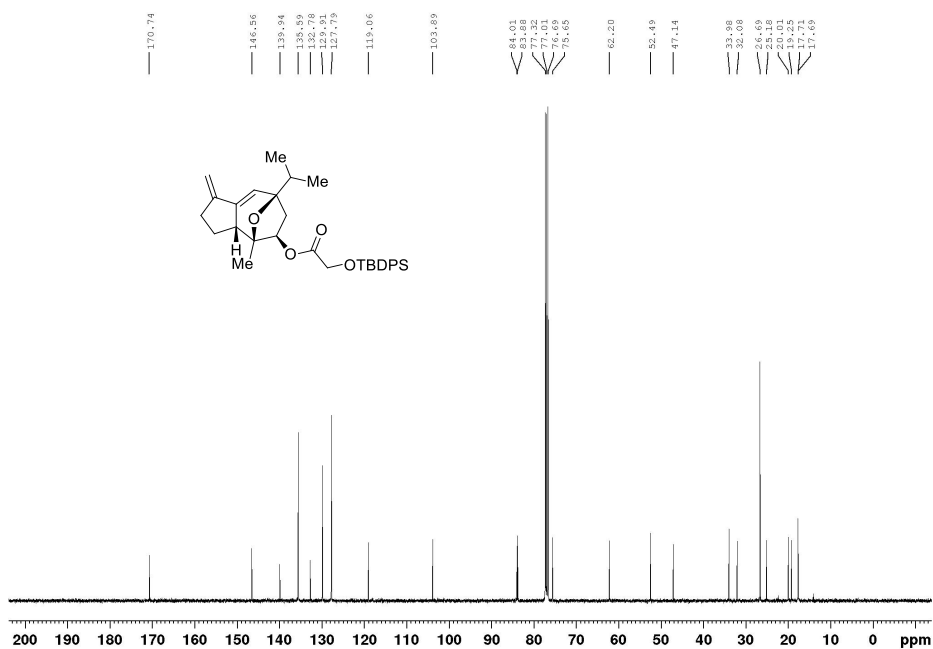
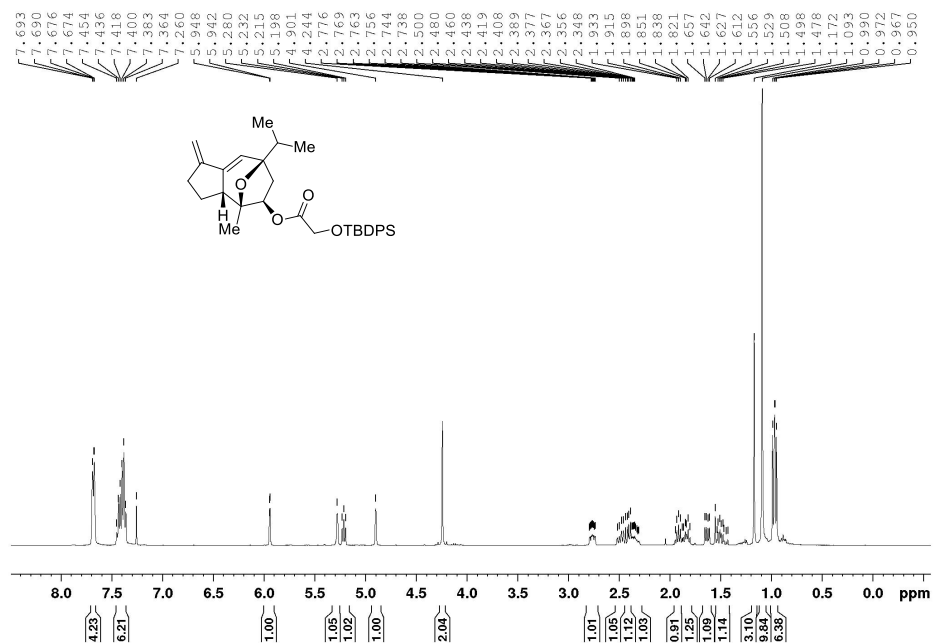
Compounds *epi-3.90*

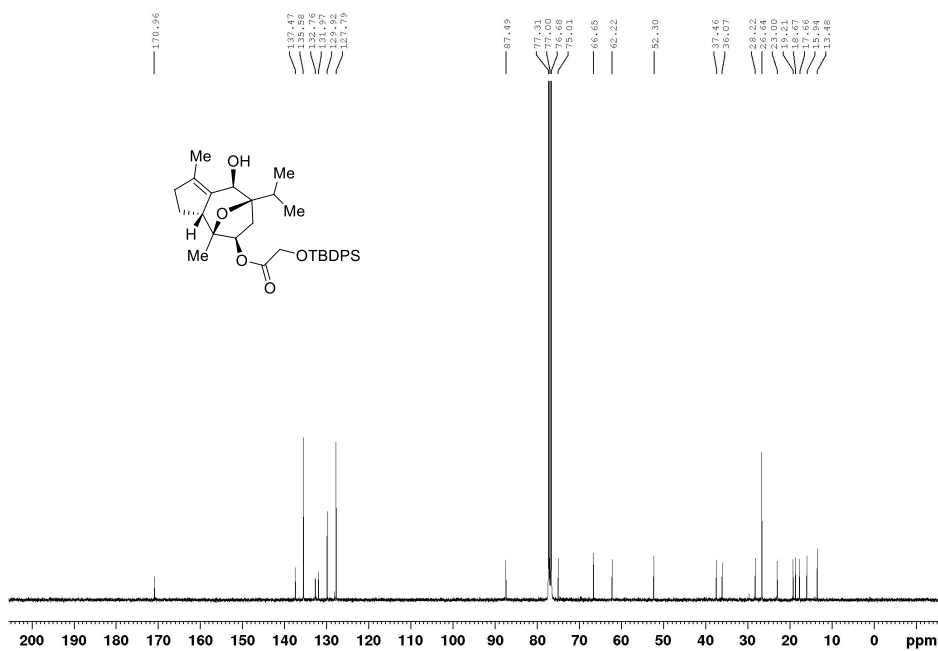
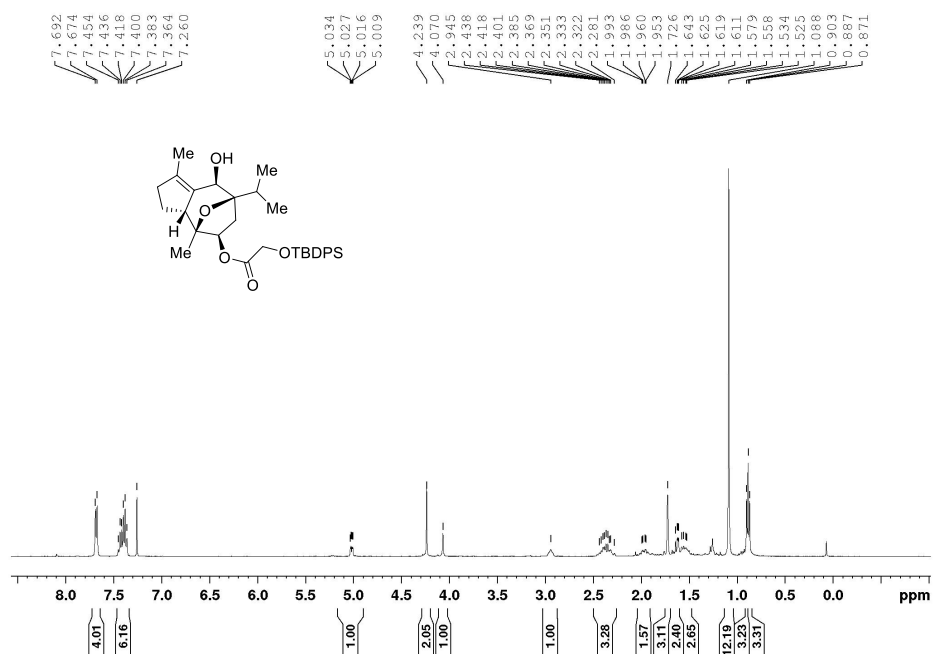
Compound 3.93

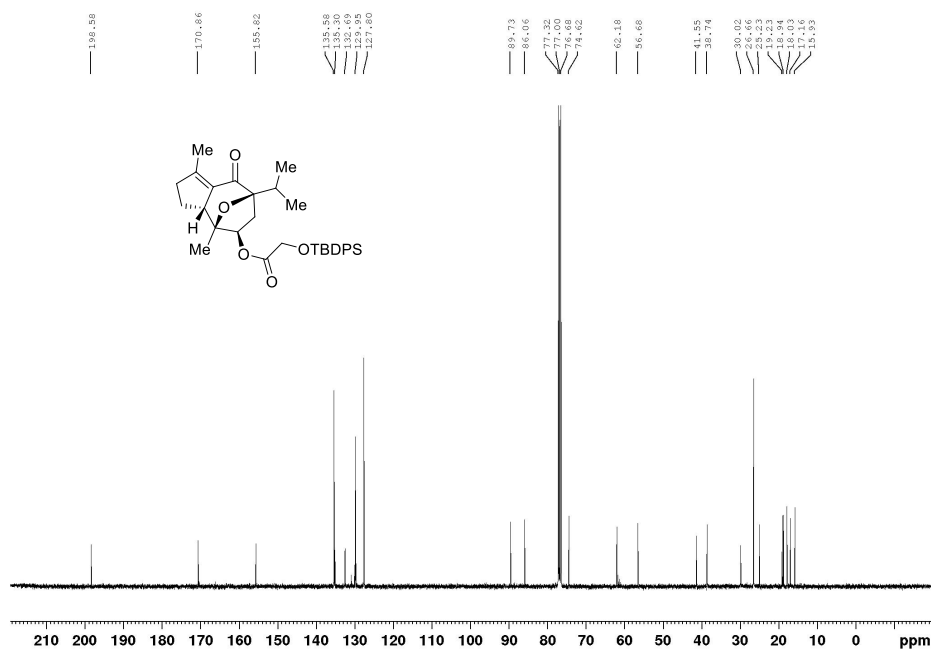
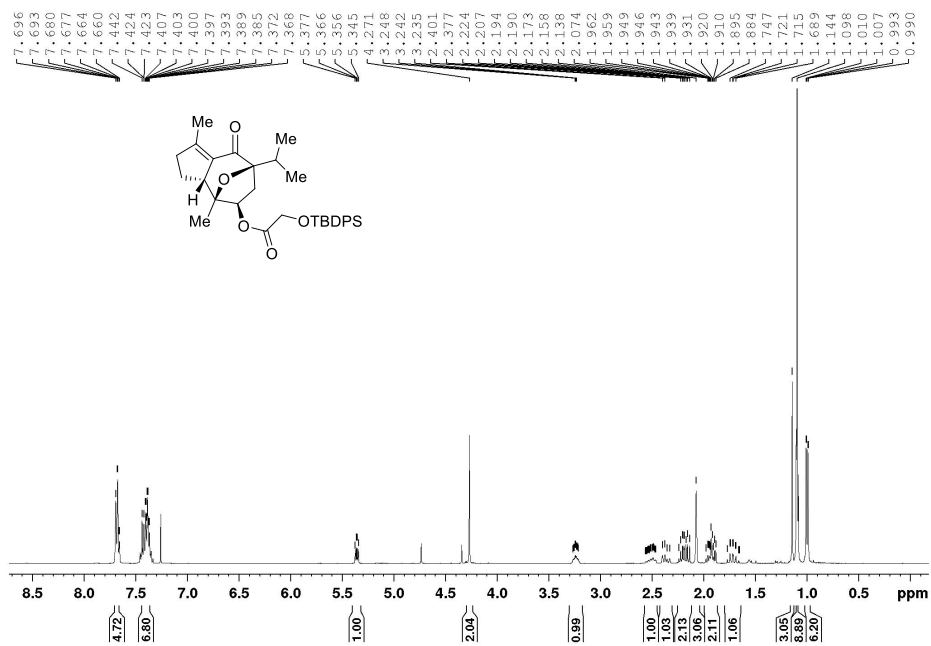


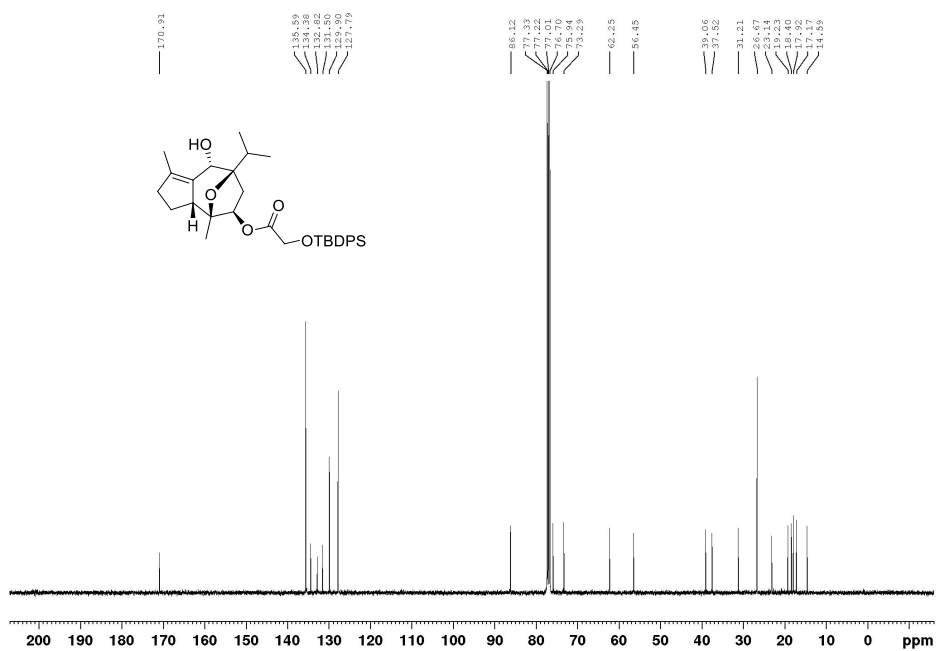
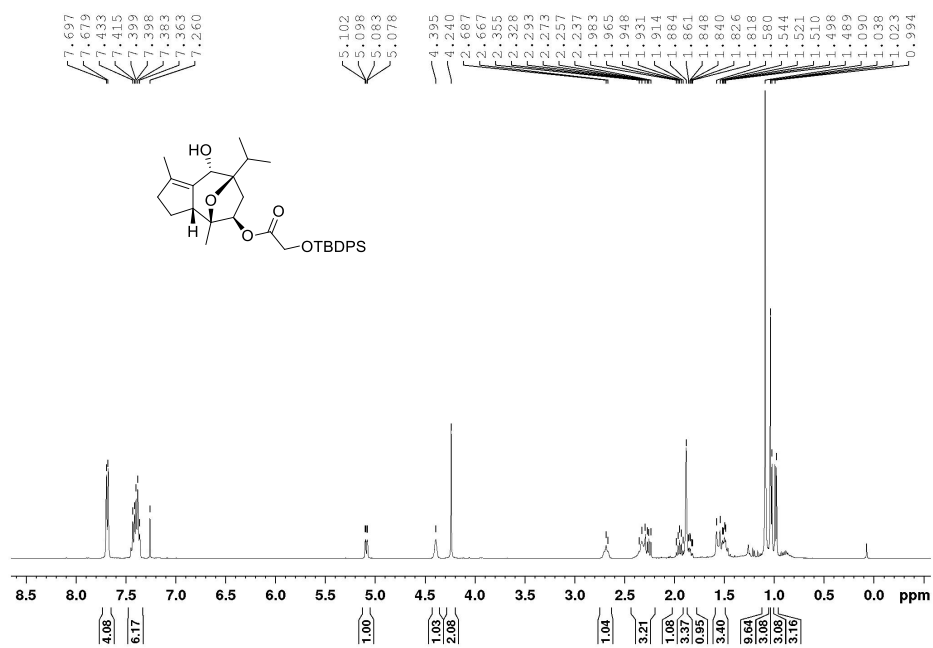
Compound **3.94**

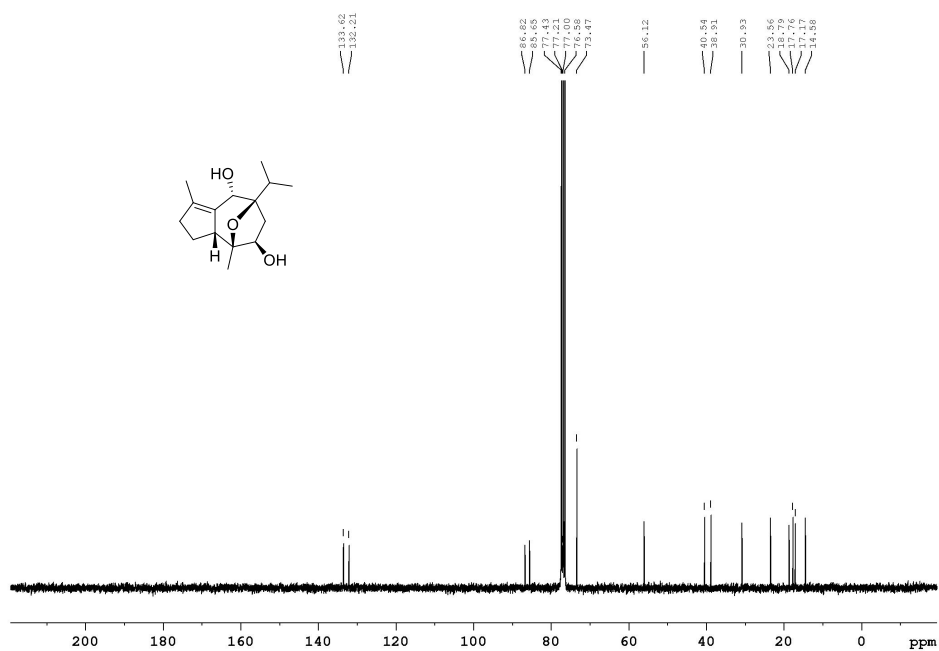
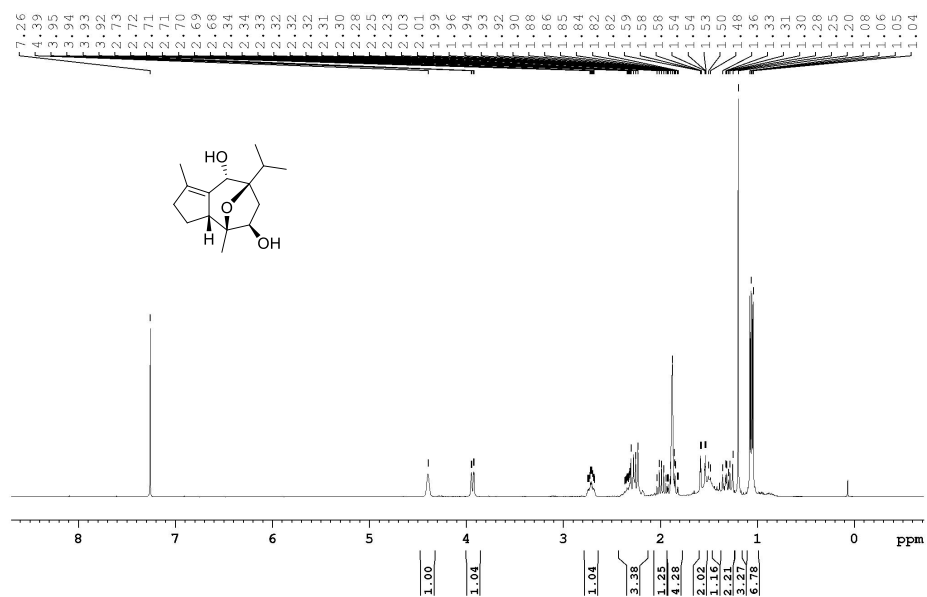
Compound 3.95

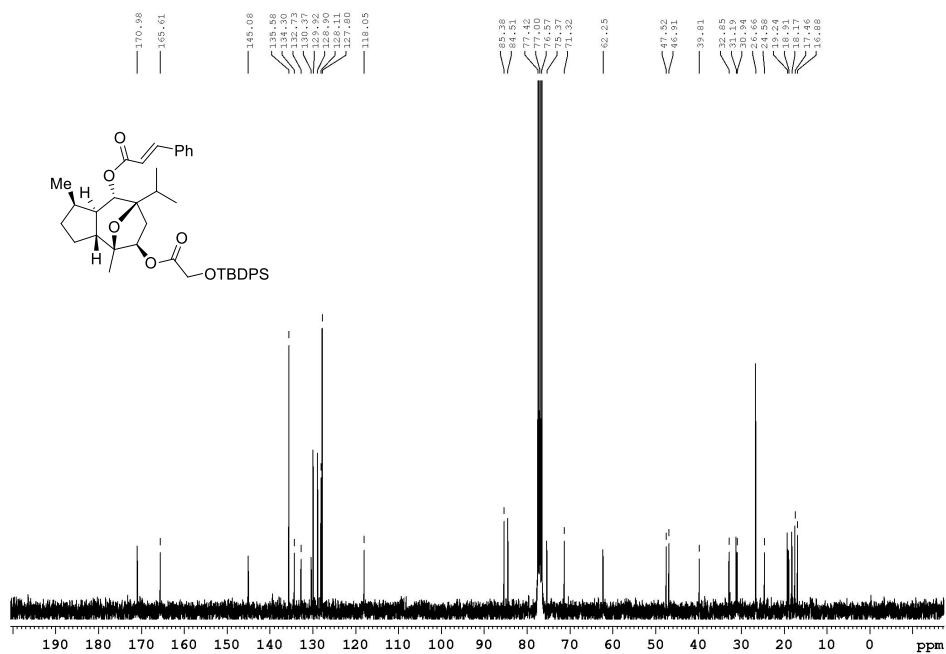
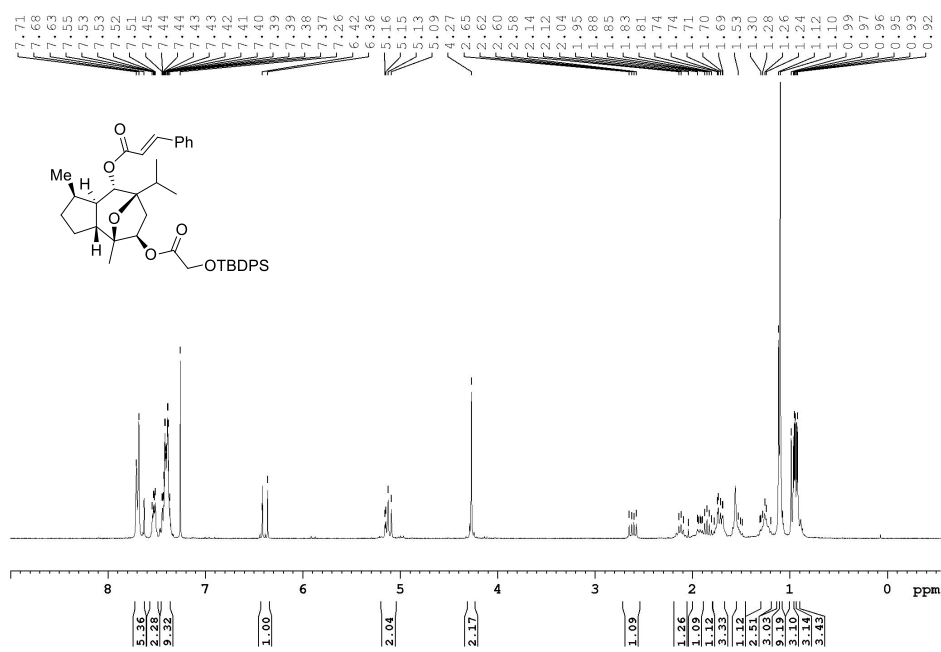


Compound **3.104**

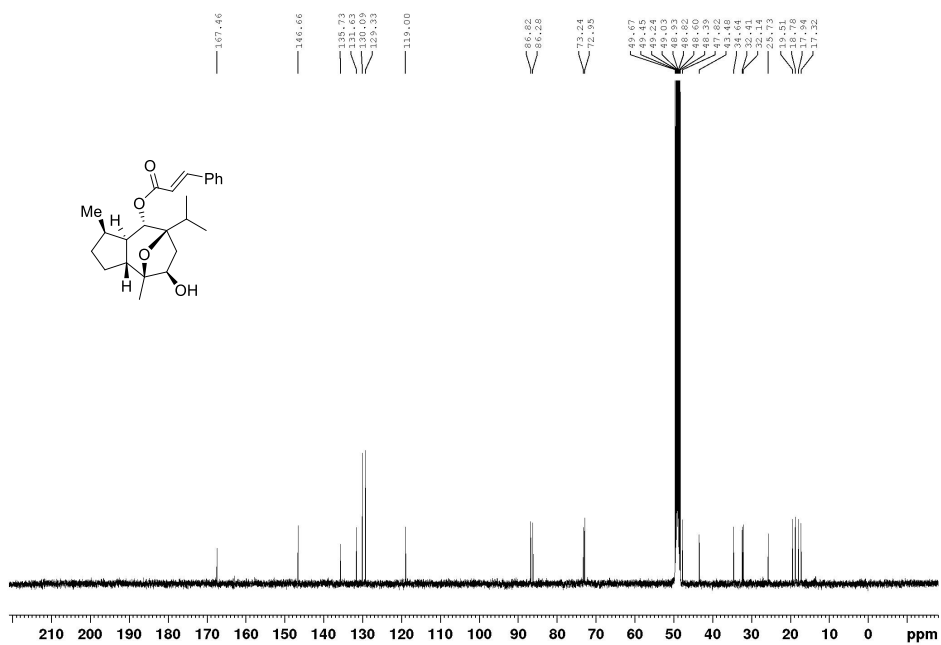
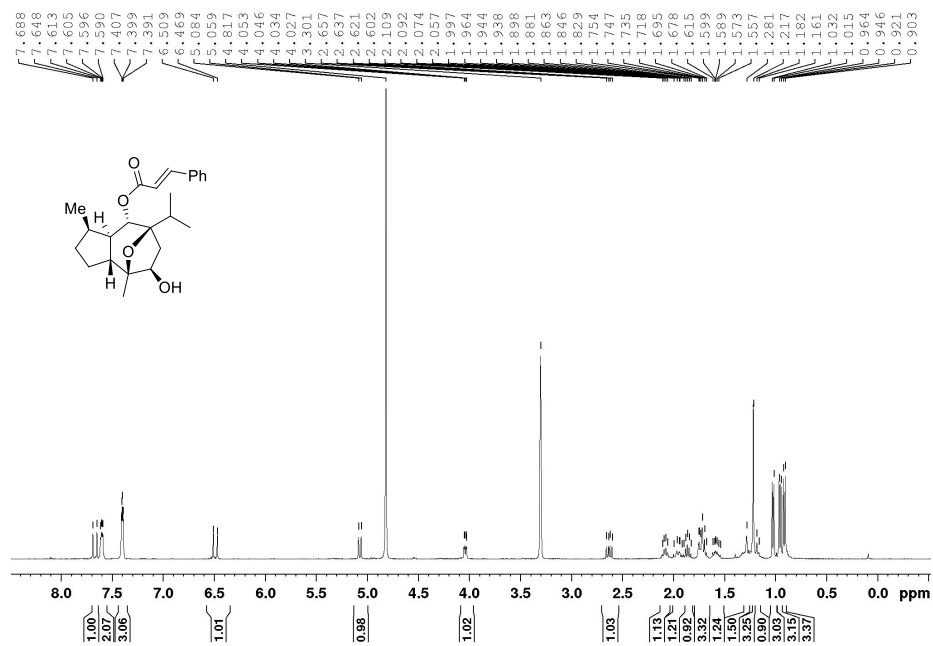
Compound **3.106**

Compound **3.105**

Compound **3.107**

Compound **3.109**

(-)-Englerin B 3.2



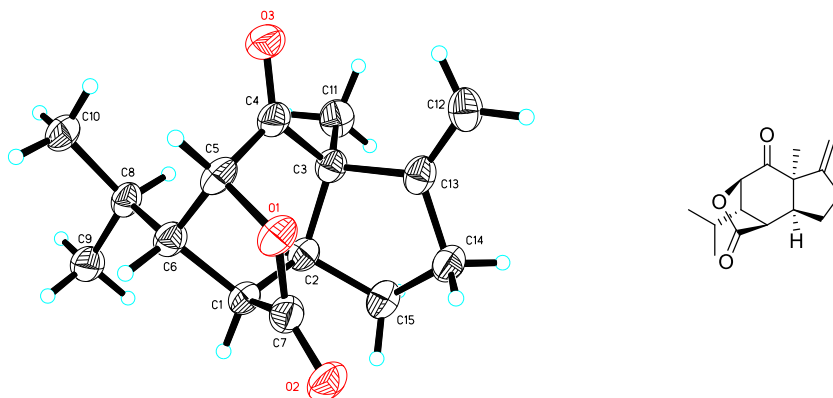
Attachment: X-ray Crystal Data**X-Ray crystal data of (+)-compound 2.73:**

Table 1. Crystal data and structure refinement for s2433lc.

Identification code	s2433lc
Empirical formula	C ₁₅ H ₂₀ O ₃
Formula weight	248.31
Temperature	130(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, P 2 ₁
Unit cell dimensions	a = 8.8202(12) Å alpha = 90° b = 6.3966(8) Å beta = 92.240(10)° c = 11.3691(14) Å gamma = 90°
Volume	640.95(14) Å ³
Z, Calculated density	2, 1.287 Mg/m ³
Absorption coefficient	0.709 mm ⁻¹
F(000)	268
Crystal size	0.16 x 0.06 x 0.03 mm
Theta range for data collection	3.89 to 63.97 deg.
Limiting indices	-10 ≤ h ≤ 5, -7 ≤ k ≤ 7, -13 ≤ l ≤ 13
Reflections collected / unique	6833 / 2066 [R(int) = 0.0661]
Completeness to theta = 63.97	98.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7469 and 0.6243
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2066 / 1 / 167
Goodness-of-fit on F ²	1.032
Final R indices [I > 2σ(I)]	R1 = 0.0388, wR2 = 0.0870
R indices (all data)	R1 = 0.0506, wR2 = 0.0917
Absolute structure parameter	0.1(3)
Extinction coefficient	0.0069(16)
Largest diff. peak and hole	0.185 and -0.133 e.Å ⁻³

Table 2. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for s2433lc.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	8399(2)	-1428(3)	4154(1)	33(1)
C(1)	8950(3)	1963(4)	3563(2)	30(1)
O(2)	8345(2)	972(3)	5589(1)	38(1)
C(2)	7515(3)	2651(4)	2846(2)	30(1)
O(3)	7250(2)	-2426(3)	1319(2)	39(1)
C(3)	6599(2)	831(4)	2236(2)	29(1)
C(4)	7526(3)	-1169(4)	2093(2)	30(1)
C(5)	8877(3)	-1466(4)	2940(2)	31(1)
C(6)	9905(3)	438(4)	2865(2)	30(1)
C(7)	8545(3)	567(4)	4570(2)	32(1)
C(8)	10337(3)	1112(4)	1625(2)	30(1)
C(9)	11376(3)	3019(4)	1694(2)	38(1)
C(10)	11084(3)	-680(4)	968(2)	36(1)
C(11)	5910(3)	1533(4)	1040(2)	38(1)
C(12)	4391(3)	-1254(4)	2938(2)	36(1)
C(13)	5317(3)	360(4)	3076(2)	32(1)
C(14)	5261(3)	2057(4)	3986(2)	36(1)
C(15)	6341(3)	3761(4)	3595(2)	37(1)

Table 3. Bond lengths [Å] and angles [deg] for s2433lc.

O(1)-C(7)	1.364(3)
O(1)-C(5)	1.460(3)
C(1)-C(7)	1.505(3)
C(1)-C(6)	1.531(3)
C(1)-C(2)	1.543(3)
C(1)-H(1)	1.0000
O(2)-C(7)	1.208(3)
C(2)-C(15)	1.540(3)
C(2)-C(3)	1.563(4)
C(2)-H(2)	1.0000
O(3)-C(4)	1.210(3)
C(3)-C(4)	1.530(4)
C(3)-C(11)	1.535(3)
C(3)-C(13)	1.538(3)
C(4)-C(5)	1.514(3)
C(5)-C(6)	1.522(4)
C(5)-H(5)	1.0000
C(6)-C(8)	1.537(3)
C(6)-H(6)	1.0000
C(8)-C(9)	1.526(3)
C(8)-C(10)	1.531(3)
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800

C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-C(13)	1.322(3)
C(12)-H(12A)	0.9500
C(12)-H(12B)	0.9500
C(13)-C(14)	1.503(4)
C(14)-C(15)	1.525(4)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(7)-O(1)-C(5)	108.42(18)
C(7)-C(1)-C(6)	99.6(2)
C(7)-C(1)-C(2)	110.90(19)
C(6)-C(1)-C(2)	111.36(18)
C(7)-C(1)-H(1)	111.5
C(6)-C(1)-H(1)	111.5
C(2)-C(1)-H(1)	111.5
C(15)-C(2)-C(1)	113.2(2)
C(15)-C(2)-C(3)	103.98(19)
C(1)-C(2)-C(3)	114.9(2)
C(15)-C(2)-H(2)	108.1
C(1)-C(2)-H(2)	108.1
C(3)-C(2)-H(2)	108.1
C(4)-C(3)-C(11)	110.21(19)
C(4)-C(3)-C(13)	108.13(19)
C(11)-C(3)-C(13)	109.37(18)
C(4)-C(3)-C(2)	113.62(18)
C(11)-C(3)-C(2)	110.8(2)
C(13)-C(3)-C(2)	104.50(18)
O(3)-C(4)-C(5)	120.7(2)
O(3)-C(4)-C(3)	122.6(2)
C(5)-C(4)-C(3)	116.6(2)
O(1)-C(5)-C(4)	110.49(17)
O(1)-C(5)-C(6)	103.51(18)
C(4)-C(5)-C(6)	108.66(19)
O(1)-C(5)-H(5)	111.3
C(4)-C(5)-H(5)	111.3
C(6)-C(5)-H(5)	111.3
C(5)-C(6)-C(1)	98.07(18)
C(5)-C(6)-C(8)	116.4(2)
C(1)-C(6)-C(8)	117.3(2)
C(5)-C(6)-H(6)	108.1
C(1)-C(6)-H(6)	108.1
C(8)-C(6)-H(6)	108.1
O(2)-C(7)-O(1)	121.1(2)
O(2)-C(7)-C(1)	130.6(2)
O(1)-C(7)-C(1)	108.30(19)

C(9)-C(8)-C(10)	110.77(19)
C(9)-C(8)-C(6)	110.33(19)
C(10)-C(8)-C(6)	111.37(19)
C(9)-C(8)-H(8)	108.1
C(10)-C(8)-H(8)	108.1
C(6)-C(8)-H(8)	108.1
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(8)-C(10)-H(10A)	109.5
C(8)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(8)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(3)-C(11)-H(11A)	109.5
C(3)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(3)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(13)-C(12)-H(12A)	120.0
C(13)-C(12)-H(12B)	120.0
H(12A)-C(12)-H(12B)	120.0
C(12)-C(13)-C(14)	127.5(2)
C(12)-C(13)-C(3)	123.0(2)
C(14)-C(13)-C(3)	109.3(2)
C(13)-C(14)-C(15)	106.12(18)
C(13)-C(14)-H(14A)	110.5
C(15)-C(14)-H(14A)	110.5
C(13)-C(14)-H(14B)	110.5
C(15)-C(14)-H(14B)	110.5
H(14A)-C(14)-H(14B)	108.7
C(14)-C(15)-C(2)	105.9(2)
C(14)-C(15)-H(15A)	110.6
C(2)-C(15)-H(15A)	110.6
C(14)-C(15)-H(15B)	110.6
C(2)-C(15)-H(15B)	110.6
H(15A)-C(15)-H(15B)	108.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for s2433lc.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

U11	U22	U33	U23	U13	U12
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O(1)	41(1)	35(1)	25(1)	2(1)	7(1)	5(1)
C(1)	31(1)	36(1)	23(1)	-2(1)	6(1)	0(1)
O(2)	41(1)	50(1)	22(1)	-2(1)	6(1)	5(1)
C(2)	34(1)	30(1)	27(1)	1(1)	6(1)	2(1)
O(3)	45(1)	41(1)	33(1)	-8(1)	8(1)	-5(1)
C(3)	30(1)	31(1)	26(1)	2(1)	3(1)	2(1)
C(4)	33(1)	34(1)	24(1)	-1(1)	10(1)	-4(1)
C(5)	39(1)	34(1)	22(1)	-1(1)	8(1)	7(1)
C(6)	32(1)	34(1)	23(1)	0(1)	4(1)	3(1)
C(7)	29(1)	37(2)	31(1)	-2(1)	2(1)	5(1)
C(8)	31(1)	37(1)	23(1)	2(1)	7(1)	4(1)
C(9)	38(1)	44(2)	33(1)	-2(1)	10(1)	-5(1)
C(10)	38(1)	45(2)	27(1)	-5(1)	9(1)	2(1)
C(11)	39(1)	48(2)	28(1)	7(1)	2(1)	0(1)
C(12)	31(1)	43(1)	34(1)	9(1)	4(1)	1(1)
C(13)	31(1)	38(1)	26(1)	5(1)	4(1)	6(1)
C(14)	35(1)	44(2)	31(1)	-4(1)	8(1)	2(1)
C(15)	39(1)	36(1)	38(1)	0(1)	9(1)	6(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for s2433lc.

	x	y	z	U(eq)
H(1)	9563	3194	3844	36
H(2)	7830	3644	2221	36
H(5)	9437	-2783	2767	38
H(6)	10861	143	3338	36
H(8)	9386	1515	1173	36
H(9A)	11695	3377	903	57
H(9B)	12272	2702	2199	57
H(9C)	10829	4202	2023	57
H(10A)	12008	-1123	1406	55
H(10B)	11344	-205	182	55
H(10C)	10378	-1860	896	55
H(11A)	5260	419	708	58
H(11B)	6725	1829	503	58
H(11C)	5303	2798	1145	58
H(12A)	3577	-1434	3452	43
H(12B)	4540	-2235	2326	43
H(14A)	5588	1513	4771	44
H(14B)	4217	2614	4030	44
H(15A)	6846	4444	4287	45
H(15B)	5784	4835	3125	45

Table 6. Torsion angles [deg] for s2433lc.

C(7)-C(1)-C(2)-C(15)	56.6(3)
C(6)-C(1)-C(2)-C(15)	166.60(19)
C(7)-C(1)-C(2)-C(3)	-62.7(3)

C(6)-C(1)-C(2)-C(3)	47.3(3)
C(15)-C(2)-C(3)-C(4)	-144.2(2)
C(1)-C(2)-C(3)-C(4)	-19.9(3)
C(15)-C(2)-C(3)-C(11)	91.1(2)
C(1)-C(2)-C(3)-C(11)	-144.56(19)
C(15)-C(2)-C(3)-C(13)	-26.6(2)
C(1)-C(2)-C(3)-C(13)	97.8(2)
C(11)-C(3)-C(4)-O(3)	-27.9(3)
C(13)-C(3)-C(4)-O(3)	91.6(2)
C(2)-C(3)-C(4)-O(3)	-152.9(2)
C(11)-C(3)-C(4)-C(5)	149.1(2)
C(13)-C(3)-C(4)-C(5)	-91.4(2)
C(2)-C(3)-C(4)-C(5)	24.1(3)
C(7)-O(1)-C(5)-C(4)	-93.5(2)
C(7)-O(1)-C(5)-C(6)	22.7(2)
O(3)-C(4)-C(5)-O(1)	-125.1(2)
C(3)-C(4)-C(5)-O(1)	57.8(3)
O(3)-C(4)-C(5)-C(6)	121.9(2)
C(3)-C(4)-C(5)-C(6)	-55.1(3)
O(1)-C(5)-C(6)-C(1)	-41.7(2)
C(4)-C(5)-C(6)-C(1)	75.8(2)
O(1)-C(5)-C(6)-C(8)	-167.62(18)
C(4)-C(5)-C(6)-C(8)	-50.2(3)
C(7)-C(1)-C(6)-C(5)	44.2(2)
C(2)-C(1)-C(6)-C(5)	-72.9(2)
C(7)-C(1)-C(6)-C(8)	169.6(2)
C(2)-C(1)-C(6)-C(8)	52.5(3)
C(5)-O(1)-C(7)-O(2)	-173.6(2)
C(5)-O(1)-C(7)-C(1)	7.0(2)
C(6)-C(1)-C(7)-O(2)	147.2(2)
C(2)-C(1)-C(7)-O(2)	-95.4(3)
C(6)-C(1)-C(7)-O(1)	-33.4(2)
C(2)-C(1)-C(7)-O(1)	84.0(2)
C(5)-C(6)-C(8)-C(9)	-179.5(2)
C(1)-C(6)-C(8)-C(9)	64.9(3)
C(5)-C(6)-C(8)-C(10)	-56.1(3)
C(1)-C(6)-C(8)-C(10)	-171.7(2)
C(4)-C(3)-C(13)-C(12)	-50.7(3)
C(11)-C(3)-C(13)-C(12)	69.4(3)
C(2)-C(3)-C(13)-C(12)	-172.0(2)
C(4)-C(3)-C(13)-C(14)	132.6(2)
C(11)-C(3)-C(13)-C(14)	-107.4(2)
C(2)-C(3)-C(13)-C(14)	11.2(2)
C(12)-C(13)-C(14)-C(15)	-167.8(2)
C(3)-C(13)-C(14)-C(15)	8.8(3)
C(13)-C(14)-C(15)-C(2)	-25.9(3)
C(1)-C(2)-C(15)-C(14)	-92.8(2)
C(3)-C(2)-C(15)-C(14)	32.6(2)

Symmetry transformations used to generate equivalent atoms:

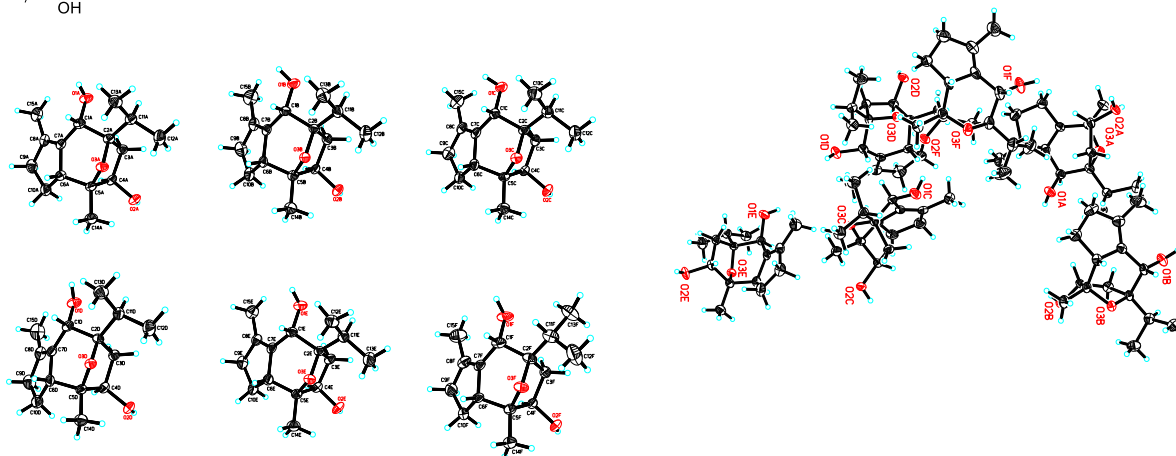
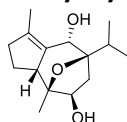
X-Ray crystal data of compound (-)-3.107:

Table 1. Crystal data and structure refinement for s2644lc.

Identification code	s2644lc - Sample: GL-VII-081-3
Empirical formula	C ₁₅ H ₂₄ O ₃
Formula weight	252.34
Temperature	130(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, C 2
Unit cell dimensions	a = 45.5324(12) Å alpha = 90° b = 10.8332(3) Å beta = 112.449(2)° c = 18.3881(5) Å gamma = 90°
Volume	8382.8(4) Å ³
Z, Calculated density	24, 1.200 Mg/m ³
Absorption coefficient	0.652 mm ⁻¹
F(000)	3312
Crystal size	0.13 x 0.08 x 0.06 mm

Theta range for data collection	2.10 to 66.49 deg.
Limiting indices	-53 ≤ h ≤ 53, -12 ≤ k ≤ 12, -21 ≤ l ≤ 21
Reflections collected / unique	59155 / 14082 [R(int) = 0.0976]
Completeness to theta = 66.49	98.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7140 and 0.6407
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	14082 / 2 / 1046
Goodness-of-fit on F ²	1.010
Final R indices [I > 2σ(I)]	R1 = 0.0478, wR2 = 0.0929
R indices (all data)	R1 = 0.0833, wR2 = 0.1030
Absolute structure parameter	0.10(13)
Extinction coefficient	0.000145(13)
Largest diff. peak and hole	0.258 and -0.193 e.Å ⁻³

Table 2. Atomic coordinates (x 10⁴) and equivalent isotropic

displacement parameters ($\text{\AA}^2 \times 10^3$) for s2644lc.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

x	y	z	U(eq)	
O(1A)	1060(1)	9363(2)	3913(1)	30(1)
C(1A)	805(1)	9963(3)	3295(2)	24(1)
O(2A)	-148(1)	8005(2)	2571(1)	27(1)
C(2A)	505(1)	9873(2)	3491(2)	21(1)
O(3A)	245(1)	10460(2)	2854(1)	23(1)
C(3A)	400(1)	8516(3)	3441(2)	23(1)
C(4A)	160(1)	8326(3)	2589(2)	23(1)
C(5A)	155(1)	9595(3)	2192(2)	23(1)
C(6A)	416(1)	9684(3)	1873(2)	25(1)
C(7A)	740(1)	9414(3)	2499(2)	23(1)
C(8A)	920(1)	8763(3)	2216(2)	27(1)
C(9A)	744(1)	8428(3)	1364(2)	37(1)
C(10A)	399(1)	8823(3)	1187(2)	34(1)
C(11A)	539(1)	10505(3)	4264(2)	24(1)
C(12A)	223(1)	10626(3)	4367(2)	36(1)
C(13A)	693(1)	11787(3)	4370(2)	30(1)
C(14A)	-167(1)	9999(3)	1599(2)	30(1)
C(15A)	1266(1)	8422(3)	2606(2)	36(1)
O(1B)	653(1)	9302(2)	7219(1)	31(1)
C(1B)	903(1)	8424(3)	7530(2)	23(1)
O(2B)	1859(1)	9343(2)	7408(1)	25(1)
C(2B)	1217(1)	9136(2)	7944(2)	21(1)
O(3B)	1462(1)	8210(2)	8293(1)	20(1)
C(3B)	1316(1)	9756(3)	7320(2)	24(1)
C(4B)	1542(1)	8849(2)	7163(2)	20(1)
C(5B)	1534(1)	7695(3)	7644(2)	22(1)
C(6B)	1252(1)	6863(3)	7190(2)	24(1)
C(7B)	944(1)	7584(3)	6925(2)	23(1)
C(8B)	764(1)	7361(3)	6174(2)	31(1)
C(9B)	920(1)	6475(3)	5805(2)	39(1)
C(10B)	1255(1)	6263(3)	6433(2)	33(1)
C(11B)	1209(1)	10009(3)	8590(2)	26(1)
C(12B)	1545(1)	10510(3)	9090(2)	37(1)
C(13B)	1072(1)	9438(3)	9144(2)	33(1)
C(14B)	1843(1)	6989(3)	8003(2)	28(1)
C(15B)	432(1)	7813(3)	5685(2)	47(1)
O(1C)	2315(1)	4645(2)	3949(1)	31(1)
C(1C)	2559(1)	5085(3)	3710(2)	22(1)
O(2C)	3498(1)	6283(2)	5595(1)	26(1)
C(2C)	2882(1)	4628(3)	4309(2)	22(1)
O(3C)	3121(1)	5033(2)	4012(1)	22(1)
C(3C)	2966(1)	5347(3)	5086(2)	24(1)
C(4C)	3176(1)	6426(3)	5030(2)	22(1)
C(5C)	3168(1)	6358(2)	4191(2)	21(1)

C(6C)	2874(1)	6992(3)	3598(2)	25(1)
C(7C)	2571(1)	6462(3)	3645(2)	25(1)
C(8C)	2368(1)	7338(3)	3641(2)	27(1)
C(9C)	2495(1)	8620(3)	3592(2)	37(1)
C(10C)	2843(1)	8397(3)	3688(2)	30(1)
C(11C)	2905(1)	3223(3)	4414(2)	26(1)
C(12C)	3250(1)	2812(3)	4863(2)	35(1)
C(13C)	2762(1)	2486(3)	3649(2)	34(1)
C(14C)	3469(1)	6736(3)	4092(2)	29(1)
C(15C)	2037(1)	7216(3)	3630(2)	39(1)
O(1D)	2712(1)	5759(2)	1304(1)	30(1)
C(1D)	2433(1)	5903(3)	1477(2)	22(1)
O(2D)	1486(1)	6483(2)	-570(1)	24(1)
C(2D)	2151(1)	5198(3)	859(2)	21(1)
O(3D)	1880(1)	5336(2)	1084(1)	20(1)
C(3D)	2047(1)	5862(3)	64(2)	24(1)
C(4D)	1786(1)	6768(3)	51(2)	23(1)
C(5D)	1766(1)	6584(3)	867(2)	22(1)
C(6D)	2010(1)	7427(3)	1475(2)	25(1)
C(7D)	2338(1)	7233(3)	1474(2)	24(1)
C(8D)	2481(1)	8289(3)	1448(2)	31(1)
C(9D)	2273(1)	9387(3)	1416(2)	41(1)
C(10D)	1954(1)	8840(3)	1357(2)	36(1)
C(11D)	2217(1)	3820(3)	814(2)	27(1)
C(12D)	1921(1)	3109(3)	287(2)	41(1)
C(13D)	2347(1)	3185(3)	1607(2)	33(1)
C(14D)	1439(1)	6670(3)	889(2)	28(1)
C(15D)	2809(1)	8508(3)	1465(2)	48(1)
O(1E)	3944(1)	9483(2)	1060(1)	30(1)
C(1E)	4195(1)	9976(3)	1729(2)	23(1)
O(2E)	5143(1)	7973(2)	2535(1)	29(1)
C(2E)	4511(1)	9842(3)	1600(2)	21(1)
O(3E)	4759(1)	10385(2)	2288(1)	23(1)
C(3E)	4600(1)	8467(3)	1644(2)	25(1)
C(4E)	4829(1)	8244(3)	2497(2)	25(1)
C(5E)	4824(1)	9474(3)	2915(2)	24(1)
C(6E)	4542(1)	9536(3)	3174(2)	27(1)
C(7E)	4228(1)	9352(3)	2484(2)	25(1)
C(8E)	4030(1)	8654(3)	2679(2)	28(1)
C(9E)	4179(1)	8204(3)	3516(2)	34(1)
C(10E)	4530(1)	8596(3)	3791(2)	38(1)
C(11E)	4506(1)	10486(3)	855(2)	26(1)
C(12E)	4363(1)	11773(3)	734(2)	30(1)
C(13E)	4840(1)	10555(3)	836(2)	36(1)
C(14E)	5134(1)	9832(3)	3569(2)	34(1)
C(15E)	3687(1)	8357(3)	2204(2)	38(1)
O(1F)	593(1)	4110(2)	2076(1)	37(1)
C(1F)	849(1)	3249(3)	2393(2)	28(1)
O(2F)	1816(1)	4447(2)	2454(1)	25(1)
C(2F)	1153(1)	3922(3)	2926(2)	26(1)

O(3F)	1399(1)	2979(2)	3216(1)	26(1)
C(3F)	1283(1)	4757(3)	2453(2)	26(1)
C(4F)	1499(1)	3949(2)	2185(2)	21(1)
C(5F)	1493(1)	2673(3)	2562(2)	24(1)
C(6F)	1225(1)	1873(3)	2013(2)	25(1)
C(7F)	910(1)	2545(3)	1762(2)	27(1)
C(8F)	737(1)	2390(3)	1006(2)	34(1)
C(9F)	908(1)	1634(3)	605(2)	40(1)
C(10F)	1245(1)	1472(3)	1230(2)	32(1)
C(11F)	1112(1)	4506(3)	3644(2)	35(1)
C(12F)	1417(1)	4606(4)	4345(2)	58(1)
C(13F)	956(1)	5789(3)	3465(2)	46(1)
C(14F)	1808(1)	1998(3)	2896(2)	29(1)
C(15F)	400(1)	2785(4)	534(2)	50(1)

Table 3. Bond lengths [Å] and angles [deg] for s2644lc.

O(1A)-C(1A)	1.435(3)
O(1A)-H(1AA)	0.80(4)
C(1A)-C(7A)	1.501(4)
C(1A)-C(2A)	1.541(4)
C(1A)-H(1A)	1.0000
O(2A)-C(4A)	1.434(3)
O(2A)-H(2A)	0.95(4)
C(2A)-O(3A)	1.457(3)
C(2A)-C(11A)	1.531(4)
C(2A)-C(3A)	1.538(4)
O(3A)-C(5A)	1.465(3)
C(3A)-C(4A)	1.543(4)
C(3A)-H(3A1)	0.9900
C(3A)-H(3A2)	0.9900
C(4A)-C(5A)	1.552(4)
C(4A)-H(4A)	1.0000
C(5A)-C(6A)	1.516(4)
C(5A)-C(14A)	1.518(4)
C(6A)-C(7A)	1.516(4)
C(6A)-C(10A)	1.547(4)
C(6A)-H(6A)	1.0000
C(7A)-C(8A)	1.327(4)
C(8A)-C(9A)	1.506(4)
C(8A)-C(15A)	1.507(4)
C(9A)-C(10A)	1.538(4)
C(9A)-H(9A1)	0.9900
C(9A)-H(9A2)	0.9900
C(10A)-H(10A)	0.9900
C(10A)-H(10B)	0.9900
C(11A)-C(12A)	1.525(4)
C(11A)-C(13A)	1.535(4)

C(11A)-H(11A)	1.0000
C(12A)-H(12A)	0.9800
C(12A)-H(12B)	0.9800
C(12A)-H(12C)	0.9800
C(13A)-H(13A)	0.9800
C(13A)-H(13B)	0.9800
C(13A)-H(13C)	0.9800
C(14A)-H(14A)	0.9800
C(14A)-H(14B)	0.9800
C(14A)-H(14C)	0.9800
C(15A)-H(15A)	0.9800
C(15A)-H(15B)	0.9800
C(15A)-H(15C)	0.9800
O(1B)-C(1B)	1.428(3)
O(1B)-H(1BB)	0.94(4)
C(1B)-C(7B)	1.503(4)
C(1B)-C(2B)	1.542(4)
C(1B)-H(1B)	1.0000
O(2B)-C(4B)	1.438(3)
O(2B)-H(2B)	0.80(3)
C(2B)-O(3B)	1.456(3)
C(2B)-C(11B)	1.529(4)
C(2B)-C(3B)	1.538(4)
O(3B)-C(5B)	1.464(3)
C(3B)-C(4B)	1.529(4)
C(3B)-H(3B1)	0.9900
C(3B)-H(3B2)	0.9900
C(4B)-C(5B)	1.539(4)
C(4B)-H(4B)	1.0000
C(5B)-C(14B)	1.510(4)
C(5B)-C(6B)	1.532(4)
C(6B)-C(7B)	1.513(4)
C(6B)-C(10B)	1.541(4)
C(6B)-H(6B)	1.0000
C(7B)-C(8B)	1.332(4)
C(8B)-C(9B)	1.502(4)
C(8B)-C(15B)	1.514(4)
C(9B)-C(10B)	1.537(4)
C(9B)-H(9B1)	0.9900
C(9B)-H(9B2)	0.9900
C(10B)-H(10C)	0.9900
C(10B)-H(10D)	0.9900
C(11B)-C(13B)	1.517(4)
C(11B)-C(12B)	1.550(4)
C(11B)-H(11B)	1.0000
C(12B)-H(12D)	0.9800
C(12B)-H(12E)	0.9800
C(12B)-H(12F)	0.9800
C(13B)-H(13D)	0.9800
C(13B)-H(13E)	0.9800

C(13B)-H(13F)	0.9800
C(14B)-H(14D)	0.9800
C(14B)-H(14E)	0.9800
C(14B)-H(14F)	0.9800
C(15B)-H(15D)	0.9800
C(15B)-H(15E)	0.9800
C(15B)-H(15F)	0.9800
O(1C)-C(1C)	1.425(3)
O(1C)-H(1CC)	0.880(19)
C(1C)-C(7C)	1.498(4)
C(1C)-C(2C)	1.544(4)
C(1C)-H(1C)	1.0000
O(2C)-C(4C)	1.443(3)
O(2C)-H(2C)	0.85(4)
C(2C)-O(3C)	1.456(3)
C(2C)-C(11C)	1.534(4)
C(2C)-C(3C)	1.541(4)
O(3C)-C(5C)	1.469(3)
C(3C)-C(4C)	1.539(4)
C(3C)-H(3C1)	0.9900
C(3C)-H(3C2)	0.9900
C(4C)-C(5C)	1.530(4)
C(4C)-H(4C)	1.0000
C(5C)-C(14C)	1.508(4)
C(5C)-C(6C)	1.529(4)
C(6C)-C(7C)	1.529(4)
C(6C)-C(10C)	1.543(4)
C(6C)-H(6C)	1.0000
C(7C)-C(8C)	1.321(4)
C(8C)-C(15C)	1.507(4)
C(8C)-C(9C)	1.521(4)
C(9C)-C(10C)	1.546(4)
C(9C)-H(9C1)	0.9900
C(9C)-H(9C2)	0.9900
C(10C)-H(10E)	0.9900
C(10C)-H(10F)	0.9900
C(11C)-C(13C)	1.529(4)
C(11C)-C(12C)	1.534(4)
C(11C)-H(11C)	1.0000
C(12C)-H(12G)	0.9800
C(12C)-H(12H)	0.9800
C(12C)-H(12I)	0.9800
C(13C)-H(13G)	0.9800
C(13C)-H(13H)	0.9800
C(13C)-H(13I)	0.9800
C(14C)-H(14G)	0.9800
C(14C)-H(14H)	0.9800
C(14C)-H(14I)	0.9800
C(15C)-H(15G)	0.9800
C(15C)-H(15H)	0.9800

C(15C)-H(15I)	0.9800
O(1D)-C(1D)	1.433(3)
O(1D)-H(1DD)	0.91(4)
C(1D)-C(7D)	1.504(4)
C(1D)-C(2D)	1.552(4)
C(1D)-H(1D)	1.0000
O(2D)-C(4D)	1.439(3)
O(2D)-H(2D)	0.92(3)
C(2D)-O(3D)	1.449(3)
C(2D)-C(11D)	1.531(4)
C(2D)-C(3D)	1.532(4)
O(3D)-C(5D)	1.450(3)
C(3D)-C(4D)	1.536(4)
C(3D)-H(3D1)	0.9900
C(3D)-H(3D2)	0.9900
C(4D)-C(5D)	1.550(4)
C(4D)-H(4D)	1.0000
C(5D)-C(14D)	1.508(4)
C(5D)-C(6D)	1.537(4)
C(6D)-C(7D)	1.513(4)
C(6D)-C(10D)	1.553(4)
C(6D)-H(6D)	1.0000
C(7D)-C(8D)	1.324(4)
C(8D)-C(15D)	1.501(4)
C(8D)-C(9D)	1.506(4)
C(9D)-C(10D)	1.536(4)
C(9D)-H(9D1)	0.9900
C(9D)-H(9D2)	0.9900
C(10D)-H(10G)	0.9900
C(10D)-H(10H)	0.9900
C(11D)-C(13D)	1.513(4)
C(11D)-C(12D)	1.536(4)
C(11D)-H(11D)	1.0000
C(12D)-H(12J)	0.9800
C(12D)-H(12K)	0.9800
C(12D)-H(12L)	0.9800
C(13D)-H(13J)	0.9800
C(13D)-H(13K)	0.9800
C(13D)-H(13L)	0.9800
C(14D)-H(14J)	0.9800
C(14D)-H(14K)	0.9800
C(14D)-H(14L)	0.9800
C(15D)-H(15J)	0.9800
C(15D)-H(15K)	0.9800
C(15D)-H(15L)	0.9800
O(1E)-C(1E)	1.425(3)
O(1E)-H(1EE)	0.92(4)
C(1E)-C(7E)	1.499(4)
C(1E)-C(2E)	1.550(4)
C(1E)-H(1E)	1.0000

O(2E)-C(4E)	1.434(3)
O(2E)-H(2E)	0.88(3)
C(2E)-O(3E)	1.461(3)
C(2E)-C(11E)	1.529(4)
C(2E)-C(3E)	1.538(4)
O(3E)-C(5E)	1.459(3)
C(3E)-C(4E)	1.534(4)
C(3E)-H(3E1)	0.9900
C(3E)-H(3E2)	0.9900
C(4E)-C(5E)	1.543(4)
C(4E)-H(4E)	1.0000
C(5E)-C(14E)	1.515(4)
C(5E)-C(6E)	1.531(4)
C(6E)-C(7E)	1.519(4)
C(6E)-C(10E)	1.541(4)
C(6E)-H(6E)	1.0000
C(7E)-C(8E)	1.326(4)
C(8E)-C(15E)	1.505(4)
C(8E)-C(9E)	1.506(4)
C(9E)-C(10E)	1.540(4)
C(9E)-H(9E1)	0.9900
C(9E)-H(9E2)	0.9900
C(10E)-H(10I)	0.9900
C(10E)-H(10J)	0.9900
C(11E)-C(12E)	1.519(4)
C(11E)-C(13E)	1.537(4)
C(11E)-H(11E)	1.0000
C(12E)-H(12M)	0.9800
C(12E)-H(12N)	0.9800
C(12E)-H(12O)	0.9800
C(13E)-H(13M)	0.9800
C(13E)-H(13N)	0.9800
C(13E)-H(13O)	0.9800
C(14E)-H(14M)	0.9800
C(14E)-H(14N)	0.9800
C(14E)-H(14O)	0.9800
C(15E)-H(15M)	0.9800
C(15E)-H(15N)	0.9800
C(15E)-H(15O)	0.9800
O(1F)-C(1F)	1.429(3)
O(1F)-H(1FF)	0.95(4)
C(1F)-C(7F)	1.500(4)
C(1F)-C(2F)	1.540(4)
C(1F)-H(1F)	1.0000
O(2F)-C(4F)	1.438(3)
O(2F)-H(2F)	0.86(3)
C(2F)-O(3F)	1.461(3)
C(2F)-C(3F)	1.524(4)
C(2F)-C(11F)	1.537(4)
O(3F)-C(5F)	1.459(3)

C(3F)-C(4F)	1.533(4)
C(3F)-H(3F1)	0.9900
C(3F)-H(3F2)	0.9900
C(4F)-C(5F)	1.552(4)
C(4F)-H(4F)	1.0000
C(5F)-C(14F)	1.512(4)
C(5F)-C(6F)	1.525(4)
C(6F)-C(7F)	1.513(4)
C(6F)-C(10F)	1.539(4)
C(6F)-H(6F)	1.0000
C(7F)-C(8F)	1.321(4)
C(8F)-C(9F)	1.501(5)
C(8F)-C(15F)	1.509(4)
C(9F)-C(10F)	1.535(4)
C(9F)-H(9F1)	0.9900
C(9F)-H(9F2)	0.9900
C(10F)-H(10K)	0.9900
C(10F)-H(10L)	0.9900
C(11F)-C(12F)	1.496(4)
C(11F)-C(13F)	1.538(5)
C(11F)-H(11F)	1.0000
C(12F)-H(12P)	0.9800
C(12F)-H(12Q)	0.9800
C(12F)-H(12R)	0.9800
C(13F)-H(13P)	0.9800
C(13F)-H(13Q)	0.9800
C(13F)-H(13R)	0.9800
C(14F)-H(14P)	0.9800
C(14F)-H(14Q)	0.9800
C(14F)-H(14R)	0.9800
C(15F)-H(15P)	0.9800
C(15F)-H(15Q)	0.9800
C(15F)-H(15R)	0.9800
C(1A)-O(1A)-H(1AA)	106(3)
O(1A)-C(1A)-C(7A)	113.0(2)
O(1A)-C(1A)-C(2A)	108.0(2)
C(7A)-C(1A)-C(2A)	110.0(2)
O(1A)-C(1A)-H(1A)	108.6
C(7A)-C(1A)-H(1A)	108.6
C(2A)-C(1A)-H(1A)	108.6
C(4A)-O(2A)-H(2A)	107(2)
O(3A)-C(2A)-C(11A)	108.3(2)
O(3A)-C(2A)-C(3A)	103.3(2)
C(11A)-C(2A)-C(3A)	113.8(2)
O(3A)-C(2A)-C(1A)	107.8(2)
C(11A)-C(2A)-C(1A)	113.9(2)
C(3A)-C(2A)-C(1A)	109.1(2)
C(2A)-O(3A)-C(5A)	105.81(19)
C(2A)-C(3A)-C(4A)	105.8(2)
C(2A)-C(3A)-H(3A1)	110.6

C(4A)-C(3A)-H(3A1)	110.6
C(2A)-C(3A)-H(3A2)	110.6
C(4A)-C(3A)-H(3A2)	110.6
H(3A1)-C(3A)-H(3A2)	108.7
O(2A)-C(4A)-C(3A)	111.2(2)
O(2A)-C(4A)-C(5A)	111.3(2)
C(3A)-C(4A)-C(5A)	103.7(2)
O(2A)-C(4A)-H(4A)	110.1
C(3A)-C(4A)-H(4A)	110.1
C(5A)-C(4A)-H(4A)	110.1
O(3A)-C(5A)-C(6A)	105.7(2)
O(3A)-C(5A)-C(14A)	107.4(2)
C(6A)-C(5A)-C(14A)	112.8(2)
O(3A)-C(5A)-C(4A)	103.1(2)
C(6A)-C(5A)-C(4A)	111.3(2)
C(14A)-C(5A)-C(4A)	115.5(2)
C(7A)-C(6A)-C(5A)	111.9(2)
C(7A)-C(6A)-C(10A)	103.5(2)
C(5A)-C(6A)-C(10A)	118.4(2)
C(7A)-C(6A)-H(6A)	107.5
C(5A)-C(6A)-H(6A)	107.5
C(10A)-C(6A)-H(6A)	107.5
C(8A)-C(7A)-C(1A)	132.3(3)
C(8A)-C(7A)-C(6A)	111.8(3)
C(1A)-C(7A)-C(6A)	115.8(2)
C(7A)-C(8A)-C(9A)	112.0(3)
C(7A)-C(8A)-C(15A)	129.2(3)
C(9A)-C(8A)-C(15A)	118.7(3)
C(8A)-C(9A)-C(10A)	104.3(2)
C(8A)-C(9A)-H(9A1)	110.9
C(10A)-C(9A)-H(9A1)	110.9
C(8A)-C(9A)-H(9A2)	110.9
C(10A)-C(9A)-H(9A2)	110.9
H(9A1)-C(9A)-H(9A2)	108.9
C(9A)-C(10A)-C(6A)	105.5(2)
C(9A)-C(10A)-H(10A)	110.6
C(6A)-C(10A)-H(10A)	110.6
C(9A)-C(10A)-H(10B)	110.6
C(6A)-C(10A)-H(10B)	110.6
H(10A)-C(10A)-H(10B)	108.8
C(12A)-C(11A)-C(2A)	112.8(2)
C(12A)-C(11A)-C(13A)	108.3(2)
C(2A)-C(11A)-C(13A)	113.6(2)
C(12A)-C(11A)-H(11A)	107.3
C(2A)-C(11A)-H(11A)	107.3
C(13A)-C(11A)-H(11A)	107.3
C(11A)-C(12A)-H(12A)	109.5
C(11A)-C(12A)-H(12B)	109.5
H(12A)-C(12A)-H(12B)	109.5
C(11A)-C(12A)-H(12C)	109.5

H(12A)-C(12A)-H(12C)	109.5
H(12B)-C(12A)-H(12C)	109.5
C(11A)-C(13A)-H(13A)	109.5
C(11A)-C(13A)-H(13B)	109.5
H(13A)-C(13A)-H(13B)	109.5
C(11A)-C(13A)-H(13C)	109.5
H(13A)-C(13A)-H(13C)	109.5
H(13B)-C(13A)-H(13C)	109.5
C(5A)-C(14A)-H(14A)	109.5
C(5A)-C(14A)-H(14B)	109.5
H(14A)-C(14A)-H(14B)	109.5
C(5A)-C(14A)-H(14C)	109.5
H(14A)-C(14A)-H(14C)	109.5
H(14B)-C(14A)-H(14C)	109.5
C(8A)-C(15A)-H(15A)	109.5
C(8A)-C(15A)-H(15B)	109.5
H(15A)-C(15A)-H(15B)	109.5
C(8A)-C(15A)-H(15C)	109.5
H(15A)-C(15A)-H(15C)	109.5
H(15B)-C(15A)-H(15C)	109.5
C(1B)-O(1B)-H(1BB)	109(2)
O(1B)-C(1B)-C(7B)	114.3(2)
O(1B)-C(1B)-C(2B)	108.2(2)
C(7B)-C(1B)-C(2B)	108.4(2)
O(1B)-C(1B)-H(1B)	108.6
C(7B)-C(1B)-H(1B)	108.6
C(2B)-C(1B)-H(1B)	108.6
C(4B)-O(2B)-H(2B)	107(2)
O(3B)-C(2B)-C(11B)	109.0(2)
O(3B)-C(2B)-C(3B)	103.6(2)
C(11B)-C(2B)-C(3B)	114.1(2)
O(3B)-C(2B)-C(1B)	106.4(2)
C(11B)-C(2B)-C(1B)	113.7(2)
C(3B)-C(2B)-C(1B)	109.3(2)
C(2B)-O(3B)-C(5B)	106.10(18)
C(4B)-C(3B)-C(2B)	105.7(2)
C(4B)-C(3B)-H(3B1)	110.6
C(2B)-C(3B)-H(3B1)	110.6
C(4B)-C(3B)-H(3B2)	110.6
C(2B)-C(3B)-H(3B2)	110.6
H(3B1)-C(3B)-H(3B2)	108.7
O(2B)-C(4B)-C(3B)	111.6(2)
O(2B)-C(4B)-C(5B)	111.2(2)
C(3B)-C(4B)-C(5B)	104.4(2)
O(2B)-C(4B)-H(4B)	109.8
C(3B)-C(4B)-H(4B)	109.8
C(5B)-C(4B)-H(4B)	109.8
O(3B)-C(5B)-C(14B)	107.3(2)
O(3B)-C(5B)-C(6B)	105.3(2)
C(14B)-C(5B)-C(6B)	112.8(2)

O(3B)-C(5B)-C(4B)	102.7(2)
C(14B)-C(5B)-C(4B)	116.2(2)
C(6B)-C(5B)-C(4B)	111.4(2)
C(7B)-C(6B)-C(5B)	110.7(2)
C(7B)-C(6B)-C(10B)	104.6(2)
C(5B)-C(6B)-C(10B)	116.4(2)
C(7B)-C(6B)-H(6B)	108.3
C(5B)-C(6B)-H(6B)	108.3
C(10B)-C(6B)-H(6B)	108.3
C(8B)-C(7B)-C(1B)	132.6(3)
C(8B)-C(7B)-C(6B)	111.6(3)
C(1B)-C(7B)-C(6B)	115.8(2)
C(7B)-C(8B)-C(9B)	111.9(3)
C(7B)-C(8B)-C(15B)	129.5(3)
C(9B)-C(8B)-C(15B)	118.5(3)
C(8B)-C(9B)-C(10B)	105.1(2)
C(8B)-C(9B)-H(9B1)	110.7
C(10B)-C(9B)-H(9B1)	110.7
C(8B)-C(9B)-H(9B2)	110.7
C(10B)-C(9B)-H(9B2)	110.7
H(9B1)-C(9B)-H(9B2)	108.8
C(9B)-C(10B)-C(6B)	105.5(3)
C(9B)-C(10B)-H(10C)	110.6
C(6B)-C(10B)-H(10C)	110.6
C(9B)-C(10B)-H(10D)	110.6
C(6B)-C(10B)-H(10D)	110.6
H(10C)-C(10B)-H(10D)	108.8
C(13B)-C(11B)-C(2B)	114.0(2)
C(13B)-C(11B)-C(12B)	108.1(2)
C(2B)-C(11B)-C(12B)	111.6(2)
C(13B)-C(11B)-H(11B)	107.6
C(2B)-C(11B)-H(11B)	107.6
C(12B)-C(11B)-H(11B)	107.6
C(11B)-C(12B)-H(12D)	109.5
C(11B)-C(12B)-H(12E)	109.5
H(12D)-C(12B)-H(12E)	109.5
C(11B)-C(12B)-H(12F)	109.5
H(12D)-C(12B)-H(12F)	109.5
H(12E)-C(12B)-H(12F)	109.5
C(11B)-C(13B)-H(13D)	109.5
C(11B)-C(13B)-H(13E)	109.5
H(13D)-C(13B)-H(13E)	109.5
C(11B)-C(13B)-H(13F)	109.5
H(13D)-C(13B)-H(13F)	109.5
H(13E)-C(13B)-H(13F)	109.5
C(5B)-C(14B)-H(14D)	109.5
C(5B)-C(14B)-H(14E)	109.5
H(14D)-C(14B)-H(14E)	109.5
C(5B)-C(14B)-H(14F)	109.5
H(14D)-C(14B)-H(14F)	109.5

H(14E)-C(14B)-H(14F)	109.5
C(8B)-C(15B)-H(15D)	109.5
C(8B)-C(15B)-H(15E)	109.5
H(15D)-C(15B)-H(15E)	109.5
C(8B)-C(15B)-H(15F)	109.5
H(15D)-C(15B)-H(15F)	109.5
H(15E)-C(15B)-H(15F)	109.5
C(1C)-O(1C)-H(1CC)	105(3)
O(1C)-C(1C)-C(7C)	114.3(2)
O(1C)-C(1C)-C(2C)	108.4(2)
C(7C)-C(1C)-C(2C)	108.9(2)
O(1C)-C(1C)-H(1C)	108.4
C(7C)-C(1C)-H(1C)	108.4
C(2C)-C(1C)-H(1C)	108.4
C(4C)-O(2C)-H(2C)	108(2)
O(3C)-C(2C)-C(11C)	108.7(2)
O(3C)-C(2C)-C(3C)	103.8(2)
C(11C)-C(2C)-C(3C)	113.8(2)
O(3C)-C(2C)-C(1C)	106.2(2)
C(11C)-C(2C)-C(1C)	114.1(2)
C(3C)-C(2C)-C(1C)	109.3(2)
C(2C)-O(3C)-C(5C)	106.1(2)
C(4C)-C(3C)-C(2C)	105.2(2)
C(4C)-C(3C)-H(3C1)	110.7
C(2C)-C(3C)-H(3C1)	110.7
C(4C)-C(3C)-H(3C2)	110.7
C(2C)-C(3C)-H(3C2)	110.7
H(3C1)-C(3C)-H(3C2)	108.8
O(2C)-C(4C)-C(5C)	110.4(2)
O(2C)-C(4C)-C(3C)	110.8(2)
C(5C)-C(4C)-C(3C)	104.7(2)
O(2C)-C(4C)-H(4C)	110.3
C(5C)-C(4C)-H(4C)	110.3
C(3C)-C(4C)-H(4C)	110.3
O(3C)-C(5C)-C(14C)	107.5(2)
O(3C)-C(5C)-C(6C)	105.4(2)
C(14C)-C(5C)-C(6C)	112.4(2)
O(3C)-C(5C)-C(4C)	102.6(2)
C(14C)-C(5C)-C(4C)	115.8(2)
C(6C)-C(5C)-C(4C)	112.0(2)
C(7C)-C(6C)-C(5C)	110.8(2)
C(7C)-C(6C)-C(10C)	104.1(2)
C(5C)-C(6C)-C(10C)	117.2(2)
C(7C)-C(6C)-H(6C)	108.1
C(5C)-C(6C)-H(6C)	108.1
C(10C)-C(6C)-H(6C)	108.1
C(8C)-C(7C)-C(1C)	132.1(3)
C(8C)-C(7C)-C(6C)	111.9(3)
C(1C)-C(7C)-C(6C)	115.9(2)
C(7C)-C(8C)-C(15C)	129.1(3)

C(7C)-C(8C)-C(9C)	112.1(3)
C(15C)-C(8C)-C(9C)	118.7(3)
C(8C)-C(9C)-C(10C)	104.3(2)
C(8C)-C(9C)-H(9C1)	110.9
C(10C)-C(9C)-H(9C1)	110.9
C(8C)-C(9C)-H(9C2)	110.9
C(10C)-C(9C)-H(9C2)	110.9
H(9C1)-C(9C)-H(9C2)	108.9
C(6C)-C(10C)-C(9C)	105.8(2)
C(6C)-C(10C)-H(10E)	110.6
C(9C)-C(10C)-H(10E)	110.6
C(6C)-C(10C)-H(10F)	110.6
C(9C)-C(10C)-H(10F)	110.6
H(10E)-C(10C)-H(10F)	108.7
C(13C)-C(11C)-C(2C)	114.7(2)
C(13C)-C(11C)-C(12C)	109.4(2)
C(2C)-C(11C)-C(12C)	111.3(2)
C(13C)-C(11C)-H(11C)	107.0
C(2C)-C(11C)-H(11C)	107.0
C(12C)-C(11C)-H(11C)	107.0
C(11C)-C(12C)-H(12G)	109.5
C(11C)-C(12C)-H(12H)	109.5
H(12G)-C(12C)-H(12H)	109.5
C(11C)-C(12C)-H(12I)	109.5
H(12G)-C(12C)-H(12I)	109.5
H(12H)-C(12C)-H(12I)	109.5
C(11C)-C(13C)-H(13G)	109.5
C(11C)-C(13C)-H(13H)	109.5
H(13G)-C(13C)-H(13H)	109.5
C(11C)-C(13C)-H(13I)	109.5
H(13G)-C(13C)-H(13I)	109.5
H(13H)-C(13C)-H(13I)	109.5
C(5C)-C(14C)-H(14G)	109.5
C(5C)-C(14C)-H(14H)	109.5
H(14G)-C(14C)-H(14H)	109.5
C(5C)-C(14C)-H(14I)	109.5
H(14G)-C(14C)-H(14I)	109.5
H(14H)-C(14C)-H(14I)	109.5
C(8C)-C(15C)-H(15G)	109.5
C(8C)-C(15C)-H(15H)	109.5
H(15G)-C(15C)-H(15H)	109.5
C(8C)-C(15C)-H(15I)	109.5
H(15G)-C(15C)-H(15I)	109.5
H(15H)-C(15C)-H(15I)	109.5
C(1D)-O(1D)-H(1DD)	109(3)
O(1D)-C(1D)-C(7D)	112.3(2)
O(1D)-C(1D)-C(2D)	109.9(2)
C(7D)-C(1D)-C(2D)	108.3(2)
O(1D)-C(1D)-H(1D)	108.8
C(7D)-C(1D)-H(1D)	108.8

C(2D)-C(1D)-H(1D)	108.8
C(4D)-O(2D)-H(2D)	105.2(19)
O(3D)-C(2D)-C(11D)	108.8(2)
O(3D)-C(2D)-C(3D)	103.8(2)
C(11D)-C(2D)-C(3D)	113.7(2)
O(3D)-C(2D)-C(1D)	107.2(2)
C(11D)-C(2D)-C(1D)	113.1(2)
C(3D)-C(2D)-C(1D)	109.5(2)
C(2D)-O(3D)-C(5D)	105.8(2)
C(2D)-C(3D)-C(4D)	105.6(2)
C(2D)-C(3D)-H(3D1)	110.6
C(4D)-C(3D)-H(3D1)	110.6
C(2D)-C(3D)-H(3D2)	110.6
C(4D)-C(3D)-H(3D2)	110.6
H(3D1)-C(3D)-H(3D2)	108.8
O(2D)-C(4D)-C(3D)	111.7(2)
O(2D)-C(4D)-C(5D)	110.7(2)
C(3D)-C(4D)-C(5D)	103.5(2)
O(2D)-C(4D)-H(4D)	110.2
C(3D)-C(4D)-H(4D)	110.2
C(5D)-C(4D)-H(4D)	110.2
O(3D)-C(5D)-C(14D)	107.7(2)
O(3D)-C(5D)-C(6D)	105.7(2)
C(14D)-C(5D)-C(6D)	112.9(2)
O(3D)-C(5D)-C(4D)	103.8(2)
C(14D)-C(5D)-C(4D)	116.1(2)
C(6D)-C(5D)-C(4D)	109.6(2)
C(7D)-C(6D)-C(5D)	110.9(2)
C(7D)-C(6D)-C(10D)	104.2(2)
C(5D)-C(6D)-C(10D)	116.8(2)
C(7D)-C(6D)-H(6D)	108.2
C(5D)-C(6D)-H(6D)	108.2
C(10D)-C(6D)-H(6D)	108.2
C(8D)-C(7D)-C(1D)	133.2(3)
C(8D)-C(7D)-C(6D)	112.3(3)
C(1D)-C(7D)-C(6D)	114.5(2)
C(7D)-C(8D)-C(15D)	129.3(3)
C(7D)-C(8D)-C(9D)	112.0(3)
C(15D)-C(8D)-C(9D)	118.7(3)
C(8D)-C(9D)-C(10D)	105.1(3)
C(8D)-C(9D)-H(9D1)	110.7
C(10D)-C(9D)-H(9D1)	110.7
C(8D)-C(9D)-H(9D2)	110.7
C(10D)-C(9D)-H(9D2)	110.7
H(9D1)-C(9D)-H(9D2)	108.8
C(9D)-C(10D)-C(6D)	105.7(3)
C(9D)-C(10D)-H(10G)	110.6
C(6D)-C(10D)-H(10G)	110.6
C(9D)-C(10D)-H(10H)	110.6
C(6D)-C(10D)-H(10H)	110.6

H(10G)-C(10D)-H(10H)	108.7
C(13D)-C(11D)-C(2D)	113.8(2)
C(13D)-C(11D)-C(12D)	107.8(3)
C(2D)-C(11D)-C(12D)	112.3(2)
C(13D)-C(11D)-H(11D)	107.6
C(2D)-C(11D)-H(11D)	107.6
C(12D)-C(11D)-H(11D)	107.6
C(11D)-C(12D)-H(12J)	109.5
C(11D)-C(12D)-H(12K)	109.5
H(12J)-C(12D)-H(12K)	109.5
C(11D)-C(12D)-H(12L)	109.5
H(12J)-C(12D)-H(12L)	109.5
H(12K)-C(12D)-H(12L)	109.5
C(11D)-C(13D)-H(13J)	109.5
C(11D)-C(13D)-H(13K)	109.5
H(13J)-C(13D)-H(13K)	109.5
C(11D)-C(13D)-H(13L)	109.5
H(13J)-C(13D)-H(13L)	109.5
H(13K)-C(13D)-H(13L)	109.5
C(5D)-C(14D)-H(14J)	109.5
C(5D)-C(14D)-H(14K)	109.5
H(14J)-C(14D)-H(14K)	109.5
C(5D)-C(14D)-H(14L)	109.5
H(14J)-C(14D)-H(14L)	109.5
H(14K)-C(14D)-H(14L)	109.5
C(8D)-C(15D)-H(15J)	109.5
C(8D)-C(15D)-H(15K)	109.5
H(15J)-C(15D)-H(15K)	109.5
C(8D)-C(15D)-H(15L)	109.5
H(15J)-C(15D)-H(15L)	109.5
H(15K)-C(15D)-H(15L)	109.5
C(1E)-O(1E)-H(1EE)	111(2)
O(1E)-C(1E)-C(7E)	113.3(2)
O(1E)-C(1E)-C(2E)	108.4(2)
C(7E)-C(1E)-C(2E)	109.1(2)
O(1E)-C(1E)-H(1E)	108.6
C(7E)-C(1E)-H(1E)	108.6
C(2E)-C(1E)-H(1E)	108.6
C(4E)-O(2E)-H(2E)	109(2)
O(3E)-C(2E)-C(11E)	109.5(2)
O(3E)-C(2E)-C(3E)	104.0(2)
C(11E)-C(2E)-C(3E)	113.7(2)
O(3E)-C(2E)-C(1E)	106.6(2)
C(11E)-C(2E)-C(1E)	113.3(2)
C(3E)-C(2E)-C(1E)	109.1(2)
C(5E)-O(3E)-C(2E)	105.59(19)
C(4E)-C(3E)-C(2E)	105.6(2)
C(4E)-C(3E)-H(3E1)	110.6
C(2E)-C(3E)-H(3E1)	110.6
C(4E)-C(3E)-H(3E2)	110.6

C(2E)-C(3E)-H(3E2)	110.6
H(3E1)-C(3E)-H(3E2)	108.7
O(2E)-C(4E)-C(3E)	110.8(2)
O(2E)-C(4E)-C(5E)	110.9(2)
C(3E)-C(4E)-C(5E)	103.9(2)
O(2E)-C(4E)-H(4E)	110.4
C(3E)-C(4E)-H(4E)	110.4
C(5E)-C(4E)-H(4E)	110.4
O(3E)-C(5E)-C(14E)	107.5(2)
O(3E)-C(5E)-C(6E)	105.9(2)
C(14E)-C(5E)-C(6E)	112.5(2)
O(3E)-C(5E)-C(4E)	103.1(2)
C(14E)-C(5E)-C(4E)	115.4(2)
C(6E)-C(5E)-C(4E)	111.5(2)
C(7E)-C(6E)-C(5E)	111.5(2)
C(7E)-C(6E)-C(10E)	103.9(2)
C(5E)-C(6E)-C(10E)	118.0(2)
C(7E)-C(6E)-H(6E)	107.6
C(5E)-C(6E)-H(6E)	107.6
C(10E)-C(6E)-H(6E)	107.6
C(8E)-C(7E)-C(1E)	132.0(3)
C(8E)-C(7E)-C(6E)	111.6(3)
C(1E)-C(7E)-C(6E)	116.4(3)
C(7E)-C(8E)-C(15E)	128.8(3)
C(7E)-C(8E)-C(9E)	112.0(3)
C(15E)-C(8E)-C(9E)	119.0(3)
C(8E)-C(9E)-C(10E)	104.5(2)
C(8E)-C(9E)-H(9E1)	110.9
C(10E)-C(9E)-H(9E1)	110.9
C(8E)-C(9E)-H(9E2)	110.9
C(10E)-C(9E)-H(9E2)	110.9
H(9E1)-C(9E)-H(9E2)	108.9
C(9E)-C(10E)-C(6E)	105.4(2)
C(9E)-C(10E)-H(10I)	110.7
C(6E)-C(10E)-H(10I)	110.7
C(9E)-C(10E)-H(10J)	110.7
C(6E)-C(10E)-H(10J)	110.7
H(10I)-C(10E)-H(10J)	108.8
C(12E)-C(11E)-C(2E)	114.2(2)
C(12E)-C(11E)-C(13E)	108.9(3)
C(2E)-C(11E)-C(13E)	111.5(2)
C(12E)-C(11E)-H(11E)	107.3
C(2E)-C(11E)-H(11E)	107.3
C(13E)-C(11E)-H(11E)	107.3
C(11E)-C(12E)-H(12M)	109.5
C(11E)-C(12E)-H(12N)	109.5
H(12M)-C(12E)-H(12N)	109.5
C(11E)-C(12E)-H(12O)	109.5
H(12M)-C(12E)-H(12O)	109.5
H(12N)-C(12E)-H(12O)	109.5

C(11E)-C(13E)-H(13M)	109.5
C(11E)-C(13E)-H(13N)	109.5
H(13M)-C(13E)-H(13N)	109.5
C(11E)-C(13E)-H(13O)	109.5
H(13M)-C(13E)-H(13O)	109.5
H(13N)-C(13E)-H(13O)	109.5
C(5E)-C(14E)-H(14M)	109.5
C(5E)-C(14E)-H(14N)	109.5
H(14M)-C(14E)-H(14N)	109.5
C(5E)-C(14E)-H(14O)	109.5
H(14M)-C(14E)-H(14O)	109.5
H(14N)-C(14E)-H(14O)	109.5
C(8E)-C(15E)-H(15M)	109.5
C(8E)-C(15E)-H(15N)	109.5
H(15M)-C(15E)-H(15N)	109.5
C(8E)-C(15E)-H(15O)	109.5
H(15M)-C(15E)-H(15O)	109.5
H(15N)-C(15E)-H(15O)	109.5
C(1F)-O(1F)-H(1FF)	108(2)
O(1F)-C(1F)-C(7F)	112.3(2)
O(1F)-C(1F)-C(2F)	110.0(2)
C(7F)-C(1F)-C(2F)	110.2(2)
O(1F)-C(1F)-H(1F)	108.0
C(7F)-C(1F)-H(1F)	108.0
C(2F)-C(1F)-H(1F)	108.0
C(4F)-O(2F)-H(2F)	111(2)
O(3F)-C(2F)-C(3F)	102.1(2)
O(3F)-C(2F)-C(11F)	107.6(2)
C(3F)-C(2F)-C(11F)	116.5(3)
O(3F)-C(2F)-C(1F)	106.2(2)
C(3F)-C(2F)-C(1F)	111.7(2)
C(11F)-C(2F)-C(1F)	111.6(3)
C(5F)-O(3F)-C(2F)	106.61(19)
C(2F)-C(3F)-C(4F)	106.5(2)
C(2F)-C(3F)-H(3F1)	110.4
C(4F)-C(3F)-H(3F1)	110.4
C(2F)-C(3F)-H(3F2)	110.4
C(4F)-C(3F)-H(3F2)	110.4
H(3F1)-C(3F)-H(3F2)	108.6
O(2F)-C(4F)-C(3F)	110.9(2)
O(2F)-C(4F)-C(5F)	111.5(2)
C(3F)-C(4F)-C(5F)	104.0(2)
O(2F)-C(4F)-H(4F)	110.1
C(3F)-C(4F)-H(4F)	110.1
C(5F)-C(4F)-H(4F)	110.1
O(3F)-C(5F)-C(14F)	107.7(2)
O(3F)-C(5F)-C(6F)	105.2(2)
C(14F)-C(5F)-C(6F)	112.9(2)
O(3F)-C(5F)-C(4F)	103.1(2)
C(14F)-C(5F)-C(4F)	115.9(2)

C(6F)-C(5F)-C(4F)	110.9(2)
C(7F)-C(6F)-C(5F)	110.8(2)
C(7F)-C(6F)-C(10F)	103.8(2)
C(5F)-C(6F)-C(10F)	117.4(2)
C(7F)-C(6F)-H(6F)	108.1
C(5F)-C(6F)-H(6F)	108.1
C(10F)-C(6F)-H(6F)	108.1
C(8F)-C(7F)-C(1F)	131.8(3)
C(8F)-C(7F)-C(6F)	111.9(3)
C(1F)-C(7F)-C(6F)	116.3(2)
C(7F)-C(8F)-C(9F)	112.0(3)
C(7F)-C(8F)-C(15F)	129.4(3)
C(9F)-C(8F)-C(15F)	118.4(3)
C(8F)-C(9F)-C(10F)	104.6(3)
C(8F)-C(9F)-H(9F1)	110.8
C(10F)-C(9F)-H(9F1)	110.8
C(8F)-C(9F)-H(9F2)	110.8
C(10F)-C(9F)-H(9F2)	110.8
H(9F1)-C(9F)-H(9F2)	108.9
C(9F)-C(10F)-C(6F)	105.5(3)
C(9F)-C(10F)-H(10K)	110.6
C(6F)-C(10F)-H(10K)	110.6
C(9F)-C(10F)-H(10L)	110.6
C(6F)-C(10F)-H(10L)	110.6
H(10K)-C(10F)-H(10L)	108.8
C(12F)-C(11F)-C(2F)	113.2(3)
C(12F)-C(11F)-C(13F)	108.7(3)
C(2F)-C(11F)-C(13F)	112.7(3)
C(12F)-C(11F)-H(11F)	107.3
C(2F)-C(11F)-H(11F)	107.3
C(13F)-C(11F)-H(11F)	107.3
C(11F)-C(12F)-H(12P)	109.5
C(11F)-C(12F)-H(12Q)	109.5
H(12P)-C(12F)-H(12Q)	109.5
C(11F)-C(12F)-H(12R)	109.5
H(12P)-C(12F)-H(12R)	109.5
H(12Q)-C(12F)-H(12R)	109.5
C(11F)-C(13F)-H(13P)	109.5
C(11F)-C(13F)-H(13Q)	109.5
H(13P)-C(13F)-H(13Q)	109.5
C(11F)-C(13F)-H(13R)	109.5
H(13P)-C(13F)-H(13R)	109.5
H(13Q)-C(13F)-H(13R)	109.5
C(5F)-C(14F)-H(14P)	109.5
C(5F)-C(14F)-H(14Q)	109.5
H(14P)-C(14F)-H(14Q)	109.5
C(5F)-C(14F)-H(14R)	109.5
H(14P)-C(14F)-H(14R)	109.5
H(14Q)-C(14F)-H(14R)	109.5
C(8F)-C(15F)-H(15P)	109.5

C(8F)-C(15F)-H(15Q)	109.5
H(15P)-C(15F)-H(15Q)	109.5
C(8F)-C(15F)-H(15R)	109.5
H(15P)-C(15F)-H(15R)	109.5
H(15Q)-C(15F)-H(15R)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for s2644lc.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
O(1A)	19(1)	30(1)	34(1)	3(1)	2(1)	4(1)
C(1A)	22(2)	22(2)	27(2)	-2(1)	7(1)	0(1)
O(2A)	17(1)	26(1)	37(1)	-2(1)	9(1)	-4(1)
C(2A)	19(2)	17(2)	25(2)	5(1)	5(1)	5(1)
O(3A)	20(1)	19(1)	25(1)	2(1)	3(1)	1(1)
C(3A)	20(2)	22(2)	26(2)	3(1)	6(1)	0(1)
C(4A)	17(2)	23(2)	31(2)	0(1)	11(1)	2(1)
C(5A)	17(2)	25(2)	24(2)	0(1)	5(1)	-1(1)
C(6A)	21(2)	27(2)	25(2)	0(1)	7(1)	-3(1)
C(7A)	21(2)	21(2)	28(2)	1(1)	11(1)	-3(1)
C(8A)	29(2)	24(2)	33(2)	0(1)	17(2)	-1(1)
C(9A)	46(2)	37(2)	35(2)	-6(2)	23(2)	-3(2)
C(10A)	35(2)	42(2)	29(2)	-4(2)	16(2)	-8(2)
C(11A)	22(2)	22(2)	26(2)	2(1)	7(1)	0(1)
C(12A)	37(2)	41(2)	37(2)	0(2)	23(2)	3(2)
C(13A)	31(2)	31(2)	27(2)	-4(1)	10(1)	2(2)
C(14A)	24(2)	30(2)	31(2)	4(1)	5(1)	-3(1)
C(15A)	38(2)	29(2)	49(2)	0(2)	25(2)	5(2)
O(1B)	19(1)	32(1)	39(1)	6(1)	9(1)	4(1)
C(1B)	19(2)	23(2)	28(2)	5(1)	11(1)	4(1)
O(2B)	21(1)	31(1)	21(1)	4(1)	7(1)	-6(1)
C(2B)	18(2)	20(2)	24(2)	3(1)	8(1)	4(1)
O(3B)	20(1)	20(1)	22(1)	4(1)	10(1)	1(1)
C(3B)	27(2)	19(2)	25(2)	6(1)	9(1)	1(1)
C(4B)	16(2)	22(2)	21(2)	1(1)	6(1)	-4(1)
C(5B)	22(2)	24(2)	23(2)	3(1)	13(1)	-1(1)
C(6B)	26(2)	18(2)	32(2)	3(1)	15(1)	-5(1)
C(7B)	23(2)	22(2)	24(2)	4(1)	10(1)	-5(1)
C(8B)	35(2)	28(2)	28(2)	1(1)	10(2)	-6(2)
C(9B)	54(2)	37(2)	27(2)	-5(2)	16(2)	-3(2)
C(10B)	40(2)	29(2)	35(2)	-6(2)	20(2)	-10(2)
C(11B)	29(2)	20(2)	30(2)	1(1)	13(1)	-2(1)
C(12B)	40(2)	32(2)	34(2)	-8(2)	10(2)	-7(2)

C(13B)	40(2)	33(2)	29(2)	0(2)	16(2)	0(2)
C(14B)	29(2)	27(2)	32(2)	7(1)	17(1)	3(1)
C(15B)	43(2)	57(2)	28(2)	7(2)	-1(2)	-1(2)
O(1C)	21(1)	42(1)	29(1)	3(1)	9(1)	-6(1)
C(1C)	22(2)	27(2)	18(1)	-2(1)	7(1)	-2(1)
O(2C)	21(1)	31(1)	21(1)	-6(1)	1(1)	4(1)
C(2C)	18(2)	28(2)	21(1)	-1(1)	9(1)	-2(1)
O(3C)	22(1)	24(1)	20(1)	-4(1)	9(1)	-2(1)
C(3C)	26(2)	28(2)	17(1)	-1(1)	7(1)	1(1)
C(4C)	17(2)	25(2)	21(2)	-1(1)	4(1)	3(1)
C(5C)	20(2)	20(2)	23(2)	-5(1)	6(1)	-5(1)
C(6C)	27(2)	27(2)	18(2)	1(1)	5(1)	1(1)
C(7C)	20(2)	34(2)	16(2)	-2(1)	3(1)	1(2)
C(8C)	26(2)	35(2)	16(2)	-6(1)	4(1)	-1(2)
C(9C)	38(2)	31(2)	37(2)	-6(2)	9(2)	3(2)
C(10C)	31(2)	24(2)	28(2)	2(1)	4(1)	0(1)
C(11C)	27(2)	28(2)	24(2)	1(1)	12(1)	1(1)
C(12C)	36(2)	34(2)	33(2)	8(2)	13(2)	7(2)
C(13C)	38(2)	25(2)	36(2)	-4(1)	13(2)	-2(2)
C(14C)	28(2)	34(2)	25(2)	-5(1)	9(1)	-6(1)
C(15C)	33(2)	50(2)	35(2)	-10(2)	13(2)	5(2)
O(1D)	20(1)	37(1)	36(1)	8(1)	11(1)	2(1)
C(1D)	19(2)	26(2)	20(2)	5(1)	6(1)	-1(1)
O(2D)	20(1)	32(1)	18(1)	4(1)	3(1)	-4(1)
C(2D)	18(2)	23(2)	23(2)	1(1)	11(1)	1(1)
O(3D)	19(1)	22(1)	20(1)	4(1)	8(1)	2(1)
C(3D)	22(2)	32(2)	19(2)	2(1)	8(1)	2(1)
C(4D)	21(2)	24(2)	19(2)	3(1)	4(1)	-1(1)
C(5D)	20(2)	24(2)	19(2)	2(1)	5(1)	3(1)
C(6D)	31(2)	25(2)	16(1)	-2(1)	6(1)	4(1)
C(7D)	23(2)	25(2)	19(2)	1(1)	2(1)	0(1)
C(8D)	35(2)	29(2)	27(2)	1(1)	10(1)	-7(2)
C(9D)	57(2)	25(2)	38(2)	2(2)	16(2)	-1(2)
C(10D)	42(2)	29(2)	28(2)	0(1)	4(2)	6(2)
C(11D)	27(2)	31(2)	23(2)	-4(1)	9(1)	0(1)
C(12D)	43(2)	30(2)	43(2)	-8(2)	7(2)	-6(2)
C(13D)	33(2)	30(2)	35(2)	4(2)	12(2)	1(2)
C(14D)	28(2)	34(2)	23(2)	6(1)	11(1)	6(1)
C(15D)	55(2)	41(2)	53(2)	2(2)	26(2)	-18(2)
O(1E)	22(1)	28(1)	32(1)	-1(1)	1(1)	0(1)
C(1E)	22(2)	20(2)	25(2)	0(1)	6(1)	3(1)
O(2E)	19(1)	21(1)	48(1)	6(1)	16(1)	6(1)
C(2E)	19(2)	20(2)	23(2)	-3(1)	5(1)	-1(1)
O(3E)	22(1)	21(1)	23(1)	-1(1)	4(1)	0(1)
C(3E)	22(2)	19(2)	33(2)	-2(1)	10(1)	3(1)
C(4E)	20(2)	24(2)	32(2)	2(1)	11(1)	2(1)
C(5E)	22(2)	24(2)	23(2)	2(1)	6(1)	5(1)
C(6E)	26(2)	30(2)	26(2)	2(1)	12(1)	5(2)
C(7E)	23(2)	23(2)	29(2)	2(1)	12(1)	9(1)
C(8E)	28(2)	23(2)	33(2)	2(1)	13(2)	5(1)

C(9E)	44(2)	28(2)	38(2)	9(2)	23(2)	7(2)
C(10E)	39(2)	46(2)	35(2)	11(2)	22(2)	16(2)
C(11E)	27(2)	28(2)	24(2)	1(1)	11(1)	-1(1)
C(12E)	32(2)	27(2)	29(2)	4(1)	9(2)	0(1)
C(13E)	36(2)	38(2)	38(2)	3(2)	19(2)	1(2)
C(14E)	27(2)	36(2)	32(2)	-2(2)	4(1)	5(2)
C(15E)	36(2)	30(2)	49(2)	-5(2)	18(2)	-9(2)
O(1F)	25(1)	37(1)	51(1)	18(1)	18(1)	16(1)
C(1F)	25(2)	29(2)	36(2)	14(2)	16(1)	8(2)
O(2F)	19(1)	32(1)	23(1)	2(1)	7(1)	-7(1)
C(2F)	29(2)	23(2)	29(2)	10(1)	14(1)	11(1)
O(3F)	26(1)	29(1)	26(1)	8(1)	12(1)	9(1)
C(3F)	25(2)	18(2)	32(2)	4(1)	9(1)	1(1)
C(4F)	18(2)	21(2)	22(2)	2(1)	6(1)	-2(1)
C(5F)	21(2)	27(2)	24(2)	2(1)	10(1)	0(1)
C(6F)	19(2)	21(2)	37(2)	8(1)	14(1)	1(1)
C(7F)	19(2)	22(2)	41(2)	8(1)	13(2)	-2(1)
C(8F)	25(2)	37(2)	38(2)	11(2)	10(2)	0(2)
C(9F)	36(2)	36(2)	41(2)	-4(2)	8(2)	-1(2)
C(10F)	29(2)	27(2)	41(2)	-9(2)	13(2)	-3(2)
C(11F)	38(2)	36(2)	36(2)	4(2)	19(2)	10(2)
C(12F)	72(3)	43(2)	47(2)	-13(2)	10(2)	5(2)
C(13F)	60(3)	42(2)	41(2)	0(2)	25(2)	16(2)
C(14F)	26(2)	30(2)	31(2)	6(1)	12(1)	3(1)
C(15F)	35(2)	68(3)	39(2)	9(2)	7(2)	10(2)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for s2644lc.

	x	y	z	U(eq)
H(1AA)	1197(9)	9870(40)	4080(20)	66(15)
H(1A)	860	10854	3284	29
H(2A)	-170(9)	7130(40)	2490(20)	80(14)
H(3A1)	299	8347	3820	28
H(3A2)	585	7959	3557	28
H(4A)	238	7671	2324	27
H(6A)	419	10553	1693	30
H(9A1)	757	7530	1282	45
H(9A2)	832	8877	1023	45
H(10A)	264	8095	1163	41
H(10B)	309	9266	678	41
H(11A)	680	9973	4703	28
H(12A)	88	11224	3986	54
H(12B)	262	10910	4902	54
H(12C)	117	9822	4279	54

H(13A)	572	12309	3919	45
H(13B)	912	11707	4403	45
H(13C)	693	12165	4854	45
H(14A)	-317	10081	1863	45
H(14B)	-247	9381	1180	45
H(14C)	-145	10795	1372	45
H(15A)	1344	8647	3164	54
H(15B)	1388	8866	2350	54
H(15C)	1290	7531	2556	54
H(1BB)	461(8)	8950(30)	7200(20)	52(11)
H(1B)	861	7907	7930	27
H(2B)	1884(7)	9560(30)	7017(17)	25(9)
H(3B1)	1128	9912	6832	29
H(3B2)	1424	10551	7518	29
H(4B)	1461	8639	6590	24
H(6B)	1240	6190	7551	29
H(9B1)	932	6831	5321	47
H(9B2)	800	5689	5669	47
H(10C)	1417	6656	6273	39
H(10D)	1301	5370	6513	39
H(11B)	1073	10730	8327	31
H(12D)	1677	9837	9402	55
H(12E)	1527	11159	9442	55
H(12F)	1642	10852	8741	55
H(13D)	849	9217	8850	50
H(13E)	1085	10033	9557	50
H(13F)	1193	8695	9385	50
H(14D)	2007	7530	8362	42
H(14E)	1909	6700	7585	42
H(14F)	1811	6278	8295	42
H(15D)	353	8319	6014	70
H(15E)	291	7104	5480	70
H(15F)	438	8310	5245	70
H(1CC)	2137(7)	4750(40)	3537(19)	99(17)
H(1C)	2526	4720	3184	27
H(2C)	3525(8)	6790(30)	5970(20)	56(12)
H(3C1)	2772	5657	5142	29
H(3C2)	3083	4813	5542	29
H(4C)	3086	7229	5115	26
H(6C)	2869	6830	3058	30
H(9C1)	2485	9157	4018	44
H(9C2)	2372	9010	3078	44
H(10E)	2892	8850	3280	36
H(10F)	2991	8678	4213	36
H(11C)	2783	2997	4746	31
H(12G)	3375	2973	4541	52
H(12H)	3255	1927	4977	52
H(12I)	3341	3274	5357	52
H(13G)	2535	2671	3395	50
H(13H)	2791	1602	3767	50

H(13I)	2869	2714	3296	50
H(14G)	3643	6192	4407	44
H(14H)	3521	7591	4268	44
H(14I)	3439	6669	3536	44
H(15G)	1895	6896	3118	59
H(15H)	1961	8027	3719	59
H(15I)	2039	6646	4046	59
H(1DD)	2833(9)	5150(40)	1610(20)	76(14)
H(1D)	2475	5546	2009	27
H(2D)	1476(7)	6990(30)	-980(20)	42(10)
H(3D1)	1964	5265	-375	29
H(3D2)	2228	6311	16	29
H(4D)	1850	7634	-4	27
H(6D)	2015	7207	2008	30
H(9D1)	2246	9906	951	49
H(9D2)	2368	9897	1896	49
H(10G)	1786	9019	836	43
H(10H)	1889	9190	1770	43
H(11D)	2380	3742	576	33
H(12J)	1982	2273	195	62
H(12K)	1822	3538	-218	62
H(12L)	1769	3060	546	62
H(13J)	2196	3279	1866	50
H(13K)	2550	3560	1935	50
H(13L)	2378	2306	1534	50
H(14J)	1304	6020	557	42
H(14K)	1347	7479	691	42
H(14L)	1454	6566	1431	42
H(15J)	2914	7714	1482	72
H(15K)	2932	8992	1932	72
H(15L)	2795	8961	991	72
H(1EE)	3778(8)	10030(30)	880(20)	55(11)
H(1E)	4153	10874	1772	28
H(2E)	5182(7)	7190(30)	2640(18)	41(10)
H(3E1)	4409	7942	1510	30
H(3E2)	4706	8278	1275	30
H(4E)	4749	7556	2736	30
H(6E)	4539	10381	3391	32
H(9E1)	4160	7296	3541	41
H(9E2)	4076	8592	3845	41
H(10I)	4666	7875	3813	45
H(10J)	4602	8979	4319	45
H(11E)	4372	9972	396	32
H(12M)	4477	12283	1196	45
H(12N)	4138	11721	661	45
H(12O)	4380	12146	267	45
H(13M)	4825	10866	323	54
H(13N)	4935	9729	922	54
H(13O)	4972	11112	1252	54
H(14M)	5305	9834	3366	51

H(14N)	5185	9234	4000	51
H(14O)	5114	10657	3763	51
H(15M)	3629	8670	1666	57
H(15N)	3553	8748	2446	57
H(15O)	3657	7461	2189	57
H(1FF)	429(10)	3870(40)	2240(20)	81(15)
H(1F)	789	2642	2723	34
H(2F)	1858(7)	4740(30)	2070(20)	44(11)
H(3F1)	1405	5447	2783	31
H(3F2)	1107	5103	1993	31
H(4F)	1409	3877	1598	25
H(6F)	1210	1113	2306	29
H(9F1)	913	2070	137	48
H(9F2)	803	824	439	48
H(10K)	1398	1994	1106	39
H(10L)	1313	600	1257	39
H(11F)	968	3957	3793	42
H(12P)	1499	3777	4525	86
H(12Q)	1380	5042	4769	86
H(12R)	1573	5064	4202	86
H(13P)	1109	6390	3418	68
H(13Q)	891	6037	3893	68
H(13R)	769	5758	2970	68
H(14P)	1962	2501	3309	43
H(14Q)	1886	1845	2476	43
H(14R)	1778	1208	3120	43
H(15P)	306	3127	889	74
H(15Q)	276	2070	256	74
H(15R)	400	3415	151	74

Table 6. Torsion angles [deg] for s2644lc.

O(1A)-C(1A)-C(2A)-O(3A)	-178.8(2)
C(7A)-C(1A)-C(2A)-O(3A)	-55.1(3)
O(1A)-C(1A)-C(2A)-C(11A)	61.0(3)
C(7A)-C(1A)-C(2A)-C(11A)	-175.3(2)
O(1A)-C(1A)-C(2A)-C(3A)	-67.3(3)
C(7A)-C(1A)-C(2A)-C(3A)	56.4(3)
C(11A)-C(2A)-O(3A)-C(5A)	-162.0(2)
C(3A)-C(2A)-O(3A)-C(5A)	-41.0(3)
C(1A)-C(2A)-O(3A)-C(5A)	74.4(2)
O(3A)-C(2A)-C(3A)-C(4A)	22.7(3)
C(11A)-C(2A)-C(3A)-C(4A)	139.9(2)
C(1A)-C(2A)-C(3A)-C(4A)	-91.8(3)
C(2A)-C(3A)-C(4A)-O(2A)	-117.4(2)

C(2A)-C(3A)-C(4A)-C(5A)	2.4(3)
C(2A)-O(3A)-C(5A)-C(6A)	-74.2(2)
C(2A)-O(3A)-C(5A)-C(14A)	165.2(2)
C(2A)-O(3A)-C(5A)-C(4A)	42.7(2)
O(2A)-C(4A)-C(5A)-O(3A)	93.2(2)
C(3A)-C(4A)-C(5A)-O(3A)	-26.5(3)
O(2A)-C(4A)-C(5A)-C(6A)	-153.9(2)
C(3A)-C(4A)-C(5A)-C(6A)	86.4(3)
O(2A)-C(4A)-C(5A)-C(14A)	-23.6(3)
C(3A)-C(4A)-C(5A)-C(14A)	-143.3(3)
O(3A)-C(5A)-C(6A)-C(7A)	56.7(3)
C(14A)-C(5A)-C(6A)-C(7A)	173.7(2)
C(4A)-C(5A)-C(6A)-C(7A)	-54.6(3)
O(3A)-C(5A)-C(6A)-C(10A)	176.9(2)
C(14A)-C(5A)-C(6A)-C(10A)	-66.0(3)
C(4A)-C(5A)-C(6A)-C(10A)	65.7(3)
O(1A)-C(1A)-C(7A)-C(8A)	-23.0(5)
C(2A)-C(1A)-C(7A)-C(8A)	-143.8(3)
O(1A)-C(1A)-C(7A)-C(6A)	160.4(2)
C(2A)-C(1A)-C(7A)-C(6A)	39.6(3)
C(5A)-C(6A)-C(7A)-C(8A)	141.1(3)
C(10A)-C(6A)-C(7A)-C(8A)	12.5(3)
C(5A)-C(6A)-C(7A)-C(1A)	-41.5(3)
C(10A)-C(6A)-C(7A)-C(1A)	-170.1(2)
C(1A)-C(7A)-C(8A)-C(9A)	-179.5(3)
C(6A)-C(7A)-C(8A)-C(9A)	-2.8(4)
C(1A)-C(7A)-C(8A)-C(15A)	-4.4(6)
C(6A)-C(7A)-C(8A)-C(15A)	172.4(3)
C(7A)-C(8A)-C(9A)-C(10A)	-8.3(4)
C(15A)-C(8A)-C(9A)-C(10A)	176.0(3)
C(8A)-C(9A)-C(10A)-C(6A)	15.4(3)
C(7A)-C(6A)-C(10A)-C(9A)	-16.7(3)
C(5A)-C(6A)-C(10A)-C(9A)	-141.3(3)
O(3A)-C(2A)-C(11A)-C(12A)	48.8(3)
C(3A)-C(2A)-C(11A)-C(12A)	-65.4(3)
C(1A)-C(2A)-C(11A)-C(12A)	168.7(2)
O(3A)-C(2A)-C(11A)-C(13A)	-74.9(3)
C(3A)-C(2A)-C(11A)-C(13A)	170.9(2)
C(1A)-C(2A)-C(11A)-C(13A)	45.0(3)
O(1B)-C(1B)-C(2B)-O(3B)	176.7(2)
C(7B)-C(1B)-C(2B)-O(3B)	-58.8(3)
O(1B)-C(1B)-C(2B)-C(11B)	56.7(3)
C(7B)-C(1B)-C(2B)-C(11B)	-178.8(2)
O(1B)-C(1B)-C(2B)-C(3B)	-72.1(3)
C(7B)-C(1B)-C(2B)-C(3B)	52.4(3)
C(11B)-C(2B)-O(3B)-C(5B)	-160.6(2)
C(3B)-C(2B)-O(3B)-C(5B)	-38.8(2)
C(1B)-C(2B)-O(3B)-C(5B)	76.4(2)
O(3B)-C(2B)-C(3B)-C(4B)	19.3(3)
C(11B)-C(2B)-C(3B)-C(4B)	137.7(2)

C(1B)-C(2B)-C(3B)-C(4B)	-93.8(3)
C(2B)-C(3B)-C(4B)-O(2B)	-114.6(2)
C(2B)-C(3B)-C(4B)-C(5B)	5.6(3)
C(2B)-O(3B)-C(5B)-C(14B)	165.4(2)
C(2B)-O(3B)-C(5B)-C(6B)	-74.2(2)
C(2B)-O(3B)-C(5B)-C(4B)	42.5(2)
O(2B)-C(4B)-C(5B)-O(3B)	92.1(2)
C(3B)-C(4B)-C(5B)-O(3B)	-28.5(3)
O(2B)-C(4B)-C(5B)-C(14B)	-24.7(3)
C(3B)-C(4B)-C(5B)-C(14B)	-145.2(2)
O(2B)-C(4B)-C(5B)-C(6B)	-155.7(2)
C(3B)-C(4B)-C(5B)-C(6B)	83.8(3)
O(3B)-C(5B)-C(6B)-C(7B)	56.6(3)
C(14B)-C(5B)-C(6B)-C(7B)	173.3(2)
C(4B)-C(5B)-C(6B)-C(7B)	-54.0(3)
O(3B)-C(5B)-C(6B)-C(10B)	175.9(2)
C(14B)-C(5B)-C(6B)-C(10B)	-67.4(3)
C(4B)-C(5B)-C(6B)-C(10B)	65.3(3)
O(1B)-C(1B)-C(7B)-C(8B)	-12.2(5)
C(2B)-C(1B)-C(7B)-C(8B)	-133.0(3)
O(1B)-C(1B)-C(7B)-C(6B)	165.6(2)
C(2B)-C(1B)-C(7B)-C(6B)	44.9(3)
C(5B)-C(6B)-C(7B)-C(8B)	133.5(3)
C(10B)-C(6B)-C(7B)-C(8B)	7.3(3)
C(5B)-C(6B)-C(7B)-C(1B)	-44.8(3)
C(10B)-C(6B)-C(7B)-C(1B)	-170.9(2)
C(1B)-C(7B)-C(8B)-C(9B)	177.0(3)
C(6B)-C(7B)-C(8B)-C(9B)	-0.9(4)
C(1B)-C(7B)-C(8B)-C(15B)	-6.4(6)
C(6B)-C(7B)-C(8B)-C(15B)	175.7(3)
C(7B)-C(8B)-C(9B)-C(10B)	-6.0(4)
C(15B)-C(8B)-C(9B)-C(10B)	177.0(3)
C(8B)-C(9B)-C(10B)-C(6B)	10.0(3)
C(7B)-C(6B)-C(10B)-C(9B)	-10.4(3)
C(5B)-C(6B)-C(10B)-C(9B)	-133.0(3)
O(3B)-C(2B)-C(11B)-C(13B)	-72.1(3)
C(3B)-C(2B)-C(11B)-C(13B)	172.7(2)
C(1B)-C(2B)-C(11B)-C(13B)	46.4(3)
O(3B)-C(2B)-C(11B)-C(12B)	50.7(3)
C(3B)-C(2B)-C(11B)-C(12B)	-64.5(3)
C(1B)-C(2B)-C(11B)-C(12B)	169.2(2)
O(1C)-C(1C)-C(2C)-O(3C)	176.5(2)
C(7C)-C(1C)-C(2C)-O(3C)	-58.7(3)
O(1C)-C(1C)-C(2C)-C(11C)	56.6(3)
C(7C)-C(1C)-C(2C)-C(11C)	-178.5(2)
O(1C)-C(1C)-C(2C)-C(3C)	-72.1(3)
C(7C)-C(1C)-C(2C)-C(3C)	52.8(3)
C(11C)-C(2C)-O(3C)-C(5C)	-160.1(2)
C(3C)-C(2C)-O(3C)-C(5C)	-38.6(3)
C(1C)-C(2C)-O(3C)-C(5C)	76.7(2)

O(3C)-C(2C)-C(3C)-C(4C)	18.7(3)
C(11C)-C(2C)-C(3C)-C(4C)	136.7(2)
C(1C)-C(2C)-C(3C)-C(4C)	-94.3(3)
C(2C)-C(3C)-C(4C)-O(2C)	-112.5(2)
C(2C)-C(3C)-C(4C)-C(5C)	6.6(3)
C(2C)-O(3C)-C(5C)-C(14C)	165.3(2)
C(2C)-O(3C)-C(5C)-C(6C)	-74.6(2)
C(2C)-O(3C)-C(5C)-C(4C)	42.8(2)
O(2C)-C(4C)-C(5C)-O(3C)	90.1(2)
C(3C)-C(4C)-C(5C)-O(3C)	-29.2(3)
O(2C)-C(4C)-C(5C)-C(14C)	-26.6(3)
C(3C)-C(4C)-C(5C)-C(14C)	-145.9(2)
O(2C)-C(4C)-C(5C)-C(6C)	-157.3(2)
C(3C)-C(4C)-C(5C)-C(6C)	83.4(3)
O(3C)-C(5C)-C(6C)-C(7C)	55.7(3)
C(14C)-C(5C)-C(6C)-C(7C)	172.5(2)
C(4C)-C(5C)-C(6C)-C(7C)	-55.1(3)
O(3C)-C(5C)-C(6C)-C(10C)	175.0(2)
C(14C)-C(5C)-C(6C)-C(10C)	-68.2(3)
C(4C)-C(5C)-C(6C)-C(10C)	64.2(3)
O(1C)-C(1C)-C(7C)-C(8C)	-13.0(4)
C(2C)-C(1C)-C(7C)-C(8C)	-134.3(3)
O(1C)-C(1C)-C(7C)-C(6C)	165.0(2)
C(2C)-C(1C)-C(7C)-C(6C)	43.7(3)
C(5C)-C(6C)-C(7C)-C(8C)	135.1(3)
C(10C)-C(6C)-C(7C)-C(8C)	8.2(3)
C(5C)-C(6C)-C(7C)-C(1C)	-43.3(3)
C(10C)-C(6C)-C(7C)-C(1C)	-170.2(2)
C(1C)-C(7C)-C(8C)-C(15C)	-5.9(5)
C(6C)-C(7C)-C(8C)-C(15C)	176.0(3)
C(1C)-C(7C)-C(8C)-C(9C)	177.9(3)
C(6C)-C(7C)-C(8C)-C(9C)	-0.2(3)
C(7C)-C(8C)-C(9C)-C(10C)	-7.9(3)
C(15C)-C(8C)-C(9C)-C(10C)	175.4(2)
C(7C)-C(6C)-C(10C)-C(9C)	-12.5(3)
C(5C)-C(6C)-C(10C)-C(9C)	-135.3(3)
C(8C)-C(9C)-C(10C)-C(6C)	12.5(3)
O(3C)-C(2C)-C(11C)-C(13C)	-76.3(3)
C(3C)-C(2C)-C(11C)-C(13C)	168.6(2)
C(1C)-C(2C)-C(11C)-C(13C)	42.1(3)
O(3C)-C(2C)-C(11C)-C(12C)	48.6(3)
C(3C)-C(2C)-C(11C)-C(12C)	-66.5(3)
C(1C)-C(2C)-C(11C)-C(12C)	167.0(2)
O(1D)-C(1D)-C(2D)-O(3D)	177.7(2)
C(7D)-C(1D)-C(2D)-O(3D)	-59.3(3)
O(1D)-C(1D)-C(2D)-C(11D)	57.7(3)
C(7D)-C(1D)-C(2D)-C(11D)	-179.3(2)
O(1D)-C(1D)-C(2D)-C(3D)	-70.3(3)
C(7D)-C(1D)-C(2D)-C(3D)	52.7(3)
C(11D)-C(2D)-O(3D)-C(5D)	-161.7(2)

C(3D)-C(2D)-O(3D)-C(5D)	-40.3(2)
C(1D)-C(2D)-O(3D)-C(5D)	75.6(2)
O(3D)-C(2D)-C(3D)-C(4D)	22.5(3)
C(11D)-C(2D)-C(3D)-C(4D)	140.6(2)
C(1D)-C(2D)-C(3D)-C(4D)	-91.7(3)
C(2D)-C(3D)-C(4D)-O(2D)	-117.2(2)
C(2D)-C(3D)-C(4D)-C(5D)	1.9(3)
C(2D)-O(3D)-C(5D)-C(14D)	165.3(2)
C(2D)-O(3D)-C(5D)-C(6D)	-73.7(2)
C(2D)-O(3D)-C(5D)-C(4D)	41.7(2)
O(2D)-C(4D)-C(5D)-O(3D)	94.1(2)
C(3D)-C(4D)-C(5D)-O(3D)	-25.7(3)
O(2D)-C(4D)-C(5D)-C(14D)	-23.9(3)
C(3D)-C(4D)-C(5D)-C(14D)	-143.7(2)
O(2D)-C(4D)-C(5D)-C(6D)	-153.3(2)
C(3D)-C(4D)-C(5D)-C(6D)	86.9(3)
O(3D)-C(5D)-C(6D)-C(7D)	58.0(3)
C(14D)-C(5D)-C(6D)-C(7D)	175.5(2)
C(4D)-C(5D)-C(6D)-C(7D)	-53.3(3)
O(3D)-C(5D)-C(6D)-C(10D)	177.1(2)
C(14D)-C(5D)-C(6D)-C(10D)	-65.4(3)
C(4D)-C(5D)-C(6D)-C(10D)	65.8(3)
O(1D)-C(1D)-C(7D)-C(8D)	-10.5(4)
C(2D)-C(1D)-C(7D)-C(8D)	-132.0(3)
O(1D)-C(1D)-C(7D)-C(6D)	167.3(2)
C(2D)-C(1D)-C(7D)-C(6D)	45.7(3)
C(5D)-C(6D)-C(7D)-C(8D)	132.0(3)
C(10D)-C(6D)-C(7D)-C(8D)	5.6(3)
C(5D)-C(6D)-C(7D)-C(1D)	-46.2(3)
C(10D)-C(6D)-C(7D)-C(1D)	-172.6(2)
C(1D)-C(7D)-C(8D)-C(15D)	-4.5(5)
C(6D)-C(7D)-C(8D)-C(15D)	177.7(3)
C(1D)-C(7D)-C(8D)-C(9D)	177.0(3)
C(6D)-C(7D)-C(8D)-C(9D)	-0.7(3)
C(7D)-C(8D)-C(9D)-C(10D)	-4.5(3)
C(15D)-C(8D)-C(9D)-C(10D)	176.8(3)
C(8D)-C(9D)-C(10D)-C(6D)	7.6(3)
C(7D)-C(6D)-C(10D)-C(9D)	-7.9(3)
C(5D)-C(6D)-C(10D)-C(9D)	-130.5(3)
O(3D)-C(2D)-C(11D)-C(13D)	-69.8(3)
C(3D)-C(2D)-C(11D)-C(13D)	175.0(2)
C(1D)-C(2D)-C(11D)-C(13D)	49.2(3)
O(3D)-C(2D)-C(11D)-C(12D)	52.9(3)
C(3D)-C(2D)-C(11D)-C(12D)	-62.3(3)
C(1D)-C(2D)-C(11D)-C(12D)	172.0(2)
O(1E)-C(1E)-C(2E)-O(3E)	178.6(2)
C(7E)-C(1E)-C(2E)-O(3E)	-57.6(3)
O(1E)-C(1E)-C(2E)-C(11E)	58.1(3)
C(7E)-C(1E)-C(2E)-C(11E)	-178.1(2)
O(1E)-C(1E)-C(2E)-C(3E)	-69.7(3)

C(7E)-C(1E)-C(2E)-C(3E)	54.1(3)
C(11E)-C(2E)-O(3E)-C(5E)	-160.4(2)
C(3E)-C(2E)-O(3E)-C(5E)	-38.5(3)
C(1E)-C(2E)-O(3E)-C(5E)	76.6(2)
O(3E)-C(2E)-C(3E)-C(4E)	18.6(3)
C(11E)-C(2E)-C(3E)-C(4E)	137.7(2)
C(1E)-C(2E)-C(3E)-C(4E)	-94.8(3)
C(2E)-C(3E)-C(4E)-O(2E)	-112.5(3)
C(2E)-C(3E)-C(4E)-C(5E)	6.6(3)
C(2E)-O(3E)-C(5E)-C(14E)	165.2(2)
C(2E)-O(3E)-C(5E)-C(6E)	-74.4(3)
C(2E)-O(3E)-C(5E)-C(4E)	42.9(2)
O(2E)-C(4E)-C(5E)-O(3E)	89.6(2)
C(3E)-C(4E)-C(5E)-O(3E)	-29.5(3)
O(2E)-C(4E)-C(5E)-C(14E)	-27.3(3)
C(3E)-C(4E)-C(5E)-C(14E)	-146.4(3)
O(2E)-C(4E)-C(5E)-C(6E)	-157.2(2)
C(3E)-C(4E)-C(5E)-C(6E)	83.8(3)
O(3E)-C(5E)-C(6E)-C(7E)	54.9(3)
C(14E)-C(5E)-C(6E)-C(7E)	172.0(2)
C(4E)-C(5E)-C(6E)-C(7E)	-56.6(3)
O(3E)-C(5E)-C(6E)-C(10E)	175.1(2)
C(14E)-C(5E)-C(6E)-C(10E)	-67.8(3)
C(4E)-C(5E)-C(6E)-C(10E)	63.6(3)
O(1E)-C(1E)-C(7E)-C(8E)	-18.5(5)
C(2E)-C(1E)-C(7E)-C(8E)	-139.4(3)
O(1E)-C(1E)-C(7E)-C(6E)	162.1(2)
C(2E)-C(1E)-C(7E)-C(6E)	41.2(3)
C(5E)-C(6E)-C(7E)-C(8E)	139.7(3)
C(10E)-C(6E)-C(7E)-C(8E)	11.5(3)
C(5E)-C(6E)-C(7E)-C(1E)	-40.7(3)
C(10E)-C(6E)-C(7E)-C(1E)	-169.0(2)
C(1E)-C(7E)-C(8E)-C(15E)	-6.5(6)
C(6E)-C(7E)-C(8E)-C(15E)	172.9(3)
C(1E)-C(7E)-C(8E)-C(9E)	178.2(3)
C(6E)-C(7E)-C(8E)-C(9E)	-2.3(4)
C(7E)-C(8E)-C(9E)-C(10E)	-7.9(4)
C(15E)-C(8E)-C(9E)-C(10E)	176.3(3)
C(8E)-C(9E)-C(10E)-C(6E)	14.4(3)
C(7E)-C(6E)-C(10E)-C(9E)	-15.6(3)
C(5E)-C(6E)-C(10E)-C(9E)	-139.7(3)
O(3E)-C(2E)-C(11E)-C(12E)	-74.2(3)
C(3E)-C(2E)-C(11E)-C(12E)	169.9(2)
C(1E)-C(2E)-C(11E)-C(12E)	44.6(3)
O(3E)-C(2E)-C(11E)-C(13E)	49.7(3)
C(3E)-C(2E)-C(11E)-C(13E)	-66.2(3)
C(1E)-C(2E)-C(11E)-C(13E)	168.6(2)
O(1F)-C(1F)-C(2F)-O(3F)	-179.6(2)
C(7F)-C(1F)-C(2F)-O(3F)	-55.1(3)
O(1F)-C(1F)-C(2F)-C(3F)	-69.1(3)

C(7F)-C(1F)-C(2F)-C(3F)	55.3(3)
O(1F)-C(1F)-C(2F)-C(11F)	63.4(3)
C(7F)-C(1F)-C(2F)-C(11F)	-172.2(2)
C(3F)-C(2F)-O(3F)-C(5F)	-42.1(3)
C(11F)-C(2F)-O(3F)-C(5F)	-165.3(2)
C(1F)-C(2F)-O(3F)-C(5F)	75.0(3)
O(3F)-C(2F)-C(3F)-C(4F)	26.3(3)
C(11F)-C(2F)-C(3F)-C(4F)	143.2(2)
C(1F)-C(2F)-C(3F)-C(4F)	-86.8(3)
C(2F)-C(3F)-C(4F)-O(2F)	-122.6(2)
C(2F)-C(3F)-C(4F)-C(5F)	-2.7(3)
C(2F)-O(3F)-C(5F)-C(14F)	163.7(2)
C(2F)-O(3F)-C(5F)-C(6F)	-75.6(2)
C(2F)-O(3F)-C(5F)-C(4F)	40.6(3)
O(2F)-C(4F)-C(5F)-O(3F)	97.5(2)
C(3F)-C(4F)-C(5F)-O(3F)	-22.1(3)
O(2F)-C(4F)-C(5F)-C(14F)	-19.9(3)
C(3F)-C(4F)-C(5F)-C(14F)	-139.5(2)
O(2F)-C(4F)-C(5F)-C(6F)	-150.4(2)
C(3F)-C(4F)-C(5F)-C(6F)	90.0(3)
O(3F)-C(5F)-C(6F)-C(7F)	56.9(3)
C(14F)-C(5F)-C(6F)-C(7F)	174.1(2)
C(4F)-C(5F)-C(6F)-C(7F)	-53.8(3)
O(3F)-C(5F)-C(6F)-C(10F)	175.9(2)
C(14F)-C(5F)-C(6F)-C(10F)	-66.8(3)
C(4F)-C(5F)-C(6F)-C(10F)	65.2(3)
O(1F)-C(1F)-C(7F)-C(8F)	-16.1(5)
C(2F)-C(1F)-C(7F)-C(8F)	-139.2(3)
O(1F)-C(1F)-C(7F)-C(6F)	164.1(2)
C(2F)-C(1F)-C(7F)-C(6F)	41.0(3)
C(5F)-C(6F)-C(7F)-C(8F)	137.8(3)
C(10F)-C(6F)-C(7F)-C(8F)	10.8(3)
C(5F)-C(6F)-C(7F)-C(1F)	-42.4(3)
C(10F)-C(6F)-C(7F)-C(1F)	-169.3(2)
C(1F)-C(7F)-C(8F)-C(9F)	177.9(3)
C(6F)-C(7F)-C(8F)-C(9F)	-2.3(4)
C(1F)-C(7F)-C(8F)-C(15F)	-6.4(6)
C(6F)-C(7F)-C(8F)-C(15F)	173.4(3)
C(7F)-C(8F)-C(9F)-C(10F)	-7.2(4)
C(15F)-C(8F)-C(9F)-C(10F)	176.5(3)
C(8F)-C(9F)-C(10F)-C(6F)	13.4(3)
C(7F)-C(6F)-C(10F)-C(9F)	-14.5(3)
C(5F)-C(6F)-C(10F)-C(9F)	-137.2(3)
O(3F)-C(2F)-C(11F)-C(12F)	35.2(4)
C(3F)-C(2F)-C(11F)-C(12F)	-78.6(4)
C(1F)-C(2F)-C(11F)-C(12F)	151.5(3)
O(3F)-C(2F)-C(11F)-C(13F)	159.1(3)
C(3F)-C(2F)-C(11F)-C(13F)	45.3(4)
C(1F)-C(2F)-C(11F)-C(13F)	-84.7(3)

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