Part I. Studies of Stereoselective C-H Amination

Part II. Synthetic Studies of Edaxadiene

Part III. Studies towards the Synthesis of Alchivemycin A

Part IV. The Formal Synthesis of (-)-Englerin A by RRCM and Etherification

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Part I. Various polysaccharides and glycosidic antibiotics including anthracycline and vancomycin have been widely used to treat cancer or infection. Amino sugars are often found in their structures and play an important role in biological activities. C-H amination is one of valuable methods to streamline the synthesis of C-N bond. Regio-, stereoselective C-H amination has been studied to produce useful amino sugars from glycals and alkynol carbamates.

Part II. Edaxadiene was considered as a new diterpene that had biological activities to inhibit the infection process of Mycobacterium tuberculosis. We describe a design to access a bicyclic backbone, which is the core structure of this compound by an intramolecular Diels-Alder (IMDA) reaction.
Part III. Progress toward the synthesis of a key moiety of alchivemycin A, which was isolated from a plant-derived actinomycete Streptomyces sp and displayed selective and potent antibiotic activity against Micrococcus luteus, has been focused on the construction of a bicyclic structure by the IMDA reaction.

Part IV. (−)-Englerin A is a natural product from phyllathus engleri, a plant common in east Africa. It showed an interesting biological activity in its ability to inhibit the growth of kidney cancer cell lines in the NCI-60 screen. The useful bioactivity and unique structure of (−)-englerin A have inspired many scientists to develop synthetic approaches to understand the structure-activity relationship (SAR). We reported the formal synthesis of (−)-englerin A and established an efficient synthetic route by a relay ring closing metathesis (RRCM) reaction and etherification. This study includes the efficient opening of the epoxide ring of a β-substituted α-epoxy alcohol under the lithium acetylide reagent, the relay ene-yne-ene metathesis method for the preparation of a diene that is disubstituted on both ends, and the transannular stereo- and regio-specific oxymercuration of the C-6, C-7 olefin in the guaiane ring system.
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<tbody>
<tr>
<td>α</td>
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<td>±</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
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DET  Diethyl tartrate
DIBAL-H  Diisobutylaluminum hydride
DIPEA  Diisopropylethylamine
DIPET  Diisopropyl tartrate
DMF  N,N-Dimethylformamide
DMSO  Dimethylsulfoxide
ee  Enantiomeric excess
eq.  Equivalent
Et  Ethyl
Et₂O  Diethyl ether
EtOAc  Ethyl acetate
g  Gram
h  Hour(s)
HMPA  Hexamethylphosphoramide
Hz  Hertz
I(Collins)₂PF₆  Bis(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate
IC₅₀  Concentration for 50 % inhibition
IMDA  Intramolecular Diels-Alder reaction
iPr  Isopropyl
IR  Infrared spectroscopy
J  First order coupling constant (NMR)
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<td>Relay ring closing metathesis</td>
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Part I.

Studies of Stereoselective C-H Amination
1.1. Introduction

1.1.1. 3-Amino hexoses

Various polysaccharide and glycosidic antibiotics have been widely used to treat cancer or bacterial infection. These antibiotics including daunorubicin (1), doxorubicin (2), and vancomycin (3) contain amino sugars, 2,3,6-trideoxy-3-aminohexoses (Figure 1), which play an important role in their biological activities.¹

Daunorubicin (1)

Doxorubicin (2)

Vancomycin (3)

Figure 1. Examples of glycosidic and polysaccharide antibiotics
These amino hexoses were generally isolated through hydrolysis of the parent antibiotics and some amino hexoses are not naturally found in nature, but had been obtained as minor products in other synthetic studies. Among them, are the simple amino hexoses represented in Figure 2.¹

![Chemical structures of amino hexoses](image)

**Figure 2.** Examples of representative simple amino hexoses

Like daunorubicin (1) and doxorubicin (2), epirubicin (12), one of the more famous anthracycline drugs has been used against various cancers such as breast tumor, ovarian tumor, and lung tumor.² Epirubicin (12) is a synthetic analogues of doxorubicin (2), but it contains 2,3,6-trideoxy-3-aminohexose called L-acosamine (8), which was first isolated from the antibiotic actinoidin by Lomakina and co-workers.¹ It (12) has almost the same structure as doxorubicin (2), but shows fewer side effects while having similar antitumor activity.³ The only difference between epirubicin (12) and doxorubicin (2) is aminohexose that the former has namely L-acosamine (8) rather than L-daunosamine (4).
Figure 3. The structure of epirubicin (12)

Therefore, L-acosamine (8) is very important moiety in its relationship to the impressive biological activity of epirubicin (12). Some amino sugars such as L-acosamine (8) and L-3-epi-daunosamine (10) (Figure 2) have the anti-configuration between the amine and hydroxyl groups and 10 does not occur naturally. Many synthetic analogues of anthracycline have been synthesized in an attempt to reduce cytotoxicity or enhance antitumor activity, but there are not many examples where this has been successful.3-4 Thus, it would be valuable to investigate efficient and simple methods to produce precursors of L-acosamine (8) or other amino sugar analogues. These glycoside precursors can yield amino sugars moieties by glycosylation.4d,4f,4k,4m

1.1.2. Glycosylation

To introduce the amino sugar moiety, several glycosidic bond formations have been developed to provide glycosides from derivatives of 3-aminohexoses (Figure 2). For example, Lowary et al.4f introduced daunorubicin (1) analogues 15, 16, 18, and 19, which have azido sugars, by glycosylation in 2007 (Scheme 1).
Scheme 1. Syntheses of daunorubicin (1) analogues, which have azido sugars by glycosylation

After removal of acetate groups, the azido sugars 20 and 22 were transformed to give the L-acosamine moiety (8) in daunorubicin (1) analogues 21 and 23 by Staudinger reduction (Scheme 2).
Scheme 2. Syntheses of daunorubicin (1) analogues 21 and 23 by the Lowary et al.\textsuperscript{4f} 

In addition, 3-amino glycals can be valuable glycoside precursors to introduce amino sugars. They also produced a mixture of glycosides, but sometimes, only the \( \alpha \)-glycoside was obtained from glycals. Monneret et al.\textsuperscript{5} demonstrated an example to show usefulness of 3-amino glycal 25 in 1998 (Scheme 3).

Scheme 3. Synthesis of \( \alpha \)-glycoside from 3-amino glycal 25 by Monneret et al.\textsuperscript{5}

Those examples show the usefulness of derivatives of 3-aminohexoses to obtain glycosides.
1.1.3. Previous synthetic approaches to precursors of L-acosamine (8)

Originally, these promising intermediates, related to L-acosamine (8) and 3-amino glycals, were prepared from carbohydrates, especially L-rhamnal in 1980.\textsuperscript{1,4g} For example, the Boivin group in 1980 reported the preparation of protected L-acosamine derivative 30, from the protected L-rhamnal derivative 27 by acid catalyzed azide addition (Scheme 4).\textsuperscript{4g}

Scheme 4. Synthesis of protected L-acosamine derivative 30 by Boivin et al.\textsuperscript{4g}

Pelyvas et al.\textsuperscript{4h} also reported another procedure to prepare L-acosamine derivative 34 by selective oxidation with Fetizon’s reagent (Ag\textsubscript{2}CO\textsubscript{3} precipitated on Celite) from L-rhamnal (31) in 1980 (Scheme 5).

Scheme 5. Synthesis of protected L-acosamine derivative 34 by Pelyvas et al.\textsuperscript{4h}
Several strategies have been tried to synthesize derivatives of L-acosamine (8) from non-carbohydrates. Firstly, Wovkulich et al. introduced an asymmetric synthesis of L-acosamine derivatives 42 by an enantioselective intramolecular [3+2] cycloaddition of a chiral nitrone in 1981 (Scheme 6).

![Scheme 6. Asymmetric synthesis of L-acosamine derivative 42 from non-carbohydrate 35](image)

On the other hand, Trost et al. also synthesized the chiral L-acosamine derivative 49 from 2-oxazolidone 46, which was prepared from the optically pure vinyl epoxide 45 obtained via a palladium-mediated vicinal hydroxyamination in 1987 (Scheme 7).
Scheme 7. Synthesis of L-acosamine derivatives 49 by Trost et al.\textsuperscript{4i}

The Fiebig group in 2000 developed a strategy, by which they convert L-rhamnal diacetate (50) to a precursor of L-acosamine derivative 52.\textsuperscript{4l} They used hydrolysis to obtain alcohol 51 from 50 and sodium azide as a nitrogen source to introduce the amine moiety of 52. The stereoselectivity of addition of azide was only moderate (52 / 53 = 2 / 1) (Scheme 8).

Scheme 8. Synthesis of a precursor of L-acosamine derivative 52 by Fiebig et al.\textsuperscript{4l}
The Pucko group in 2006 demonstrated the synthesis of protected L-acosamine glycal 55. Isocyanate was used to convert 54 to a chlorosulfonyl compound, which is an valuable intermediate for the synthesis of L-acosamine glycal 55 (Scheme 9).

**Scheme 9.** Synthesis of protected L-acosamine glycal 55 by the Pucko group

Zhang and co-workers in 2007 developed a different approach, which uses a α,β-unsaturated lactone 56 as a key intermediate. It was prepared by a reaction with BF₃.OEt₂ and mCPBA from L-rhamnal diacetate (50). The treatment with diphenylphosphoryl azide (DPPA) produced azido sugar 59 that is one of precursors to prepare L-acosamine (8) (Scheme 10).

**Scheme 10.** Synthesis of L-acosamine derivative 59 by Zhang et al.
In 2007, McLeod and co-workers reported a synthesis of protected L-acosamine glycal 63 from a non-carbohydrate 60 via asymmetric aminohydroxylation (Scheme 11).  

![Scheme 11. Synthesis of L-acosamine glycal 63 by the McLeod group](image)

Finally, Bagal et al. 4p reported an asymmetric synthesis of a derivative of L-acosamine 8 and the β-amino ester 64 was converted to the lactone 67 that was subjected to a reduction with DIBAL-H to produce 69 (Scheme 12).

![Scheme 12. Synthesis of L-acosamine derivative 69 by Bagal et al.](image)

ratio (67 : 68 = 7 : 3)
1.1.4. Previous syntheses of 3-amino sugar intermediate by C-H amination

Recently, intramolecular amination of C-H bond, especially Du Bois reaction\(^7\) (Scheme 13), has been ultimately developed ranging from catalysts to reagents to synthesize nitrogen-containing molecules and amine-derived natural products.\(^8\)

![Scheme 13](image)

**Scheme 13.** The intramolecular C-H amination by the Du Bois group

In 2003 and 2005, the Parker group\(^9\) demonstrated that the intramolecular C-H amination using the Du Bois reaction, can be applied to produce valuable 3-amino glycals derivatives such as L-daunosamine (73), D-saccharosamine (75), L-ristosamine (77), and L-vancosamine (79) from glycals 72, 74, 76, and 78 with high stereoselectivity (Scheme 14).
Scheme 14. Synthesized protected 3-amino glycals by the Du Bois reaction

The white group also reported new allylic C-H amination and the preparation of a key intermediate, which allowed Trost and co-workers to synthesize L-acosamine. The oxazolidinone was prepared from carbamate via allylic C-H amination with a palladium catalyst (Scheme 15).
These examples prove usefulness of C-H amination methods to provide various amino sugars. Thus, studies of stereoselectivity of C-H amination of appropriate substituents would be valuable to develop application of amino sugars syntheses.

1.1.5. A new investigation of the intermolecular C-H amination of glycal

As we discussed, previously the Parker group demonstrated that the regiospecific C-H insertions of glycal (see Scheme 14) and allylic positions are preferred other sites. However, the intramolecular C-H amination on a cyclic system cannot be applied to the preparation of 3,4-trans-3-aminoglycal from deoxy glycal because it produces cis-addition products. Therefore, the intramolecular C-H amination cannot give L-acosamine glycal and 3-epi-daunosamine (see Scheme 17).

In 2007, Du Bois et al. also introduced the intermolecular C-H amination (Scheme 16) and some of the examples showed stereoselective insertions of C-H bond (Table 1).
Scheme 16. The intermolecular C-H amination developed by Du Bois et al.\textsuperscript{12}

Table 1. Examples for a stereoselective intermolecular amination by the Du Bois group

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>(\text{CH}_2\text{CH}_3\text{NHces})</td>
<td>46</td>
</tr>
<tr>
<td>87</td>
<td>(\text{CH}_2\text{CH}_3\text{NHces})</td>
<td>74</td>
</tr>
<tr>
<td>88</td>
<td>(\text{PhCH}_2\text{OAc})</td>
<td>10</td>
</tr>
</tbody>
</table>

Thus, we wanted to build a new efficient way to synthesize them from glycals via the intermolecular C-H amination. Due to steric hindrance, we expected that stereoselectivity would
be controlled by the intermolecular C-H amination to provide useful other 3-amino sugars including L-rhodinose glycal (92) and L-amicetose glycal (94) if allylic positions were more reactive than other sites. (Scheme 17).

Scheme 17. Retrosynthetic analyses for syntheses of 3-amino glycals 93 and 95

To investigate them, we needed to prepare glycals 93 and 95 as precursors. There are few methods for the preparation of L-rhodinose glycal (93) and L-amicetose glycal (95). Efficient methods has been developed by McDonald et al. in 1998 and Trost et al. in 2002 (Scheme 18).

Scheme 18. Syntheses of glycals 93 and 95 by the McDonald group and the Trost group

Both methods can produce two glycals 93 and 95 by tungsten or rhodium-catalyzed cycloisomerization, but precursors 96 and 97 are not prepared by asymmetric syntheses.
When the Parker group synthesized L-ristosamine (77), 99 was prepared by asymmetric synthesis (see scheme 21).9a We believe that the intermediate 97 could be obtained after protection and deprotection of the alcohol 99. (Scheme 19)

Scheme 19. Retrosynthetic analysis of alkynol 99

In progress of synthesis of the alkynol 97, asymmetric procedure was reported by Schmidt and co-worker.15 L-Rhodinose glycal (93) and L-amicetose glycal (95) were prepared from the ethyl lactate (107) via a ring closing metathesis isomerization. These new methods seem to be efficient and useful, so we adopted their procedures and prepared L-rhodinose glycal (93). Finally, the intermolecular C-H amination was applied to know the stereoselective C-H insertion of a glycal.

1.1.6. A new investigation of the intramolecular C-H amination of alkynol carbamates

As we discussed, Trost and White groups showed preparations of the oxazolidinone 46 as the key intermediate to synthesize L-acosamine (8) from the epoxide 45 and the carbamate 80 (Scheme 20).

Scheme 20. The key precursor 46 of L-acosamine derivative 49

We focused on another possibility to access the intermediate oxazolidinone 46 from an alkyne 102 (see Scheme 23) by the intramolecular C-H amination (Du Bois reaction).
When the Parker group disclosed a preparation of L-ristosamine glycal (77), they also developed a procedure to provide a carbamate 102 (Scheme 21)\(^9\), but the regioselectivity of C-H amination of the alkynol carbamate 102 was not explored.

\[
\begin{align*}
\text{OH} & \quad 1) \text{Sharpless AE} \quad \text{OTBDPS} \\
100 & \quad 2) \text{TBDPS, base} \\
& \quad \text{42\%, 90\% ee} \\
\text{OTBDPS} & \quad \text{TMS} \quad \equiv \quad \text{H} \\
101 & \quad \text{BuLi, Et}_2\text{AlCl} \\
& \quad \text{79\%} \\
\text{OTBDPS} & \quad \text{TMS} \\
99 & \quad \text{OH}
\end{align*}
\]

**Scheme 21.** Asymmetric synthesis of the carbamate 102 by the Parker group

At that time, there was no example to expect results from C-H amination, but we could expect two possible products (Scheme 22).

\[
\begin{align*}
\text{R', R}'' & = \text{H} \\
\text{103} & \quad \leftrightarrow \quad \text{102} \\
\text{104} & \quad \leftrightarrow
\end{align*}
\]

**Scheme 22.** Expected products from C-H amination of alkynol carbamates

When it provides the insertion of a nitrène into a propargylic C-H bond, we expected that a precursor of oxazolidinone 103 might be produced from the carbamate 102, which will subjected to a reduction of alkyne 103 to provide a valuable intermediate 46\(^j\) for L-Acosamine (8) (Scheme 23). The stereoselectivity could be controlled by cis-addition of the intramolecular C-H amination.
Scheme 23. Retrosynthetic analysis of the oxazolidinone 46 by the Du Bois reaction

In addition, another expected product 104 was an aminal structure, which has amine and alcohol functional group on the same carbon atom. A wide variety of natural products, which show incredible bioactivities for cancer cells, have aminal structures as a key moiety such as pederin (105) and psymberin (106). Preparing the aminal moiety and control of its stereochemistry are the central problems in their syntheses.\textsuperscript{16} If we would control the stereoselectivity of aminal structures, it could be a new strategy to produce valuable natural compounds (Figure 4).

Figure 4. Natural products, which have aminal structures

Thus, we have investigated reactivity and selectivity of alkynol carbamates of intramolecular C-H amination.
1.2. Result and discussion

1.2.1. Intermolecular C-H amination of L-rhodinose glycals (93)

1.2.1.1. Synthesis of L-rhodinose glycals (93)

To investigate the stereoselectivity of the intermolecular C-H amination of L-rhodinose glycal (93) and L-amicetose glycal (95), we decided to follow procedures developed by Schmidt group\textsuperscript{15}. They produced 93 and 95 from ethyl lactate (107) via the RCM-isomerization. The first step was a synthesis of allyl ethyl lactate 108\textsuperscript{17} from the ethyl lactate (107) via a palladium-catalyzed O-allylation with allyl ethyl carbonate. Reduction of the allyl ethyl lactate 108, and then addition of vinyl magnesium bromide produced alcohol 109. Benzyl protection of the alcohol 109 afforded benzyl ether 110. However, we were not able to prepare L-rhodinose glycal (93) from 110 through the RCM-isomerization. Instead of 93, a dihydropyran 111 was obtained. We also used other reagents such as NaH and NaBH\textsubscript{4} instead of NaOH for the RCM-isomerization\textsuperscript{18}, but all reactions produced the only dihydropyran 111 (Scheme 24).
**Scheme 24.** Preparation of the dihydropyran 111 from the ethyl lactate 107

In 1973, Corey group reported the isomerization of allyl ether that Wilkinson’s catalyst, RhCl(PPh₃)₃, can catalyze isomerization of allyl ether 112 to 1-propenyl ether 113 (Scheme 25).¹⁹

**Scheme 25.** Isomerization of allyl ether with Rh catalyst

Thus, the dihydropyran 111 was treated with Wilkinson’s catalyst and finally we could obtain the protected L-rhodinose glycal 93 (Scheme 26).¹⁹-²⁰

**Scheme 26.** Synthesis of the protected L-rhodinose glycal 93 by isomerization with Rh catalyst
1.2.1.2. Intermolecular C-H amination of L-rhodinose glycal (93)

After preparing C-H amination reagents such as TcesNH₂, PhI(O₂CtBu)₂, and Rh₂(esp)₂, we investigated the selectivity of the intermolecular C-H amination of the protected L-rhodinose glycal 93 to know if L-epi-daunosamine glycal (92) could be produced from the protected L-rhodinose glycal 93. However, we found that the product was not the 3-amino glycal 92 but the 2-aminosugar 114 (Scheme 27).

**Scheme 27.** Synthesis of 2-aminosugar 114 from the protected L-rhodinose glycal 93

On the basis of a reference, we believe that a rhodium nitrene insertion prefers forming an aziridine ring with a double bond of 93 to C-H amination of C3-H bond of 93, and 2-aminosugar 114 was produced via an aziridine ring opening by (t-BuCO₂) generated from a reagent, PhI(CO₂tBu)₂ (Scheme 28).

**Scheme 28.** Formation of 2-aminosugar 114 via aziridine ring opening

So far, there are not so many examples to prepare 2-amino glycosides. Our approach would be good access to introduce 2-amino sugar moiety for natural products analogues.
1.2.2. Intermolecular C-H amination of alkylnol carbamates

1.2.2.1. Preparation of alkylnol carbamates

First of all, the alkylnol carbamate 115 was prepared from 3-buten-2-ol (100) using the procedure developed by the Parker group. The epoxide was produced from 3-buten-2-ol (100) by Sharpless asymmetric epoxidation and the epoxy alcohol was protected by TBDPS to provide 101. The treatment of the epoxide 101 with acetylide in the presence of Lewis acid (Et₂AlCl) gave alkylnol 99 that was converted to the alkylnol carbamate 115 (Scheme 29).

\[ \text{OH} \quad 100 \quad 1) \text{Sharpless AE} \quad \text{OTBDPS} \quad 2) \text{TBDPS, base} \quad \text{OTBDPS} \quad \text{BuLi, Et₂AlCl} \quad \text{TMS} \quad \text{H} \quad \text{OH} \quad 115 \]

Scheme 29. Asymmetry synthesis of the alkylnol carbamate 115

In addition, we also applied another synthetic way to easily prepare alkylnol carbamates, two diastereomers 122 and 123. The McDonald group reported that a treatment of aldehyde 116 (R = TBS) with allenylmagnesium bromide could give a partially separable mixture of TBS-protected alkylnols 117 and 118, but it is not convenient to make allenylmagnesium bromide (Scheme 30).

\[ \text{OR} \quad 116 (R = \text{TBS}) \quad \text{MgBr} \quad \text{OTBS} \quad \text{HO}^+ \quad 117 \quad + \quad \text{HO}^+ \quad 118 \]

Scheme 30. Synthesis of alkylnols 117 and 118 with allenylmagnesium bromide
Wu et al.\textsuperscript{23} also introduced a synthesis of Bn-protected alkynols 119 and 120 from the aldehyde 116 (R = Bn) by a propargylation with Zn-dust and propargyl bromide, which is an effective and convenient method, but they gave an inseparable mixture (Scheme 31).

\begin{equation}
\begin{array}{c}
\text{OR} \\
\text{H}
\end{array}
\begin{array}{c}
\text{Zn dust} \\
\text{Br}
\end{array}
\begin{array}{c}
\text{OR} \\
\text{H}
\end{array}
\begin{array}{c}
\rightarrow
\end{array}
\begin{array}{c}
\text{OBn} \\
\text{HO}
\end{array}
\begin{array}{c}
\text{HO}
\end{array}
\begin{array}{c}
+ \\
\text{OBn}
\end{array}
\begin{array}{c}
\text{HO}
\end{array}
\begin{array}{c}
\text{116 (R = Bn)}
\end{array}
\begin{array}{c}
\text{119}
\end{array}
\begin{array}{c}
\text{120}
\end{array}
\end{equation}

\textbf{Scheme 31.} Synthesis of alkynols 119 and 120 with Zn-dust and propargyl bromide

Therefore, we decided to apply allylation with Zn-dust and propargyl bromide to produce carbamates 117 and 118 from aldehyde (R = TBS) 116 that can be separable by silica gel chromatography (Scheme 32).

\begin{equation}
\begin{array}{c}
\text{OR} \\
\text{H}
\end{array}
\begin{array}{c}
\begin{array}{c}
\rightarrow
\end{array}
\begin{array}{c}
\text{Br}
\end{array}
\begin{array}{c}
\text{Zn dust}
\end{array}
\end{array}
\begin{array}{c}
\text{OTBS} \\
\text{HO}
\end{array}
\begin{array}{c}
\text{HO}
\end{array}
\begin{array}{c}
\text{TBS}
\end{array}
\begin{array}{c}
\text{116 (R = TBS)}
\end{array}
\begin{array}{c}
\text{117}
\end{array}
\begin{array}{c}
\text{118}
\end{array}
\end{equation}

\textbf{Scheme 32.} Synthesis of alkynols 117 and 118 with Zn-dust and propargyl bromide

(-)-Ethyl lactate (107) was simply converted to TBS-protected ethyl lactate 121. The DIBAL-H reduction of TBS-protected ethyl lactate 121 gave an aldehyde 116.\textsuperscript{24} The treatment of the aldehyde 116 with Zn dust and propargyl bromide provided alkynols as two diastereomers 117 and 118 that were partially separated by silica gel chromatography. Finally, an addition of isocyanate to each alkynol 117 and 118 followed by filtration throughout $\text{Al}_2\text{CO}_3$\textsuperscript{25} resulted in two diastereomers, carbamates 122 and 123 (Scheme 33).
Scheme 33. Preparation of two alkynol carbamates diastereomers 122 and 123

1.2.2.2. C-H amination of alkynol carbamates

We had been investigating the C-H amination of carbamate 115 under the Du Bois reaction condition\(^7\). After several experiments, although this reaction just gave small amount of a product 124 (12%), it showed that the carbamate 115 had reactivity for C-H amination and the product is the aminal 124 (Scheme 34) (Table 2).
Scheme 34. Synthesis of aminal 124 from carbamate 115

Table 2. Results of C-H amination of alkynol carbamate 115

<table>
<thead>
<tr>
<th>Catalyst (% mol)</th>
<th>PhI(OAc)₂ (eq.)</th>
<th>MgO (eq.)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(OAc)₄ 5%</td>
<td>1.4</td>
<td>2.3</td>
<td>40</td>
<td>CH₂Cl₂</td>
<td>no rxn</td>
</tr>
<tr>
<td>Rh₂(OAc)₄ 10%</td>
<td>1.4</td>
<td>2.3</td>
<td>40</td>
<td>CH₂Cl₂</td>
<td>no rxn</td>
</tr>
<tr>
<td>Rh₂(OAc)₄ 20%</td>
<td>1.4</td>
<td>2.4</td>
<td>40</td>
<td>CH₂Cl₂</td>
<td>no rxn</td>
</tr>
<tr>
<td>Rh₂(OAc)₄ 20% X 2</td>
<td>1.4 X 2</td>
<td>2.4 X 2</td>
<td>90</td>
<td>Toluene</td>
<td>Y = 12 %</td>
</tr>
</tbody>
</table>

After we obtained a small amount of product, we prepared two carbamate diastereomers 122 and 123 and another catalyst, Rh₂(tpa)₄, to examine the regio and stereoselectivity of C-H amination for carbamates. Firstly, the carbamate 123 that has the same stereo configuration as the carbamate 115 was examined and it gave us only aminal structure 125 like 124 in 52% yield. The Rh₂(tpa)₄ catalyst⁷,²⁶ is more efficient and powerful than the Rh₂(OAc)₄ for the carbamate 123 in C-H amination reaction. The relative stereochemistry of the aminal 125 was assigned on the basis of nuclear Overhauser effects (Scheme 35) (Table 3).

Scheme 35. Synthesis of aminal 125 from carbamate 123
Table 3. Results of C-H amination of alkynol carbamate 123

<table>
<thead>
<tr>
<th>Catalyst (% mol)</th>
<th>Phl(OAc)$_2$ (eq.)</th>
<th>MgO (eq.)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>20%</td>
<td>1.4</td>
<td>2.4</td>
<td>50</td>
<td>benzene conversion 50%</td>
</tr>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>20%</td>
<td>1.4</td>
<td>2.4</td>
<td>90</td>
<td>toluene no product and no</td>
</tr>
<tr>
<td>Rh$_2$(tpa)$_4$</td>
<td>20%</td>
<td>1.4</td>
<td>2.4</td>
<td>50</td>
<td>benzene Y = 40%, no starting</td>
</tr>
<tr>
<td>Rh$_2$(tpa)$_4$</td>
<td>3%</td>
<td>1.4</td>
<td>2.4</td>
<td>50</td>
<td>benzene Y = 52%, 19% starting recovered</td>
</tr>
</tbody>
</table>

On the other hand, another diastereomer 122 did not give any product, although several reaction conditions including different catalysts were tried (Scheme 36) (Table 4).

Scheme 36. C-H amination of carbamate 122

Table 4. Results of C-H amination of alkynol carbamate 122

<table>
<thead>
<tr>
<th>Catalyst (% mol)</th>
<th>Phl(OAc)$_2$ (eq.)</th>
<th>MgO (eq.)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>20%</td>
<td>1.4</td>
<td>2.4</td>
<td>40</td>
<td>CH$_2$Cl$_2$ no rxn</td>
</tr>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>20%</td>
<td>1.4</td>
<td>2.4</td>
<td>80</td>
<td>benzene no rxn</td>
</tr>
<tr>
<td>Rh$_2$(tpa)$_4$</td>
<td>4%</td>
<td>1.4</td>
<td>2.0</td>
<td>40</td>
<td>benzene 96% 122 recovered</td>
</tr>
<tr>
<td>Rh$_2$(tpa)$_4$</td>
<td>10%</td>
<td>1.8</td>
<td>2.4</td>
<td>50</td>
<td>benzene no rxn</td>
</tr>
<tr>
<td>Rh$_2$(tpa)$_4$</td>
<td>40%</td>
<td>1.8</td>
<td>3.0</td>
<td>40</td>
<td>benzene no 122 and no product</td>
</tr>
<tr>
<td>Rh$_2$(tpa)$_4$</td>
<td>20%</td>
<td>3.5</td>
<td>6.0</td>
<td>50</td>
<td>benzene no 122 and no product</td>
</tr>
</tbody>
</table>
Under the same reaction condition, the anti-alkynol carbamate 123 just gave aminal product 125, but the syn-alkynol 122 was not reactive and did not give products. To confirm previous results for selective amination, a mixture of 122 and 123 (1:1 ratio) was examined under the Du Bois reaction and this experiment gave us more a reliable result that the anti-alkynol carbamate 123 could just do C-H insertion and the syn-alkynol carbamate 122 did not give any C-H insertion product on based of NMR analysis (Scheme 37).

\[
\text{OTBS} \quad \begin{array}{c}
\text{O} \\
\text{NH}_2 \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{10 mol\% Rh}_2(tpa)_4 \\
\text{PhI(OAc)}_2, \text{MgO}
\end{array} \quad \text{Benzene, 50\degree C}
\]

**Scheme 37.** C-H amination of a mixture of diastereomers of 122 and 123

\[
\text{OTBS} \quad \begin{array}{c}
\text{O} \\
\text{NH}_2 \\
\text{O}
\end{array} + \begin{array}{c}
\text{OTBS} \\
\text{O} \\
\text{NH}_2 \\
\text{O}
\end{array} + \begin{array}{c}
\text{OTBS} \\
\text{O} \\
\text{NH}
\end{array}
\]

**Ratio**

\[
122/123/125 = 1.4/1.0/0.4
\]
1.3. Conclusion

In conclusion, in attempting to examine the stereoselectivity of intermolecular C-H amination for L-rhodinose glycal (93), we discovered that the 2-amino sugar 114 was produced from the glycal 93 in 57 % yield. This experimental result clearly shows that the intermolecular C-H amination of glycals prefer 2-amino sugars to 3-amino sugars. We can explain that the intermolecular C-H amination by the formation of an aziridine ring intermediate instead of nitrene C-H insertion and thereafter aziridine ring opening would provide the 2-amino sugar 93.

In addition, we had investigated and discovered that the intramolecular C-H amination of anti-alkynol carbamates 115 and 123 give aminal structures 124 and 125 with high regio-, and stereoselectivity, but the isomeric syn-alkynol carbamates 122 do not provide any product. Experimental result also showed that the Rh$_2$(tpa)$_4$ catalyst is more reactive than the Rh$_2$(OAc)$_4$ for the C-H amination of alkynol carbamates. Further studies of the C-H amination of alkynol carbamates are needed to allow the syntheses of aminal subunits in valuable natural compounds.
1.4. Reference


(o) Bodkin, J. A.; Bacskay, G. B.; McLeod, M. D.: The Sharpless asymmetric aminohydroxylation reaction: optimising ligand/substrate control of regioselectivity for the synthesis of 3- and 4-aminosugars, *Organic & Biomolecular Chemistry* 2008, 6, 2544


1.5. Experimental section

General Information

All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 µm layer aluminum-supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å, 230-400 mesh, surface area 500-600 m²/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH₂Cl₂ on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ¹H), a Varian Inova-500 (500 MHz for ¹H and 125 MHz for ¹³C), Bruker-400 (400 MHz for ¹H and 100 MHz for ¹³C), Varian Inova-400 (400 MHz for ¹H and 100 MHz for ¹³C), or Gemini-2300 (300 MHz for ¹H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.
1.5.1. Experimental Procedure for intermolecular C-H amination of glycals

![Chemical structure](image)

**Allyl ethyl lactate 108.** To a solution of ethyl lactate (107) (0.590 g, 5.00 mmol) in THF (5 mL) was added a solution of allyl ethyl carbonate (1.30 g, 10.0 mmol) and Pd(PPh₃)₄ (0.144 g, 0.125 mmol) in THF (5 mL) via a cannula. The mixture was stirred and heated to reflux for 5 h. The reaction was allowed to cool to ambient temperature and then filtered through a short pad of silica followed by washing with ethyl ether. After evaporation, the crude product was purified on silica gel chromatography (elution with petroleum ether / EtOAc = 9 : 1) to give allyl ethyl lactate 108 (0.63 g, 80%) as colorless liquid. ¹H NMR (300 MHz, CDCl₃) δ 5.89 (dddd, 1H, J = 17.2, 10.4, 6.0, 5.5 Hz), 5.26 (ddd, 1H, J = 16.9, 3.4, 1.5 Hz), 5.16 (dt, J = 10.4, 1.4 Hz, 1H), 4.18 (dq, J = 7.2 Hz, 2H), 4.11 (ddt, J = 12.5, 5.5, 1.4 Hz, 1H), 3.97 (q, J = 6.9 Hz, 1H), 3.91 (ddt, J = 12.5 Hz, 6.0 Hz, 1.4 Hz, 1H), 1.38 (d, J = 6.9 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). Spectroscopic properties were in agreement with literature values.¹⁷

![Chemical structure](image)

**Alcohol 109.** A solution DIBAL-H (1.0 M in hexane, 1.23 mL, 1.23 mmol) was added at -90°C to a solution of lactate 108 (0.142 mg, 0.900 mmol) in CH₂Cl₂ (5 ml). After stirring at this temperature for 30 min, TLC (EtOAc : hexanes = 1 : 20) indicated complete consumption of the starting material. Vinyl magnesium bromide (0.7 M solution in THF, 2.51 mL, 1.76 mmol) was then added via syringe and the mixture was allowed to warm to ambient temperature. It was then poured onto water and diethyl ether, and the precipitate was dissolved with a saturated solution
of K tartrate. The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were dried with MgSO₄. After evaporation, the crude product was purified on silica gel chromatography (elution with EtOAc : hexane = 1 : 20) to give alcohol 109 (85 mg, 67 %). ¹H NMR (300 MHz, CDCl₃): δ 5.89 (ddddd, J = 17.3, 10.5, 5.5, 5.5 Hz, 1H) 5.79 (ddd, J = 17.3, 10.5, 6.5 Hz, 1H), 5.34 (dd, J = 17.3, 1.5 Hz, 1H), 5.25 (ddm, J = 17.3 Hz, 1H), 5.19 (ddd, J = 10.5, 1.5, 1.5 Hz, 1H), 5.15 (dmm, J = 10.5 Hz, 1H), 4.12 (ddddd, J = 12.8, 5.5, 1.3, 1.3 Hz, 1H), 3.93 (dddd, J = 12.8, 5.5, 1.3, 1.3 Hz, 1H), 3.89 (dd, J = 7.0, 6.5 Hz, 1H), 3.32 (dq, J = 7.0, 6.3 Hz, 1H), 2.80 (br s, 1H), 1.11 (d, J = 6.3 Hz, 1H). Spectroscopic properties were in agreement with literature values.¹⁶,²⁸

Benzyl protected benzyl ether 110.¹⁵ NaH (60 % dispersion in mineral oil, 3.0 mg, 0.08 mmol) was added to a solution of 109 (9.0 mg, 0.06 mmol) in THF (2.5 mL) and the mixture was heated to reflux for 30 min. Benzyl bromide (13.2 mg, 0.077 mmol) was added, and the mixture was heated to reflux for 30 min again. NaH (60 % dispersion in mineral oil, 3.0 mg, 0.08 mmol) was 2 times more added until TLC (EtOAc : hexane = 1 : 7) indicated complete consumption of the starting material. After evaporation, the crude product was purified on silica gel chromatography (elution with EtOAc : hexane = 1 : 20) to afford benzyl ether 110 (13.5 mg, 92 %). ¹H NMR (300 MHz, CDCl₃): δ 7.40 - 7.25 (m, 5H), 5.93 (ddddd, J = 17.0, 10.5, 5.7, 5.4 Hz, 1H), 5.82 (ddd, J = 17.2, 10.2, 7.5 Hz, 1H), 5.36 - 5.24 (m, 3H), 5.16 (dmm, J = 10.5 Hz, 1H), 4.64 (d, J = 12.3 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.10 - 4.07 (dt, J = 2.4, 2H), 3.83 - 3.78 (m, 1H), 3.58 (dq, J = 6.2, 6.2 Hz, 1H), 1.13 (d, J = 6.6 Hz, 3H). Spectroscopic properties were in agreement with literature values.¹⁵
3,6-Dihydropyran 111. Grubb’s 1st generation catalyst (2.3 mg, 5.0 mol %) was added to a solution of ether 110 (13 mg, 0.056 mmol) in toluene (1.5 mL). The solution was stirred at ambient temperature, until the starting material was fully consumed as indicated by TLC and all volatiles were evaporated. The residue was purified by silica gel column chromatography (elution with EtOAc : hexanes = 1 : 20) to give colorless oil 111 (6.0 mg, 53 %). $^1$H NMR (400 MHz) $\delta$ 7.34 - 7.25 (m, 5H), 5.98 (m, 2H), 4.60 (dd, $J = 12.0$ Hz, 2H), 4.18 (m, 2H), 3.67 (m, 1H), 3.63 (m, 1H), 1.35 (d, $J = 2.4$ Hz, 3H).

L-Rhodinose glycal (93). To a solution of dihydropyran 111 (6.0 mg, 29 µmol) in absolute EtOH (3 mL) was added RhCl(PPh$_3$)$_3$ (5.4 mg, 5.9 µmol) and DBU (1.1 µL, 7.4 µmol). The mixture was heated to 70 $^\circ$C. After 16 h, the reaction temperature was increased to 85 $^\circ$C. The catalyst (5.4 mg, 5.9 µmol) and DBU (7 µL) were added more and stirred for 2.5 h at the same temperature. After evaporation, the residue was purified by silica gel column chromatography (elution with EtOAc : hexanes = 1 : 20) to give colorless oil 93 (5.0 mg, 83 %). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.35 (m, 5H), 6.31 (m, 1H), 4.66 (d, $J = 12.2$ Hz,1H), 4.61 (m, 1H), 4.53 (d, $J = 12.2$ Hz, 1H), 4.13 (dq, $J = 2.7$ Hz, 1H), 3.67 (dt, $J = 2.7$, 5.7 Hz, 1H), 2.27 - 2.11 (m, 2H), 1.28 (d, $J = 6.5$ Hz, 3H). Spectroscopic properties were in agreement with literature values.
2-Amino sugar 114. To a solution of glycal 93 (14.3 mg, 0.070 mmol) in benzene (0.8 mL) was added Rh$_2$(esp)$_4$ 84 (4.0 mg, 0.005 mmol) and NH$_2$Tces 83 (10.2 mg, 0.070 mmol) under argon and then a solution of PhI(O$_2$CtBu)$_2$ (56.9 mg, 0.140 mmol) in benzene (0.5 mL) was added dropwise for 3 h with a syringe pump. The reaction mixture was stirred for 3 hr and sat. thiourea solution was added. The mixture was separated, extracted with CH$_2$Cl$_2$ (3 times), and dried over anhydrous MgSO$_4$. The combined organic extract was concentrated under reduced pressure and purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 20) to give white solid 114 (21 mg, 57%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.30 - 7.30 (m, 5H), 6.19 (d, $J = 3.6$ Hz, 1H), 4.74 (d, $J = 12.0$ Hz, 1H), 4.62 (s, 2H), 4.56 (d, $J = 9.9$ Hz, 1H), 4.42 (d, $J = 11.7$ Hz, 1H), 4.25 - 4.15 (m, 1H), 3.90 (qd, $J = 6.6$, 1.2 Hz, 1H), 3.49 (s, 1H), 2.50 (dt, $J = 14.4$, 0.9 Hz, 1H), 1.82 (td, $J = 12.9$, 2.1 Hz, 1H), 1.25 (s, 9H), 1.21 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.6, 137.8, 128.7, 128.2, 93.5, 91.0, 78.5, 76.9, 73.7, 71.6, 68.7, 48.5, 39.6, 29.6, 27.3, 16.7.

1.5.2. Experimental Procedure for intramolecular of C-H amination of alkynol carbamates

Epoxide 101$^{9a}$ Powdered 3Å molecular sieves (500 mg) were placed in a flask and heated at 300 °C under reduced pressure (ca. 0.5 mmHg) for 3 h. To the cooled flask, maintained under argon, were added CH$_2$Cl$_2$ (100 mL), 3-butene-2-ol (100) (2.0 mL, 23 mmol), and L-(+) DIPT
(730 μL, 3.5 mmol). The stirred mixture was cooled to -20 °C and treated with Ti(O-i-Pr)$_4$ (680 μL, 2.3 mmol). After 30 min, TBHP in decane (6.0 M, 1.73 mL, 10 mmol), dried with activated 3Å molecular sieves prior to use, was added dropwise. The reaction mixture was stirred at -20 °C for 21 h and then diluted with CH$_2$Cl$_2$ (50 mL). To the stirred mixture at -20 °C were added imidazole (4.7 g, 69 mmol), and TBDPS-Cl (9.0 mL, 35 mmol) in CH$_2$Cl$_2$ (50 mL). The reaction mixture was slowly warmed to rt and stirred for 12 h. Then 10 % saturated aqueous NaHCO$_3$ (20 mL) was added, and the mixture was filtered through a short Celite column and concentrated. The residue was extracted with hexane (2 × 20 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (elution with EtOAc : hexanes = 1 : 150) on silica gel, that had been treated with Et$_3$N (0.1 mL per 100 mL gel) in hexane before use, to afford epoxide 101 (2.7 g, 38 % for two steps, theoretical yield: 45 %). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.68 (m, 4H), 7.40 (m, 6H), 3.59 (m, 1H), 2.86 (m, 1H), 2.55 (m, 1H), 2.26 (m, 1H), 1.20 (d, $J$ = 5.9 Hz, 3H), 1.06 (s, 9H). Spectroscopic properties were in agreement with literature values.$^{9a}$

**Alkynol 99.$^{9a}$** To the solution of trimethylsilyl acetylene (1.83 mL, 12.9 mmol) in toluene (13 mL) was added n-BuLi in hexane (1.6 M, 8.09 mL, 13 mmol) and the mixture was stirred at -35 °C. After 15 min, the white suspension was warmed to 0 °C and Et$_2$AlCl in toluene (1.8 M, 7.19 mL, 13 mmol) was added. The mixture was vigorously stirred at 0 °C for 1 h and epoxide 101 (2.11 g, 6.47 mmol) in toluene (9 mL) was added via cannula. The mixture was slowly warmed to 10 °C and stirred for 12 h. Then, it was quenched with saturated aqueous NH$_4$Cl (4 mL) and water (10 mL). The organic layer was separated and the aqueous phase was extracted with ether (5 × 5 mL). The combined organic solution was dried over MgSO$_4$, concentrated, and purified by silica gel flash column chromatography on silica gel (elution with EtOAc : hexanes = 1 : 60) to provide alcohol 99 (2.2 g, 63 %) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.67 (m, 4H), 7.41 (m, 6H), 3.98 (dd, $J$ = 4.4, 1H), 3.74 (dt, $J$ = 6.8, 4.4, 1H), 2.48 (dd, $J$ = 17.0, 6.8 Hz, 1H), 2.36 (dd, $J$
= 16.8, 6.8 Hz, 1H), 1.04 (s, 9H), 0.90 (d, J = 6.0 Hz, 3H), 0.07 (s, 9H). Spectroscopic properties were in agreement with literature values.\(^\text{9a}\)

**Carbamate 115.** To a solution of alcohol 99 (56.8 mg, 0.134 mmol) in CH\(_2\)Cl\(_2\) was added isocyanate (20.5 \(\mu\)L, 0.167 mmol)\(^\text{9a}\) dropwise at 0 °C under argon. The mixture was slowly warmed to rt, and stirred at rt for 1 hr. The mixture was filtered throughout Al\(_2\)O\(_3\) with CH\(_2\)Cl\(_2\) and then concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (elution with EtOAc : n-hexane = 1 : 50) to afford carbamate 115 (55 mg, 88 %) as colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.33 - 7.45 (m, 6H), 7.65 - 7.71 (m, 4H), 4.76 - 4.81 (m, 1H), 4.44 (br, 2H), 4.10 - 4.07 (m, 1H), 2.76 - 2.58 (m, 2H), 1.06 (s, 9H), 1.02 (d, J = 6.4 Hz, 3H), 0.12 (s, 9H); IR (neat) \(\nu_{\text{max}}\) 3501, 3341, 2958, 2929, 2179, 1728, 1590, 1427, 1389, 1250, 1112 cm\(^{-1}\). Spectroscopic properties were in agreement with literature values.\(^\text{9a}\)

**TBS - protected ethyl lactate 121.**\(^\text{24}\) To a solution of ethyl lactate 107 (0.50 g, 3.2 mmol) in THF (5 ml) was added Et\(_3\)N (0.83 g, 8.2 mmol), DMAP (37 mg, 0.30 mmol) and TBS-Cl (0.63 g, 4.3 mmol) under argon, and the mixture was stirred at rt for 20 hr. The mixture was concentrated under reduced pressure. Ethyl ether was added, and salts were removed by filtration. The filtrate was washed with 15 % acetic acid, water, Saturated aq. NaHCO\(_3\), and water and then dried over MgSO\(_4\). The combined mixture was concentrated under reduced pressure to give the crude product 121 (744 mg, 91.0 %). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.28 (q, J = 6.9 Hz, 1H),
4.23 - 4.10 (m, 2H), 1.37 (d, \( J = 6.9 \) Hz, 3H), 1.26 (t, \( J = 6.9 \) Hz, 3H), 0.88 (s, 9H), 0.06 (d, \( J = 8.7 \) Hz, 6H) Spectroscopic properties were in agreement with literature values.²⁹

![Chemical Structures](image)

**Aldehyde 116.**²⁹,²⁴ To a solution of TBS-protected ethyl ester 121 (500 mg, 2.15 mmol) in \( \text{CH}_2\text{Cl}_2 \) (10 mL) was cooled to -55 °C ~ -65 °C, and then DIBAL-H (2.9 mL, 2.88 mmol, 1.3 ~ 1.5 M solution in \( \text{CH}_2\text{Cl}_2 \)) was added dropwise for 20 min. The mixture was stirred at -60 °C for 20 min, and then \( \text{H}_2\text{O} \) was added dropwise. The mixture was filtered to remove white solid, dried over \( \text{MgSO}_4 \), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with \( \text{CH}_2\text{Cl}_2 : \text{hexane} = 1 : 1 \)) to afford aldehyde 116 (0.34 mg, 84 %). \(^1\text{H} \) NMR (300 MHz, \( \text{CDCl}_3 \)) \( \delta \): 9.61 (d, \( J = 0.9 \) Hz, 1H), 4.09 (qd, \( J = 1.2, 6.9 \) Hz, 1H), 1.28 (d, \( J = 3.3 \) Hz, 3H), 0.92 (s, 9H), 0.10 (d, \( J = 3.9 \) Hz, 6H). Spectroscopic properties were in agreement with literature values.²⁹

![Chemical Structures](image)

**Alkynol 117 and 118.** To a solution of aldehyde 116 (0.46 mg, 1.97 mmol) in a mixed solvent (8 mL, DMF and ethyl ether = 1:1) was added activated Zn dust (0.387 mg, 5.92 mmol) and propargyl bromide (0.59 mg, 3.95 mmol)²³ and the reaction was stirred at rt for 14 hr. The reaction mixture was filtered to remove Zn dust and saturated aq. \( \text{NH}_4\text{Cl} \) solution was added. The organic phase was separated and the aqueous layer was extracted with ethyl ether (5 mL X 2). The combined organic layers were washed with brine and dried over anhydrous \( \text{MgSO}_4 \).
crude oil was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with pentene : ethyl ether = 100 : 1 and then 20 : 1) to afford 117 (90.9 mg, 20 %), 118 (51 mg, 11 %), and the mixture of 117 and 118 (142 mg, 32 %).

Akynol 117\textsuperscript{13}: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 3.97 (dq, \(J = 3.3, 6.3\) Hz, 1H), 3.50 (m, 1H), 2.40 (dd, \(J = 2.7, 6.5\) Hz, 2H), 2.02 (t, \(J = 2.4, 1H\)), 1.2 (d, \(J = 6.3, 3H\)), 0.90 (s, 9H), 0.11 (s, 6H).

Alkynol 118\textsuperscript{13}: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 3.89 (m, 1H), 3.65 (m, 1H), 2.41 (m, 2H), 2.27 (br, 1H), 2.03 (t, \(J = 2.7\) Hz, 1H), 1.15 (d, \(J = 6.2\) Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H).

Spectroscopic properties were in agreement with literature values.\textsuperscript{13}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{carbamate_diagram}
\caption{Carbamate 122.}
\end{figure}

Carbamate 122. To a solution of alcohol 117 (77 mg, 0.34 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5.0 mL) was cooled to 0 °C and added isocyanate (69 mg, 0.37 mmol) dropwise.\textsuperscript{9a} The reaction was slowly warmed to rt and stirred for 1 hr. The reaction mixture was filtered throughout Al\textsubscript{2}O\textsubscript{3}\textsuperscript{25} and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : n-hexane = 1 : 20) to afford 122 (82 mg, 90 %). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 4.75 - 4.70 (m, 3H), 4.12 (q, \(J = 7.2\) Hz, 1H), 2.51 (dddd, \(J = 24.9, 16.8, 5.7, 2.7\) Hz, 2H), 1.97 (t, \(J = 2.7\) Hz, 1H), 1.15 (d, \(J = 6.3\) Hz, 3H), 0.89 (s, 9H), 0.08 (d, \(J = 3.0\) Hz), 0.08 (d, \(J = 3.0\) Hz); IR (neat) \(\nu_{\text{max}}\) 3482, 3313, 2928, 2857, 1725, 1599, 1389, 1257, 1109 cm\textsuperscript{-1}.

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**Carbamate 123.** To a solution of alcohol 118 (50.5 mg, 0.221 mmol) in CH$_2$Cl$_2$ (5.0 mL) was cooled to 0 °C and added isocyanate dropwise (45.8 mg, 0.243 mmol).\textsuperscript{9a} The reaction was slowly warmed to rt and stirred for 1 hr. The reaction mixture was filtered throughout Al$_2$O$_3$\textsuperscript{25} and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : n-hexane = 1 : 20) to afford 123 (55 mg, 91\%). \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 4.86 (br, 1H), 4.65 (q, $J$ = 5.4, 1H), 4.00 (app. quintet, $J$ = 6.3 Hz, 2H), 2.63 - 2.48 (m, 2H), 1.96 (t, $J$ = 2.7 Hz, 1H), 1.15 (d, $J$ = 6.3 Hz, 3H), 0.88 (s, 9H), 0.06 (d, $J$ = 3.0 Hz, 6H); IR (neat) $\nu_{\text{max}}$ 3314, 2925, 2853, 1724, 1463, 1379, 1259, 1074 cm$^{-1}$.

**Oxazolidinone 124.** To a dried vial were added the carbamate 115 (8.0 mg, 0.017 mmol), toluene (3 ml), MgO (3 mg, 0.074 mmol), Phl(OAc)$_2$ (7.7 mg, 0.025 mmol), and Rh$_2$(OAc)$_4$ (1.5 mg, 0.0034 mmol).\textsuperscript{7} The mixture was stirred at 90 °C for 36 hr, and then cooled to rt. MgO (3.0 mg, 0.074 mmol), Phl(OAc)$_2$ (7.7 mg, 0.025 mmol), and Rh$_2$(OAc)$_4$ (1.5 mg, 0.0034 mmol) were additionally added. The mixture was stirred at 90 °C for 18 hr again. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 4) to afford oxazolidinone 124 (1.0 mg, 12\%). \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71 (m, 4H), 7.50 - 7.39 (m, 6H), 4.81 (s, 1H), 4.35 (dd, $J$ = 9.0, 6.0 Hz, 1H), 3.06 (dd, $J$ = 18.0, 9.0 Hz, 1H), 2.90 (dd, $J$ = 15.0, 3.0 Hz, 1H), 1.51 (s, 3H), 1.07 (s, 9H), 0.20 (s, 9H); IR (neat) $\nu_{\text{max}}$ 3274, 3071, 2960, 2926, 2181, 1775 cm$^{-1}$.

---

1. Carbamate 123. To a solution of alcohol 118 (50.5 mg, 0.221 mmol) in CH$_2$Cl$_2$ (5.0 mL) was cooled to 0 °C and added isocyanate dropwise (45.8 mg, 0.243 mmol). The reaction was slowly warmed to rt and stirred for 1 hr. The reaction mixture was filtered throughout Al$_2$O$_3$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : n-hexane = 1 : 20) to afford 123 (55 mg, 91\%). \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 4.86 (br, 1H), 4.65 (q, $J$ = 5.4, 1H), 4.00 (app. quintet, $J$ = 6.3 Hz, 2H), 2.63 - 2.48 (m, 2H), 1.96 (t, $J$ = 2.7 Hz, 1H), 1.15 (d, $J$ = 6.3 Hz, 3H), 0.88 (s, 9H), 0.06 (d, $J$ = 3.0 Hz, 6H); IR (neat) $\nu_{\text{max}}$ 3314, 2925, 2853, 1724, 1463, 1379, 1259, 1074 cm$^{-1}$.

2. Oxazolidinone 124. To a dried vial were added the carbamate 115 (8.0 mg, 0.017 mmol), toluene (3 ml), MgO (3 mg, 0.074 mmol), Phl(OAc)$_2$ (7.7 mg, 0.025 mmol), and Rh$_2$(OAc)$_4$ (1.5 mg, 0.0034 mmol). The mixture was stirred at 90 °C for 36 hr, and then cooled to rt. MgO (3.0 mg, 0.074 mmol), Phl(OAc)$_2$ (7.7 mg, 0.025 mmol), and Rh$_2$(OAc)$_4$ (1.5 mg, 0.0034 mmol) were additionally added. The mixture was stirred at 90 °C for 18 hr again. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 4) to afford oxazolidinone 124 (1.0 mg, 12\%). \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71 (m, 4H), 7.50 - 7.39 (m, 6H), 4.81 (s, 1H), 4.35 (dd, $J$ = 9.0, 6.0 Hz, 1H), 3.06 (dd, $J$ = 18.0, 9.0 Hz, 1H), 2.90 (dd, $J$ = 15.0, 3.0 Hz, 1H), 1.51 (s, 3H), 1.07 (s, 9H), 0.20 (s, 9H); IR (neat) $\nu_{\text{max}}$ 3274, 3071, 2960, 2926, 2181, 1775 cm$^{-1}$.
Representative procedure for intramolecular C-H amination

Oxazolidinone 125. To a solution of carbamate 123 (55.0 mg, 0.203 mmol) in benzene (1 mL) were added Rh\textsubscript{2}(tpa)\textsubscript{4} (8.2 mg, 0.007 mmol), PhI(OAc)\textsubscript{4} (99.6 mg, 0.309 mmol), and MgO (21.3 mg, 0.528 mmol) and then stirred at 50 °C for 3 hr. The mixture was cooled to rt and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 4) to afford 125 (23 mg, 52 %) and recovered starting material 123 (10 mg, 19 %). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 6.42 (br, 1H), 4.34 (dd, \(J = 8.0, 4.0\), 1H), 2.75 - 2.63 (m, 2H), 2.15 (t, \(J = 2.7\) Hz, 1H), 1.62 (s, 3H), 0.90 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 157.0, 86.2, 84.6, 78.8, 70.62, 27.3, 25.5, 18.9, 18.0, -3.6. IR (neat) \(\nu_{\text{max}}\) 3313, 2926, 2854, 1762, 1724, 1587, 1462, 1260, 1037 cm\textsuperscript{-1}.

Difference NOE for compound 125.

<table>
<thead>
<tr>
<th>Inverted peak (ppm)</th>
<th>Enhanced peaks (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH (4.34)</td>
<td>CH\textsubscript{2} (2.75 - 2.63), CH\textsubscript{3} (1.62)</td>
</tr>
<tr>
<td>CH\textsubscript{2} (2.70)</td>
<td>CH (4.34), CH (2.15), C\textsubscript{4}H\textsubscript{9} (0.90)</td>
</tr>
<tr>
<td>CH\textsubscript{3} (1.62)</td>
<td>CH (4.34), C\textsubscript{4}H\textsubscript{9} (0.90), CH\textsubscript{3} (0.17), CH\textsubscript{3} (0.16)</td>
</tr>
</tbody>
</table>
Part II.

Synthetic Studies of Edaxadiene (129)
2.1. Introduction

2.1.1. Background

Tuberculosis (TB) is an infectious disease and an incredibly serious problem around the world. It is caused by mycobacteria, mainly Mycobacterium tuberculosis. This tuberculosis is a pathogenic bacteria species, and more than one-third of global population has been infected.\(^1\) In 2009, Mann and co-workers reported that they found a new bioactive diterpene \(129\), which inhibits endosomal progression to suppress phagosome maturation in the infection process of Mycobacterium tuberculosis.\(^2\) Subverting phagosomal processing allows the bacterium to enter and reside in its host cell macrophage. Mycobacterium tuberculosis also prevents phagosomal maturation, and an enzyme encoded by Rv3377c plays an important role for Mycobacterium tuberculosis to enter into macrophage at initial stage.

The Rv3378c enzyme produces halimadienyl diphosphate \((127)\). Mann and co-workers expected that an enzyme encoded by Rv3378c could give a further product from halimadienyl diphosphate \((127)\). Finally, they got a single diterpene \(129\) (Scheme 38).

\[
\text{Halimadienyl diphosphate} \quad \text{Rv3378c/MtEDS} \quad \text{B:} \quad \text{Purported Edaxadiene or "PE"} \quad \text{Scheme 38. Catalyzed cyclization of 127 to 129 by Rv3378c/MtEDS and proposed a mechanism 128}
\]

However, it is difficult to do a large scale incubation of Rv3378c encoded enzyme because this enzyme is unstable. Therefore, they developed the biomimetic synthesis of “PE” \((129)\) from tuberculosinol \((130)\) (Scheme 39).
Scheme 39. Corresponding biomimetic synthesis of “PE” (129) from tuberculosinol (130)

After characterization of the structure of “PE” (129), they proposed the structure and named it edaxadiene (129).

Later, Maugel and Mann et al.\textsuperscript{3} questioned the structure of “PE” (129), so they synthesized another possible structure, nosyberkol (isotuberculosinol) (131) and elucidated that the diterpene is not “PE” (129), but nosyberkol (isotuberculosinol) (131), which was isolated by Kashman et al.\textsuperscript{4} in 2004 from the Nosy be Islands sponge Raspailia sp. (Figure 5).

Figure 5. Revised structure 131 of the diterpene 129

2.1.2. Synthetic approaches to nosyberkol (131) and “PE” (129)

In 2010, (±)-nosyberkol (131) was synthesized by Maugel et al.\textsuperscript{3a} to compare the spectra data of the diterpene 129 they isolated to nosyberkol (131) (Scheme 36). A bicyclic structure 134 was prepared by an intermolecular Diels-Alder reaction (Scheme 40).
Scheme 40. Construction of a backbone 134 of (±)-nosyberkol (131) by Maugel et al.3a

From a bicyclic compound 134, they demonstrated syntheses of tuberculosinol (130) and (±)-nosyberkol (131) (Scheme 41).

Scheme 41. Syntheses of tuberculosinol (130) and (±)-nosyberkol (131) by Maugel et al.3a

In 2010, Sorensen group displayed a synthesis of the [3.3.1] bicyclic core 142 of “PE” (129) by an intramolecular ketone allylation.5 A Diels-Alder reaction in thermal condition with a modified Rawal diene 136 and tiglaldehyde 137 provided silyl enol ether 138, which was subjected to methylation and Suzuki-Miyaura coupling to give a right linear piece of alkene chain 139. After TBS-deprotection, the oxazolidinone was removed to afford α,β-unsaturated ketone 140, which was treated with Mn and Cu in AcOH-benzene to produce bicycles 141. After
a reduction and dehydration, they showed the synthesis of bicyclic core 142 by an intramolecular ketone allylation (Scheme 42).

![Scheme 42. Synthesis of the [3.3.1] bicyclic core 142 of “PE” (129) by Sorensen group](image)

In the progress of their research, Maugel et al.\(^3\) revised the structure of 129, so Sorensen group changed the target compound “PE” (129) to tuberculosinol (130) and (±)-nosyberkol (131) and also confirmed the structure of 129. A Diels-Alder reaction in thermal condition produced inseparable products 144 in favor of a desired major product (Scheme 43).

![Scheme 43. Construction of a backbone 144 of (±)-nosyberkol (131) by Sorensen group](image)
In addition, they demonstrated biomimetic conversion of tuberculosinol (130) into nosyberkol (131) (See Scheme 38). They found that this reaction is a Lewis acid-mediated allylic transposition and the treatment of tuberculosinol (130) with CuCl₂ produced nosyberkol (131) in 34 % yield (Scheme 44).

Scheme 44. Syntheses of nosyberkol (131) from tuberculosinol (130) by Sorensen group

When we started a synthesis of “PE” (129), we focused on the preparation of a bicyclic core by an intramolecular Diels-Alder reaction, but in the progress of our research, we found that the diterpene (129) is nosyberkol (131). Therefore, we also changed a target compound “PE” (129) to nosyberkol (131) and examined a procedure to convert tuberculosinol (130) to 131.

2.1.3. A new synthetic approach to a key core of “PE” (129)

We envisioned that the bicyclic core 145, of “PE” (129) could be prepared by the intramolecular Diels-Alder (IMDA) reaction of triene 146. This was an attractive approach because a powerful fragmentation approach provided 146 from a commercially available epoxide 147 (Scheme 45).
The intramolecular Diels-Alder reaction (IMDA)\(^7\) could have 4 possible transition states to produce a diastereomers mixture. Desired products \(150\) and \(151\) would be produced throughout endo-transition state as an isomeric mixture in thermal condition (Scheme 46).
Scheme 46. Proposed transition states of the intramolecular Diels-Alder reaction

Based on our expectation, we designed a retrosynthetic approach to access a precursor of an IMDA. We focused on synthesis of methyl ketone 153 reported by Skorianetz et al.\(^8\) It was simply prepared from an epoxide, 4-(1,3,3-trimethylbicyclo[4.1.0]hept-2-yl)-3-Buten-2-one 147, a commercially available material by two steps (Scheme 47).

Scheme 47. Preparation the methyl ketone 153 from the epoxide 147 by Skorianetz et al.\(^8\)
In addition, the haloform reaction has been widely used to convert ketones 154 to carboxylic acids 155 (Scheme 48).\textsuperscript{9a}

\[
\begin{array}{c}
\text{R} \quad \text{(154)} \\
\text{O} \\
\text{X}_2 \quad \text{NaOH} \\
\text{R} \quad \text{OH} \quad \text{(155)} \\
\text{X} = \text{halogen}
\end{array}
\]

**Scheme 48.** Conversion ketones 154 to carboxylic acids 155 by haloform reaction

Therefore, we believed that haloform reaction would give us carboxylic acid 157 from methyl ketone 153. Reduction of carboxylic acid 157 followed by oxidation could produce aldehyde 156, which would be subjected to Wittig reaction to prepare a precursor 146 for an IMDA reaction (Scheme 49).

**Scheme 49.** Retrosynthetic analysis of a precursor 146

Furthermore, after we proved the usefulness of our simple procedure, introducing a chiral auxiliary to a precursor for an IMDA would control stereoselectivity to provide a desired product 151. Based on our retrosynthetic analysis, we started the synthetic approach of “PE” (129).
2.1.4. A new approach for the preparation of nosyberkol (131) from tuberculosinol (130)

In the progress of our research, it was elucidated that the diterpene 129 isolated by Mann et al. is nosyberkol (131). Therefore, we examined a synthetic route to obtain nosyberkol (131) from tuberculosinol (130) because we also wanted to confirm the structure of “PE” (129) by the synthesis of nosyberkol (131) from tuberculosinol (130) using a promising synthetic method for 1,3-transposition of primary allylic alcohols. There are some methods to convert primary allylic alcohols to vinyl tertiary alcohols.\(^\text{10}\) Especially, we focused on sulfoxide-sulfenate ester rearrangement (Scheme 50).\(^\text{11}\)

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{S} & \quad \text{O} \\
\text{158} & \quad \text{159}
\end{align*}
\]

Scheme 50. Sulfoxide-sulfenate ester rearrangement

Thus, we envisioned another promising method to nosyberkol (131) from tuberculosinol (130) by sulfoxide-sulfenate ester rearrangement (Scheme 51).

\[
\begin{align*}
\text{Nosyberkol (131)} & \quad \text{160} & \quad \text{Tuberculosinol (130)}
\end{align*}
\]

Scheme 51. Retrosynthetic approaches of nosyberkol (131) from tuberculosinol (130)

We used a model compound, farnesol (164), and explored synthetic methods with this rearrangement to obtain a vinyl tertiary alcohol 161 (Scheme 52).
Scheme 52. Retrosynthetic analysis of a tertiary alcohol 161 from farnesol (164)
2.2. Result and Discussion

2.2.1. Studies of synthesis of “PE” (129)

As we envisioned retrosynthetic analysis of “PE” (129), the mixtures of diastereomers 152 were obtained from the epoxide 147 by reduction with LiAlH₄. After dehydration, the mixture 155 gave the methyl ketone 153 as one product in 78 % for 2 steps (Scheme 53). 

![Scheme 53. Preparation of the methyl ketone 153 from the epoxide 147](image)

To convert the methyl ketone 153 to a carboxylic acid, the haloform reaction ⁹⁺ was examined to give a product. When it was treated with bromine, a desired product was obtained. The crude acid was directly used to the next step, reduction with LiAlH₄, to produce an alcohol 165 in 45 % for 2 steps (Scheme 54).

![Scheme 54. Preparation of the alcohol 165 from the methyl ketone 153](image)
The treatment of the alcohol 165 with PCC afforded an aldehyde 156, which was subjected to Wittig reaction to provide an ester 166, a precursor of the IMDA reaction (Scheme 55).

\[
\text{PCC} \quad \text{CH}_2\text{Cl}_2 \quad \text{Ph} \quad \text{Ph} \quad \text{Et} \quad \text{Ph} \quad \text{benzene, 80 °C} \quad 73\% \ (2 \text{ steps})
\]

**Scheme 55.** Preparation of the triene 166 from the alcohol 165

Finally, in thermal condition, the IMDA reaction was applied to the ester 166 to produce a bicyclic core and we believed that products 167 were an inseparable mixture of diastereomers (Scheme 56).

**Scheme 56.** Preparation of the bicyclic compounds 167 from the triene 166

### 2.2.2. Studies of synthesis of nosyberkol (131) from tuberculosinol (130)

A sulfide 163 was synthesized from an allylic alcohol 164, farnesol, which is a commercially available compound. Farnesol (164) was treated with diphenyl sulfide\(^\text{13}\), tributyl phosphine, and pyridine to provide a sulfide 163 (Scheme 57). Other phosphine reagents were explored, but tributyl phosphine gave high conversion (Table 5).
Farnesol (164) \[\text{Ph-S-S- Ph} \quad \text{(n-Bu)}_3\text{P, Pyridine}}\]

\[\text{CH}_2\text{Cl}_2, 83\%\]

**Scheme 57.** Synthesis of the sulfide 163 from the farnesol (164)

**Table 5.** Results of synthesis of the sulfide 163

<table>
<thead>
<tr>
<th>Phosphine reagent</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triphenyl phosphine</td>
<td>CH(_2)Cl(_2)</td>
<td>RT</td>
<td>No rxn</td>
</tr>
<tr>
<td>Triphenyl phosphine</td>
<td>CH(_2)Cl(_2)</td>
<td>Reflux</td>
<td>No rxn</td>
</tr>
<tr>
<td>Tris(dimethylamino)phosphine</td>
<td>CH(_2)Cl(_2)</td>
<td>RT</td>
<td>Conversion 23%</td>
</tr>
<tr>
<td>Tris(dimethylamino)phosphine</td>
<td>C(_2)H(_4)Cl(_2)</td>
<td>reflux</td>
<td>Conversion 35%</td>
</tr>
<tr>
<td>Tributyl phosphine</td>
<td>CH(_2)Cl(_2)</td>
<td>RT</td>
<td>Conversion ~ 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Y = 83%</td>
</tr>
</tbody>
</table>

RT = room temperature

In addition, a treatment of the sulfide 163 with mCPBA provided a sulfoxide 162 (scheme 58).\(^{14}\)

**Scheme 58.** Preparation of the sulfoxide 162 from the sulfide 163

Finally, a vinyl tertiary alcohol 161 was produced from the sulfoxide 162 by sulfoxide- sulfenate ester rearrangement\(^{11a,b}\) and sulfenate cleavage. P(OMe)\(_3\) was used as thiophile\(^{15}\) (Scheme 59). The tertiary alcohol 161 was successfully synthesized from the model compound, farnesol (164).
Scheme 59. Synthesis of the vinyl tertiary alcohol 161 from the sulfoxide 162

We obtained a vinyl tertiary alcohol 161 in 61% yield for 3 steps and proved sulfoxide-sulfenate ester rearrangement is a mild reaction to provide vinyl tertiary alcohols from allylic alcohols. However, the progress of their research, Sorensen group also proved the structure of “PE” (129), so we did not try to synthesize nosyberkol (isotuberculosinol) (131) from tuberculosinol (130).
2.3. Conclusion

In conclusion, a bicyclic structure 167, which would be a key structure of natural products, was simply constructed from epoxide 147, a commercially available material, by seven steps. Our procedure would be applied to syntheses of other natural products. In addition, we also demonstrated that the vinyl tertiary alcohol 161 can prepared from the farnesol (164) via the sulfoxide-sulfenate ester rearrangement and total yields for 3 steps were 61 %. Nosyberkol (131) could be prepared from tuberculosinol (130) by our developed process.
2.4. Reference


2.5. Experimental Section

General Information

All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum -supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å, 230-400 mesh, surface area 500-600 m²/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH₂Cl₂ on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ¹H), a Varian Inova-500 (500 MHz for ¹H and 125 MHz for ¹²C), Bruker-400 (400 MHz for ¹H and 100 MHz for ¹³C), Varian Inova-400 (400 MHz for ¹H and 100 MHz for ¹³C, or Gemini-2300 (300 MHz for ¹H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.
**Methyl ketone 153.** To a stirred solution of LiAlH₄ (LAH) (155 mg, 155 mmol) in THF (10 mL) was added dropwise epoxide 147 (300 mg, 1.44 mmol) solution in THF (5 mL). The reaction mixture was heated to 35 °C for 6.5 h and cooled to rt. To a reaction mixture was added dropwise EtOAc under an ice bath and then ice water was added. Volatile organic mixture was evaporated and EtOAc (20 mL) was added again. After separation of the organic layer, the aqueous phase was extracted with EtOAc (15 mL X 2). The combined organic layer was washed with aq. NaCl and dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 20 to 1 : 1) to provide a mixture of diastereomers 152. ¹H NMR (300 MHz, CDCl₃) δ 5.71 (m, 1H), 5.51 (m, 1H), 4.35 (quint, J = 6.0, 1H), 1.74 (m, 2H), 1.57 – 1.34 (m, 7H), 1.53 (d, J = 10.2, 1H), 1.46 (m, 1H), 1.29 (d, J = 6.3, 3H), 1.08 (m, 3H), 1.00 (m, 3H), 0.79 (m, 3H); IR (neat) 3386, 2928, 1458 cm⁻¹. Without a further purification, it was directly used to the next step. To a stirred solution of mixture products 152 in CH₂Cl₂ (15 mL) was added p-TsOH (30 mg) and stirred at rt for 19 h. The reaction mixture was washed with brine and extracted with CH₂Cl₂ (10 mL). The combined organic solution was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20) to afford methyl ketone 153 (197 mg, 78 % for 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 5.87 – 6.06 (m, 2H), 5.55 – 5.66 (m, 1H), 5.49 (d, J = 15.0 Hz, 1H), 2.37 (t, J = 7.5 Hz, 2H), 2.12 (s, 3H), 1.73 (dd, J = 6.9, 1.5 Hz, 3H), 1.54 – 1.43 (m, 2H), 1.27 – 1.21 (m, 2H), 0.99 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 209.3, 141.6, 132.1, 127.2, 126.7, 44.6, 42.8, 36.0, 30.1, 27.4, 19.4, 18.3.
Alcohol 165. To a stirred solution of NaOH (265 mg, 6.60 mmol) in H₂O (2.2 mL) was cooled to 0 °C and bromine (0.086 mL, 1.7 mmol) was added dropwise for 5 min. The reaction mixture was stirred for 7 min and dioxane (1.5 mL) was added dropwise for 5 min. Then, to a reaction mixture were added dropwise the solution of methyl ketone 153 in dioxane (2.5 mL) and H₂O (0.7 mL) at 0 °C. The reaction solution was slowly warmed to rt over 3 h and stirred at rt for 2 h. Na₂SO₃ (63 mg, 0.50 mmol) and H₂O (0.06 mL) were added and then the resulting mixture was immersed in a pre-heated oil bath 90 °C for 15 min and cooled to rt. After evaporation, the residue was washed with Et₂O (10 mL) and 25 % H₂SO₄ was added and extracted with Et₂O (20 mL X 2). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure to give a product, crude carboxylic acid, (106 mg). ¹H NMR (400 MHz, CDCl₃) δ 5.87 – 6.03 (m, 2H), 5.58 (m, 1H), 5.46 (d, J = 15.6, 1H), 2.28 (t, J = 7.6 Hz, 2H), 1.71 (dd, J = 6.8, 1.2 Hz, 3H), 1.71 – 1.49 (m, 2H), 1.31 – 1.28 (m, 2H), 0.98 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 180.6, 141.4, 132.2, 127.3, 126.8, 42.7, 36.0, 34.9, 27.3, 20.3, 18.2.; IR (neat) 2500 - 3700, 2960, 1713 cm⁻¹. To a stirred solution of LiAlH₄ (131 mg, 3.45 mmol) was added dropwise the carboxylic acid (106 mg) solution in THF (10 mL) for 10 min and stirred at rt for 4 h. H₂O (1 mL) was added dropwise very carefully and then aq. 10 % NaOH was added. The resulting mixture was filtered throughout Celite and rinsed with E₂O, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20 to 7 : 1) to afford alcohol 165 (44 mg, 45 % for 2 steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 6.06 – 5.97 (m, 1H), 5.89 (m, 1H), 3.63 (t, J = 6.6 Hz, 2H), 1.73 (dd, J = 6.9, 1.5 Hz, 3H), 1.55 - 1.49 (m, 2H), 1.33 – 1.22 (m, 2H), 0.99 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 142.0, 132.2, 127.1, 126.5, 63.2, 43.3, 36.1, 33.7, 27.4, 21.1, 18.2.; IR (neat) 3364, 2933 cm⁻¹.
Ester 166. To a stirred solution of alcohol 165 (81.6 mg, 0.447 mmol) in CH₂Cl₂ (6.5 mL) was added PCC (Pyridinium chlorochromate) reagent (156 mg, 1.79 mmol) and stirred at rt. After 5 h, the reaction mixture was concentrated under reduced pressure and ethyl ether was added. The resulting mixture was filtered throughout Celite and concentrated under reduced pressure again. Then the residue was purified by a short silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20) to give crude aldehyde 156. ¹H NMR (400 MHz, CDCl₃) δ 9.69 (t, J = 1.6 Hz, 1H), 6.01 – 5.85 (m, 2H), 5.56 (m, 1H), 5.44 (d, J = 15.2 Hz, 1H), 2.33 (td, J = 7.2, 1.6 Hz, 2H), 1.69 (dd, J = 6.8, 1.2 Hz, 3H), 1.55 – 1.47 (m, 2H), 1.28 – 1.22 (m, 2H), 0.97 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 141.3, 132.1, 127.4, 127.0, 44.7, 42.8, 36.1, 29.9, 27.3, 17.7; IR (neat) 2959, 1727 cm⁻¹. To a stirred solution of crude aldehyde 156 in benzene (9 mL) was added triphenyl phosphorane (162 mg, 0.468 mmol). The reaction mixture was heated and stirred at 80 °C. After 9 h, the resulting mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by a short silica gel column chromatography (elution with EtOAc : Hexane = 1 : 100 to 1 : 50) to provide ester 166 (86 mg, 73 %). ¹H NMR (400 MHz, CDCl₃) δ 6.72 (tq, J = 1.2, 7.2, 1H), 6.07 - 5.86 (m, 2H), 5.60 (m, 1H), 5.45 (d, J = 15.2, 1H), 4.14 (q, J = 7.2, 2H), 2.08 (q, J = 6.8, 2H), 1.78 (s, 3H), 1.70 (dd, J = 6.4, 0.8, 3H), 1.35 - 1.24 (m, 7H), 0.95 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 168.2, 142.0, 141.5, 131.9, 127.7, 126.9, 126.4, 60.3, 42.9, 35.8, 29.3, 27.2, 23.8, 18.0, 14.5, 12.5; IR (neat) 2959, 1712 cm⁻¹.
**Bicyclic compounds 167.** The solution of ester 166 (15.4 mg, 0.0582 mmol) in toluene (6.0 mL) was heated to 160 °C. After 24 h, the reaction solution was concentrated under reduced pressure and purified by a short silica gel column chromatography (elution with EtOAc : Hexane = 1 : 100) to give crude esters. This crude was purified again by Plate TLC to provide diastereomer mixtures 167 (7 mg, 46 %). ¹H NMR (600 MHz, CDCl₃) δ 5.64 – 5.57 (m, 2H), 4.21 – 4.03 (m, 2H), 2.91 – 2.89 (m, 0.5H), 2.30 (dt, J = 12.6 Hz, 0.5 H), 2.02 (m, 0.5H), 1.89 (td, J = 10.8, 2.4, 0.5H, 1.71 – 1.67 (m, 1H), 1.58 – 1.48 (m, 4H), 1.43 – 1.35 (m, 1H), 1.27 – 1.23 (m, 3H), 1.22 (s, 3H), 1.18 – 1.14 (m, 3H), 1.01 – 0.99 (m, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.86 (d, J = 6.6 Hz, 1H), 0.81 (s, 1H); IR (neat) 2961, 1729 cm⁻¹.

**Sulfide 163.** To a stirred solution of farnesol (164) (18.6 mg, 0.0840 mmol) in CH₂Cl₂ (1 mL) were added phenyl sulfide (55.3 mg, 0.251 mmol) and pyridine (33.0 mg, 0.418 mmol). The mixture was cooled to 0°C and tributyl phosphine (63 μL, 0.251 mmol) was added dropwise. The reaction mixture was slowly warmed to rt and stirred for 14 hr. NaBH₄ (14.5 mg, 0.251 mmol) was added and stirred for 1 hr. Then, 10% NaOH solution was added and the mixture was separated. After extraction with CH₂Cl₂ (2 times), the combined organic extract was treated with 25 % H₂SO₄ and NaHCO₃. The mixture was washed with H₂O, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by Plate TLC (elution with EtOAc : n-hexane = 1 : 4) to afford sulfide 163 (22 mg, 83%). ¹H NMR (300 MHz, CDCl₃)
δ 7.14 ~ 7.36 (m, 5H), 5.31 (m, 1H), 5.09 (m, 2H), 3.55 (d, J = 7.5 Hz, 2H), 2.02 (m, 8H), 1.68 (d, J = 1.2 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 9H).

**Sulfoxide 163.** mCPBA (4.2 mg, 0.019 mmol) was added to a solution of sulfide 163 (6.0 mg, 0.019 mmol) in CH₂Cl₂ (0.8 mL). The reaction mixture was stirred under argon for 1 hr, and H₂O was added. The organic phase was separated and extracted with CH₂Cl₂ (2 times). The combined organic extract was dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (elution with EtOAc : hexane = 1 : 20) to afford 162 (5.2 mg, 83 %). ¹H NMR (300 MHz, CDCl₃) δ 7.60 ~ 7.63 (m, 2H), 7.48 ~ 7.50 (m, 3H), 5.06 (m, 3H), 3.59 (qd, J = 16.5, 8.1 Hz, 2H), 2.08 (m, 8H), 1.67 (d, J = 1.2 Hz, 3H), 1.59 (d, J = 1.5 Hz, 6H), 1.42 (d, J = 1.5 Hz, 3H).

**Vinyl tertiary alcohol 161.** To a solution of sulfoxide 162 (2.0 mg, 0.0061 mmol) in MeOH (1.0 mL) was added P(OMe)₃ (11.0 mg, 0.089 mmol). The mixture was stirred at 55 °C for 12 hr under argon. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (elution with EtOAc : hexane = 1 : 4) to afford vinyl tertiary alcohol 161 (1.2 mg, 88%). ¹H NMR (600 MHz, CDCl₃) δ 5.92 (dd, J = 10.2 Hz, 1H), 5.22 (d, J = 11.4 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 5.07 (m, J = 2.7 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 6H), 1.28 (s, 3H); IR (neat) 3416, 2969, 2926, 1450, 1375, 1109 cm⁻¹.
Part III.

Studies Towards the Synthesis of Alchivemycin A (168)
3.1. Introduction

3.1.1. Background

Alchivemycin A (168), a bioactive polycyclic polyketide, was discovered from the culture extract of a Streptomyces strain from a leaf of a Chinese chive by Furuma et al.\(^1\) in 2010. Strain TP-A0867 produced was cultured in A-11 M medium 30 °C for 6 days and was extracted with 1-butanol to produce Alchivemycin A (168) (Figure 6). It showed not only a selective antimicrobial activity for Micrococcus luteus in MIC value of 50 nM, but also bioactivity for a murine colon carcinoma with an IC\(_{50}\) of 0.34 µM without cytotoxic effects.

![Alchivemycin A (168)](image_url)

**Figure 6.** The structure of Alchivemycin A (168)

A structure of Alchivemycin A (168) was determined and showed a highly interesting core and a 2H-tetrahydro-4,6-dioxo-1,2-oxazine ring 172. Furuma and co-workers also suggested a possible biogenesis of that oxazine ring (scheme 60).
Scheme 60. A possible biogenesis of oxazine ring 172 proposed by the Furuma group

We focused on a bicyclic structure that would be a good starting point to construct alchivemycin A (168) and could be prepared by a Diels-Alder reaction, especially an intramolecular Diels-Alder (IMDA) reaction\(^2\) or a transannular Diels-Alder (TADA) reaction\(^3\) (Scheme 61). Generally, expectations with transition state conformations predicted products and transition state conformations would be controlled by reaction conditions and an appropriate design of precursors.

Scheme 61. Retrosynthetic analysis of alchivemycin A (168)

3.1.2. Stereochemistry of the intramolecular and transannular Diels-Alder reaction

The intramolecular Diels-Alder (IMDA) reactions have produced a wide variety of bicyclic cores of many natural products and demonstrated valuable IMDA applications. In spite of a large number of examples of these reactions, the control of stereoselectivity of IMDA reactions has been not fully understood and it is still very important to discover the origin of
stereoselectivity. In principle, IMDA reactions would have 2 transition states of endo and exo to generate trans-fused or cis-fused products. Thermal cyclization could provide cis-fused products by exo-mode cyclization or a mixture of trans and cis-fused rings. For example, Roush and co-worker in 1981 displayed some examples. In thermal condition, products depend on precursors of IMDA reactions, but cis-fused products can be generated as one of the major products (Scheme 62).

\[ \text{Scheme 62. Intramolecular Diels-Alder reactions by the Roush group} \]

The Vederas group reported bicyclic structure syntheses by IMDA reactions in 1996. The IMDA reaction can have endo and exo transition states and each provides two diastereomers in which methyl the group is pseudoaxial and pseudoequatorial at C-6. Both thermal and Lewis
acid (EtAlCl₂)⁶ catalyzed conditions were applied to a triene 184. Thermal condition gave two products (186 and 188) from endo and exo transition states and the Lewis acid condition produced the endo product 186 selectively. None of the reactions showed any product from transition states in which the methyl at C-6 is pseudoaxial. Therefore, comparing endo and exo transition states of triene (184) can sometimes allow us to predict products from IMDA reactions (Scheme 63).

\[ \text{E,E,E-triene (184)} \]

\[ X = \text{CO}_2\text{Et} \]

**Scheme 63.** Endo and exo products 186 and 188 from IMDA reactions

The Shing group also reported the synthesis of (-)-oblongolide by the IMDA reaction.⁷ They also showed similar results for stereoselectivity controlled by a methyl group at C-6 (Schemes 64 and 65)
Scheme 64. Bicyclic compounds from the IMDA reaction in the thermal condition by the Shing group

Scheme 65. Bicyclic compounds from the IMDA reaction in the thermal condition by the Shing group

Based on their results, methyl group at C6 would play an important role to control stereoselectivity of bicyclic structures from IMDA reactions.
In addition, there are other examples of controlling endo and exo transition states to obtain desired products by the transannular Diels-Alder (TADA) reaction. TADA reactions can produce a tricycle 197 from a macrocycle 196. The stereochemistry of the tricycles can be predicted and controlled by geometry of double bonds and substituents of macrocycles (Scheme 66).

**Scheme 66.** Transannular Diels-Alder reaction (TADA)

The Toró group investigated a stereocontrol of TADA reactions and showed syntheses of bicyclic cores. In macrocycles, both exo transition states are sterically prohibited and only endo transition conformations can be applied to provide products. As expected, two endo products (199 and 200) from 198 were isolated, but the major product was 200 (Scheme 67). The endo product 204 was produced from 203 (Scheme 68). The results were a little surprising because the -OTBS at C3 and the methyl group at C4 of 198 and 204 would be axial in a transition state TS-2 and TS-4 to product 200 and 204. This experiment demonstrated that the steric effects of the substituent -OTBS and methyl groups are not enough to control a stereoselectivity of products and they suggested -COOMe group and -CN group would prefer to be inside of boat-like conformation.
Scheme 67. Bicyclic cores 199 and 200 produced by the TADA reaction in thermal condition by the Toró group

Scheme 68. Bicyclic cores 202 and 204 produced by TADA reactions with Et₂AlCl by the Toró group
The Shing group displayed usefulness of TADA reactions in the synthesis of (-)-oblongolide from (E,E,E)-macrocyle (205) in 1995.\textsuperscript{7b} This triene gave the only bicyclic core 206 from the macrocycle (205) by endo-mode cyclization (Scheme 69).

\begin{center}
\textbf{Scheme 69.} A synthesis of a backbone of (-)-oblongolide from a (E,E,E)-macrocycle (205) by a TADA reactions
\end{center}

The Nakada group demonstrated a synthesis of (+)-phomopsidin from (E,Z,E)-triene 207 and 210 by the TADA reaction (Scheme 70).\textsuperscript{10} The only difference between 207 and 210 is the stereochemistry of the OTIPS groups. The major products were 209 and 211 in spite of axial hydroxyl and methyl groups in transition states.
Scheme 70. Bicyclic cores and proposed transition states by the TADA reaction by the Nakada group

These syntheses clearly demonstrate that the bicyclic cores of natural products can be constructed by Diels-Alder reactions and that stereoselectivity would be determined by various factors including the preference for an equatorial position of substituents and the geometry of double bonds of macrocycles.
3.1.3. A new synthetic approach to a key core of Alchivemycin A (168)

In intramolecular Diels-Alder (IMDA) reactions, trans-fused products have been produced predominately in many cases, but cis-fused products can be obtained from proper precursors in thermal reaction conditions. To construct a key moiety of Alchivemycin A (168), we also need to prepare cis-fused rings and control transition states to prohibit trans-fused products, so three trienes (213, 215, and 216) were designed to investigate possible precursors and reaction conditions to produce a moiety of Alchivemycin A (168) by IMDA or TADA reactions (Scheme 71).

\[
\text{(E,E,E)-triene (213)} \quad \leftrightarrow \quad \text{214} \quad \rightarrow \quad \text{(E,E,Z)-triene (215)}
\]

\[
\text{(E,E,E)-triene (216)}
\]

**Scheme 71.** Designed precursors to investigate IMDA and TADA reactions

In addition, dienes 217 can be common precursors to prepare three trienes (213, 215, and 216) (Scheme 72).
Scheme 72. Retrosynthetic analyses of trienes (213, 215, and 216)

We believed that dienes 217 can be prepared by cross coupling reactions\(^\text{11}\) (e.g. Negishi and Suzuki - Miyaura coupling reactions) from known compounds 219\(^\text{12}\) and 220\(^\text{13}\) (Scheme 73).

Scheme 73. Retrosynthetic analysis of the diene 213
Further, after investigation of three trienes (213, 215, and 216), the next triene will be other macrolactons like a (E,Z,E)-triene 221 (Scheme 74).

Scheme 74. The Structure of the (E,Z,E)-triene (221)
3.2. Result and Discussion

3.2.1. Synthetic approach to precursors of IMDA and TADA reactions

To efficiently investigate precursors to prepare a target structure 214 by the IMDA reaction, the (E,E,E)-triene 213, the (E,E,Z)-triene 215, and the macrolactone 216 were prepared as racemic mixtures.

The left and the right pieces were prepared by known procedures. First, an iododiene 225 was synthesized by the literature method.\textsuperscript{12-13} Alkyne 223 was treated with catecholborane and water to generate boronic acid 224. The treatment of 224 with I\textsubscript{2} and NaOH solution produced the iodo alcohol 225 as a left piece (Scheme 75).

\begin{center}
\begin{tikzpicture}
    \node[reactor] (a) {OH \textasciitilde \textasciitilde \textasciitilde \textasciitilde} edge[reaction] node[near start, above] {1) Catecholborane} edge[reaction] node[near end, below] {2) H\textsubscript{2}O, 54 \%} (b);
    \node[reactor] (c) at (2.5,0) {OH \textasciitilde \textasciitilde \textasciitilde \textasciitilde} edge[reaction] node[near start, above] {3 N NaOH} edge[reaction] node[near end, below] {I\textsubscript{2}, Et\textsubscript{2}O, 57 \%} (d);

    \node at (a) {223};
    \node at (b) {224};
    \node at (c) {225};

    \draw[arrow] (a) -- (b);
    \draw[arrow] (b) -- (c);
    \draw[arrow] (c) -- (d);
\end{tikzpicture}
\end{center}

\textbf{Scheme 75.} Preparation of the iododiene 225

Next, we synthesized an iodide 233. A diester 226 was treated with a bromoester 227 to produce a triester 228, which was subject to hydrolysis with acid and lactonization with acetic anhydride to give an anhydride mixture. It was treated with DIPEA in EtOAc and recrystallized at -20 °C to generate a meso compound 230 as a white solid.\textsuperscript{14,15} Reduction with lithium aluminium hydride provided diol 231 \textsuperscript{16}. Finally, the selective protection of the diol 231 with TBSCl gave the racemate 232 at low temperature\textsuperscript{17}, which was subjected to Appel type reaction to afford the corresponding right piece 233\textsuperscript{18}. Herein, if we use an enzyme and vinyl acetate, it will provide an acetate protected alcohol from the diol 231 as an enantiomer (Scheme 76).\textsuperscript{16,19}
After preparing precursors \((224, 225\) and \(233\)), we examined the Negishi and Suzuki-Miyaura coupling reactions to obtain a common precursor \(234\) (Scheme 77).

**Scheme 76.** Preparation of the iodo alkane \(233\)

**Scheme 77.** Preparation of the common precursor \(234\)
There are a few examples to show sp\(^3\) - sp\(^2\) cross coupling reactions, so we decided to do model tests with a commercially available iodo alkane 235 instead of the right piece iodide 233 because left pieces 224 and 225 are easily prepared by one or two steps, but the right piece 233 demands six steps.

Firstly, Suzuki-Miyaura coupling reaction with Ni(COD)\(_2\) catalyst developed by the Fu group\(^{20}\) was tested with 235, but in spite of several trials, we did not isolate any product from this reaction conditions (Scheme 78).

![Scheme 78](image)

**Scheme 78.** The model test by Suzuki coupling reaction with Ni(COD)\(_2\) catalyst

Next, Negishi coupling\(^{21}\) was applied and we could isolate a desire product 236 in 37 % yield (Scheme 79). However, it demanded the excess amount of the iodo alkane 235 (more than 2 equivalent of dienol 225) to produce 236 and the isolated yield was not high.

![Scheme 79](image)

**Scheme 79.** The model test by Negishi coupling reaction

Finally, diene 236 was also produced by Suzuki-Miyaura coupling reaction\(^{22}\) with 9-OMe-9-BBN. However, inseparable by-products were generated (Scheme 80).
Scheme 80. The model test by Suzuki-Miyaura coupling reaction using 9-OMe-9-BBN

Although the product 236 included inseparable unknown products, this reaction gives more advantages that the excess amount of the iodo alkane 235 can be used and the reaction condition is mild (9-BBN complex with 235 is not sensitive for moisture). Therefore, this reaction condition was applied to our real substituents 225 and 233. It gave us 234 and concomitant impurities (Scheme 81).

Scheme 81. Preparation of 234 by Suzuki-Miyaura coupling reaction using 9-OMe-9-BBN

After the alcohol protection of 234 with acetate, we could remove almost all of impurities from coupling reactions. After deprotection of TBS group, we prepared an alcohol 238, which was subjected to Dess-Martin oxidation to give the aldehyde 239 (Scheme 82).
Scheme 82. Preparation of the aldehyde 239

From the aldehyde 239, the (E,E,E)-triene 242 and the (E,E,Z)-triene 243, two precursors of IMDA reactions, were synthesized by Wittig reaction and the Still-Gennari olefination (Scheme 83).

Scheme 83. Preparation of the (E,E,E)-triene 242 and the (E,E,Z)-triene 243

On the other hand, the macrocyclic lactone (216) was generated by an intramolecular Horner-Wadsworth-Emmons reaction. Suzuki-Miyaura coupling gave the same alcohol 234, followed by
treatment with diethylphosphonoacetic acid\textsuperscript{10a} 244 to produce the phosphorane 245. Deprotection of TBS group followed by Dess-Martin oxidation gave an aldehyde 247, which was subjected to Horner-Wadsworth-Emmons reaction to provide a macrocyclic lactone (216) (Scheme 84).

\begin{align*}
\text{HO} & \quad \text{TBSO} \\
\text{234} & \quad \begin{array}{c}
\text{EtO} \quad \text{PO} \\
\text{OEt} & \text{244}
\end{array} \\
\text{CBr}_4, \text{PPH}_3, \text{py, CH}_2\text{Cl}_2 & \quad \begin{array}{c}
\text{RO} \\
\text{TBSO} \\
\text{245}
\end{array}
\end{align*}

\begin{align*}
\text{TBAF} & \quad \text{RO} \\
\text{THF} & \quad \text{246} \\
\text{246} & \quad \begin{array}{c}
\text{HO} \\
\text{Dess-Martin} \\
\text{78 \%}
\end{array} \\
\text{RO} & \quad \text{O} \\
\text{247}
\end{align*}

\begin{align*}
\text{LiCl, DIPEA} & \quad \text{AcCN, rt, 42 \%}
\end{align*}

Macrolactone 216

\textbf{Scheme 84.} Preparation of the macrolactone 216

\subsection*{3.2.2. Investigation of an intramolecular Diels-Alder (IMDA) reactions}

From the (E,E,E)-triene 242, the IMDA reaction gave us an inseparable mixture of two diastereomers 248 under thermal conditions (Scheme 85). After the IMDA reaction, we isolated one spot on TLC by a silica gel column chromatography, but the \textsuperscript{1}H NMR spectrum showed two strong methyl peaks of acetate groups, so we believed that it was a mixture 248 of diastereomers.
Scheme 85. Two diastereomers produced by the IMDA reaction

From the IMDA reaction of (E,E,E)-triene 242, we expected 4 possible diastereomers (Scheme 86).

Scheme 86. Proposed transition states and products of the IMDA reaction from the (E,E,E)-triene 242

We had tried to separate the mixture 248 to identify each diastereomer. After deprotection of the alcohols, we could separate two products from the mixture 248. One of products was a lactone 255 and we believe that after hydrolysis, an alcohol 253 spontaneously underwent the
lactonization reaction\textsuperscript{7b} to provide 255. 1D NOE and COSY spectrum data explained the relative stereochemistry of the lactone 255, so we believe that 255 is a trans-fused bicyclic product from the endo chair transition state, which is also energetically favored. The stereochemical assignment of another product was established by \textsuperscript{1}H, \textsuperscript{13}C, COSY, NOESY, and HMQC and we confirmed that it was the cis-fused product 254 from an exo chair transition state. Therefore, we could confirm that the mixture 248 gave two products (249 and 251) and we elucidated the relative stereochemistry of these compounds (Scheme 87). The preferred equatorial position of both methyl groups would be a key factor to control a stereoselectivity of 253 and 254.

Scheme 87. The lactone 255 and the alcohol 254 separated by deprotection of acetate of 248

The (E,E,Z)-triene (243) was also subjected to thermal conditions and it appeared to give only one product 256 because a methyl group of acetate showed one peak in the \textsuperscript{1}H NMR spectrum data (Scheme 88).
Scheme 88. Bicyclic core 243 from the (E,E,Z)-triene 256 by the IMDA reaction

From the IMDA reaction of (E,E,Z)-triene 236, we also expected four possible diastereomers (Scheme 89)

Scheme 89. Proposed transition states and products of the IMDA reaction from the (E,E,Z)-triene (243)
The product 256 had few impurities. We removed the acetate group and obtained one product 261 (Scheme 90). Its structure was assigned by $^1$H, COSY, and 1D NOE. This product 261 would be a trans-fused ring produced from 257 (See Scheme 89) through the endo transition state because of the preferred equatorial position of both methyl groups and steric hindrance between the methyl group at C8 and -CH$_2$OAc.

![Chemical structure](image)

**Scheme 90.** The alcohol 261 by separated by deprotection of acetate of 256
3.3. Conclusion

In conclusion, the valuable intermediate 234 was efficiently prepared by the Suzuki-Miyaura coupling reaction. From 234, two model compounds 242 and 243 were successfully synthesized and examined to give bicyclic cores by the intramolecular Diels-Alder reactions. The (E,E,E)-triene 242 produced the inseparable mixture but after deprotection of alcohols, we could isolate products 254 and 255. From these compounds, we could assign relative stereochemistry to the cycloaddition products. In addition, only one diastereomer 256 was synthesized from the (E,E,Z)-triene 243 and we also confirmed a stereochemistry of 243 after deprotection of an acetate group. Although the stereochemistry of the bicyclic cores was consistent with expectations, none had the relative stereochemistry required for alchivemycin A (168). We began the preparation of the macrolactone 216 and it will be examined soon. Control the stereochemistry of bicyclic cores of alchivemycin A (168) will be supported by future experiments.
3.4. Reference


(16) (a) Prusov, E.; Röhm, H.; Maier, M. E.: Chemoenzymatic Synthesis of the C10-C23 Segment of Dictyostatin, *Org. Lett.* 2006, 8, 1025 (b) Schmidt, Y.; Lehr, K.; Breuninger,


3.5. Experimental section

General Information

All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum -supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å, 230-400 mesh, surface area 500-600 m²/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH₂Cl₂ on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ¹H), a Varian Inova-500 (500 MHz for ¹H and 125 MHz for ¹³C), Bruker-400 (400 MHz for ¹H and 100 MHz for ¹³C), Varian Inova-400 (400 MHz for ¹H and 100 MHz for ¹³C), or Gemini-2300 (300 MHz for ¹H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.
**Boronic acid 225.** To the alcohol 223 (484 mg, 5.89 mmol) was added catecholborane (1.484 g, 12.37 mmol) at 0 °C under argon, allowing release for hydrogen. The reaction mixture was stirred for 2 h. It was stored at -20 ~ 25 °C for 16 h. The cold water (12 mL) was added and stirred for 4.5 h. The resulting solution was saturated with NaCl and extracted with EtOAc (10 mL X 5). The combined organic solution was dried over MgSO$_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 1 to CH$_2$Cl$_2$ : MeOH = 95 : 5) to produce 224 (408 g, 54 %). To a stirred solution of 224 (408 mg, 3.19 mmol) in ethyl ether (10 mL) was added 3N NaOH at 0 ° and then I$_2$ (891 mg, 3.52 mmol) solution in ethyl ether (10 mL). The reaction mixture was slowly warmed to rt and stirred for 1 h and quenched by addition of saturated aq. Na$_2$S$_2$O$_3$ solution. The aqueous layer was extracted with (6 mL X 3) and the combined organic layer was dried over MgSO$_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 3) to give 225 (381 mg, 57 %) as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.05 (dd, $J$ = 10.5, 1H), 6.36 (dd, $J$ = 14.4, 0.6 Hz, 1H), 6.20 (dd, $J$ = 15.3, 10.5 Hz, 1H), 5.86 (dt, $J$ = 14.4, 5.4 Hz, 1H), 4.17 (t, $J$ = 4.8 Hz, 2H). Spectroscopic properties were in agreement with literature values.

**Diacid 229.** To ethanol (28 mL) was added Na (1.055 g, 44.89 mmol) and the resulting solution was heated to reflux. Malonate 226 (7.959 g, 45.23 mmol) was bromide 227 (9.121 g, 46.7 mmol) were added and stirred at 90 °C (an oil bath temperature). After 5 h, the reaction mixture was cooled to rt and concentrated under reduced pressure. Ethyl ether (25 mL) and water...
(4 mL) were added and the aqueous layer was extracted with ethyl ether (15 mL X 3). The combined organic layer was dried over MgSO4 and concentrated under reduced pressure to give a crude product the triester 228 (11.09 g). Conc. HCl was added to 228 (11.09 g) and stirred at 100 °C for 8 h and stored at -25 °C for 1 day. A white solid was filtered and dissolved in ethyl ether. The ether layer was dried over MgSO4 and concentrated under reduced pressure to give the white solid 229 (3.07 g). The filtrate was extracted with ethyl ether and the combined organic layer was concentrated under reduced pressure. Hexane was added and stored at -25 °C for 1 day. A white solid was filtered and followed the same procedure above to give the 229 (0.397 g) as white solid. The white solids 229 were combined (3.46 g, 48 % for 2 steps). $^1$H NMR (300 MHz, CDCl3) δ 2.71 (sext, $J = 6.9$ Hz, 1H), 2.54 (m, 1H), 1.97 (dd, $J = 5.7, 6.3$ Hz, 1H), 1.21 (d, $J = 5.7$ Hz, 3H) 1.20 (d, $J = 6.0$ Hz, 3H). Spectroscopic properties were in agreement with literature values.$^{14-15}$

Diol 231.$^{14,15-16}$ A stirred solution of diacid 229 (3.39 g, 21.16 mmol) in acetic anhydride (10 mL) was heated to 115 °C (an oil bath temperature). After 24 h, the reaction mixture was cooled to rt and then acetic acid and acetic anhydride were distilled to give a white solid (2.6 g). EtOAc (3.1 mL) and DIPEA (0.6 mL) were added and stirred at rt for 14 h. The mixture was cooled to -30 °C for 1 day. The white solid was filtered and washed with EtOAc (pre-cooled to -30 °C). The white solid 230 (580 mg) was obtained. The filtrate was concentrated under reduced pressure. The residue was added EtOAc and recrystallized again to produce 230 (610 mg). The filtrate was reused to obtain 230. Crystallized white solid 230 (1.19 g, 40 %) from$^{1}$st and $^{2}$nd recrystallization.$^ {1}$H NMR (500 MHz, CDCl3) δ 2.83 - 2.63 (m, 2H), 2.06 (dt, $J = 13.6, 5.3$ Hz, 1H), 1.69 - 1.58 (m, 1H), 1.37 (dd, $J = 6.9, 0.5$ Hz, 6H). To stirred solution of 230 (658 mg, 4.63 mmol) in Et2O was added LiAlH4 (351 mg, 9.25 mmol) and stirred for 1 h at rt. To the resulting mixture was added Et2O (15 mL) and water (3 mL) carefully and then 10 % NaOH (1.2 mL). The mixture was filtered through Celite and Et2O was added. The organic layer was concentrated under reduced
pressure to give a crude product 231 (454 mg, 74 %). \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.93 (ddt, \( J = 17.3, 10.4, 5.7 \) Hz, 1H), 5.45 - 5.39 (m, 1H), 5.28 (dq, \( J = 17.2, 1.7 \) Hz, 1H), 5.18 (dq, \( J = 10.4, 1.4 \) Hz, 1H), 4.98 (d, \( J = 1.4 \) Hz, 1H), 4.85 (s, 1H), 4.07 - 3.94 (m, 6H), 2.70 (dd, \( J = 11.6, 3.1 \) Hz, 1H), 2.46 - 2.24 (m, 3H), 2.11 (ddd, \( J = 34.8, 14.4, 9.8 \) Hz, 2H), 1.92 (dt, \( J = 13.0, 6.9, 3.4 \) Hz, 1H), 1.68 (d, \( J = 1.3 \) Hz, 3H), 1.17 - 1.04 (m, 13H), 0.14 (s, 9H). Spectroscopic properties were in agreement with literature values.\(^{14}\)

\[ \text{HO--OTBS} \rightleftharpoons \text{HO--OTBS} \]

**Iodide 233.** To a stirred solution of diol 231(267 mg, 2.017 mmol) in THF (4 mL) was added n-BuLi (1.34 mL, 2.14 mmol, 1.6 M in hexane) dropwise at -78 °C and stirred for 30 min. TBS-Cl solution in THF (2 mL) was added dropwise at -78 °C for 40 min and stirred for 4 h at -78 °C and stored at -30 °C for 14h. It was quenched with saturated aq. NH\(_4\)Cl (2.5 mL) and Ethyl ether (5 mL) were added. The aqueous layer was extracted with ethyl ether (1 mL X 3). The combined organic phase was washed with brine and water and dried over MgSO\(_4\). After concentration, the crude product was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to provide 232\(^{17}\) (427 mg, 86 %) and the recovered starting 231 (38 mg, 14 %). \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.46 - 3.32 (m, 4H), 2.01 (s, 1H), 1.69 (quint, \( J = 5.6 \) Hz, 2H), 1.41 (quint, \( J = 6.8 \) Hz, 1H), 0.92 (d, \( J = 6.8 \) Hz, 3H), 0.89 - 0.87 (m, 13H), 0.02 (s, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 68.3, 68.0, 37.3, 33.2, 33.2, 25.9, 18.3, 17.8, 17.7, -5.4. To a stirred solution of iodine (520.6 mg, 2.051 mmol) in CH\(_2\)Cl\(_2\) (10 mL) were added imidazole (151.3 mg, 2.222 mmol) and PPh\(_3\) (538 mg, 2.051 mmol) at 0 °C under argon. The reaction mixture was stirred for 10 min, and then the solution of 232 (419.3 mg, 1.701 mmol) in CH\(_2\)Cl\(_2\) (4 mL) was added and the syringe was rinsed with CH\(_2\)Cl\(_2\) (1 mL). The resulting mixture was warmed to rt and stirred for 2 h. It was concentrated under reduced pressure and purified with silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to give a iodo alkane 233\(^{18}\) (489 mg, 80 %). \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 3.44 (dd, \( J = 9.6, 5.7 \) Hz, 1H), 3.35 (dd, \( J = 9.6, 6.9 \) Hz, 1H), 3.26 (dd, \( J = 9.6, 3.9 \) Hz, 1H), 3.10 (dd, \( J = 6.9, 6.0 \) Hz, 1H), 1.75 - 1.15 (m, 3H), 1.06 - 0.79 (m, 16H), 0.893 (s, 6H). Spectroscopic properties were in agreement with literature values.\(^{17-18}\)
Diene 237. To a stirred solution of 233 (16.2 mg, 0.0455 mmol) was Et₂O (0.6 mL) was added B-OMe-9-BBN (0.21 mL, 0.21 mmol) at -78 °C under argon and stirred for 10 min. t-BuLi (0.13 mL, 0.21 mmol, 1.6 M pentane) was added and stirring for 15 min at -78 °C. THF (0.9 mL) was added dropwise and stirring for 20 min. The resulting mixture was slowly warmed to rt and stirred for 2.5 h. To the solution were added 3 M Cs₂CO₃ (0.05 mL, 0.16 mmol), PdCl₂(dppf)Cl₂ (3.7 mg, 0.0046 mmol), diene 225 (13.4 mg, 0.0636 mmol) solution in DMF (0.9 mL), and AsPh₃ (2.1 mg, 0.0068 mmol) for 36 h. It was quenched with saturated aq. NaCl (1.0 mL) and Et₂O (3 mL) was added. The resulting mixture was extracted with Et₂O (3 mL X 3) and the combined organic phase was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to provide the crude 234 (25.3 mg). ¹H NMR (500 MHz, CDCl₃) δ 6.22 (dd, J = 15, 10.5 Hz, 1H), 6.03 (dd, J = 15, 10.5 Hz, 1H), 5.71 (m, 2H), 4.17 (m, 2H), 3.43 (dd, J = 9.5, 5 Hz, 1H), 3.32 (dd, J = 9.5, 6.5 Hz, 1H), 2.11 (m, 1H), 1.87 (m, 1H), 1.58 - 1.72 (m, 2H), 1.34 (quint, J = 6.5 Hz, 1H), 1.26 (m, 2H), 0.89 (s, 9H), 0.88 (m, 6H), 0.03 (s, 6H); IR (neat) νmax 3377.1, 2925.3, 2858.7 cm⁻¹. To a stirred solution of 234 (25.3 mg) in CH₂Cl₂ was added Et₃N (10.6 mg, 0.105 mmol), DMAP (1.0 mg, 0.008 mmol), and acetic anhydride (9.1 mg, 0.089 mmol) and stirred for 14 h at rt. It was quenched with saturated aq. NaHCO₃ and water was added. The resulting mixture was extracted with CH₂Cl₂ (3 mL X 2) and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 20) to provide the pure 237 (10 mg, 60 % for 2 steps). ¹H NMR (500 MHz, CDCl₃) δ 6.26 (dd, J = 15.0, 10.0 Hz, 1H), 6.02 (dd, J = 15.0, 10.0 Hz, 1H), 5.61 - 5.75 (m,
2H), 4.57 (d, J = 5.0 Hz, 2H), 3.43 (dd, J = 9.8, 5.4 Hz, 1H), 3.32 (dd, J = 9.7, 6.5 Hz, 1H), 2.15 - 2.03 (m, 4H), 1.87 (dt, J = 14.5, 7.6 Hz, 1H), 1.73 - 1.55 (m, 3H), 1.34 (dt, J = 13.7, 6.8 Hz, 1H), 1.25 (s, 1H), 0.95 - 0.91 (m, 1H), 0.89 (s, 9H), 0.86 (d, J = 5.0 Hz, 6H), 0.03 (s, 6H); IR (neat) νmax 2956, 2928, 2856, 1744 cm⁻¹.

**Alcohol 238.** To a stirred solution of 237 (10 mg, 0.027 mmol) in THF (1.0 mL) was added TBAF (0.05 mL, 0.05 mmol, 1.0 M in THF). The reaction mixture was stirred for 3 h at rt and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to provide 238 (6.4 mg, 94 %). 1H NMR (500 MHz, CDCl3) δ 6.29 - 6.24 (m, 1H), 6.05 - 6.00 (m, 1H), 5.74 - 5.61 (m, 2H), 4.57 (d, J = 6.5 Hz, 2H), 3.51 (dd, J = 10.5, 5.5 Hz, 1H), 3.38 (dd, J = 10.5, 7.0 Hz, 1H), 2.15 - 2.10 (m, 1H), 2.06 (s, 3H), 1.89 (quint, J = 7.0 Hz, 1H), 1.71 (sext, J = 6.5 Hz, 1H), 1.66 - 1.59 (m, 1H), 1.37 - 1.28 (m, 2H), 0.99 - 0.94 (m, 1H), 0.92 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H).

**Aldehyde 239.** To a stirred solution of 239 (6.4 mg, 0.027 mmol) in CH2Cl2 (4.0 mL) was added Dess-Martin periodinane (18.2 mg, 0.042 mmol). The reaction mixture was stirred for 14 h at rt and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to provide 239 (5.1 mg, 79 %). 1H NMR (500 MHz, CDCl3) δ 9.57 (d, J = 2.5 Hz, 1H), 6.26 (dd, J = 15.0, 10.0 Hz, 1H), 6.04
(dd, \( J = 15.0, 10.0 \) Hz, 1H), 5.72 - 5.63 (m, 2H), 4.58 (d, \( J = 6.0 \) Hz, 2H), 2.41 - 2.48, (m, 1H), 2.13 - 2.08 (m, 1H), 2.07 (s, 3H), 2.02 - 1.92 (m, 1H), 1.77 - 1.71 (m, 1H), 1.65 - 1.59 (m, 1H), 1.21 - 1.11 (m, 1H), 1.09 (d, \( J = 7.5 \) Hz, 3H), 0.90 (d, \( J = 6.5 \) Hz, 3H).

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\text{(E,E,E)-triene 242. To a stirred solution of aldehyde 239 (10.9 mg, 0.046 mmol) in CH}_2\text{Cl}_2 (3.3 mL) was added 240 (71.8 mg, 0.206 mmol). The reaction mixture was stirred for 17 h and 240 (14.6 mg, 0.0419 mmol) was added more. After 3 h, the mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to provide 242 (12.2 mg, 87 %).}^{1}H \text{ NMR (300 MHz, CDCl}_3) \delta 6.78 (dd, \( J = 15.7, 8.5 \) Hz, 1H), 6.34 - 6.18 (m, 1H), 6.09 - 5.94 (m, 1H), 5.86 - 5.56 (m, 3H), 4.57 (dd, \( J = 6.7, 1.2 \) Hz, 2H), 4.25 - 4.10 (m, 2H), 2.49 - 2.33 (m, 1H), 2.14 - 1.84 (m, 6H), 1.61 (d, \( J = 3.0 \) Hz, 1H), 1.53 - 0.97 (m, 11H), 0.97 - 0.79 (m, 4H). IR (neat) \( \nu_{\text{max}} \) 2960, 2915, 1741, 1719 cm\(^{-1}\).

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\text{(E,E,Z)-triene 243. To a stirred solution of 241 (27.2 mg, 0.0794 mmol) in THF (1 mL) was added 18-crown-6 (24.5 mg, 0.0926 mmol) and cooled at 0 °C. To the reaction mixture was added dropwise KHMDS (0.08 mL, 0.08 mmol, 1 M in THF) and stirred at 0 °C. The mixture was cooled to -78 °C and aldehyde 239 (6.3 mg, 0.026 mmol) solution in THF (1 mL) was added dropwise and the syringe was rinsed with THF (0.05 mL). The resulting mixture was stirred for 1}
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h at -78 °C and stored at -25 °C for 15 h. It was quenched with saturated aq. NH₄Cl (0.5 mL) and EtOAc (3 mL) was added. The aqueous phase was extracted with EtOAc (3 mL X 2). The combined organic mixture was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to provide 242 (6.2 mg, 76 %). ¹H NMR (400 MHz, CDCl₃) δ 6.26 (dd, J = 15.6, 10.1 Hz, 1H), 6.10 - 5.84 (m, 2H), 5.82 - 5.58 (m, 3H), 4.57 (d, J = 6.6 Hz, 2H), 4.16 (qd, J = 7.2, 1.3 Hz, 2H), 3.65 (tt, J = 10.5, 5.3 Hz, 1H), 2.06 (d, J = 1.3 Hz, 4H), 1.94 (dq, J = 14.1, 6.7 Hz, 1H), 1.57 (d, J = 1.3 Hz, 1H), 1.44 (tq, J = 13.4, 7.4 Hz, 1H), 1.35 - 1.19 (m, 4H), 1.19 - 0.82 (m, 7H).

Phosphorane 245. To a stirred solution of the crude alcohol 233 (28.0 mg, 0.090 mmol) in CH₂Cl₂ were added pyridine (14.2 mg, 0.179 mmol), CBr₄ (44.6 mg, 0.134 mmol), PPh₃ (32.9 mg, 0.125 mmol), and acid 244 (21.0 mg, 0.108 mmol). The mixture was stirred for 18 h and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7 to 1 : 2) to provide 245 (17.5 mg, 60 %, b.r.s.m) and recovered 233 (9.4 mg). δ 6.27 (dd, J = 15.3, 10.4 Hz, 1H), 6.01 (dd, J = 15.2, 10.4 Hz, 1H), 5.76 - 5.58 (m, 2H), 4.64 (d, J = 6.7 Hz, 2H), 4.16 (m, 4H), 3.42 (dd, J = 9.6, 5.4 Hz, 1H), 3.33 (dd, J = 9.6, 6.8 Hz, 1H), 3.00 (d, J = 24, 2H), 2.13 - 2.07 (m, 1H), 1.90 - 1.83 (m, 1H), 1.70 - 1.57 (m, 3H), 1.34 (m, 7H), 0.90 (s, 9H), 0.87 (d, J = 1.6 Hz, 3H), 0.86 (d, J = 2.0 Hz, 3H), 0.2 (s, 6H). IR (neat) νmax 3419, 2956, 1738, 1443 cm⁻¹.
**Alcohol 246.** To a stirred solution of 245 (17.4 mg, 0.0355 mmol) in THF (1.5 mL) was added TBAF (0.09 mL, 0.09 mmol, 1.0 M in THF). The reaction mixture was stirred for 15 h at rt and it was concentrated under reduced pressure. The residue was purifed by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 2 to 1 : 1) to provide 246 (7.1 mg, 93 %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.29 (dd, $J = 15.2$, 10.4 Hz, 1H), 6.02 (dd, $J = 15.1$, 10.4 Hz, 1H), 5.68 (ddt, $J = 34.8$, 14.7, 7.0 Hz, 2H), 4.65 (d, $J = 6.7$ Hz, 2H), 4.17 (quint, $J = 7.3$ Hz, 4H), 3.53 - 3.37 (m, 2H), 2.98 (d, $J = 21.6$, 2H), 2.16 - 2.09 (m, 1H), 1.89 (dt, $J = 14.6$, 7.7 Hz, 1H), 1.79 - 1.61 (m, 2H), 1.43 (s, 3H), 1.34 (t, $J = 7.2$ Hz, 6H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H).

**Aldehyde 216.** To a stirred solution of 246 (5.3 mg, 0.014 mmol) in CH$_2$Cl$_2$ (2.0 mL) was added Dess-Martin periodinane (9.0 mg, 0.021 mmol). The reaction mixture was stirred for 5 h at rt and it was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 1) to provide 247 (4.1 mg, 78 %). To a stirred solution of 247 (4.1 mg, 0.011 mmol) in CH$_3$CN (10.0 mL) was added LiCl (10.0 mg, 0.229 mmol) and DIPEA (28.3 mg, 0.219 mmol). The reaction mixture was stirred. After 3 days, it was concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford 216 (1.0 mg, 42 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.76 (ddd, $J = 15.8$, 8.6, 1.8 Hz, 1H), 6.25 (t, $J = 12.9$ Hz, 3H).

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1H), 6.09 - 5.98 (m, 1H), 5.81 - 5.63 (m, 3H), 4.72 (dd, J = 13.5, 6.1 Hz, 1H), 4.61 (dd, J = 13.5, 5.9 Hz, 1H), 2.42 (s, 1H), 1.97 (q, J = 8.0 Hz, 1H), 1.43 (m, 2H), 1.15 - 0.97 (m, 4H), 0.91 (dd, J = 19.6, 6.3 Hz, 3H).

**Diastereomer mixture 248.** The solution of 242 (11.5 mg, 0.037 mmol) in toluene (3.7 mL) was heated to 150 °C for 20 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to afford the mixture 248 (8.4 mg, 73%).
Lactone 255 and alcohol 254. To a stirred solution of the mixture of 248 (8.4 mg, 0.027 mmol) in absolute EtOH (1.5 mL) was added K$_2$CO$_3$ (2.5 mg, 0.018 mmol). The reaction mixture was stirred for 11 h. It was quenched with saturated aq. NH$_4$Cl and Et$_2$O was added. The mixture was concentrated under reduced pressure. To residue was added CH$_2$Cl$_2$ and water. The organic layer was separated and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford the mixture 255 (2.9 mg, 35 % for 2 steps) and 254 (3.4 mg, 34 %).

255: $^1$H NMR (400 MHz, CDCl$_3$) δ 5.83 (dt, $J = 9.3$, 3.0 Hz, 1H), 5.64 (dt, $J = 9.3$, 2.8 Hz, 1H), 4.41 - 4.21 (m, 2H), 2.96 (ddt, $J = 8.4$, 5.8, 2.8 Hz, 1H), 2.72 - 2.62 (m, 1H), 1.94 - 1.84 (m, 1H), 1.78 - 1.64 (m, 2H), 1.55 (s, 5H), 1.41 (tdd, $J = 12.8$, 6.2, 4.2 Hz, 1H), 1.32 - 0.68 (m, 13H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.6, 139.1, 127.7, 71.6, 46.0, 44.9, 43.8, 40.8, 39.6, 38.4, 36.76, 32.2, 22.3, 20.1.; IR (neat) ν$_{max}$ 2915, 1765, 1456 cm$^{-1}$.

254: $^1$H NMR (400 MHz, CDCl$_3$) δ 5.67 - 5.53 (m, 2H), 4.15 (qd, $J = 7.1$, 4.7 Hz, 2H), 3.69 (dd, $J = 10.5$, 6.4 Hz, 1H), 3.50 (t, $J = 9.7$ Hz, 1H), 2.98 (t, $J = 2.4$ Hz, 1H), 2.77 (ddt, $J = 9.0$, 6.1, 2.8 Hz, 1H), 2.39 (s, 1H), 1.70 (td, $J = 13.3$, 12.7, 6.5 Hz, 2H), 1.63 - 1.46 (m, 6H), 1.33 - 1.12 (m, 5H), 0.95 (d, $J = 6.3$ Hz, 3H), 0.85 (d, $J = 6.5$ Hz, 3H), 0.69 (q, $J = 11.8$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.2, 133.1, 125.4, 65.4, 60.5, 44.4, 42.9, 41.2, 40.0, 38.7, 32.6, 30.1, 27.8, 22.5, 20.2, 14.2.

Difference NOE chart for compound 255
<table>
<thead>
<tr>
<th>Inverted peak</th>
<th>Enhanced peaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.68 ppm</td>
<td>2.95 ppm, 1.08 ppm</td>
</tr>
<tr>
<td>2.95 ppm</td>
<td>5.66 ppm, 4.38 ppm, 1.70 ppm</td>
</tr>
<tr>
<td>4.37 ppm</td>
<td>2.68 ppm</td>
</tr>
</tbody>
</table>

Difference NOESY chart for compound **254**

Diene **261.** The solution of **243** (5.0 mg, 0.016 mmol) in toluene (3 mL) was heated to 150 °C for 21 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 7) to afford the impure **248** (3.5 mg). Without further purification, it was used to the next reaction. To a stirred solution of the mixture of **248** (3.5 mg) in absolute EtOH (2.5 mL) was added K$_2$CO$_3$ (2.0 mg, 0.014 mmol). The reaction mixture was stirred for 11 h. It was quenched with saturated aq. NH$_4$Cl and Et$_2$O was added. The mixture was concentrated under reduced pressure. To
residue was added CH₂Cl₂ and water. The organic layer was separated and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford 261 (2.0 mg, 46 % for 2 steps). ¹H NMR (400 MHz, CDCl₃) δ 5.66 - 5.63 (d, J = 10.0 Hz, 1H), 5.53 - 5.49 (dt, J = 10.0, 3.0 Hz, 1H), 4.22 - 4.02 (m, 2H), 3.65 (d, J = 11.1 Hz, 1H), 3.46 (t, J = 9.6 Hz, 1H), 3.06 (d, J = 3.9 Hz, 1H), 2.58 (s, 1H), 2.08 (t, J = 12.0 Hz, 1H), 1.75 (ddt, J = 23.4, 13.2, 3.0 Hz, 2H), 1.47 (d, J = 33.5 Hz, 13H), 1.33 - 1.13 (m, 4H), 1.04 - 0.82 (m, 8H), 0.79 - 0.61 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 135.3, 123.6, 65.6, 60.0, 45.3, 44.4, 41.9, 41.3, 41.0, 36.7, 33.7, 32.2, 30.3, 22.4, 19.4, 14.3.

Difference NOE chart for compound 255

<table>
<thead>
<tr>
<th>Inverted peak</th>
<th>Enhanced peaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.58 ppm</td>
<td>5.55 ppm, 3.69 ppm, 3.66 ppm</td>
</tr>
<tr>
<td>3.06 ppm</td>
<td>1.02 ppm</td>
</tr>
<tr>
<td>2.08 ppm</td>
<td>5.65 ppm, 1.55 ppm</td>
</tr>
</tbody>
</table>
Part IV.

The Formal Synthesis of (-)-Englerin A (267)

by RRCM and Etherification
4.1. Introduction

4.1.1. Background

Nature is a major source for useful medical products. Many natural products have been isolated from various natural sources ranging from plants to marine sponges; some have been developed as valuable drugs such as aspirin, penicillin and taxol (262) to treat a wide spectrum of human diseases. Throughout the ages, plants, in particular, have been major natural sources for important drugs. For example, the record for Egyptian medicine, which was written in “Ebers Papyrus”, shows that the Egyptians used more than 700 drugs from natural sources, mostly plant origins, to treat many diseases around 1500 BCE. Until now a number of natural products from plants have been used without modification.\(^1\) Although the number of natural compounds isolated from medical plants have been rapidly decreasing since early 1981’s, they have played a pivotal role in the development of valuable drugs such as taxol (262), camptothecin (263), and podophyllotoxin (264) (Figure 7).\(^2\)

![Chemical structures of Taxol, Camptothecin, and Podophyllotoxin](image)

**Figure 7.** Valuable drugs from plant origin sources
Recently, new guaiane sesquiterpenes such as (+)-oriental F (265), (±)-pubinernoid B (266), (-)-englerin A (267) and (-)-englerin B (268) were reported (Figure 8).

Among them, (-)-englerin A (267) and B (268) were firstly isolated from root and stem bark of *Phyllanthus engleri* that is a very popular plant in East Africa, particularly Tanzania and Zimbabwe by the Beutler group in 2008. Extraction yields from the plant, *Phyllanthus engleri* are not high; the yields were 0.24% (2.4 g/kg) from root bark and 0.12% (1.2 g/kg) from stem bark. (-)-Englerin A (267) displayed excellent biological activities to inhibit the growth of kidney cancer cell lines. The Beutler group also demonstrated their structures and relative stereoconfigurations of (-)-englerin A (267) and B (268). They have tricyclic cores, which have also oxa-cyclic substructures and show interesting structure-activity relationship (SAR). Englerin A (267) and B (268) have almost the same structure except a substituent at C9 position (Figure 8), but Englerin B (268) showed low activity and selectivity for renal cancer cells. In 2009, Christmann and co-workers synthesized unnatural (+)-englerin A and confirmed an absolute
stereochemistry of (-)-englerin A (267). Various research groups have also reported efficient strategies to provide (-)-englerin A (267) and its analogues.

Our research group has been also interested in this unique structure and excellent bioactivity and it allowed us to invent a new process to obtain the key core structure of (-)-englerin A (267). We have believed that it would contribute to study preliminary structure-activity relationship (SAR) and launch a new kidney cancer drug.

4.1.2. Biological activities of (-)-englerin A (267) and analogues of (-)-englerin A (267)

The biological activity and selectivity of (-)-englerin A (267) has attracted many scientists because the medical treatment of renal cancer is very difficult and challenging task and there are no satisfactory medicines. Although there are some medicines such as bevacizumab (269), sunitinib\(^8\) (270), and sorafenib (271)\(^9\) (Figure 9) to treat renal cancers, they have serious side effects or no medicinal effects.\(^5\)

![Chemical structures of Sunitinib (270) and Sorafenib (271)]

**Figure 9.** Drugs for kidney cancers

The Beutler group reported biological tests of (-)-englerin A (267) that showed high selective and potent for kidney cancer cell line panel at concentrations under 20 nM (Table 6).
Table 6. Renal Cancer Cell Growth Inhibition Data of (-)-englerin A (267)

<table>
<thead>
<tr>
<th>Renal cell line</th>
<th>(-)-Englerin A (267)</th>
<th>Taxol (262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>786-0</td>
<td>&lt; 0.01</td>
<td>0.034</td>
</tr>
<tr>
<td>A498</td>
<td>&lt; 0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>ACHN</td>
<td>&lt; 0.01</td>
<td>0.65</td>
</tr>
<tr>
<td>CAKI-1</td>
<td>15.5</td>
<td>0.35</td>
</tr>
<tr>
<td>RXF-393</td>
<td>0.011</td>
<td>0.041</td>
</tr>
<tr>
<td>SN12C</td>
<td>0.087</td>
<td>0.018</td>
</tr>
<tr>
<td>TK-10</td>
<td>15.5</td>
<td>0.11</td>
</tr>
<tr>
<td>UO-31</td>
<td>&lt; 0.01</td>
<td>0.45</td>
</tr>
</tbody>
</table>

(Mean GI50 in μM)

In addition, (-)-englerin A (267) and B (268) displayed impressive structure-activity relationship (SAR). Therefore exploring the SAR will be helpful to find and develop a new kidney cancer drug. Many research groups have prepared various analogues of (-)-englerin A (267) and tried to elucidate SAR.

Nicolaou and co-workers in 2010 reported biological studies for (±)-englerin A (272) and (±)-analognes against cancer cell lines including breast (MCF-7), lung (NCI-H460), and renal (ACHN, A498, and UO31).10 (±)-Englerin A (272) displayed high potency and selectivity toward renal cancer cells. (±)-Englerin B (273), (±)-englerin B acetate (274), and (±)-analognes showed no or little activities (Figure 10) (Table 7).
Figure 10. Structures of (±)-englerin B acetate (274), hydroxy acetate (275), TBS-ether (276), and hydrogenated englerin A (277)

Table 7. Cytotoxicity of (±)-Englerin A (272) and Englerin A analogues

<table>
<thead>
<tr>
<th>Compound</th>
<th>MCF-7</th>
<th>NCI-H460</th>
<th>ACHN</th>
<th>A498</th>
<th>UO31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>0.066 ± 0.004</td>
<td>0.010 ± 0.000</td>
<td>0.072 ± 0.006</td>
<td>0.243 ± 0.062</td>
<td>0.693 ± 0.221</td>
</tr>
<tr>
<td>Taxol</td>
<td>0.007 ± 0.001</td>
<td>0.006 ± 0.001</td>
<td>0.076 ± 0.008</td>
<td>0.078 ± 0.006</td>
<td>0.721 ± 0.146</td>
</tr>
<tr>
<td>(±)-Englerin A (272)</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>0.113 ± 0.071</td>
<td>0.045 ± 0.004</td>
<td>0.037 ± 0.005</td>
</tr>
<tr>
<td>(±)-Englerin B (273)</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>(±)-Englerin B acetate (274)</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>6.341 ± 0.229</td>
<td>9.275 ± 0.013</td>
</tr>
<tr>
<td>Hydroxy acetate (275)</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>TBS-ether (276)</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Hydrogenated englerin A (277)</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>0.745 ± 0.166</td>
<td>0.287 ± 0.139</td>
<td>0.359 ± 0.006</td>
</tr>
</tbody>
</table>

(GI₅₀ values in µM)

Christmann and co-workers had prepared (-)-englerin A (267) and 32 analogues to test cytotoxicity with A498 kidney cancer cell lines to extend SAR study to find new potential compounds. First, they changed cinnamoyl ester of (-)-englerin A (267) and found 3 analogues (279, 280, and 285) that are twice as potent as (-)-englerin A (267) (Figure 11) (Table 8). They
proved that cinnamoyl ester of (-)-englerin A (267) can be replaced and changed to improve activities.

Figure 11. Structure of (-)-Englerin A analogues (278)

Table 8. The cytotoxicity of 32 englerin A analogues (278) was tested with the A498 by the Christmann group

<table>
<thead>
<tr>
<th>R¹ (IC₅₀ value)</th>
<th>(-)-englerin A (267) (45 nM)</th>
<th>279 (25 nM)</th>
<th>280 (26 nM)</th>
<th>281 (&gt; 10 µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>282 (&gt; 10 µM)</td>
<td>283 (&gt; 10 µM)</td>
<td>284 (92 nM)</td>
<td>285 (24 nM)</td>
<td></td>
</tr>
<tr>
<td>286</td>
<td>287</td>
<td>288 (0.28 µM)</td>
<td>289 (&gt; 10 µM)</td>
<td>290 (&gt; 10 µM)</td>
</tr>
<tr>
<td>X = Cl (4.59 µM)</td>
<td>X = H (&gt; 10 µM)</td>
<td>X = Cl (1.48 µM)</td>
<td>X = F (&gt; 10 µM)</td>
<td>X = NO₂ (1.84 µM)</td>
</tr>
<tr>
<td>X = Br (&gt; 10 µM)</td>
<td>X = F (&gt; 10 µM)</td>
<td>X = NO₂ (1.84 µM)</td>
<td>X = Br (&gt; 10 µM)</td>
<td>X = Br (&gt; 10 µM)</td>
</tr>
<tr>
<td>X = F (0.72 µM)</td>
<td>X = NO₂ (1.84 µM)</td>
<td>X = Br (&gt; 10 µM)</td>
<td>X = Br (&gt; 10 µM)</td>
<td>X = Br (&gt; 10 µM)</td>
</tr>
<tr>
<td>291 (4.88 µM)</td>
<td>292 (&gt; 10 µM)</td>
<td>293 (&gt; 10 µM)</td>
<td>294 (&gt; 10 µM)</td>
<td>295 (&gt; 10 µM)</td>
</tr>
</tbody>
</table>
Secondly, the glycolate ester was replaced. The resulting analogues (294) gave extremely decreased activities (Figure 12) (Table 9). They showed that the glycolate ester part is very sensitive for a modification.

![Figure 12. Structure of (-)-Englerin A analogues (294)](image)

**Table 9.** The cytotoxicity of 32 englerin A analogues (294) was tested with the A498 by Christmann group

<table>
<thead>
<tr>
<th>R² (IC₅₀ value)</th>
<th>R² (IC₅₀ value)</th>
<th>R² (IC₅₀ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>295 (0.23 µM)</td>
<td>296 (4.61 µM)</td>
<td>297 (1.54 µM)</td>
</tr>
<tr>
<td>298 (5.23 µM)</td>
<td>299 (&gt;10 µM)</td>
<td>300 (&gt;10 µM)</td>
</tr>
<tr>
<td>301 (0.65 µM)</td>
<td>302 (5.04 µM)</td>
<td>303 (&gt;10 µM)</td>
</tr>
<tr>
<td>-CH₂OMe</td>
<td>-CH₂NHCH₃</td>
<td>-CH₂N(Boc)Me</td>
</tr>
</tbody>
</table>

Thirdly, replacing the isopropyl group with methyl and ethyl groups dramatically decreases biological activities. Therefore, this part is also important to obtain high activity.

The Chan group in 2011 also introduced biological evaluation of (±)-englerin analogues. They changed the cinnamoyl ester of (±)-englerin A (272). Analogues (305) and (309) showed similar or slightly improved activities (Figure 13) (Table 10).
Figure 13. Structure of (±)-englerin analogues 304

Table 10. The cytotoxicity of englerin A (272) analogues by the Chans group

<table>
<thead>
<tr>
<th>R₁</th>
<th>UO31</th>
<th>A498</th>
<th>R₁</th>
<th>UO31</th>
<th>A498</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-englerin A (272)</td>
<td>0.037</td>
<td>0.045</td>
<td>305</td>
<td>0.040</td>
<td>0.032</td>
</tr>
<tr>
<td>306</td>
<td>0.150</td>
<td>0.340</td>
<td>307</td>
<td>0.071</td>
<td>0.060</td>
</tr>
<tr>
<td>308</td>
<td>0.014</td>
<td>0.086</td>
<td>309</td>
<td>0.007</td>
<td>0.049</td>
</tr>
<tr>
<td>310</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>311</td>
<td>8.6</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

(GI₅₀ values in µM)

They also replaced the glycolate. However, two analogues 313 and 314 gave no activities (Figure 14) (Table 11). Although these analogues did not give significant improvement of activities, they showed a role of structure of (±)-englerin A (272).
Figure 14. Structure of (±)-Englerin A analogues (312)

Table 11. The cytotoxicity of englerin A analogues (312) by the Chan group

<table>
<thead>
<tr>
<th>R₂</th>
<th>UO31</th>
<th>A498</th>
<th>R₂</th>
<th>UO31</th>
<th>A498</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CH₂OC(O)CH₂OH 313</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>- CO₂H 314</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>- C(O)OCH₂CH₂OH 315</td>
<td>0.035</td>
<td>0.048</td>
<td></td>
<td>0.047</td>
<td>0.020</td>
</tr>
</tbody>
</table>

(GI₅₀ values in µM)

Theodorakis and co-workers finally reported SAR of truncated englerins (Figure 15). Truncated englerin 317 and 319 compounds did not give any activity in A498 cancer cell, so they suggested that a five membered ring of englerin A (267) is essential to inhibit a growth of renal cancer cells. Antiproliferative activity of (−)-englerin A (267) and truncated englerin analogues in CEM T-cell acute lymphoblastic leukemia cells was also evaluated. (−)-Englerin A (267) and 320 that have additional rings showed no or little cytotoxicity in 20 µM, but 321 and 322 analogues, which have single ring gave high cytotoxicity against leukemia cells in low concentration (GI₅₀ = 1-3 µM). They explained a role of structures of (−)-englerin A (267) (Figure 15).
4.1.3. Previous synthetic approaches to englerin A

The Beutler group in 2008 reported the natural product, (-)-englerin A (267) and demonstrated the relative stereochemistry of this compound. The absolute configuration of (-)-englerin A (267) was established by Christmann and co-workers in 2009. They introduced the first synthetic route for (+)-englerin A from (+)-cis,trans-neopetalactone 323 using key strategies such as an epoxylactone rearrangement, a stereoselective Barbier addition, and a ring-closing metathesis (RCM) reaction (Scheme 91).

In addition, they demonstrated that (-)-englerin A (267) can be synthesized from (-)-cis,trans-neopetalactone (see Scheme 101) by the same strategies in 2011.
Scheme 91. The total synthesis of (+)-Englerin A

After the Christmann group identified the absolute configuration of (-)-englerin A (267), the research groups of Ma and Echavarren reported the total synthesis of (-)-englerin (267) by a gold-catalyzed cyclization in 2010.

Echavarren et al.\textsuperscript{14} generated a tricyclic alcohol 332 from a protected ketone 331 by the gold-catalyzed cyclization (Scheme 92).
Scheme 92. The mechanism of the backbone synthesis of (-)-Englerin A (267) by the Echavarren group

Ma et al.\textsuperscript{15} also showed the synthesis of (-)-englerin A (267) from an unprotected alcohol 333 by the Au-catalyzed cyclization. The tricyclic alcohol 335, the backbone of (-)-englerin A (267), was constructed from the free alcohol 333 (Scheme 93).

Scheme 93. The mechanism of the backbone synthesis of (-)-Englerin A (267) by the Ma group

Nicolaou and co-workers introduced a [5+2] cycloaddition for the construction of a seven-membered ring (337) in 2010 (Scheme 94).\textsuperscript{10}
Scheme 94. The construction of the 7-memebred ring (337) by Nicolaou and co-workers

In addition, they showed stereoselective [5+2] cycloaddition using the chiral auxiliary 339 to obtain the optically pure 340 (Scheme 95).

Scheme 95. Stereoselective [5+2] cycloaddition using the chiral auxiliary 339 by Nicolaou and co-workers

The oxatricyclic structure 343 was formed by the aldol condensation followed by reduction (Scheme 96).

Scheme 96. The synthesis of the oxatricyclic structure 343 by Nicolaou and co-workers
The Theodorakis group reported a formal synthesis of (-)-englerin A (267). They used the [4+3] cycloaddition for construction of the 7-membered oxabicycle 346 (Scheme 97) and the aldol condensation to generate the tricyclic core 349 (Scheme 98). The origin of diastereoselectivity of [4+3] cycloaddition was controlled by an interaction between the carbonyl group of the auxiliary of 344 and rhodium carbenoid generated from diazo compound of 344.

Scheme 97. The synthesis of the oxabicycle 346 by the Theodorakis group

The adol condensation provided the tricyclic intermediate 348 from a diketone 347. After 8 steps, 348 was converted to the known compound 349 reported by Ma et al. (Scheme 98).

Scheme 98. The synthesis of the oxatricyclic structure 349 by the Theodorakis group

The Chain group in 2011 displayed the most efficient synthesis. A 5-membered ring 351 was prepared from lithium enolates by Michael addition and 7-membered oxatricyclic core 352 was constructed through a reductive carbonyl-alkene cyclization. 3-Furanone 349 was treated with LDA to produce lithium enolate that was subjected to Michael addition with an aldehyde 350 to give inseparable 5-membered rings in favor of a desired product 351 in d.r. 2:1. A reductive carbonyl-alkene cyclization with SmI2 gave the valuable ketone 352 that is a known compound synthesized by the Ma group. It is very a concise synthetic strategy to furnish (-)-englerin A (267) (Scheme 99).
Scheme 99. The synthesis of (-)-englerin A (267) by the Chain group

Lin and co-workers showed a formal synthesis of (+)-englerin A by organocatalytic [4+3]-cycloaddition (Scheme 100).\textsuperscript{18}
Scheme 100. Preparation of oxabicycle by organocatalytic [4+3]-cycloaddition by the Lin group

The Christmann group in 2011 used the same strategy, which was used to synthesize (+)-englerin A, to prepare (-)-englerin A (267) (Scheme 101).11
Scheme 101. The total synthesis of (−)-englerin A (267) by the Christmann group

Recently, Cook and co-worker reported a reductive-Heck approach to key cores of (±)-englerin A (272). A hydroazulene ring 369 was constructed by the Heck reaction. They showed a preparation of a known alcohol 335 reported by the Ma group (Scheme 102).[^19]

Scheme 102. The formal synthesis of (±)-englerin A (272) by the Cook group
4.1.4. Previous syntheses of guaiane cores of englerins

The Maier group used carbonyl ylide-alkyne 1,3-dipolar cycloaddition to generate a oxo-bridged guaiane 376. A 5-membered ring 374 was prepared from 372 by Favorskii rearrangement and Barton-McCombie protocol. They utilized carbonyl ylide-alkyne 1,3-dipolar cycloaddition to build a 7-membered ring 376 from diazoketone 375 (Scheme 103).

Scheme 103. Preparation of a oxo-bridged guaiane structure 376

The synthesis of analogue, (-)-9-deoxy-englerin A (380) was reported by the same group (Scheme 104). They used intramolecular epoxide opening of a ketone enolate for the construction of a bicyclic ketone 378. Oxymercuration of 379 followed by reduction gave the oxygen-bridged structure 380.
Scheme 104. Preparation of a bicyclic ketone 380

As we discussed, there have been a lot of synthetic approaches to prepare englerin A and because of selective and potential biological activities of (-)-englerin A (267) for renal cancer cells and studies for SAR to disclose new potential compounds from (-)-englerin A (267). Herein, we describe a new strategy for a formal synthesis of (-)-englerin A (267) by a relay ring closing metathesis (RRCM) reaction and transannular etherification.\textsuperscript{22} Now, asymmetric syntheses of (-)-englerin A (267) can be summarized\textsuperscript{23} as follows (Scheme 105).

\textbf{Scheme 104.} Preparation of a bicyclic ketone 380

As we discussed, there have been a lot of synthetic approaches to prepare englerin A and because of selective and potential biological activities of (-)-englerin A (267) for renal cancer cells and studies for SAR to disclose new potential compounds from (-)-englerin A (267). Herein, we describe a new strategy for a formal synthesis of (-)-englerin A (267) by a relay ring closing metathesis (RRCM) reaction and transannular etherification.\textsuperscript{22} Now, asymmetric syntheses of (-)-englerin A (267) can be summarized\textsuperscript{23} as follows (Scheme 105).
Scheme 105. Asymmetric syntheses of (-)-englerin A (267)

4.1.5. A new approach to a key core of (-)-englerin (267) A by RRCM and transannular etherification

A cascade metathesis has been investigated for some time and it is well known to produce easily various bicyclic dienes (Scheme 106).24
Scheme 106. Preparation of various bicyclic dienes by a cascade metathesis

There are also some examples of dienyne metathesis from optically pure dienyne (Scheme 107).

Scheme 107. Examples of dienyne metathesis from optically active dienyne
Therefore, we believed that optically active hydroazulene 381 can be prepared by ene-yne-ene metathesis and an important structure to synthesize (-)-englerin A (267). In addition, based on our analysis, transannular etherification was expected to produce an oxa-bicyclic structure 392 from a hydroazulene 381, which can be probably converted to the key intermediates to synthesize (-)-englerin A (267) (Scheme 108).

Scheme 108. Retrosynthetic analysis of (-)-englerin A (267) by RCM and transannular etherification

First, we designed an acetylene diol precursor 393 to obtain the hydroazulene 381 by the cascade metathesis and found two problems. A desired diene 381 would be a major product because a less hindered site might be more reactive with a catalyst, but it has a possibility to have another diene 394 (Scheme 109).

Scheme 109. Possible two diene products from a ring closing metathesis (RCM) reaction
In addition, it cannot be easy to initiate a ring closing metathesis because geminally substituted terminal alkenes are unreactive with a relay ring closing (RCM) catalysts. Therefore, to give more promising results, we decided to introduce a relay metathesis step to give high reactivity and regio selectivity of ene-yne-ene metathesis. Hoye and co-workers developed relay metathesis to resolve reactivity (Scheme 110) and selectivity (Scheme 111) problems of terminal alkenes 395 that are geminally substituted.26

![Scheme 110](image1)

**Scheme 110.** The relay ring closing metathesis reaction for unreactive geminally substituted alkenes

![Scheme 111](image2)

**Scheme 111.** Regioselectivity of the relay ring closing metathesis
Therefore, it is prudent to initiate site-specific ruthenium carbene to produce a desired diene 381, so we decided to use the relay ring closing metathesis (RRCM) to construct hydroazulene 381 (Scheme 112).

Scheme 112. The Synthesis of the hydroazulene 381 by the RRCM reaction

After a construction of 381, we postulated that the oxa-bicyclic structure 392 would be approached by transannular etherification. Hydroxyl nucleophile would not only attack C-7 because this site is more positive than C-6, but also approach from front side of C-7 of unstrained conformations because backside attack would not be possible due to a ring strain (Scheme 113).
Thus, the final retrosynthetic analysis of (-)-englerin (267) is as follows (Scheme 114).

Based on our expectation, we designed two retrosynthetic strategies to access the diol 406 to prepare the hydroazulene 381.

The first retrosynthetic plan of 406 is to use Sharpless asymmetric kinetic resolution\textsuperscript{27} to control stereoselectivity of the hydroazulene 381 (Scheme115). An aldehyde 408 can be prepared from Geraniol 409, a commercially available starting material, by selenium oxidation. Optically pure epoxy alcohol 407 would be obtained by Sharpless asymmetric kinetic resolution from a secondary allylic alcohol made by a Barbier addition based. Although the maximum yield would be 50 % from epoxidation, another diastereomer recovered from Sharpless epoxidation might be easily separable and reused by oxidation and stereoselective reduction. Finally, the target precursor of RRCM, diol 406, would be prepared by stereo-, regio selective epoxide opening reaction because generally less hinder site of epoxide has more reactive in nucleophilic addition reaction.
Scheme 115. The first retrosynthetic plan to prepare diol 406

The second retrosynthetic plan of 406 is to use Sharpless asymmetric epoxidation to introduce stereoselectivity of hydroazulene 381 (Scheme 116). Our second retrosynthetic scheme would be alternative to produce the same intermediate, the diol 406. Herein, stereoselectivity of an epoxy alcohol could be controlled by Sharpless epoxidation and epoxide opening could provide 410. Oxidation and a Barbier coupling reaction would produce the mixture of diastereomers 406, but a desired diastereomer could be produced as a major product through non-chelation transition state.
Scheme 116. The second retrosynthetic plan to prepare diol 406

Based on our synthetic analysis of (-)-englerin A (267), we decided to apply the first strategies (Scheme 115) to produce acetylene diol 406, but we found that epoxide opening of 407 did not give desired product 406. Therefore, we have prepared three model compounds, epoxy alcohols, and investigated epoxide opening reactions. After examination, the second method (Scheme 116) was applied to obtain the hydroazulene 381 and we proved that 381 can be converted to the key structure 392 of (-)-englerin A (267) by transannular etherification.
4.2. Result and discussion

4.2.1. Investigation of preparation of diol acetylene (406)

4.2.1.1. The first-generation approach (Scheme 115)

To investigate a relay ring closing metathesis (RRCM) reaction to construct the hydroazulene 381, we needed to prepare the diol 406 with a desired stereochemistry (See Scheme 112). First, allyl ether 412 was synthesized from a geraniol 409 to give a moiety of the relay ring closing metathesis by two methods (Scheme 117). Both methods gave us high yields; the 2nd method is more convenient for a large scale experiment, so we decided to use the 2nd method.

\[
\begin{align*}
\text{Scheme 117. Preparation of allyl ether 412} \\
\text{After o-allylation of a geraniol 409, we have explored SeO}_2 \text{ oxidation to provide the aldehyde 408 from allyl ether 412. After several examinations}^{29} \text{, we decided to use catalytic SeO}_2 \text{ oxidation method}^{29b} \text{ to produce an alcohol 411 and the aldehyde 408 because other reaction conditions showed low conversion or low yield. PDC oxidation was applied to convert the alcohol 411 to the aldehyde 408 in 65 % yield (Scheme 118).}
\end{align*}
\]
Scheme 118. SeO₂ oxidation to prepare alcohol 411 and aldehyde 408

The aldehyde 408 was treated with 2-bromo-methyl-3-methyl-1-butene (326) to afford an alcohol 413 by a Barbier addition. We tested reaction conditions and found that when 3 equivalent of allyl bromide 326 was used in a solvent mixture of THF and saturated aq. NH₄Cl, the yield of 413 was increased to 95 % (Scheme 119) (Table 12).

Scheme 119. Preparation of the alcohol 413 by a Barbier addition
Table 12. Results of synthesis of the alcohol 413 by a Barbier addition

<table>
<thead>
<tr>
<th>Activated Zn (eq.)</th>
<th>Bromide 326 (eq.)</th>
<th>Solvent (v/v)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>THF / NH₄Cl (sat.) = 2/1</td>
<td>Y = 85 - 90 %</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>THF / NH₄Cl (sat.) = 2/1</td>
<td>Y &gt; 95 %</td>
</tr>
</tbody>
</table>

(v/v = volume / volume)

In addition, the bromide 326 was prepared from an alcohol 416 by a literature method. Firstly, the alcohol 416 was prepared from an ester 415 by a literature method, but a synthesis of 416 was not easy to obtain enough because of a low yield and by-products in a large scale (Scheme 120).

![Scheme 120](image)

Scheme 120. Preparation of bromide 326 by literature methods

Thus, another route was developed to provide the alcohol 416. An aldehyde 418 was prepared from a literature method and a simple reduction of 418 with NaBH₄ gave us the alcohol 416, which is a precursor to make the bromide 326 (Scheme 121).

![Scheme 121](image)

Scheme 121. Preparation the alcohol 416 from the aldehyde 417

Sharpless kinetic resolution was used to give a chiral epoxide 407 from the secondary alcohol 413. Epoxidation of one of isomers would be faster and give an optically pure epoxy alcohol 407. The epoxy alcohol 407 was obtained in 42% yield and 419 was recovered in 47%
yield. We did not identify an enantiomeric excess of 407 because it would be easy to confirm an absolute stereochemistry of 407 after an epoxide opening reaction (Scheme 122).

![Scheme 122. Preparation the epoxy alcohol 407 from the secondary alcohol 413](image)

After obtaining the epoxy alcohol 407, representative methods had been tested to open an epoxide ring of 407 to provide a chirality of alcohol position and desired stereochemistry of alkyne of 406 (see Scheme 115). However, acetylene did not attack the epoxide ring of 407 to produce the acetylene diol 406. When the epoxy alcohol 407 was treated with TMS-acetylene and Et₂AlCl, it gave an unknown product 420. The ¹H NMR spectrum of 420 did not show proton peaks from a double bond of isobutene structure of 407. It might be possible that a double bond of isobutene of 407 would attack the epoxide ring to afford a cyclized product 420. In addition, when 407 was treated with TMS-acetylene and BF₃OEt or Li-acetylene diamine complex, Payne rearrangements was occurred to produce a mixture of 407 and 421 that were an inseparable mixture and ratio (1:1) was determined by the ¹H NMR spectrum (Scheme 123).
Scheme 123. Epoxide opening reactions from the epoxy alcohol 407

Representative procedures to open epoxides did not give us the desired product 406 and there are few references to open an acetylide opening of a 2-alkyl-2,3-epoxy alcohol and their examples are not exactly match with our epoxy alcohol 407.\textsuperscript{37} Therefore, more experiments was required to find efficient methods to provide the desired acetylene diol 406 and we started to investigate epoxide opening reactions with model compounds.

4.3.1.2. Model test of epoxide ring opening

We synthesized six model compounds that are free or Bn-protected epoxy alcohols (Figure 16).
Figure 16. Structures of six model compounds

Firstly, secondary epoxide alcohols (422, 423, 424, and 425) were prepared from 10-undecenal (428) by general methods. Horner–Wadsworth–Emmons reaction gave a α,β-unsaturated ketone 430 and a reduction of 430 with NaBH₄ produced an allylic alcohol 431 that was subjected to epoxidation with Ti(i-OPr)₄ to give anti- and syn-epoxy alcohols 422 and 424 in a ratio (2:1 or 1:2). Relative configuration of epoxy alcohols 422 and 424 was not determined by other experiments, but the major product would be the anti-epoxy alcohol 422 based on references 38, which showed that Ti(i-OPr)₄ catalyst can produce anti-epoxy alcohols as a major product and most of all anti-epoxy alcohols gave proton peaks of epoxide in down field of ¹H NMR more than syn-epoxy alcohols. When the alcohol 431 was treated with mCPBA, it gave a 1:1 mixture of syn- and anti-epoxy alcohols 422 and 424. After separation, we also prepared benzyl protected alcohols 423 and 425 from two isomers 422 and 424 (Scheme 124).
After preparation of four epoxy alcohols, we tested the anti-epoxy alcohol 422, which has the same relative configuration as the epoxy alcohol 407 (Scheme 123), with Et₂AlCl or Li-acetylene diamine complex to open an epoxide ring, but we could not get acetylene diols (433 or 434). Bn-protected the anti-epoxy alcohols 423 had been also investigated to explore epoxide opening reactions with various Lewis acids (Et₂AlCl, Me₂AlCl³⁹, BF₃OEt₂, and AlMe₃⁴⁰) and Li-acetylene diamine complex. We realized that Li-acetylene diamine complex can give the acetylene 1,2-diol 432 from the protected epoxy alcohol 423 when a reaction temperature was increased at 50 °C, but the reaction conversion was 50 % (Scheme 125). When we increased a reaction temperature to 70 °C, the conversion was increased to 85-90%, but an unknown by-product was formed (Table 13).
Scheme 125. Preparation of acetylene diol 432 with Li-acetylene diamine complex from 423

The experiment results were summarized as follows (Scheme 126) (table 13).

Table 13. Results of epoxide opening reactions from anti-epoxy alcohols 422 and 423

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Reaction condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>Li-acetylide (10 eq.), DMSO / HMPA, rt, 2 days</td>
<td>No reaction</td>
</tr>
<tr>
<td>H</td>
<td>TMS</td>
<td>TMS-acetylene (3.8 eq.), n-BuLi (3.8 eq.), Et₂AlCl(3.8 eq.), rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide (10-15 eq.), DMSO / HMPA, rt, 1 day</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide (10-15 eq.), DMSO / HMPA, 50 °C, 1–3 days</td>
<td>Conversion 50 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ratio (423 : 433 = 1 : 1)</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide (10-15 eq.), DMSO, 50 °C, 1 day</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide (10-15 eq), DMSO / HMPA, 70 °C, 1-3 days</td>
<td>423 (10–15% left)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Major by-product formed</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (3 eq.), n-BuLi (3 eq.), Et₂AlCl (3 eq.), Cat. NiCl₂, 35 °C</td>
<td>Some unknown spots, but almost 423 left</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (32 eq.), n-BuLi (32 eq.), Et₂AlCl (32 eq.), rt, 4 days</td>
<td>Ratio (433 : 434 = 1 / 1) 423 (20 - 30% left)</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (2 eq), n-BuLi (2 eq), Me₃Al (1.9 eq), 4.5 hr, rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (3 eq), n-BuLi (3 eq), Me₂AlCl (2.9 eq), 14 hr, rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (5 eq), BF₃OEt₂ (2.2 eq), BuLi (4.6 eq), rt, 24 hr</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (5 eq), BF₃OEt₂ (2.2 eq), BuLi (4.6 eq), THF, 60 °C, 44 hr</td>
<td>Starting and messy unknown products</td>
</tr>
</tbody>
</table>

However, syn-epoxy alcohols 424 and 425 displayed different reactivity and results. It gave us an acetylene 2,3-diol 435 as major product in 42 % yield and an acetylene 2,4-diol 436 as a by-product in 10 - 15 % yield when it was treated with Et₂AlCl and TMS-acetylene. Li-acetylene diamine complex can also open a ring of the protected syn-epoxy alcohol 425 to give 435 even at a room temperature, although the conversion was 15-20 %. When a reaction temperature was increased to 50 °C, the conversion was 50 % after 3 days. Therefore, both epoxy alcohols 424 and 425 produced acetylene diols 435 by different methods.

The experiment results were summarized as follows (Scheme 127) (Table 14).

**Scheme 127.** Epoxide opening reactions from syn-epoxy alcohols 424 and 425
Table 14. Results of epoxide opening reactions from syn-epoxy alcohols 424 and 425

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Reaction condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>Li-acetylide, (10 eq.), DMSO / HMPA, rt, 2 days</td>
<td>No reaction</td>
</tr>
<tr>
<td>H</td>
<td>TMS</td>
<td>TMS-acetylene (3.8 eq.), n-BuLi (3.8 eq.), Et₃Al (3.8 eq.), rt</td>
<td>435 (yield : 42 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>436 (yield : 5-10%)</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide, (15 eq.), DMSO / HMPA, rt, 3 days</td>
<td>Ratio : (425 : 435 = 7 : 3 )</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide, (2 eq.), DMSO / HMPA, rt, 3 days</td>
<td>Almost starting 427 left</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide, (10 eq.), DMSO / HMPA, 50 °C, 3 days</td>
<td>Ratio (425 : 435 = 1 : 1 )</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (5 eq.), BF₃OEt₂ (2.2 eq.), BuLi (4.6 eq.), THF, 60 °C, 44 hr</td>
<td>425 and messy unknown products</td>
</tr>
</tbody>
</table>

On the other hand, the primary epoxy alcohols 426 and 427 were synthesized from the 10-undecenal (428) to explore another possible access to have the acetylene 2,3-diols 440 (Scheme 129). The 10-undecenal (428) was treated with phosphonopropionate 437 to furnish a α, β-unsaturated ester 438. The reduction of 438 followed by epoxidation with mCPBA provided the epoxy alcohol 426. Benzyl protection of 426 afforded the Bn-protected epoxy alcohol 427 (Scheme 128).

Scheme 128. Preparation of primary epoxy alcohols 426 and 427 as model compounds
This epoxy alcohol 426 was treated with Et₂AlCl and it provided the acetylene 2,3-diols 440 as a major product, but the protected alcohol 427 did not give the desired product 440. Therefore, we decided to use the second strategy (see Scheme 112) to prepare acetylene diol 406 from the primary epoxy alcohol 411 because a protection free procedure is better to save synthetic steps. The experiment results were summarized as follows (Scheme 129) (Table 15).

![Scheme 129. Epoxide opening reaction from primary epoxy alcohols 426 and 427]

Table 15. Results of epoxide opening reactions from primary epoxy alcohols 426 and 427

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Reaction condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>TMS</td>
<td>TMS-acetylene (4.3eq), n-BuLi (3.0eq), Et₂AlCl(3.0eq), rt</td>
<td>Yield 55 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ratio (440 : 441 = 5 : 1)</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide (10-15 eq), DMSO / HMPA, rt, 24 hr</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>H</td>
<td>Li-acetylide (10-15 eq), DMSO / HMPA, 50 °C, 1-3 days</td>
<td>No reaction</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (5 eq), BF₃OEt₂ (2.2 eq), BuLi (4.6 eq), THF, rt, 48 hr</td>
<td>Almost starting</td>
</tr>
<tr>
<td>Bn</td>
<td>TMS</td>
<td>TMS-acetylene (5 eq), BF₃OEt₂ (2.2 eq), BuLi (4.6 eq), THF, 60 °C, 44 hr</td>
<td>Starting and messy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unknown products</td>
</tr>
</tbody>
</table>

4.2.1.3. The second - generation approach (Scheme 116)

To introduce chirality of the primary epoxy alcohol 442, we used Sharpless epoxidation⁴¹ (Scheme 130) and enantiomeric excess was determined by ¹H NMR of its Mosher esters.
Scheme 130. Preparation the epoxy alcohol 442 from the allylic alcohol 411

The epoxide 442 was treated with Et₂AlCl and TMS-acetylene gave a 2,3-diol product 443 as a major product (ratio 1.4 : 1.0). To prohibit a formation of 2,4-diol 444, we had tried to change reaction conditions and found high reaction temperature can depress 2,4-diol formation to give more of the 2,3-diol 443. When a reaction temperature was 50 °C, it afforded a mixture of the 2,3-diol 443 and the 2,4-diol 444 as a moderate ratio (1.5 ~ 3.0 : 1.0) in 80 % yield (Scheme 131).

Scheme 131. Preparation of 2,3-diol 443 with Et₂AlCl and TMS-acetylene

The separation of two isomers 443 and 444 was difficult, but 444 can be removed by silica gel column chromatography to give 443, which has adequate purity for the next step. The oxidation of alcohol 443 with SO₃-Py complex and triethyl amine⁴² gave an aldehyde 445 in 51 % yield. We tried to use the Swern oxidation to improve a yield of 445, but the yield was 61 % yield. Finally, Parikh-Doering oxidation with diisopropyl ethyl amine (DIPEA) provided the best yield in 67 % yield (Scheme 132).
Scheme 132. Preparation of the aldehyde 445 by Parikh-Doering oxidation

The Barbier addition produced a TMS-acetylene diol 446 and 447 from the aldehyde 445 in 93 % yield. Later, the major compound was assigned structure 446. The separation of two diastereomers 446 and 447 is not easy, but we could obtain some pure 446 and 447 by silica gel column chromatography. TMS deprotection of 446 gave the diol 406 to make a diene 381 in 94 - 98 %. (Scheme 133).

Scheme 133. Preparation of the diol 406 by the Barbier addition and TMS-deprotection
The best reaction condition was found that a crude aldehyde 445 without column purification was directly subject to a Barbier addition to afford the TMS-acetylene diols (ratio 446: 447 = 2:1) in 70% for 2 steps.

In addition, we finally found another good procedure to open the epoxy alcohol 442 with high regio-selectivity. Li-acetylene diamine complex in DMSO and HMPA directly produced the only desired product 410 in 82% at 50 - 60°C (Scheme 134).

**Scheme 134.** Preparation of the diol 410 with Li-acetylene diamine complex

The acetylene diol 406 was produced from 410 by Parikh-Doering oxidation with diisopropyl ethyl amine (DIPEA) and the Barbier addition (ratio 406: 449 = 1.8: 1.0) (Scheme 135).

**Scheme 135.** Preparation of the diol 406 with Li-acetylene diamine complex
4.2.2. Investigation of RRCM and preparation of TBS-protected diol (466)

After successfully preparing the acetylene diols, a major diastereomer of diol 406 was tested to construct a guaiane structure 450 by the ring closing metathesis (RRCM) reactions. However, we could not obtain any product or just recover the starting material 406 under various reaction conditions such as a high temperature like 110 °C and high loading catalysts (20 - 30 %). (Scheme 136) (Table 16).

![Scheme 136](image)

**Scheme 136.** Construct a guaiane structure 406 by the closing metathesis (RRCM) reactions

<table>
<thead>
<tr>
<th>Table 16. Results of the RRCM reaction of 406</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalyst</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>G II</td>
</tr>
<tr>
<td>G II</td>
</tr>
<tr>
<td>G I</td>
</tr>
</tbody>
</table>

G I: Grubbs 1st catalyst, G II: Grubbs 2nd catalyst

We focused one result that the starting material 406 was just recovered when 406 was treated with 8.5 mol% of Grubbs 2nd catalyst in CH₂Cl₂ at reflux. It was very interesting because the Grubbs 2nd catalyst did not give any expected product (Scheme 137). The 2,5-dihydrofuran 400 has low boiling point, so it is not possible to detect 400, but a by-product 452 of RRCM reaction could be produced when Grubbs 2nd catalyst have a chance to react with the allyl ether moiety of 406.
Scheme 137. Expected products by ring closing metathesis (RRCM) reactions

One of possible reasons would be deactivation of catalysts by a formation of a chelate between the diol of 406 and catalysts. We tested to use Ti(OiPr)₄ reagent⁴³ because this reagent can inhibit a formation of a chelate between catalysts and functional groups. However, we could not obtain products (Table 13).

Table 13. Results of RRCM of 406 with Ti(OiPr)₄

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Mole % of catalyst</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Ti(OiPr)₄ (eq.)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>30</td>
<td>CH₂Cl₂</td>
<td>Reflux</td>
<td>14</td>
<td>10</td>
<td>Starting &amp; messy</td>
</tr>
<tr>
<td>GI</td>
<td>30</td>
<td>Toluene</td>
<td>Reflux</td>
<td>14</td>
<td>2</td>
<td>Decomposed</td>
</tr>
</tbody>
</table>

GI: Grubbs 1st catalyst

The next possibility would be conformation problems and conformational constraints could improve RCM.⁴⁴ To remove all possible problems, the diol 406 was protected as the acetonide 453 which provided metathesis products 454 and 455. After a protection, the RRCM reaction produced an unknown product, which was isolated by silica gel column chromatography, and it showed one spot on TLC. In ¹H NMR spectrum, it displayed many peaks from 5-7 ppm and the integration of each peak indicated around one proton. These peaks probably come from protons of double bonds. We suspected that it can be a mixture of a diene 455 and a 5-membered ring...
454, so it was treated with Grubbs 2\textsuperscript{nd} catalyst again in the same reaction condition. After 20 h, some peaks became smaller and other peaks became bigger in the \textsuperscript{1}H NMR spectrum, so we proved that it was an inseparable mixture. After deprotection of the mixture of 454 and 455, we could isolate the hydroazulene 450. The relative stereo configuration of 450 was determined on the basis of nuclear Overhauser effects and we confirmed that the diene 450 was a desired diene for the synthesis of (-)-Englerin A (267). Therefore, we proved that the hydroazulene 450 can be constructed by the RRCM reaction (Scheme 138).

\textbf{Scheme 138.} Preparation of the hydroazulene 450 by the RRCM reaction

Many reaction conditions had been examined to find the best condition. Grubbs 1\textsuperscript{st} and 2\textsuperscript{nd} catalysts and Hoveyda-Grubbs 2\textsuperscript{nd} catalyst had been used to improve a conversion from the 5-membered ring 454 to the diene 455. Grubbs 1\textsuperscript{st} catalyst gave less unknown by-products and was similar conversion to Grubbs 2\textsuperscript{nd} catalyst. Hoveyda-Grubbs 2\textsuperscript{nd} catalyst did give lower
conversion than Gruubs 2nd catalyst. In addition, long reaction time and high loading catalysts gave more unknown by-products (Scheme 135). However, all reactions did not give 100 % conversion from 454 to 455.

![Conversion Diagram](image)

**Scheme 139.** Preparation of the hydroazulene 455 from 453 by the RRCM reaction

**Table 17.** Results of synthesis of the hydroazulene 455 by the RRCM reaction

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Mole % of catalyst</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Concentration (M)</th>
<th>Crude NMR ratio (454 / 455)</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>G II</td>
<td>10</td>
<td>CH₂Cl₂</td>
<td>Reflux</td>
<td>20</td>
<td>0.01</td>
<td>1.5 / 1.0</td>
<td></td>
</tr>
<tr>
<td>G II</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>Reflux</td>
<td>19</td>
<td>0.01</td>
<td>0.9 / 1.0</td>
<td></td>
</tr>
<tr>
<td>G II</td>
<td>30</td>
<td>Toluene</td>
<td>60 – 70</td>
<td>60</td>
<td>0.005</td>
<td>0.4 / 1.0</td>
<td></td>
</tr>
<tr>
<td>G II</td>
<td>35</td>
<td>Toluene</td>
<td>Reflux</td>
<td>14</td>
<td>0.005</td>
<td>0.3 / 1.0</td>
<td></td>
</tr>
<tr>
<td>G I</td>
<td>30</td>
<td>Toluene</td>
<td>80</td>
<td>24</td>
<td>0.005</td>
<td>0.4 -0.5 / 1.0</td>
<td></td>
</tr>
<tr>
<td>G I</td>
<td>30</td>
<td>Toluene</td>
<td>140</td>
<td>0.5</td>
<td>0.01</td>
<td>0.3 / 1.0</td>
<td>microwave</td>
</tr>
<tr>
<td>G I</td>
<td>35</td>
<td>Toluene</td>
<td>Reflux</td>
<td>13</td>
<td>0.005</td>
<td>0.4 / 1.0</td>
<td></td>
</tr>
<tr>
<td>HG II</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>Reflux</td>
<td>36</td>
<td>0.005</td>
<td>0.8 / 1.0</td>
<td></td>
</tr>
</tbody>
</table>

* G I : Grubbs 1st catalyst, G II : Grubbs 2nd catalyst, HG II : Hoveyda-Grubbs 2nd catalyst

On the other hand, an acetonide 456 from the minor diastereomer diol 449 did produce not any diene 458, but a 5-memebred ring 457 by the RRCM reaction when 456 was treated with Grubbs 1st catalyst (Scheme 140).
Based on our experiments, we decided a reaction condition, 30% Grubbs 1st catalyst in toluene at 80 °C for 24 h because it gave fewer by-products. The RRCM reaction provided the inseparable mixture of 454 and 455. After deprotection, we isolated the diene 450 in 35% yield for 2 steps and the deprotection yield was moderate (~ 75%) from 455. We also tried to obtain the 5-membered ring 451 (see Scheme 137) from deprotection of 454 to reuse 451, but we could not separate 451 because the hydrolysis of the mixture of 454 and 455 gave messy products (Scheme 141).

Scheme 140. RRCM of the acetonide 456 from the diastereomer diol 449

Scheme 141. Synthesis of the hydroazulene 450 from the acetonide 453
Therefore, we decided to use carbonate protecting groups to protect the diol 406 that can be easily removed in a mild condition. We used the mixture of diastereomers (406 and 449) and obtained carbonates 459 in 83% when it was treated with CDI (1,1’-carbonyldiimidazole) in THF at reflux or toluene at 80°C, but the yield of 459 was increased to 92% when it was treated with CDI and NaH in DMF at rt (Scheme 142).

\[
\text{406} + \text{449} \xrightarrow{\text{CDI, NaH, DMF, rt}} \text{Mixture 459}
\]

ratio: 1.4 / 1.0

Scheme 142. Synthesis of carbamates mixture 459 from the mixture of 406 and 449

Carbonates 459 were tested under the same reaction condition (30% Grubbs 1st catalyst, toluene, 80°C). The result was little disappointing because the conversion from the 5-membered ring 460 to the diene 461 was 50%. However, surprisingly, we can separate the 5-membered ring 460 by silica gel column chromatography. After the deprotection of carbonates, the hydroazulene 450 and a five-membered ring 463 were easily isolated by silica gel column chromatography. Deprotection of carbonate groups was very simple and clean to produce the hydroazulene 450 (Scheme 143).


Scheme 143. Synthesis of the hydroazulene 450 from carbonates mixture 459

Although the carbonate 459 gave the lower yield of 450 (18% for 2 steps) and the low conversion (∼50% from 460 to 461), deprotection and isolation procedures were more efficient and easier than acetonide experiments. In addition, the isolated 5-membered ring 460 was reused to provide diene 461. It was treated with Grubbs 1st catalyst again and showed 77% conversion to afford 461 (Scheme 144).

Scheme 144. Synthesis of the hydroazulene 461 from carbonates mixture 460

Therefore, we decided to use the carbonate protection and to continue to try to find more a reactive catalyst to give quantitative conversion from this carbonates 459
One of more reactive RCM catalysts, Stewart-Grubbs catalyst (465)\(^ {45} \), was tested for RRCM. When 459 was treated with 20 % Stewart-Grubbs catalyst 465, it provided two dienes (460 and 463) and two 5-membered rings (461 and 459) from both of stereoisomers 458. Each product could be isolated after deprotection of carbonates (Scheme 145).

**Scheme 145.** Synthesis of the hydroazulene 450 from carbonates mixture 459 with Stewart-Grubbs catalyst 465
Therefore, we found that both dienes 461 and 464 can be produced by Stewart-Grubbs catalyst 465 and the carbonates 459 can also give a high conversion and yields. Finally, when we used 30 % Stewart-Grubbs catalyst 464, it gave a quantitative conversion from carbonates 459 to dienes 461 and 464. The relative stereochemistry of both dienes 461 and 464 were assigned on the basis of nuclear Overhauser effects (Scheme 146).

![Scheme 146. Synthesis of the dienes 461 and 464 from carbonates 459 with 30 % Stewart-Grubbs catalyst 465](image)

This result gave us strong points that we do not have to isolate diastereomer diols 406 and 449 after the Barbier addition (see Scheme 133) because they were easily isolated after the RRCM reaction. The epimer diene 464 could be used to develop new structures or changed to the desired hydroazulene 450 by general methods after deprotection of carbonate groups.

The desired diene 461 was easily hydrolyzed by a treatment of base, NaOH in dioxane and gave the hydroazulene 450 in 97 % yield. The secondary alcohol of the hydroazulene 450 was protected with TBS group to afforded TBS–protected diene 466 in 93 % yield (Scheme 147).

![Scheme 147. Synthesis of TBS–protected diene 466 from 461](image)
4.2.3. Investigation of transannular etherification and the synthesis of an oxa-bicyclic structure (469)

After preparing the TBS-protected diene 466, we have developed procedures to provide the oxa-bicyclic structure 392 that is an important intermediate for the synthesis of (-)-englerin A (267) (Scheme 148).

Scheme 148. Synthesis of 392 by transannular etherification

Various methods have been tested to initiate a transannular cyclization that would affect conversion of 466 to 392. An epoxidation with mCPBA provided a product in which the olefinic proton was retained. Treatments of 466 with I$_2$, NIS$^{25a,47}$, NBS$^{48}$, PhI(O$_2$CCF$_3$)$_2$,$^{49}$ and (Coll)$_2$IPF$_6$,$^{50}$ did not provide the oxa-bicyclic compound 392 (Table 18). After several experiments, we realized that oxymercuration of 466 with Hg(O$_2$CCF$_3$)$_2$,$^{51}$ affords a transannular cyclized product 392.
Table 18. Results of synthesis of the oxa-bicyclic compound 392 by transannular etherification

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Reaction condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhI(O₂CCF₃)₂</td>
<td>2.4 eq., CH₂Cl₂, rt, 4 h</td>
<td>TLC (no spots), Crude NMR (showed peaks from reagents)</td>
</tr>
<tr>
<td></td>
<td>1.0 eq., CH₂Cl₂, rt, 4 -20 h</td>
<td>TLC (no spots), crude NMR (showed 466 peaks and some small peaks)</td>
</tr>
<tr>
<td></td>
<td>1.2 eq., CH₂Cl₂, rt, 18 h</td>
<td>TLC (466 spot), crude NMR (showed 466 and some small peaks)</td>
</tr>
<tr>
<td>NIS</td>
<td>K₂CO₃ (5.5 eq.), CH₂Cl₂, rt, 38 h</td>
<td>TLC (messy, 466 spot), crude NMR (showed 466 and some very small peaks)</td>
</tr>
<tr>
<td></td>
<td>CSA (1.0 eq.), 2,4,6-collidine</td>
<td>TLC (messy, 466 spot), crude NMR showed 466 and some very small peaks)</td>
</tr>
<tr>
<td></td>
<td>(1.0 eq.), rt, 20 h</td>
<td>Crude NMR showed 466 and some very small peaks)</td>
</tr>
<tr>
<td></td>
<td>AcCN, rt, 5 h</td>
<td>TBS deprotected 466 ( = 450)</td>
</tr>
<tr>
<td>I₂</td>
<td>KI, K₂CO₃, THF, rt, 5 h</td>
<td>466 was recovered</td>
</tr>
<tr>
<td></td>
<td>KI, K₂CO₃, THF, 50 °C, 10 h</td>
<td>466 was recovered.</td>
</tr>
<tr>
<td></td>
<td>NaHCO₃, AcCN, rt, 12 h</td>
<td>Messy unknown products</td>
</tr>
<tr>
<td>I(Collidine)₂PF₆</td>
<td>1.6 eq., CH₂Cl₂, rt, 21 h, 35°C, 20 h</td>
<td>466 was recovered</td>
</tr>
<tr>
<td></td>
<td>1.6 eq., CH₂Cl₂, 35 °C, 20 h</td>
<td>466 was recovered</td>
</tr>
<tr>
<td></td>
<td>10 eq., ClCH₂CH₂Cl, 50 °C, 3.5 h</td>
<td>465 was recovered</td>
</tr>
<tr>
<td></td>
<td>10 eq., ClCH₂CH₂Cl, 60-64 °C, 15 h</td>
<td>TLC (466 spot), Crude NMR (466 and showed some small peaks).</td>
</tr>
<tr>
<td></td>
<td>2 eq., toluene, 100 °C</td>
<td>466 was recovered</td>
</tr>
<tr>
<td>NBS (4.5 eq.)</td>
<td>4A MS, CH₂Cl₂, rt, 1 h</td>
<td>Messy unknown products</td>
</tr>
<tr>
<td>Hg(O₂CF₃)₂</td>
<td>AcCN, 0 °C</td>
<td>392 (R = HgCl), yield = 45 %</td>
</tr>
<tr>
<td></td>
<td>CH₂Cl₂/MeOH (cat.), -78 °C (12 h) over 0 °C (5 °C)</td>
<td>392 (R = HgCl), a very clean product</td>
</tr>
</tbody>
</table>

Oxymercuration gave expected regio- and stereoselective addition of C6-C7 olefin and the hydroxyl group at C10 exactly attached to C7 position in Hg complex with the diene 466, so it provided the only product 467. This result showed that the hydroxyl nucleophile effects ring opening by attack at C-7 and a backside attack is not allowed (Scheme 149).
Scheme 149. Synthesis of the alkyl Hg compound 467 by transannular etherification

After the construction of the alkyl Hg(O₂CCF₃) intermediate 392 in situ condition, we found that saturated aq. NaCl solution was doing rapid reversion to the starting material 466 and it would be because of aq. CF₃COOH generated by aq. NaCl solution.⁵¹a Therefore, a chloromercurial compound 467 was produced by the treatment with saturated aq. NaCl solution after neutralizing the acid with saturated aq. NaHCO₃ solution. This chloromercurial compound 467 was very stable, so we isolated 467 by silica gel column chromatography and identified 467 by ¹H NMR spectrum. This spectrum showed that a proton peak from double bond of C6 and C7 had disappeared and a new peak had appeared; therefore we proved the highly regio, stereoselective etherification from the diene 466. To improve yields and reduce by-products, we tried to optimize reaction conditions. The reaction temperature was cooling down to 0 ℃ and it gave 45 % yield and showed fewer by-products on TLC. Therefore, we believed that low temperature can depress the formation of by-products and decided to use CH₂Cl₂ / MeOH solvents system at low temperature (-78 ℃). After 12 h, the reaction showed the only product, but 466 was still left on TLC, so 0.3 eq. Hg(O₂CCF₃)₂ was added more and slowly warmed to 5 ℃ over 4 h, and then starting completely disappeared. Finally, we obtained a very clean a crude product (TLC showed the only product) (Scheme 150). For the next reaction, the purification of chloromercurial was not necessary, so it was directly used without purification.
Scheme 150. Synthesis of the alkyl Hg compound 467 at low temperature

The second, we desired to convert the chloromercurial 467 to the alcohol 470. Until now, there are two methods to do oxidative demercuration. One is to use O₂ and another is to use O₂ and TEMPO. Both methods are radical reactions. We expected they could produce the secondary alcohol 470 directly from chloromercurial 467. However, after several tries, we found that radical generated from oxygen was trapped at the tertiary position and produced tertiary alcohols. Both methods gave us the same products, but O₂ and TEMPO provided a low yield.

The chloromercurial 467 was treated with NaBH₄ and O₂ in DMF to produce a mixture of stereoisomeric tertiary alcohols 468 and 469 (Scheme 151).

Scheme 151. Synthesis of tertiary alcohols 468 and 469 by oxidative demercuration

Although we would have preferred to obtain the known alcohol 470 directly, the alcohol 468 has been produced by oxidative demercuration through the radical intermediate. However, the major product 468 is also the valuable known alcohol, which has been converted to (-)-englerin A (267) in seven steps by way of alcohol 470. Therefore, access to alcohol 468 completes a formal synthesis of (-)-englerin A (267) (Scheme 152).
Scheme 152. The synthesis of (-)-englerin A (267) from the alcohol 468
4.3. Conclusion

In conclusion, we illustrated the efficient strategies to approach the key core of (-)-englerin A (267). First of all, we introduced the epoxide opening reaction to access the acetylene diol 406 from alkyl-2,3-epoxide derivatives with lithium acetylide condition. In addition, the optically pure hydroazulene 450, which has disubstituted olefins both side, was synthesized by the relay ene-yne-ene metathesis reaction. The carbamate from the sterically hindered diol 449 was also converted to the hydroazulene 464 by Stewart-Grubbs catalyst. Furthermore, we demonstrated that the oxa-bicyclic structure 468 can be constructed by transannular etherification with Hg(O$_2$CCF$_3$)$_2$ and oxidative demercuration. It also proved that ionic transannular oxymercuration of 466 gave the regio specific halomercurial 467.
4.4. Reference


4.5. Experimental Section

General Information

All air- and moisture sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum supported flexible plates. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å, 230-400 mesh, surface area 500-600 m²/g, bulk density 0.4 g/mL, pH range 6.5-7.5). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids or dissolved in CH₂Cl₂ on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ¹H), a Varian Inova-500 (500 MHz for ¹H and 125 MHz for ¹³C), Bruker-400 (400 MHz for ¹H and 100 MHz for ¹³C), Varian Inova-400 (400 MHz for ¹H and 100 MHz for ¹³C), or Gemini-2300 (300 MHz for ¹H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. COSY and NOE experiments were measured on Bruker-400, Varian Inova-400 and Varian Inova-600 spectrometer. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.
Ether 412. To a stirred solution of geraniol (409, 5.00 g, 32.4 mmol) in THF (50 mL) were added allyl bromide (4.71 g, 38.9 mmol) and slowly NaH (1.43 g, 60 %, 35.7 mmol) under argon. The reaction mixture achieved a gentle reflux and then it was allowed to cool down to room temperature. After stirring for 14 h, the mixture was filtered through Celite to remove a solid and the filter cake was washed with THF. The resulting solution was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with hexane) to give allyl ether 412 (5.98 g, 95 %). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 5.93 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H), 5.35 (tdd, J = 6.9, 2.4, 1.2 Hz, 1H), 5.27 (ddt, J = 17.4, 1.7 Hz, 1H), 5.17 (dm, J = 10.2 Hz, 1H), 5.09 (m, 1H), 3.99 (dd, J = 6.9, 0.9 Hz, 2H), 3.96 (dt, J = 5.7, 1.4 Hz, 2H), 1.98 – 2.15 (m, 4H), 1.67 (d, J = 1.2 Hz, 3H), 1.66 (m, 3H), 1.60 (d, J = 0.3 Hz, 3 H). The \(^1\)H NMR data were consistent with the reported values.\(^{28}\)

Aldehyde 408 and alcohol 411. To a stirred solution of SeO\(_2\) (2.3 mg, 0.62 mmol) in CH\(_2\)Cl\(_2\) (3 mL) were added salicylic acid (14.2 mg, 0.10 mmol), t-BuOOH (477 mg, 70 % in H\(_2\)O, 3.71 mmol), and ether 412 (200 mg, 1.03 mmol) under Ar. The mixture was stirred for 46 h. Then volatile compounds were removed under reduced pressure and the residue was diluted with Et\(_2\)O (10 mL). The organic solution was washed with 10 % NaOH (5 mL X 3) and brine, dried over MgSO\(_4\), and concentrated under reduced pressure. The crude oil was purified by silica gel
column chromatography (elution with EtOAc : Hexane = 1:20 to 1:2) to give alcohol 411 (104.4 mg, 48 %) as an oil, the corresponding aldehyde 408 (17.4 mg, 8 %), and recovered 412 (42.3 mg, 21 %).

**Alcohol 411:** $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.92 (m, 1H), 5.37 (quintet d, $J$ = 6.6, 1.2 Hz, 1H), 5.26 (dd, $J$ = 16.8, 1.2 Hz, 1H), 5.17 (dd, $J$ = 10.8, 1.2 Hz, 1H), 3.97 (m, 6H), 2.17 (q, $J$ = 7.2 Hz, 2H), 2.07 (t, $J$ = 7.8 Hz, 2H), 1.66 (s, 3H), 1.65 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 13.7, 16.4, 25.7, 39.1, 66.5, 69.0, 71.0, 117.0, 121.1, 125.6, 135.0, 135.1, 139.7.; IR (neat) $\nu_{\text{max}}$ 3397, 2918, 2857, 1670, 1448, 1383 cm$^{-1}$. HRMS[ES+] calcd for C$_{13}$H$_{22}$O$_2$ [M + Na]$^+$ 233.1517, found 233.1523.

**Aldehyde 408:** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.34(s, 1H), 6.43 (tdd, $J$ = 7.5, 2.7, 1.2 Hz, 1H), 5.88 (ddt, $J$ = 17.4, 10.5, 5.7 Hz, 1H), 5.37 (tdd, $J$ = 6.6, 2.7, 1.2 Hz, 1H), 5.23 (ddt, $J$ = 17.4, 1.5 Hz, 1H), 5.16 (m, 0.5H), 5.12 (m, 0.5H), 3.95 (dd, $J$ = 6.9, 0.9 Hz, 2H), 3.93 (ddd, $J$ = 6.0, 1.5 Hz, 2H), 2.46 (m, 2H), 2.19 (t, 2H), 1.70 (dt, $J$ = 2.1, 0.9 Hz, 3H), 1.66 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 9.1, 16.3, 26.9, 37.7, 66.3, 71.0, 117.0, 121.9, 134.7, 138.3, 139.4, 153.7, 195.1. IR (neat) $\nu_{\text{max}}$ 2924, 2853, 2711, 1687, 1645, 1447, 1360 cm$^{-1}$.

**Alcohol 413.** To a stirred solution of 408 (781 mg, 2.70 mmol) in THF (7 mL) and saturated aq. NH$_4$Cl (3.5 mL) were added Zn dust (530 mg, 8.10 mmol) and bromide 326 (880 mg, 5.40 mmol). After 16 h, to the reaction mixture were added Zn dust (176 mg, 2.70 mmol) and bromide 326 (440 mg, 2.70 mmol) and stirred for 5 h. To the resulting mixture were added Et$_2$O (5 mL) and water (3 mL) and the aqueous layer was extracted with Et$_2$O (20 mL x 3). The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel.
column chromatography (elution with EtOAc : Hexane = 1:20 to 1:2) to provide alcohol 413 (750 mg, 95 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.98 - 5.85 (m, 1H), 5.45 - 5.30 (m, 2H), 5.26 (dq, $J$ = 17.1, 1.8 Hz, 1H), 5.16 (ddt, $J$ = 10.2, 1.8, 1.2 Hz, 1H), 4.88 (t, $J$ = 1.2 Hz, 1H), 4.80 (d, $J$ = 1.2 Hz, 1H), 4.09 (q, $J$ = 4.5 Hz, 1H), 3.98 - 3.94 (m, 4H), 2.32 - 2.03 (m, 7H), 1.88 (s, 1H), 1.63 (dm, $J$ = 11.1 Hz, 6H), 1.04 (d, $J$ = 6.9 Hz, 3H), 1.02 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 211.1, 152.6, 139.7, 136.9, 134.9, 125.6, 120.9, 117.0, 110.0, 74.9, 71.0, 66.0, 41.3, 39.0, 33.2, 25.7, 21.6, 16.4, 11.6.; IR (neat) $\nu_{\text{max}}$ 3445, 2961, 2928, 2870, 1668, 1641, 1449, 1380 cm$^{-1}$. HRMS[ES+] calcd for C$_{19}$H$_{32}$O$_2$ [M + Na]$^+$ 315.2296, found 315.2300.

Alcohol 416. To a stirred solution of aldehyde 418$^{33}$ (3.04 g, 30.1 mmol) in MeOH (50 mL) was added NaBH$_4$ (1.17 g, 30.1 mmol) at 0 $^\circ$C. After stirring at room temperature for 1 h, the reaction was quenched with saturated NH$_4$Cl (8 mL). The resulting mixture was diluted with H$_2$O (12 mL) and Et$_2$O (20 mL) then filtered through Celite to remove the white solids. Volatile organic solvent was carefully removed under reduced pressure (note the volatility of the product) and the residue was extracted with CH$_2$Cl$_2$ (15 mL X 4). The combined organic solution was concentrated and purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 9) to provide 416 (2.51 g, 81 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.94 (m, 1H), 4.82 (m, 1H), 4.05 (s, 2H), 2.43 (br s, 1H), 2.26 (sept, $J$ = 6.8 Hz, 1H), 1.01 (s, 3H), 1.00 (s, 3H). $^1$H NMR data were consistent with the reported values.$^{32}$ 2-Bromo-methyl-3-methyl-1-butene (326) was prepared from this alcohol according to Barton et al.$^{31}$

\[
\text{418} \xrightarrow{\text{NaBH}_4, \text{MeOH, O}^\circ\text{C}} \text{416}
\]
Epoxide 407. To a stirred suspension of activated 4 Å molecular sieves (0.5 g) in CH$_2$Cl$_2$ (45 mL) were added alcohol 413 (845 mg, 2.90 mmol) and D-(-)-DIPT (104 mg, 0.435 mmol) under Ar. The resulting mixture was stirred and cooled to -20 °C. The solution of Ti(O’i-Pr)$_4$ (82.4 mg, 0.290 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise and stirred at -20 °C for 30 min. TBHP (0.34 mL, 1.88 mmol, 5.5 M in decane with molecular sieves) was added dropwise and the resulting mixture was cooled to -25 °C for 20 h. It was warmed to 0 °C and water (1 mL) was added and then warmed to room temperature. Aqueous NaOH solution 30 % saturated NaCl (0.2 mL) was added and the resulting mixture was stirred vigorously for 30 min. The resulting mixture was filtered through Celite and the filter cake was washed with CH$_2$Cl$_2$. The combined organic solution was concentrated under reduced pressure and purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20 to 1 : 10) to afford epoxide 407 (379 mg, 42 %) as colorless oil and recovered 419 (402 mg, 47 %). 

Epoxide 407: $^1$H NMR (400 MHz, CDCl$_3$) δ $^1$H NMR (400 MHz,CDCl$_3$) δ 5.91 (ddt, $J$ = 17.1, 10.3, 5.7 Hz, 1H), 5.41 (tq, $J$ = 6.8, 1.3 Hz, 1H), 5.31 - 5.12 (m, 2H), 4.86 (dt, $J$ = 17.5, 1.3 Hz, 2H), 4.01 - 3.92 (m, 4H), 3.59 (ddd, $J$ = 9.6, 2.9, 1.3 Hz, 1H), 2.95 (t, $J$ = 6.8 Hz, 1H), 2.42 - 2.03 (m, 6H), 1.80 - 1.62 (m, 5H), 1.28 (s, 3H), 1.04 (t, $J$ = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.2, 138.9, 134.8, 121.6, 117.0, 109.3, 72.0, 71.1, 66.4, 62.4, 60.3, 38.2, 36.1, 33.2, 26.2, 21.9, 21.5, 16.4, 13.6.; IR (neat) $\nu_{max}$ 3462, 3081, 2961, 2870, 1643, 1460, 1382 cm$^{-1}$. HRMS[ES+] calcd for C$_{19}$H$_{32}$O$_3$[M + Na]$^+$ 331.2249, found.331.2246.
Methyl Ketone 430. To a stirred solution of a phosphonate 429 (1.155 g, 6.412 mmol) in THF (35 ml) was added Ba(OH)$_2$ (5.000 g, 29.14 mmol) and 10-undecenal (428) (1.116 g, 5.829 mmol). The reaction mixture was stirred for 5 min and hold for 16 h. To the resulting mixture was added saturated aq. NaHCO$_3$ and CH$_2$Cl$_2$, and then filtered. The aqueous later was extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure and purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20) to give a product 430 (1.1 g, 92 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.88 (t, $J$ = 7.2 Hz, 1H), 5.86 - 5.76 (m, 1H), 5.01 - 4.91 (m, 1H), 2.30 (s, 3H), 2.22 (q, $J$ = 7.3 Hz, 2H), 2.01 - 2.06 (m, 1H), 1.76 (s, 3H), 1.48 - 1.30 (m, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.0, 144.0, 139.1, 137.6, 114.1, 33.8, 29.4, 29.3, 29.1, 29.0, 28.9, 28.6, 25.4, 11.1; IR (neat) $\nu_{\max}$ 2926, 1670 cm$^{-1}$. HRMS[ES+] calcd for C$_{15}$H$_{26}$O [M + H]$^+$ 223.2062, found 223.2062.
Alcohol 431. To a stirred solution of the methyl ketone 430 (1.05 g, 5.38 mmol) in MeOH (20 mL) was added CeCl₃·H₂O (2.05 g, 5.38 mmol). The reaction mixture was cooled to 0 °C and NaBH₄ (204 mg, 5.38 mmol) was added and stirred for 1 h at 0 °C. The resulting mixture was quenched with saturated aq. NH₄Cl (5 mL) and concentrated under reduced pressure. The residue was extracted with Et₂O (15 mL X 3). The combined organic layer was washed with brine, and dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 20 to 1 : 10) to give alcohol 431 (945 mg, 95%). 

1H NMR (500 MHz, CDCl₃) δ 5.85 - 5.75 (m, 1H), 5.40 (t, J = 7.2 Hz, 1H), 5.03 - 4.89 (m, 3H), 4.25 - 4.16 (m, 1H), 2.08 - 1.96 (m, 4H), 1.62 (s, 3H), 1.35 - 1.23 (m, 16H).

13C NMR (100 MHz, CDCl₃) δ 139.2, 138.3, 125.4, 114.0, 73.5, 33.8, 29.5, 29.5, 29.4, 29.3, 29.1, 28.9, 27.5, 21.6, 11.4.; IR (neat) νmax 3343, 2925 cm⁻¹. HRMS[EI] calcd for C₁₅H₂₆O [M]+ 224.21353, found 224.21353.

Epoxy alcohols 422 and 424 (model compounds). To a stirred suspension of activated 4 Å molecular sieves (0.4 g) in CH₂Cl₂ (34 mL) were added alcohol 431 (0.975 g, 4.97 mmol) and cooled at -20 °C. Ti reagent was added and the reaction mixture was stirred for 0.5 h. TBHP (2.2 mL, 0.993 mmol, 5.5 M) was added and the resulting mixture was stirred for 5 h at -20 °C. The mixture was quenched with water and warmed to rt. The mixture was filtered and extracted with CH₂Cl₂. The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20 to 1: 4) to
afford the anti-epoxy alcohol 422 (690 mg, 58 % : the fast moving isomer) and 424 (315 mg, 31 % : the slow moving isomer).

**Anti - epoxy alcohol 422:** \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.86 - 5.73 (m, 1H), 5.05 – 4.86 (m, 2H), 3.77 (q, \(J = 6.3\), 1H), 3.02 (t, \(J = 6.0\) Hz, 1H), 2.23 (s, 1H), 2.10 - 1.96 (m, 2H), 1.62 - 1.25 (m, 17H), 1.20 (d, \(J = 6.3\), 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.2, 114.1, 68.5, 63.6, 59.0, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.1, 26.4, 18.4, 14.3.; IR (neat) \(\nu_{\text{max}}\) 3450, 2926, 2855 cm\(^{-1}\). HRMS[El] calcd for C\(_{15}\)H\(_{28}\)O\(_2\) [M]\(^+\) 241.21676, found 241.21609.

**Syn- epoxy alcohol 424:** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.88 - 5.78 (m, 1H), 4.98 (dd, \(J = 17.2, 2.0\) Hz, 1H), 4.95 (m, 1H), 3.47 - 3.41 (m, 1H), 2.88 (t, \(J = 6.0\) Hz, 1H), 2.12 (d, \(J = 4.8\) Hz, 1H), 2.04 (q, \(J = 7.0\) Hz, 2H), 1.61 - 1.27 (m, 17H), 1.22 (d, \(J = 9.0\) Hz, 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.2, 114.1, 72.3, 63.9, 61.8, 33.8, 29.5, 29.4, 29.3, 28.9, 28.1, 26.4, 18.7, 11.3.; IR (neat) \(\nu_{\text{max}}\) 3418, 2926, 2856 cm\(^{-1}\). HRMS[ES+] calcd for C\(_{15}\)H\(_{28}\)O\(_2\) [M + Na]\(^+\) 263.1996, found 263.1987.

**Bn-protected alcohol 423.** To a stirred solution of epoxide 422 (457 mg, 2.02 mmol) in THF (9 mL) was added BnBr (414 mg, 2.43 mmol) and NaH (96.9 mg, 2.42 mmol, 60 %). The reaction mixture was stirred for 21 h. The resulting mixture was quenched with water (1 mL) and Et\(_2\)O (3 mL) was added. After separation, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 10 : 100 to 1: 20) to afford epoxide 423 (442 mg, 91 %). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.39 - 7.25 (m, 5H), 5.85 - 5.78 (m, 1H), 4.99 (dd, \(J = 17.4, 1.8\) Hz, 1H), 4.94 - 4.92 (m, 1H), 4.59 (d, \(J = 11.9\) Hz, 1H), 4.48 (d, \(J = 11.8\) Hz, 1H), 3.13 (q, \(J = 6.4\) Hz, 1H), 2.82 (t, \(J = 6.0\) Hz, 1H), 2.05 (m, 2H), 1.58 - 1.27 (m, 20H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.1, 138.5, 128.3, 127.5, 127.4, 114.1, 79.0, 71.1, 64.0, 61.0, 33.7, 29.4, 29.3, 28.1, 28.4, 26.4, 16.4, 11.4.; IR (neat) \(\nu_{\text{max}}\)
3065, 3030, 2976, 2926, 2855 cm⁻¹. HRMS[ES+] calcd for C₂₂H₃₄O₂ [M + Na]⁺ 353.2457, found 353.2449.

Bn-protected alcohol 425. To a stirred solution of epoxide 424 (74.9 mg, 0.312 mmol) in THF (1 mL) was added BnBr (63.9 mg, 0.374 mmol) and NaH (17.4 mg, 0.436 mmol, 60 %). The reaction mixture was stirred for 14 h. The resulting mixture was quenched with water (0.3 mL) and added Et₂O (3 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20) to afford epoxide 425 (89 mg, 91 %). ¹H NMR (400 MHz, CDCl₃) δ 7.38 - 7.23 (m, 5H), 5.86 - 5.76 (m, 1H), 4.99 (dd, J = 17.2, 1.6 Hz, 1H), 4.95 - 4.92 (m, 1H), 4.75 (d, J = 11.9 Hz, 1H), 4.53 (d, J = 11.9 Hz, 1H), 3.15 (q, J = 6.6 Hz, 1H), 2.61 (m, 1H), 2.04 (m, 2H), 1.68 - 1.30 (m, 17H), 1.20 (d, J = 6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 139.2, 138.7, 128.3, 127.6, 127.4, 114.1, 80.2, 71.1, 63.2, 59.0, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.0, 26.4, 17.9, 11.0; IR (neat) νₘₐₓ 3064, 3031, 2976, 2925, 2854 cm⁻¹. HRMS[ES+] calcd for C₂₂H₃₄O₂ [M + Na]⁺ 353.2457, found 353.2463.

Diol 433: To a stirred solution of epoxide 423 (31.5 mg, 0.10 mmol) in DMSO (0.35 mL) were added HMPA (0.35 mL) and Li-acetylene diamine complex (153 mg, 1.66 mmol). The reaction
mixture was stirred at 50 °C for 24 h. To the mixture were added saturated aq. NH₄Cl (1 mL) and H₂O (1 mL), and saturated aq. LiCl (1 mL). After separation, the organic layer was concentrated under reduced pressure and purified by a silica gel column chromatography to provide 433 (2.4 mg, 7%). ¹H NMR (400 MHz, CDCl₃) δ 7.36 - 7.31 (m, 5H), 5.74 - 5.88 (m, 1H), 5.03 - 4.90 (m, 3H), 4.68 (d, J = 11.4 Hz, 1H), 4.44 (d, J = 11.4 Hz, 1H), 3.66 (q, J = 6.3 Hz, 1H), 3.48 (q, J = 3.51 - 3.44 (m, 1H), 2.07 (d, J = 2.4 H, 1H), 1.30 - 1.25 (m, 19). ¹³C NMR (100 MHz, CDCl₃) δ 139.3, 128.4, 127.8, 127.7, 114.1, 85.1, 79.1, 75.4, 71.5, 71.2, 39.1, 33.8, 29.7, 29.5, 29.4, 29.1, 28.9, 28.6, 28.1, 20.6, 12.8.; IR (neat) νₘₐₓ 3307, 2926, 2854 cm⁻¹. HRMS[ES+] calcd for C₂₄H₃₆O₂ [M + Na]⁺ 379.2613, found 379.2615.

Diol 435 (X = TMS): To a stirred solution of TMS-acetylene (0.15 mL, 1.1 mmol) was added n-BuLi (0.43 mL, 0.696 mmol, 1.6 M) dropwise at - 15 °C and stirred for 30 min at the same temperature. Et₂AlCl (0.43 mL, 0.70 mmol) was added dropwise. The reaction mixture was warmed to O °C and stirred for 1.5 h at the same temperature. The epoxy alcohol 424 was added, and the resulting mixture was warmed to rt and stirred for 12 h. The reaction mixture was quenched with saturated aq. NH₄Cl solution and Et₂O was added. After separation, the organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 7) to afford diol 435 (26 mg, 42%). ¹H NMR (400 MHz, CDCl₃) δ 5.86 - 5.76 (m, 1H), 5.01 - 4.91 (m, 2H), 4.03 (d, J = 5.5 Hz, 1H), 2.58 (d, J = 9.9 Hz, 2H), 2.22 (s, 1H), 2.08 (s, 1H), 2.04 (q, J = 6.9 Hz, 2H), 1.43 - 1.36 (m, 14H), 1.17 (d, J = 6.4 Hz, 3H), 1.14 (s, 3H), 0.15 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 139.2, 114.1, 107.8, 88.5, 75.6, 70.9, 41.5, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.7, 28.1, 19.4, 17.0, 0.07.; IR (neat) νₘₐₓ 3392, 2923, 2852, 2161 cm⁻¹. HRMS[ES+] calcd for C₂₀H₃₈O₅Si [M + H]⁺ 339.2719, found 339.2722.
Ester 438. To a stirred solution of phosphonate 437 (4.72 g, 19.7 mmol) in THF (25 ml) was added NaH (0.984 mg, 24.6 mmol) at 0 °C and slowly warmed. The reaction mixture was stirred for 1 h at rt and cooled to 0 °C. 10-undecenal (428) (3.15 g, 16.45 mmol) was added and then the resulting mixture was warmed to rt. After 20 h, the mixture was quenched with water. After separation, the aqueous layer was extracted with Et<sub>2</sub>O (20 mL x 3). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20 to 1: 4) to afford ester 438 (3.24 g, 72 %).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.73 (t, <i>J</i> = 7.5 Hz, 1H), 5.77 (ddt, <i>J</i> = 17.0, 10.2, 6.7 Hz, 1H), 4.97 - 4.87 (m, 2H), 4.18 - 4.12 (q, <i>J</i> = 7.1 Hz, 2H), 2.13 (q, <i>J</i> = 7.4 Hz, 2H), 2.00 (q, <i>J</i> = 6.9 Hz, 2H), 1.79 (s, 3H), 1.42 - 1.24 (m, 15H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.1, 142.2, 138.9, 127.6, 114.0, 60.2, 33.7, 29.3, 29.2, 29.0, 28.8, 28.6, 28.5, 14.2, 12.2.; IR (neat) v<sub>max</sub> 2928, 1714 cm<sup>-1</sup>. HRMS[ES+] calcd for C<sub>16</sub>H<sub>28</sub>O<sub>2</sub> [M + H]<sup>+</sup> 253.2168, found 253.2170.

Alcohol 439. To a solution of the ester 438 (2.04 g, 8.09 mmol) in THF (95 mL) was added LAH (very slowly) (321 mg, 8.45 mmol) and stirred at rt. After 24 h, it was quenched with water (15 mL) and extracted with Et<sub>2</sub>O (20 mL x 3). The combined organic mixture was concentrated reduced pressure and purified by silica gel column chromatography (eluent with EtOAc : hexane = 1 : 20) to give alcohol 439 (941 mg, 55 %).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.86 - 5.76 (m, 1H), 5.41 (td, <i>J</i> = 7.2, 1.2, 1H), 4.99 (dddd, <i>J</i> = 17.2, 3.6, 1.6, 1H), 4.93 (dm, <i>J</i> = 10.2, 1H), 4.00 (s, 2H), 2.03 (quint, <i>J</i> = 7.1, 4H), 1.66 (s, 3H), 1.39 - 1.28 (m, 12H).<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)
Epoxide 426. To the alcohol 439 (225 mg, 1.07 mmol) solution in CH$_2$Cl$_2$ (3 ml) was added mCPBA (251 mg, 1.12 mmol, max 77%) at 0 °C and stirred for 1 h. 10 % KOH solution was added and extracted with CH$_2$Cl$_2$ (5 ml X 2) and dried over MgSO$_4$ and concentrated under reduced pressure. After silica gel column chromatography, 211 mg epoxide 426 was obtained in 88 % yield. $^1$H NMR (300 MHz, CDCl$_3$) δ $^1$H NMR (400 MHz, CDCl$_3$) δ 5.85 - 5.75 (m, 1H), 4.98 (ddd, $J$ = 17.1, 3.6, 1.6 Hz, 1H), (dm, $J$ = 10.2 Hz, 1H), 3.67 (dd, $J$ = 12.2, 3.7 Hz, 1H), 3.56 (dd, $J$ = 12.2, 8.1 Hz, 1H), 3.02 (m, 1H), 2.03 (q, $J$ = 6.8 Hz, 2H), 1.71 (s, 1H), 1.58 - 1.27 (m, 17). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.0, 114.0, 65.5, 60.9, 60.3, 33.7, 29.3, 29.2, 29.0, 28.8, 28.1, 26.3, 14.1. ; IR (neat) $\nu$$_{\text{max}}$ 3418, 3077, 2924 cm$^{-1}$.

Bn-protected alcohol 427. To a stirred solution of epoxide 426 (183 mg, 0.809 mmol) in THF (3 mL) was added BnBr (168 mg, 0.971 mmol) and NaH (38.9 mg, 0.971 mmol, 60 %). The reaction mixture was stirred for 21 h and it was quenched with water (1 mL) and Et$_2$O was added. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent with EtOAc : hexane = 1: 20) to afford the Bn-protected epoxy alcohol 427 (249 mg, 97 %). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42 - 7.23 (m, 5H), 5.88 - 5.75 (m, 1H), 5.03 - 4.91 (m, 2H), 4.59 (d, $J$ = 12.3 Hz, 1H), 4.53 (d, $J$ = 12.0 Hz, 1H), 3.50 (d, $J$ = 10.9 Hz, 1H), 3.44 (d, $J$ = 10.9 Hz, 1H), 2.87 - 2.84 (m, 1H), 1.59 - 1.30 (m, 17H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.2, 138.1, 128.3, 127.7, 114.1, 74.9, 73.1, 61.1, 59.7, 33.8, 29.5, 29.4,
29.3, 29.1, 28.9, 28.2, 26.5, 14.5.; IR (neat) $\nu_{\text{max}}$ 3065, 3031, 2926, 2854 cm$^{-1}$. HRMS[ES+] calcd for C$_{21}$H$_{32}$O$_2$ [M + Na]$^+$ 339.2300, found 339.2305.

**Diol 440**: To a stirred solution of TMS-acetylene (0.15 mL, 1.1 mmol) was added n-BuLi (0.44 mL, 0.70 mmol, 1.6 M) dropwise at -30 °C and stirred for 30 min at the same temperature. The resulting mixture was warmed to 0 °C and added Et$_2$AlCl (0.70 mL, 0.70 mmol, 1.0 M) dropwise and stirred for 1.5 h at 0 °C. The epoxy alcohol 426 (53 mg, 0.23 mmol) was added and the mixture was warmed to rt and stirred for 17 h. The reaction mixture was quenched with saturated aq. NH$_4$Cl (1 mL) and Et$_2$O (2 mL) were added. After separation, the aqueous layer was extracted with Et$_2$O (3 mL X 4). The combined organic layer was concentrated under reduced pressure and purified by a silica gel column chromatography (eluent with EtOAc : hexane = 1 : 7) to afford diol 440 (41 mg, 55%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.81 (ddt, $J = 17.0, 10.2, 6.7$ Hz, 1H), 4.99 (dd, $J = 17.1, 1.6$ Hz, 1H), 4.92 (d, $J = 9.5$ Hz, 1H), 3.78 (d, $J = 11.0$ Hz, 1H), 3.48 (d, $J = 11.0$ Hz, 1H), 2.53 - 2.50 (m, 1H), 2.06 - 2.01 (m, 2H), 2.26 (br s, 1H), 2.13 (br, 1H), 1.71 - 1.60 (m, 1H), 1.37 - 1.29 (m, 13H), 1.19 (s, 3H), 0.14 (s, 9H). NMR (100 MHz, CDCl$_3$) $\delta$ 139.2, 114.1, 107.2, 88.3, 74.0, 68.8, 41.2, 33.8, 29.5, 29.4, 29.3, 29.1, 28.9, 28.6, 28.1, 20.2, - 0.05.; IR (neat) $\nu_{\text{max}}$ 3343, 2921, 2850, 2159 cm$^{-1}$. HRMS[ES+] calcd for C$_{19}$H$_{36}$O$_2$Si [M + H]$^+$ 325.2563, found 325.2568.
**Epoxy Alcohol 442.** Regio- and stereoselective epoxidation was accomplished by the catalytic procedure of Sharpless. To a stirred suspension of activated 4 Å molecular sieves (1.6 g) in CH$_2$Cl$_2$ (124 mL) under argon were added alcohol 411 (2.59 g, 12.3 mmol) and D-(-)-DET (381 mg, 1.85 mmol). The resulting mixture was stirred and cooled to -20 °C. A solution of Ti(OiPr)$_4$ (350 mg, 1.23 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise and stirred at -20 °C for 30 min. Then TBHP (4.50 mL, 24.7 mmol, 5.5 M in decane with molecular sieves) was added dropwise and the resulting mixture was cooled to -26 to -30 °C. After 2.5 h, it was warmed to 0 °C, water (7 mL) was added, and the solution was allowed to warm to room temperature. A 30% NaOH solution saturated with solid NaCl was prepared. Of this, 1.4 mL was added to the reaction mixture. Vigorous stirring was continued for 30 min. Then the reaction mixture was filtered through Celite and the filter cake was washed with CH$_2$Cl$_2$. The combined organic solution was concentrated under reduced pressure and subjected to silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4 to 1 : 1) to afford epoxide 442 (2.42 g, 83 %) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.28 (s, 3 H), 1.69 (s, 3 H), 1.79 – 1.65 (m, 2H), 1.84 (d, $J = 5.0$ Hz, 1H), 2.20 (m, 1H), 3.03 (t, $J = 6.5$ Hz, 1H), 3.60 (dd, $J = 12.3$, 8.3 Hz, 1H), 3.61 (dd, $J = 12.5$, 4.3 Hz, 1H), 3.98 (t, 4H), 5.18 (d, $J = 10.5$ Hz, 1H), 5.27 (d, $J = 17.5$ Hz, 1H), 5.41 (t, $J = 6.5$ Hz, 1H), 5.92 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.2, 16.3, 26.3, 36.1, 60.0, 60.9, 65.6, 66.4, 71.1, 117.0, 121.5, 134.8, 138.9.; IR (neat) $\nu_{max}$ 3441, 2925, 2857, 1741, 1670, 1647, 1449, 1384 cm$^{-1}$. HRMS[ES+] calcd for C$_{13}$H$_{22}$O$_3$ [M + Na]$^+$ 249.1467, found 249.1456. The enantiomeric excess was determined to be 93 % ee by comparison of the $^1$H NMR of the (S)-MTPA and the (R)-MTPA ester.
Diols 443 and 444. To a solution of TMS-acetylene (1.33 mL, 9.31 mmol) in toluene (12 mL) was added n-BuLi (2.8 mL, 6.98 mmol, 2.5 M) for 3 min at -60 °C. The reaction mixture was warmed to 0 °C. Et₂AlCl (7.0 mL, 6.98 mmol, 1.0 M) was added dropwise for 20 min and the resulting mixture was stirred for 1h at 0 °C and an ice bath was removed. The solution of epoxide 442 (535 g, 2.27 mmol) in toluene (7 mL) was added and the mixture was directly immersed a pre-heated (50 - 60 °C) oil bath. The reaction mixture was stirred overnight. The mixture was quenched with saturated aq. NH₄Cl and water. Et₂O was added and the aqueous layer was extracted with Et₂O (15 mL X 3 times). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue (a ratio of 443 : 444 = 3.5 : 1.0) was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 4) to give 443 (484 mg, a ratio of 443 : 444 = 2.6 : 1.0, 66 %) and 444 (118 mg, a ratio of 443 : 444 = 1 : 1, 16 %).

Slow moving isomer 443: ¹H NMR (400 MHz, CDCl₃) δ 5.97 - 5.88 (m, 1H), 5.41 (td, J = 6.8, 1.2 Hz, 1H), 5.27 (dq, J = 17.2, 1.6 Hz, 1H), 5.20 (dd, J = 10.4, 1.2 Hz, 1H), 4.02 – 3.95 (m, 4H), 3.77 (d, J = 11.2 Hz, 1H), 3.47 (d, J = 11.2 Hz, 1H), 2.50 (dd, J = 12.0, 3.2 Hz, 1H), 2.36 - 2.30 (m, 3H), 2.12 - 2.04 (m, 1H), 1.84 (dddd, J = 12.8, 10.1, 7.2, 3.3 Hz, 1H), 1.68 (s, 3H), 1.52 - 1.43 (m, 1H), 1.18 (s, 3H), 0.14 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 140.0, 135.0, 121.3, 117.2, 107.0, 88.4, 74.0, 71.1, 68.9, 66.5, 40.2, 37.8, 26.7, 19.9, 16.5, 0.04.; IR (neat) νmax 3408, 2958, 2167 cm⁻¹. HRMS[ES+] calcd for C₁₈H₃₂O₃Si [M + Na]+ 347.2018, found 347.2015.


Mixture of isomer 443 and 444 (ratio = 1 : 1) : ¹H NMR (400 MHz, CDCl₃) δ 5.98 - 5.88 (m, 1H), 5.45 - 5.40 (m, 1H), 5.27 (dd, J = 17.2, 0.6 Hz, 1H), 5.18 (d, J = 10.4, 1H), 4.06 – 3.97 (m,
Aldehyde 445. To a solution of 443 (660 g, 2.04 mmol, a ratio of 443 : 444 = 2.6 : 1.0) in CH₂Cl₂ was added DIPEA (1.368 g, 10.58 mmol) and DMSO (1.670 g, 21.37 mmol) and cooled to 0 °C. SO₃Py complex (992 mg, 6.107 mmol) was added and stirred for 30 min at 0 °C. The reaction mixture was warmed to 10 °C and stirred for 4 h. 1N HCl was added to adjust pH 3 ~ 4. After separation, CH₂Cl₂ (5 mL) was added and washed with NaHCO₃ (sat.) and brine. It was dried over MgSO₄ and concentrated under reduced pressure. The crude aldehyde 445 (908 g) was directly used in a Barbier addition. ¹H NMR (400 MHz, CDCl₃) δ 9.74 (d, J = 0.7 Hz, 1H), 5.92 (ddt, J = 16.9, 10.3, 5.6 Hz, 1H), 5.39 (t, J = 6.4 Hz, 1H), 5.27 (dd, J = 17.2, 1.6 Hz, 1H), 5.18 (dd, J = 10.4, 0.8, 1H), 3.97 (t, J = 7.2 Hz, 4H), 3.16 (br s, 1H), 2.47 (dd, J = 11.6, 3.6 Hz, 1H), 2.34 - 2.28 (m, 1H), 2.12 - 2.04 (m, 1H), 1.73 - 1.58 (m, 1H), 1.65 (s, 3H), 1.38 (s, 3H), 0.16 (d, J = 0.8 Hz, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 139.9, 135.0, 121.4, 121.5, 117.3, 107.2, 88.6, 74.2, 71.2, 69.0, 66.7, 66.6, 40.4, 37.9, 26.9, 20.1, 20.0, 16.6, 16.5, 0.2.; IR (neat) ν_max 3422, 2959, 2169, 1734, 1251 cm⁻¹.
Diols 446 and 447. To a solution of aldehyde 445 (908 g) in THF (18 mL) were added saturated aq. NH₄Cl (9 mL), bromide 326 (896 mg, 5.49 mmol), and Zn dust (599 mg). The resulting mixture was stirred for 20 h. If 445 is left, Zn dust and bromide will be added more (the conversion should be checked by proton NMR because TLC does not show clearly a progress of the reaction). The reaction mixture was extracted with Et₂O (10 mL X 3 times) and filtered throughout Celite to remove Zinc dust. The organic layer was washed with brine and dried over MgSO₄ and concentrated under reduced pressure. The residue (a ratio of 446 : 447 = 2 : 1) was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 9) to provide 446 (165 mg, 28 % for 2 steps based on 443), and 447 (132 mg, 22 % for 2 steps based on 443), and the mixture of 446 and 447 (121 mg, 20 % for 2 steps based on 443).

Slower moving isomer (major 446): ¹H NMR (300 MHz, CDCl₃) δ 6.00 - 5.86 (m, 1H), 5.44 - 5.40 (m, 1H), 5.28 (dq, J = 17.4, 1.5 Hz, 1H), 5.18 (dm, J = 10.2 Hz, 1H), 4.83 (s, 1H), 4.04 - 3.93 (m, 4H), 3.78 (d, J = 10.8 Hz, 1H), 2.60 (d, J = 13.6 Hz, 1H), 2.46 (dd, J = 11.4, 3.3 Hz, 1H), 2.42 – 2.21 (m, 3H), 2.18 – 2.00 (m, 3H), 1.99 – 1.86 (m, 1H), 1.69 (s, 3H), 1.57 - 1.49 (m, 1H), 1.31 (s, 3H), 1.11 - 1.09 (d, J = 4.5 Hz, 3H), 1.07 (d, J = 4.5 Hz, 3H), 0.13 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 153.3, 140.0, 135.0, 116.9, 110.8, 106.7, 88.2, 76.7, 74.8, 72.1, 71.0, 66.5, 39.6, 37.8, 36.3, 32.9, 27.1, 22.4, 21.5, 20.7, 16.5, 0.04.

Faster moving isomer (minor 447): ¹H NMR (500 MHz, CDCl₃) δ 5.97 - 5.90 (m, 1H), 5.42 (t, J = 6.5 Hz, 1H), 5.28 (dq, J = 17.0, 1.5 Hz, 1H), 5.18 (dq, J = 10.5, 1.5 Hz, 1H), 4.98 (s, 1H), 4.85 (s, 1H), 4.04 (dd, J = 11.0, 2.5 Hz, 1H), 4.01 - 3.96 (m, 4H), 2.70 (dd, J = 11.5, 3.0 Hz, 1H), 2.42 (d, J = 13.5 Hz, 1H), 2.38 - 2.31 (m, 1H), 2.28 (quint, J = 7.0 Hz, 1H), 2.14 (dd, J = 11.0 Hz, 1H), 2.11 - 2.05 (m, 1H), 1.96 - 1.90 (m, 1H), 1.68 (s, 3H), 1.55- 1.47 (m, 1H), 1.15 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.14 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ
153.0, 139.9, 135.0, 121.2, 116.9, 110.6, 108.0, 87.7, 75.3, 71.2, 70.9, 66.5, 40.8, 38.1, 36.4, 33.4, 26.7, 22.1, 21.5, 17.8, 16.4, 0.04.; IR (neat) ν\text{max} 3397, 3082, 2963, 2164, 1640, 1452, 1250 cm\textsuperscript{-1}.

406 : To a stirred solution of 446 (165 mg, 0.405 mmol) in THF (12 mL) was added TBAF (0.47 mL, 0.461 mmol, 1.0 M). The reaction mixture was stirred for 5 h and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent with EtOAc : hexane = 1 : 4) to provide 446 (138 mg, 99 %). The \textsuperscript{1}H NMR data were consistent with the reported values of the same product, which was synthesized from 448.

Diol 410. To a stirred solution of epoxide 442 (933 mg, 3.95 mmol) in DMSO (13 mL) and HMPA (13 mL) under argon was added Li-acetylide-ethylenediamine complex (2.02 g, 19.8 mmol, 90 %) at room temperature. The mixture was warmed to 55 °C and stirred for 3.5 h. The reaction mixture was carefully quenched with saturated aq. NH\textsubscript{4}Cl (3 mL) at 0 °C and the resulting mixture was diluted with Et\textsubscript{2}O (45 mL). Then saturated aq. LiCl was added very carefully. The resulting mixture was separated and the aqueous solution was extracted with Et\textsubscript{2}O (20 mL X 5). The combined organic solution was dried over MgSO\textsubscript{4}, decolorized with activated
charcoal, and concentrated under reduced pressure. Silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 1) provided diol 410 (814 mg, 82 %) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.10 (s, 3H), 1.43 (m, 1H), 1.61 (s, 3H), 1.84 (s, 1H), 2.03 (m, 1H), 2.07 (d, $J$ = 2.8 Hz, 1H), 2.28 (m, 1H), 2.43 (dt, $J$ = 11.6, 2.6 Hz, 1H), 3.05 (br, 1H), 3.40 (d, $J$ = 11.2 Hz, 1H), 3.70 (d, $J$ = 11.2 Hz, 1H), 3.92 (m, 4H), 5.12 (dd, $J$ = 10.4, 4.0 Hz, 1H), 5.21 (dd, $J$ = 17.2, 1.2 Hz, 1H), 5.35 (td, $J$ = 7.2, 1.2 Hz, 1H), 5.85 (ddt, $J$ = 17.2, 10.4, 5.6 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 16.3, 19.3, 26.3, 37.5, 38.3, 66.3, 68.4, 70.8, 71.4, 73.9, 84.5, 117.0, 120.9, 134.6, 139.6.; IR (neat) $\nu$$_{\text{max}}$ 3418, 3080, 2935, 2110, 1668, 1646, 1455, 1381 cm$^{-1}$. HRMS[ES+] calcd for C$_{15}$H$_{24}$O$_3$ [M + Na]$^+$ 275.1623, found 275.1615.

**Aldehyde 448.** Oxidation was performed by the Parikh-Doering method. To a stirred solution of diol 410 (200 mg, 0.793 mmol) in CH$_2$Cl$_2$ (5.5 mL) were added DMSO (495 mg, 6.34 mmol) and N,N-diisopropylamine (DIPEA) (410 mg, 3.17 mmol). Then the reaction mixture was cooled to 0 °C under argon. The SO$_3$·Py complex (322 mg, 1.98 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. Then it was warmed to 10 °C and stirred for 2 h. Additional DMSO (0.14 mL, 1.97 mmol), DIPEA (0.10 mL, 0.57 mmol), and SO$_3$·Py complex (130 mg, 98%, 0.80 mmol) were added and stirring was continued for 1 h. The reaction mixture was quenched with 1N HCl (3 mL) and extracted with CH$_2$Cl$_2$ (5 mL X 2). The combined organic solution was washed with saturated aq. NaHCO$_3$ and brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford aldehyde 448 as a colorless oil (142 mg, 71 %). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.34 (s, 3H), 1.59 (s, 3H), 1.61 (m, 1H), 2.01 - 2.10 (m, 1H), 2.18 (d, $J$ = 2.4 Hz, 1H), 2.24 - 2.31 (m, 1H), 2.46 (dd, $J$ = 10.4, 4.4, 2.4 Hz, 1H), 3.35 (br, 1H), 3.91 (m, 4H), 5.12 (dd, $J$ = 10.2, 1.6 Hz, 1H), 5.21 (dd, $J$ = 17.2, 1.6 Hz, 1H), 5.34 (td, $J$ = 6.4, 0.8 Hz,
1H), 5.86 (m, 1H), 9.66 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.2, 19.6, 26.8, 36.9, 38.4, 66.2, 70.8, 73.2, 78.0, 81.9, 116.8, 121.7, 134.8, 138.6, 203.3.; IR (neat) $\nu_{\text{max}}$ 3430, 3295, 3080, 2935, 2859, 1732, 1669, 1646, 1452, 1349 cm$^{-1}$. HRMS[ES+] calcd for C$_{13}$H$_{22}$O$_3$ [M + H]$^+$ 251.1647, found 251.1657.

Diols 406 and 449. The allylation procedure of Luche et al. was used. To a stirred solution of aldehyde 448 (374 mg, 1.43 mmol) in THF (10 mL) and saturated aq. NH$_4$Cl (5 mL) were added 2-bromo-methyl-3-methyl-1-butene (326) (1.07 g, 6.57 mmol) and activated Zn dust (683 mg, 10.5 mmol). The reaction mixture was stirred for 12 h under argon and diluted with Et$_2$O (10 mL). The resulting mixture was filtered through Celite and the filter cake was washed with Et$_2$O. After separation of the layers, the aqueous phase was extracted with Et$_2$O (10 mL X 3). The combined organic solution was washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was subjected to column chromatography (elution with EtOAc : Hexane = 1 : 4) to afford a mixture of 5a and 13a (398 mg, 80 %, d.r. 5a : 13a = 1.8 : 1.0).

A sample of the mixture was subjected to additional chromatography and spectroscopic data were obtained for each isomer.

Slower moving isomer, later shown to be 406 (colorless oil) : $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.07 (d, $J = 7.0$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.32 (s, 3H), 1.57 (m, 1H), 1.69 (s, 3H), 1.97 (m, 1H), 2.02 (m, 1H), 2.07 – 2.14 (m, 3H), 2.29 (m, 1H), 2.37 (m, 1H), 2.47 (dt, $J = 11.5$, 2.6 Hz, 1H), 2.58 (d, $J = 13.5$ Hz, 1H), 3.79 (dd, $J = 9.0$, 2.0 Hz, 1H), 3.98 (dd, $J = 11.5$, 6.0 Hz, 4H), 4.84 (s, 1H), 4.98 (s,1H), 5.17 (d, $J = 10.5$ Hz, 1H), 5.27 (dd, $J = 15.5$, 1.5, 1H), 5.43 (td, $J = 5.5$, 1.0 Hz, 1H), 5.89 – 5.97 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 16.5, 20.7, 21.4, 22.2, 26.9,
33.0, 36.2, 37.7, 38.4, 66.5, 70.9, 71.8, 71.9, 74.7, 84.2, 110.8, 116.9, 121.3, 135.0, 139.7, 153.2.; IR (neat) $\nu_{\text{max}}$ 3454, 3307, 3081, 2962, 2871, 1640, 1455, 1379 cm$^{-1}$. HRMS[ES+] calcd for C$_{21}$H$_{34}$O$_3$ [M + Na]$^+$ 357.2406, found 357.2398.

**Faster moving isomer, later shown to be 449** (white solid): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.07 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.16 (s, 3H), 1.53 (m, 1H), 1.68 (s, 3H), 1.96 (m, 1H), 2.05 – 2.11 (m, 1H), 2.11 (d, $J = 2.4$ Hz, 1H), 2.13 – 2.19 (m, 1H), 2.18 (d, $J = 2.0$ Hz, 1H), 2.25 (s, 1H), 2.25 – 2.30 (m, 1H), 2.33 – 2.40 (m, 1H), 2.41 (d, $J = 14.0$ Hz, 1H), 2.71 (dt, $J = 11.6$, 2.8 Hz, 1H), 3.96 (dt, $J = 6.0$, 1.2 Hz, 2H), 3.99 – 4.02 (m, 3H), 4.85 (s, 1H), 4.99 (s, 1H), 5.17 (dd, $J = 10.4$, 1.6 Hz, 1H), 5.27 (dq, $J = 17.6$, 1.6 Hz, 1H), 5.42 (td, $J = 6.8$, 0.8 Hz, 1H), 5.93 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.5, 17.6, 21.5, 22.2, 26.7, 33.3, 36.4, 37.9, 39.5, 66.5, 70.8, 70.9, 71.3, 75.2, 85.3, 110.6, 116.9, 121.3, 135.0, 139.8, 153.0.; IR (neat) $\nu_{\text{max}}$ 3382, 3304, 3229, 2961, 2916, 2850, 1643, 1455, 1391 cm$^{-1}$. HRMS[ES+] calcd for C$_{21}$H$_{34}$O$_3$ [M + Na]$^+$ 357.2401. mp = 53 - 55 °C.

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**Acetonide 453:** To a stirred solution of diol 406 (200 mg, 0.602 mmol) in CH$_2$Cl$_2$ (6.0 mL) were added 2,2-dimethyloxypropane (0.15 mL, 1.2 mmol) and p-TsOH (11.5 mg, 0.0602 mmol). The reaction mixture was stirred for 2 h at rt. The mixture was quenched with saturated aq. NaHCO$_3$ to adjust pH 7. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL X 2). The combined organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with EtOAc : Hexane = 1 : 20) to provide 453 (196 mg, 93 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.95 - 5.85 (m, 1H), 5.41 (td, $J = 6.8$, 0.8 Hz, 1H), 5.25 (dq, $J = 17.2$, 1.2, 1H), 4.85 (d, $J = 3.6$, 2H), 3.98 - 3.93 (m, 5H), 2.62 (d, $J = 15.6$ Hz, 1H), 2.49 (dt, $J = 11.6$, 2.4 Hz, 1H), 2.38
- 2.26 (m, 3H), 2.13 (d, $J = 2.4$ Hz, 1H), 2.08 - 2.00 (m, 2H), 1.66 (s, 3H), 1.34 (s, 6H), 1.33 (s, 3H), 1.04 (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 152.8, 139.4, 134.9, 121.4, 116.8, 107.7, 106.8, 85.3, 83.1, 82.5, 72.2, 70.8, 66.5, 37.3, 35.8, 33.9, 33.8, 28.2, 27.4, 26.5, 21.7, 21.6, 19.9, 16.5.; IR (neat) $\nu_{\text{max}}$ 3308, 3081, 2982, 2935, 2871, 1645, 1378 cm$^{-1}$.

**Acetonide 456:** To a stirred solution of diol 449 (24.4 mg, 0.071 mmol) in CH$_2$Cl$_2$ (3.5 mL) were added 2,2-dimethoxypropane (14.7 mg, 0.14 mmol) and $p$-TsOH (1.4 mg, 0.007 mmol). The reaction mixture was stirred for 2 h at rt. The mixture was quenched with saturated aq. NaHCO$_3$ to adjust pH 7. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL X 2). The combined organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : Hexane = 1 : 20) to provide 453 (25 mg, 99 %). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.00 - 5.86 (m, 1H), 5.43 (td, $J = 6.9, 1.2$ Hz, 1H), 5.27 (dq, $J = 17.1, 1.8$ Hz, 1H), 5.18 (dm, $J = 10.5, 1H$), 4.90 (d, $J = 1.5$ Hz, 1H), 4.86 (s, 1H), 2.02 (dd, $J = 10.2, 1.5$ Hz, 1H), 4.01 - 3.95 (m, 4H), 2.61 (d, $J = 15.9$ Hz, 1H), 2.38 (dt, $J = 11.4, 2.7$ Hz, 1H), 2.33 - 2.20 (m, 3H), 2.12 (d, $J = 2.7$ Hz, 1H), 2.16 - 2.10 (m, 1H), 1.99 - 1.93 (m, 1H), 1.68 (s, 3H), 1.56 - 1.53 (m, 1H), 1.41 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H), 1.06 (d, $J = 2.1$ Hz, 3H), 1.04 (d, $J = 1.8$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 135.0, 139.3, 135.0, 121.5, 116.9, 106.7, 84.1, 82.5, 81.9, 72.1, 71.0, 66.5, 41.5, 37.3, 35.6, 33.7, 28.6, 27.8, 26.6, 21.8, 21.7, 17.4, 16.4.
Five membered ring 437: To a solution of 456 (18.8 mg, 0.0521 mmol) was added Grubb’s 1st catalyst (12.9 mg, 0.0156 mmol). The reaction mixture was heated by a microwave (setting temp. 150 °C, W = 100). The temperature of the microwave was increased to 115 °C for 10 min and to 139 °C for 30 min. The resulting mixture was cooled to 65 °C for 20 min. The mixture was concentrated under reduced pressure. The residue was purified by PTLC (eluent with EtOAc : hex = 20 : 1) to provide 457 (6.4 mg, 40 %). \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 6.54 (dd, \(J = 17.4, 11.4\) Hz, 1H), 5.09 (d, \(J = 17.4\) Hz, 1H), 5.05 (d, \(J = 11.2\) Hz, 1H), 4.87 (d, \(J = 7.1\) Hz, 2H), 4.11 (t, \(J = 5.8\) Hz, 1H), 3.03 (d, \(J = 8.8\) Hz, 1H), 2.53 - 2.47 (m, 1H), 2.25 (quint, \(J = 6.6\) Hz, 1H), 2.16 - 2.12 (m, 3H), 2.08 - 2.05 (m, 1H), 1.95 - 1.89 (m, 1H), 1.81 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.06 (s, 3H), 1.03 (d, \(J = 7.2\) , 6H).

Carbonates 5b+13b. To a stirred solution of the mixture of 5a and 13a (177 mg, 0.528 mmol) in DMF (1.7 mL) under argon was added NaH (44.3 mg, 60%, 1.11 mmol). The reaction mixture was stirred for 15 min and then 1,1’-carbonyldiimidazole (CDI) (530 mg, 3.17 mmol) was added slowly. The resulting mixture was stirred at room temperature for 4 h. Et\(_2\)O and saturated aq. NH\(_4\)Cl were added and the resulting mixture was stirred for 10 min. After separation of the two
layers, the organic solution was washed with water (1.5 mL X 3) and brine and then dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution with EtOAc : hexane = 1 : 4) to provide a mixture of carbonates 5b and 13b (175 mg, 92 %) as a colorless oil. Without further purification, the mixture of carbonate 5b and 13b was directly used for the next step.

For the purpose of characterization, each carbonate isomer was prepared from the corresponding diol (see above).

**Major product**: ¹H NMR (600 MHz, CDCl₃) δ 1.04 (t, J = 6.6 Hz, 6H), 1.56 (s, 3H), 1.65 (m, 1H), 1.66 (s, 3H), 1.87 – 1.94 (m, 1H), 2.11 (m, 1H), 2.24 – 2.37 (m, 4H), 2.69 (d, J = 11.4 Hz, 1H), 2.81 (d, J = 15.0 Hz, 1H), 3.97 (dd, J = 12.6, 6.0 Hz, 4H), 4.46 (d, J = 12.0, 1H), 4.85 (s, 1H), 4.93 (s, 1H), 5.15 (d, J = 10.2 Hz, 1H), 5.28 (d, J = 18.0 Hz, 1H), 5.41 (t, J = 6.6 Hz, 1H), 5.87 – 5.94 (m, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 16.3, 20.5, 21.4, 21.6, 27.4, 33.5, 33.7, 35.3, 36.9, 66.3, 71.0, 73.5, 81.9, 84.9, 85.7, 110.6, 116.9, 122.2, 134.8, 149.5, 153.4.; IR (neat) νₘₐₓ 3288, 3083, 2964, 2872, 1808, 1646, 1455, 1384 cm⁻¹. HRMS[ES+] calcd for C₂₂H₃₂O₄ [M + Na]⁺ 383.2198, found 383.2199

**Minor product**: ¹H NMR (400 MHz, CDCl₃) δ 1.04 (d, J = 4.8 Hz, 3H), 1.06 (d, J = 4.8 Hz, 3H), 1.43 (s, 3H), 1.59 (m, 1H), 1.67 (s, 3H), 1.86 – 1.94 (m, 1H), 2.12 (m, 1H), 2.22 (d, J = 2.4 Hz, 1H), 2.26 – 2.38 (m, 2H), 2.40 (d, J = 10.4 Hz, 1H), 2.51 (d, J = 15.2 Hz, 1H), 2.65 (dt, J = 8.8, 2.4 Hz, 1H), 3.98 (m, 4H), 4.64 (dd, J = 8.0, 2.4 Hz, 1H), 4.90 (s, 1H), 4.94 (s, 1H), 5.18 (dd, J = 10.4, 1.2 Hz, 1H), 5.28 (dd, J = 17.6, 1.6 Hz, 1H), 5.42 (t, J = 6.4 Hz, 1H), 5.88 – 5.98 (m, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 15.7, 16.3, 21.5, 21.6, 27.0, 33.5, 35.4, 36.9, 41.3, 66.5, 71.1, 73.5, 81.2, 83.8, 85.8, 110.5, 117.0, 122.4, 134.9, 138.2, 149.9, 153.2.; IR (neat) νₘₐₓ 3288, 2962, 2871, 1805, 1646, 1455, 1385 cm⁻¹. HRMS[ES+] calcd for C₂₂H₃₂O₄ [M + Na]⁺ 383.2198, found 383.2194.
Bicyclic dienes 461 and 464. To a stirred solution of the mixture of carbonates 459 (31.7 mg, 0.088 mmol) in toluene (8.8 mL) under Argon was added 30 mol % Stewart -Grubbs catalyst (15.0 mg, 0.026 mmol). The resulting mixture was stirred at 80 °C for 24 h. After cooling down to room temperature, the reaction mixture was concentrated. The residue was subjected to silica gel flash column chromatography (elution with EtOAc : hexane = 1 : 4) to give diene 461 (10.3 mg, 45 %) as an oil and diene 464 (7.4 mg, 32 %) as an oil.

461: 1H NMR (400 MHz, CDCl3) δ 1.26 (d, 3.2 Hz, 1H), 1.35 (d, J = 3.6 Hz, 3H), 1.33 (s, 3H), 1.74 (s, 3H), 1.89 – 1.95 (m, 1H), 1.99 – 2.07 (m, 1H), 2.31 (dd, J = 14.8, 4.0 Hz, 1H), 2.35 – 2.37 (m, 3H), 2.97 (t, J = 12.8 Hz, 1H), 3.64 (d, J = 8.0 Hz, 1H), 4.27 (dd, J = 12.2, 3.8 Hz, 1H), 6.07 (s, 1H). 13C NMR (100 MHz, CDCl3) δ 14.2, 20.9, 20.9, 21.2, 23.3, 30.2, 37.5, 37.8, 50.8, 84.6, 87.1, 120.1, 131.2, 139.3, 139.6, 153.9.; IR (neat) νmax 2960, 2927, 1805, 1466, 1383 cm⁻¹. HRMS[ES+] calcd for C16H22O3 [M + Na]⁺ 285.1467, found 285.1462.

464: 1H NMR (400 MHz, CDCl3) δ 1.04 (t, J = 7.6 Hz, 6H), 1.17 (s, 3H), 1.73 – 1.78 (m, 1H), 1.77 (s, 3H), 2.03 (m, 1H), 2.38 (sext, 4H), 2.67 (dd, J = 17.2, 4.4 Hz, 1H), 3.03 (m, 1H), 4.42 (dd, J = 12.0, 4.4 Hz, 1H), 6.19 (s, 1H). 13C NMR (100 MHz, CDCl3) δ 13.0, 14.5, 21.5, 22.1, 23.8, 28.4, 37.7, 39.0, 54.9, 84.9, 87.5, 118.5, 129.4, 137.1, 142.6, 154.9.; IR (neat) νmax 2961, 2930, 1809, 1462, 1382 cm⁻¹. HRMS[ES+] calcd for C16H22O3 [M + Na]⁺ 285.1467, found 285.1470.
**Diol 450.** To a stirred solution of carbonate 461 (67.2 mg, 0.256 mmol) in dioxane (3.2 mL) was added 1N NaOH (0.7 mL) and the resulting mixture was stirred for 14 h at room temperature. The reaction was quenched with saturated aq. NH₄Cl and the resulting mixture was diluted with Et₂O. After separation of layers, the aqueous layer was extracted with Et₂O (5 mL X 2) and the combined organic solution was washed with brine and water, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to provide diol 450 (58.7 mg, 97 %) as a colorless oil. $^1$H NMR (600 MHz, CDCl₃) δ 1.02 (s, 3H), 1.04 (s, 3H), 1.13 (s, 3H), 1.73 (s, 3H), 1.90 – 2.02 (m, 2H), 2.06 (dd, $J = 16.8, 1.2$ Hz, 1H), 2.14 (s, 1H), 2.20 (dd, $J = 16.8, 9.6$ Hz, 1H), 2.33 (quint, $J = 6.6$ Hz, 1H), 2.41 (quint, $J = 8.4$ Hz, 1H), 2.56 (br, 1H), 2.73 (dd, $J = 16.2, 10.2$ Hz, 1H), 3.04 (d, $J = 9.0$ Hz, 1H), 3.45 (d, $J = 9.0$ Hz, 1H), 6.03 (s, 1H). $^{13}$C NMR (100 MHz, CDCl₃) δ 14.4, 20.7, 21.1, 21.5, 24.3, 34.4, 37.6, 37.8, 53.7, 76.8, 77.2, 119.0, 132.7, 137.2, 144.6.; IR (neat) $\nu_{\text{max}}$ 3396, 2959, 2924, 1714, 1557, 1463, 1379 cm⁻¹. HRMS[ES+] calcd for C₁₅H₂₄O₂ [M + Na]⁺ 259.1674, found 259.1685.

**Cyclization Substrate 466.** To a stirred solution of diol 450 (R = H) (8.5 mg, 36 µmol) in CH₂Cl₂ (2.0 mL) under argon was added 2,6-lutidine (9.2 mg, 86 µmol). Then TBSOTf (11.4 mg, 43.0 µmol) was added dropwise and the resulting mixture was stirred for 2 h, quenched with water, and diluted with CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (1 mL X 3) and
the combined organic solution was dried over MgSO₄, concentrated under reduced pressure, and subjected to silica gel flash column chromatography (elution with EtOAc : hexane = 1 : 20). Alcohol 466 (11.7 mg, 93 %) was isolated as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.03 (dd, J = 6.8, 1.6 Hz, 6H), 1.04 (s, 3H), 1.74 (s, 3H), 1.81 (dd, J = 20.8, 1.6 Hz, 1H), 1.90 – 1.98 (m, 1H), 2.02 – 2.07 (m, 1H), 2.17 (dd, J = 16.7, 9.6 Hz, 1H), 2.31 (quint, J = 6.8 Hz, 1H), 2.37 – 2.46 (m, 1H), 2.89 (dd, J = 16.8, 9.6, 1H), 3.03 (d, J = 4.8 Hz, 1H), 3.11 (s, 1H), 3.43 (dd, J = 10.8, 1.6 Hz, 1H), 6.02 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ -4.8, -3.8, 14.3, 18.0, 21.2, 21.5, 21.9, 24.7, 25.9, 34.3, 37.8, 37.9, 53.1, 76.0, 78.8, 119.1, 133.1, 136.8, 145.2. IR (neat) νmax 3544, 2956, 2930, 2857, 1651, 1472, 1361 cm⁻¹. HRMS[ES+] calcd for C₂₁H₃₈O₂Si [M + Na]⁺ 373.2539, found 373.2535.

Alcohols 468 and 469. Oxymercuration was carried out according to a hybrid procedure derived from related literature.⁹ To a stirred solution of alcohol 466 (16.0 mg, 45.6 µmol) in CH₂Cl₂ (2 mL) under argon was added MeOH (5.0 mg) at room temperature. The reaction mixture was cooled to -78 °C, Hg(O₂CCF₃)₂ (23.8 mg, 54.8 µmol) was added, and stirring was continued for 24 h. Then additional Hg(O₂CCF₃)₂ (5.9 mg, 14 µmol) was added and the reaction mixture was

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slowly warmed to 5 °C over 3.5 h. The reaction was quenched with saturated aq. NaHCO₃ (2 mL) and then saturated aq. NaCl (2 mL). The resulting mixture was stirred at room temperature for 2 h, and then extracted with Et₂O (5 mL X 3). The ether solution was washed with brine and then with water, dried over MgSO₄, and concentrated under reduced pressure to provide an organomercurial intermediate 467. Without further purification, the crude product was directly used for the next step. 467: ¹H NMR (600 MHz, CDCl₃) δ 0.02 (s, 3H), 0.30 (s, 3H), 0.88 (s, 9H), 1.2 (d, J = 6.0 Hz, 1H), 1.45 (s, 3H), 1.17 (d, J = 6.6 Hz, 1H), 1.26 – 1.34 (m, 1H), 1.81 – 1.96 (m, 4H), 2.00 (s, 3H), 2.31 – 2.40 (m, 2H), 2.71 (m, 1H), 2.93 (s, 1H), 3.99 (dd, J = 7.2, 3.0 Hz, 1H).

Oxidative demercuration was accomplished according to Hill and Whitesides. A stream of oxygen gas was bubbled into a solution of NaBH₄ (9.5 mg, 0.11 mmol) in DMF (3.5 mL) at 0°C for 30 min. To the resulting mixture was added dropwise a solution of the alkylmercurial 467 in DMF (0.7 mL) by syringe pump at 0°C for 1 h. During this time, oxygen bubbling was continued. The syringe was filled with DMF (0.2 mL) and this wash was added dropwise (oxygen bubbling continued). When addition was complete, the resulting mixture was warmed slowly to room temperature over 2.5 h (oxygen bubbling continued). The reaction mixture was quenched with 1N HCl, diluted with Et₂O (15 mL), and filtered through Celite. Water and Et₂O were added to the filtrate and the layers were separated. The organic solution was dried over MgSO₄ and concentrated under reduced pressure. The residue was subjected to silica gel Flash column chromatography (elution with EtOAc : hexane = 1 : 3) to afford the known 468 (9.2 mg, 55% for 2 steps) as an oil and its isomer 469 (6.2 mg, 37% for 2 steps), also as an oil.

Compound 468: ¹H NMR (600 MHz, CDCl₃) δ 0.02 (s, 6H), 0.88 (s, 9H), 0.93 (d, J = 6.0 Hz, 3H), 0.97 (d, J = 6.0 Hz, 3H), 1.26 (s, 3H), 1.36 (s, 3H), 1.39 – 1.41 (m, 1H), 1.56 – 1.58 (m, 2H), 1.73 – 1.78 (m, 3H), 1.91 (hept, J = 6.6 Hz, 1H), 2.30 (dd, J = 11.4, 7.8 Hz, 1H), 2.70 (m, 1H), 4.13 (t, J = 6.0, 1H), 5.72 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ -4.9, -4.5, 17.8, 17.7, 18.0, 20.7, 23.5, 25.8, 28.0, 34.1, 41.0, 50.2, 51.0, 73.4, 77.4, 83.3, 85.1, 119.3, 148.9; IR (neat) ν max 3419, 2959, 2929, 2857, 1472, 1386 cm⁻¹. ¹H NMR and ¹³C NMR data were consistent with the reported values.¹⁴

Compound 469: ¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.88 (s, 9H), 0.94 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.17 – 1.24 (m, 1H), 1.26 (s, 3H), 1.37 (s, 3H), 1.60 (m, 1H), 1.70 (m, 1H), 1.84 – 1.97 (m, 1H), 2.26 (dd, J = 11.2, 7.2, 1H), 3.07 (td, J = 9.2, 2.4 Hz,
1H), 4.01 (m, 1H), 5.65 (d, J = 2.8 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) -5.0, -4.5, 17.7, 17.8, 18.0, 20.7, 22.9, 25.5, 25.8, 34.0, 40.8, 49.5, 50.8, 73.4, 77.1, 83.1, 85.2, 120.0, 146.7.; IR (neat) $\nu_{\text{max}}$ 3373, 2959, 2930, 2857, 1463, 1386 cm$^{-1}$.

Difference NOE for compound 461

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<th>Enhanced peaks (C$_{\text{number}}$, ppm)</th>
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Difference NOE for compound **464**

![Compound Diagram](image)

### Difference NOE Chart for Compound **464**

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<th>Enhanced peaks (C\textsubscript{number}, ppm)</th>
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<tr>
<td>CH (1, 3.03)</td>
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<tr>
<td>CH (9, 4.42)</td>
<td>CH\textsubscript{3} (7b, 1.04), CH (10a, 1.17), CH\textsubscript{2} (2.38), CH\textsubscript{2} (8, 2.67), CH (1, 3.03), CH (6, 6.19)</td>
</tr>
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</table>
Part I.


**Part II.**


**Part III.**


Part IV.


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(a) Adam, W.; Kumar, R.; Reddy, T. I.; Renz, M.: Chemo- and Diastereoselective Epoxidation of Chiral Allylic Alcohols with the Urea Hydrogen Peroxide Adduct,


Appendix