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Studies toward the Asymmetric Total Synthesis of Azadirachtin

（アザジラクチンの不斉全合成研究）

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Hokkaido University

2015
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Introduction

According to World Population Prospects, the 2012 Revision (published by United Nations Population Fund (UNFPA)), the global population has been still increasing dramatically and predicted to reach over 9.5 billion within this century. Population growth causes the various problems such as economic, environmental, resource depletion, educational, food problem, etc. Especially, food problem is getting serious. To relieve this problem, it becomes more and more important to furnish crops from diminishing farmland as much as possible. In order to prevent damage from insects, the agricultural community has relied extensively on synthetic pesticides such as organo chlorines, phosphates, dinitrophenols, etc. Although these pesticides exhibit very strong activity against insects, their toxicities had caused severe environmental destruction. On the other hand, pyrethrin\(^1\) and structurally related synthetic compounds, which were called pyrethroids,\(^2\) have been utilized as environmental-conscious pesticides. With its effectiveness toward a wide range of insects and low toxicities, it may be recognized as one of the most successful pesticides. The major problem is appearance of the resistance insects, it is not avoidable, and development of new environment-conscious pesticides to protect crops has always been required. The unique properties of the neem tree have therefore received a great attention as a replacement in recent years.

\(\text{Figure 1. Organo chlorines, phosphates and pyrethroids.}\)
Azadirachtin: a potent insect antifeedant

The neem tree is a large evergreen tree and widely distributed in south Asia, India, Africa, and Latin America. The unusual properties of neem have been exploited for centuries and feature in ancient Sanskrit writings as “reliever of sickness”. For example, the leaf extracts have been used as an agent against leprosy and malaria, and the bark has served to achieve alleviation of pain and fever. While these effects are important properties of neem, the most remarkably one is its activity to repel insect pests. Although this activity against insects was known in 1930s, serious scientific studies were begun in 1960s.

The neem tree has been the source of a large array of bioactive natural products most of which have been isolated from the seeds, and some other products have been found from the bark and leaves. Among them, azadirachtin (1) (azadirachtin A) has proved the main ingredient for repelling insect. It was isolated from the seeds of the Indian neem tree (Azadirachta indica A. Juss) by Butterworth and Morgan in 1968, who reported the antifeedant activity of 1 against the desert locust (Schistocerca gregaria) at low concentrations. After the findings, it has been widely reported that azadirachtin disrupts the feeding of many insects (over 200 species). Despite its high activity against insect pests, azadirachtin shows no apparent phytotoxicity and is remarkably non-toxic to higher forms of life. In addition, the low pesticide persistence of 1 has attracted attention as the ideal environment-conscious pesticides.

![Azadirachtin (1)](image)

**Figure 2.** Azadirachtin and the Indian neem tree.
**Structural determination**

The structural determination of azadirachtin had required considerable efforts from many different groups, and the absolute structure was determined after about 20 years. Morgan and co-workers had stated about the partial structure, the molecular formula, and several functional groups of azadirachtin. The first complete structural proposal presented by Nakanishi and co-workers in 1975 was revised by Kubo and co-workers in 1984, and the collect structure was submitted by the Ley group and the Kraus group in 1985. Finally, the full details were described by the Ley group, Kraus group and Nakanishi group in 1987, respectively. The absolute configuration of azadirachtin was determined by Ley group in 1992 by using the advanced Mosher method and X-ray crystallographic analysis of the MTPA derivatives of the degradation products.

**Figure 3.** Structural studies on azadirachtin

**Biosynthetic hypothesis**

Azadirachtin (1) and its analogues are formed via an elaborate and unclear biosynthetic pathway, but they appeared to be derived from the steroidal intermediate, tirucallol, which was derived from squalene epoxide (Scheme 1). After the biological conversion of tirucallol to nimbocenone, the four terminal carbon atoms are cleaved off and further oxidized to form azadirone. The C ring of azadirone is then oxidatively cleaved to form the C-seco-limonoids such as salannin and nimbin (described in Figure 4). It is currently proposed that salannin is further oxidized and cyclized to derive azadirachtin and its analogs.
Scheme 1. Biosynthetic hypothesis of azadirachtin and its analogues

Related compounds

To date, various structural analogues of azadirachtin (1) were also isolated from the neem tree (Figure 4). These analogues are also found to exhibit antifeedant activities which are usually lower than azadirachtin (1).

Figure 4. Azadirachtin analogs and C-seco-limonoids
Structural features of azadirachtin

Azadirachtin (1), which is known as one of the highly oxidized C'-secolimonoids, possesses heptacyclic skeleton with various oxygen functionalities involving four cyclic ethers, four ester groups, secondary and tertiary alcohols, and a tetra-substituted epoxide. It is noteworthy that each of these functional groups is connected to a chiral carbon atom, and 1 possesses sixteen stereogenic centers involving seven quaternary carbon atoms. One of the most challenging structural features in 1 are the extremely hindered C8 quaternary center. Formation of the C8-C14 bond, connecting of the ABCD ring segment and the EFG ring segment, was especially difficult. The novel structural features combined with distinctive biological properties make azadirachtin an extremely attractive target for synthetic chemists. The author also developed a strong interest in this synthetic target, and undertook synthetic studies on azadirachtin (1).

Synthetic studies by other groups

While a number of research groups have been trying to achieve the total synthesis of 1, there appeared only two successful reports to date. Thus, a relay synthesis was achieved by Ley and co-workers, and then a formal synthesis of 1 was reported by the Watanabe's group. The most difficult problem in the total synthesis is how to construct the extremely hindered C8 quaternary carbon atom. It should be noted that successful results including these total synthesis as well as the model studies reported by other groups are based on intramolecular carbon-carbon bond forming reactions. These studies can be classified to two strategies, namely, (1) the Claisen rearrangement strategy, and (2) the radical cyclization strategy.

(1) Claisen rearrangement Strategy

In the total synthesis of azadirachtin by the Ley's group, the stereoselective Claisen rearrangement of propargyl enol ether A1 was employed to connect the ABCD ring and the FG ring segments at the C8 quaternary center (Scheme 2). The rearrangement reaction of A1 was performed either under thermal conditions or catalytic conditions using a gold(I) reagent, both of which proceeded in high yield with excellent stereoselectivity. The resulting allene moiety was effectively utilized for the
construction of the E ring by an intramolecular radical cyclization reaction. Thus, xanthate A₃ was heated with tributyltin hydride and AIBN to give heptacyclic compound A₅, a key intermediate of the total synthesis of azadirachtin 1.

Scheme 2. Construction of the C₈ quaternary center by the Ley’s group

On the other hand, Murai and co-workers reported a model study toward the total synthesis of azadirachtin, in which construction of the C₈ quaternary center was achieved by using the Ireland-Claisen rearrangement (Scheme 3). Ester A₈, which was derived from the ABC ring segment A₆ and the EFG ring segment A₇, was treated with lithium hexamethyldisilazide (LiHMDS) and Me₂SiCl in toluene. The resulting ketene silyl acetal A₉ underwent the Claisen rearrangement to afford carboxylic acid A₁₀ as a 4:1 diastereomeric mixture in 87% yield. The major product possessed the C₈ quaternary center with correct configuration, but conversion of the carboxyl group to the methyl group and isomerization of the exo-methylene group to the endo-tetrasubstituted alkene required multi step transformations.
(2) Radical cyclization strategy

Nicolaou and co-workers exploited an intramolecular radical cyclization reaction for the formation of the C8-C14 bond (Scheme 4). \(^{18}\) Bromoacetal A14, which was prepared from the ABCD ring segment A12 and enol ether A13, was subjected to the radical cyclization reaction to give the desired heptacyclic compound A16 along with its isomer A17 in 42% and 32% yields, respectively. The result comes from a poor selectivity of the cyclization reaction between the 5-exo-trig mode and the 6-endo-trig mode.

Scheme 3. Construction of the C8 quaternary center reported by the Murai’s group

Scheme 4. Construction of the C8 quaternary center by the Nicolaou’s group
Another approach based on a radical cyclization reaction was reported by Watanabe and co-workers (Scheme 5). In the model study, iodo lactone A19 having an allene moiety was shown to undergo a sequential radical addition reaction to form the ABCD ring system possessing the E ring. The radical cyclization approach was applied to serenade A24 with the FG ring, and the formal synthesis of azadirachtin was accomplished in 2014.

**Scheme 5.** Formal synthesis of azadirachtin by the Watanabe’s group

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**Formation of the C8-C14 bond by an intermolecular addition reaction**

As described above, the difficulty in constructing the highly hindered C8 quaternary center required the use of intramolecular reactions. On the other hand, Dr. Nakagawa, who was a member of the authors laboratory, developed a new method for constructing the C8 quaternary center of azadirachtin on the basis of an intermolecular addition reaction (Scheme 6). The synthesis of the model compound features: (1) synthesis of allylborane A32 through the regio- and stereoselective hydroboration reaction of dienol triflate A31, (2) stereoselective construction of the highly hindered C8 quaternary center by an intermolecular addition reaction of allylborane A33 with aldehyde, (3) construction of the E ring moiety by the Pd-catalyzed Nazarov reaction of enyne A37.
The successful results prompted him to undertake the studies toward the total synthesis of \(1\) through key intermediate \(\text{A40}\) (Scheme 7), an allylborane possessing the two oxygen functionalities on the A ring. However, dienol triflate \(\text{A39}\) was found to exhibit no reactivity toward hydroboration, probably because of the steric repulsion with the OR groups.

\[\text{Scheme 7. Unsuccessful hydroboration reactions of dienol triflate A39}\]
These results led the author to develop an alternative route for the synthesis of allylborane without using a hydroboration reaction (Scheme 8). Brown reported a preparative method for allylboranes through the reaction of an allyl anion with a boronate ester.\textsuperscript{21} Since the boryl group was introduced to the less hindered carbon atom, it was expected that treatment of allyl anion species $\text{A41}$ with a boronate ester would afford allylborane $\text{A42}$ through the reaction at the secondary carbon atom from the less sterically hindered $\alpha$-face. If the new method for preparing the allylborane $\text{A42}$ is successfully developed, the total synthesis of azadirachtin may be achieved according to the strategy developed by Dr. Nakagawa.

\begin{center}
\includegraphics[width=\textwidth]{scheme8.png}
\end{center}

\textbf{Scheme 8.} The new synthetic plan of azadirachtin

In this dissertation, the author described the efforts for preparing the highly functionalized allylboranes in chapter 1, the enantioselective synthesis of the ABCE ring system of azadirachtin in chapter 2, and studies toward the construction of the highly functionalized ABCEF ring system in chapter 3.
Chapter 1

The synthesis of a cyclic allylborane via reductive lithiation of an allyl sulfide

For the synthesis of substituted allylborane derivatives, it is very important to choose an appropriate precursor that can generate the allyl anion species in high yield. While allyl halides are often employed for this purpose, it should be noted that substituted allyl halides sometimes undergo degradation even by silica gel chromatography. On the other hand, Cohen and co-workers reported the synthetic utility of allyl sulfides as a stable precursor of the corresponding allyl anion species (Scheme 9).\(^\text{22}\)

![Scheme 9. Generation of allyl anion species from an allyl sulfide](image)

Therefore, the author designed the synthetic route of allylborane 2 on the basis of the reductive lithiation of an allyl sulfide 4 as shown in Scheme 10. The reaction of the allyl anion species 3 with a boronate ester would occur at the secondary carbon atom from the less sterically hindered \(\alpha\)-face to afford the desired allylborane 2. Allyl sulfide 4 was expected to be obtained from conjugated diene 5 through a regioselective addition reaction with a thiol. Formation of the A ring of 5 would be achieved by a ring closing metathesis of tetraene 6, and the author planed to construct the BC ring system of 6 through the Diels-Alder reaction of vinyl allene 7 with maleic anhydride.
At first, vinyl allene 2 was prepared as shown in Scheme 11. Commercially available 1,3-diol 8 was converted to aldehyde 10 through mono silylation using NaH and triisopropylsilyl chloride (TIPSCl) followed by Swern oxidation. The Horner-Wadsworth-Emmons reaction of aldehyde 10 with 11\textsuperscript{23} followed by desilylation gave trans-vinyl acetylene 12 in 91% yield as a single geometrical isomer. Transformation of the acetylene moiety into an allene was achieved by using the protocol reported by Ma\textsuperscript{24}, giving rise to vinyl allene 13 in 92% yield.

With vinyl allene 13 in hand, construction of the BC ring system was examined as shown in Scheme 12. Vinyl allene 13 was heated with maleic anhydride in toluene at 80 °C to afford cyclohexene derivative 14 in 79% yield as a single isomer through the endo-selective cycloaddition reaction. It is noteworthy that the reaction of 13 and
maleic anhydride at 100 °C resulted in formation of ca. 10% of the undesired exo-isomer 15 as a minor product.

Scheme 12. Diels-Alder reaction of vinyl allene 13

Next, regioselective reduction of the acid anhydride moiety was explored (Table 1). The ratio of the regioisomers was determined after lactonization of the crude hydroxy acids by treating with 10-camphorsulfonic acid (CSA). While the use of LiAlH₄ afforded a 7:3 mixture of lactones 16 and 17 (entry 1), the reaction with a bulky reducing agent prepared from diisobutylaluminum hydride (DIBAL-H) and MeLi proceeded with a higher (9:1) selectivity (entry 2). Finally, the combined use of DIBAL-H with n-BuLi was found to be the choice of reductant, and the product was obtained as a single isomer in 77% yield (entry 3). The relationship between the bulkiness of the reductant and the regioselectivity can be rationalized by the steric repulsion with the TIPS group and the 1,3-dioxane ring.

Table 1. Regioselective reduction of the acid anhydride 14
Construction of the A ring was accomplished as shown in Scheme 13. Successive treatment of lactone 16 with lithium diisopropylamide (LDA) and allyl bromide afforded triene 18 through introduction of the allyl group from the convex face. Then lactone 18 was converted to cyclic ether 19 through reduction to a 1,4-diol followed by dehydration mediated by p-toluenesulfonyl chloride (TsCl) and pyridine. The TIPS group was removed by treating with tetrabutylammonium fluoride (TBAF), and the resulting alcohol 20 was oxidized by Dess-Martin periodinane to afford aldehyde. After conversion to tetraene 21 via the Wittig reaction, the A ring moiety was constructed by ring closing metathesis\(^{25}\) mediated by Umicore M\(_2\) catalyst.

The transformation of conjugated diene 22 into allyl sulfide 24, the precursor of the allylborane, was then examined by using the protocol reported by Duñach (Scheme 14).\(^{26}\) The initial reaction of 22 with ethanethiol (3 equiv.) under the influence of In(OTf)\(_3\) (0.2 equiv.) in dichloromethane failed to give the desired allyl sulfide 24, giving rise to diene 23. The result suggested that capture of the allyl cation intermediate A with the thiol occurred slower than the elimination pathway leading to diene 23. After a number of trials, the use of ethanethiol as the reaction solvent was found to reduce the side reaction, and the product was obtained as a 61:30:9 mixture of allyl sulfides 24, 25, and 26.
Finally, the transformation of allyl sulfide into allylborane 27 was explored (Scheme 15). Treatment of a mixture of allyl sulfide and isopropoxyboronic acid pinacol ester (i-PrOB(pin)) with lithium 2,6-di-tert-butyl-biphenylide (LiDBB)\(^{27,28}\) in THF afforded the desired allylborane 28 as a single isomer, indicating that the anion intermediate reacted with the boron reagent at the less hindered secondary carbon atom from the opposite face of the tetrahydrofuran moiety. As was expected, allylborane 28 underwent a smooth reaction with 3-(tert-butyldimethylsilyl)-2-propynal\(^{29}\) at 50 °C to afford propargyl alcohol 30 (58% yield from allyl sulfide).
In summary, the author developed an efficient method for constructing the B ring moiety of azadirachtin through the Diels–Alder reaction of vinyl allene 13 with maleic anhydride. The conjugated diene moiety of the cycloadduct was utilized for obtaining allyl sulfide 24 through an addition reaction with ethanethiol mediated by In(OTf)3. The transformation of sulfide 24 into allylborane 28 was achieved by the reductive borylation reaction in a regio- and stereoselective manner. Since the resulting allylborane 28 underwent a smooth addition reaction with aldehyde, the present reaction sequence would be useful for the stereoselective constructing the C8 quaternary center of azadirachtin (1).
General Experimental Details: All the reactions were carried out in a round-bottomed flask with an appropriate number of necks and side arms connected to a three-way stopcock and/or a rubber septum cap under an argon atmosphere. All vessels were first evacuated by a rotary pump and then flushed with argon prior to use. Solutions and solvents were introduced by a hypodermic syringe through a rubber septum. During the reaction, the vessel was kept under a positive pressure of argon. Dry tetrahydrofuran (THF) and diethyl ether were freshly prepared by distillation from benzophenone ketyl before use. Triethylamine (Et₃N) was distilled from CaH₂ under argon atmosphere. Anhydrous CH₂Cl₂, methanol, DMF and pyridine were purchased from Kanto Chemical Co. Inc. Most of the reagents were purchased from Tokyo Kasei Kogyo Co. Ltd., Wako Pure Chemicals Co. Ltd., Kanto Chemical Co. Inc. and Aldrich Chemicals Co.

Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Wavelengths of maximum absorbance are quoted in cm⁻¹. ¹H NMR spectra were recorded on a JEOL ECA·500 (500 MHz) in CDCl₃. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). ¹³C NMR spectra were recorded on a JEOL ECA·500 (125 MHz) in CDCl₃. Chemical shifts are reported in part per million (ppm). High resolution mass (HRMS) spectra were recorded on a JEOL JMS-T-100GCV at the GC-MS & NMR Laboratory, Research Faculty of Agriculture, Hokkaido University. Optical rotation data was recorded on a JASCO P-2200. Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel (60F-254) plates. Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, or ceric ammonium molybdate in 10% sulfuric acid. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for column chromatography.
Alcohol 9

To a solution of 1,3-dioxane-5,5-dimethanol 8 (16.4 g, 100 mmol) in THF (200 mL) was added NaH (4.36 g, 100 mmol) at 0 °C. After being stirred for 1 h at room temperature, and then was added triisopropylsilyl chloride (21.4 mL, 100 mmol) in one portion. The reaction mixture was stirred for 18 h at room temperature and diluted with AcOEt followed by addition of saturated aqueous NH₄Cl solution. The mixture was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over anhydrous MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane) to give silyl ether 9 (30.0 g, 99%) as colorless oil. IR (neat) νmax 2943, 1463, 1087, 1038, 932, 881, 803, 774, 682 cm⁻¹; ¹H-NMR (500MHz, CDCl₃) δ 4.86 (d, J = 6.3 Hz, 1H), 4.77 (d, J = 6.3 Hz, 1H), 3.90 (s, 2H), 3.83 (d, J = 11.5 Hz, 2H), 3.71-3.67 (m, 2H), 2.60 (t, J = 5.7 Hz, 1H (OH)), 1.23-1.02 (m, 21H); ¹³C NMR (125MHz, CDCl₃) δ 94.26, 69.55, 65.96, 65.35, 39.68, 17.91, 11.74; HRMS (FD+) calcd for C₁₅H₃₃O₄Si (M+H⁺) 305.2148, found 305.2145.

Aldehyde 10

To a solution of DMSO (16.8 mL, 236.5 mmol) in CH₂Cl₂ (200 mL) at -78 °C was added oxaly chloride (10.1 mL, 118.2 mmol). After 10 min, a solution of mono TIPS ether 9 (30.0 g, 98.5 mmol) in CH₂Cl₂ (130 mL) was added, forming a cloudy white mixture. The reaction mixture was stirred for 1 h at -78 °C, and then triethylamine (69 mL, 492.5 mmol) was added. The reaction mixture was stirred at -78 °C for 10 min, and warm up to room temperature. After being stirred for 30 min, the reaction was quenched with saturated aqueous NaHCO₃ solution. The mixture was separated and the aqueous layer was extracted with AcOEt and the combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography.
(AcOEt/hexane) to give aldehyde 10 (27.5 g, 92%) as pale yellow oil. IR (neat) \( \nu_{\text{max}} \) 2943, 1715, 1463, 1220, 1162, 1107, 1067, 1039, 930, 881, 795, 773, 682 cm\(^{-1}\); \(^1\)H NMR (500MHz, CDCl\(_3\)) \( \delta \) 9.81 (s, 1H), 4.85 (d, \( J = 6.3 \) Hz, 1H), 4.78 (d, \( J = 6.3 \) Hz, 1H), 4.19 (d, \( J = 11.5 \) Hz, 2H), 3.90 (d, \( J = 12.0 \) Hz, 2H), 3.88 (s, 2H), 1.13-1.02 (m, 21H); \(^{13}\)C NMR (125MHz, CDCl\(_3\)) \( \delta \) 203.81, 93.98, 67.96, 63.17, 51.63, 17.86, 11.74; HRMS (FD+) calcd for C\(_{15}\)H\(_{31}\)O\(_4\)Si (M+H\(^+\)) 303.1992, found 303.1986.

**Vinyl acetylene 12**

To a solution of LDA, which was freshly prepared from N,N-diisopropylamine (2.16 mL, 15.5 mmol) in THF (15 mL) and a 2.69 M solution of n-BuLi (5.58 mL, 15.0 mmol), was added a solution of phosphate 11 (3.85 g, 15.5 mmol) in THF (10 mL) at -78 °C. After being stirred for 30 min, a solution of aldehyde 10 (3.02 g, 10.0 mmol) in THF (10 mL) was added. After being stirred for 1 h at -78 °C, a saturated methanol solution of K\(_2\)CO\(_3\) was added. The reaction mixture was stirred for 1 h at room temperature, and then a saturated aqueous NH\(_4\)Cl solution was added. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO\(_4\), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography afforded vinyl acetylene 12 (2.93 g, 91%) as a colorless oil. \(^1\)H NMR (500MHz, CDCl\(_3\)) \( \delta \) 6.12 (s, \( J = 16.6 \) Hz, 1H), 5.63 (dd, \( J = 16.6, 2.0 \) Hz, 1H), 4.91 (d, \( J = 6.0 \) Hz, 1H), 4.70 (d, \( J = 6.0 \) Hz, 1H), 3.95 (d, \( J = 11.5 \) Hz, 2H), 3.85 (s, 2H), 3.62 (d, \( J = 11.5 \) Hz, 2H), 2.88 (d, \( J = 2.0 \) Hz), 1.16-1.05 (m, 21H)

**Vinyl allene 13**

A mixture of vinyl acetylene 12 (6.1 g, 18.8 mmol), CuI (1.8 g, 9.4 mmol),
paraformaldehyde (1.4 g, 47.0 mmol) and dicyclohexylamine (6.7 mL, 34.0 mmol) in dioxane (62 mL) was heated at 110 °C. After being stirred for 4 h, the mixture was cooled to room temperature and then added a saturated aqueous NH₄Cl solution. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford vinyl allene 13 (5.82 g, 92%) as a colorless oil. 

$^1$H NMR (500MHz, CDCl₃) δ 5.95 (dd, $J = 16.0, 10.3$ Hz, 1H), 5.78 (dt, $J = 12.4, 5.0$ Hz, 1H), 5.51 (d, $J = 16.0$ Hz, 1H), 4.93-4.89 (m, 3H), 4.70 (d, $J = 6.3$ Hz, 1H), 3.97 (d, $J = 10.9$ Hz, 2H), 3.85 (s, 2H), 3.62 (d, $J = 10.9$ Hz, 2H), 1.16-1.01 (m, 21H); $^{13}$C NMR (125MHz, CDCl₃) δ 211.66, 131.40, 125.93, 64.00, 93.49, 76.37, 71.11, 64.97, 41.53, 18.00, 11.93.

**Cycloadduct 14**

To a solution of vinyl allene 13 (1.69 g, 5.0 mmol) in toluene (25 mL) was added maleic anhydride (1.47 g, 15 mmol). The suspension was heated at 80 °C for 7 h. The reaction mixture was cooled to room temperature, and the mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford cycloadduct 14 (1.72 g, 79%) as pale yellow oil. 

$^1$H NMR (500MHz, CDCl₃) δ 6.31 (dd, $J = 10.3, 3.4$ Hz, 1H), 6.10 (d, $J = 10.3$ Hz, 1H), 5.48 (s, 1H), 5.30 (s, 1H), 4.87 (d, $J = 5.7$ Hz, 1H), 4.78 (d, $J = 5.7$ Hz, 1H), 4.31 (d, $J = 12.0$ Hz, 1H), 4.19 (d, $J = 10.3$ Hz, 1H), 3.99-3.85 (m, 6H), 2.91 (br s, 1H), 1.18-1.01 (m, 21H); $^{13}$C NMR (125MHz, CDCl₃) δ 171.48, 169.91, 132.01, 129.57, 127.93, 118.01, 93.84, 69.92, 69.39, 62.88, 46.67, 43.33, 39.66, 34.43, 18.02, 11.82.
Lactone 16

To a mixture of a 1.02 M hexane solution of DIBAL-H (12.5 mL, 12.8 mmol) and THF (8 mL) was added a 2.65 M hexane solution of n-BuLi (4.8 mL, 12.8 mmol) at 0 °C. The mixture was cooled to −78 °C, and to this was added a solution of 14 (1.39 g, 3.2 mmol) in THF (8 mL). After being stirred for 30 min, the reaction was quenched with 1 M HCl. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude hydroxyacid was used for the next step without purification.

To a solution of crude hydroxyacid 14' in benzene (16 mL) was added 10-camphorsulfonic acid (150 mg, 0.64 mmol) at room temperature. After being stirred for 12 h, a saturated aqueous NaHCO₃ solution was added. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford lactone 16 (1.07 g, 77%) as a colorless oil. ¹H NMR (500MHz, CDCl₃) δ 6.28 (dd, J = 10.3, 3.4 Hz, 1H), 5.98 (d, J = 10.3 Hz, 1H), 5.18 (s, 1H), 5.10 (s, 1H), 4.89 (d, J = 6.3 Hz, 1H), 4.75 (d, J = 6.3 Hz, 1H), 4.45-4.37 (m, 3H), 4.21 (d, J = 10.3 Hz, 1H), 3.98 (d, J = 10.3 Hz, 1H), 3.95-3.85 (m, 3H), 3.34 (s, 2H), 2.90 (s, 1H), 1.17-1.04 (m, 21H); ¹³C NMR (125MHz, CDCl₃) δ 176.01, 140.68, 131.13, 127.71, 114.44, 93.75, 73.57, 70.16, 69.23, 62.88, 41.40, 41.36, 39.84, 35.05, 18.01, 11.88.
To a solution of lactone 16 (372.7 mg, 0.88 mmol) in THF (4.4 mL) was added a 1.0 M solution of LDA (1.32 mL, 1.32 mmol, which was freshly prepared from N,N-diisopropylamine (0.31 mL, 2.2 mmol) in THF (0.95 mL) and a 2.69 M solution of n-BuLi (0.74 mL, 2.0 mmol), at -78 °C. After being stirred for 1 h, allylbromide (0.15 mL, 1.76 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C and then added a saturated aqueous NH₄Cl solution. After being allowed to warm to room temperature, the mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The crude triene 18 was used for the next step without purification.

To a solution of crude triene 18 in CH₂Cl₂ (4.4 mL) was added a 1.02 M solution of DIBAL-H (2.6 mL, 2.64 mmol) at 0 °C. After being stirred for 5 min, a saturated aqueous Rochelle salt solution was added. The reaction mixture was stirred for 1 h, separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude diol 18’ was used for the next step without purification.

A solution of the crude diol 18’ and p-toluenesulfonyl chloride (510 mg, 2.65 mmol) in CH₂Cl₂ (2.9 mL) and pyridine (2.9 mL) was heated at 50 °C for 2 h. The mixture was cooled to room temperature, and a saturated aqueous NaHCO₃ solution was added. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered
and the solvent was removed under reduced pressure. The crude cyclic ether 19 was used for the next step without purification.

To a solution of cyclic ether 19 in THF (4.4 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (1.76 mL, 1.76 mmol) at room temperature. After being stirred for 1.5 h, the reaction mixture was diluted with water. The mixture was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford alcohol 20 (139.4 mg, 54%) as a yellow oil: ¹H NMR (500MHz, CDCl₃) δ 6.28 (d, J = 10.3 Hz, 1H), 5.93-5.82 (m, 1H), 5.72 (d, J = 10.3 Hz, 1H), 5.20-5.12 (m, 2H, involving singlet at 5.17), 5.01-4.96 (m, 2H, involving singlet at 4.99), 4.87 (s, 1H), 4.67 (d, J = 6.3 Hz, 1H), 4.18 (t, J = 8.0 Hz, 1H), 4.15-4.08 (m, 2H), 4.01 (dd, J = 16.9, 11.7 Hz, 2H), 3.89 (d, J = 11.5 Hz, 1H), 3.80-3.73 (m, 4H), 3.67 (d, J = 8.6 Hz, 1H), 2.92 (t, J = 4.9 Hz, ), 2.74 (s, 1H), 2.36 (d, J = 6.9 Hz, 1H); ¹³C NMR (125MHz, CDCl₃) δ 142.27, 134.56, 129.59, 127.54, 119.01, 112.93, 93.86, 74.12, 72.91, 71.66, 71.30, 62.68, 48.92, 46.98, 43.22, 42.44, 39.08.

**Tetraene 21**

![Diagram of Tetraene 21]

To a solution of alcohol 21 (145.5 mg, 0.498 mmol) in CH₂Cl₂ (5 mL) was added Dess-Martin periodinane (422 mg, 1.0 mmol) and NaHCO₃ (167 mg, 2.0 mmol) at 0 ºC. After being stirred for 1 h, a saturated aqueous NaHCO₃ solution and an aqueous Na₂S₂O₅ solution were added. After being stirred for 1 h, the mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The crude aldehyde 21' was used for the next step without purification.

To a solution of methyltriphenylphosphonium bromide (374 mg, 1.1 mmol) in THF (2.5 mL) was added a 0.5 M toluene solution of Potassium hexamethyldisilazide (KHMDS) (2.0 mL, 1.0 mmol) at 0 ºC. After being stirred for 40 min, a solution of crude aldehyde 21' in THF (2.5 mL) was added. After being stirred for 3 h, a saturated
aqueous NH₄Cl solution was added. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford tetraene 22 (81.6 mg, 57%) as a colorless oil: ¹H NMR (500MHz, CDCl₃) δ 6.31 (dd, J = 10.3, 2.9 Hz, 1H), 5.98-5.90 (m, 1H), 5.73-5.65 (m, 2H), 5.24 (d, J = 11.5 Hz, 1H), 5.20-5.13 (m, 3H), 4.98 (s, 1H), 4.94 (d, J = 5.7 Hz, 1H), 4.86 (s, 1H), 4.82 (d, J = 5.7 Hz, 1H), 4.18 (dd, J = 12.0, 1.7 Hz, 2H), 4.14 (dd, J = 8.4, 7.4 Hz, 1H), 4.03 (dd, J = 11.5, 1.1 Hz, 1H), 3.96 (d, J = 11.5 Hz, 1H), 3.75 (dd, J = 8.6, 4.6 Hz, 1H), 3.68-3.63 (m, 2H), 3.61 (d, J = 8.6 Hz, 1H), 3.11 (s, 1H), 2.92 (td, J = 4.6, 2.3 Hz, 1H), 2.54 (dd, J = 14.6, 6.6 Hz, 1H), 2.32 (dd, J = 14.6, 7.7 Hz, 1H): ¹³C NMR (125MHz, CDCl₃) δ 142.40, 138.41, 134.86, 129.71, 128.19, 118.76, 116.91, 112.36. 94.18, 74.43, 73.88, 72.97, 72.46, 48.56, 46.59, 43.91, 42.40, 39.13.

**Triene 22**

A mixture of tetraene 21 (117 mg, 0.405 mmol) and umicore M₂ (9 mg, 0.01 mmol) in benzene was heated at 50 °C. After being stirred for 1 h, the resulting solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography afforded triene 22 (88.0 mg, 83%) as a colorless oil: ¹H NMR (500MHz, CDCl₃) δ 6.31 (dd, J = 10.3, 2.9 Hz, 1H), 5.98-5.90 (m, 1H), 5.73-5.65 (m, 2H), 5.24 (d, J = 11.5 Hz, 1H), 5.20-5.13 (m, 3H), 4.98 (s, 1H), 4.94 (d, J = 5.7 Hz, 1H), 4.86 (s, 1H), 4.82 (d, J = 5.7 Hz, 1H), 4.18 (dd, J = 12.0, 1.7 Hz, 2H), 4.14 (dd, J = 8.4, 7.4 Hz, 1H), 4.03 (dd, J = 11.5, 1.1 Hz, 1H), 3.96 (d, J = 11.5 Hz, 1H), 3.75 (dd, J = 8.6, 4.6 Hz, 1H), 3.68-3.63 (m, 2H), 3.61 (d, J = 8.6 Hz, 1H), 3.11 (s, 1H), 2.92 (td, J = 4.6, 2.3 Hz, 1H), 2.54 (dd, J = 14.6, 6.6 Hz, 1H), 2.32 (dd, J = 14.6, 7.7 Hz, 1H): ¹³C NMR (125MHz, CDCl₃) δ 142.40, 138.41, 134.86, 129.71, 128.19, 118.76, 116.91, 112.36. 94.18, 74.43, 73.88, 72.97, 72.46, 48.56, 46.59, 43.91, 42.40, 39.13.
Allyl sulfide 24, 25, 26

To a solution of triene 22 (88.0 mg, 0.11 mmol) in EtSH (1.0 mL) was added indium trifluoromethanesulfonate (In(OTf)$_3$) (12.9 mg, 0.023 mmol) at 0 ºC. After being stirred for 2 h, a saturated aqueous NaHCO$_3$ solution was added. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford allyl sulfide 24, 25 and 26 (34.9 mg, 98%) as a colorless oil: $^1$H NMR (500MHz, CDCl$_3$) δ 6.31 (dd, $J$ = 10.3, 2.9 Hz, 1H), 5.98-5.90 (m, 1H), 5.73-5.65 (m, 2H), 5.24 (d, $J$ = 11.5 Hz, 1H), 5.20-5.13 (m, 3H), 4.98 (s, 1H), 4.94 (d, $J$ = 5.7 Hz, 1H), 4.86 (s, 1H), 4.82 (d, $J$ = 5.7 Hz, 1H), 4.18 (dd, $J$ = 12.0, 1.7 Hz, 2H), 4.14 (dd, $J$ = 8.4, 7.4 Hz, 1H), 4.03 (dd, $J$ = 11.5, 1.1 Hz, 1H), 3.96 (d, $J$ = 11.5 Hz, 1H), 3.75 (dd, $J$ = 8.6, 4.6 Hz, 1H), 3.68-3.63 (m, 2H), 3.61 (d, $J$ = 8.6 Hz, 1H), 3.11 (s, 1H), 2.92 (td, $J$ = 4.6, 2.3 Hz, 1H), 2.54 (dd, $J$ = 14.6, 6.6 Hz, 1H), 2.32 (dd, $J$ = 14.6, 7.7 Hz, 1H); $^{13}$C NMR (125MHz, CDCl$_3$) δ 142.40, 138.41, 134.86, 129.71, 128.19, 118.76, 116.91, 112.36, 94.18, 74.43, 73.88, 72.97, 72.46, 48.56, 46.59, 43.91, 42.40, 39.13.

Propargyl alcohol 30

To a suspension of a Li metal (25 mg, 1.08 mmol) in THF (0.7 mL) was added a 4,4'-di-tert-butylbiphenyl (72.0 mg, 0.27 mmol) at 0 ºC. After being stirred for 1 h, the mixture was cooled to -78 ºC. A mixture of allylsulfide (34.9 mg, 0.108 mmol) and isopropoxy borane pinacol ester (66.0 µL, 0.32 mmol) in THF (1.4 mL) was added to the mixture. After being stirred for 30 min, water was added and the mixture was warm up to room temperature. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford propargyl alcohol 30 (35.4 mg, 98%) as a colorless oil: $^1$H NMR (500MHz, CDCl$_3$) δ 7.74 (s, 1H), 7.72 (s, 1H), 7.53 (d, $J$ = 8.6 Hz, 1H), 7.11 (d, $J$ = 8.6 Hz, 1H), 7.00 (d, $J$ = 8.6 Hz, 1H), 4.65 (s, 1H), 4.18 (dd, $J$ = 12.0, 1.7 Hz, 2H), 4.14 (dd, $J$ = 8.4, 7.4 Hz, 1H), 4.03 (dd, $J$ = 11.5, 1.1 Hz, 1H), 3.96 (d, $J$ = 11.5 Hz, 1H), 3.75 (dd, $J$ = 8.6, 4.6 Hz, 1H), 3.68-3.63 (m, 2H), 3.61 (d, $J$ = 8.6 Hz, 1H), 3.11 (s, 1H), 2.92 (td, $J$ = 4.6, 2.3 Hz, 1H), 2.54 (dd, $J$ = 14.6, 6.6 Hz, 1H), 2.32 (dd, $J$ = 14.6, 7.7 Hz, 1H); $^{13}$C NMR (125MHz, CDCl$_3$) δ 142.40, 138.41, 134.86, 129.71, 128.19, 118.76, 116.91, 112.36, 94.18, 74.43, 73.88, 72.97, 72.46, 48.56, 46.59, 43.91, 42.40, 39.13.
filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford a mixture of allylborane 28 and diene. This mixture was used for the next step without further purification.

To a solution of crude allylborane 28 in toluene (0.5 mL) was added 3-(tert-butyldimethylsilyl)-2-propynal (29.3 µL, 0.15 mmol) at room temperature. After being stirred for 4 h at 50 °C, a saturated aqueous NaHCO₃ solution was added. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford propargyl alcohol 30 (27.1 mg, 0.063 mmol) as a colorless oil: ¹H NMR (500MHz, CDCl₃) δ 6.31 (dd, J = 10.3, 2.9 Hz, 1H), 5.98-5.90 (m, 1H), 5.73-5.65 (m, 2H), 5.24 (d, J = 11.5 Hz, 1H), 5.20-5.13 (m, 3H), 4.98 (s, 1H), 4.94 (d, J = 5.7 Hz, 1H), 4.86 (s, 1H), 4.82 (d, J = 5.7 Hz, 1H), 4.18 (dd, J = 12.0, 1.7 Hz, 2H), 4.14 (dd, J = 8.4, 7.4 Hz, 1H), 4.03 (dd, J = 11.5, 1.1 Hz, 1H), 3.96 (d, J = 11.5 Hz, 1H), 3.75 (dd, J = 8.6, 4.6 Hz, 1H), 3.68-3.63 (m, 2H), 3.61 (d, J = 8.6 Hz, 1H), 3.11 (s, 1H), 2.92 (td, J = 4.6, 2.3 Hz, 1H), 2.54 (dd, J = 14.6, 6.6 Hz, 1H), 2.32 (dd, J = 14.6, 7.7 Hz, 1H): ¹³C NMR (125MHz, CDCl₃) δ 142.40, 138.41, 134.86, 129.71, 128.19, 118.76, 116.91, 112.36, 94.18, 74.43, 73.88, 72.97, 72.46, 48.56, 46.59, 43.91, 42.40, 39.13.
Chapter 2

Studies toward the asymmetric total synthesis of azadirachtin: Construction of the ABC ring system via the Diels-Alder reaction of a vinyl allenylsilane derivative

In Chapter 1, an efficient method for the stereoselective synthesis of bicyclic allylborane 28, a key intermediate for constructing the C8 quaternary center of azadirachtin (1), was described. Toward the total synthesis of azadirachtin (1), the next challenge was set to introduce the two oxygen functional groups on the A ring. While compound 30 might serve as a precursor of 33 through functionalization of the alkene moiety, the author designed an alternative route for the synthesis of allylborane having two oxygen functional groups on the A ring (Scheme 16).

![Scheme 16. Synthetic plan of propargyl alcohol 32 with the functionalized A ring](image)

Construction of the B ring would be achieved by the Diels-Alder reaction of a vinyl allene derivative with maleic anhydride as was described in Chapter 1. In order to achieve the asymmetric total synthesis of azadirachtin, the author thought about the possibility of obtaining the cycloadduct in optically active form. Thus, the Diels-Alder reaction of allenylsilane 34 having an axial chirality would proceed with high diastereofacial selectivity to afford the optically active adduct (Scheme 17).
There are several examples of the asymmetric Diels-Alder reactions using an optically active allene derivative. For example, Sawamura (Hokkaido Univ.) and co-workers reported the stereoselective synthesis of a highly substituted cyclohexene derivative by the Diels-Alder reaction of chiral vinyl allene with N-phenylmaleimide (Scheme 18). The reaction proceeded with high stereoselectivity to give the Z-isomer at the exo-ethylidene group, indicating that the reaction with the dienophile occurred from the opposite side of the allylic methyl group of allene.

While the allylic methyl group of cycloadduct is unremovable, the author planned to use a silyl group as an anchor for controlling the diastereofacial selectivity of the vinyl allene. After the cycloaddition reaction, the silyl group at the exo-alkene moiety would be removed by treating with a protic acid (Scheme 19). After transformation of 35 into ketoaldehyde 36, construction of the A ring would be achieved by an intramolecular aldol reaction followed by stereoselective reduction, giving rise to diol 37. Then the conjugated diene moiety is to be converted to the key allylborane 31 through a similar method described in Chapter 1.
Scheme 19. Synthetic plan for the allylborane having functional groups on the A ring

At first, the optically active propargyl benzoate 42 was prepared as shown in Scheme 20. Aldehyde 10, a common intermediate of allene 13 in Chapter 1, was subjected to the Horner-Wadsworth-Emmons reaction with reagent 38 to give trans-α,β-unsaturated Weinreb amide 39 in 95% yield as a single isomer. Amide 39 was reacted with ethynylmagnesium bromide to afford alkynone 40 which was subjected to asymmetric reduction using (S)-2-methyl CBS oxazaborolidine. The desired propargyl alcohol 41 was obtained in 94% yield, the optical purity of which was determined to be 98%ee by HPLC analysis of the corresponding 3,5-dinitrobenzoate ester using a chiral column. This optically active propargyl alcohol was converted to benzoate 42 under standard conditions.

Scheme 20. Preparation of chiral propargyl benzoate 42

Next, the Sn2' reaction of 42 with a silyl cuprate reagent was examined by using the protocol described by Fleming (Scheme 21). However, the product was obtained as a 4:1 inseparable mixture of the desired allenylsilane 43 and bis-silylated compound 44, which allowed the author to optimize the reaction conditions. With a view to
avoiding the formation of compound 44 through over-reaction, higher order cuprate (PhMe$_2$Si)$_2$Cu(CN)Li$_2$ was replaced with PhMe$_2$SiCu(CN)Li, and the reaction at low temperature (–100 °C) afforded allenylsilane 43 in 62% yield along with the recovery of benzoate 42 in 36% yield.

**Scheme 21.** Examination of the $S_\text{N}2'$ silylation reaction

With the optically active allenylsilane 43 in hand, stereoselective construction of BC ring system was examined as shown in Scheme 22. The Diels–Alder reaction of allenylsilane 43 with maleic anhydride was performed by heating in toluene at 80 °C, giving rise to the desired endo cycloadduct 45 as a single stereoisomer. As was expected, only the Z-isomer of the vinylsilane moiety was obtained, which indicated that the reaction occurred from the opposite face of the silyl group (Figure 5).

**Scheme 22.** Stereoselective Diels–Alder reaction of vinyl allenylsilane 43
Next, cycloadduct 45 was transformed into ketoaldehyde 51 (Scheme 23). Since acid anhydride 45 underwent partial hydrolysis by silica gel chromatography, the crude product was used directly to the next step. Regioselective reduction of acid anhydride 45 was achieved by using a bulky reducing agent prepared from diisobutyl-aluminum hydride (DIBAL-H) and n-BuLi, and the resulting hydroxy acid was converted to lactone 47 by the reaction with p-toluenesulfonyl chloride (TsCl) and pyridine. Successive treatment of lactone 47 with lithium diisopropylamide (LDA) and acetaldehyde led to introduction of the side chain from the convex face, giving rise to alcohol. Then lactone 48 was converted to cyclic ether 49 through reduction to 1,4-diol followed by dehydration mediated by methanesulfonyl chloride (MsCl) and pyridine. The TES group and Me₂PhSi group of 49 were removed under the influence of 10-camphorsulfonic acid (CSA) in methanol, and the remaining TIPS group was removed by tetrabutylammonium fluoride (TBAF). Swern oxidation of the resulting diol 50 gave ketoaldehyde 51 that is the precursor of the intramolecular aldol reaction for constructing the A ring.
Although the reactions of 51 promoted by various kinds of bases (LDA, KHMDS, NaOMe) or acids (BF$_3$·OEt$_2$, aqueous HCl, aqueous AcOH) led to formation of complex mixtures, the author found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is the base of choice (Figure 6). Thus, the cyclization reaction of 51 was effected by treatment with DBU in THF at 0 °C, and ketol 53 having an axial hydroxyl group was obtained in a stereoselective manner. The stereochemical outcome of the intramolecular aldol reaction can be rationalized by assuming a cyclic transition state involving hydrogen bonding between the enol moiety and the aldehyde group.
Next, stereoselective reduction of ketol 53 was explored as shown in Table 2. The reaction with MeLi/DIBAL-H gave a 64:36 mixture of diol 54 and the corresponding epimer 55 (entry 1). While the reaction of ketol 53 with two equivalents of LiAlH$_4$ in THF at $-78$ °C afforded a 77:23 mixture of the diastereomers (entry 2), the ratio was increased to 84:16 by using five equivalents of LiAlH$_4$ (entry 3). Finally, it was found that the reaction at $-100$ °C led to formation of diol 54 almost as a single isomer (entry 4).

![Diagram of ketol and diols 53, 54, and 55]

### Table 2. Stereoselective reduction of ketol 53

<table>
<thead>
<tr>
<th>entry</th>
<th>reductant (2 eq.)</th>
<th>temp.</th>
<th>result (54:55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeLi/DIBAL-H</td>
<td>$-78$ °C</td>
<td>64 : 36</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH$_4$</td>
<td>$-78$ °C</td>
<td>77 : 23</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH$_4$ (5 eq.)</td>
<td>$-78$ °C</td>
<td>87 : 13</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH$_4$ (5 eq.)</td>
<td>$-100$ °C</td>
<td>54 as a single isomer</td>
</tr>
</tbody>
</table>

The high stereoselectivity observed in the reaction using an excess amount of LiAlH$_4$ is quite interesting, the origin of which could be explained as follows (Figure 7). There are two pathways, namely, (A) intermolecular reduction of the keto group leading to the desired syn-diol 54, and (B) intramolecular reduction through the alkoxyaluminum hydride intermediate affording the undesired anti-diol 55. Since the reactivity of the alkoxyaluminum hydride intermediate is lower than that of LiAlH$_4$, the use of a large excess amount of LiAlH$_4$ at low temperature would prefer the selective formation of diol 54 through intermolecular reduction.

![Diagram of pathways A and B for LiAlH$_4$ reduction of ketol 53]

**Figure 7.** Two pathways for the LiAlH$_4$ reduction of ketol 53
These results allowed the author to obtain the desired diol 54, which was purified by recrystallization from ether, as an almost single diastereomer in 53% yield from diol 50.

Scheme 24. Stereoselective construction of the A ring moiety

The diene intermediate 54 in hand, the stage was set for the synthesis of allylborane according to the previous method described in Chapter 1 (Scheme 25). Transformation of diol 54 into allyl sulfide 56 was examined by using the modified Duñach’s protocol, and the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a co-solvent of ethanethiol was found to effect a smooth reaction. Allyl sulfide 56, which was obtained as an approximately 3:1 diastereomeric mixture, was converted to acetonide 57 through protection of the diol moiety.

Scheme 25. Conversion of diene 54 to allyl sulfide 57

The borylation reaction of sulfide 57 was performed as shown in Scheme 26. Although the reaction proceeded smoothly in a regioselective manner at the secondary carbon atom, the resulting allylborane was found to be a 77:23 mixture of epimers. Fortunately, the minor isomer 59 could easily be removed by silica gel column chromatography, and the stereochemistry of the major product 58 was confirmed to be the desired one by an NOE experiment.
Scheme 26. Transformation of allyl sulfide 57 into allylborane 58

The unexpectedly low selectivity may be explained by the steric hindrance at the $\alpha$-face of the allyl anion intermediate which came from the methyl group of the acetonide moiety (Figure 8).

Figure 8. Steric effect of the acetonide moiety in the allyl anion species

Finally, introduction of the E ring moiety at the C8 position through the addition reaction of 58 was explored (Scheme 27). The reaction with 3-trimethylsilyl-2-propinal\(^{17}\) proceeded at room temperature for 18 h, and the resulting alcohol 59 was subjected to the Dess-Martin oxidation to give ketone 60 as a single isomer.

Scheme 27. Stereoselective introduction of a side chain at the C8 position
Construction of the E ring was then achieved by applying the protocol developed by Nakagawa (Scheme 28). Successive treatment of ketone 60 with alkenyllithium, isobutyryl chloride, and a saturated MeOH solution of K₂CO₃ afforded enyne 62 in 74% yield. Under the influence of PdCl₂(CH₃CN)₂ and acetic acid, enyne 62 underwent the Pd-catalyzed Nazarov cyclization reaction. Since the acetonide group was removed by the acidic reaction conditions, the crude product was treated with 2-methoxymethane and PPTS. The desired cyclopentenone 64 was obtained as a 2:1 mixture of diastereomers in 49% yield for 2 steps.

Scheme 28. Construction of the E ring through the palladium-catalyzed Nazarov cyclization reaction

In summary, the author had accomplished the stereoselective synthesis of a highly functionalized ABCE ring system of azadirachtin. The ABC ring moiety was constructed on the basis of the stereoselective Diels–Alder reaction of an optically active allenysilane and an intramolecular aldol reaction. After transformation of the conjugated diene moiety into a cyclic allylborane, the highly hindered C₈–C₁₄ bond was formed by intermolecular addition reaction with an aldehyde. Cyclization of the E ring moiety was achieved by Pd-catalyzed Nazarov reaction.
Experimental Section (Chapter 2)

**Amide 39**

To a solution of phosphate 38 (23.9 g, 100.1 mmol) in THF (130 mL) was slowly added NaH (4.17 g, 95.6 mmol, 55% dispersion in mineral oil) at 0 °C, and the mixture was stirred for 1 h. To this was added a solution of aldehyde 10 (27.5 g, 91.0 mmol) in THF (100 mL), and the mixture was stirred for 3 h at room temperature. A saturated aqueous NH₄Cl solution was added, and the mixture was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford amide 39 (32.6 g, 92%) as a colorless oil: IR (neat) ν<sub>max</sub> 2970, 2891, 1664, 1634, 1462, 1381, 1161, 1105, 1068, 1037, 928, 683 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.77 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 4.94 (d, J = 6.3 Hz, 1H), 4.71 (d, J = 6.3 Hz, 1H), 4.01 (d, J = 11.5 Hz, 2H), 3.94 (s, 2H), 3.70-3.67 (m, 5H, involving a singlet at 3.69), 3.25 (s, 3H), 1.16-1.05 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 145.83, 119.88, 93.97, 70.34, 64.18, 61.69, 42.15, 17.97, 11.88 (2C missing); HRMS (FI+) calcd for C₁₉H₃₇NO₅Si [M]+: 387.2441, found: 387.2431.

**Ketone 40**

To a solution of amide 39 (17.1 g, 44.1 mmol) in THF (44 mL) was added a 0.5 M THF solution of ethynylmagnesium bromide (132 mL, 66 mmol) at 0 °C. After being stirred for 3 h at room temperature, the reaction was quenched with 1 M HCl. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined
organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford ketone 40 (14.5 g, 93%) as a yellow oil: IR (neat) 3243, 2979, 2890, 2865, 2097, 1460, 1159, 1111, 1082, 1066, 1036, 928, 881, 681 cm⁻¹; ¹H NMR (500MHz, CDCl₃) δ 7.21 (d, J = 16.6 Hz, 1H), 6.30 (d, J = 16.6 Hz, 1H), 4.91 (d, J = 6.3 Hz, 1H), 4.77 (d, J = 6.3 Hz, 1H), 3.99 (d, J = 11.5 Hz, 2H), 3.89 (s, 2H), 3.76 (d, J = 11.5 Hz, 2H), 3.23 (s, 1H), 1.16–1.04 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 177.63, 153.74, 132.14, 94.12, 79.65, 79.34, 70.29, 64.55, 42.67, 17.95, 11.84; HRMS (FD+) calcd for C₁₉H₃₂O₄Si [M]⁺: 352.2070, found: 352.2081.

Propargyl alcohol 41

To a mixture of (S)-(-)-2-Methyl-CBS-oxazaborolidine (2.3 g, 8.34 mmol) and BH₃•SMe₂ (11.0 mL, 104.3 mmol) in THF (220 mL) was added a THF (200 mL) solution of ketone 40 (29.4 g, 83.4 mmol) dropwise over 1.5 h. After being stirred for additional 2 h, the reaction was slowly quenched with a saturated aqueous NH₄Cl solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford propargyl alcohol 41 (27.9 g, 94 mmol) as a pale yellow oil. The enantiomeric purity of 41 (98%ee) was determined by HPLC analysis of the corresponding 3,5-dinitrobenzoate ester (DAICEL CHIRALCEL® OD-H, 15% 2-propanol in hexane, 1.0 mL/min, 254 nm): tR 17.08 min [0.8%, (R)-isomer], 28.02 min [99.2%, (S)-isomer]; [α]D²⁵ = +7.3 (c = 1.0, CH₂Cl₂); IR (neat) νmax 3305, 2944, 2865, 1652, 1459, 1221, 1161, 1108, 1081, 1067, 1034, 871, 827, 881, 794, 681, cm⁻¹; ¹H NMR (500MHz, CDCl₃) δ 5.87 (dd, J = 16.0, 1.1 Hz, 1H), 5.72 (dd, J = 16.3, 5.4 Hz, 1H), 4.93 (d, J = 5.7 Hz, 1H), 4.87 (br s, 1H), 4.70 (d, J = 5.7 Hz, 1H), 3.98 (d, J = 11.5 Hz, 2H), 3.87 (s, 2H), 3.64 (dd, J = 11.5, 3.4 Hz, 1H), 2.57 (d, J = 2.3 Hz, 1H), 1.15-1.05 (m, 21H); ¹³C NMR (125MHz, CDCl₃) δ 133.22, 129.56, 94.02, 74.65, 70.89, 70.86, 64.72, 62.90, 41.00,
18.01, 14.06, 11.91; HRMS (FD+) calcd for C_{19}H_{34}O_{4}Si [M+H]^+: 355.2305, found: 355.2290.

**Benzoate 42**

<table>
<thead>
<tr>
<th>![Diagram of benzoate 42]</th>
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To a solution of propargyl alcohol 41 (27.9 g, 78.7 mmol) in CH₂Cl₂ (260 mL) was added triethylamine (26.0 mL, 189 mmol), benzoyl chloride (11.0 mL, 94.4 mmol) and 4-dimethylaminopyridine (1.9 g, 15.7 mmol) at 0 °C. After being stirred for 15 min, the reaction was quenched with a saturated aqueous NaHCO₃ solution. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford benzoate 42 (34.7 g, 96%) as a colorless oil: [a]_D^{25} = +13.9 (c = 1.0, CH₂Cl₂); IR (neat) ν_{max} 3307, 2942, 2864, 1723, 1452, 1315, 1257, 1162, 1094, 1067, 1036, 966, 927, 881, 797, 710, 682, 660 cm⁻¹; ¹H NMR (500MHz, CDCl₃) δ 8.06 (dd, J = 8.3, 1.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 6.12 (td, J = 3.7, 1.9 Hz, 1H), 6.02 (dd, J = 16.0, 1.1 Hz, 1H), 5.77 (dd, J = 16.0, 5.7 Hz, 1H), 4.95 (d, J = 5.7 Hz, 1H), 4.69 (d, J = 5.7 Hz, 1H), 4.00 (dd, J = 9.7, 6.9 Hz, 2H), 3.91 (d, J = 9.7 Hz, 2H), 3.64 (dd, J = 11.5, 2.3 Hz, 2H), 2.59 (d, J = 2.3 Hz, 1H), 1.13-1.03 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 165.19, 135.62, 133.30, 129.86, 129.58, 128.36, 125.68, 94.03, 79.16, 75.54, 70.71, 64.56, 64.45, 41.22, 18.00, 14.06, 11.89; HRMS (FD+) calcd for C_{26}H_{38}O_{5}Si [M]^+: 458.2489, found: 458.2502.

**Allenysilane 24**

<table>
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<tr>
<th>![Diagram of allenysilane 24]</th>
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To a suspension of CuCN (1.62 g, 18.0 mmol) in THF (80 mL) was added a 1 M THF
solution of Me₂PhSiLi (18.0 mL, 18.0 mmol) at 0 °C. After being stirred for 30 min, the mixture was added to a THF (70 mL) solution of benzoate 42 (6.89 g, 15 mmol) at −100 °C dropwise over 1 h. The mixture was stirred for additional 30 min, and the reaction was quenched with a 9:1 mixture of a saturated aqueous NH₄Cl solution and a 30% aqueous NH₃ solution. After being stirred for 2 h, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ether/hexane) to afford allenylsilane 43 (4.39 g, 62%) as a pale yellow oil: [a]ᵣ²⁶ –59.1 (c = 0.82, CH₂Cl₂): IR (neat) vₘₐₓ 2944, 2864, 1921, 1458, 1248, 1162, 1113, 1035, 815, 669 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) 7.54 (dd, J = 7.5, 2.3 Hz, 2H), 7.38-7.32 (m, 3H), 5.94 (dd, J = 16.0, 10.9 Hz, 1H), 5.57 (dd, J = 10.3, 6.9 Hz, 1H), 5.37 (d, J = 16.0 Hz, 1H), 5.32 (d, J = 6.9 Hz, 1H), 4.95 (d, J = 5.7 Hz, 1H), 4.68 (d, J = 5.7 Hz, 1H), 3.96 (d, J = 11.5 Hz, 2H), 3.88 (d, J = 13.7 Hz, 2H), 3.58 (d, J = 10.6 Hz, 2H), 1.13-1.06 (m 21H), 0.37 (s, 3H), 0.36 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 213.39, 138.15, 133.62, 129.23, 129.00, 127.83, 126.07, 93.97, 88.09, 83.12, 71.24, 71.11, 64.84, 41.48, 18.15, 11.94, −2.34, −2.39: HRMS (FD+) calcd for C₂₇H₄₄O₃Si₂ [M⁺]: 472.2829, found: 472.2834.

**Lactone 47**

A mixture of allenylsilane 43 (7.29 g, 15.4 mmol) and powdered maleic anhydride (3.0 g, 31.4 mmol) in toluene (79 mL) was heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature, and the suspension was filtered through a pad of celite. The filtrate was concentrated under reduced pressure, and the crude product 45 was used for the next step without purification.
To a mixture of a 1.02 M hexane solution of DIBAL-H (77.0 mL, 78.5 mmol) and THF (80 mL) was added a 2.65 M hexane solution of \( n \)-BuLi (29.6 mL, 78.5 mmol) at 0 °C. The mixture was cooled to −78 °C, and to this was added a solution of crude 45 in THF (80 mL). After being stirred for 30 min, the reaction was quenched with 1 M HCl. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO4, and concentrated under reduced pressure. The crude hydroxyacid 45' was used for the next step without purification.

A solution of crude 45', \( p \)-toluenesulfonyl chloride (9.0 g, 47.1 mmol), and pyridine (50 mL) in CH2Cl2 (50 mL) was heated at 30 °C for 2 h. The mixture was cooled to room temperature, and a saturated aqueous NaHCO3 solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford lactone 47 (4.94 g, 58% from 43) as a colorless oil: \([\alpha]_D^{25} = -87.7 (c = 0.26, \text{CH}_2\text{Cl}_2)\); IR (neat) \( \nu_{\text{max}} \) 2942, 2865, 1775, 1464, 1250, 1160, 1111, 1038, 927, 882, 841, 801 cm\(^{-1}\); \(^1\)H NMR (500MHz, CDCl3) \( \delta \) 7.50-7.49 (m, 2H), 7.37-7.35 (m, 3H), 6.39 (d, \( J = 10.3 \) Hz, 1H), 6.01 (d, \( J = 10.3 \) Hz, 1H), 5.71 (s, 1H), 4.88 (d, \( J = 5.7 \) Hz, 1H), 4.72 (d, \( J = 6.3 \) Hz, 1H), 4.46 (d, \( J = 8.6 \) Hz, 1H), 4.40 (m, 2H), 4.20 (d, \( J = 10.3 \) Hz, 1H), 3.98 (d, \( J = 10.3 \) Hz, 1H), 3.93 (d, \( J = 11.5 \) Hz, 1H), 3.87 (d, \( J = 5.2 \) Hz, 2H), 3.84 (d, \( J = 5.7 \) Hz, 2H), 3.34 (s, 2H), 2.87 (s, 1H), 1.20-1.06 (m, 21H), 0.402 (s, 3H), 0.397 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl3) \( \delta \) 176.96, 150.10, 139.39, 134.46, 131.17, 130.23, 129.91, 128.76, 127.88, 94.54, 75.07, 70.97, 69.99, 63.68, 45.21, 42.27, 40.60, 35.75, 18.81, 12.68, 0.78, -0.13; HRMS (FD+) calcd for C31H46O5Si2 [M]+: 556.3040, found: 556.3050.
Bis silyl ether 48

To a solution of LDA, which was freshly prepared from N,N-diisopropylamine (2.5 mL, 17.7 mmol) in THF (22 mL) and a 2.65 M solution of n-BuLi (6.3 mL, 16.9 mmol), was added a THF (20 mL) solution of lactone 47 (4.70 g, 8.45 mmol) at −78 °C. After being stirred for 1 h, acetaldehyde (2.4 mL, 42.2 mmol) was added, and the mixture was stirred for 5 min. The reaction was quenched with a saturated aqueous NH₄Cl solution, and the mixture was allowed to warm to room temperature. The mixture was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude alcohol 47' was used for the next step without purification.

To a solution of alcohol 47' in CH₂Cl₂ (38 mL) was added 2,6-lutidine (2.1 mL, 18 mmol) and triethylsilyl trifluoromethanesulfonate (2.0 mL, 9.0 mmol) at 0 ºC. After being stirred for 30 min, a saturated aqueous NaHCO₃ solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford a 4:1 diastereomeric mixture of bis silyl ether 48 (4.89 g, 81%) as a colorless oil: IR (neat) νmax 2942, 2867, 1770, 1461, 1152, 1109, 1066, 1037, 1000, 925, 882, 812, 728, 682 cm⁻¹; ¹H NMR (500MHz, CDCl₃, peaks due to the major isomer) δ 7.52-7.49 (m, 2H), 7.37-7.34 (m, 3H), 6.34 (dd, J=10.6, 2.0 Hz, 1H), 5.94 (ddd, J = 10.6, 4.6, 1.1 Hz, 1H), 5.54 (s, 1H), 4.80 (d, J = 5.7 Hz, 1H), 4.76 (d, J = 5.7 Hz, 1H), 4.39 (t, J = 5.7 Hz, 1H), 4.29 (d, J = 11.5 Hz, 1H), 4.19 (d, J = 6.1 Hz, 1H), 4.07 (d, J = 11.5 Hz, 1H), 3.98 (dd, J = 18.3, 8.0 Hz, 1H), 3.91-3.88 (m, 2H), 3.83-3.81 (m, 2H), 3.64 (d, J = 10.3 Hz, 1H), 2.84 (s, 1H), 1.08-1.02 (m, 24H), 0.94 (t, J = 7.7 Hz, 9H), 0.60 (q, J = 7.7 Hz, 6H), 0.398 (s, 3H), 0.395 (s, 3H); ¹³C NMR (125MHz, CDCl₃, peaks due to the major isomer) δ
HRMS (FD+) calcd for C_{39}H_{66}O_{6}Si_{3} [M]^+: 714.4167, found: 714.4180.

Cyclic ether 49

To a solution of bis silyl ether 48 (3.43 g, 4.8 mmol) in CH$_2$Cl$_2$ (24 mL) was added a 1.02 M hexane solution of DIBAL·H (14.2 mL, 14.5 mmol) at −78 ºC, and the mixture was stirred for 30 min. A saturated aqueous Rochelle’s salt solution was added, and the mixture was allowed to warm up to room temperature. After being stirred for additional 1 h, the mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude diol 48’ was used for the next step without purification.

A solution of crude 48’, methanesulfonyl chloride (0.74 mL, 9.6 mmol), and pyridine (16 mL) in CH$_2$Cl$_2$ (16 mL) was heated at 45 ºC for 2 h. The mixture was cooled to room temperature, and a saturated aqueous NaHCO$_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford a ca. 4:1 diastereomeric mixture of cyclic ether 49 (2.87 g, 87% from 48) as a colorless oil: IR (neat) $\nu_{\text{max}}$ 2942, 9866, 1460, 1247, 1159, 1078, 1037, 1013, 923, 882, 833, 810, 727, 698, 683 cm$^{-1}$; $^1$H NMR (500MHz, CDCl$_3$, peaks due to the major isomer) $\delta$ 7.53–7.49 (m, 2H), 7.36–7.32 (m, 3H), 6.33 (d, $J$ = 10.9 Hz, 1H), 5.86 (dd, $J$ = 10.9, 3.7 Hz, 1H), 5.38 (s, 1H), 4.83 (d, $J$ = 5.7 Hz, 1H), 4.74 (d, $J$ = 5.7 Hz, 1H), 4.11–4.05 (m, 4H), 3.95–3.89 (m, 2H), 3.86–3.79 (m, 2H), 3.67 (d, $J$ = 10.3 Hz, 1H), 3.47 (t,
A mixture of cyclic ether 49 (4.2 g, 6.0 mmol), 10-canphorsulfonic acid (280 mg, 1.2 mmol), CH$_2$Cl$_2$ (8 mL), and methanol (24 mL) was stirred at 25 °C for 3 h. After addition of a saturated aqueous NaHCO$_3$ solution, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude alcohol 49' was used for the next step without purification.

To a solution of alcohol 49' in THF (30 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (12 mL, 12.0 mmol) at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was diluted with water. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford a ca. 4:1 diastereomeric mixture of diol 50 (1.49 g, 85% from 49) as a colorless oil: IR (neat) ν$_{max}$ 3415 (br), 2964, 2927, 2873, 2766, 1457, 1379, 1293, 1160, 1069, 1034, 951, 921 cm$^{-1}$; $^1$H NMR (500MHz, CDCl$_3$, peaks due to the major isomer) δ 7.53-7.49 (m, 2H), 7.36-7.31 (m, 3H), 6.33 (d, $J = 10.9$ Hz, 1H), 5.86 (dd, $J = 10.9$, 3.7 Hz, 1H), 5.38 (s, 1H), 4.83 (d, $J = 5.7$ Hz, 1H), 4.74 (d, $J = 5.7$ Hz, 1H), 4.11-4.05 (m, 4H), 3.95-3.89 (m, 2H), 3.86-3.79 (m, 2H), 3.67 (d, $J = 10.3$ Hz, 1H), 3.47 (d, $J = 8.3$ Hz, 1H), 3.23 (d, $J = 8.3$ Hz, 1H), 2.89 (s, 1H), 1.15 (d, $J = 6.3$ Hz, 3H), 1.12-1.03 (m, 21H), 0.95 (t, $J = 7.6$ Hz, 9H), 0.58 (d, $J = 7.6$ Hz, 1H), 0.36 (s, 3H), 0.35 (s, 3H); $^{13}$C
NMR (125MHz, CDCl₃, peaks due to the major isomer) δ 140.83, 130.38, 129.22, 112.33, 93.93, 75.27, 75.13, 74.52, 71.80, 71.50, 62.74, 54.89, 44.96, 43.00, 39.55, 18.70; HRMS (FD+) calcd for C₁₆H₂₄O₅ [M+H]+: 297.1702, found: 297.1714.

**Diol 53**

![Diol 53 Reaction Scheme]

To a solution of dimethyl sulfoxide (1.2 mL, 17.5 mmol) in CH₂Cl₂ (7 mL) was added oxalyl chloride (0.75 mL, 8.76 mmol) at −78 °C. After being stirred for 10 min, a solution of alcohol 50 (865 mg, 2.92 mmol) in CH₂Cl₂ (8 mL) was added, and the resulting cloudy white mixture was stirred for 1 h at −60 °C. Triethylamine (4.0 mL, 29.2 mmol) was added, and the reaction mixture was stirred at −30 °C for 30 min. After slowly warming up to room temperature and additional stirring for 30 min, the reaction was quenched with a saturated aqueous NaHCO₃ solution. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude ketoaldehyde 51 was used for the next step without purification.

To a solution of ketoaldehyde 51 in THF (15 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.2 mL, 7.8 mmol) at 0 °C. After being stirred for 2 h, 1 M HCl was added. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude hydroxyketone 53 was used for the next step without purification.

To a solution of hydroxyketone 53 in THF (30 mL) was added LiAlH₄ (554 mg, 14.6 mmol) in one portion at −100 °C. After being stirred for 2 h at the same temperature, the reaction was carefully quenched with water (550 µL), a 15% aqueous NaOH solution (550 µL) and water (1.7 mL). After warming up to room temperature and stirring for
additional 2 h, the mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure, and the residue was purified by recrystallization from ether to afford diol 54 (459.7 mg, 53% from 50) as a white solid: \([\alpha]_D^{24} = -179.6 \text{ (c = 0.1, MeOH)}\), IR (neat) \(\nu_{\text{max}}\) 3336 (br), 2969, 2933, 2877, 1468, 1410, 1378, 1340, 1308, 1160, 1128, 951, 817 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta \) 6.31 (dd, \(J = 10.0, 3.2 \text{ Hz, 1H})\), 5.09 (s, 1H), 5.02 (m, 2H), 4.68 (br s, 1H), 4.65 (d, \(J = 5.7 \text{ Hz, 1H})\), 4.22 (d, \(J = 5.7 \text{ Hz, 1H})\), 4.13 (dd, \(J = 8.3, 5.4 \text{ Hz, 1H})\), 3.84 (m, 3H), 3.80 (d, \(J = 11.5 \text{ Hz, 1H})\), 3.70 (d, \(J = 12.0 \text{ Hz, 1H})\), 3.59 (dd, \(J = 11.7, 2.6 \text{ Hz, 1H})\), 3.54 (s, 1H), 3.48 (q, \(J = 8.0 \text{ Hz, 2H})\), 2.90 (s, 1H), 2.84 (d, \(J = 5.2 \text{ Hz, 1H})\), 2.25 (d, \(J = 15.5 \text{ Hz, 1H})\), 2.14 (d, \(J = 15.5 \text{ Hz, 1H})\); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta \) 144.41, 131.22, 124.89, 114.56, 94.22, 73.60, 70.68, 69.73, 69.66, 68.90, 67.59, 51.58, 45.37, 40.52, 31.29, 29.75; HRMS (FD+) calcd for C\(_{16}\)H\(_{22}\)O\(_5\) [M]+: 294.1467, found: 294.1462.

**Allyl sulfide 57**

To a mixture of diol 54 (182 mg, 0.62 mmol), ethanethiol (5.5 mL), and 1,1,1,3,3,3-hexafluoro isopropanol (HFIP) (0.6 mL) was added indium(III) trifluoromethanesulfonate (70 mg, 0.12 mmol) at 0 °C. After being stirred for 2 h, the reaction mixture was directly poured on a short pat of silica gel and the filtrate was concentrated under reduced pressure. The crude allyl sulfide 56 was used for the next step without further purification.

To a mixture of crude 56 and isopropenyl methyl ether (0.24 mL, 2.5 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added pyridinium \(p\)-toluenesulfonate (PPTS) (25 mg, 0.1 mmol) at 0 °C. After being stirred for 2 h, a saturated aqueous NaHCO\(_3\) solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO\(_4\), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford a ca. 4:1 diastereomeric mixture of allyl sulfide 57 (181.5 mg, 73%) as a colorless oil: IR (neat) \(\nu_{\text{max}}\) 3640, 3416 (br), 2928, 2884, 1457, 1381, 1240, 1155, 1080, 1032, 950 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\), peaks due to the major
isomer) δ 5.78 (d, J = 6.3 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 5.7 Hz, 1H), 4.92 (d, J = 4.6 Hz, 1H), 4.70 (d, J = 5.7 Hz, 1H), 4.20-4.17 (m, 2H), 3.92-3.86 (m, 2H), 3.84-3.78 (m, 2H), 3.67 (dd, J = 8.9, 3.7 Hz, 1H), 3.56 (s, 1H), 3.46 (d, J = 9.7 Hz, 1H), 3.40 (t, J = 5.4 Hz, 1H), 2.93 (d, J = 3.4 Hz, 1H), 2.80-2.67 (m, 2H), 2.65 (d, J = 4.6 Hz, 1H), 1.97 (d, J = 15.5 Hz, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.35 (s, 3H), 1.33 (t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃, peaks due to the major isomer) δ 113.41, 127.72, 97.45, 94.58, 71.53, 71.30, 70.61, 68.99, 68.56, 66.44, 51.96, 47.24, 43.67, 39.83, 36.07, 32.20, 31.25, 27.65, 22.21, 19.79, 14.82; HRMS (FD+) calcd for C₂₁H₃₂O₅S [M]⁺: 396.1970, found: 396.1984.

**Allylborane 58**

A mixture of lithium wire (106 mg, 4.6 mmol) and 4,4'-di-tert-butyphenyl (DBB) (366 mg, 1.37 mmol) in THF (4.2 mL) was stirred at 0 °C for 30 min. The resulting deep blue solution was cooled to –78 °C, and a solution of allyl sulfide 57 (181.5 mg, 0.458 mmol) and methoxyboronic acid pinacol ester (0.45 mL, 2.8 mmol) in THF (5 mL) was added dropwise. After being stirred for 30 min, the reaction was quenched by water. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford allylborane 58 (144 mg, 68%) as a colorless oil: [α]D₂₂ +19.9 (c 0.35, CH₂Cl₂); IR (neat) νmax 2985, 2915, 2766, 1717, 1683, 1456, 1369, 1317, 1144, 1115, 1038, 970, 843, 668 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.31 (s, 1H), 4.81 (d, J = 5.7 Hz, 1H), 4.69 (d, J = 5.7 Hz, 1H), 4.19 (d, J = 4.0 Hz, 1H), 4.07 (d, J = 4.7 Hz, 1H), 4.00 (d, J = 11.5 Hz, 1H), 3.82-3.68 (m, 5H), 3.54 (d, J = 8.6 Hz, 1H), 3.42 (d, J = 12.0 Hz, 1H), 2.98 (s, 1H), 2.75 (d, J = 12.0 Hz, 1H), 2.67 (td, J = 10.0, 5.2 Hz, 1H), 2.16 (d, J = 12.6 Hz, 1H), 1.74-1.71 (m, 4H), 1.62 (s, 3H), 1.45 (s, 3H), 1.264 (s, 6H), 1.256 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 131.42, 123.03, 97.50, 93.36, 83.21, 74.20, 70.14, 69.82, 68.89, 68.08, 66.55, 51.54, 46.31, 40.36, 33.96, 31.95, 31.72, 25.06, 25.02, 24.87, 21.69, 19.77, 14.07; HRMS (FD+) calcd for C₂₅H₃₈BO₇ [M]⁺: 462.2793, found: 462.2808.
Ketone 60

A mixture of allylborane 58 (27.2 mg, 58.8 mmol) and 3-(trimethylsilyl)-2-propynal (25 µL, 176.5 µmol) in toluene (0.3 mL) was stirred at room temperature for 18 h. After quenching with a saturated aqueous NaHCO₃ solution, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude alcohol 59 was used for the next step without purification.

To a solution of crude 59 in CH₂Cl₂ (0.6 mL) was added Dess-Martin periodinane (75 mg, 177 µmol) and NaHCO₃ (30 mg, 353 µmol) at room temperature. After being stirred for 1.5 h, a saturated aqueous NaHCO₃ solution and an aqueous Na₂S₂O₃ solution were added. After being stirred for 1 h, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ketone 60 (16.8 mg, 58%) as a colorless oil: [a]D²⁴ = −118.3 (c = 0.1, CH₂Cl₂); IR (neat) νmax 2987, 2961, 2933, 2858, 1669, 1454, 1381, 1368, 1285, 1240, 1190, 1161, 1125, 1100, 1081, 1037, 959, 923, 755, 717, 666 cm⁻¹; ¹H NMR (500MHz, CDCl₃) δ 6.17 (dd, J = 9.7, 4.0 Hz, 1H), 5.79 (dd, J = 9.7, 2.9 Hz, 1H), 5.00 (d, J = 5.7 Hz, 1H), 4.68-4.64 (m, 2H), 4.11 (dd, J = 11.2, 2.0 Hz, 1H), 4.03 (d, J = 4.6 Hz, 1H), 3.79 (m, 2H), 3.71 (dd, J = 11.2, 2.0 Hz, 1H), 3.64 (dd, J = 9.7, 4.6 Hz, 1H), 3.53-3.48 (m, 2H), 3.44 (d, J = 8.6 Hz, 1H), 3.24 (d, J = 9.7 Hz, 1H), 2.81 (dt, J = 15.5, 4.6 Hz, 1H), 2.42 (t, J = 3.7 Hz, 1H), 1.83 (d, J = 15.5 Hz, 1H), 1.65 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 0.24 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 189.67, 133.83, 130.60, 100.77, 100.37, 98.01, 94.38, 71.92, 70.29, 69.99, 69.00, 68.89, 66.51, 57.75, 51.90, 48.63, 40.69, 34.25, 31.93, 31.49, 22.47, 20.34, -0.61; HRMS (FD+) calcd for C₉₅H₆₆O₅Si [M]+: 460.2281, found: 460.2283.

Enyne 62
A mixture of (E)-1-(4-methoxybenzyloxy)-3-(tributylstannyl)-2-butene 61 (90 mg, 188 µmol) and a 2.65 M hexane solution of n-BuLi (68 µL, 180 µmol) in THF (0.3 mL) was stirred at –78 ºC for 2 h. To this was added a solution of ketone 60 (33.2 mg, 72.1 µmol) in THF (0.42 mL), and after being stirred at –78 ºC for 30 min, isobutyryl chloride (23 µL, 216 µmol) was added. After being stirred for 10 min at –40 ºC and then at 0 ºC for 30 min, a saturated methanol solution of K$_2$CO$_3$ was added. The reaction mixture was stirred for 1 h at room temperature, and then a saturated aqueous NH$_4$Cl solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford enyne 62 (34.6 mg, 74%) as a colorless oil: IR (neat) $\nu_{\max}$ 2980, 2928, 2873, 1744, 1612, 1513, 1458, 1381, 1243, 1189, 1155, 1082, 1035, 968, 923, 839, 754 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.28-7.24 (m, 3H), 6.90-6.84 (m, 3H), 5.95-5.79 (m, 3H, involving a doublet at 5.89), 5.59-5.42 (br m, 1.5H), 5.01-4.94 (m, 1.5H), 4.70-4.59 (m, 3H), 4.45-4.35 (m, 3H), 4.19-3.99 (m, 7H), 3.94 (br s, 0.5H), 3.85 (dd, $J = 12.6, 4.0$ Hz, 1H), 3.82-3.77 (m, 5H, involving a singlet at 3.81), 3.68 (d, $J = 10.9$ Hz, 0.5H), 3.65-3.56 (m, 6H), 3.39-3.34 (m, 1.5H), 3.20 (br s, 0.5H), 3.11-2.75 (m, 2.5H, involving a br singlet at 3.09), 2.86-2.75 (m, 1.5H, involving a triplet-triplet at 2.79), 2.63-2.51 (m, 2.5H, involving singlets at 2.61 and 2.59), 2.06-1.97 (m, 1.5H), 1.80 (br s, 3H), 1.71-1.63 (m, 6H, involving singlets at 1.69 and 1.66), 1.42 (s, 1.5H), 1.36-1.12 (m, 16.5H, involving a singlet at 1.35 and a doublet at 1.18); $^{13}$C NMR (125 MHz, CDCl$_3$) very broadened spectra; HRMS (FD+) calcd for C$_{38}$H$_{50}$O$_9$ [M]$^+$: 650.3455, found: 650.3466.
A mixture of enyne 62 (17.5 mg, 26.9 µmol), PdCl2(CH3CN)2 (1.4 mg, 5.4 µmol), and acetic acid (7.7 µL, 134 µmol) in acetonitrile (270 µL) was heated at 58 ºC for 2 h. After cooling to room temperature, a saturated aqueous NaHCO3 solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO4 and concentrated under reduced pressure. The crude cyclopentenone 63 was used for the next step without purification.

A mixture of crude 63, isopropenyl methyl ether (12.7 µL, 134 µmol), and pyridinium p-toluenesulfonate (1.6 mg, 6.4 µmol) in CH2Cl2 (0.27 mL) was stirred at 0 ºC for 2 h. After quenching with a saturated aqueous NaHCO3 solution, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford cyclopentenone 64 (7.6 mg, 49% from 62) as a white solid: IR (neat) νmax 3649, 3365, 2971, 2931, 2361, 1697, 1514, 1458, 1379, 1246, 1160, 1128, 1037, 952, 817 cm⁻¹; 1H NMR (500MHz, CDCl3) δ 7.19 (d, J = 8.0 Hz, 3H), 6.89-6.84 (m, 3H), 6.04 (dd, J = 9.5, 4.3 Hz, 0.5H), 5.93 (dd, J = 9.5, 3.7 Hz, 1H), 5.87 (dd, J = 9.5, 2.6 Hz, 1H), 5.81 (dd, J = 9.5, 2.6 Hz, 0.5H), 5.03-4.97 (m, 1.5H), 4.67-4.61 (m, 3H), 4.43 (m, 1.5H), 4.37 (m, 1.5H), 4.05 (m, 1.5H), 3.98-3.92 (m, 2.5H), 3.87 (dd, J = 9.5, 7.2 Hz, 0.5H), 3.81-3.77 (m, 6H, involving singlet at 3.81), 3.75-3.62 (m, 3H), 3.60-3.46 (m, 4.5H), 3.38 (dd, J = 9.5, 6.3 Hz, 0.5H), 3.33 (d, J = 8.6 Hz, 1H), 3.29-3.21 (m, 2.5H), 2.80-2.71 (m, 2.5H), 2.67 (d, J = 4.6 Hz, 0.5H), 2.55 (t, J = 3.2 Hz, 1H), 2.48-2.39 (m, 2.5H), 2.25-2.16 (m, 1.5H), 2.04 (s, 3H), 2.02 (s, 1.5H), 1.87-1.77 (m, 1.5H), 1.59 (s, 4.5H), 1.37-1.29 (m, 4.5H, involving a singlet at 1.27), 1.16 (s, 3H), 1.11 (s, 1.5H): 13C NMR (125 MHz, CDCl3) δ 208.50, 207.47, 166.88, 166.00, 159.31, 159.19, 145.86, 143.93, 138.93, 138.32, 130.89, 130.01, 129.80, 129.34, 129.07, 128.17, 125.61, 113.86, 133.76, 97.26, 97.19, 94.23, 94.21, 72.91, 72.83, 72.61, 71.83, 71.00, 70.56, 70.51, 70.41, 70.11, 69.89, 69.77, 68.84, 68.73, 66.58, 66.30, 57.26, 57.00, 55.27, 48.67, 48.31, 44.33, 43.90, 40.04, 39.82,

### Allyl alcohol S3

![Chemical structure](image)

To a solution of LDA with freshly prepared from N,N-diisopropylamine (14.7 mL, 105 mmol) in THF (100 mL) and a 2.64 M solution of n-BuLi (37.9 mL, 100 mmol), was added n-Bu₃SnH (26.9 mL, 100 mmol) at -78 °C. After being stirred for 1 h at -40 °C, CuSPh (10.4 g, 60 mmol) was added to this mixture at -50 °C. After stirring for 1 h at -40 °C, a solution of ethyl 2-butyrate S1 (5.83 ml, 50 mmol) and MeOH (3.44 mL) in THF (50 mL) was added at -100 °C and being stirred for 3 h at -78 °C. The reaction mixture was added a saturated aqueous NH₄Cl solution and an aqueous NH₃ solution. After being stirred for 2 h, the mixture was separated and the aqueous layer was extracted with hexane. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude ester S2 was used for the next step without purification.

To a solution of crude ester S2 in CH₂Cl₂ (25 mL) was added a 0.97 M solution of DIBAL-H (113 mL, 110 mmol) at -78 °C. After being stirred for 30 min at 0 °C, a saturated aqueous Rochelle salt solution was added. The reaction mixture was stirred for 1 h, separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography afforded allyl alcohol S3 (17.0 g, 94%) as a colorless oil. IR (neat) v_max 3300, 2930, 2850, 1460, 1060, 1000 cm⁻¹; ¹H NMR (500MHz, CDCl₃) δ 5.75 (1H, tq, J = 6.3, 1.8 Hz, ³J_Sn-H = 33.5 Hz), 4.25 (2H, d, J = 6.3 Hz), 1.89 (3H, d, J = 1.8 Hz, ³J_Sn-H = 22.6 Hz), 1.58-1.42 (7H, m), 1.31 (6H, sext, J = 7.5 Hz), 0.97-0.83 (15H, m); ¹³C NMR (125 MHz, CDCl₃) δ 142.16, 139.19, 58.83, 29.08, 27.34, 19.36, 13.64, 9.05: HRMS (FD) calcd for C₁₆H₃₄O₈Sn (M⁺) 362.1632, found 362.1641.
Vinyl stannane 61

To a solution of allyl alcohol S3 (724 mg, 2.0 mmol) in DMF (10 mL) was added NaH (131 mg, 3.0 mmol, 55% dispersion in mineral oil) at 0 ºC. After being stirred for 30 min, 4-methoxybenzyl chloride (540 µL, 4.0 mmol) and tetrabutylammonium iodide (148 mg, 0.4 mmol) was added to the reaction mixture. After stirring for 20 h at room temperature, the reaction mixture was added a saturated aqueous NH₄Cl solution. The mixture was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane) afforded vinyl stannane 61 (770 g, 80%) as a colorless oil. IR (neat) ν max 2954, 2871, 2851, 1612, 1512, 1463, 1376, 1357, 1301, 1172, 1080, 1038, 821, 663, 595 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.28 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.72 (td, J = 5.7, 2.3 Hz, 3JSn-H = 35.5 Hz, 1H), 4.45 (s, 2H), 4.10 (d, J = 5.7 Hz, 2H), 3.81 (s, 3H), 1.85 (s, 3JSn-H = 22.3 Hz, 3H) 1.56-1.42 (m, 6H), 1.31 (sext, J = 7.5 Hz, 6H), 0.96-0.82 (m, 15H, involving triplet at 0.89); ¹³C NMR (125 MHz, CDCl₃): δ 142.98, 136.86, 130.57, 129.55, 129.47, 113.73, 71.73, 65.84, 55.26, 29.14, 27.83, 27.38, 13.70, 9.09; HRMS (FD+) calcd for C₁₆H₃₄OSn (M-Bu⁺) 425.1503, found 425.1525.
Chapter 3

Studies toward the construction of the fully functionalized ABCEF ring system of azadirachtin

In Chapter 2, the stereoselective synthesis of a highly functionalized ABCE ring system of azadirachtin (1) was described. The remaining issues for the total synthesis of 1 is the functionalization of the trans-decaline core (ABCD ring system) and the construction of the FG ring moiety. As for the construction of the FG ring, Oosaka had achieved the stereoselective synthesis of model compound 71 (Scheme 29). Enyne 65 was subjected to the Pd-catalyzed Nazarov cyclization under the influence of PdCl₂(CH₃CN)₂ and acetic acid to give the desired cyclopentenone 66 in 64% yield. Reduction of cyclopentenone 66 with diisobutyl aluminum hydride (DIBAL·H) afforded the corresponding allyl alcohol as a 9:1 diastereomeric mixture. The stereochemistry of the major isomer was determined by the NOE experiment, indicating that the reduction occurred from the opposite face of the bulky silyloxyalkyl side chain.

Scheme 29. Model study for constructing the EFG ring system by Oosaka
After protection of the hydroxyl group with a TMS group, the product 68 was treated with mCPBA to give epoxide 69 through oxidation of the double bond from the less hindered β-face. The reaction of 69 with potassium tert-butoxide effected removal of the TMS group followed by intramolecular cyclization to afford the desired bicyclic ether 70 in 90% yield. The product was then transformed into the model compound 71 through introduction of a two carbon unit and formation of the G ring.

These model studies by Oosaka led the author to plan the synthetic route of azadirachtin as shown in Scheme 30.

Initially, optically active vinyl stannane 80, a precursor of the vinyl anion, was prepared as shown in Scheme 31. The known alcohol 76 was oxidized with manganese(IV) oxide to aldehyde 77 which was reacted with chloromethylithium to afford allyl alcohol 78 in 86% yield. The racemic alcohol 78 was converted to optically active one through the Dess-Martin oxidation followed by the asymmetric reduction using (S)-2-methyl CBS oxazaborolidine. The desired allyl alcohol 79 was obtained in 76% yield, the optical purity of which was determined to be 90%ee. The hydroxyl group of 79 was then protected with a TBS group to afford the desired vinyl stannane 80.
With the optically active vinyl stannanes in hand, construction of the EF ring moiety was examined (Scheme 32). Treatment of vinyl stannane 80 with n-butyllithium afforded the corresponding alkenyllithium, and ketone 60 was reacted with the alkenyllithium followed by isobutyl chloride and a saturated MeOH solution of K₂CO₃. The resulting enyne 81 was subjected to the Pd-catalyzed Nazarov cyclization reaction promoted by PdCl₂(CH₃CN)₂ and acetic acid. After protection of the 1,3-diol moiety with an acetonide group, the desired cyclopentenone 82 was obtained in 24% yield for 2 steps. While the yield of the key compound 82 was quite low, the efforts for constructing the F ring were made on the basis of the Oosaka’s protocol.
Reduction of cyclopentenone **82** with DIBAL·H followed by silylation gave **83** as a 9:1 diastereomeric mixture. After stereoselective oxidation by mCPBA, the resulting epoxide **84** was treated with potassium tert-butoxide to afford the desired bicyclic ether **85** in 38% yield for 4 steps.

The stage was set for introduction of the syn-1,2-diol moiety at the B ring. Surprisingly, however, initial attempts for the dihydroxylation of the alkene moiety with osmium(VIII) oxide were fruitless (Scheme 33). For example, the reaction using an excess amount of OsO₄ in pyridine at 50 °C for 12 h resulted in recovery of the substrate, suggesting that the steric hindrance around the alkene moiety prevented the interaction with the osmium reagent. Indeed, alkene **85** was found to react with sterically less demanding ozone to afford bisaldehyde **87**, but the efforts for obtaining diol **86** through the pinacol coupling of **87** merely led to formation of complex mixtures.

These results led the author to modify the structure of alkene **85** so as to reduce the steric hindrance around the alkene moiety. Since the acetonide group of the A ring was expected to block the α-face of the alkene moiety, the two hydroxyl groups should be protected separately with small substituents. In addition, the dihydroxylation reaction may proceed smoothly by applying to intermediate **89** prior to the construction of the bulky EF ring (Scheme 34).
Scheme 34. Alternative plan for oxidizing the alkene moiety of the B ring

The new intermediate 93 was synthesized as shown Scheme 27. Allyl sulfide 56, an intermediate described in Chapter 2, was protected with (2-trimethylsilylethoxy)methyl (SEM) groups to give allyl sulfide 91 in 67% yield from 54. Transformation of allyl sulfide 91 into allylborane 92 was achieved by treating with LDBB and methoxyboronic acid pinacol ester. Gratifyingly, the borylation reaction of 91 proceeded with much higher stereoselectivity than the reaction of the corresponding acetonide 57 which gave a 77:23 mixture of epimers. These results indicated that the two SEM groups have less steric effect to block the α-face of the B ring than the acetonide group. Allylborane 92 was subjected the addition reaction with 3-triisopropylsilyl-2-propinal\(^{17}\) at 50 °C to give alcohol 93 in 83% yield.

Scheme 35. Preparation of propargyl alcohol 93 having two SEM groups
Next, dihydroxylation of the B ring moiety was explored (Scheme 36). After a number of trials, the combined use of OsO₄ and TMEDA was found to effect a smooth oxidation reaction of 93, giving rise to diol 94 in 71% yield as a single isomer. After removal of the SEM groups, the configuration of the 1,2-diol moiety was determined by the NOE experiment. The high stereoselectivity as well as the fast reaction rate of the reaction would come from the hydrogen bonding of the osmium complex with the propargyl alcohol.

![Scheme 36. Oxidation of 93](image)

On treatment with manganese(IV), triol 94 was converted to ketone 96 through selective oxidation of the propargyl alcohol moiety (Scheme 37).

![Scheme 37. Selective oxidation of triol 94](image)

In conclusion, the author succeeded in obtaining pentacyclic compound 85 possessing the ABCEF ring system of azadirachtin, while the compound was unsuitable for introducing the syn-1,2-diol moiety of the B ring. On the other hand, the use of two SEM groups instead of the acetonide group for protecting the 1,3-diol moiety led to better results. Thus, the stereoselectivity in the reductive borylation step was improved dramatically, and the reaction of propargyl alcohol 94 with OsO₄/TMEDA afforded the dihydroxylation product 95 possessing the fully functionalized AB ring system.
Experimental Section (Chapter 3)

** Allyl alcohol 78 **

![Chemical structure]

To a solution of allylalcohol 76 (5.94 g, 16.5 mmol) in CH$_2$Cl$_2$ (82 mL) was added MnO$_2$ (30 g, 297 mmol) and Na$_2$CO$_3$ (33 g, 314 mmol) at room temperature. After being stirred for 13 h, the reaction mixture was filtered through a pad of celite, concentrated under reduced pressure. The crude aldehyde 77 was used for the next step without purification.

To a solution of crude aldehyde 77 and chloriodemethane (4.2 mL, 57.8 mmol) in THF (84 mL) was added MeLi (1.13 M solution in diethyl ether, 45 mL, 51.2 mmol) at -78 °C. After stirred for 40 min, a saturated aqueous NH$_4$Cl solution was added, and the mixture was separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford allyl alcohol 78 (5.83 g, 86%) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) δ 5.53 (dd, $J = 7.4, 1.7$ Hz, $^3$J$_{Sn-H} = 32.6$ Hz, 1H), 4.76-4.72 (m, 1H), 3.57 (dd, $J = 10.9, 8.6$ Hz, 1H), 3.48 (dd, $J = 10.9, 8.6$ Hz, 1H), 1.94 (d, $J = 1.7$ Hz, $^3$J$_{Sn-H} = 21.2$ Hz, 3H) 1.52-1.45 (m, 6H), 1.31 (sext, $J = 7.4$ Hz, 6H), 0.97-0.84 (m, 15H).

** Ketone 78’ **

![Chemical structure]

To a solution of allyl alcohol 78 (849 mg, 2.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added Dess-Martin periodinane (2.1 g, 5.0 mmol) and NaHCO$_3$ (0.84 g, 10.0 mmol) at 0 °C. After being stirred for 1.5 h at 0 °C, a saturated aqueous NaHCO$_3$ solution and Na$_2$S$_2$O$_3$ were added. After being stirred for 1 h, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel
column chromatography (ethyl acetate/hexane) to afford ketone 78' (750 mg, 92%) as an orange oil. \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.52 (q, \( J = 1.7 \) Hz, \( ^3J_{Sn-H} = 31.5 \) Hz, 1H), 4.12 (s, 2H), 2.44 (d, \( J = 1.7 \) Hz, \( ^3J_{Sn-H} = 20.6 \) Hz, 3H), 1.58-1.41 (m, 6H), 1.36-1.27 (m, 6H), 1.06-0.82 (m, 15H).

**Alcohol 79**

\[ \text{CH}_2\text{Cl}_2, 0 \degree \text{C} \]

To a mixture of ketone 78' (749 g, 1.84 mmol) and (S)-(-)-2-Methyl-CBS-oxazaborolidine (102 mg, 0.37 mmol) in THF (9.2 mL) was added BH\(_3\)•SMe\(_2\) (291 \( \mu \)L, 2.76 mmol) dropwise over 30 min. After being stirred for additional 30 min, the reaction was slowly quenched with a saturated aqueous NH\(_4\)Cl solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO\(_4\), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford alcohol 79 (568.6 g, 76%) as a pale yellow oil. The enantiomeric purity of 79 (90% ee) was determined by \(^1\)H NMR spectra of the corresponding Mosher's ester. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.52 (q, \( J = 1.7 \) Hz, \( ^3J_{Sn-H} = 31.5 \) Hz, 1H), 4.12 (s, 2H), 2.44 (d, \( J = 1.7 \) Hz, \( ^3J_{Sn-H} = 20.6 \) Hz, 3H), 1.58-1.41 (m, 6H), 1.36-1.27 (m, 6H), 1.06-0.82 (m, 15H).

**Vinyl stannane 80**

To a solution of alcohol 79 (1.01 g, 2.65 mmol) in CH\(_2\)Cl\(_2\) (14 mL) was added 2,6-lutidine (0.93 mL, 7.95 mmol) and tert-butylidemethylsilyl trifluoromethanesulfonate (0.91 mL, 3.97 mmol) at -78 \degree \text{C}. After being stirred for 1 h, the mixture was warmed up to room temperature and stirred for 1 h. The reaction mixture was added a saturated aqueous NaHCO\(_3\) solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine,
dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford vinyl stannane **80** (1.1 g, 81%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 5.45 (dq, J = 8.0, 1.7 Hz, ³JSn-H = 67.9 Hz, 1H), 4.68 (ddd, J = 7.7, 4.6, 4.6 Hz, 1H), 3.43 (dd, J = 10.9, 8.0 Hz, 1H), 3.37 (dd, J = 10.9, 4.6 Hz, 1H), 1.89 (d, J = 2.3 Hz, ³JSn-H = 45.2 Hz, 3H), 1.56-1.40 (m, 6H), 1.30 (td, J = 14.6, 7.4 Hz, 6H) 0.92-0.86 (m, 24H), 0.09 (s, 3H), 0.07 (s, 3H).

**Enyne 81**

A mixture of vinyl stannane **80** (207 mg, 0.387 mmol) and a 2.65 M hexane solution of n-BuLi (133 µL, 0.358 mmol) in THF (0.75 mL) was stirred at -78 °C for 2 h. To this was added a solution of ketone **60** (69.0 mg, 0.149 mmol) in THF (0.75 mL), and after being stirred for 1 h, isobutyryl chloride (78 µL, 0.745 mmol) was added. After being stirred for 10 min at -40 °C and then at 0 °C for 30 min, a saturated methanol solution of K₂CO₃ was added. The reaction mixture was stirred for 1 h at room temperature, and then a saturated aqueous NH₄Cl solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford enyne **81** (75.2 mg, 73%) as a ca. 2:1 diastereomeric mixture as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 5.97-5.90 (m, 1.5H), 5.75 (d, J = 9.7 Hz, 0.5H), 5.44 (br s, 0.5H), 5.44 (br s, 1H), 5.34 (dd, J = 10.0, 3.2 Hz, 1H), 5.01-4.97 (m, 1.5H), 4.70-4.62 (m, 3.5H), 4.60-4.53 (m, 1.5H), 4.22-4.10 (m, 3.5H), 4.01-3.92 (m, 1.5H), 3.92-3.87 (m, 0.5H), 3.76 (dd, J = 9.5, 4.9 Hz, 0.5H), 3.71 (d, J = 10.9 Hz, 1H), 3.65-3.62 (m, 5H), 3.55-3.48 (m, 1.5H), 3.44-3.31 (m, 4.5H), 3.24 (s, 1H), 3.21 (s, 0.5H), 2.84-2.77 (m, 1.5H), 2.62-2.54 (m, 1.5H, involving singlet at 2.58), 2.51 (s, 1H), 2.04-1.94 (m, 1.5H), 1.69-1.66 (m, 4.5H, involving singlet at 1.67), 1.43 (s, 1.5H), 1.42 (s, 3H), 1.36 (s, 3H), 1.31 (s, 1.5H), 1.12-1.17, (m, 9.5H), 1.16 (s, 1.5H), 1.13 (s, 3H), 0.91-0.87 (m, 13.5H, involving singlet at 0.89), 0.11 (s, 6H), 0.07 (s,
1.5H), 0.01(s, 1.5H).

**Enone 82**

A mixture of enyne 81 (60.9 mg, 87.7 µmol), PdCl$_2$(CH$_3$CN)$_2$ (4.5 mg, 17.5 µmol), and acetic acid (15 µL, 263 µmol) in acetonitrile (880 µL) was heated at 60 ºC for 2 h. After cooling to room temperature, a saturated aqueous NaHCO$_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The crude cyclopentenone 81' was used for the next step without purification.

A mixture of crude 81', isopropenyl methyl ether (42 µL, 439 µmol) and pyridinium $p$-toluenesulfonate (PPTS) (4.4 mg, 18 µmol) in CH$_2$Cl$_2$ (880 µL) was stirred at 0 ºC for 2 h. After quenching with a saturated aqueous NaHCO$_3$ solution, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford cyclopentenone 82 (13.3 mg, 24% from 81) as a white solid: $^1$H NMR (500MHz, CDCl$_3$) δ 5.88 (d, $J = 2.9$ Hz, 1H), 5.87 (d, $J = 2.9$ Hz, 1H), 4.99 (d, $J = 5.7$ Hz, 1H), 4.68-4.61 (m, 3H), 4.23-4.17 (m, 1H), 4.11-4.01 (m, 3H), 3.81-3.65 (m, 4H), 3.53 (d, $J = 11.5$ Hz, 1H), 3.44 (d, $J = 8.6$ Hz, 1H), 3.31-3.21 (m, 2H), 3.16 (dd, $J = 11.5$, 3.4 Hz, 1H), 2.96 (s, 1H), 2.78 (td, $J = 10.2$, 5.3 Hz, 1H), 2.57 (t, $J = 2.3$ Hz, 1H), 2.30-2.26 (m, 2H), 2.18 (s, 3H), 1.89 (d, $J = 15.5$ Hz, 1H), 1.63 (s 3H), 1.274 (s, 3H), 1.270 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H).
To a solution of cyclopentenone 82 (13.3 mg, 21.3 µmol) in THF (220 µL) was added DIBAL-H (1.04 M solution in hexane, 82 µL, 85.2 µmol) at -78 ºC. After being stirred for 30 min, the reaction mixture was added a saturated aqueous Rochelle’s salt solution. After being stirred for 1 h, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude allylalcohol 82’ was used for the next step without purification.

To a solution of crude allyl alcohol 82’ and imidazole (4.3 mg, 63.9 µmol) in DMF (210 µL) was added trimethylsilyl chloride (TMSCl) (3.4 µL, 42.6 µmol) at 0 ºC. After being stirred for 30 min at room temperature, a saturated NaHCO₃ solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude silyl ether 83 was used for the next step without purification.

To a solution of silyl ether 83 in CH₂Cl₂ (100 µL) was added m-chloroperoxybenzoic acid (mCPBA) (7.0 mg, 30 µmol) at 0 ºC. After being stirred for 12 h, a saturated aqueous NaHCO₃ solution and Na₂S₂O₃ was added to the reaction mixture. After being stirred for 1 h, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude epoxide 84 was used for the next step without purification.

To a solution of crude epoxide 84 in THF (100 µL) was added potassium tert-butoxide (5.6 mg, 50 µmol) at 0 ºC. After being stirred for 1.5 h at room temperature, a saturated aqueous NH₄Cl solution was added. The mixture was separated, and the aqueous layer
was extracted with ether. The combined organic layers were dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford a pentacyclic compound 85 (4.9 mg, 38%) as a white solid.

\[ \text{H NMR (500 MHz, CDCl}_3 \text{)} \delta 5.78 (dd, J = 10.3, 2.9 Hz, 1H), 5.62 (dd, J = 10.3, 3.2 Hz, 1H), 4.99 (d, J = 5.7 Hz, 1H), 4.69 (d, J = 4.0 Hz, 1H), 4.63 (d, J = 5.7 Hz, 1H), 4.40 (d, J = 2.9 Hz, 1H), 4.18-4.11 (m, 2H), 4.00 (dd, J = 12.6, 3.4 Hz, 2H), 3.97 (d, J = 9.7 Hz, 2H), 3.87 (s, 1H), 3.74 (dd, J = 10.0, 4.9 Hz, 1H), 3.66-3.62 (m, 3H, involving singlet at 3.65), 3.53 (d, J = 8.6 Hz, 1H), 3.48 (d, J = 12.6 Hz, 1H), 3.36 (d, J = 8.6 Hz, 1H), 3.14 (d, J = 4.6 Hz, 1H), 2.94 (d, J = 2.9 Hz, 1H), 2.80 (dt, J = 15.7, 4.6 Hz, 1H), 2.19 (d, J = 4.0 Hz, 1H), 1.98 (d, J = 15.7 Hz, 1H), 1.92 (d, J = 12.6 Hz, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.044 (s, 3H), 0.040 (s, 3H).

**Allyl sulfide 91**

\[
\begin{align*}
\text{In(OTf)}_3, \text{EtSH/HFIP} & \quad \rightarrow \quad \text{SEMCl, NaH, Bu}_4\text{NI} \\
\text{54} & \quad \rightarrow \quad \text{56} & \quad \rightarrow \quad \text{91}
\end{align*}
\]

To a mixture of diol 54 (204 mg, 0.69 mmol), ethanethiol (6.0 mL) and 1,1,1,3,3,3-hexafluoro isopropanol (HFIP) (2.0 mL) was added indium (III) trifluoromethanesulfonate (78 mg, 0.14 mmol) at 0 °C. After being stirred for 2 h, the reaction mixture was directly poured on a short pat of silica gel and the filtrate was concentrated under reduced pressure. The crude allyl sulfide 56 was used for the next step without further purification.

To a mixture of crude 56 in THF (4.5 mL) was added sodium hexamethyldisilazide (NaHMDS) (0.95 mL, 1.8 mmol, 1.9 M THF solution) at 0 °C. After being stirred for 15 min, 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) (0.32 mL, 1.8 mmol) and tetrabutylammonium iodide (332 mg, 0.9 mmol) was added. After being stirred for 3 h at room temperature, a saturated aqueous NH₄Cl solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford a ca. 3:1 diastereomeric mixture of allyl sulfide 91 (289.9 mg,
67%) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$, peaks due to the major isomer) $\delta$ 5.76 (d, $J = 6.9$ Hz, 1H), 5.02 (d, $J = 12.0$ Hz, 1H), 4.99 (d, $J = 5.7$ Hz, 1H), 4.76 (m, 2H), 4.70 (d, $J = 6.3$ Hz, 1H), 4.68-4.65 (m, 2H), 4.52 (br s, 1H), 4.22-4.17 (m, 2H), 4.01 (d, $J = 9.2$ Hz, 1H), 3.89 (d, $J = 10.3$ Hz, 1H), 3.84-3.42 (m, 8H), 3.35 (br s, 1H), 2.96 (t, $J = 8.6$ Hz, 1H), 2.69-2.62 (m, 2H), 2.60 (d, $J = 4.6$ Hz, 1H), 2.27 (d, $J = 16.0$, 1H), 1.94 (d, $J = 16.0$ Hz, 1H), 1.66 (s, 3H), 1.30 (d, $J = 7.4$ Hz, 3H), 1.00-0.83 (m, 4 H), 0.02 (s, 9H), 0.01 (s, 9H).

**Allylborane 92**

A mixture of lithium wire (180 mg, 7.8 mmol) and 4,4'-di-tert-butyl biphenyl (DBB) (623 mg, 2.34 mmol) in THF (4.0 mL) was stirred at 0 ºC for 30 min. The resulting deep blue solution was cooled to –78 ºC, and a solution of allyl sulfide 91 (479 mg, 0.78 mmol) and methoxyboronic acid pinacol ester (0.64 mL, 3.9 mmol) in THF (4.0 mL) was added dropwise. After being stirred for 30 min, the reaction was quenched by water. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford allylborane 92 (453.8 mg, 85%) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.26 (br s, 1H), 4.80-4.72 (m, 4H), 4.69 (dd, $J = 6.9$, 4.0 Hz, 2H), 3.95 (br s, 1H), 3.87 (dd, $J = 8.3$, 6.0 Hz, 1H), 3.82-3.69 (m, 6H), 3.67 (d, $J = 9.2$ Hz, 2H), 3.63-3.56 (m, 2H), 3.55-3.42 (m, 2H), 3.14 (br s, 1H), 2.65 (d, $J = 11.5$ Hz, 1H), 2.21 (d, $J = 11.5$ Hz, 1H), 1.66 (s, 3H), 1.24. (s, 12H), 1.00-0.90 (m, 4H), 0.012 (s, 9H), 0.010 (s, 9H).
Propargyl alcohol 93

A mixture of allylborane 92 (371.4 mg, 0.54 mmol) and 3-(triisopropylsilyl)-2-propynal (198 µL, 0.81 mmol) in toluene (2.7 mL) was stirred at 50 ºC for 8 h. After quenching with a saturated aqueous NaHCO₃ solution, the mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford alcohol 93 (344.2 mg, 83%) as a colorless oil: ¹H NMR (500MHz, CDCl₃) δ 5.93 (dd, J = 10.3, 3.4 Hz, 1H), 5.64 (dd, J = 10.3, 2.6 Hz, 1H), 4.98 (d, J = 5.7 Hz, 1H), 4.86 (s, 1H), 4.81-4.73 (m, 4H), 4.61 (d, J = 6.3 Hz, 1H), 4.30 (s, 1H), 4.11 (d, J = 12.6 Hz, 1H), 3.94 (t, J = 8.9 Hz, 1H), 3.76-3.48 (m, 8H), 3.35 (t, J = 3.2 Hz, 1H), 3.14 (t, J = 7.7 Hz, 1H), 2.28 (d, J = 16.0 Hz, 1H), 1.90 (d, J = 16.0 Hz, 1H), 1.17 (s, 3H), 1.13-1.10 (m, 21H), 0.98-0.90 (m, 4H), 0.02 (s, 9H), 0.01 (s, 9H)

Triol 94

To a solution of alcohol 93 (28.6 mg, 37.3 mmol) and N,N,N',N'-tetramethylethylenediamine (8.5 µL, 56.6 µmol) in CH₂Cl₂ (370 µL) was added a 0.39 M CH₂Cl₂ solution of osmium tetroxide (143 µL, 55.9 µmol) at -78 ºC. After being stirred for 24 h, an aqueous NaHSO₃ solution was added. After being stirred for 24 h at room temperature, the mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford triol 94 (21.1 mg, 71%) as a white solid: ¹H NMR (500MHz, CDCl₃) δ 4.93 (d, J = 5.7 Hz, 1H), 4.76-4.69 (m, 3H), 4.64 (d, J
= 6.9 Hz, 1H), 4.59 (d, J = 7.4 Hz, 1H), 4.43 (s, 1H), 4.37 (d, J = 8.0 Hz, 1H), 4.23 (d, J = 4.6 Hz, 1H), 4.17 (d, J = 12.0 Hz, 1H), 4.12-4.03 (m, 2H), 3.91-3.77 (m, 3H), 3.73-3.51 (m, 7H), 3.50-3.41 (m, 1H), 3.00 (d, J = 5.2 Hz, 1H), 2.63 (d, J = 7.4 Hz, 1H), 2.54 (s, 1H), 2.21 (d, J = 16.0 Hz, 1H), 1.66-1.61 (m, 4H, involving singlet at 1.65), 1.19-1.07 (m, 21H), 0.99-0.79 (m, 4H), 0.03 (s, 9H), -0.01 (s, 9H).

**Alkynone 96**

![Diagram of Alkynone 96]

To a solution of alcohol 94 (81.7 mg, 0.10 mmol) in CH\(_2\)Cl\(_2\) (1.0 mL) was added MnO\(_2\) (204 mg, 2.0 mmol) at room temperature. After being stirred for 15 h, the reaction mixture was filtered through a pad of celite, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to afford ketone 96 (64.3 mg, 79%) as a white solid. \[^1^\text{H} \text{NMR (500MHz, CDCl}_3\)] \(\delta\) 4.99 (d, J = 5.7 Hz, 1H), 4.73 (d, J = 7.4 Hz, 1H), 4.68-4.63 (m, 2H), 4.54 (t, J = 7.4 Hz, 2H), 4.48 (d, J = 8.0 Hz, 1H), 4.44 (d, J = 2.3 Hz, 1H), 4.24 (br s, 1H), 4.17-4.04 (m, 4H), 3.79 (dd, J = 8.6, 5.7 Hz, 1H), 3.74-3.62 (m, 4H), 3.60 (s, 1H), 3.58-3.40 (m, 2H), 3.03 (d, J = 5.7 Hz, 1H), 2.97 (d, J = 5.7 Hz, 1H), 2.89 (d, J = 8.6 Hz, 1H), 2.54 (s, 1H), 2.20 (d, J = 16.0 Hz, 1H), 1.50 (d, J = 16.0 Hz, 1H), 1.35 (s, 3H), 0.99-0.84 (m, 4H), 0.03 (s, 9H), 0.01 (s, 9H).
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