Development of a synthetic method for terpene scaffolds via stereoselective construction of quaternary carbon centers

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(Doctor's course)

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Contents

Chapter 1. General Introduction

1-1. Natural products and total synthesis

In living organisms, in addition to the primary metabolites essential for survival, species-specific secondary metabolites are also biosynthesized. These secondary metabolites, commonly referred to as natural products, are studied in the field known as natural product chemistry.[1)] Many natural products have roles that remain to be fully elucidated. However, it is well-established that natural products exhibit diverse biological activities when introduced into the human body, functioning as either drugs or toxins. This activity arises from their specific interactions with target proteins in biological systems. By unraveling the mechanisms underlying these interactions, compounds demonstrating pharmacological activity can be developed into therapeutic agents, while those with toxic effects can serve as tools for probing biological phenomena. Due to this potential, the study of natural products continues to be an active area of research. Among these efforts, total synthesis refers to the artificial construction of natural products through the power of organic synthesis.

In living organisms, complex carbon frameworks and diverse functional groups of natural products are efficiently biosynthesized from amino acids, sugars, and isoprenes through enzyme-mediated reactions. In contrast, total synthesis involves the artificial assembly of natural products starting from commercially available and inexpensive materials. At first glance, extracting natural products directly from their biological sources may seem more efficient if biosynthesis is straightforward. At first glance, if a target natural product can be easily synthesized within a living organism, extracting it directly from the producing organism may seem more efficient. However, there are research advancements that are uniquely possible through total synthesis. The primary research objectives of total synthesis can be summarized as follows: 1) determination of the structure of natural products, 2) quantitative supply, 3) elucidation of structure-activity relationships through the synthesis of derivatives, and 4) validation of biosynthetic pathways.[1)] Among these, the synthesis of derivatives and the study of structure–activity relationships (SAR) are particularly noteworthy. Biosynthesis in living organisms is constrained by the available starting materials, often leading to fixed stereochemistry and substitution patterns in intermediates. This limitation makes it challenging to generate a diverse array of derivatives. In contrast, total synthesis allows for facile modification of stereochemistry and molecular structures, enabling the creation of non-natural compounds. Remarkably, some of these non-natural compounds exhibit higher biological activity than their natural counterparts. For example, non-natural analogs of antitumor agents such as halichondrin B (**1**), epothilone (**3**), and bryostatin (**5**) demonstrate enhanced bioactivity through structural modifications or simplifications of their parent molecules (Figure 1).[2)] Therefore, total synthesis remains a vigorously pursued field of research.

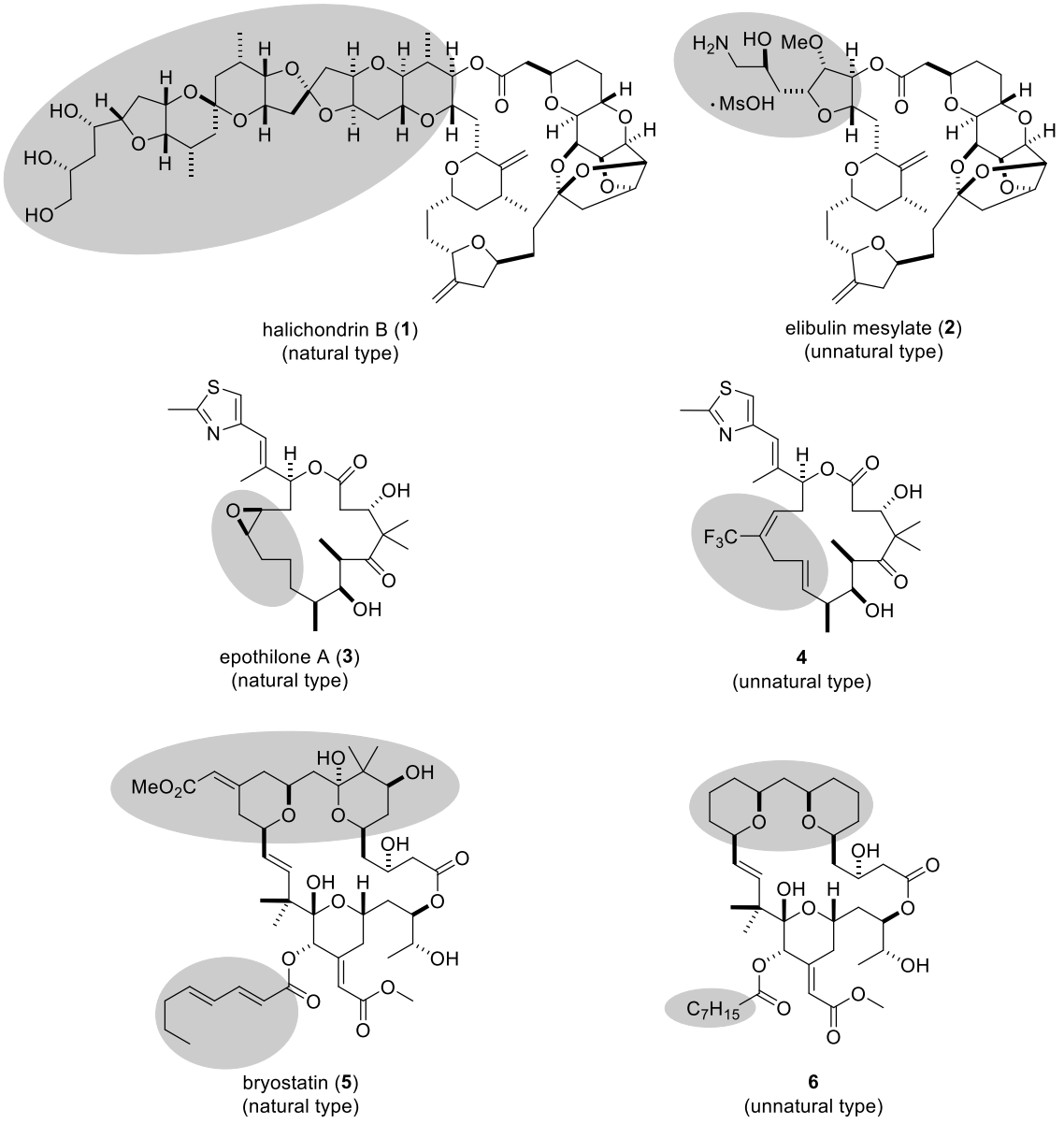
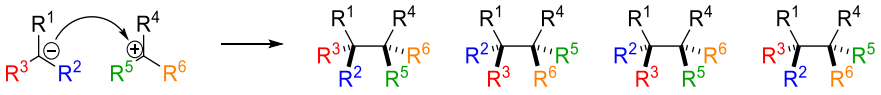


Figure 1. Structures of antitumor natural and unnatural products

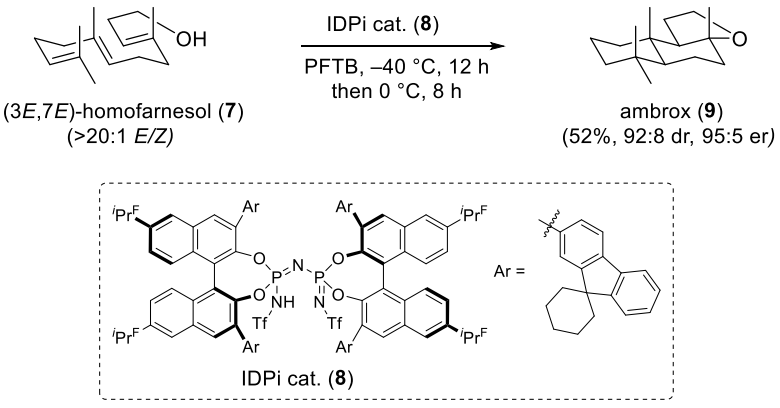
1-2. Construction of quaternary carbon centers

The stereoselective construction of quaternary carbon centers is a challenging task. For instance, when a nucleophile reacts with a tertiary carbocation to form a quaternary carbon, two enantiomers are typically generated unless a chiral environment is established. In the synthesis of simple compounds, this issue can sometimes be addressed using chiral catalysts. However, when constructing sterically congested quaternary carbons or contiguous quaternary carbon centers, the steric hindrance between bulky substituents makes the formation of such bonds energetically unfavorable. Achieving stereoselectivity under these conditions becomes even more difficult (Scheme 1).



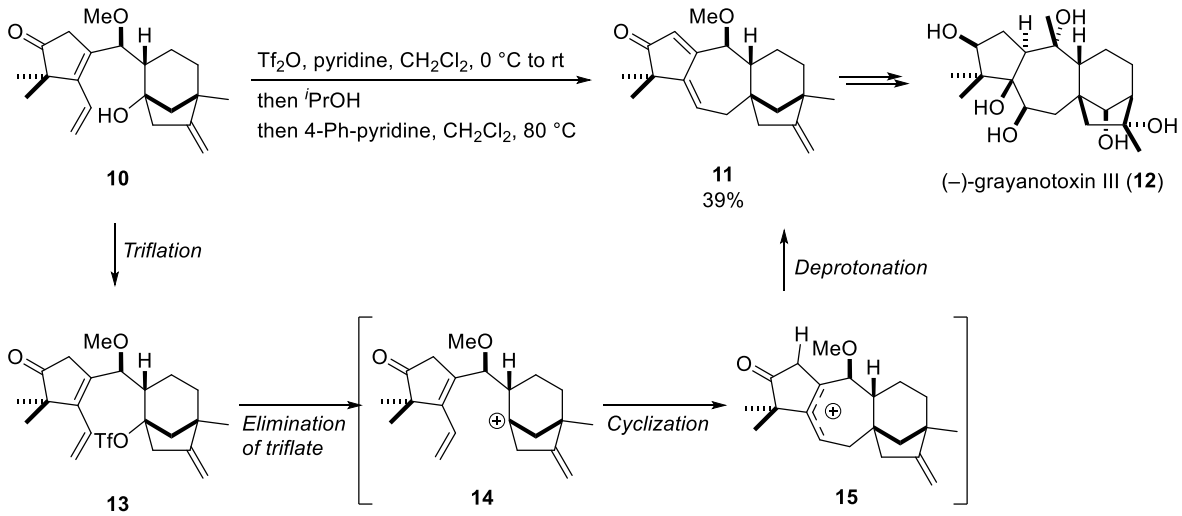
Scheme 1. Construction of quaternary carbon center by using intermolecular reaction

Here, the focus is placed on the stereoselective construction of quaternary carbons in total synthesis. One example is polyene cyclization. Polyene cyclization is a reaction in which multiple carbon-carbon bonds, ring structures, and stereocenters are formed in a single step from simple acyclic compounds. For example, List and colleagues reported that (−)-ambrox (**9**) could be stereoselectively synthesized via polyene cyclization by treating (3*E*,7*E*)-homofarnesol (**7**) with an imidodiphosphorimidate (IDPi) catalyst **8** in perfluoro-*t*-butanol (PFTB) (Scheme 2).[3)]



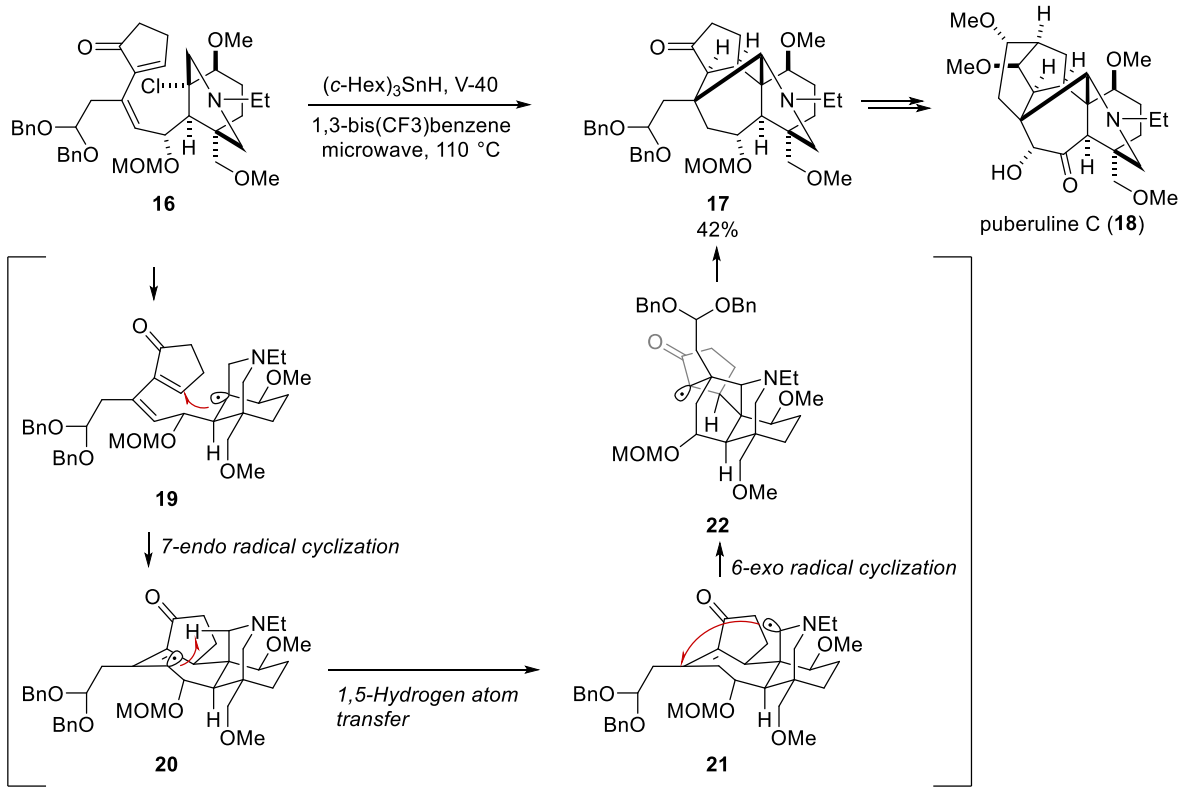
Scheme 2. Stereoselective polyene cyclization

Additionally, Luo and colleagues utilized the rigidity of the bicyclo[3.2.1]octane framework to stereoselectively construct quaternary carbons in the total synthesis of three natural products, including (−)-Grayanotoxin III (**12**) (Scheme 3).[4)] A major challenge in this reaction was the high reactivity of the resulting bridgehead carbocation **14**. Luo resolved this issue by designing a system where the carbocation was intercepted by an intramolecular alkene and subsequently deprotonated using 4-phenylpyridine as a base.



Scheme 3. Stereoselective cyclization using bridgehead carbocation

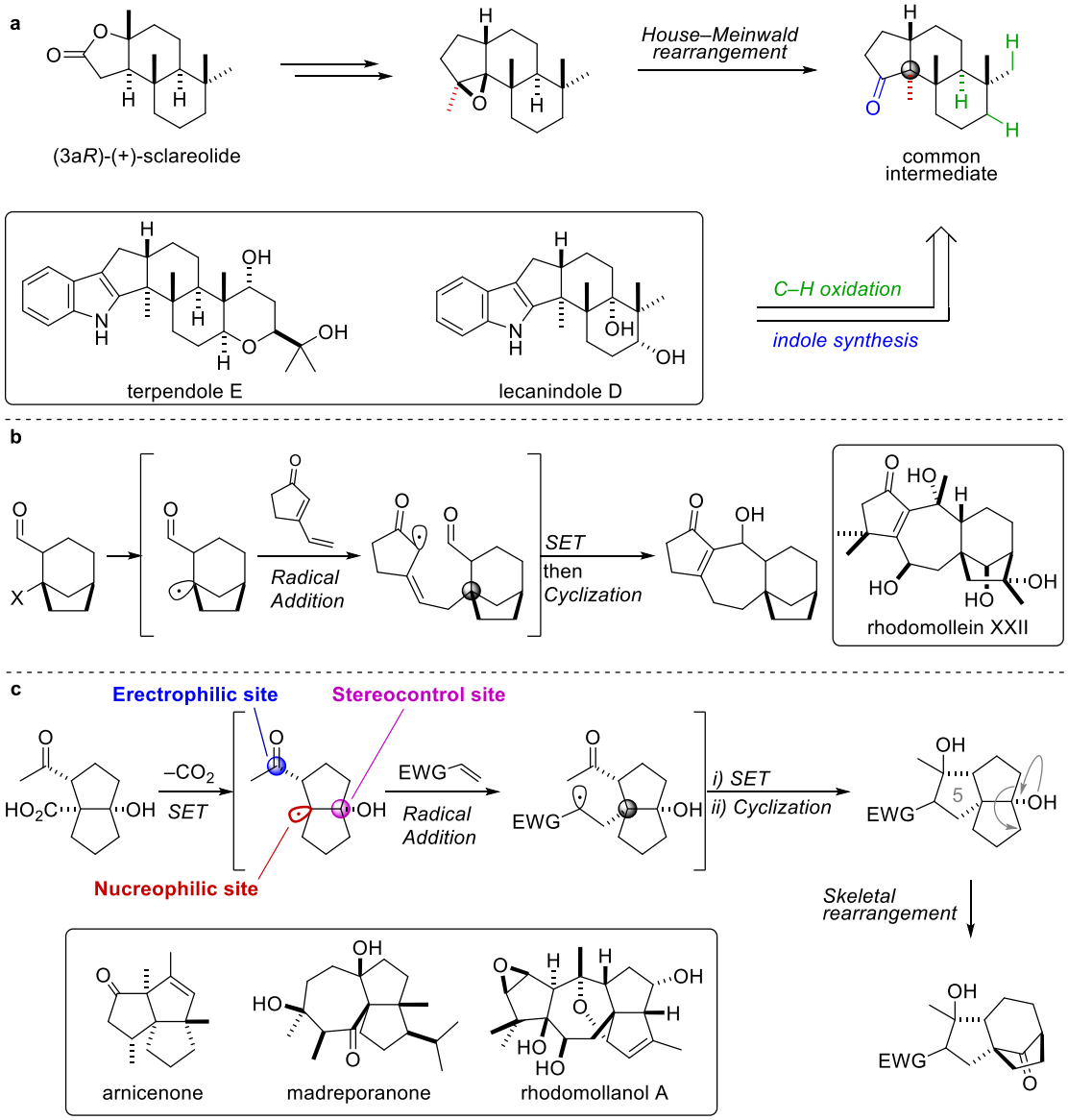
As another strategy, Inoue and colleagues employed sterically robust radical species to simultaneously construct two quaternary carbons in their total synthesis of puberuline C (**18**) (Scheme 4).[5] In this reaction, the bridgehead radical **19** generated from compound **16** underwent intramolecular cyclization to form the first quaternary carbon. Subsequently, a 1,5-hydrogen atom transfer of intermediate **20** led to another intramolecular radical cyclization, completing the construction of the second quaternary carbon.



Scheme 4. Stereoselective radical cyclization

1-3. Outline of this study

This study investigated methods for the stereoselective construction of quaternary carbons with potential applications in natural product synthesis. In Chapter 2, attention was focused on the contiguous asymmetric quaternary carbons, a structural feature of indole terpenes, and efforts were made to develop a construction method using the House–Meinwald rearrangement (Scheme 5a). In Chapter 3, the target was natural products with a bicyclo[3.2.1]octane framework. The study aimed to develop an annulation strategy that simultaneously induces the addition of two components followed by cyclization using the bridgehead position of the bicyclo[3.2.1]octane ring (Scheme 5b). In Chapter 4, the goal was to develop a strategy combining annulation using bicyclo[3.3.0]octane as a building block with a skeletal rearrangement that converts the bicyclo[3.3.0]octane framework to a bicyclo[3.2.1]octane framework (Scheme 5c).



Scheme 5. Synthetic strategy to the construction of stereoselective quaternary carbon centers

1-3. Reference

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Chapter 2. Toward the Synthesis of Paspaline-type Indole-terpenes: Stereoselective Construction of Core Scaffold with Contiguous Asymmetric Quaternary Carbon Centers

2-1. Abstract

The core scaffold of paspaline-type indole-terpenes was synthesized by using the House–Meinwald rearrangement as a key step. Rearrangement of the epoxide methyl group in the precursor with methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) as a Lewis acid proceeded smoothly to construct contiguous asymmetric quaternary carbon centers by a 1,2-chirality transfer.

2-2. Introduction

2-2-1. Syntheses of natural products with contiguous asymmetric quaternary carbon centers

Indole terpenoids isolated from fungi and actinomycetes are known to exhibit a wide range of biological activities (Figure 1). For example, among the indole sesquiterpenoids, sespendole (**23**)[1] demonstrates macrophage foam cell formation inhibitory activity, while lecanindole D (**24**)[2] is considered a promising progesterone receptor agonist. Additionally, in the category of indole diterpenoids, terpendole E (**25**)[3] shows inhibitory activity against the microtubule motor protein Eg5, and nodulisporic acid A (**26**)[4] exhibits insecticidal activity. A notable structural feature of these indole terpenoids is the presence of contiguous quaternary stereogenic centers adjacent to the indole ring. Even with the advancements in modern organic synthetic chemistry, the stereoselective construction of quaternary carbon centers remains a formidable challenge. Focusing on this unique structural characteristic, the author aimed to develop a comprehensive synthetic methodology for indole terpenoids, employing an innovative approach for constructing contiguous quaternary stereogenic centers distinct from conventional methods.

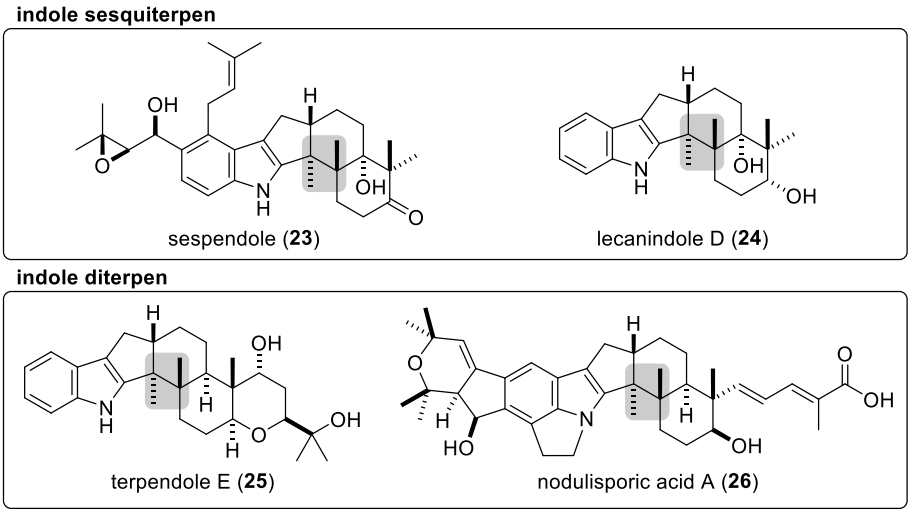
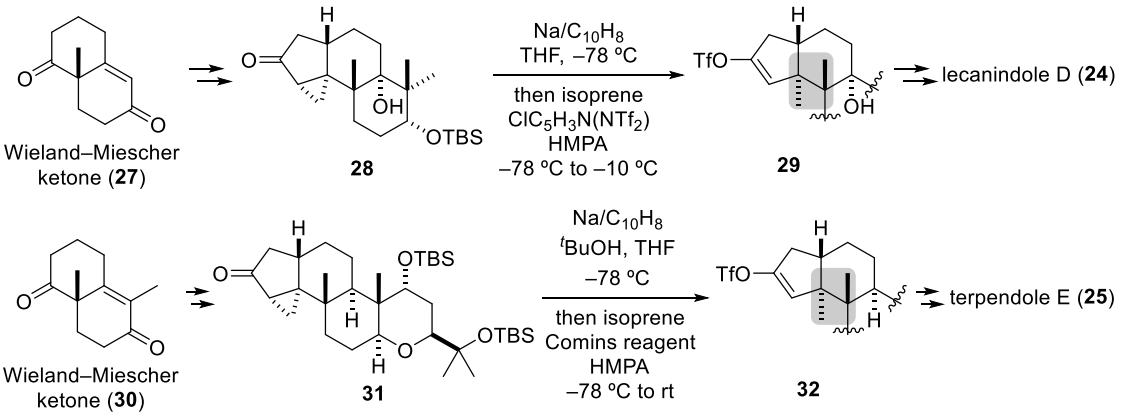


Figure 1. Structures of indole terpenes with contiguous asymmetric quaternary carbon centers

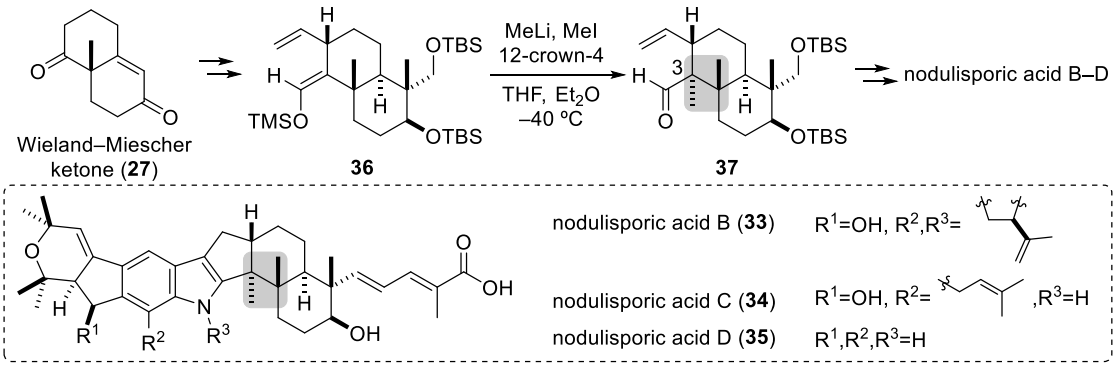
The currently reported synthetic routes for indole terpenoids are illustrated in Scheme 1. In 2013, Kuwahara and colleagues achieved the total synthesis of racemic lecanindole D (**24**).[5] This synthetic route utilizes Wieland–Miescher ketone (**27**) as the starting material, where the construction of contiguous quaternary carbon centers is accomplished through single-electron

reduction-induced ring-opening of the cyclopropane moiety in ketone **28**. Using a similar strategy, the racemic synthesis of terpendole E (**25**) has also been reported. These methodologies demonstrate the utility of cyclopropane ring-opening reactions in the synthesis of indole terpenoids with challenging quaternary carbon frameworks.[6)]



Scheme 1. Kuwahara's synthesis of contiguous asymmetric quaternary carbon centers

On the other hand, Smith and colleagues achieved the asymmetric synthesis of nodulisporic acid D (**35**) in 2015, and nodulisporic acids B (**33**) and C (**34**) in 2018 (Scheme 2).[7,8)] These syntheses utilized silyl enol ether **36**, derived from Wieland–Miescher ketone (**27**). By treating **36** with MeLi, a silicon–lithium exchange was induced, generating an enolate, which subsequently underwent nucleophilic attack on MeI. This reaction enabled the stereoselective introduction of a methyl group at C3 position, facilitating the construction of contiguous quaternary stereogenic centers. This approach successfully provided access to various nodulisporic acids with intricate stereochemical architectures. Also, total syntheses of indole terpenes using diverse strategies for constructing contiguous quaternary carbon centers have been reported.[9)]



Scheme 2. Smith's synthesis of contiguous asymmetric quaternary carbon centers

A common feature of these reported syntheses is the use of the Wieland–Miescher ketone as the starting material. The Wieland–Miescher ketone is frequently employed in terpenoid synthesis due to its structural attributes, including a ketone and an enone group that serve as

versatile handles for functional group transformations. Additionally, the presence of a quaternary stereogenic methyl group at the ring junction makes it particularly suitable for constructing terpenoid frameworks. Typically, optically active Wieland–Miescher ketones are synthesized via Robinson annulation using proline as a chiral catalyst. However, this method often yields the ketone with only about 70% ee.[10] To achieve higher optical purity, additional steps such as recrystallization or optical resolution are required.

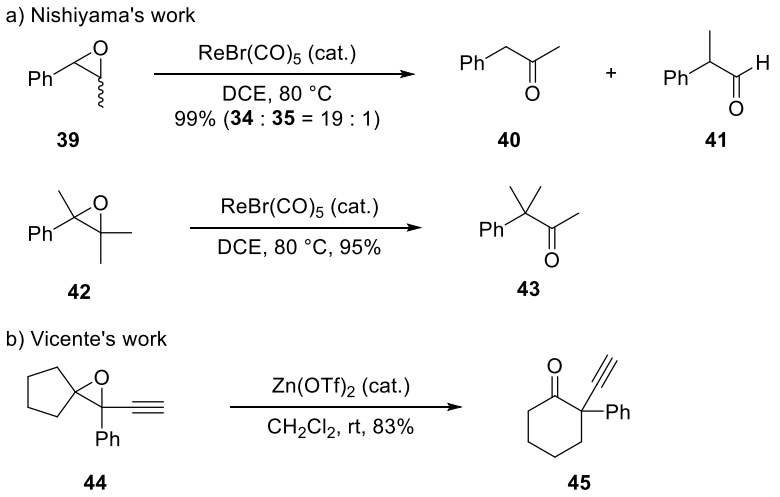
2-2-2. The concept of this study

As mentioned above, Wieland–Miescher ketone is often used as a starting material in the total synthesis of indole terpenes. This is due to its ease of synthesis, variety of functional groups, and the presence of a quaternary carbon center. However, obtaining it with high optical purity involves effort. So the author focused on (3a*R*)-(+)-sclareolide (**38**). This compound not only shares a carbon framework corresponding to the D–E ring system of indole terpenes but also features a methyl group at the C4 position. Additionally, it contains a lactone ring, which serves as a foundation for constructing the A–C ring system, making (3a*R*)-(+)-sclareolide (**38**) a valuable building block. However, introducing the methyl group at the C3 position to (3a*R*)-(+)-sclareolide (**38**) is challenging same as Wieland–Miescher ketone. Furthermore, many indole terpenes possess oxygen functionalities adjacent to the gem-dimethyl group on the E ring, while (3a*R*)-(+)-sclareolide (**38**) lacks a suitable functional group as a starting point. To overcome these challenges, the author focused on the House–Meinwald rearrangement as a strategy for constructing quaternary carbon center and employed C-H oxidation reactions for introducing oxygen functionalities.

Figure 2. Structure of core skeleton of indole terpene and (3a*R*)-(+)-sclareolide (**38**)

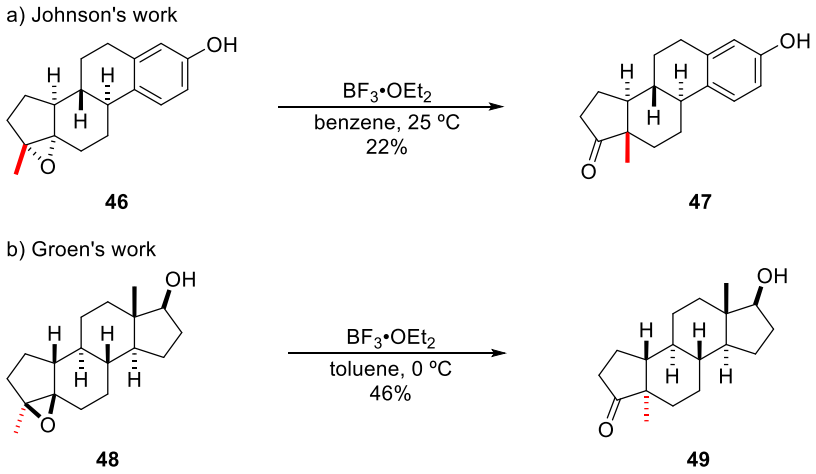
2-2-3. House–Meinwald rearrangement

House–Meinwald rearrangement is a reaction in which an epoxide is treated with an acid catalyst to yield a carbonyl compound.[11] During this process, a functional group on one carbon atom of the epoxide rearranges to the other carbon atom. For example, Nishiyama and colleagues have reported that the House–Meinwald rearrangement of epoxides proceeds using $ReBr(CO)_5$ as a Lewis acid (Scheme 3a).[12] Similarly, Vicente and coworkers have described an expanded-ring variant of the House–Meinwald rearrangement using $Zn(OTf)_2$ (Scheme 3b).[13] While various forms of the House–Meinwald rearrangement have been documented, examples where the methyl group is selectively migrated remain scarce.



Scheme 3. House–Meinwald rearrangement

As an example of applying this rearrangement to natural product synthesis, Johnson and colleagues used $BF_3 \cdot OEt_2$ as a Lewis acid to promote the methyl migration in epoxide **46**, achieving the stereospecific construction of a quaternary stereogenic center (Scheme 4a).[14] Similarly, Groen and coworkers synthesized ketone **49** through the stereospecific methyl migration of epoxide **48** (Scheme 4b).[15] However, in these reports, the yields of the desired rearranged products were relatively low, ranging from 22–46%.



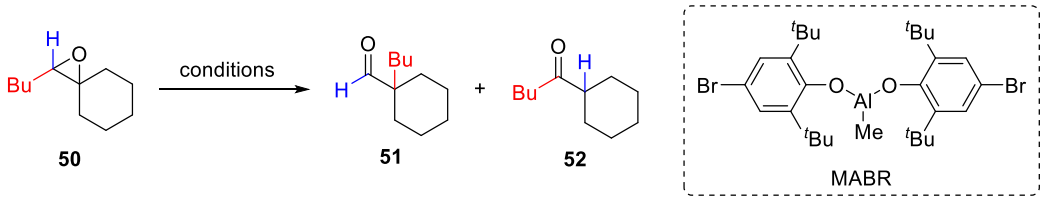
Scheme 4. Construction of asymmetric quaternary carbon center by using House–Meinwald rearrangement

2-2-4. Rearrangement reactions using super Lewis acids

Yamamoto and colleagues have reported that tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) and methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) exhibit reactivity distinct from conventional Lewis acids (Table 1).[16] Specifically, when $BF_3 \cdot OEt_2$, a typical Lewis acid, is applied to epoxide **50**, hydride migration is favored. In contrast, the use of $B(C_6F_5)_3$ or MABR promotes alkyl group migration with both high yield and high selectivity. Yamamoto and colleagues have referred to these reagents as "super Lewis acids". If the rearrangement of a

methyl group proceeds with high yield and stereoselectivity using a super Lewis acid, it could become a powerful method for constructing quaternary carbon centers in the synthesis of complex natural products.

Table 1. Chemoselective rearrangement of alkyl group by using super Lewis acid

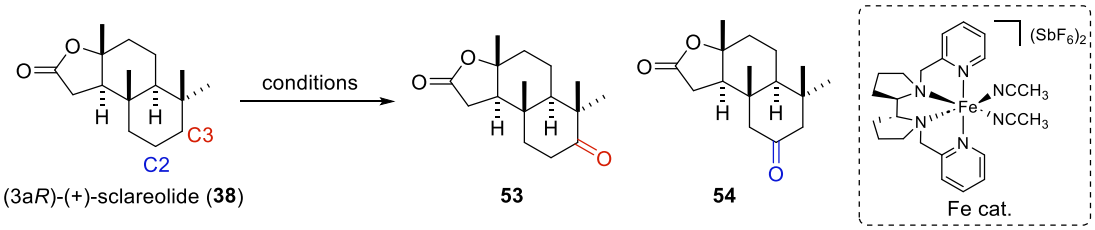


conditions	Results	
	yield (%)	**51** : **52**
$BF_3{\cdot}OEt_2$ (200 mol%), benzene, 25 ºC	55	33 : 67
MABR (200 mol%), CH_2Cl_2, –20 ºC	73	100 : 0
$B(C_6F_5)_3$ (1 mol%), toluene, 60 ºC	>99	98 : 2

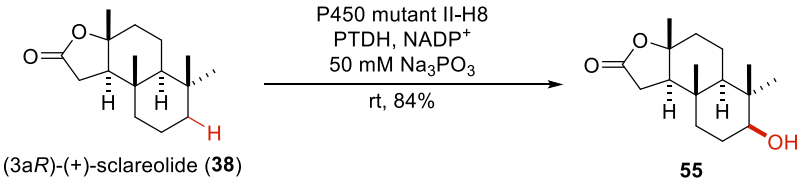
2-2-5. C3-selective C–H functionalization of (3a*R*)-(+)-sclareolide (38)

C-H oxidation is a highly powerful reaction capable of converting not only reactive C-H bonds, such as those at allylic positions, benzylic positions, or α-positions of carbonyl groups, but also inert C-H bonds, such as those in alkanes, into C-O bonds. While numerous examples have been reported, this focuses on discussing the C-H oxidation reaction of (3a*R*)-(+)-sclareolide (**38**). Baran and colleagues have reported that the C–H oxidation at the C2 and C3 positions of (3a*R*)-(+)-sclareolide (**38**) proceeds via an electrochemical reaction using carbon and nickel electrodes in the presence of atmospheric oxygen (Table 2).[17] Additionally, they demonstrated that the oxidation at the C3 position could be achieved with high yield by employing methyl(trifluoromethyl)dioxirane (TFDO) as the oxidant.[17] White and coworkers further reported that the C2 and C3 positions of (3a*R*)-(+)-sclareolide (**38**) could be oxidized with high conversion efficiency using hydrogen peroxide in the presence of an Fe complex.[18] Meanwhile, Fasan and colleagues showed that the C3 position of (3a*R*)-(+)-sclareolide (**38**) could be selectively and efficiently oxidized using the P450 mutant II-H8 enzyme as a biocatalyst (Scheme 5).[19] By employing such C–H oxidation reactions to introduce oxygen functional groups adjacent to the *gem*-dimethyl group, it becomes possible to synthesize a wide variety of indole terpenoids.

Table 2. C–H oxidation of (3a*R*)-(+)-sclareolide (**38**) by chemical synthesis



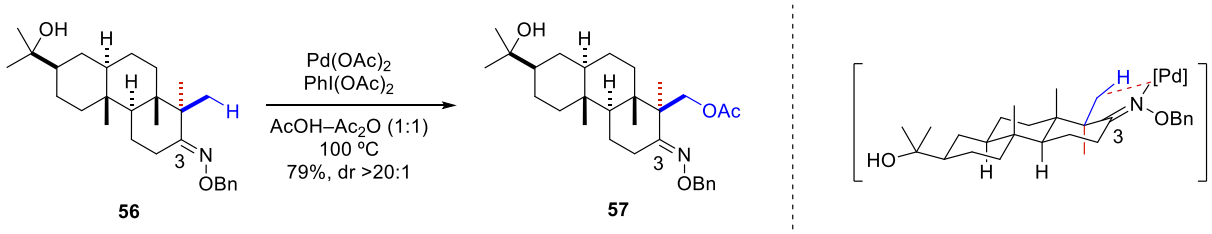
conditions	results (%)		
	53 (C3)	**54** (C2)	recovered **38**
quinuclidine, $Me_4N{\cdot}BF_4$, HFIP, air RVC anode/ Ni cathode, MeCN constant current: 25 mA/mmol	9	42	30
TFDO, CH_2Cl_2, 0 ºC	37	10	–
Fe cat., AcOH, H_2O_2, MeCN, rt	33	46	9



Scheme 5. C–H oxidation at C3 position in (3a*R*)-(+)-sclareolide (**38**) using P450

2-2-6. Equatorial selective C–H functionalization of the *gem*-dimethyl group

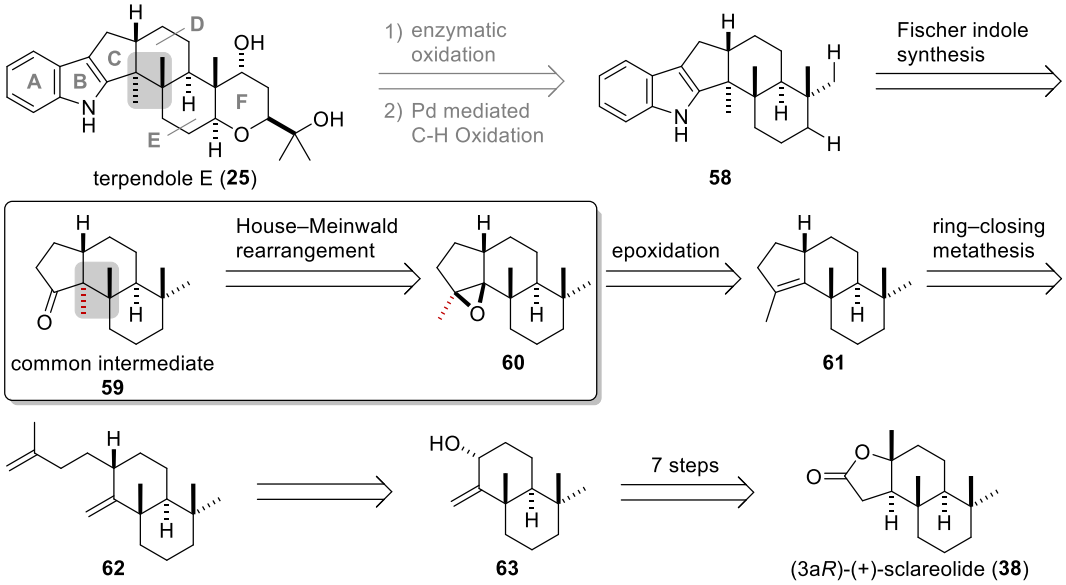
Many indole terpenoids possess an F ring. Therefore, in addition to C–H oxidation at the C3 position, it is necessary to selectively oxidize the equatorial methyl group of the *gem*-dimethyl group. Johnson and colleagues reported that the equatorial position of a *gem*-dimethyl group is oxidized selectively by introducing an oxime group as a directing group and using a Pd(II) catalyst (Scheme 6).[20] Inspired by this strategy, the author hypothesized that this approach could be applied to construct the F ring. Specifically, the ketone produced via C–H oxidation at the C3 position, as described earlier, could be converted into an oxime. Subsequent treatment with a Pd(II) catalyst could enable selective oxidation of the equatorial methyl group of the gem-dimethyl group, facilitating F-ring construction.



Scheme 6. Regioselective C–H oxidation by using Pd(II) catalyst

2-2-7. Retrosynthetic pathway targeting terpendole E (25)

Based on the previously described findings, a retrosynthetic pathway targeting terpendole E (**25**) is outlined in Scheme 7. The F ring of terpendole E (**25**) is planned to be derived from indole **58** using enzymatic oxidation or Pd-catalyzed C–H oxidation reactions. The indole moiety corresponding to the A–B rings will be introduced via Fischer indole synthesis starting from the common intermediate, ketone **59**. The contiguous quaternary stereogenic centers in the common intermediate **59** will be constructed using House–Meinwald rearrangement of a methyl group promoted by a super Lewis acid, as described earlier. The rearrangement precursor, epoxide **60**, will be obtained through the epoxidation of tricyclic olefin **61**, which in turn will be synthesized via a ring-closing metathesis reaction of diene **62**. Diene **62** is planned to be synthesized from the known allyl alcohol **63**, with commercially available (3a*R*)-(+)-sclareolide (**38**) serving as the starting material.[21,22] In this study, C-H oxidation was not performed.



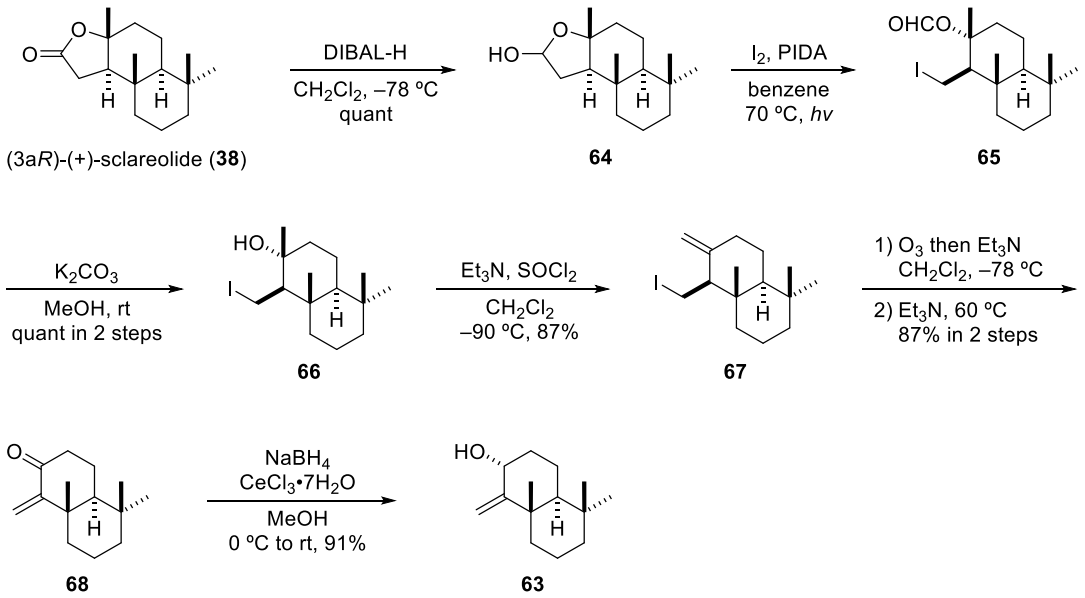
Scheme 7. Retrosynthetic pathway of terpendole E (**25**)

2-3. Results and discussions

2-3-1. Synthesis of diene 62 using 2,3-Wittig rearrangement

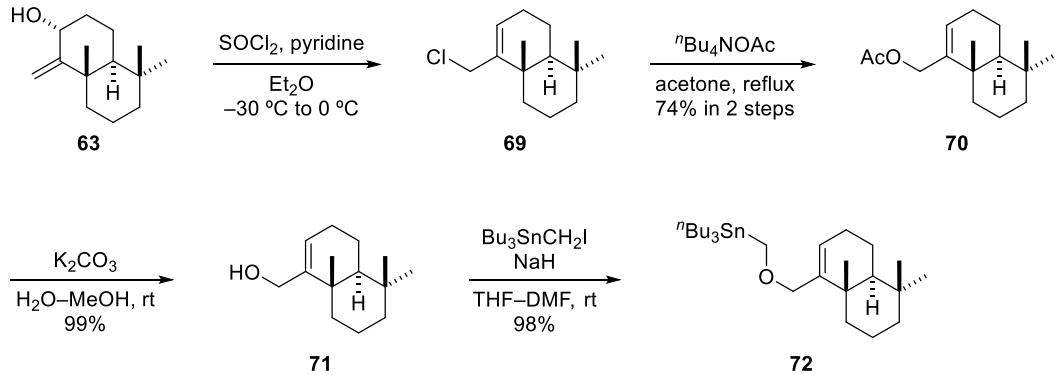
To synthesize the precursor for the House–Meinwald rearrangement, I prepared the known allyl alcohol **63** (Scheme 8). Following the protocol reported by Baran et al., (3a*R*)-(+)-sclareolide (**38**) was reduced using DIBAL, providing scalarol (**64**) quantitatively.[21] The obtained **64** was then converted to formate **65** by treatment with I_2 and PIDA under irradiation with a halogen lamp at 60 °C, followed by hydrolysis to yield hydroxyiodide **66** quantitatively. Next, according to the work of Yang et al., hydroxyiodide **66** was treated with $SOCl_2$ in the presence of Et_3N at –90 °C, affording exo-methylene compound **67** in 87% yield.[22] Subsequently, **67** underwent ozonolysis followed by E1cB elimination using Et_3N, producing

unsaturated ketone **68** with a two-step yield of 87%. Finally, Luche reduction of **68** provided allyl alcohol **63** in 91% yield as a single stereoisomer.



Scheme 8. Synthesis of allyl alcohol **63**

With the known allyl alcohol **63** successfully synthesized, the preparation of diene **62** was undertaken (Scheme 9).[23] Allyl alcohol **63** was first converted into allyl chloride **69** by treatment with $SOCl_2$ in the presence of pyridine. Subsequent reaction with $^{n}Bu_4NOAc$ provided allyl acetate **70** in a two-step yield of 74%. The acetyl group in **70** was then hydrolyzed in a mixed solvent of methanol and water in the presence of K_2CO_3, affording allyl alcohol **71**. The resulting **71** was subsequently converted into stannyl methyl ether **72** as a precursor for the 2,3-Wittig rearrangement.

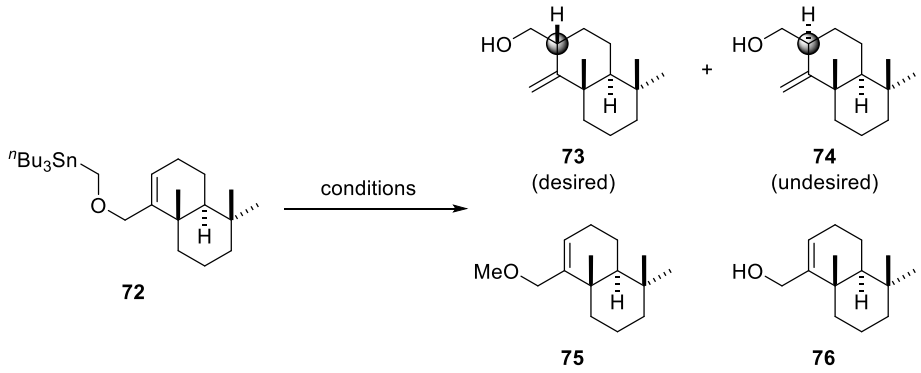


Scheme 9. Synthesis of stannyl methyl ether **72**

To introduce the side chain at the C16 position stereoselectively, the 2,3-Wittig rearrangement of precursor **72** was investigated (Table 3). Based on previous reports, THF or hexane was used as the solvent, and different bases and temperatures were examined.[23] In entry 1, THF was selected as the solvent, while hexane was used in entry 2. *n*-BuLi was employed as

the base, and the reaction temperature was gradually increased from –78 ºC to –10 ºC. In entry 1, the 2,3-Wittig rearrangement did not proceed, leading to the formation of methyl ether **75** via tin-lithium exchange and alcohol **76**, where the tributyltin methyl group was removed. In contrast, entry 2 showed that the 2,3-Wittig rearrangement proceeded, albeit with low yield. The stereochemistry of the resulting alcohols **73** and **74** was confirmed using NOESY spectra, revealing that the undesired diastereomer **74** was the major product (Figure 3). In entries 3 and 4, MeLi was used as the base. In THF (entry 3), the desired alcohol **73** was obtained, but a significant amount of byproducts were formed. Conversely, in hexane (entry 4), the 2,3-Wittig rearrangement proceeded exclusively, yielding a combined 63% of alcohol **73** and diastereomer **74**. However, even under these conditions, diastereomer **74** remained the major product. The results from entries 1–4 indicated that using MeLi in hexane allowed the 2,3-Wittig rearrangement to proceed without byproduct formation. Subsequently, the reaction temperature under these conditions was investigated. Increasing the reaction temperature from 0 ºC to room temperature improved the yield and led to an almost equal ratio of alcohols **73** and **74** (entry 5). In entry 6, raising the reaction temperature to 10 ºC slightly improved the diastereoselectivity. Further attempts to improve stereoselectivity were made by adding additives. In entry 7, the reaction was conducted in THF with HMPA as an additive, which resulted in a lower overall yield (57%) and decreased diastereoselectivity (**73**:**74** = 1:8.0). To explore the hypothesis that trace amounts of LiBr in MeLi acted as a Lewis acid, the MeLi·LiBr complex was used (entry 8). Although the yield was high, the diastereoselectivity remained low. Due to these investigations, it was concluded that improving the stereoselectivity was hard. The obtained alcohols **73** and **74** were separated by silica gel column chromatography and used for a subsequent step.

Table 3. Investigation of 2,3-Wittig rearrangement of stannyl methyl ether **62**



entry	conditions			yield (%)			
	base	solv.	temp.	**73**	**74**	**75**	**76**
1	^{n}BuLi	THF	–78 to –10 ºC	—	—	32	1
2		hexane		10	22	—	—
3	MeLi	THF	–78 to –10 ºC	6	27	21	45
4		hexane		23	40	—	—
5		hexane	0 ºC to rt	48	52	—	—
6		hexane	10 °C to rt	50	45	—	—
7	MeLi, HMPA	THF	0 ºC to rt	11	89	—	—
8	MeLi•LiBr	hexane	0 ºC to rt	30	70	—	—

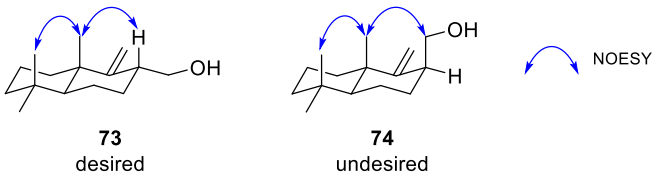
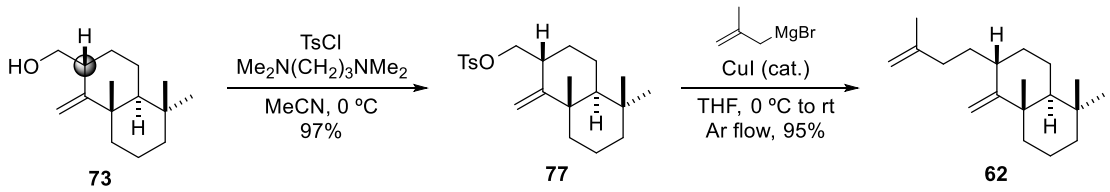


Figure 3. Determination of the stereochemistries of alcohols **73** and **74**

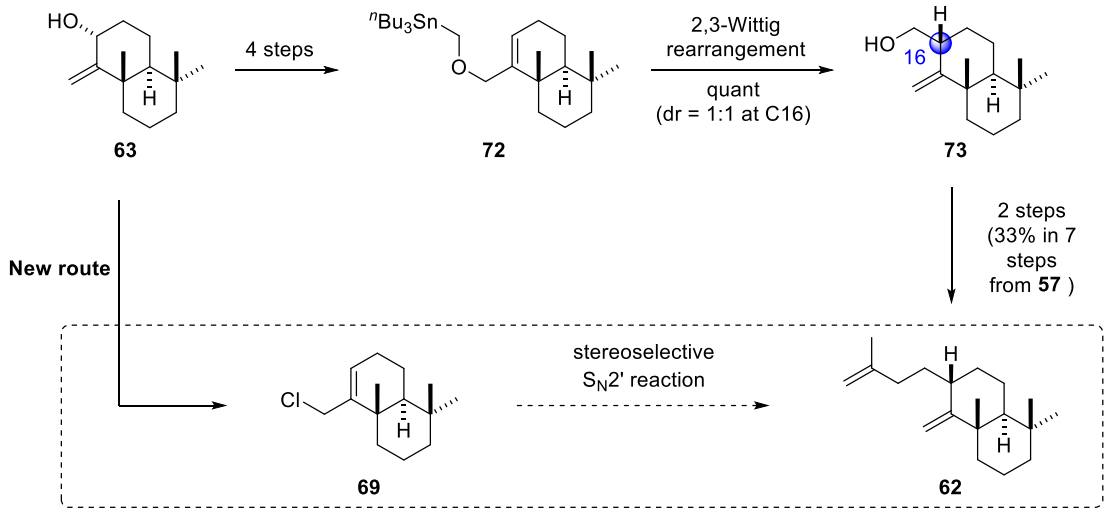
The 2,3-Wittig rearrangement product **73** was subjected to tosylation using the Tanabe method, yielding tosylate **77** (Scheme 10). The resulting tosylate **77** was then treated with a methallyl Grignard reagent in the presence of a catalytic amount of CuI, successfully affording the target diene **62**.



Scheme 10. Synthesis of diene **62**

2-3-2. Synthesis of diene 62 using stereoselective S_N2' reaction

As discussed in the previous section, although the desired diene **62** was obtained, several issues remained. The lack of stereoselectivity at the C16 position during the 2,3-Wittig rearrangement was a significant limitation, and the separation of allyl alcohols **73** and **74** proved challenging. Additionally, the introduction of the side chain required seven steps, making the process inefficient. To address these challenges, an alternative synthetic route was devised (Scheme 11). Specifically, starting from the known allyl alcohol **63**, allyl chloride **69** would be prepared using the same method as in Scheme 11. Subsequently, a stereoselective S_N2' reaction using an organocopper reagent would be employed to introduce the side chain, enabling the synthesis of diene **62** in just two steps.

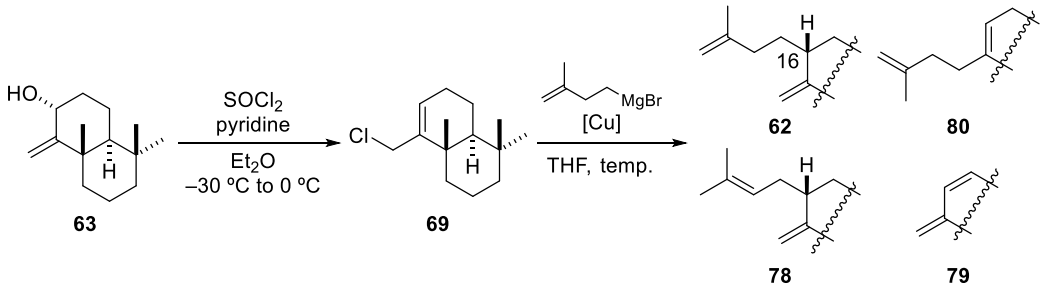


Scheme 11. Modified synthetic route of diene **62**

To investigate the stereoselective S_N2' reaction, a series of experiments were conducted (Table 4). In entry 1, following the report by Alexakis, the reaction was performed using a 3-methyl-3-butenyl magnesium bromide and CuTC as the catalyst.[24] The desired diene **62** was obtained, albeit in low yield. On the other hand, the byproducts predominantly formed were isomer **78**, in which the terminal olefin had isomerized internally, and **79**, resulting from E2 elimination. In entries 2 and 3, the reaction was performed using CuI and $CuBr \cdot SMe_2$, respectively, as copper(I) halides. In both cases, the desired product **62** was preferentially obtained despite the formation of **78** and **79** as by-products. Notably, the C16 stereochemistry was consistent and matched the desired configuration, as confirmed by NMR spectroscopy

comparison with the previously synthesized **62** from Scheme 13. Considering ease of handling, the reaction conditions using CuI (entry 3) were selected for optimization. To suppress isomerization and elimination reactions, lower reaction temperatures were examined. In entry 4, performing the reaction at 0 °C resulted in a slight increase in the yield of **62**, but the formation of **78** and **79** persisted. Lowering the temperature to –20 °C (entry 5) yielded results similar to those at 0 °C. When the reaction was conducted at –40 °C (entry 6), a slight improvement in the yield of **62** was observed. However, at –78 °C (entry 7), the desired product **62** was not obtained, and the S_N2 product **80** became the major product. Based on these results, the optimal reaction conditions were determined to be at –40 °C, providing moderate yields of **62**. The observed stereoselectivity is likely attributed to steric hindrance from the C4 methyl group at the ring junction, which directs the reaction pathway (Figure 4). Compared to the original synthesis route in Scheme 11, this revised pathway reduced the number of steps by five and improved overall yields. This led to the establishment of a more practical and efficient synthetic route (Scheme 12).

Table 4. Investigation of stereoselective S_N2' reaction of allyl chloride **69**



entry	[Cu]	temp.	results (%) [a]			
			desired **62**	**78**	**79**	**80**
1	CuTC	rt	11	23	23	–
2	$CuBr{\cdot}SMe_2$	rt	36	25	9	–
3	CuI	rt	31	25	9	–
4	CuI	0 °C	36	25	10	–
5	CuI	–20 °C	38	21	10	–
6	CuI	–40 °C	41	20	13	–
7	CuI	–78 °C	–	7	13	42

[a] calculated by ^{1}H NMR

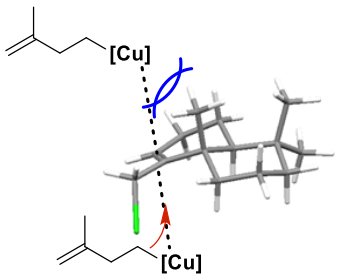
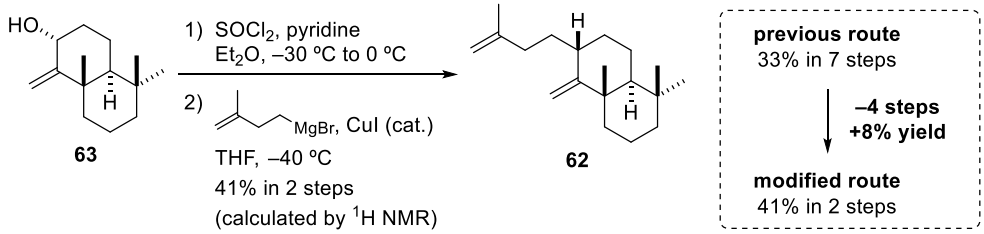


Figure 4. Plausible mechanism of the S_N2' reaction of **69**
(DFT optimized structure of **69** at B3LYP/6-31G* level)

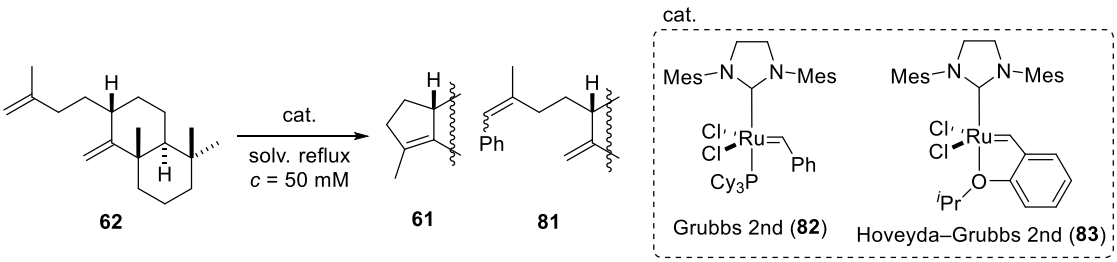


Scheme 12. Synthesis of diene **62** by using a new pathway

2-3-3. Investigation of the synthesis of tricyclic olefin 61 using ring-closing metathesis reaction

The construction of the C-ring via ring-closing metathesis (RCM) of diene **62** was investigated (Table 5). In entries 1 and 2, Grubbs 2nd generation catalyst (**82**) and Hoveyda–Grubbs 2nd generation catalyst (**83**) were used, respectively, with toluene as the solvent under reflux conditions. However, neither catalyst yielded the desired tricyclic olefin **61**.[25] Upon analyzing the products from entry 1, it was found that a cross-metathesis reaction occurred between the terminal olefin of **62** and the phenylmethylene moiety of the Grubbs 2nd catalyst, forming compound **81**. This indicated that the exo-methylene group in **62** did not participate in the reaction, likely due to conformational constraints. To address this issue, alternative solvents were examined to modify the conformation of the substrate. In entries 3 and 4, dichloromethane was used as the solvent, while in entries 5 and 6, 1,2-dichloroethane was employed. In all cases, the desired product **41** was not obtained, and the recovery rate of starting material **62** increased. Since cross-metathesis product **81** was most prominent in entries 1 and 2, the reaction was repeated using octafluorotoluene, where all protons of toluene were replaced with fluorine. However, the results showed no significant improvement compared to those with dichloromethane. From these results, it was concluded that the substantial steric hindrance around the exo-methylene group of **62** prevented the intramolecular RCM, favoring an intermolecular reaction instead. Consequently, a change in the synthetic strategy was deemed necessary.

Table 5. Investigation of RCM of diene **62**



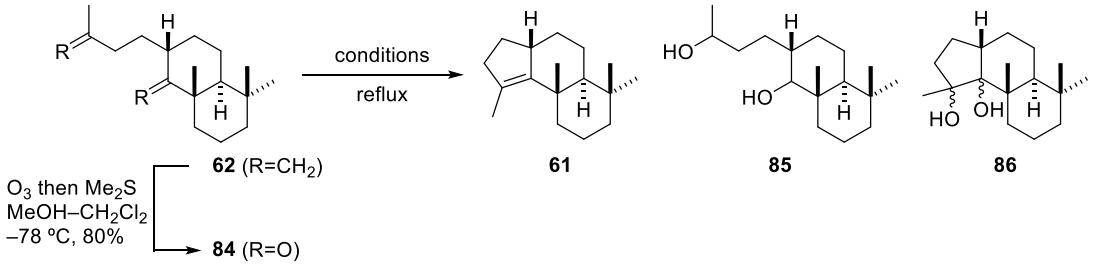
entry	cat.	solv.	results (%)	
			recovered 6**2**	**81**
1	Grubbs 2nd	toluene	34	20
2	Hoveyda–Grubbs 2nd		37	–
3	Grubbs 2nd	CH_2Cl_2	66	4
4	Hoveyda–Grubbs 2nd		76	–
5	Grubbs 2nd	DCE	90	trace
6	Hoveyda–Grubbs 2nd		85	–
7	Grubbs 2nd	$C_6F_5(CF_3)$	61	11
8	Hoveyda–Grubbs 2nd		64	–

2-3-4. Synthesis of tricyclic olefin 61 using intramolecular McMurry coupling

As discussed in the previous section, the synthesis of tricyclic olefin **61** via ring-closing metathesis proved challenging. Therefore, the synthetic strategy was revised. Diene **62** was converted into diketone **84** through ozonolysis, and the formation of **61** was attempted via intramolecular McMurry coupling. Since McMurry coupling proceeds via a radical mechanism, it was expected to be less affected by steric hindrance. Specifically, diketone **84** was synthesized by ozonolysis of **62** in dichloromethane, and intramolecular McMurry coupling of **84** was investigated (Table 6). In entry 1, following the report by Almstead et al., a sodium naphthalene solution was prepared, and $TiCl_4$ was added to the reaction mixture.[26] However, the reaction resulted in a complex mixture. Product analysis revealed that diol **85**, resulting from ketone reduction, and diol **86**, formed by intramolecular pinacol coupling, were the primary products. In entry 2, based on the report by Condroski et al., $TiCl_3$ and a Zn–Cu alloy were used.[27] This approach successfully yielded a small amount of the desired product **61**. In entry 3, the reaction was conducted using $TiCl_4$, zinc, and pyridine, following the method of List et al..[28] Under

these conditions, the yield improved, and **61** was obtained in 25% yield. Pyridine is known to coordinate with low-valent titanium, facilitating back-donation of electrons from the titanium d-orbitals to the π-conjugated system of pyridine, thereby reducing the electron density on titanium.[29] This effect helps to control the reactivity of low-valent titanium, suppressing side reactions and improving the yield of the desired product. However, the yield remained low, prompting further optimization. In entry 4, the solvent was changed to THF. While this did not improve the yield of **61**, the yield of the intermediate pinacol coupling product **86** increased, resulting in an overall improvement in recovery. Based on these results, THF was chosen as the solvent for further optimizations. The cause of the reaction stalling at the pinacol coupling stage was hypothesized to be the reaction of the low-valent titanium species with dissolved oxygen in the system. In entry 5, the reaction was conducted under deoxygenated conditions by using Ar-bubbled THF and maintaining an Ar atmosphere during the reaction. These conditions significantly improved the yield, and **61** was obtained in 51% yield.

Table 6. Investigation of intramolecular McMurry coupling of diketone **84**



entry	conditions		results (%)			
	reagents	solv.	**61**	**85**	**86**	recovered **84**
1	$TiCl_4$, $Na/C_{10}H_8$	THF	complex mixture (including **85** and **86**)			
2	$TiCl_3$, Zn–Cu	DME	5	–	30	59
3	$TiCl_4$, Zn, pyridine	DME	25	–	9	12
4	$TiCl_4$, Zn, pyridine	THF	22	–	41	–
5 [a,b]	$TiCl_4$, Zn, pyridine	THF [c]	51	–	<49	–

[a] under Ar flow

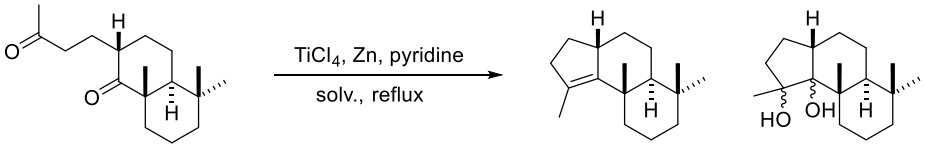
[b] 100 mg scale

[c] degassed solvent via Ar bubbling

However, when scaling up the reaction (from 100 mg to 500 mg), reproducibility decreased. This issue was attributed to potential inaccuracies in the amount of pyridine added during scale-

up. To address this, the optimal amount of pyridine was examined at a 100 mg scale (Table 7). In the initial conditions (Table 6), 2.5 equivalents of pyridine were used. Suspecting that this might be excessive, the reaction was conducted with 1.0 equivalent of pyridine (entry 1). However, no significant change in yield was observed. In entry 2, the amount of pyridine was increased to 3.5 equivalents, resulting in an improved yield of 63% for the tricyclic olefin **61**. Further increasing the pyridine amount to 10 equivalents (entry 3) led to a significant decrease in yield. This likely occurred because excessive electron back-donation from titanium to pyridine significantly reduced the reactivity of the titanium species during the deoxygenation step. Based on these findings, the optimal pyridine amount was determined to be 3.5 equivalents. When the reaction was scaled up to 500 mg under these optimized conditions (entry 4), **61** was obtained with good reproducibility.

Table 7. Investigation of equivalents of pyridine in McMurry coupling of diketone **84**



84 **61** **86**

entry	pyridine (eq.)	yield (%)	
		61	**86**
1	1.0	48	<52
2	3.5	63	<37
3	10	29	62
4 [a]	3.5	60	<40

[a] 500 mg scale

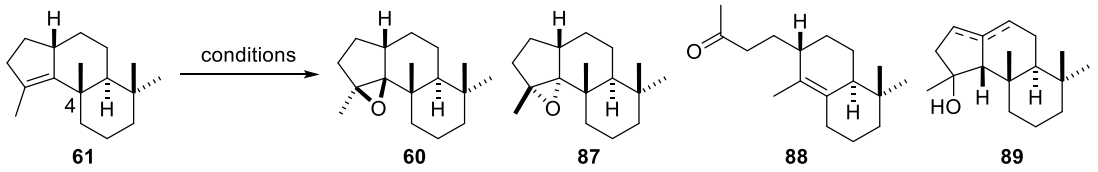
2-3-5. Investigation of stereoselective epoxidation

To synthesize epoxide **60**, the precursor for the House–Meinwald rearrangement, the stereoselective epoxidation of tricyclic olefin **61** was investigated (Table 8). In entry 1, the reaction was conducted using the common oxidant *m*CPBA. This resulted in a 43% yield with a diastereomeric ratio (dr) of 1:2.9, favoring the undesired diastereomer **87**. The stereochemistry of epoxides **60** and **87** could not be determined and was inferred from the stereochemistry of the products obtained in the subsequent House–Meinwald rearrangement. In entries 2–5, the method reported by Mukaiyama et al. was employed, wherein a divalent or trivalent metal reagent (Mn(II), Ni(II), Co(II), or Fe(III)) and ^{i}PrCHO were used under an oxygen atmosphere.[30] While these conditions improved the overall yields, the diastereoselectivity still favored the undesired diastereomer **87**. In entry 6, following the report

by Kimura et al., $Fe(acac)_3$ and 30% hydrogen peroxide were used as the oxidant.[31] Although the epoxide was obtained in high yield under these conditions, the diastereoselectivity remained unchanged, still favoring the formation of **87**.

In entries 1–6, the undesired diastereomer **87** was preferentially formed during the epoxidation of tricyclic olefin **61**. Initially, it was assumed that oxidation would proceed from the convex face of the substrate based on the stable conformation of **61**, yielding the desired stereochemistry for **60**. However, it is likely that the steric hindrance caused by the methyl group at the C4 position diverted the oxidant to approach from the concave face, favoring the formation of **87** (Figure 5). Based on the example by Zeelen et al., where epoxidation proceeds with the same stereochemistry as the α-quaternary carbon of the alkene, the reaction was conducted using TBHP and $Mo(CO)_6$ (entry 7).[32] This condition yielded the desired stereoisomer **60** with a diastereomeric ratio of 3:1 and a yield of 25%. However, reproducibility was poor, and byproducts such as ketone **88** (from methyl migration and ring cleavage) and alcohol **89** (hydride shift of **87**) were observed. To overcome steric hindrance and improve selectivity, DMDO was employed as the oxidant. Due to its small size, DMDO was expected to enable oxidation from the convex face. Following Dondoni's report, DMDO was generated in situ using acetonitrile as the solvent (entry 8).[33] Although epoxides were formed in low yield with a 1:1 diastereomeric ratio, this confirmed the viability of using DMDO. Changing the solvent to dichloromethane (entry 9) improved the conversion rate, but diastereoselectivity remained unchanged. Using ethyl acetate as the solvent (entry 10) resulted in a recovery rate improvement, despite no significant changes in conversion or diastereoselectivity. Using acetone as the solvent (entry 11) provided the highest yield of **60** and **87**, albeit with a reduction in recovery compared to entry 10.[34] Since DMDO reactions are known to be concentration-dependent, the reaction concentration was increased from 0.42 M in entry 10 to 1.3 M in entry 12.[35] This adjustment improved the yield to 70%, with a diastereomeric ratio of 1:0.8 for **60** and **87**. Finally, the more reactive TFDO (600 times more reactive than DMDO) was tested (entries 13–14). However, significant decomposition of the product was observed under all conditions, leading to reduced recovery. Based on these investigations, the conditions in entry 12 (1.3 M DMDO in ethyl acetate) were determined to be optimal. While these conditions did not achieve diastereoselectivity, they provided the best balance of yield, recovery, and reproducibility, making them the most practical choice for synthesizing epoxide **60**.

Table 8. Investigation of epoxidation of tricyclic olefin **61**



entry	conditions			results (%)	
	reagents	solv.	temp.	epoxide (**60** : **87**) [a]	Recovered **61**
1	*m*CPBA	DCE	rt	<43 (1 : 2.9)	–
2	$Mn(acac)_2$, O_2 ^{i}PrCHO	DCE	rt	81 (1 : 3.8)	–
3	$Ni(acac)_2$, O_2 ^{i}PrCHO	DCE	rt	53 (1 : 1.8)	–
4	$Co(acac)_2$, O_2 ^{i}PrCHO	DCE	rt	50 (1 : 1.9)	–
5	$Fe(acac)_3$, O_2 ^{i}PrCHO	DCE	rt	<40 (–) [b]	–
6	$Fe(acac)_3$ 30% H_2O_2 aq.	MeCN	40 °C	84 (1 : 8.0)	–
7	$Mo(CO)_6$, TBHP	toluene	80 °C	10–40 (1 : 0–3.0 : 1)	–
8 [c]	acetone Oxone® aq., $NaHCO_3$	MeCN	rt	10 (1 : 1.0)	78
9 [c]	acetone Oxone® aq., $NaHCO_3$	CH_2Cl_2	rt	43 (1 : 1.2)	40
10 [c]	acetone Oxone® aq., $NaHCO_3$	EtOAc	rt	35 (1.1 : 1)	56
11 [c]	acetone Oxone® aq., $NaHCO_3$	–	rt	66 (1 : 1.0)	–
12 [d]	acetone Oxone® aq., $NaHCO_3$	EtOAc	rt	70 (1.3 : 1)	–
13 [c]	1,1,1-trifluoroacetone Oxone® aq., $NaHCO_3$	–	rt	34 (2.0 : 1)	22
14 [c]	1,1,1-trifluoroacetone Oxone® aq., $NaHCO_3$	EtOAc	rt	16 (1 : <1.0)	48

[a] Calculated by ^{1}H NMR

[b] Not determined

[c] These reactions were carried out at the substrate concentration of 0.42 M.

[d] This reaction was carried out at the substrate concentration of 1.3 M.

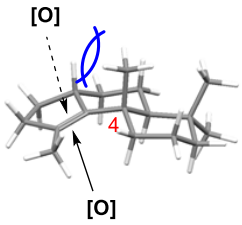
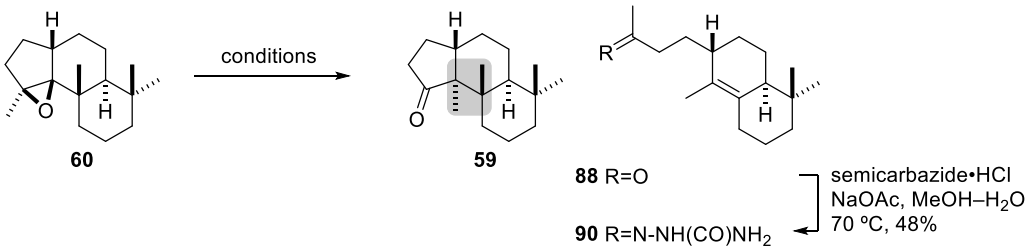


Figure 5. A plausible mechanism of the epoxidation of **61**
(DFT optimized structure of **61** at B3LYP/6-31G* level)

2-3-6. Construction of contiguous asymmetric quaternary carbon centers using House–Meinwald rearrangement

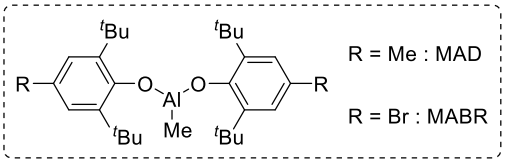
With epoxide **60** synthesized as the precursor, the House–Meinwald rearrangement was investigated (Table 9). Initially, $BF_3 \cdot OEt_2$, a commonly used Lewis acid in natural product synthesis, was employed in toluene at –78 °C (entry 1). However, the desired ketone **59** was not obtained. Instead, ketone **88**, resulting from methyl migration followed by ring cleavage, was formed (Scheme 13). The structure of **88** was confirmed by derivatization into semicarbazone **90** and subsequent X-ray crystallographic analysis (Figure 6). Next, $B(C_6F_5)_3$ as a super Lewis acid was tested (entry 2). While it exhibited higher reactivity, the reaction predominantly yielded **88** in high yield, indicating that boron-based Lewis acids were unsuitable for promoting the desired rearrangement.[16] Given the limitations of boron-based Lewis acids, aluminum-based Lewis acids were explored, focusing on their size and reactivity (entries 3–6). A small Lewis acid, Me_3Al, was used, but the rearrangement did not proceed (entry 3). A bulkier Lewis acid, MAD, was tested, but again, no reaction was observed (entry 4). When a stronger Lewis acid, Et_2AlCl, was employed, the desired ketone **59** was detected (entry 5). However, the reaction still predominantly produced **88**. Finally, MABR, a bulkier and stronger Lewis acid than MAD, was tested (entry 6). Under these conditions, ketone **59** was obtained with good yield and selectivity, as the major product. The stereochemistry of compound **59** was determined using NOESY spectroscopy (Figure 7). These investigations successfully established a method for constructing the contiguous quaternary stereogenic centers common to indole terpenoids. Among the tested conditions, the use of MABR (entry 6) proved to be the most effective, yielding ketone **59** in good yield and selectivity. This represents a significant advancement in the stereoselective synthesis of complex natural products.

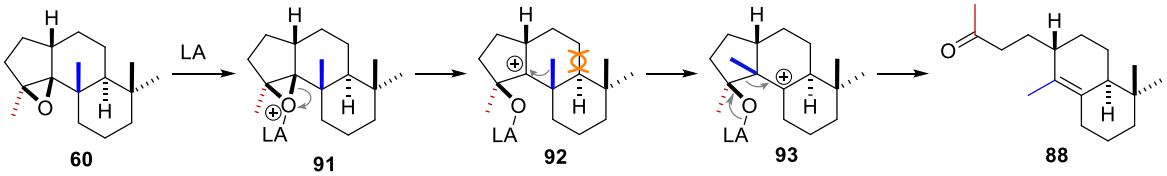
Table 9. Investigation of House–Meinwald rearrangement of epoxide **60**



entry	conditions			yield (**59** : **88**) [a]
	Lewis acid	solv.	temp.	
1	$BF_3{\cdot}OEt_2$	toluene	–78 °C to rt	47 (0 : 1.0)
2	$B(C_6F_5)_3$	↓	60 °C	98 (0 : 1.0)
3	Me_3Al	CH_2Cl_2	reflux	no reaction
4	MAD	↓	reflux	no reaction
5	Et_2AlCl	↓	rt	51 (1 : 2.2)
6	MABR	↓	rt	79 (5.0 : 1)

[a] calculated by ^{1}H NMR





Scheme 13. Mechanism of ring cleavage

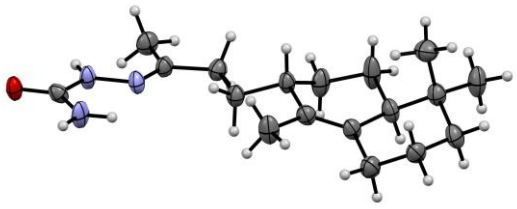


Figure 6. X-ray crystallographic structure of semicarbazone **90**.

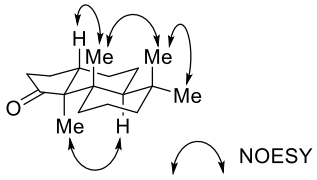
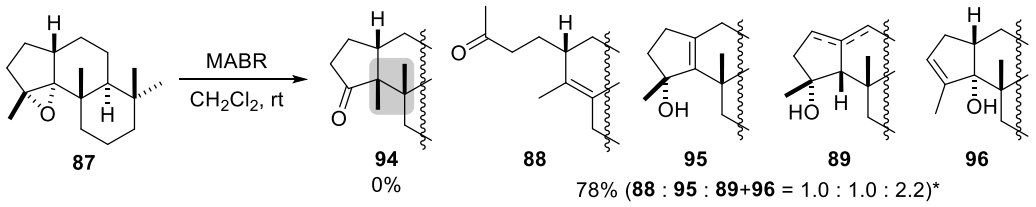


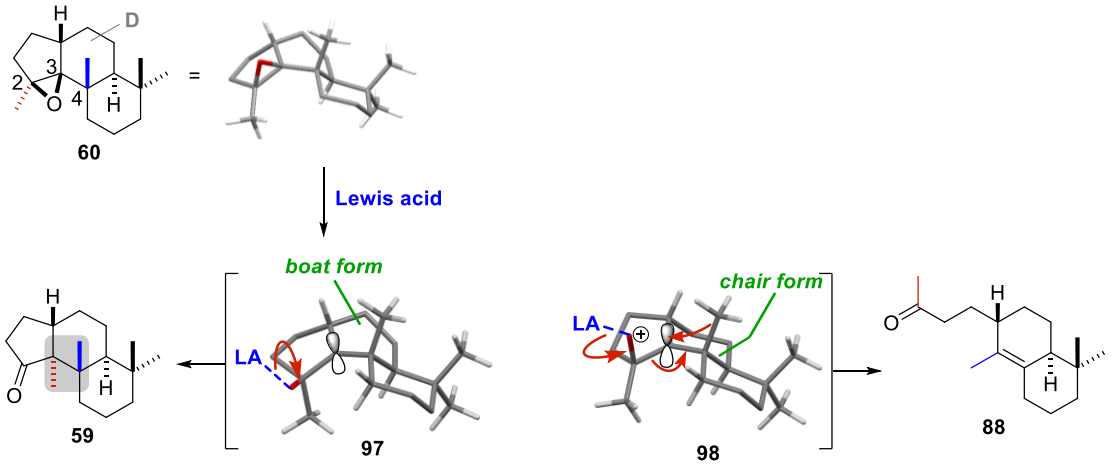
Figure 7. NOESY spectrum of ketone **59**.

To investigate the reaction mechanism, the House–Meinwald rearrangement of epoxide **87**, the diastereomer of epoxide **60**, was performed using MABR (Scheme 14). Contrary to expectations, product **94** was not obtained. Instead, the reaction yielded a mixture of products similar to those observed when epoxide **60** was used. These included the ring-cleavage product **88**, allyl alcohol **95**, and alcohols **89** and **96**, which resulted from the stereospecific migration of the hydride or methyl group at the ring junction. This outcome suggests that the reaction pathway is highly sensitive to the stereochemistry of the substrate and likely proceeds through a complex network of competing mechanisms. The formation of multiple products highlights the influence of both steric and electronic factors in directing the migration and cleavage steps during the rearrangement



Scheme 14. House–Meinwald rearrangement of epoxide **87**

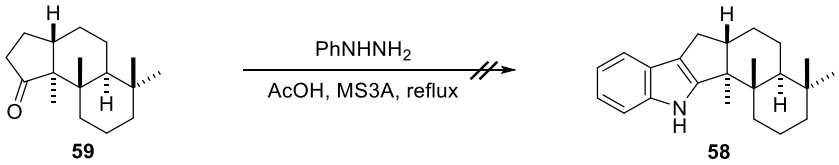
Based on the experimental results, the mechanism of the House–Meinwald rearrangement was analyzed (Scheme 15). Two possible mechanisms for forming the desired rearrangement product **59** were considered: a concerted mechanism and a stepwise mechanism. In the concerted mechanism, the Lewis acid activates the epoxide, positioning the C2 methyl group on the axial side. This alignment facilitates a stereospecific rearrangement of the methyl group, leading directly to the formation of the desired product **59**. The stepwise mechanism is supported by the formation of the ring-cleavage product **88**. In this pathway, Lewis acid activation of the epoxide generates a tertiary carbocation intermediate at the ring junction. The migration of the C2 methyl group leads to the formation of **59**, while the migration of the C4 methyl group results in **88**, following subsequent ring cleavage. DFT calculations provided further insights, suggesting that the conformation of the D ring in the carbocation intermediate significantly influences the reaction pathway. In a conformation **97**, the C–O bond cleavage positions the D ring in a boat conformation. This alignment allows the C2 methyl group's C–C σ bond to overlap with the empty p orbital of the carbocation, enabling the migration of the C2 methyl group and yielding **59** as the product. In the chair flipped conformation **98**, the C4 methyl group's C-C σ bond overlaps with the carbocation's empty p orbital. This leads to the rearrangement of the C4 methyl group, followed by ring cleavage, resulting in **88**. This is attributed to the stabilization of the boat-like conformation of the carbocation intermediate **97**, caused by the steric repulsion between the bulky MABR and the C4 methyl group, which facilitated the desired rearrangement reaction.



Scheme 15. Plausible reaction mechanism of House–Meinwald rearrangement of epoxide **60** (DFT optimized structure of **97** and **98** at B3LYP/6-31G** level)

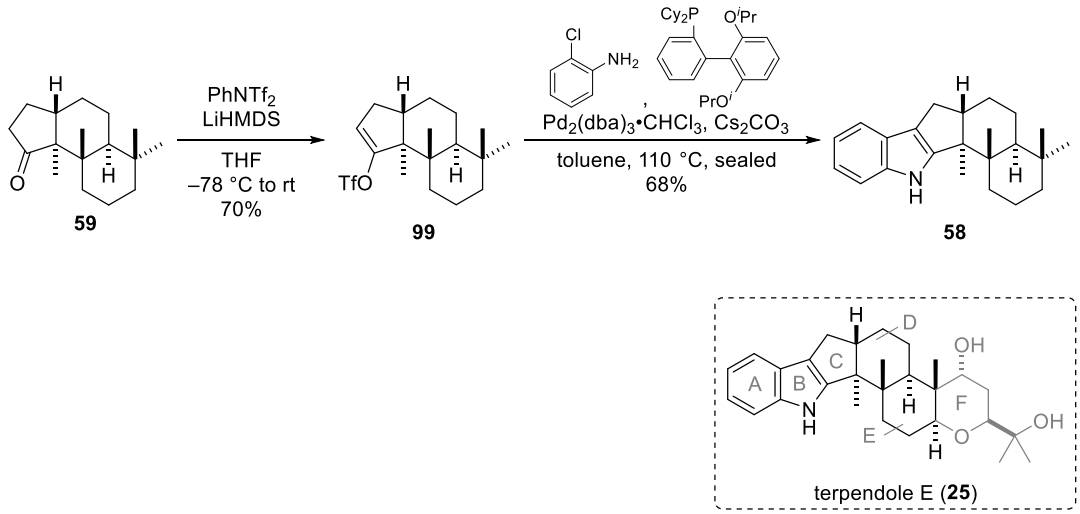
2-3-7. Construction of the A-E ring portion of terpendole E (25) by introducing the Indole moiety

With the desired ketone **59** in hand, the introduction of the indole moiety was explored. Initially, the Fischer indole synthesis was attempted to introduce the indole group (Scheme 16).[28] Ketone **59** was treated with phenylhydrazine in acetic acid under reflux conditions. However, the desired reaction did not proceed, and 80% of the starting material was recovered. The absence of the hydrazone intermediate suggested that steric hindrance around the carbonyl group prevented the reaction from progressing. Based on this observation, the synthetic strategy was revised.



Scheme 16. Fischer indole synthesis

Following Smith et al.'s report, the synthesis of indole **58** was pursued by first converting ketone **59** into its enol triflate, followed by the Barluenga–Smith indole synthesis (Scheme 17).[7] First, ketone **59** was treated with LiHMDS to generate the corresponding enolate, which was then reacted with $PhNTf_2$ to yield enol triflate **99** in 70% yield. Subsequently, **99** was reacted with 2-chloroaniline in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ as the catalyst, successfully synthesizing the desired indole **58** in 68% yield. X-ray crystallographic analysis of **58** confirmed its structure, including the stereochemistry of the methyl group introduced during the House–Meinwald rearrangement (Figure 8). This result demonstrated the successful construction of the A–E ring system of terpendole E (**25**).



Scheme 17. Synthesis of indole **58** by using Barluenga–Smith indole synthesis

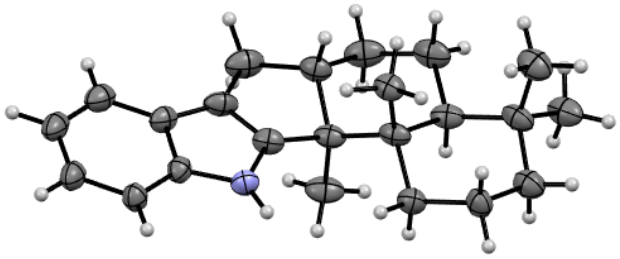
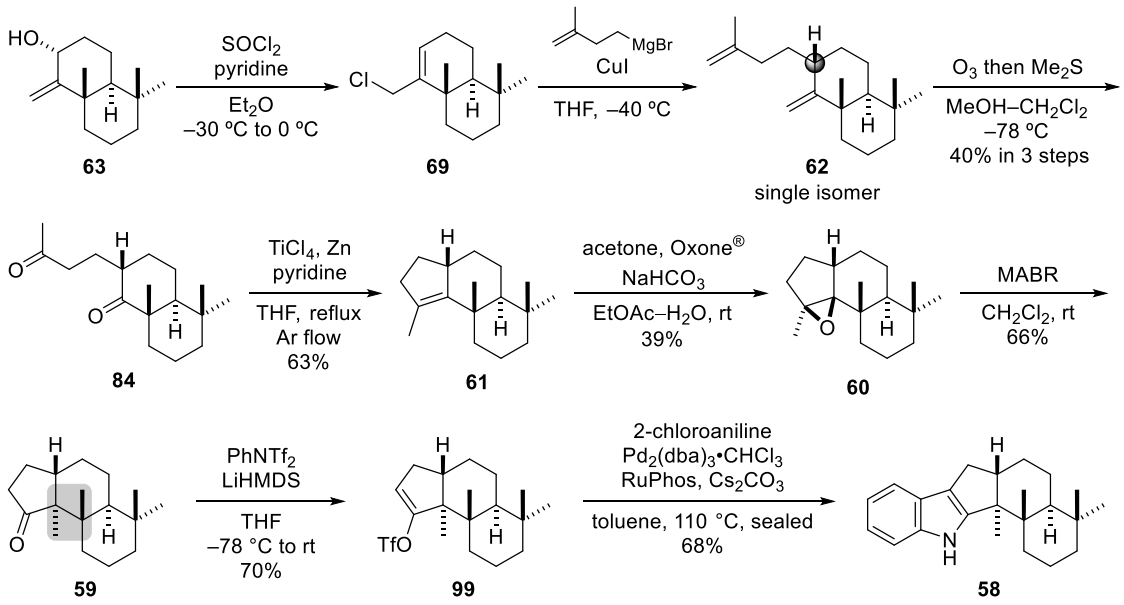


Figure 8. X-ray crystallographic structure of indole **58**.

2-4. Conclusion

In this study, we aimed to comprehensively synthesize indole terpenoids and investigate the construction method of contiguous asymmetric quaternary carbon centers, which are their common structural feature (Scheme 18). Starting from known allylic alcohol **63**, we synthesized diketone **84** and obtained tricyclic olefin **61** through intramolecular McMurry coupling. Epoxidation of the obtained **61** followed by treatment with the super Lewis acid MABR yielded ketone **59**, thereby establishing a method for constructing contiguous asymmetric quaternary carbon centers common to indole terpenoids. Subsequently, enol triflation of ketone **59** followed by Barluenga–Smith indole synthesis allowed us to establish the construction method of the A-E ring portion of Terpendole E (**25**). If site-selective C-H oxidation can be achieved, this synthetic route is expected to be extended to the synthesis of various indole terpenes starting from ketone **59**.



Scheme 18. Synthesis of indole **58**

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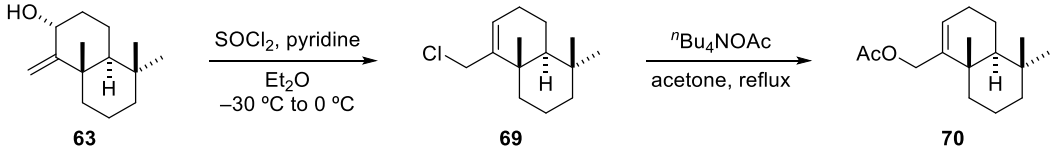
2-6. Experimental section

General Experimental Information

All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with toluene before use. For the reactions that require heating, an oil bath was used. All chemicals were used as obtained from commercial supplies unless otherwise noted. Anhydrous acetone, CH_2Cl_2, DMF, Et_2O, MeCN, MeOH, pyridine, THF, and toluene were purchased from Wako Pure Chemical Industries Ltd. or KANTO Chemical Co., Inc. and used without further drying. Anhydrous hexane for 2,3-Wittig rearrangement was distilled from CaH. TLC analyses were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel PSQ 100B or PSQ 60B was used for column chromatography unless otherwise noted. Melting points were measured on a J-SCIENCE RFS-10 micromelting point apparatus and are uncorrected. Optical rotations were measured with a HORIBA SEPA-300 polarimeter. IR spectra were recorded on a SHIMADZU FTIR-8400, and only selected peaks are reported in wavenumbers (cm^{-1}). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian NMR System 600, a Varian 400-MR spectrometer, or a JEOL ECZ 600R (equipped with a Supercool probe) (600 MHz). The ^1H and $^{13}C\{^1H\}$ chemical shifts were referenced to the solvent peaks, δ_H 7.26 (residual $CHCl_3$) and δ_C 77.0 ppm ($CDCl_3$). *J* values are given in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High-resolution electrospray ionization/time-of-flight (ESI/TOF) mass spectra and an APCI mass spectra were recorded on a Bruker micrOTOF II spectrometer. X-ray single-crystal analyses of **62** and **40** were conducted with a Rigaku VariMax with Saturn.

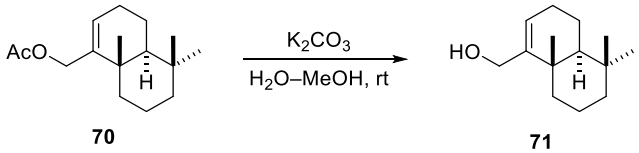
((4a*S*,8a*S*)-5,5,8a-Trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl Acetate (70).



To a stirred solution of allyl alcohol **63** (5.77 g, 27.7 mmol) in Et_2O (580 mL) were added pyridine (6.75 mL, 83.6 mmol) and $SOCl_2$ (3.00 mL, 41.3 mmol) at −30 °C. The reaction mixture was allowed to warm to 0 °C. After being stirred at the same temperature for 20 min, the reaction mixture was diluted with saturated aqueous NH_4Cl (100 mL) and extracted with Et_2O (150 mL × 3). The combined extracts were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated. The crude allyl chloride **69** (6.81 g) was used for the next reaction without further purification.

To a stirred solution of crude allyl chloride **69** (6.48 g) in acetone (100 mL) was added $^{n}Bu_4NOAc$ (25.2 g, 83.4 mmol) at room temperature. After being stirred at reflux for 16 h, the reaction mixture was concentrated. The mixture was diluted with EtOAc (50 mL) and H_2O (50 mL) and extracted with EtOAc (100 mL × 3). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (10 g, ^{n}hexane−EtOAc 100:1 → 75:1) to afford allyl acetate **70** (5.11 g, 74% in two steps) as a yellow oil: $[\alpha]^{21}_D$ +69.2 (*c* = 0.73, $CHCl_3$); IR (neat) 2941, 1740, 1466, 1366, 1229, 1047, 1022, 959, 854, 794, 606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, *J* = 3.2, 3.2 Hz, 1H), 4.56−4.45 (m, 2H), 2,17 (m, 1H), 2.13−2.00 (m, 4H), 1.73−1.65 (m, 2H), 1.60 (dddd, *J* = 17.0, 6.7, 3.4, 3.4 Hz, 1H), 1.51−1.39 (m, 3H), 1.29−1.13 (m, 3H), 1.07 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 142.4, 126.2, 65.2, 51.2, 41.7, 37.5, 36.1, 33.3, 33.2, 26.6, 21.6, 21.2, 20.8, 18.7, 18.3; HRMS (ESI) *m/z* 273.1813, calcd for $C_{16}H_{26}O_2$ $[M + Na]^+$ 273.1825.

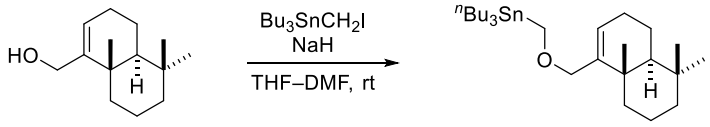
((4a*S*,8a*S*)-5,5,8a-Trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methanol (71).



To a stirred solution of allyl acetate **70** (3.40 g, 13.6 mmol) in MeOH (100 mL) and H_2O (25 mL) was added K_2CO_3 (5.63 g, 40.8 mmol) at room temperature. After being stirred at room temperature for 4 h, the reaction mixture was concentrated, diluted with EtOAc (100 mL) and brine (100 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL × 2). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4 g, ^{n}hexane−EtOAc 10:1 → 5:1) to afford allyl alcohol **71** (2.79 g, 99%) as a colorless solid: $[\alpha]^{24}_D$ +61.1 (*c* = 0.39,

$CHCl_3$); mp 56.8−59.6 °C; IR (neat) 3613, 3397, 2924, 2367, 1701, 1458, 1389, 1215, 1132, 1098, 1051, 999, 854, 758, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (m, 1H), 4.09 (dd, *J* = 4.4, 1.6 Hz, 2H), 2.17 (m, 1H), 2.06 (m, 1H), 1.76 (ddd, *J* = 12.4, 4.4, 3.2 Hz, 1H), 1.61 (dddd, *J* = 16.9, 6.7, 3.3, 3.3 Hz, 1H), 1.52−1.39 (m, 3H), 1.30−1.11 (m, 4H), 1.08 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H). A signal due to one proton (OH) was not observed; $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$) δ 147.7, 122.1, 63.2, 51.3, 41.8, 37.5, 36.3, 33.3, 33.2, 26.5, 21.6, 21.0, 18.7, 18.5; HRMS (ESI) *m/z* 231.1717, calcd for $C_{14}H_{24}O$ $[M+Na]^+$ 231.1719.

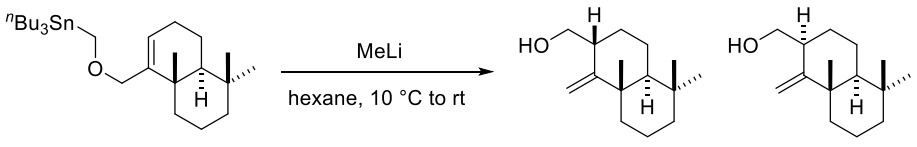
Tributyl((((4a*S*,8a*S*)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methoxy)methyl)stannane (72).



71 **72**

To a stirred solution of allyl alcohol **71** (2.17 g, 10.1 mmol) and iodomethyltributyltin (5.78 g, 13.4 mmol) in THF (20 mL) and DMF (20 mL) was added NaH (60% oil suspension, 1.02 g, 25.6 mmol) at 0 °C. After being stirred at room temperature for 6.5 h, the mixture was cooled to 0 °C, diluted with Et_2O (30 mL) and saturated aqueous NH_4Cl (30 mL), and the layers were separated (A): (1) The extract of (A) was washed with brine (50 mL) and Et_2O (50 mL); (2) the aqueous layer of (A) was extracted with Et_2O (50 mL × 3). The combined extracts were washed with brine (100 mL). The combined extracts {(1) + (2)} were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (15 g, *n*hexane⟶ *n*hexane−EtOAc 50:1) to afford tin-substituted ether **72** (5.23 g, 98%) as a colorless oil: $[\alpha]^{24}_D$ +25.9 (*c* = 0.41, $CHCl_3$); IR (neat) 2924, 1462, 1375, 1292, 1236, 1198, 1072, 1051, 959 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (dd, *J* = 2.8, 2.8 Hz, 1H), 3.82 (m, 1H), 3.72 (m, 1H), 3.69−3.62 (m, 2H), 2.16 (m, 1H), 2.00 (m, 1H), 1.73 (m, 1H), 1.69−1.38 (m, 12H), 1.35−1.24 (m, 6H), 1.23−1.12 (m, 3H), 1.06 (s, 3H), 0.97−0.80 (m, 20H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.5, 123.5, 76.5, 61.0, 51.3, 41.9, 37.5, 36.2, 33.4, 33.2, 29.2 (3C), 27.4 (3C), 26.5, 21.6, 20.8, 18.8, 18.5, 13.7 (3C), 9.0 (3C); HRMS (ESI) *m/z* 535.2925, calcd for $C_{27}H_{52}OSn$ $[M+Na]^+$ 535.2932.

((2*R*,4a*S*,8a*S*)-5,5,8a-Trimethyl-1-methylenedecahydronaphthalen-2-yl)methanol (73) and ((2*S*,4a*S*,8a*S*)-5,5,8a-Trimethyl-1-methylenedecahydronaphthalen-2-yl)methanol (74)



72 **73** **74**

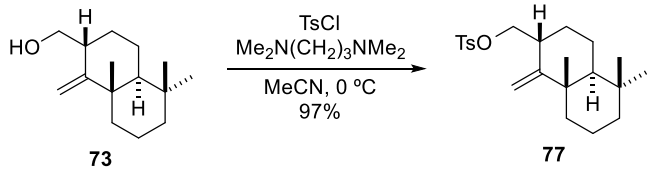
To a stirred solution of tin-substituted ether **72** (4.98 g, 9.73 mmol) in *n*hexane (25 mL) was added MeLi (3.10 M solution in DME, 15.5 μL, 48.0 μmol) at 10 °C. After being stirred at

room temperature for 1 h, the mixture was cooled to 0 °C, diluted with saturated aqueous NH_4Cl (15 mL), and extracted with EtOAc (70 mL × 3). The combined extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (200 g, *n*hexane−EtOAc 40:1) to afford desired isomer **73** (1.02 g, 50%) and C16 undesired isomers **74** (911 mg, 45%) as colorless solids, respectively.

Desired isomer **73**: $[\alpha]^{24}_{D}$ −25.4 (*c* = 0.39, $CHCl_3$); mp 48.0−49.8 °C; IR (neat) 3397, 2932, 1632, 1464, 1388, 1215, 1076, 1045, 1015, 970, 891, 758, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.72 (d, *J* = 1.6 Hz, 1H), 4.49 (d, *J* = 1.6 Hz, 1H), 3.83 (ddd, *J* = 10.8, 6.0, 5.0 Hz, 1H), 3.60 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 2.44 (m, 1H), 1.99 (ddd, *J* = 12.0, 7.2, 4.2 Hz, 1H), 1.72 (ddd, *J* = 13.8, 7.2, 3.0 Hz, 1H), 1.66 (dddd, *J* = 16.9, 6.5, 3.3, 3.3 Hz, 1H), 1.55 (m, 1H), 1.51−1.37 (m, 4H), 1.25 (s, 1H), 1.16 (ddd, *J* = 13.3, 13.3, 3.7 Hz, 1H), 1.05 (s, 3H), 1.01 (dd, *J* = 12.6, 4.2 Hz, 1H), 0.93 (dd, *J* = 12.6, 3.0 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 109.2, 65.1, 53.5, 46.6, 41.9, 39.9, 38.5, 33.7, 33.3 (2C), 28.8, 21.7, 18.7, 18.6; HRMS (ESI) *m/z* 245.1856, calcd for $C_{15}H_{26}O$ $[M+Na]^+$ 245.1876.

C16 undesired isomer **74**: $[\alpha]^{22}_{D}$ −31.6 (*c* = 0.37, $CHCl_3$); mp 47.4−50.2 °C; IR (neat) 3397, 2928, 1624, 1462, 1388, 1215, 1030, 961, 901, 758, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.86 (d, *J* = 1.6 Hz, 1H), 4.72 (dd, *J* = 1.6, 0.6 Hz, 1H), 3.66 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.58 (m, 1H), 2.54 (dd, *J* = 15.6, 7.8 Hz, 1H), 1.78−1.73 (m, 2H), 1.67 (ddd, *J* = 13.2, 6.0, 1.8 Hz, 1H), 1.62 (ddd, *J* = 13.2, 6.6, 3.0 Hz, 1H), 1.61−1.56 (m, 2H), 1.52 (m, 1H), 1.48−1.36 (m, 3H), 1.17 (ddd, *J* = 13.2, 13.2, 4.2 Hz, 1H), 1.06 (d, *J* = 0.6 Hz, 3H), 0.99 (dd, *J* = 12.0, 2.4 Hz, 1H), 0.87 (s, 3H), 0.84 (s, 3H); $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$) δ 159.1, 109.2, 65.1, 53.5, 46.6, 41.9, 39.9, 38.5 (2C), 33.7, 33.3, 28.8, 21.7, 18.7, 18.6; HRMS (ESI) *m/z* 245.1881, calcd for $C_{15}H_{26}O$ $[M+Na]^+$ 245.1876.

((2*R*,4a*S*,8a*S*)-5,5,8a-Trimethyl-1-methylenedecahydronaphthalen-2-yl)methyl 4-Methylbenzenesulfonate (77).

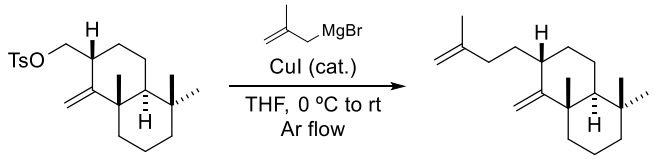


73 **77**

To a stirred solution of desired isomer **73** (296 mg, 1.42 mmol) and *p*-TsCl (407 mg, 2.14 mmol) in MeCN (10 mL) was added *N,N,N',N'*-tetramethyl-1,3-propanediamine (1.20 mL, 7.16 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h, diluted with water (10 mL), and extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (7 g, *n*hexane−EtOAc 80:1) to afford tosylate **77** (518 g, 97%) as a colorless oil: $[\alpha]^{24}_{D}$ −39.3 (*c* = 0.39, $CHCl_3$); IR (neat) 3020, 2934, 1636, 1599, 1464, 1361, 1215, 1188, 1175, 1098, 961, 853, 756, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.73 (s, 1H), 4.76 (s, 1H), 4.23 (dd, *J* = 9.6,

9.6 Hz, 1H), 3.93 (dd, *J* = 8.9, 5.5 Hz, 1H), 2.67 (ddd, *J* = 9.6, 4.8, 4.8 Hz, 1H), 2.45 (s, 3H), 1.80 (m, 1H), 1.67 (m, 1H), 1.60 (m, 1H), 1.54−1.45 (m, 3H), 1.37 (m, 1H), 1.34−1.21 (m, 2H), 1.12 (ddd, *J* = 13.8, 13.8, 4.1 Hz, 1H), 0.91 (dd, *J* = 12.4, 2.8 Hz, 1H), 0.88 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.7, 144.7, 133.2, 129.8 (2C), 127.9 (2C), 109.2, 73.3, 53.2, 43.6, 41.9, 39.5, 38.1, 33.6, 33.2, 27.9, 21.7, 21.58, 21.56, 18.7, 17.7; HRMS (ESI) *m/z* 399.1958, calcd for $C_{22}H_{32}O_3S$ $[M+Na]^+$ 399.1964.

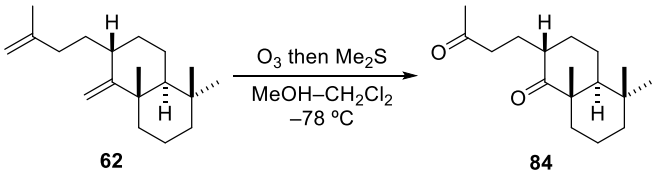
(4a*S*,6*S*,8a*S*)-1,1,4a-Trimethyl-6-(3-methylbut-3-en-1-yl)-5-methylenedecahydronaphthalene (62).



77 **62**

THF was degassed by freeze−thawing. To a stirred solution of CuI (408 mg, 2.14 mmol) in degassed THF (10 mL) was added 2-methylallylmagnesium bromide (0.500 M solution in THF, 43.0 mL, 21.5 mmol) at 0 °C. The mixture was stirred at the same temperature for 10 min to give a THF solution of the organocuprate. The above-mentioned solution of the organocuprate was added to a solution of tosylate **77** (2.71 g, 7.19 mmol) in degassed THF (15 mL) at 0 °C under an argon flow. After being stirred at room temperature for 12 h, the mixture was cooled to 0 °C, diluted with saturated aqueous NH_4Cl (30 mL), and stirred at room temperature for 30 min. The resultant reaction mixture was extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (25 g, *n*hexane) to afford diene **62** (1.79 g, 95%) as a colorless oil: $[\alpha]^{24}_D$ −53.4 (*c* = 0.37, $CHCl_3$); IR (neat) 2932, 1647, 1632, 1460, 1389, 1373, 1215, 889, 758, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71−4.68 (m, 2H), 4.67 (s, 1H), 4.51 (s, 1H), 2.15 (m, 1H), 2.10−1.95 (m, 3H), 1.80−1.60 (m, 6H), 1.59−1.36 (m, 6H), 1.32 (m, 1H), 1.25 (m, 1H), 1.16 (ddd, *J* = 8.8, 8.8, 2.4 Hz, 1H), 1.03 (d, J = 0.6 Hz, 3H), 0.92 (dd, *J* = 12.6, 3.2 Hz, 2H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 146.6, 109.5, 99.7, 54.7, 42.4, 40.5, 38.1, 37.8, 35.5, 35.2, 33.9, 33.2, 31.0, 22.5, 22.4, 21.8, 20.5, 19.2; HRMS (APCI) *m/z* 261.2532, calcd for $C_{19}H_{33}$ $[M+H]^+$ 261.2577; found 261.2532. Because diene 19 was difficult to ionize under the ESI and APCI-TOF conditions, high-resolution mass spectra within the 10 ppm acceptable error could not be obtained.

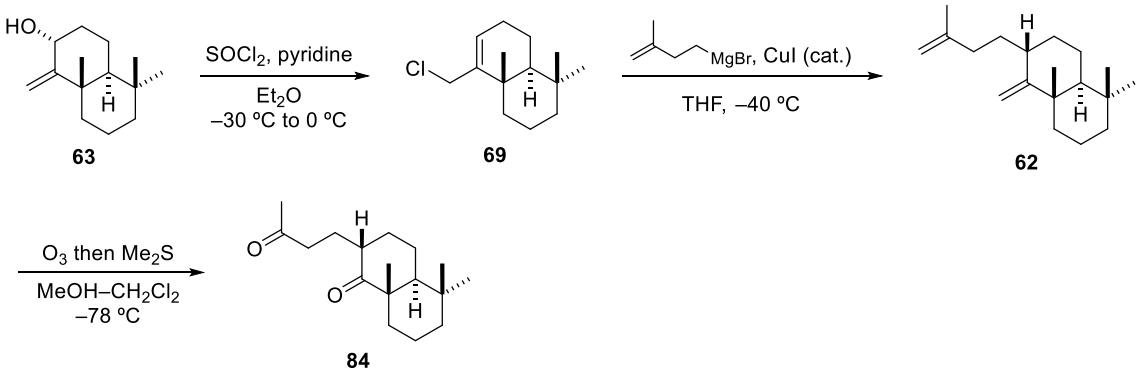
(2*S*,4a*S*,8a*S*)-5,5,8a-Trimethyl-2-(3-oxobutyl) -octahydronaphthalen-1(2H)-one (84).



62 **84**

Diene **62** (1.72 g, 6.62 mmol) was dissolved in MeOH (40 mL) and CH_2Cl_2 (20 mL) and cooled to −78 °C. A stream of ozone in oxygen was gently bubbled through this solution for 2 h. The solution was purged with argon for 30 min, and then Me_2S (2.50 mL, 34.6 mmol) was added. The resultant mixture was allowed to warm to room temperature and stirred for 1 h. Removal of the solvent afforded the crude product, which was purified by column chromatography on silica gel (20 g, *n*hexane−EtOAc 30:1) to afford diketone **84** (1.41 g, 80%) as a colorless oil: $[\alpha]^{24}{}_D$ −8.8 (*c* = 0.35, $CHCl_3$); IR (neat) 2933, 1703, 1462, 1366, 1217, 1165, 991, 966, 756, 667 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 2.64−2.57 (m, 2H), 2.54 (ddd, *J* = 17.2, 8.6, 5.9 Hz, 1H), 2.36 (ddd, *J* = 17.2, 8.6, 6.4 Hz, 1H), 2.11 (s, 3H), 2.08 (dddd, *J* = 10.0, 6.5, 3.8, 2.8 Hz, 1H), 1.88 (dddd, *J* = 14.0, 8.3, 8.3, 5.8 Hz, 1H), 1.73 (dddd, *J* = 13.6, 4.8, 4.8, 3.2 Hz, 1H), 1.72−1.60 (m, 2H), 1.57−1.49 (m, 2H), 1.45 (dddd, *J* = 13.7, 8.8, 6.4, 4.7 Hz, 1H), 1.38 (m, 1H), 1.26−1.13 (m, 2H), 1.10 (s, 3H), 1.08 (dd, *J* = 12.2, 3.5 Hz, 1H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 209.1, 54.4, 49.0, 44.4, 41.5, 41.4, 34.2, 33.9, 33.0 (2C), 29.8, 24.0, 21.9, 21.3, 18.6, 18.1; HRMS (ESI) *m/z* 287.1970, calcd for $C_{17}H_{28}O_2$ $[M+Na]^+$ 287.1982.

(2*S*,4a*S*,8a*S*)-5,5,8a-Trimethyl-2-(3-oxobutyl)-octahydronaphthalen-1(2H)-one (84).



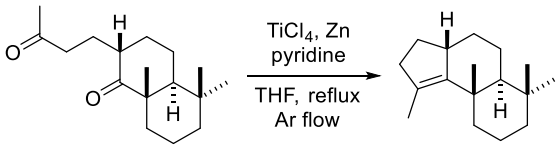
To a stirred solution of allyl alcohol **63** (2.94 g, 13.0 mmol) in Et_2O (200 mL) were added pyridine (3.15 mL, 39.0 mmol) and $SOCl_2$ (1.40 mL, 19.5 mmol) at −30 °C. The reaction mixture was allowed to warm to 0 °C. After being stirred at the same temperature for 10 min, the mixture was diluted with saturated aqueous NH_4Cl (50 mL) and extracted with hexane (30 mL × 3). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude allyl chloride **69** (2.95 g) was used for the next reaction without further purification.

THF was degassed by argon bubbling. An oven-dried two-necked flask was charged with magnesium turnings (945 mg, 38.9 mmol). The flask was heated by heat gun under reduced pressure for 10 min with vigorous stirring. The resultant activated magnesium was suspended in degassed THF (6.0 mL). To a stirred suspension of activated magnesium in THF was added 1,2-dibromoethane (100 μL, 1.30 mmol) at room temperature. After being stirred at 50 °C for 1.5 h, the mixture was added a solution of 4-bromo-2-methylbut-1-ene (3.99 g, 27.1 mmol) in THF (8.5 mL) at 50 °C via cannula and then rinsed (THF 500 μL × 1). The mixture was stirred at the same temperature for 4 h to give a THF solution of (3-methylbut-3-en-1-yl) magnesium

bromide, which was diluted with degassed THF (42.0 mL). The above-mentioned solution of (3-methylbut-3-en-1-yl)-magnesium bromide (57.1 mL, 27.1 mmol) was added slowly to a solution of crude allyl chloride **69** (2.95 g) and CuI (744 mg, 3.90 mmol) in degassed THF (15 mL) at −40 °C through by a syringe pump over 3 h. After being stirred at the same temperature for 1 h, the mixture was diluted with saturated aqueous NH_4Cl (100 mL) and stirred until turned blue. The mixture was extracted with hexane (50 mL × 3). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, *n*hexane) to afford diene **62** (2.25 g; containing a small quantity of impurity). **62** was used for next reaction without further purification.

The crude diene **62** (2.25 g) was dissolved in MeOH (30 mL) and CH_2Cl_2 (15 mL) and cooled to −78 °C. A stream of ozone in oxygen was gently bubbled through this solution for 2 h. The solution was purged with argon for 30 min, and then Me_2S (2.0 mL, 27.7 mmol) was added. The resultant mixture was allowed to warm to room temperature and stirred for 1 h. Removal of the solvent afforded the crude product, which was purified by column chromatography on silica gel (40 g, *n*hexane−EtOAc 40:1) to afford diketone **84** (1.39 g, 40% in three steps) as a colorless oil. The spectral data were in full agreement with those of our authentic sample.

(3a*S*,5a*S*,9a*S*)-1,6,6,9a-Tetramethyl-3,3a,4,5,5a,6,7,8,9,9a-decahydro-2H-cyclopenta[a]naphthalene (61).

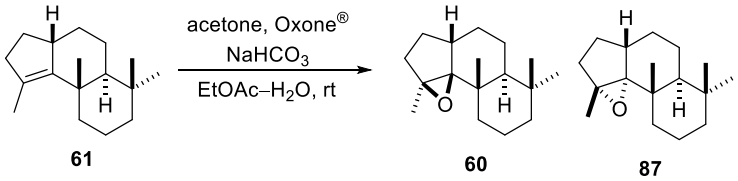


84 **61**

THF was degassed by argon bubbling. To a stirred degassed THF (15 mL) was added $TiCl_4$ (1.00 M solution in CH_2Cl_2, 3.78 μL, 3.78 μmol) at 0 °C under an argon flow. After being stirred at the same temperature for 20 min, to the resultant $TiCl_4$ solution were added Zn (500 mg, 7.64 mmol) and pyridine (105 μL, 371 μmol). The resultant mixture was stirred at reflux for 2 h and added to a solution of diketone **84** (96.9 mg, 366 μmol) in THF (10 mL) at the same temperature through by a syringe pump over 1 h. After being stirred at the same temperature for 13 h, the mixture was diluted with 10% aqueous K_2CO_3 (10 mL) and stirred until turning green. The resultant mixture was filtered through a pad of Celite. The filtrate was extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1 g, *n*hexane) to afford tricyclic compound **61** (53.4 mg, 63%) as a colorless oil: $[\alpha]_D^{24}$ −56.9 (*c* = 0.86, $CHCl_3$); IR (neat) 2930, 2864, 1460, 1387, 1371, 1329, 1204, 1008, 963 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.71 (m, 1H), 2.27−2.16 (m, 2H), 2.06 (ddd, *J* = 12.6, 4.8, 2.8 Hz, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.77 (s, 3H), 1.71 (ddd, *J* = 13.1, 13.1, 4.1 Hz, 1H), 1.65−1.57 (m, 2H), 1.43−1.34 (m, 2H), 1.20 (dd, *J* = 13.1, 4.1 Hz, 1H), 1.18−1.10 (m, 2H),

1.08 (s, 3H), 1.05 (dd, J = 12.4, 2.0 Hz, 1H), 0.98 (m, 1H), 0.85 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.2, 124.8, 53.9, 45.5, 42.1, 40.72, 40.69, 39.2, 37.0, 33.8, 33.6, 29.2, 22.4, 21.9, 20.5, 19.0, 16.2; HRMS (APCI) *m/z* 233.2252, calcd for $C_{17}H_{29}$ $[M+H]^+$ 233.2264.

(2a*S*,4a*S*,8a*S*,8b*S*,9a*S*)-5,5,8a,9a-Tetramethyldodecahydrobenzo[6,7]indeno[1,7a-b]oxirene (60) and (2a*S*,4a*S*,8a*S*,8-b*R*,9a*R*)-5,5,8a,9a-tetramethyldodecahydrobenzo[6,7]indeno[1,7a-b]oxirene (87).



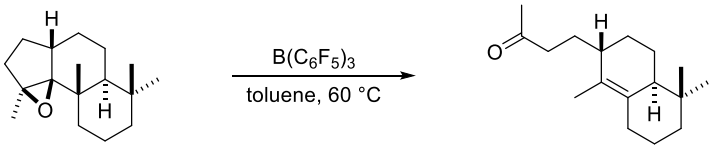
61 **60** **87**

To a mixture of tricyclic compound **61** (103 mg, 0.445 mmol) and $NaHCO_3$ (181 mg, 2.14 mmol) were added EtOAc (300 μL) and acetone (330 μL). The reaction mixture was added to 0.520 M aqueous oxone (1.77 mL, 922 μmol) at the same temperature through by a syringe pump over 1 h. After being stirred at the same temperature for 1 h, the mixture was diluted with saturated aqueous Na_2CO_3 (3 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, ^{n}hexane−Et_2O 200:1) to afford desired epoxide **60** (42.7 mg, 39%) and its diastereomer **87** (34.5 mg, 31%) as a colorless oil, respectively.

Desired epoxide **60**: $[\alpha]^{21}_D$ −16.6 (*c* = 1.10, $CHCl_3$); IR (neat) 2942, 2868, 1462, 1420, 1377, 1366, 1308, 1206, 1196, 1088, 1026, 1011, 968, 909, 870, 677 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21 (ddd, *J* = 13.1, 7.8, 5.3 Hz, 1H), 1.77−1.70 (m, 3H), 1.63 (ddd, *J* = 13.4, 6.7, 3.1 Hz, 1H), 1.60 (s, 3H), 1.55−1.51 (m, 2H), 1.50−1.36 (m, 5H), 1.29 (m, 1H), 1.15 (d, *J* = 0.7 Hz, 3H), 1.10 (dd, *J* = 12.5, 2.9 Hz, 1H), 1.05 (dd, *J* = 13.1, 4.0 Hz, 1H), 0.95 (ddd, *J* = 12.6, 7.6, 1.6 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 78.7, 71.1, 53.7, 42.5, 39.4, 38.6, 34.3, 33.7, 33.5, 33.4, 31.3, 24.0, 22.3, 21.7, 18.8, 18.5, 18.3; HRMS (ESI) *m/z* 271.2024, calcd for $C_{17}H_{28}O$ $[M+Na]^+$ 271.2032.

Undesired epoxide **87**: $[\alpha]^{21}_D$ −40.8 (*c* = 1.10, $CHCl_3$); IR (neat) 2922, 2868, 1449, 1418, 1375, 1304, 1263, 1198, 1171, 1121, 1069, 1040, 1022, 982, 974, 907, 882, 864, 853, 702, 691, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.02 (dddd, *J* = 12.3, 10.0, 7.5, 4.8 Hz, 1H), 1.81 (dddd, *J* = 12.3, 4.8, 3.2, 3.2 Hz, 1H), 1.71 (dd, *J* = 13.7, 8.1 Hz, 1H), 1.67 (m, 1H), 1.59 (m, 1H), 1.56−1.48 (m, 2H), 1.49 (s, 3H), 1.45−1.35 (m, 3H), 1.32 (ddd, *J* = 12.7, 5.8, 3.2 Hz, 2H), 1.29 (dd, *J* = 12.3, 2.1 Hz, 1H), 1.24 (dd, *J* = 12.3, 3.9 Hz, 1H), 1.20 (dd, *J* = 12.6, 4.3 Hz, 1H), 1.12 (d, *J* = 0.5 Hz, 3H), 0.87 (m, 1H), 0.87 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 69.5, 50.8, 41.6, 38.12, 38.08, 34.4, 33.42 (2C), 33.3, 33.2, 29.9, 25.0, 21.9, 21.7, 19.4, 18.3, 17.2; HRMS (ESI) *m/z* 271.2026, calcd for $C_{17}H_{28}O$ $[M+Na]^+$ 271.2032.

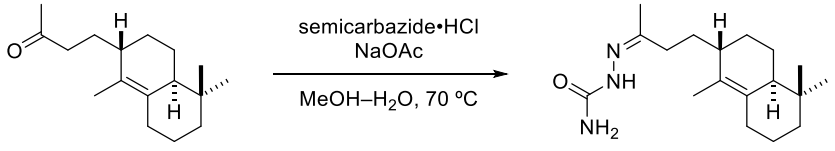
4-((2*S*,4a*S*)-1,5,5-Trimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-yl)butan-2-one (60).



60 **88**

To a stirred solution of desired epoxide **60** (61.4 mg, 247 μmol) in toluene (1.7 mL) was added a solution of $B(C_6F_5)_3$ (247 mg, 482 μmol) in toluene (1.0 mL) at room temperature. After being stirred at 60 °C for 22 h, the reaction mixture was cooled to room temperature, diluted with water (1 mL), and cooled to 0 °C. The resultant mixture was diluted with saturated aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2 g, *n*hexane−Et_2O 100:1) to afford ring-cleavage compound **88** (59.9 mg, 98%) as a colorless oil: $[\alpha]^{24}_{D}$ −4.4 (*c* = 0.14, $CHCl_3$); IR (neat) 2924, 2864, 1717, 1456, 1362, 1260, 1159, 1095, 1020, 800, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.67 (d, *J* = 13.7 Hz, 1H), 2.42 (ddd, *J* = 16.5, 10.0, 5.2 Hz, 1H), 2.35 (ddd, *J* = 16.5, 9.7, 6.2 Hz, 1H), 2.14 (s 3H), 1.88−1.82 (m, 2H), 1.73 (d, *J* = 5.5 Hz, 1H), 1.69−1.63 (m, 4H), 1.62−1.54 (m, 2H), 1.52 (m, 1H), 1.48−1.30 (m, 5H), 1.18 (m, 1H), 0.92 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.6, 132.1, 128.3, 46.5, 42.8, 41.7, 39.5, 35.9, 30.4, 30.1, 29.9, 26.4, 25.9, 22.7, 21.4, 20.8, 17.3; HRMS (ESI) *m/z* 271.2019, calcd for $C_{17}H_{28}O$ $[M+Na]^+$ 271.2032.

(*E*)-2-(4-((2*S*,4a*S*)-1,5,5-Trimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-yl)butan-2-ylidene)hydrazine-1-carboxamide (90).



88 **90**

A mixture of ring-cleavage compound **88** (17.2 mg, 69.2 μmol), semicarbazide hydrochloride (75.0 mg, 672 μmol), 2.0 M aqueous AcONa (0.75 mL), and EtOH (0.75 mL) was stirred at 70 °C for 20 min. The reaction mixture was diluted with H_2O (3.0 mL) at 70 °C and cooled to 0 °C. The resultant mixture was filtrated under reduced pressure to give crude yellow solid. The residual solid was recrystallized from $CHCl_3$–*n*hexane to afford semicarbazone **90** (10.2 mg, 48%) as colorless crystals: $[\alpha]^{24}_{D}$ +9.7 (*c* = 0.20, $CHCl_3$); mp 145.9−147.4 °C; IR (neat) 3534, 3470, 3212, 3012, 2928, 2864, 1694, 1580, 1435, 1375, 1261, 1103, 1069, 1018, 754, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.19 (brd. s, 1H), 4.74 (brd. s, 1H), 2.67 (m, 1H), 2.26 (ddd, *J* = 14.8, 10.4, 5.2 Hz, 1H), 2.16 (ddd, *J* = 14.8, 10.2, 6.2 Hz, 1H), 1.86 (brd. s, 1H), 1.80 (s, 3H), 1.77 (m, 1H), 1.68−1.64 (m, 4H), 1.62−1.56 (m, 2H), 1.53 (m, 1H), 1.47−1.41 (m, 2H), 1.41−1.29 (m, 3H), 1.30−1.24 (m, 2H), 0.93 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 157.3, 150.7, 132.0, 128.3, 46.4, 42.9, 39.6, 36.7, 35.9, 30.5, 30.1, 28.8, 25.7, 22.8, 21.5, 20.6, 17.5, 15.0; HRMS (ESI) *m/z* 328.2356, calcd for $C_{18}H_{31}N_3O$ $[M+Na]^+$ 328.2359.

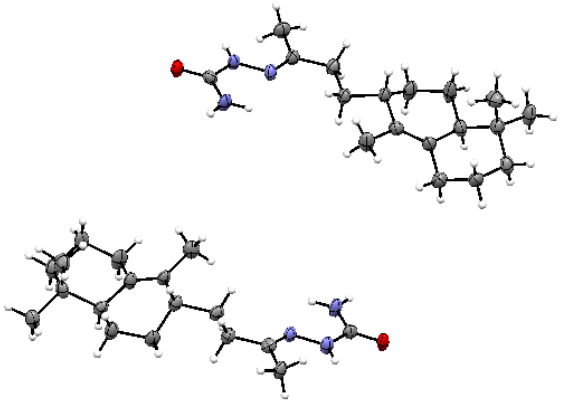
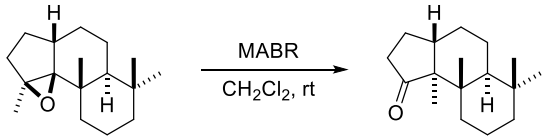


Figure 9. X-ray crystallographic structure of semicarbazone **90**.

(3a*S*,5a*S*,9a*S*,9b*S*)-6,6,9a,9b-tetramethyldodecahydro-1Hcyclopenta[a]naphthalen-1-one (59).



60 **59**

To a stirred solution of 4-bromo-2,6-di-tert-butylphenol (315 mg, 1.10 mmol) in CH_2Cl_2 (2.7 mL) was added a solution of Me_3Al (2.0 M solution in toluene, 270 μL, 540 μmol) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was cooled to −78 °C and added to a solution of desired epoxide **60** (43.4 mg, 0.175 mmol) in CH_2Cl_2 (1.5 mL) via cannula and then rinsed (THF 500 μL × 1). The mixture was allowed to warm to room temperature. After being stirred at room temperature for 1 h, the reaction mixture was diluted with 10% aqueous HCl (1 mL) and extracted with CH_2Cl_2 (2 mL × 3). The combined extracts were washed with brine (3 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2 g, nhexane−Et_2O 800:1 → 400:1 → 200:1) to afford mixture of desired rearrangement compound 6 and ring-cleavage compound 26 (34.4 mg, 79%, **59**:**8** = 5:1) as a yellow solid. The mixture of **10**:**82** was separated by next reaction.

A mixture of **59** and **88** (34.4 mg, **59**:**88** = 5:1), 2.0 M aqueous AcONa (0.50 μL), and EtOH (0.50 μL) was added to semicarbazide hydrochloride (309 mg, 277 μmol) at room temperature. After being stirred at 70 °C for 20 min, the reaction mixture was diluted with H_2O (3 mL) at the same temperature. The mixture was extracted with CH_2Cl_2 (2 mL × 3). The combined extracts were washed with brine (3 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1 g, ^{n}hexane−Et_2O 100:1) to afford desired rearrangement compound **59** (26.9 mg, 62% in two steps) as a yellow solid:

$[\alpha]^{21}{}_{D}$ −73.9 (*c* = 0.68, $CHCl_3$); mp 70.6−71.1 °C; IR (neat) 3019, 2951, 2870, 2400, 1726, 1476, 1458, 1375, 1215, 1022, 754, 669, 590 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.29 (dd, *J* = 19.2, 8.3 Hz, 1H), 2.20 (ddd, *J* = 12.5, 6.1, 3.4 Hz, 1H), 2.08 (ddd, *J* = 13.4, 5.4, 3.6 Hz, 1H), 1.98 (dddd, *J* = 19.2, 9.6, 9.6, 0.7 Hz, 1H), 1.77 (dddd, *J* = 12.3, 9.1, 6.1, 0.7 Hz, 1H), 1.68 (ddd, *J* = 12.8, 6.5, 3.5 Hz, 1H), 1.66−1.55 (m, 2H), 1.50 (m, 1H), 1.44−1.32 (m, 4H), 1.31−1.22 (m, 2H), 1.13 (ddd, *J* = 13.4, 13.4, 3.5 Hz, 1H), 0.98 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 221.6, 55.9, 47.2, 42.5, 40.5, 39.8, 37.6, 34.1, 33.4, 32.7, 26.1, 23.8, 22.6, 21.5, 18.6, 17.4, 10.4; HRMS (ESI) *m/z* 271.2033, calcd for $C_{17}H_{28}O$ $[M+Na]^+$ 271.2032.

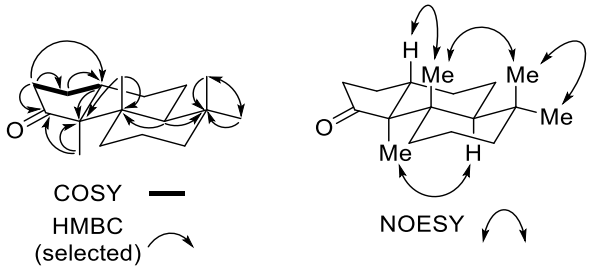
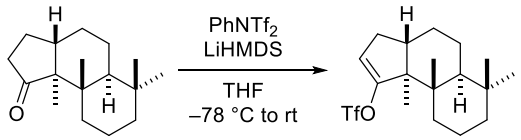


Figure 10. COSY, HMBC and NOESY spectrum of ketone **59**

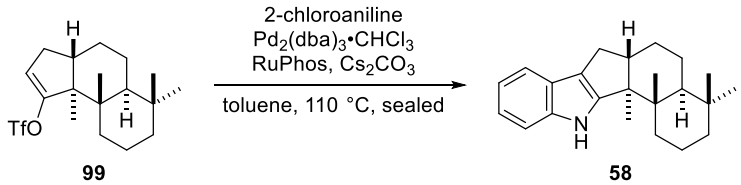
(3a*S*,5a*S*,9a*S*,9b*S*)-6,6,9a,9b-tetramethyl-3a,4,5,5a,6,7,8,9,9a,9bdecahydro-3H-cyclopenta[a]naphthalen-1-yl trifluoromethanesulfonate (99).



To a stirred solution of ketone **59** (32.0 mg, 129 μmol) in THF (2.0 mL) was added LHMDS (1.0 M solution in THF, 0.330 mL, 0.330 mmol) at −78 °C. After being stirred at the same temperature for 1 h, the reaction mixture was added to a solution of $PhNTf_2$ (182 mg, 0.509 mmol) in THF (2.0 mL) and allowed to warm to room temperature. After being stirred at room temperature for 1.5 h, the resultant mixture was added to MeOH (1.0 mL), Et_3N (0.20 mL), DMAP (32.5 mg), and acetone (15 mL) at room temperature. After being stirred at room temperature for 1.5 h, the resultant mixture was diluted with saturated aqueous NH_4Cl (2 mL) and extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1 g, *n*hexane → *n*hexane−Et_2O 1000:1) to give enol triflate **99** (34.2 mg, 70%) as a colorless oil:$[\alpha]^{18}{}_{D}$ −20.9 (*c* = 1.00, $CHCl_3$); IR (neat) 2940, 2866, 1626, 1458, 1422, 1391, 1379, 1248, 1211, 1142, 1055, 939, 897, 864, 829, 804, 766, 729, 633, 600 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.52 (dd, *J* = 3.2, 1.8 Hz, 1H), 2.29 (m, 1H), 2.16 (ddd, *J* = 15.1, 6.9, 3.4 Hz, 1H), 1.97 (ddd, *J* = 14.5, 11.0, 2.0 Hz, 1H), 1.68 (ddd, *J* = 13.1, 6.2, 3.4 Hz, 1H), 1.69−1.56 (m, 3H), 1.49−1.34 (m, 4H), 1.29−1.20 (m, 2H), 1.14 (ddd, *J* = 13.7, 13.7, 4.1 Hz, 1H), 1.06 (s, 3H), 1.05 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

158.6, 117.8 (J_{CF3} = 317 Hz), 114.0, 54.5, 47.0, 42.8, 42.4, 39.5, 34.1, 33.5, 33.1, 30.2, 24.8, 23.1, 21.1, 18.9, 17.9, 12.0; HRMS (ESI) *m/z* 403.1522, calcd for $C_{18}H_{27}F_3O_3S$ $[M+Na]^+$ 403.1525.

(4a*S*,6a*S*,12b*S*,12c*S*)-4,4,12b,12c-tetramethyl-1,2,3,4,4a,5,6,6a,7,12,12b,12c-dodecahydrobenzo[6,7]indeno[1,2-b]indole (58).



99 **58**

In a 10 mL high pressure glass vial, to a mixture of RuPhos (22.9 mg, 49.1 μmol), $Pd_2(dba)_3 \cdot CHCl_3$ (8.9 mg, 8.60 μmol), and Cs_2CO_3 (96.9 mg, 0.297 mmol) was added toluene (0.10 mL). After being stirred at room temperature for 30 min, the mixture was added to a solution of enol triflate **99** (34.2 mg, 89.9 μmol) and 2-chloroaniline (9.4 μL, 89.9 μmol) in toluene (0.10 mL). The resultant mixture was stirred at 110 °C. After being stirred at the same temperature for 23.5 h, the mixture was cooled to room temperature, diluted with degassed hexane (0.10 mL). The resultant mixture was purified by column chromatography on silica gel (1.5 g, *n*hexane−Et_2O 400:1 → 200:1) under nitrogen to afford indole **58** (19.7 mg, 68%) as a yellow solid. X-ray Analytical sample of indole **58** was prepared by recrystallization from Et_2O−*n*hexane: $[\alpha]^{18}{}_D$ −13.0 (*c* = 0.35, $CHCl_3$); mp 175.2 °C (decomposed); IR (neat) 3478, 3019, 2930, 2853, 2400, 1456, 1389, 1377, 1300, 1260, 1215, 1045, 928, 756, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.42 (m, 1H), 7.29 (m, 1H), 7.01−7.05 (m, 2H), 2.71 (m, 1H), 2.65 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.32 (dd, *J* = 13.1, 10.7 Hz, 1H), 1.84−1.72 (m, 4H), 1.63 (m, 1H), 1.56 (m, 1H), 1.52 (m, 1H), 1.45 (m, 1H), 1.36 (m, 1H), 1.30−1.18 (m, 2H), 1.09 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.4, 139.8, 125.1, 120.2, 119.4, 118.3, 118.1, 111.4, 52.9, 48.9, 46.8, 42.5, 39.7, 35.6, 33.9, 33.4, 27.5, 25.7, 23.3, 21.2, 19.1, 18.5, 14.5; HRMS (ESI) *m/z* 344.2340, calcd for $C_{23}H_{31}N$ $[M+Na]^+$ 344.2349.

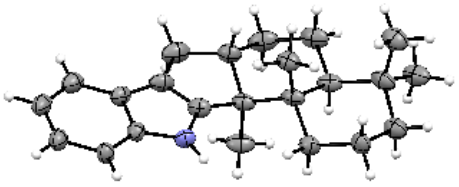


Figure 11. X-ray crystallographic structure of indole **58**

Chapter 3. Development of Convergent Synthetic Method toward Natural Products with Bicyclo[3.2.1]octane Core

3-1. Abstract

Aiming to develop a novel annulation method utilizing a bicyclo[3.2.1]octane ring as a building block for constructing natural product frameworks, research was undertaken. Initial efforts focused on synthesizing a precursor for radical-polar crossover annulation; however, the desired product could not be obtained. Therefore the strategy shifted to radical cyclization. Despite these attempts, generating a radical at the bridgehead position of the bicyclo[3.2.1]octane ring was unsuccessful. This difficulty is likely attributed to the rigidity of the bicyclo[3.2.1]octane ring and the high strength of the C–O bond.

3-2. Introduction

3-2-1. Natural products with bicyclo[3.2.1]octane ring

Many diterpenoids isolated from plants of the Ericaceae family contain a bicyclo[3.2.1]octane ring system.[1)] Natural products with this structural framework are classified into several groups based on their fused ring systems, including gibberellins, *ent*-kauranes, leucothanes, and grayananes (Figure 1). These compounds, characterized by multiple stereocenters and diverse oxygen functional groups, exhibit unique and potent biological activities, such as anti-inflammatory, antifungal, antiviral, and insecticidal properties.[2)] Due to their intricate structures and significant biological activities, this family of compounds has captivated the interest of chemists for decades.

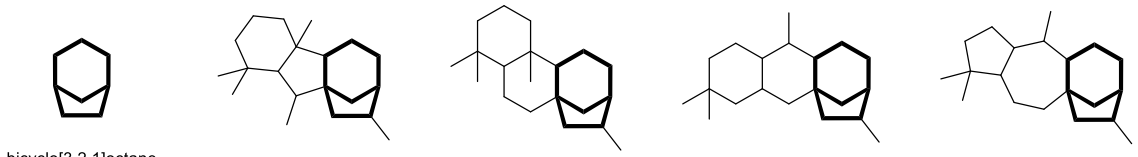
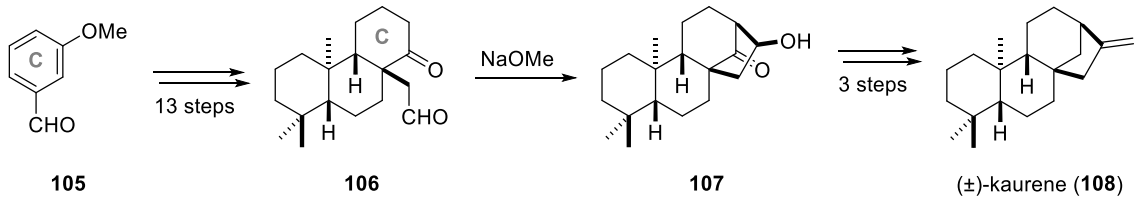


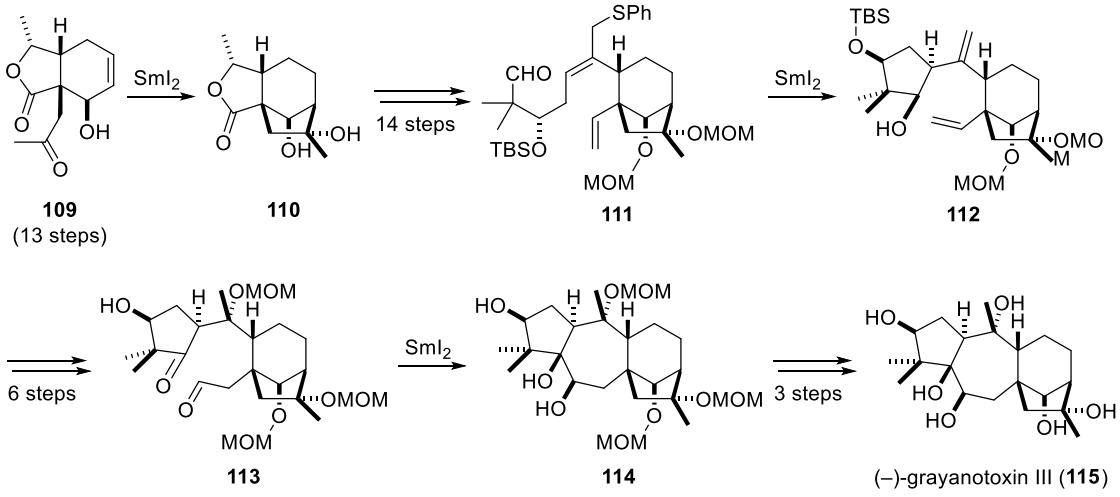
Figure 1. Natural products with bicyclo[3.2.1]octane ring

In the context of the total synthesis of natural products with the bicyclo[3.2.1]octane ring, traditional approaches have generally followed two main linear strategies[3)]: 1) constructing the fused tricyclic framework (perhydrophenanthrene) first, followed by the formation of the bicyclo[3.2.1]octane ring, or 2) assembling the bicyclo[3.2.1]octane ring before extending the fused ring system. For example, Ireland and co-workers employed the first strategy by synthesizing a keto aldehyde **106** from 3-methoxybenzaldehyde **105** in 13 steps. The bicyclo[3.2.1]octane ring was subsequently constructed via an aldol reaction, yielding the *ent*-kaurane skeleton **107**. Functional group manipulations of this skeleton led to the total synthesis of (±)-kaurene (**108**) in an additional three steps (Scheme 1).[4)]



Scheme 1. Total synthesis of (±)-kaurene (**108**) by Ireland and co-workers

On the other hand, as a representative example of the second strategy, Shirahama and co-workers accomplished the total synthesis of (–)-grayanotoxin III (**115**) by constructing the bicyclo[3.2.1]octane ring **110** at an early stage. This was achieved using SmI_2-mediated reductive cyclization from a precursor **109**, which had been synthesized in 13 steps from a commercially available starting material. The building block **110** was subsequently converted into the natural product through a stepwise assembly of the ring system (Scheme 2).[5] These studies represent pioneering efforts in the synthesis of complex natural products with the bicyclo[3.2.1]octane ring and have made significant contributions to the advancement of the field. However, these syntheses often follow lengthy and linear pathways. While effective for the production of specific compounds, they are less adaptable for synthesizing a wider range of structurally related analogs.

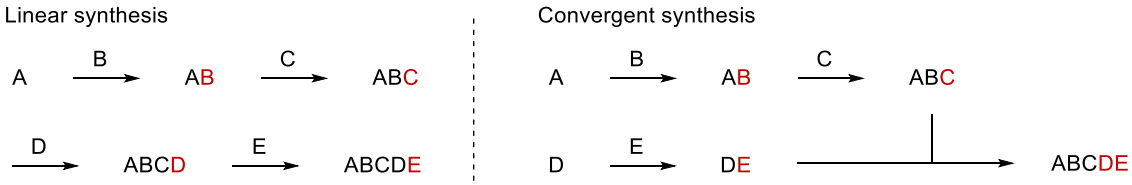


Scheme 2. Total synthesis of (–)-grayanotoxin III (**115**) by Shirahama and co-workers

3-2-2. Convergent synthetic strategy

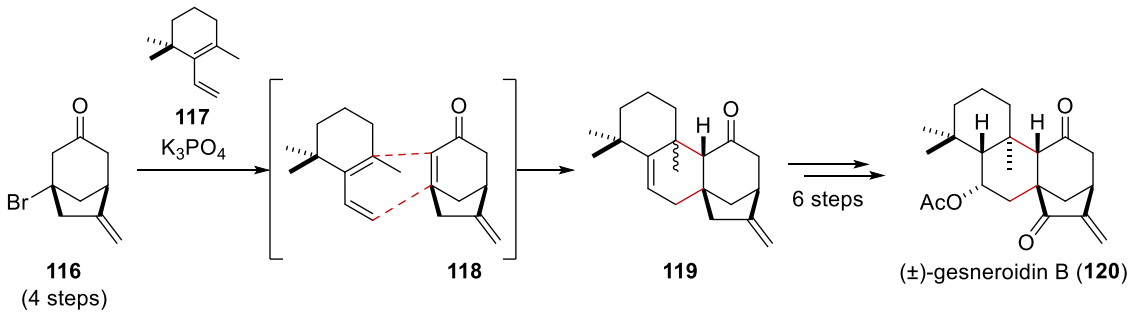
The routes toward the total synthesis of natural products can be broadly categorized into two major strategies: linear synthesis and convergent synthesis. Linear synthesis involves constructing the natural product skeleton from a simple starting material by sequentially connecting multiple building blocks. For example, the synthesis of a compound composed of ABCDE units begins with the reaction of A and B to form AB, followed by the sequential addition of C, D, and E (Scheme 3). The total synthesis examples discussed in Section 3-2-1 belong to this category. Conversely, convergent synthesis employs the coupling of larger,

advanced segments, such as ABC and DE, which are synthesized separately before the coupling stage. Assuming a yield of 70% per step, the overall yields for these methods are 24% for linear synthesis and 34% for convergent synthesis. As the number of steps increases, convergent synthesis provides higher overall yields. Furthermore, convergent synthesis enables the parallel preparation of segments ABC and DE, reducing the overall synthesis time.



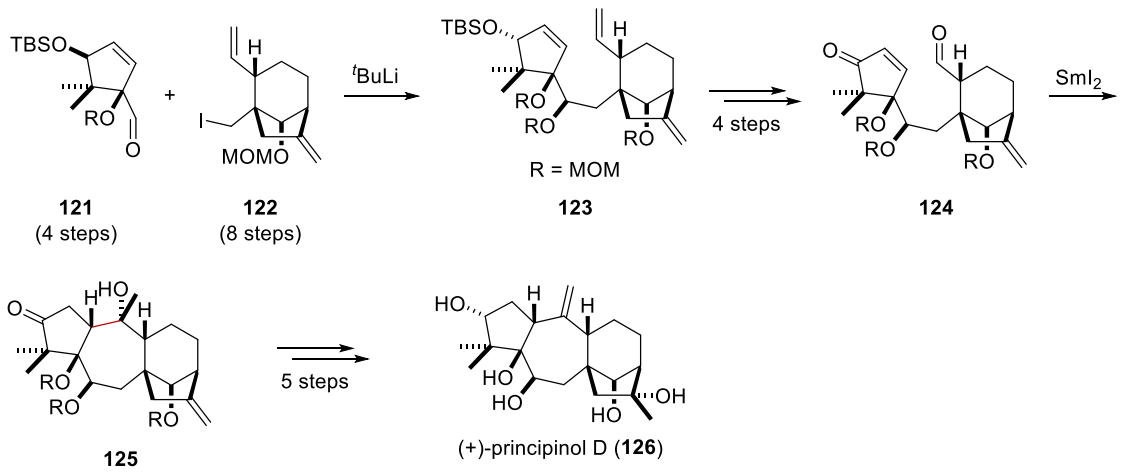
Scheme 3. Linear synthesis and convergent synthesis

The convergent synthetic strategy has also been employed in the synthesis of diterpenoids from the Ericaceae family. Recently, the convergent synthesis of *ent*-kaurane and grayanane diterpenoids utilizing the bicyclo[3.2.1]octane ring as a key building block has garnered significant attention. For instance, Ma and co-workers utilized a strained enone **118** as a reactive fragment of the bicyclic core. The enone **118** was generated *in situ* from bromide **116** through K_3PO_4 mediated elimination and subsequently applied to a Diels–Alder reaction with diene **117**, effectively constructing the *ent*-kaurane skeleton **119** (Scheme 4).[6] In 2022, Ma and colleagues also accomplished the convergent total synthesis of Napelline-type natural products using the bicyclo[3.2.1]octane ring as a building block.[7]



Scheme 4. Total synthesis of (±)-kaurene (**120**) by Ma and co-workers

Newhouse and co-workers reported the total synthesis of the grayanane diterpenoid principinol D (**126**) using a convergent coupling strategy (Scheme 5). In their approach, an aldehyde segment **121** was coupled with a bicyclo[3.2.1]octane unit **122** via the addition of an alkyl lithium reagent to the aldehyde. This was followed by an SmI_2-mediated reductive ring closure, yielding the grayanane skeleton **125**.[8] While these methods enable the short-step total synthesis of complex natural products, several challenges remain. For instance, Ma's approach is limited to the construction of six-membered rings, whereas Newhouse's method involves a multi-step coupling and cyclization sequence to form the central ring. Therefore, the development of a new convergent synthetic strategy that addresses these limitations is desirable.

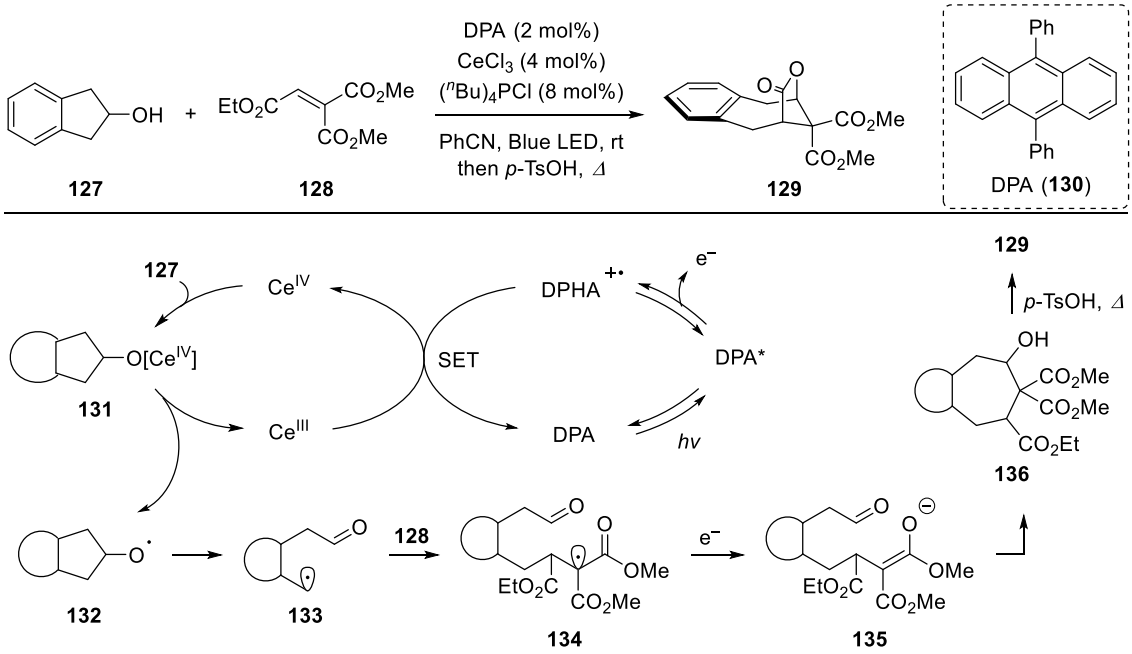


Scheme 5. Total synthesis of (+)-principinol D (**126**) by Newhouse and co-workers

3-2-3. Construction of cyclic structures via annulation reaction

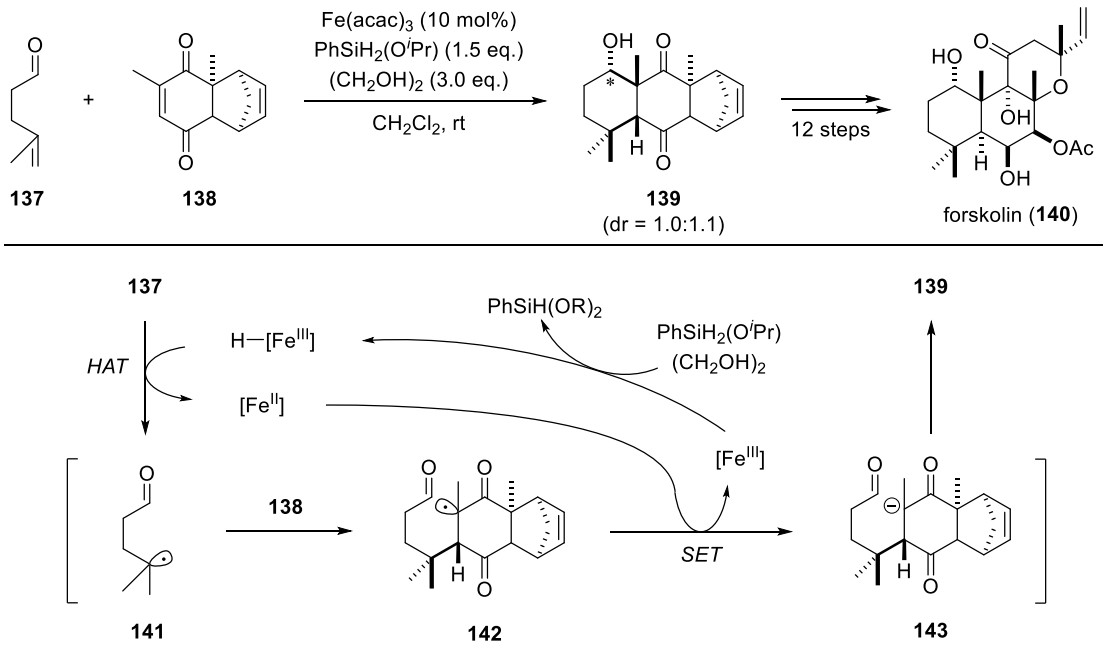
As demonstrated by Newhouse and co-workers' total synthesis, constructing cyclic structures from two molecules often requires multiple steps. This complexity arises because controlling reaction sites typically necessitates protection/deprotection steps and functional group transformations. For instance, in Newhouse's approach, the molecule design had to prevent deprotonation during the iodine–lithium exchange of **122**, and the resulting carbanion species needed to selectively undergo nucleophilic attack on the carbonyl group of **121**. Consequently, the carbonyl group used for the cyclization of **124** could not be introduced in advance, necessitating six steps from the coupling of the two components to cyclization. In contrast, annulation reactions, such as the Robinson annulation, provide an efficient method to combine coupling and cyclization into a single step. Employing annulation reactions in the synthesis of complex molecules is a powerful strategy. However, challenges related to functional group tolerance often arise, as seen in Newhouse's synthesis. To address this issue, radical-polar crossover reactions mediated by photoredox catalysts have emerged as a functional group-tolerant alternative within annulation reactions.[9] Radical-polar crossover reactions involve the generation of a radical species from one substrate, followed by radical coupling with another substrate. Subsequently, single-electron oxidation or reduction converts the radical intermediate into an ionic species, which then undergoes a polar reaction in a cascade manner. When mediated by photoredox catalysts, this process offers excellent functional group tolerance, redox neutrality, and mild reaction conditions. For example, Zuo and co-workers reported an annulation reaction between alcohol **127** and enone **128** under visible light irradiation, using DPA (**130**) and $CeCl_3$ as catalysts (Scheme 6).[10] This process begins with the formation of cerium(iv) alkoxide **131** from alcohol **127**, which undergoes homolytic cleavage to generate alkoxyl radical **132**. Fragmentation of the unstable alkoxyl radical produces carbon radical **133** through C–C bond cleavage, which undergoes Giese-type addition to the electron-poor alkene **128**. Subsequent single-electron reduction of the radical intermediate forms enolate **135**, driving aldol cyclization to afford cycloheptane ring **136**. Notably, this method provides a single-step

approach to construct a seven-membered ring-containing scaffold, which is challenging to synthesize using conventional pericyclic cycloaddition reactions.



Scheme 6. Photo-induced annulation reaction by Zuo and co-workers

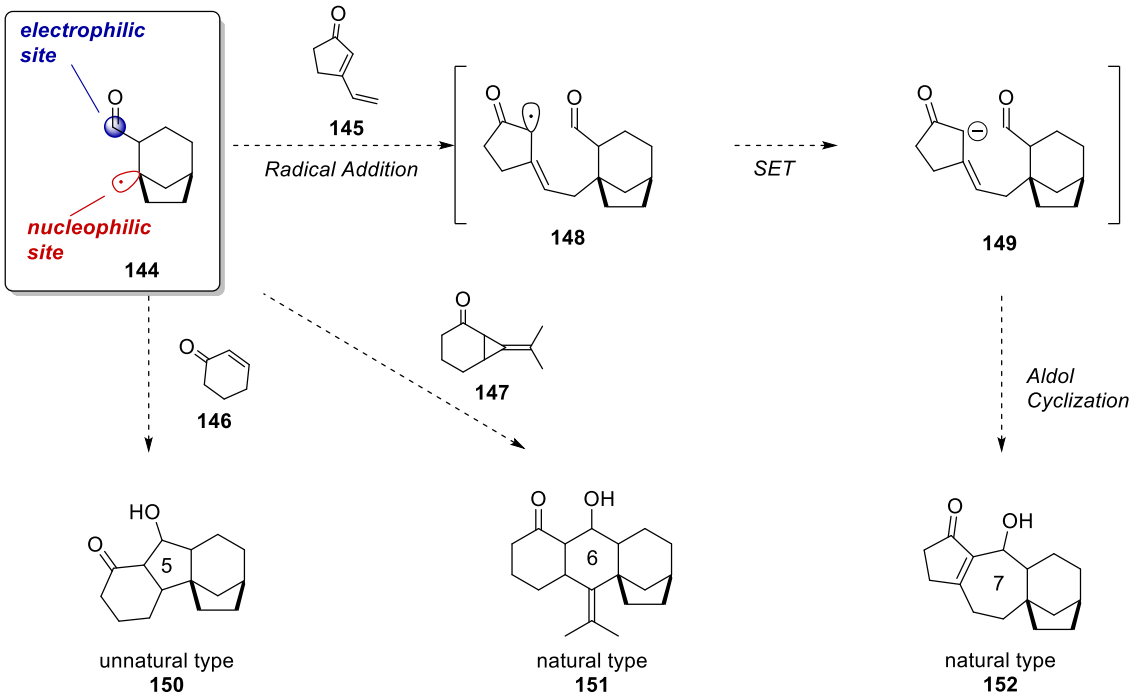
While photoredox catalysis is a widely used method for facilitating radical-polar crossover reactions, hydrogen atom transfer (HAT) has also been reported as an alternative approach to achieve these transformations. Pronin and co-workers developed a radical-polar crossover annulation of ene-aldehyde **137** and enone **138**, constructing a six-membered ring with a quaternary carbon center as a key step in the total synthesis of forskolin (**140**) (Scheme 7).[11] The cascade reaction is proposed to initiate with a metal-hydride hydrogen atom transfer (MHAT) involving an iron hydride complex generated from an iron(III) catalyst and hydrosilane. This step converts the gem-disubstituted alkene of **137** into a tertiary alkyl radical **141**. Addition of this radical to the alkene of **138** forms an electron-deficient radical **142**, which is subsequently reduced to enolate **143** via single-electron reduction. The enolate then undergoes an aldol cyclization, leading to the formation of **139**. As demonstrated in this section, radical-polar crossover annulative coupling is a powerful strategy for convergently coupling two fragments and constructing multicyclic frameworks that are inaccessible via traditional pericyclic cycloaddition reactions, such as the Diels–Alder reaction and 1,3-dipolar cycloaddition. Due to these advantageous features, the development and application of such reactions have gained significant attention in the field of expeditious total synthesis of complex natural products.



Scheme 7. HAT-induced annulation reaction by Pronin and co-worker

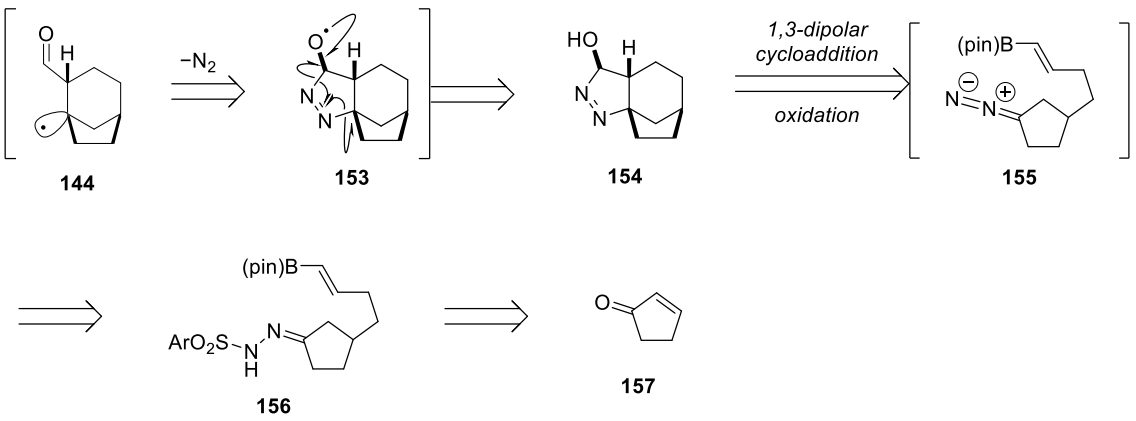
3-2-4. Synthetic strategy using bicyclo[3.2.1]octane as a building block

Inspired by the above reports, I hypothesized that applying this approach to a bicyclo[3.2.1]octane core could provide a novel synthetic strategy for natural products featuring the bicyclo[3.2.1]octane structure (Scheme 8). Specifically, I designed an active species with ampholytic character, possessing both a nucleophilic carbon radical and an electrophilic carbonyl group, such as **144**. I envisioned that this active species could undergo an addition/cyclization cascade reaction between two components in a single step. This reaction would proceed through radical addition to cyclic enones (**145**, **146**, or **147**), followed by a concomitant polar-type intramolecular cyclization after single-electron reduction. I further hypothesized that this approach could generate a variety of polycyclic molecules, including the grayanane skeleton **152**, the leucothane skeleton **151**, and the unnatural skeleton **150**, by altering the structure of the coupling partner. Additionally, the bridgehead radical of the bicyclo[3.2.1]octane scaffold is expected to construct a quaternary carbon center while preserving stereochemistry due to the inherent rigidity of the scaffold.



Scheme 8. Synthetic strategy based on the radical-polar crossover annulation of a bicyclo[3.2.1]octane building block

To realize this concept, I designed diazoalcohol **151** as a precursor for the radical species **144** (Scheme 9). I anticipated that if the alkoxyl radical **153** could be generated from the alcohol group of precursor **154**, β-scission of the carbon–nitrogen bond would occur concomitantly with denitrogenation, yielding radical species **144**. Precursor **154** would be constructed via an intramolecular 1,3-dipolar cycloaddition reaction of diazoalkane **155**, followed by oxidation of a boronic ester. Diazoalkane **155** would be generated *in situ* from hydrazone **156**, which can be synthesized from cyclopentenone **157**.

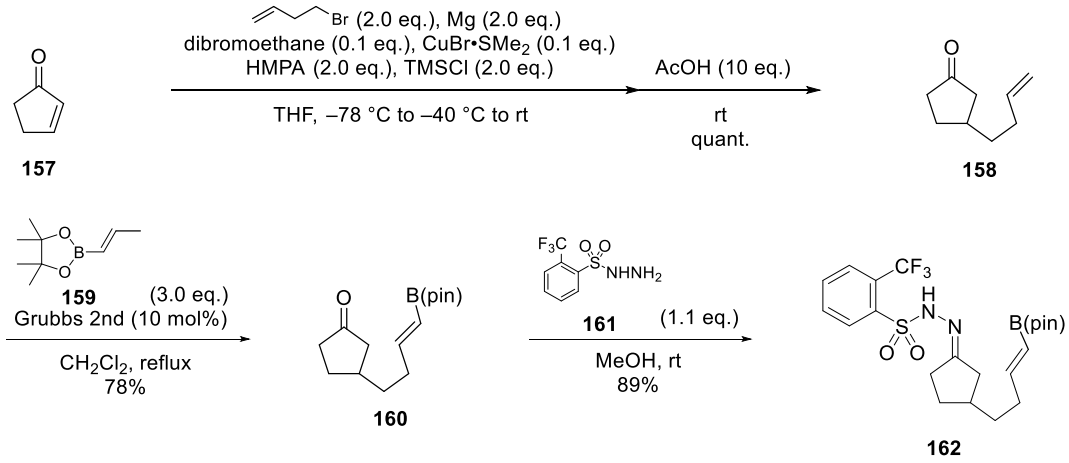


Scheme 9. retrosynthetic pathway of active species **144**

3-3. Results and discussions

3-3-1. Synthesis of precursor 154 via intramolecular 1,3-dipolar cycloaddition reaction

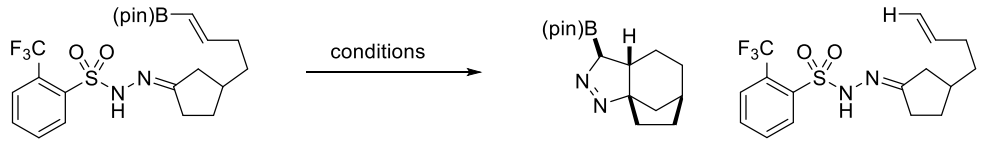
The synthesis of precursor **154** was commenced with a conjugate addition of cuprate to cyclopentenone **157**, affording ketone **158** (Scheme 10).[12] Subsequently, the cross-metathesis reaction between the terminal alkene of obtained ketone **158** and propenylboronic ester **159** yielded alkenyl boronic ester **159** in *E*-selective manner.[13] The ketone moiety of **160** was then converted to a 2-trifluoromethylbenzenesulfonyl hydrazone **162**, known to generate diazoalkane under mild conditions.[14]



Scheme 10. Synthesis of **154** for intramolecular 1,3-dipolar cycloaddition reaction

Next, I investigated the 1,3-dipolar cycloaddition reaction of the obtained hydrazone **162** (Table 1). Initially, following the report by Bi et al., I conducted the reaction under basic conditions in 1,4-dioxane.[14] Using cesium carbonate (entry 1) and sodium hydride (entry 2) as the base, the reaction resulted in the formation of a complex mixture. Given the difficulty in synthesizing the target compound under basic conditions, I decided to explore conditions using Lewis acids. Referencing the report by Rekers et al., I attempted the reaction in benzene with $BF_3 \cdot OEt_2$ (entry 3). However, the desired product was not obtained, and a complex mixture was obtained.[15] Because I detected the benzene adduct (detailed structure not determined) of the starting material in the mixture, in entry 4, I switched the solvent to 1,2-dichloroethane. In this case, only protodeborylated **164** was obtained.

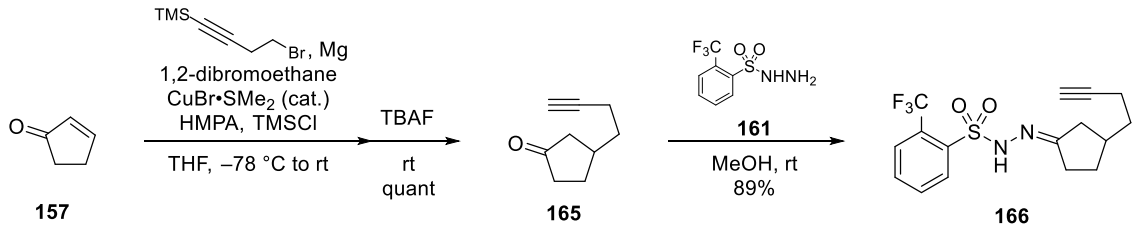
Table 1. Investigation of the 1,3-dipolar cycloaddition reaction using **162**



162 **163** **164**

entry	conditions			results
	reagent	solvent	temperature	
1	Cs_2CO_3	1,4-dioxane	80 ºC	complex mixture
2	NaH	1,4-dioxane	80 ºC	complex mixture
3	$BF_3{\cdot}OEt_2$	benzene/CH_2Cl_2	reflux	complex mixture
4	$BF_3{\cdot}OEt_2$	1,2-dichloroethane	reflux	**164**: 42%

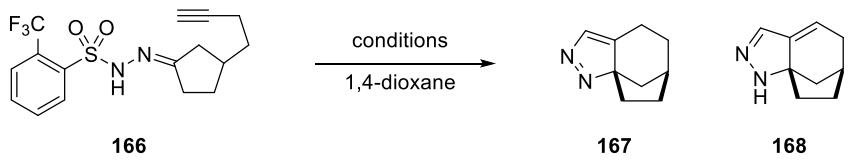
Given that the desired compound **163** could not be obtained from hydrazone **162** with a vinylboronic ester structure, I decided to investigate the cycloaddition reaction using an alkyne containing substrate **166**, which would produce **167** bearing 3H-pyrazole structure for the further functional group transformations. Using a method similar to that for the synthesis of alkene **162**, I synthesized alkyne **166** as a cyclization precursor (Scheme 11) and examined the cycloaddition reaction (Table 2). Under basic conditions, the reaction became complex, and the desired compound **167** was not obtained. Analysis of the products revealed that compounds **168** were detected in entry 2 where sodium hydride was used as the base. The result indicates that, although the 1,3-dipolar cycloaddition has proceeded, the product isomerized rapidly to a compound that cannot be converted to the designed radical precursor **168**. Consequently, I decided to modify our synthetic strategy.



157 **165** **166**

Scheme 11. Synthesis of **166** for intramolecular 1,3-dipolar cycloaddition reaction

Table 2. Investigation of the 1,3-dipolar cycloaddition reaction using **166**

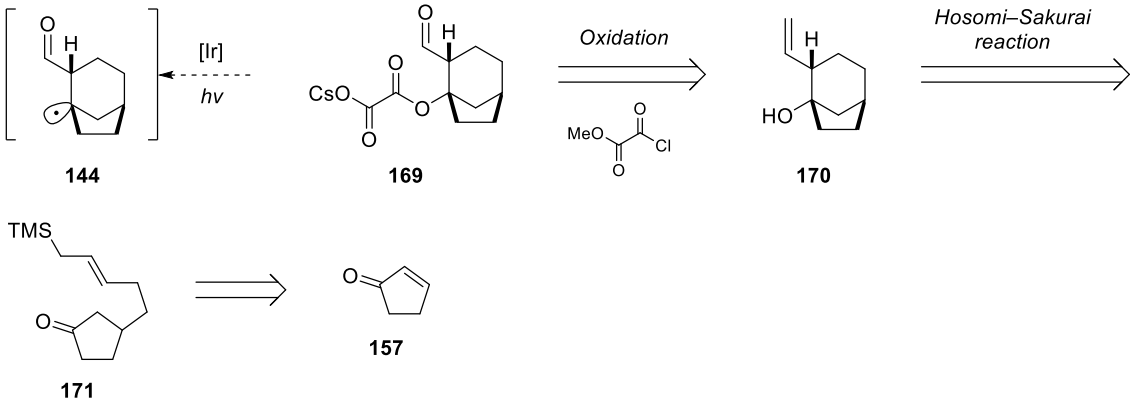


166 **167** **168**

entry	conditions		Results
	reagent	temperature	
1	Cs_2CO_3	90 ºC	complex mixture
2	NaH	reflux	complex mixture (including **168**)

3-3-2. Strategy using alcohol derivative with bicyclo[3.2.1]octane as a precursor of the radical species

I decided to use cesium oxalate ester **169** as a new precursor for the active species (Scheme 12). Cesium oxalate ester **169** is expected to generate the radical **144** upon activation by a photoredox catalyst.[16] Cesium oxalate ester **169** will be synthesized by oxidative cleavage of the alkene of alcohol **170,** followed by an introduction of the oxalate ester. Alcohol **170** will be obtained via the Hosomi–Sakurai reaction of allylsilane **171**, which is derived from cyclopentenone **157**.[17]



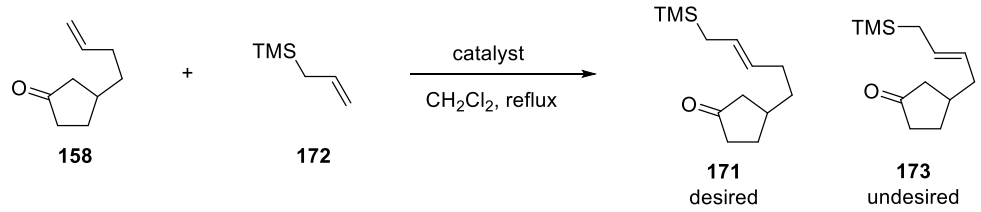
144 **169** **170** **171** **157**

Scheme 12. Synthesis of cesium oxalate ester **169**

I embarked on the synthesis of alcohol derivative **169** by the conversion of ketone **158** to **171** via a cross-metathesis reaction with allylsilane **172** (Table 3). The metathesis reaction was carried out under reflux conditions in dichloromethane using Grubbs 1st, Grubbs 2nd, or Hoveyda–Grubbs 2nd catalysts. Among these, Grubbs 1st catalyst provided the highest yield of the desired allylsilane 1**71**. Additionally, one carbon truncated compound **173** was obtained. This product would be formed by the isomerization of the double bond before undergoing metathesis. The ratio of **171** and **173** was depended on the catalyst, and with using Grubbs 2nd

catalyst, only the undesired allylsilane **173** was produced. When Hoveyda–Grubbs 2nd catalyst was employed, the desired allylsilane **171** was obtained, but the yield was lower than with Grubbs 1st. Due to the difficulty in separating the two allylsilanes **171** and **173** by silica gel column chromatography, I decided to alter the synthetic route.

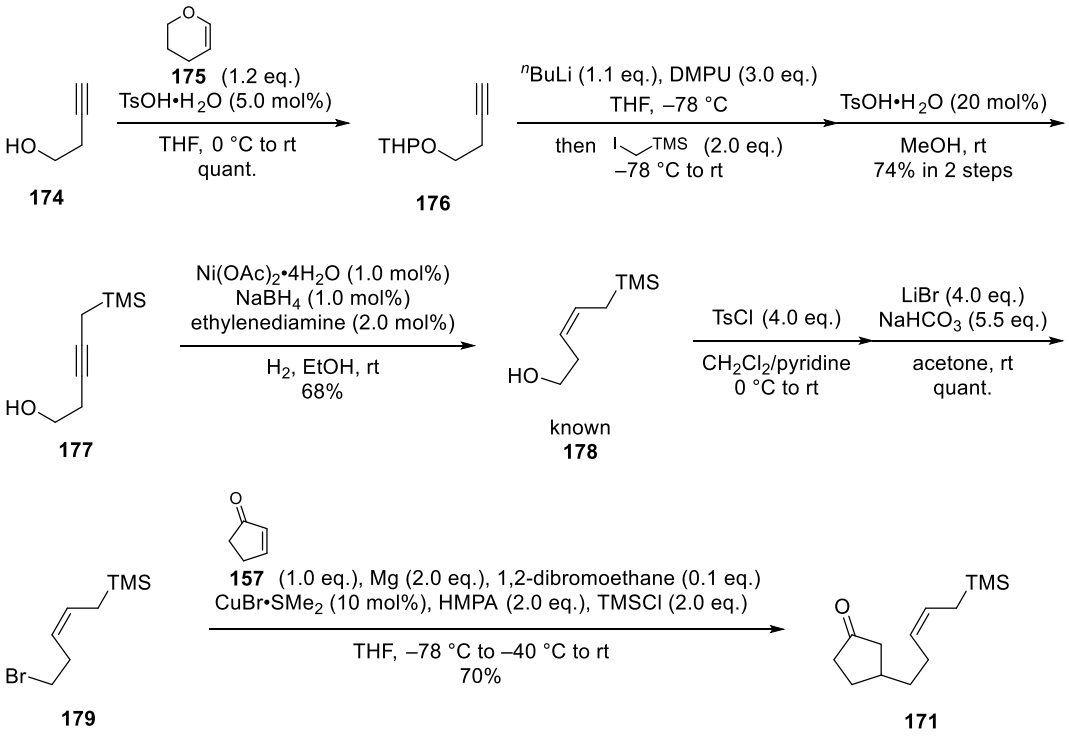
Table 3. Examination of cross-metathesis reaction



158 + **172** → **171** desired + **173** undesired

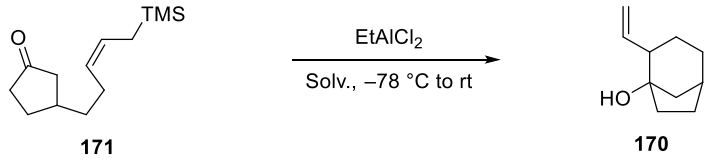
entry	catalyst	NMR yield		
		171	**173**	recovered **158**
1	Grubbs 1st	45%	22%	–
2	Grubbs 2nd	–	79%	–
3	Hoveyda–Grubbs 2nd	14%	35%	4%

Therefore, I decided to introduce the allylsilane-sidechain directly into cyclopentenone **157** (Scheme 13). Propargylsilane **177** was prepared from 3-butyn-1-ol following Aubé et al.'s procedure.[18] By following Speckamp et al.'s method, the alkyne was reduced to the alkene under a hydrogen atmosphere using nickel boride to give allylsilane **178**.[19] The primary alcohol was converted to homoallyl bromide **179** in two-steps. Addition of the cuprate generated from **179** to cyclopentenone afforded allylsilane **171**, a precursor for the Hosomi–Sakurai reaction. Hosomi–Sakurai reaction constructing bicyclo[3.2.1]octane was then examined. Based on Baran et al.'s report, I treated allylsilane **171** with $EtAlCl_2$ as a Lewis acid in toluene (Table 4). However, the desired product was not obtained, and compounds that likely reacted with toluene were produced.[17] The problem was solved by changing the solvent to dichloromethane, and desired alcohol **170** was obtained in 98% yield.



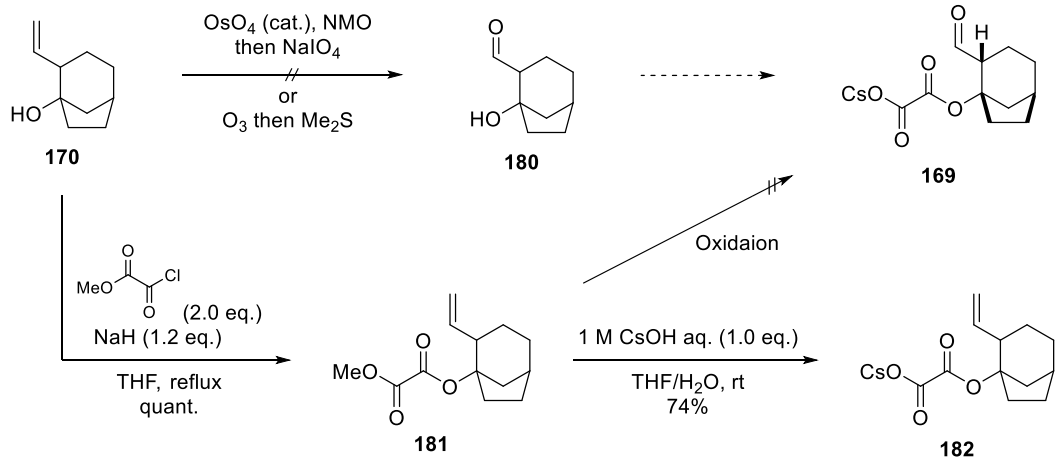
Scheme 13. Synthesis of allylsilane **171**

Table 4. Examination of Hosomi–Sakurai reaction of allylsilane **171**



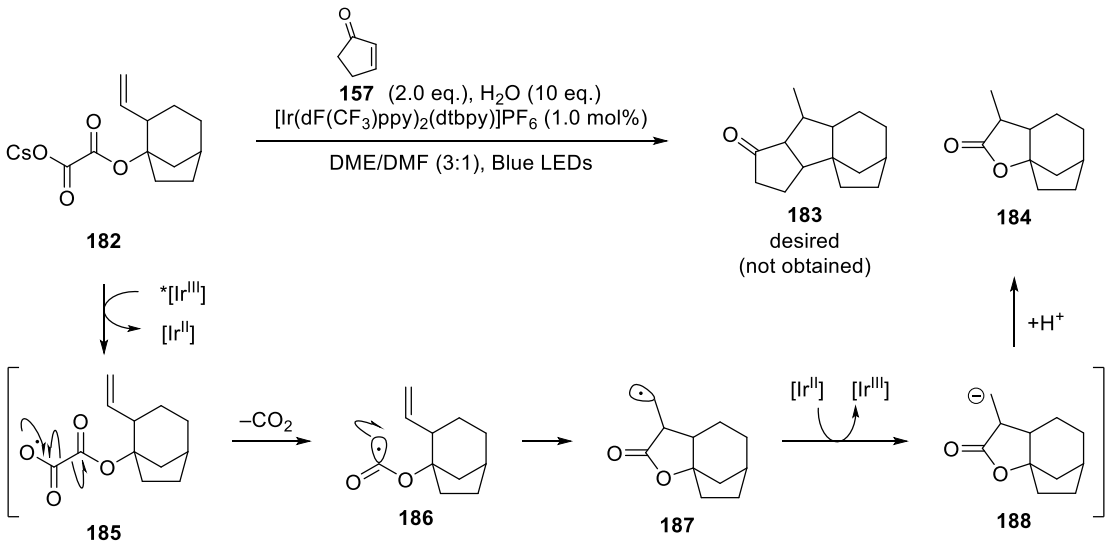
Entry	Solv.	Result
1	Toluene	Toluene adduct
2	CH_2Cl_2	98%

With bicyclic alcohol **170** in hand, I proceeded with the synthesis of precursor **169** (Scheme 14). Initially, I attempted to oxidize the alkene moiety of alcohol **170**, but neither dihydroxylation with OsO_4 followed by periodic acid cleavage nor ozonolysis yielded the desired oxidized product, and the starting material was decomposed. Therefore, I decided to introduce the oxalate ester before the oxidation of the alkene. Alcohol **170** was converted to oxalate diester **181** under basic conditions, and subjected to the oxidation of the alkene under the same conditions as above, unfortunately, the oxidation didn't produce the desired **169**, and again, decomposition was observed. Therefore, I abandoned the oxidation of the alkene moiety and shifted to a strategy utilizing radical reaction. The hydrolysis of the methyl ester group with cesium hydroxide produced cesium oxalate ester **182**.



Scheme 14. Synthesis of the precursor as a carbon radical

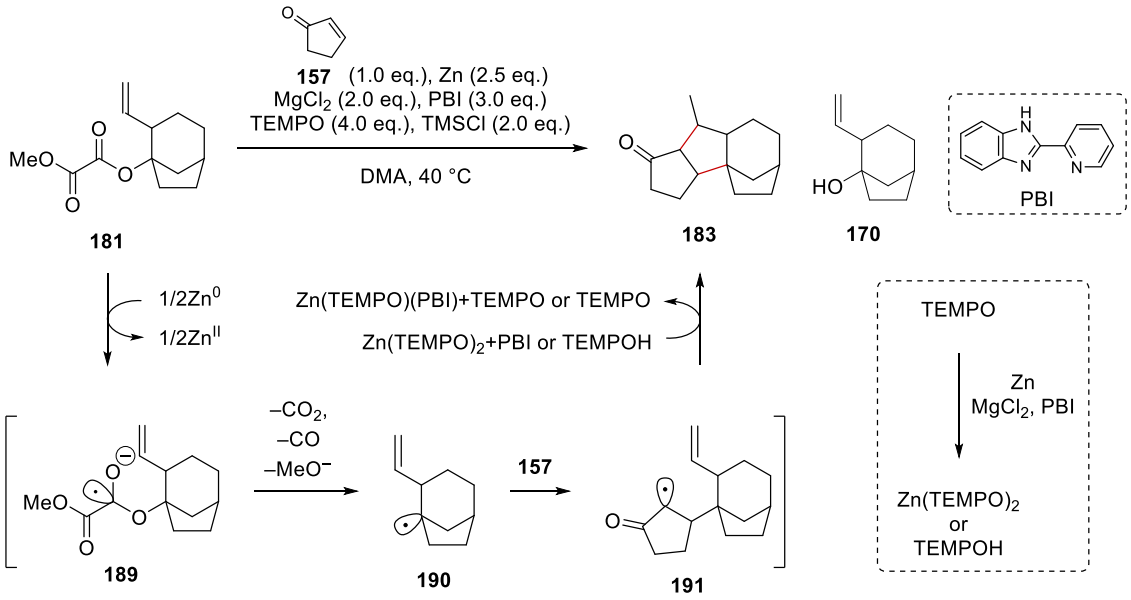
The key radical coupling was carried out using cesium oxalate ester **182** and cyclopentenone **157** (Scheme 15). Following the report by Macmillan, Overman, and co-workers, the reaction was conducted in a mixed solvent of DME and DMF under visible light irradiation in the presence of an iridium catalyst.[16] However, the desired radical coupling did not proceed and lactone **184** was obtained instead (29%). The lactone **184** would be generated by the decarboxylation of cesium oxalate ester **182,** forming a carbonyl radical **186**, followed by a 5-exo-*trig* cyclization before the second decarboxylation to give bridgehead radical. To promote the second decarboxylation and facilitate the desired reaction, I conducted the reaction under heating condition. However, this approach also resulted in either the formation of lactone **186** or the decomposition of the substrate.



Scheme 15. Radical coupling reaction of **182** with **157**

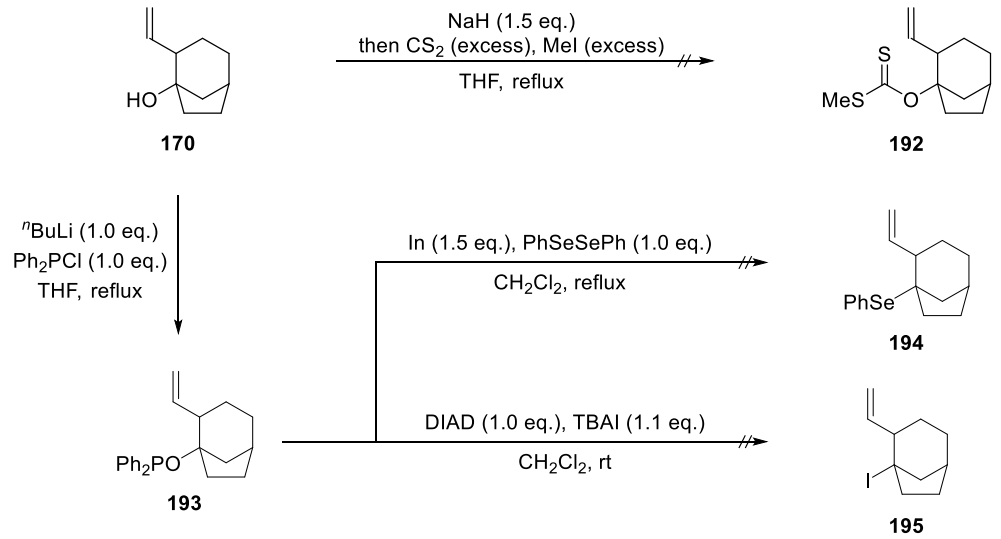
To avoid the generation of the carbonyl radical, I decided to use conditions that would directly eliminate the oxalate ester group (Scheme 16). Following the method reported by Li et

al., I conducted the reaction of **181** with **157**. The reaction is proposed to be initiated with the single-electron reduction of oxalate diester by Zn, leading to the radical C–O bond cleavage generating carbonyl radical with liberating methyl oxalate.[19] However, the desired radical coupling did not occur, and loss of the oxalate ester moiety was observed.



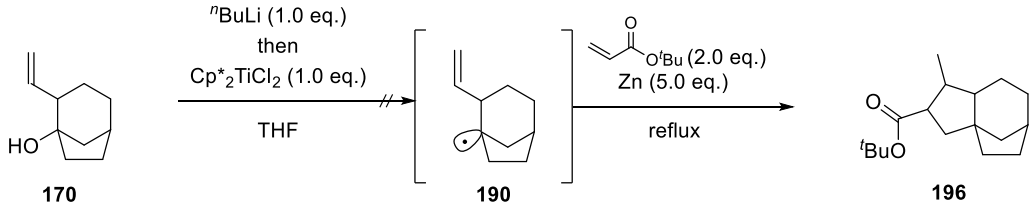
Scheme 16. Radical coupling of **181** with **157** via direct elimination of the oxalate

Based on the above results, I concluded that the strategy using oxalate ester as a leaving group was challenging. Consequently, I decided to convert the alcohol into functional groups that readily generate radicals, such as xanthate ester **192**, selenium **194**, or halogen **195** (Scheme 17). First, I attempted to convert the alcohol to xanthate ester **192**, but the starting material was recovered unchanged. Next, I tried direct selenylation, but the alcohol **170** did not react, and decomposition of the selenylating reagent was observed.[21] Therefore, I phosphinylated the alcohol **170** and then attempted selenylation under the same conditions. However, while phosphinylation proceeded, selenylation did not occur.[22] I also attempted halogenation from this intermediate, but the desired reaction did not take place in this case either.[23]



Scheme 17. Synthesis of radical precursor

Because it was difficult to convert an alcohol to other functional groups, I decided to generate the bridgehead radical directly from alcohol **170** (Scheme 18). Based on the reports by Wang, Shu, and co-workers, I attempted to generate the bridgehead radical using $Cp^*_2TiCl_2$ and Zn. However, the starting material was recovered unchanged.[24] From these investigations, it became clear that generation of the bridgehead radical of the bicyclo[3.2.1]octane ring is difficult due to their low stability, and use of this type of radical species for the annulation is not feasible. Therefore, I decided to make a major modification of the design of the radical species for the annulation.



Scheme 18. Attempt of direct generation of the bridgehead radical

For the formation of a carbon radical, it is necessary that the carbon has a certain degree of planarity. The bicyclo[3.2.1]octane ring has a rigid structure due to their carbon-ring framework, and their bridgehead carbon is fixed to a tetrahedral structure. Additionally, the C–O bond is known to be difficult to dissociate. This likely explains why the derivatives of alcohol **170** did not generate the desired carbon radicals.

3-4. Conclusion

Aiming to develop a novel annulation method utilizing a bicyclo[3.2.1]octane ring as a building block for constructing natural product frameworks, research was conducted. Efforts were initially directed toward synthesizing a precursor for radical-polar crossover type annulation, but the desired product could not be obtained. Consequently, the strategy was shifted to radical cyclization; however, generating a radical at the bridgehead position of the bicyclo[3.2.1]octane ring proved unsuccessful. This difficulty is believed to stem from the rigidity of the bicyclo[3.2.1]octane ring and the strength of the C–O bond. Therefore, the substrate design was revisited and further explored in Chapter 4.

3-5. Reference

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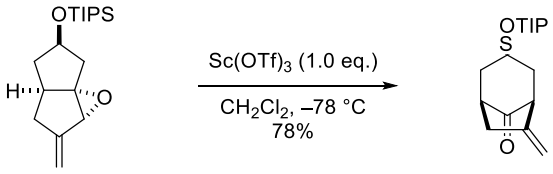
Chapter 4. Synthesis of an Angular Triquinane Structure Based on a Stereoselective Decarboxylative Giese Reaction at an Angular Position in a Diquinane Skeleton

4-1. Abstract

A chemo-, regio-, and stereo-selective method for constructing the angular triquinane core-skeleton was developed based on a radical carbon-carbon bond formation at a diquinane ring-junction as a key process. With the use of a photoredox catalyst under blue LED irradiation, the decarboxylative Giese reaction of the diquinane core with unsaturated carbonyl compounds proceeds stereoselectively to construct a quaternary carbon center at the angular position. Subsequent aldol cyclization exploiting the carbonyl group installed to a diquinane core resulted in an expeditious synthesis of the angular triquinane skeleton. In this study, an attempt was made to construct a seven-membered ring, though it was not successfully achieved.

4-2. Introduction

The challenges encountered in the research described in Chapter 3 were believed to stem from the rigid structure of the bicyclo[3.2.1]octane ring and the difficulty of cleaving its C–O bonds. Consequently, attention was turned to the bicyclo[3.3.0]octane framework, which tends to adopt a more planar structure. The ring junction of the bicyclo[3.3.0]octane system is energetically favored in the trans form compared to the cis form. This structural preference suggests the potential transmission of stereochemistry from the adjacent ring junction carbon to newly formed angular carbons.[1)] Furthermore, the transformation of a bicyclo[3.3.0]octane framework into a bicyclo[3.2.1]octane framework is considered feasible using the method reported by Leighton et al. (Scheme 1). Leighton demonstrated that treating epoxide **197** with $Sc(OTf)_3$ promotes the House–Meinwald rearrangement, converting the structure into bicyclo[3.2.1]octane **198**. The strategy of utilizing bicyclo[3.3.0]octane as a building block is significant not only as an intermediate in the synthesis of natural products with bicyclo[3.2.1]octane frameworks but also because the bicyclo[3.3.0]octane structure itself holds a privileged position in natural product frameworks.



197 **198**

Scheme 1. House–Meinwald rearrangement of bicyclo[3.3.0]octane **197** to bicyclo[3.2.1]octane **198**

4-2-1. Natural products with bicyclo[3.3.0]octane ring

Bicyclo[3.3.0]octane **100**, known as diquinane, is a common substructure in many natural products (Figure 1). Triquinane sesquiterpenes, which have an additional cyclopentane ring fusion to the diquinane, are the major class of these natural products and can be classified into linear, propellane, and angular types (**200**–**202**) depending on their ring fusion pattern.[2)] Angular triquinane sesquiterpenes with an all-carbon quaternary center at a ring-junction of

three rings can be further categorized into five sub-groups based on the positions of the four carbon substituents (Figure 1, **203**–**207**).[2h-2l] In addition, many biologically active natural products possess a polycyclic skeleton that consists of a triquinane core fused with an additional ring-system, such as waihoensene and retigeranic acid.[3] Due to the structural diversity and unique biological activities of these compounds, many researchers have targeted angular triquinane sesquiterpenoids for synthesis.[4] Reported total syntheses of angular triquinane sesquiterpenoids frequently employ strategies wherein the angular quaternary carbon is constructed through either cyclization reactions (such as the Pauson–Khand reaction, radical cyclization, electrocyclization, etc.), annulation, skeletal rearrangement, or nucleophilic addition of a cuprate to a β,β-disubstituted enone (Scheme 2).[4] Alternatively, the construction of a triquinane core through the electrophilic introduction of an angular sidechain followed by a cyclization has been reported.[5] The nucleophilic species used in this synthesis is limited to an enolate generated from an adjacent ketone. Therefore, an alternative synthetic pathway toward angular triquinanes using a ring-junction carbon nucleophilic has great potential to expand the chemical space of this class of molecules.

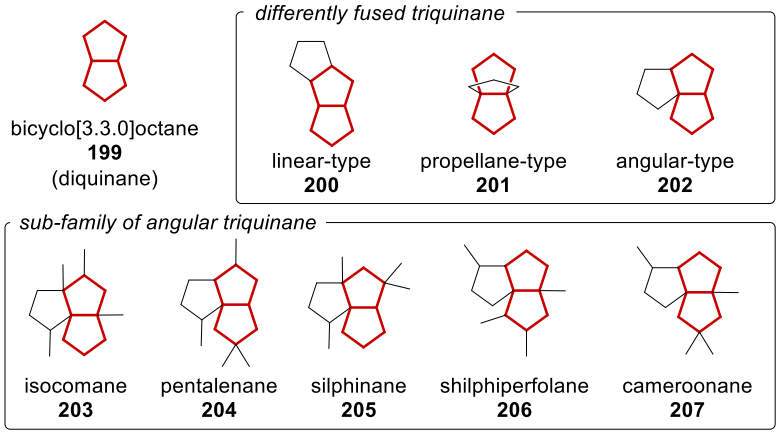
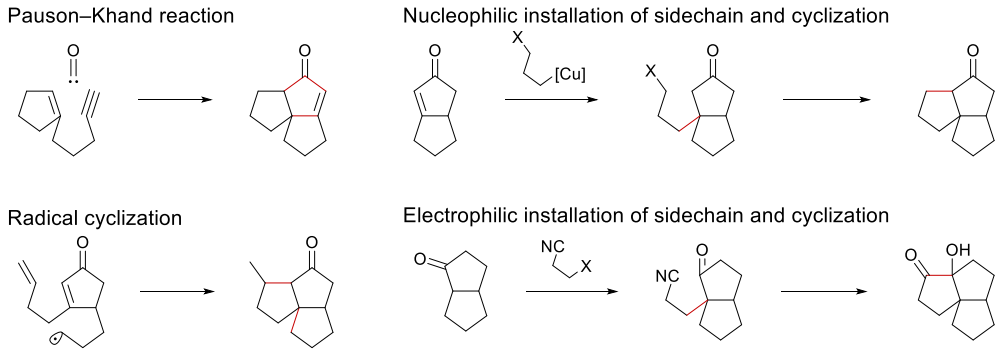


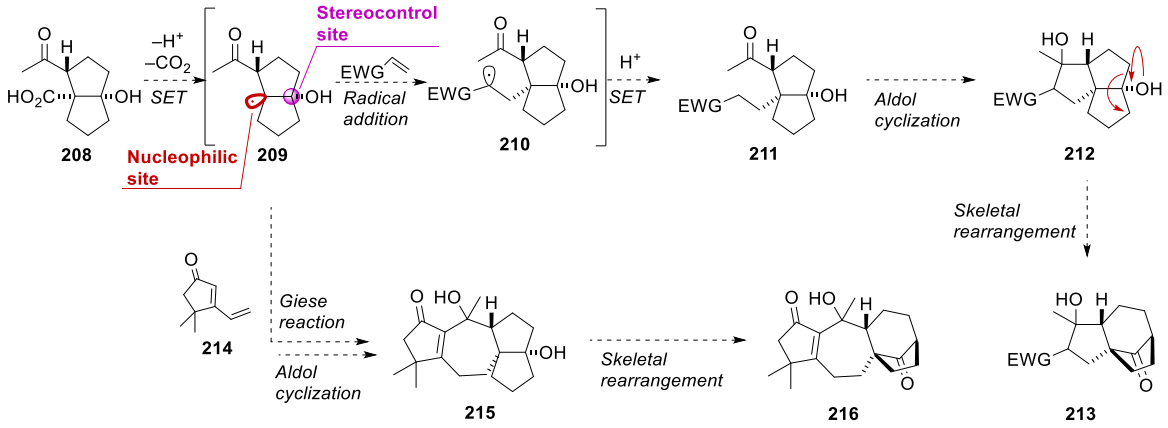
Figure 1. Triquinane sesquiterpene skeletons



Scheme 2. Reported methods for the construction of an angular triquinane core

4-2-2. New synthetic strategy using bicyclo[3.3.0]octane as a building block

In recent years, the decarboxylative Giese reaction using photoredox catalysis has been extensively studied.[6)] Commonly available aliphatic carboxylic acids can be easily converted to nucleophilic radicals which undergo radical-coupling with electron-deficient alkenes. Although this provides a powerful tool to construct complex molecular architectures, control of the stereochemistry of the formed carbon–carbon bond is challenging because of the sp^2-character of the radical. One effective solution to this issue is the use of bridgehead radicals to fix the stereochemistry.[7,8)] However, the substrates used in Chapter 3 failed to generate radicals. Therefore, a strategy was planed to utilize the bicyclo[3.3.0]octane framework to synthesize natural products containing either bicyclo[3.3.0]octane or bicyclo[3.2.1]octane frameworks. Specifically, The plan involved inducing a stereoselective decarboxylative Giese reaction between dicyclane-1-carboxylic acid **208** with methyl ketone group and acrylate or enone, followed by aldol reaction (Scheme 3). After completing the annulation reaction to form five- and seven-membered rings, the skeletal rearrangement from bicyclo[3.3.0]octane to bicyclo[3.2.1]octane was planned. This chapter focuses on developing annulation for constructing five- and seven-membered rings.



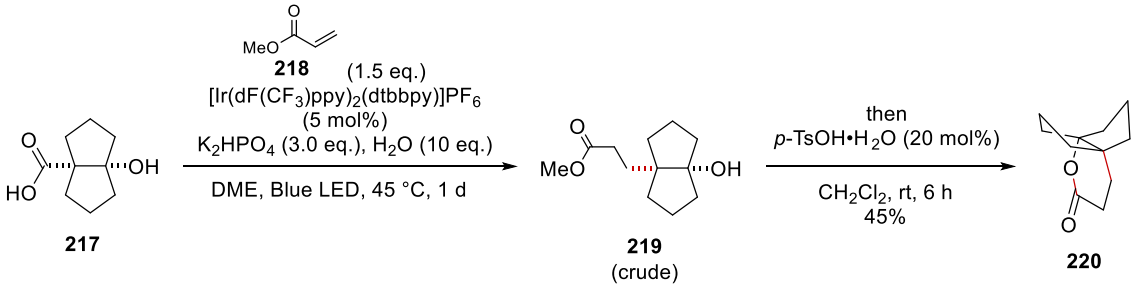
Scheme 3. Synthetic strategy using bicyclo[3.3.0]octane as a building block

4-3. Results and discussions

4-3-1. Development of a stereoselective Giese reaction using the bicyclo[3.3.0]octane ring as a building block

To verify our hypothesis, the reactivity and stereoselectivity of the decarboxylative Giese reaction of the diquinane structure were first investigated using a simple diquinane-1-carboxylic acid. Carboxylic acid **217** was subjected to Overman's decarboxylative Giese reaction conditions using an iridium photoredox catalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ and base (K_2HPO_4) under blue LED irradiation (Scheme 4).[6c)] By using methyl acrylate as a radicalophile, coupling product **219** was obtained as a single diastereomer. We found that **219** was prone to undergo cyclization to form lactone **220** during purification by silica gel column chromatography, which was not separable from **219**. Therefore, the crude material of the Giese

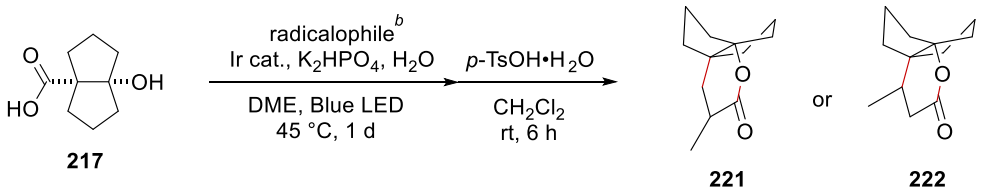
reaction was treated with a catalytic amount of *p*-TsOH to push lactonization, and after purification, lactone **220** was obtained in 45% yield as a sole product. Formation of the lactone strongly suggests that the obtained diquinane core has a cis configuration, supporting our stereoretentive radical coupling scenario.

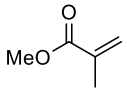
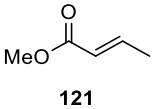


Scheme 4. Giese-type radical coupling carboxylic acid **217** with methyl acrylate **218**

Some substituted methyl acrylates were subjected to the decarboxylative Giese reaction to evaluate electronic and steric effects (Table 1). Methyl methacrylate **223** exhibited good reactivity toward the coupling to give the lactone product **221** in 85% yield. However, methyl crotonate **224** having a β-substituent showed poor reactivity, indicating that the reaction is susceptible to steric bulkiness at the β-position.

Table 1. Investigation of substrate scope of radicalophile



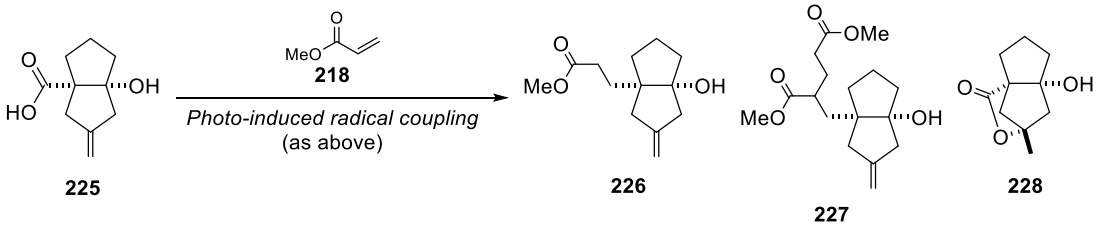
entry	radicalophile	yield
1	 **120**	**221**: 85%
2	 **121**	**222**: trace

[a] All reactions were conducted using 1.5 eq. of radicalophile, 5 mol% of Ir cat., 3.0 eq. of K_2HPO_4, 10 eq. of H_2O, and 20 mol% of *p*-TsOH·H_2O.

[b] Ir cat = $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$.

Next, bicyclic carboxylic acids with additional functional groups were examined. The radical coupling reaction was first attempted with the exo-methylene carboxylic acid **225** under the previously established conditions (Table 2). This reaction yielded the desired coupling product **226** in 26% yield (entry 1). Along with the desired product, lactone **228** was obtained as a byproduct. This result suggests that cyclization of a carboxylic radical to the alkene competes with an intended decarboxylation.[9] To promote decarboxylation and avoid undesired cyclization, the reaction temperature was increased from 45 °C to 65 °C (entry 2). While the starting material was fully consumed at the higher temperature, the reaction resulted in an over-reaction of the methyl acrylate **218**, producing a different major product **227**.

Table 2. Giese reaction of carboxylic acid **225** with exo-cyclic alkene

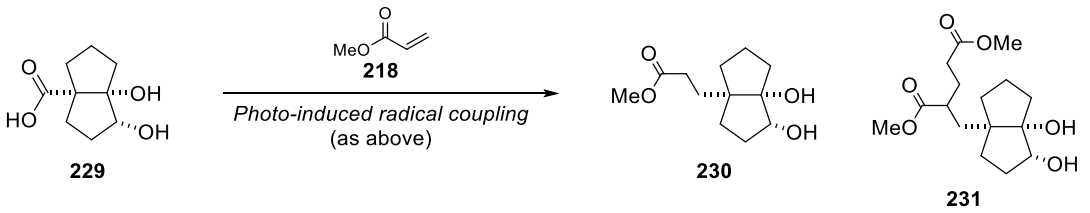


entry	temp.	yield		
		226	**227**	**228**
1	45 °C	26%	–	<17%
2	65 °C	<78 (**226**+**227**)		–

All reactions were conducted using 1.5 eq. of methyl acrylate, 5 mol% of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, 3.0 eq. of K_2HPO_4, and 10 eq. of H_2O in DME. 14 W blue LED.

The reaction was conducted using a carboxylic acid **229** with a secondary alcohol (Table 3). As a result, although a significant amount of the starting material was recovered, the desired coupling product **230** was synthesized with a yield of 33% (entry 1). When the reaction was conducted at 65 ºC, the starting material was completely consumed similar to the case with carboxylic acid **225**. Subsequently, the coupling product **230** and compound **231** formed due to excessive reaction with methyl acrylate **218** were obtained (entry 2).

Table 3. Giese reaction of carboxylic acid **229** with diol

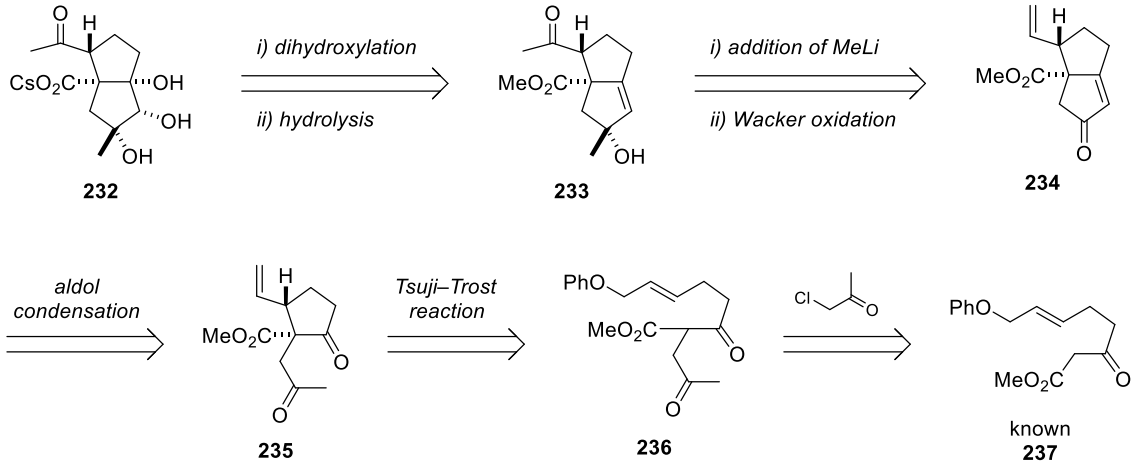


Entry	Temp.	Time	yield	
			230	**231**
1	45 °C	1 d	33%	–
2	65 °C	9 h	44%	41%

All reactions were conducted using 1.5 eq. of methyl acrylate, 5 mol% of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, 3.0 eq. of K_2HPO_4, and 10 eq. of H_2O in DME. 14 W blue LED.

4-3-2. Synthesis of radical precursor 232 with bicyclo[3.3.0]octane ring

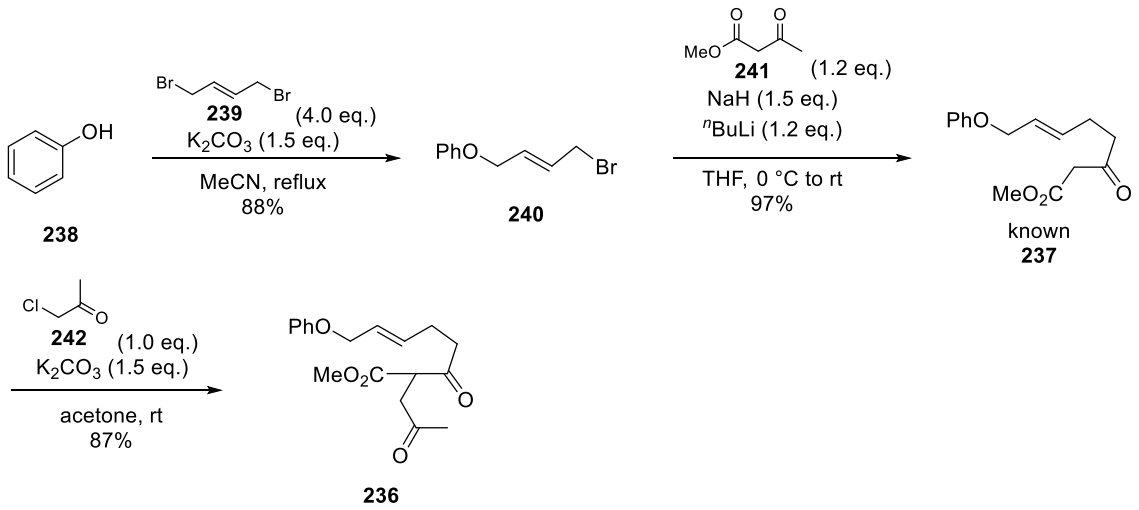
The retrosynthetic pathway for synthesizing cesium carboxylate salt **232** as a radical precursor is shown in Scheme 5. The cesium carboxylate salt **232** is synthesized from ketone **233** through dihydroxylation and ester hydrolysis. Ketone **233** is derived from enone **234** by the addition of methyl lithium and then Wacker oxidation. Enone **234** was synthesized through intramolecular aldol condensation of diketone **235**, obtained via intramolecular Tsuji–Trost reaction of tricarbonyl **236**. Tricarbonyl **236** is synthesized from known keto ester **237**.[10)]



Scheme 5. Retrosynthetic pathway of radical precursor **232** with bicyclo[3.3.0]octane ring

Allyl bromide **240** was prepared via an S_N2 reaction between phenol **238** and 1,4-dibromobutene **239**. It was then reacted with a dienolate generated from methyl acetoacetate

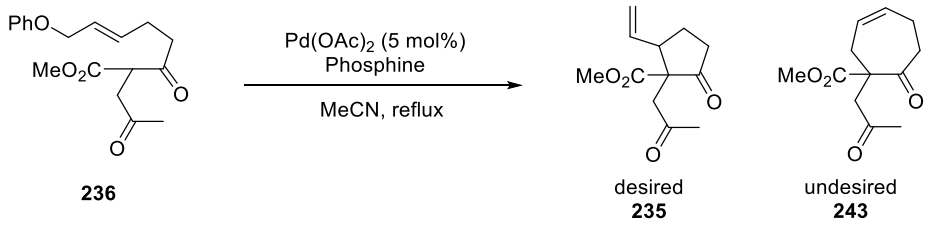
138 to afford the known β-keto ester **237** (Scheme 6).[10] The resulting keto ester **237** was subsequently treated with chloroacetone **242** under basic conditions to synthesize tricarbonyl **236**.



Scheme 6. Synthesis of tricarbonyl **236**

I investigated the intramolecular Tsuji–Trost reaction of tricarbonyl **236** (Table 4).[10] Referring to Tsuji's report, I conducted the reaction in acetonitrile with catalytic amounts of $Pd(OAc)_2$ and triphenylphosphine, obtaining the desired five-membered ring keto ester **235** in 81% yield with a diastereomeric ratio of 1.3:1 (entry 1). However, an undesired seven-membered ring keto ester **243** was also formed. To selectively obtain the five-membered ring **235**, I investigated different phosphine ligands (entries 2–4). Despite varying the bite angles of bidentate ligands, no significant improvement in selectivity was observed. Therefore, I proceeded with the conditions of entry 2, which gave the highest yield of the five-membered ring keto ester **235**.

Table 4. Intramolecular Tsuji–Trost reaction of tricarbonyl **133**

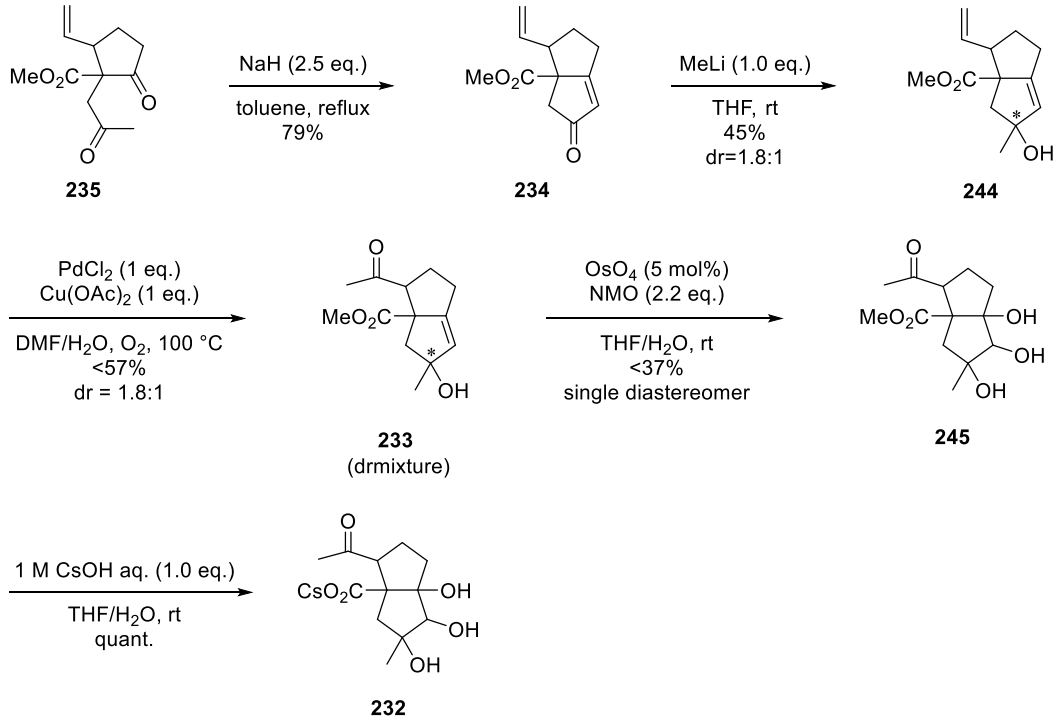


236 desired **235** undesired **243**

entry	phosphine	results	
		desired **235** (dr)	undesired **243**
1	PPh_3 (20 mol%)	81% (1.3 : 1)	6%
2[a]	dppp (10 mol%)	89% (1.3 : 1)	11%
3[a]	dppb (10 mol%)	84% (1.5 : 1)	16%
4[a]	xantphos (10 mol%)	77% (1.4 : 1)	19%

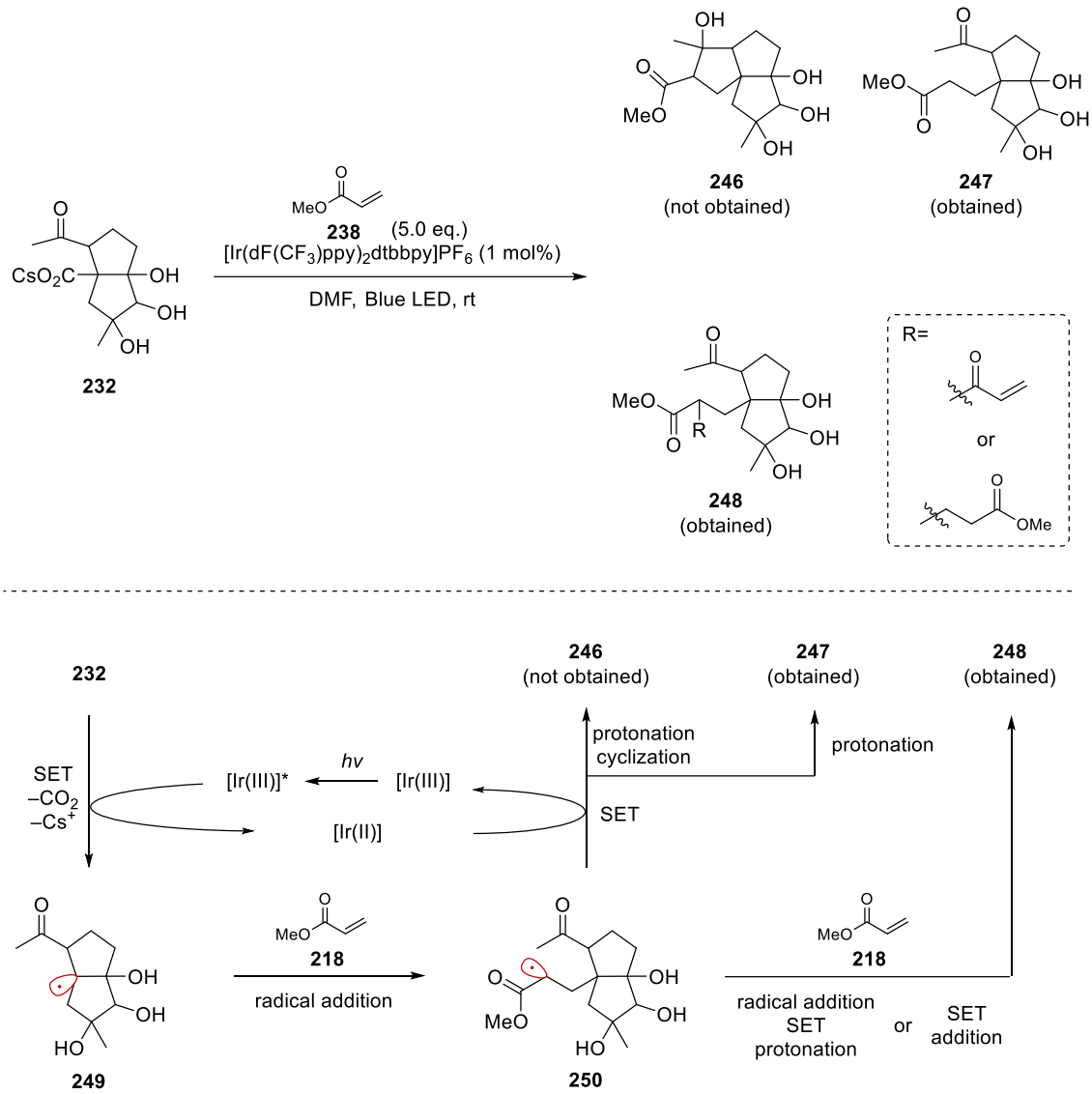
[a] Evaluated by ^{1}H NMR analysis using trichloroethylene as an internal standard

I isolated one diastereomer of the synthesized five-membered ring keto ester **235** and advanced the synthesis of the radical precursor **232** (Scheme 7). Treating keto ester **235** with sodium hydride in toluene yielded enone **234** via intramolecular aldol condensation. Although this reaction suffers from reproducibility issues, the synthesis of precursor **232** was pursued. Addition of methyl lithium to enone **234** produced allyl alcohol **244** in 45% yield with a diastereomeric ratio of 1.8:1. The allyl alcohol **244** as a diastereomeric mixture was converted into ketone **233** through Wacker oxidation. Subsequent dihydroxylation yielded triol **245** as a single stereoisomer with a yield of less than 37%. A diastereomer of triol **245** was observed in the reaction but was lost to the aqueous layer during extraction and could not be obtained. Hydrolysis of the ester group of triol **245** quantitatively yielded the cesium carboxylate salt **232**.



Scheme 7. Synthesis of the radical precursor **232**

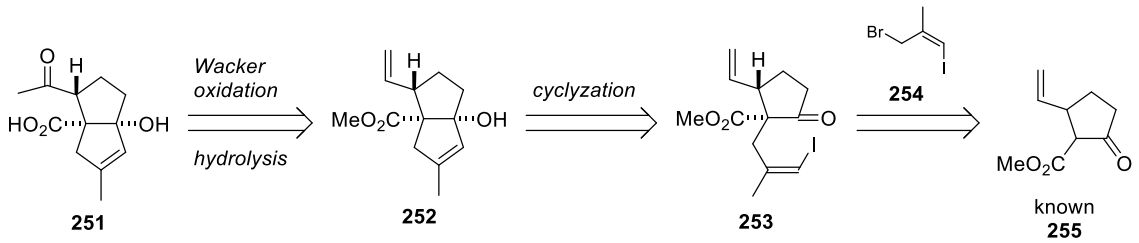
After obtaining the radical precursor **232**, the decarboxylative Giese reaction was carried out (Scheme 8). Following the reports by MacMillan and Overman, precursor **232** was reacted with methyl acrylate **218** in DMF under visible light irradiation in the presence of Ir catalyst.[11)] Although the desired annulation reaction did not proceed, coupling product **247** was obtained. Additionally, the byproduct formed through overreaction with methyl acrylate **218** was also detected. While the Giese reaction was successfully performed, challenges related to stereoselectivity, reproducibility, and yield were identified in the synthesis of precursor **232**. Therefore, improvements to the synthetic route were necessary.



Scheme 8. Giese reaction of **232** with **218**

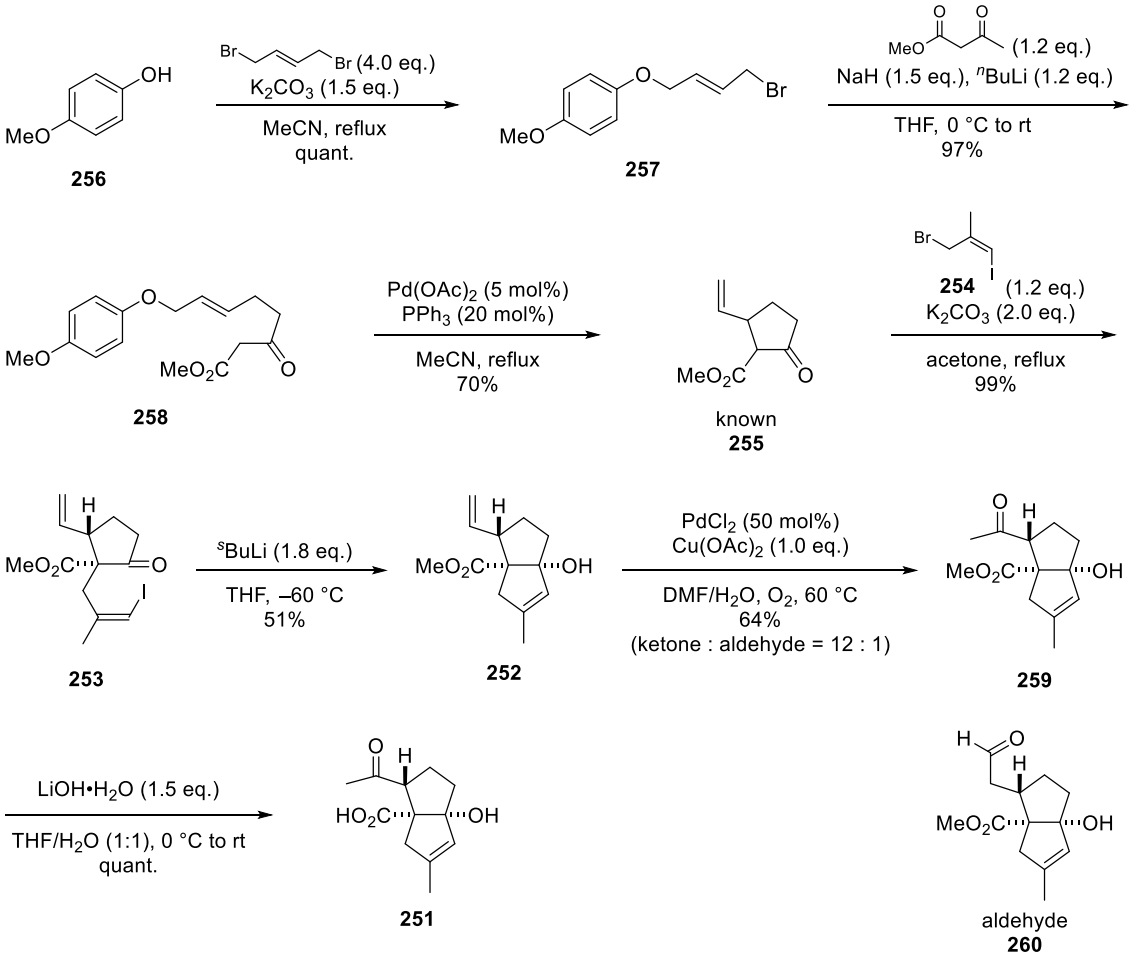
4-3-3. Synthesis of the radical precursor 251 with bicyclo[3.3.0]octane bing

The carboxylic acid **251** as a precursor was designed (Scheme 9). It was anticipated that the hydroxy group of carboxylic acid **251** at the ring-junction position would act as a directing group, allowing for the stereoselective modification of the alkene. This structure was considered advantageous for performing the subsequent skeletal rearrangement. A new synthetic route was shown in scheme 27. Using an irreversible reaction was expected to enable the reproducible synthesis of **251**. Specifically, carboxylic acid **251** was predicted to be obtained through the Wacker oxidation of alcohol **252**, followed by hydrolysis. Alcohol **252**, in turn, was expected to be synthesized via the cyclization of a ketone formed after the lithiation of vinyl iodide **253**. The starting material chosen for this sequence was the known five-membered ketone ester **255**.



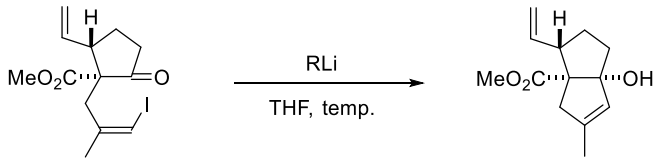
Scheme 9. Retrosynthetic pathway of Active Intermediate Precursor **251**

Ketone ester **237** was synthesized, and the intramolecular Tsuji–Trost reaction was investigated. As a result, the desired five-membered ketone ester **255** was successfully synthesized (Scheme 10). However, separating the five-membered ketone ester **255** from phenol was difficult. To address this issue, the leaving group was changed to a 4-methoxyphenyl group, and the intramolecular Tsuji–Trost reaction was occurred. This modification allowed the isolation of the five-membered ketone ester **255** in 70% yield. Next, the obtained five-membered ketone ester **255** was reacted with allyl bromide **254** in the presence of potassium carbonate to synthesize vinyl iodide **253**. Due to the steric hindrance of the vinyl group, vinyl iodide **253** was obtained as a single stereoisomer. The cyclization of vinyl iodide **253** was then explored (Table 5). Based on Piers' report, lithiation using *n*-BuLi was performed, yielding the bicyclic compound **252** in 39% yield (entry 1).[12] However, *n*-BuLi preferentially reacted with the ketone, forming an alcohol instead of lithiation. Therefore, the lithium reagent was changed to *s*-BuLi (entry 2). This modification successfully produced the desired cyclized compound **252** in 35% yield, with 44% of the starting material recovered. Further optimization revealed that using 1.8 equivalents of *s*-BuLi yielded the best results (entries 2 and 3). Scale-up of the reaction resulted in a decrease in yield, prompting an investigation of reaction temperature (entries 5–8). After the dropwise addition of *s*-BuLi at –78 ºC followed by warming, no improvement in yield was observed (entries 5 and 6). However, setting the dropwise addition temperature of *s*-BuLi to –60 ºC increased the yield of cyclized compound **252** to 51% (entry 7). No further improvement was observed at –50 ºC (entry 8). The terminal alkene of the obtained bicyclic compound **252** was converted to ketone **259** via Wacker oxidation. In this process, aldehyde **260** was also formed as a byproduct. After ketone **259** was successfully isolated using silica gel column chromatography, hydrolysis of ketone **259** yielded carboxylic acid **251**.



Scheme 10. Synthesis of Active Intermediate Precursor **251**

Table 5. Investigation of cyclization of vinyl iodide **253**



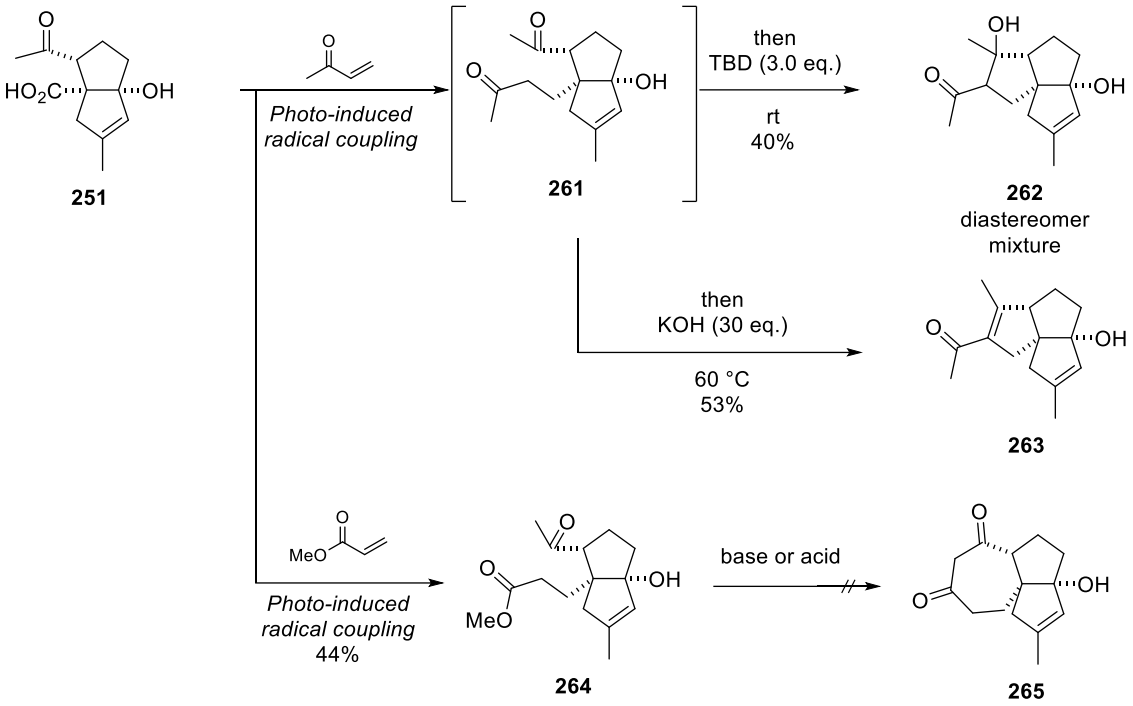
253 **252**

entry	RLi		temp.	NMR yield
	R	eq.		
1	^{n}Bu	1.5	–78 ºC	39%
2	^{s}Bu	1.5	–78 ºC	35% (brsm 63%)
3	^{s}Bu	3.0	–78 ºC	35%
4	^{s}Bu	1.8	–78 ºC	36–51%
5	^{s}Bu	1.8	–78 ºC to –60 ºC	20%
6	^{s}Bu	1.8	–78 ºC to –50 ºC	27%
7	^{s}Bu	1.8	–60 ºC	51%*
8	^{s}Bu	1.8	–50 ºC	28%

* isolated yield

4-3-4. Annulation reaction of radical precursor 251 with radicalophiles

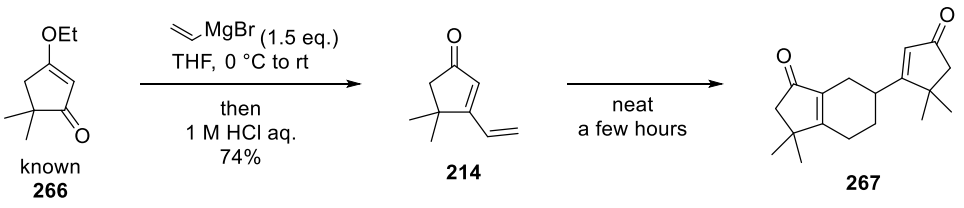
The annulation reaction using carboxylic acid **251** with methyl ketone was investigated (Scheme 11). First, a decarboxylative Giese reaction between carboxylic acid **251** and methyl vinyl ketone was performed, followed by treatment with TBD. This resulted in the successful synthesis of diol **262** with an angular tricyclane framework as a diastereomer mixture in 40% yield. When the base added after the Giese reaction was changed to potassium hydroxide, enone **263** was synthesized in 53% yield. Based on these results, an annulation reaction using the bicyclo[3.3.0]octane framework as a building block was successfully developed. Subsequently, the radicalophile was changed to methyl acrylate to target the construction of a seven-membered ring. While the Giese reaction proceeded, attempts to achieve the desired annulation using bases such as TBD or KHMDS, or acids like $TiCl_4$, resulted in either the recovery of starting material or its decomposition.



Scheme 11. Investigation of annulation reaction of radical precursor **251** with radicalophiles

4-3-5. Giese reaction of radical precursor 251 with dienylenone 214

If annulation and subsequent skeletal rearrangement using dienyl ketone **267** as the radicalophile can be achieved, this approach could be extended to the synthesis of grayanane diterpenes, as described in Chapter 3. To this end, the synthesis of dienyl enone **214** as the radicalophile was pursued (Scheme 12). By treating the known enol ether **266** with vinylmagnesium bromide, followed by work-up with hydrochloric acid, the desired dienylenone **214** was successfully synthesized.[9] Notably, it was observed that dienylenone **214** undergoes dimerization when stored in a neat condition, necessitating immediate use following purification.

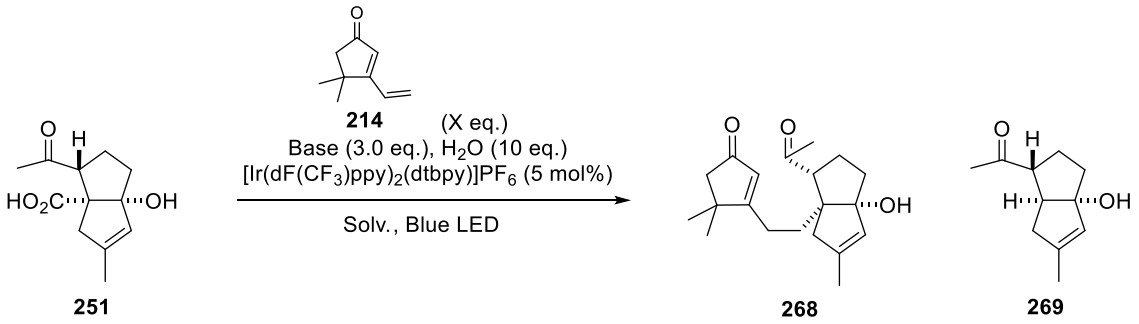


Scheme 12. Synthesis of dienylenone **214** as a radicalophile

Based on the report by Overman et al., a reaction was conducted in a mixed solvent of DME and THF (25 mM) using dienylenone **214** as the radicalophile, K_2HPO_4 as the base, $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ as the photoredox catalyst, and H_2O as an additive, under visible light irradiation conditions. As a result, radical addition product **268** was obtained with 30%

yield (Table 6, entry 1).[6c)] Additionally, it was found that the decarboxylation product **269** was formed as a byproduct. This is presumed that the formation occurred via 1,4-HAT from the hydrogen of methyl ketone to the carbon radical.[13)] To improve the yield, solvent screening was performed, revealing that using DMF, DMSO, MeCN, or CH_2Cl_2 resulted in decreased yields. In contrast, when only DME was used as the solvent, the yield improved to 40% (entry 2). Under conditions where the concentration of substrate **251** was 50 mM, decomposition of dienylenone **214** was prioritized in the system, yielding little of the target product (entry 3). TLC analysis during the reaction indicated that decomposition of dienylenone **214** progressed over time. Thus, it was decided to add dienylenone **214** every three hours from the start of the reaction (entries 4, 5). Consequently, adding dienylenone **214** after three and six hours increased the yield of the coupling product **268** to 52% (entry 5). To further enhance the yield, the base was changed to carbonate for the reaction (entries 6–9). Coupling product **268** was obtained with all bases except for Li_2CO_3 (entry 7). Although no decarboxylation product **269** was obtained with Na_2CO_3 (entry 8) and Cs_2CO_3 (entry 9), the yield of coupling product **268** did not improve under these conditions.

Table 6. Investigation of Giese reaction of carboxylic acid **251** with dienylenone **214**



entry	**214** (X eq.)	Base	Solv. (conc.)	Yield	
				268	Recovered **251**
1	1.5	K_2HPO_4	DME/THF (25 mM)	<35%	–
2	1.5	K_2HPO_4	DME (25 mM)	40%	–
3	1.5	K_2HPO_4	DME (50 mM)	trace	–
4	1.5 + 0.5[a]	K_2HPO_4	DME (25 mM)	49%	–
5	1.5 + 0.5[a] + 0.5[b]	K_2HPO_4	DME (25 mM)	52%	–
6	1.5 + 0.5[a] + 0.5[b]	K_2CO_3	DME (25 mM)	44%	–
7	1.5 + 0.5[a] + 0.5[b]	Li_2CO_3	DME (25 mM)	–	81%
8	1.5 + 0.5[a] + 0.5[b]	Na_2CO_3	DME (25 mM)	36%	<74%
9	1.5 + 0.5[a] + 0.5[b]	Cs_2CO_3	DME (25 mM)	44%	33%

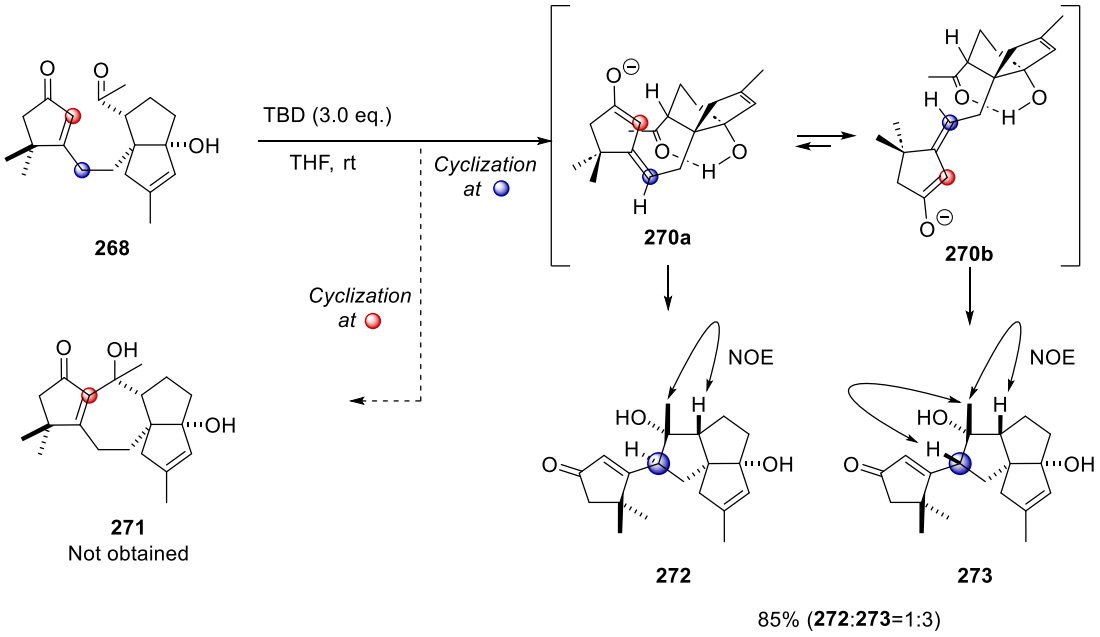
[a] Added after 3 hours from the start of the reaction

[b] Added after 6 hours from the start of the reaction

4-3-6. Investigation of the cyclization reaction of radical coupling product

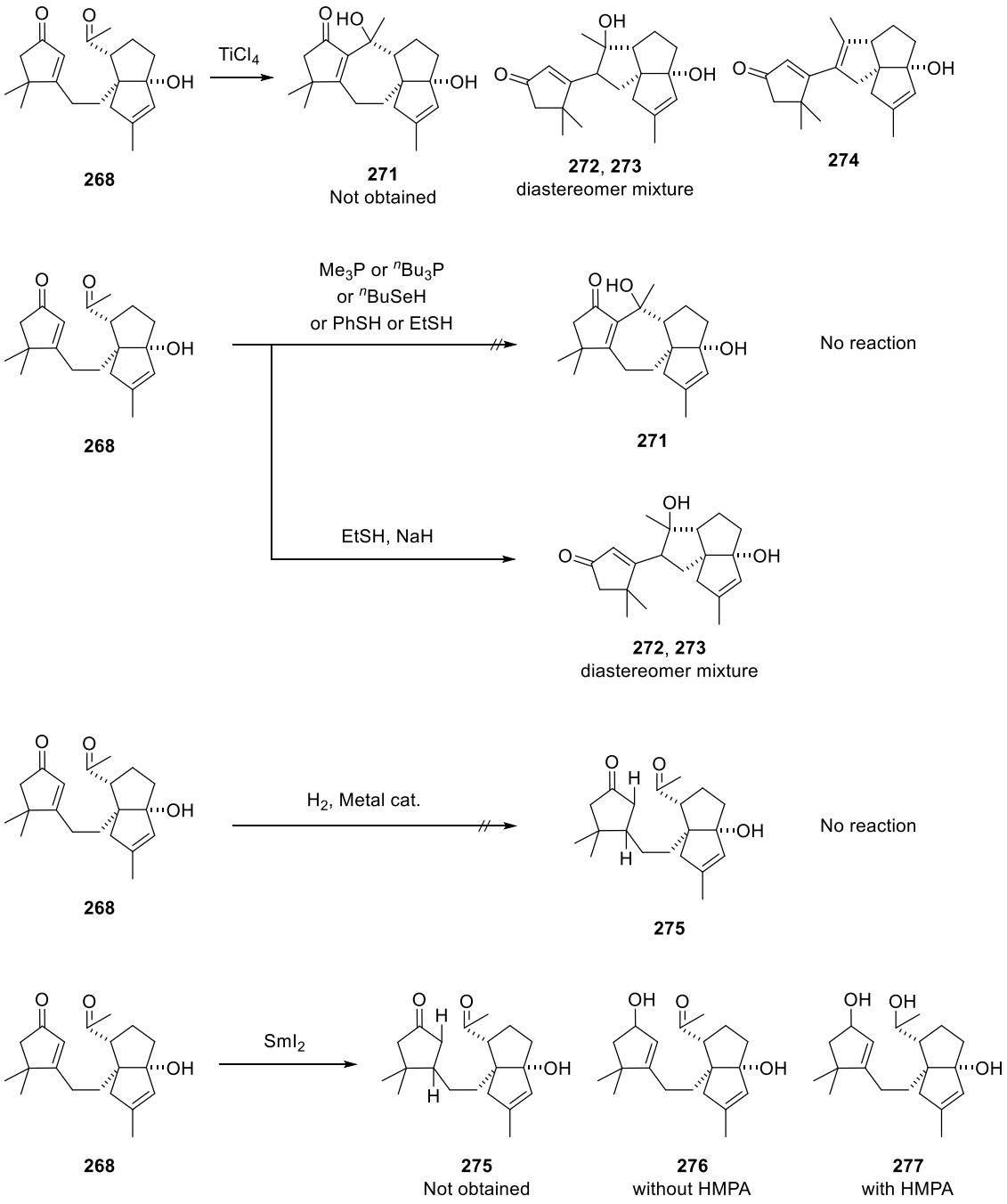
The cyclization conditions for the obtained coupling product **268** were examined (Scheme 13). Referring to the results from 4-3-4, the application of TBD as the base facilitated cyclization at the γ-position of the enone, yielding five-membered ring compounds **272** and **273** (**272**:**273** = 1:3). The identical stereochemistry of the newly formed tertiary alcohol suggests the formation of an intramolecular hydrogen bond between methyl ketone and tertiary alcohol at ring junction. Assuming that the resulting enolate **270** adopts the *E*-isomer which minimizes steric repulsion between *gem*-dimethyl group and side chain connected to bicyclo[3.3.0]octane

ring, two transition states, **270a** and **270b**, can be proposed. In **270a**, steric repulsion occurs between five-membered ring and bicyclo[3.3.0]octane ring. In contrast, in **270b**, steric repulsion arises between methyl ketone and five-membered ring. Comparing two transition states, the steric repulsion in **270a** is expected to be greater. This reasoning suggests that **273** is preferentially formed. Regarding the base, the reaction did not proceed with organic bases that had a pKa of less than 21 at room temperature.[14] For instance, MTBD and DBU, which have pKa values below 21, did not promote the reaction in THF at room temperature. Furthermore, the reaction did not proceed with anionic bases such as KHMDS.



Scheme 13. Cyclization reaction of radical coupling product **268** using TBD

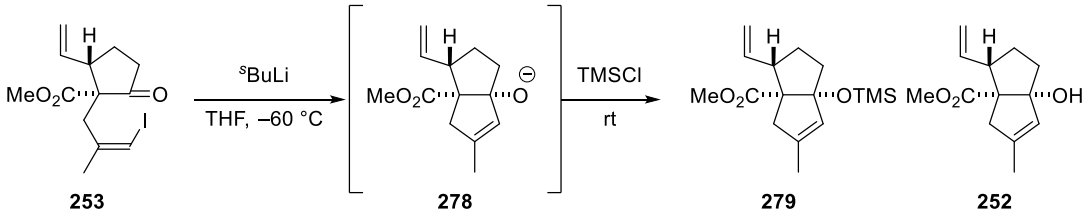
To construct a seven-membered ring through cyclization at the α-position of enone **268**, other reaction conditions were investigated, such as acid-catalyzed aldol cyclization, Morita–Baylis–Hillman reaction, and reduction/cyclization of the enone part (Scheme 14). In the acid-catalyzed aldol reaction, the formation of five-membered ring compounds **272** and **273**, and its dehydration product **274** were observed. In the Morita–Baylis–Hillman reaction, using nucleophilic catalysts such as Me_3P, $^nBu_3P$, BuSeH, PhSH, and EtSH resulted in the recovery of starting material, likely due to steric hindrance from *gem*-dimethyl group. However, when EtSH was pre-deprotonated before the reaction, it functioned as a base, leading to the formation of the five-membered ring. Consequently, a reduction of the enone part was considered to facilitate aldol reaction between ketones. However, under conditions designed for the selective catalytic reduction of the enone moiety, the starting material was recovered likely due to the steric hindrance caused by the *gem*-dimethyl group. On the other hand, reduction with SmI_2 yielded compounds **276** and **278** which are presumed to be products of the enone being converted into an allyl alcohol.



Scheme 14. Investigation of Cyclization reaction of radical coupling product **268**

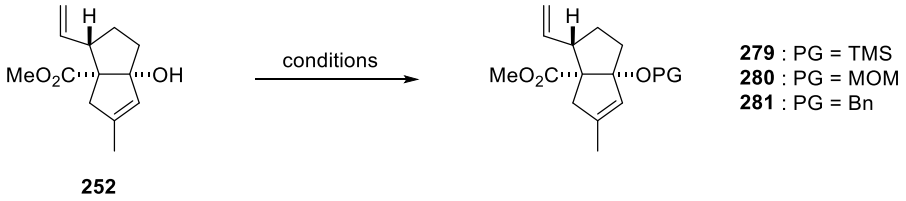
Considering that the intramolecular hydrogen bond may be fixing the conformation of the molecule and inhibiting the formation of the seven-membered ring, the decision was made to protect the tertiary alcohol. Adding TMSCl to the alkoxide **278** generated from the cyclization of **253** yielded alcohol **252**, but the desired protected product **279** was not obtained (Scheme 15). Therefore, protection to alcohol **252** was investigated (Table 7). When TMSOTf and 2,6-lutidine were reacted to compound **252**, the system became complicated (entry 1). This is thought to be due to the activation of the ester by the reagents, leading to a retro-aldol reaction.

Consequently, it was decided to introduce a protecting group under neutral or basic conditions. In entry 2, HMDS was chosen due to its ability to protect tertiary alcohols under relatively neutral conditions. When alcohol **252** was reacted with HMDS in nitromethane, the desired protected compound **279** was successfully obtained in good yield.[15] Attempts were made to introduce MOM and Bn groups under basic conditions (entries 3 and 4). When alcohol **252** was treated with MOMCl or BnCl in dichloromethane under reflux conditions with sodium hydride as the base, the starting material was recovered. On the other hand, when the solvent was changed to DMF for the Bn group introduction, the Bn-protected compound **281** was successfully obtained (entry 5). Nevertheless, the separation of the protected compound **281** from benzyl bromide was difficult. Subsequently, TMS-protected compound **279** was used in subsequent investigations.



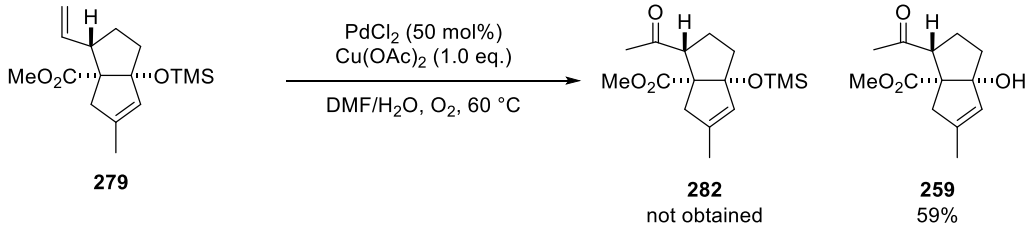
Scheme 15. Protection of alcohol **252**

Table 7. Investigation of protection of alcohol **252**



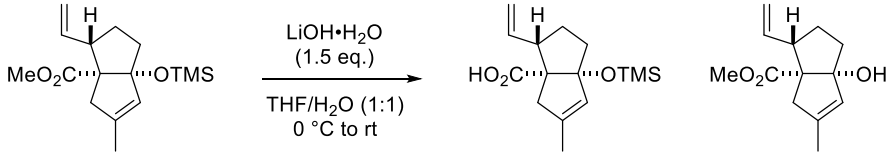
entry	conditions			PG	yield
	reagents	solv.	temp.		
1	TMSOTf (1.2 eq.) 2,6-lutidine (1.5 eq.)	CH_2Cl_2	rt	TMS	decomposed
2	HMDS (1.0 eq.)	$MeNO_2$	rt	TMS	**279**: 87%
3	NaH (1.2 eq.) MOMCl (1.5 eq.)	CH_2Cl_2	rt to reflux	MOM	no reaction
4	NaH (1.2 eq.) BnCl (1.5 eq.)	CH_2Cl_2	rt to reflux	Bn	no reaction
5	NaH (1.5 eq.), NaI (1.0 eq.) BnBr (3.0 eq.)	DMF	rt	Bn	**281**: <99% (with BnBr)

However, a problem arose during the subsequent Wacker oxidation where the TMS group was removed (Scheme 16). Thus, the order of reactions was rearranged to protect the alcohol after the Wacker oxidation, followed by hydrolysis. However, during hydrolysis of TMS-protected compound **279**, the TMS group was removed, preventing the introduction of the protecting group into the coupling precursor (Scheme 17). Based on these results, it was decided to perform alcohol protection after coupling, leading to the synthesis of TMS-protected compound **284** (Scheme 18). When TBD was applied to this protected compound **284**, the TMS was removed, resulting in the formation of the five-membered ring. Additionally, alcohol protection and cyclization were also performed on coupling product **264** with methyl acrylate (Scheme 19). Although the generation of a new compound was confirmed by TLC, its structure could not be elucidated.



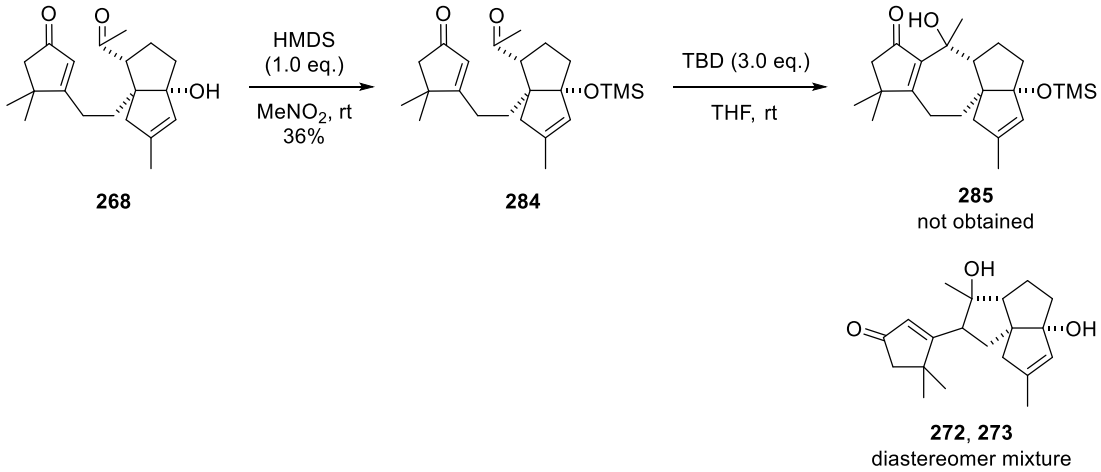
279 **282** not obtained **259** 59%

Scheme 16. Wacker oxidation of TMS-protected compound **279**



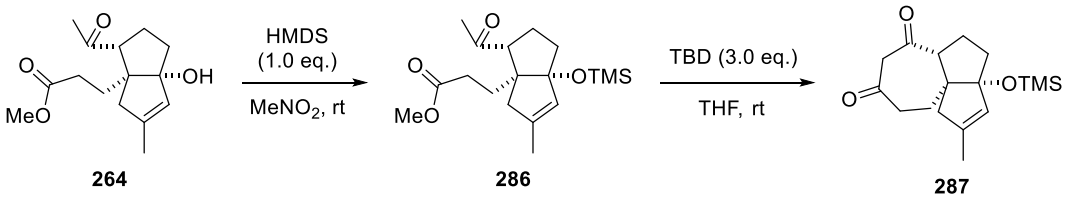
279 **283** not obtained **252** quant

Scheme 17. Hydrolysis of TMS-protected compound **279**



268 **284** **285** not obtained **272**, **273** diastereomer mixture

Scheme 18. Cyclization of TMS-protected compound **285**



Scheme 19. Cyclization of TMS-protected compound **286**

4-4. Conclusion

I have developed a concise method for the synthesis of angular triquinane, a tricyclic skeleton frequently found in bioactive terpenoids. To construct the angular quaternary carbon center stereoselectively, I have established a photoredox catalyst-mediated decarboxylative Giese reaction of bicyclo[3.3.0]octane **199** (diquinane) to form a carbon-carbon bond at a ring-junction. With using a radical-coupling precursor bearing a methyl ketone moiety, Aldol cyclization and aldol condensation of the coupling product derived from enone and dienylketone under basic conditions successfully proceed to afford the desired angular triquinanes in good yield. The application of this method for the synthesis of natural terpenoids is being studied in our group.

4-5. Reference

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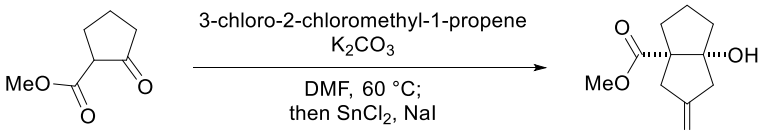
4-6. Experimental section General Experimental Information

IR spectra were recorded on a SHIMADZU FTIR-8400 spectrometer. ^{1}H NMR spectra were measured on JEOL JNMECZ600R spectrometer (600 MHz), Varian NMR System 600 PS600 spectrometer (600 MHz), and a Varian 400-MR ASW spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from the solvent resonance employed as the internal standard ($CHCl_3$ at 7.26 ppm) on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; pent = pentet/quintet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on JEOL JNMECZ600R spectrometer (150 MHz), Varian NMR System 600 PS600 spectrometer (150 MHz) and a Varian 400-MR ASW spectrometer (100 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.16 ppm). For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Kanto Chemical Co., Inc. silica gel 60 N (spherical, neutral), Fuji Silysia Chemical PSQ100B, and Kanto Chemical Co. were used. High- and low-resolution mass spectral analysis (HRMS) was measured on a Bruker micrOTOF II (ESI) at Chemical Instrument Facility, Okayama University. IR spectra were recorded on a SHIMADZU FTIR-8400, and only selected peaks are reported in wavenumbers (cm^{-1}). Dry N,N-dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), methanol (MeOH), diethyl ether (Et_2O), acetone and chloroform ($CHCl_3$) were purchased from Kanto Chemical Co., Inc. or Wako Pure Chemical Industries Ltd. as the “anhydrous” and stored under nitrogen. 1,2-dimethoxyethane (DME) was purchased from TCI Co., LTD dehydrated by molecular sieves 4A prior to use. Other materials were obtained from commercial supplies and used without further purification. All reactions were conducted in a flame-dried glassware under a nitrogen atmosphere, otherwise noted.

rac-methyl (3a*S*,6a*R*)-6a-hydroxy-2-methylenehexahydropentalene-3a(1*H*)-carboxylate (289)

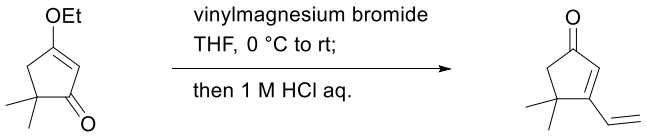


289

To the DMF (38 mL) suspension of methyl 2-oxocyclopentanecarboxylate (100 μL, 805 μmol) and K_2CO_3 (167 mg, 1.21 mmol) was added 3-chloro-2-chloromethyl-1-propene (130 μL, 1.21 mmol) at room temperature. The mixture was warmed to 60 ºC and stirred for 5 hours. To the mixture was added $SnCl_2$ (305 mg, 1.61 mmol) and NaI (241 mg, 1.61 mmol) at the same temperature and further stirred for 17 hours. [3] After cooling down to room temperature, the reaction mixture was diluted with 10% NH_4F aq. (7.3 mL) and filtrated through Celite (washed with EtOAc 20 mL). The filtrate was diluted with H_2O (36 mL) and the aqueous layer was extracted with EtOAc (22 mL×3). Combined organic extracts were washed with brine (36 mL), dried over Na_2SO_4 and filtrated. The filtrate was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (*n*-hexane:EtOAc = 15:1) to afford ester **289** (120 mg, 61.2 μmol, 76%) as a pale yellow oil.

289: IR (neat) 3460, 2943, 1703, 1643, 1449, 1412, 1261, 1207, 1179, 1111, 899, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.86 (app oct., *J* = 1.2 Hz, 1H), 4.84 (app octet, *J* = 1.2 Hz, 1H), 3.73 (s, 3H), 3.06 (app dsept., *J* = 16.2, 1.2 Hz, 1H), 2.96 (s, 1H), 2.65 (d, *J*=15.6 Hz, 1H), 2.54 (ddd, *J*=15.6, 2.4, 1.2 Hz, 1H), 2.37–2.31 (m, 1H), 2.27 (ddd, *J*=16.2, 3.0, 1.2 Hz, 1H), 1.92 (app dt, J = 13.2, 7.2 Hz, 1H), 1.87–1.76 (m, 2H), 1.66–1.59 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 147.4, 107.7, 90.6, 61.4, 52.2, 47.7, 43.5, 40.5, 36.7, 23.1; HRMS (ESI) *m/z* 219.0992, calcd for $C_{11}H_{16}NaO_3$ $[M+Na]^+$ 219.0992.

4,4-dimethyl-3-vinylcyclopent-2-en-1-one (214)



266 **214**

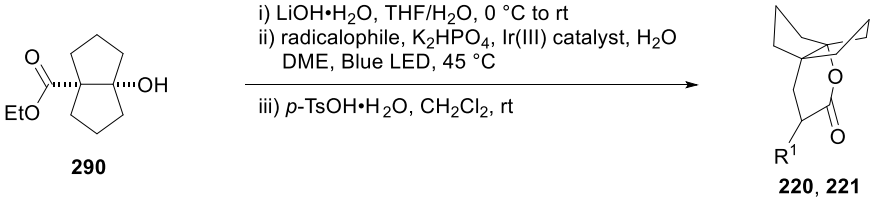
To a solution of enol ether **266** [5] (1.00 g, 6.48 mmol) in THF (32.0 mL) was added vinylmagnesium bromide (1 M solution in THF, 9.7 mL, 9.73 mmol) dropwise at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 12 hours. The reaction mixture was acidified with 1 M HCl aqueous solution (29 mL) and stirred for 1 hour. The aqueous reaction mixture was extracted with EtOAc (3 × 29 mL), and combined organic extracts were dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (*n*-hexane:EtOAc = 30:1 to 20:1) to afford dienylketone **214** (389 mg, 2.86 mmol, 44%) as a pale yellow liquid.*

* Note: **124** is unstable under high concentration because the Diels–Alder dimerization occurs.

214: IR (neat) 3466, 2963, 1686, 1605, 1447, 1364, 1329, 1277, 1169, 1078, 1020, 849, 758, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.49 (ddd, *J* = 17.6, 11.0, 0.6 Hz, 1H), 6.09 (s, 1H), 5.90 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.63 (dd, *J* = 11.0, 1.0 Hz, 1H), 2.36 (s, 2H), 1.28 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.0, 180.9, 129.2, 126.3, 124.2, 52.3, 42.1, 27.4 (2C); HRMS (ESI) *m/z* 159.0780, calcd for $C_9H_{12}NaO_1$ $[M+Na]^+$ 159.0780.

Investigation of a Decarboxylative Giese Reaction of Bicyclo[3,3,0]octane

General Procedure for Hydrolysis and Decarboxylative Giese Reaction, followed by Lactonization



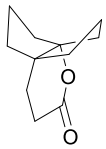
290 **220**, **221**

To the THF/ H_2O (1:1, 450 mM) solution of ester **290** (1.0 eq.) was added $LiOH·H_2O$ (1.5 eq.) at 0 ºC. The reaction mixture was warmed to room temperature and stirred at the same temperature until the starting material was consumed. The reaction was quenched with 1 M HCl aqueous solution. The aqueous layer was extracted with EtOAc (× 3), and the combined organic extracts were dried over Na_2SO_4. After the filtration, the filtrate was concentrated in vacuo to afford carboxylic acid. Carboxylic acid was used in the next reaction without purification.

To a degassed DME (50.0 mM) solution of carboxylic acid (1.0 eq.) was added H_2O (10 eq.), K_2HPO_4 (3.0 eq.), radicalophile (1.5 eq.), and $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (5.0 mol%). The resulting suspension was stirred under the irradiation of blue LED for 24 hours (Aldrich SynLED Parallel Photoreactor was used. The reaction temperature reached 45 °C due to the irradiation). After a period of time, the reaction mixture was diluted with H_2O, and the aqueous layer was extracted with EtOAc (×3). Combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude mixture containing a radical coupling product.

The crude product was dissolved in CH_2Cl_2 (150 mM) and treated with *p*-$TsOH·H_2O$ (20 mol%). After being stirred at room temperature for 6 hours, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (×3). Combined organic extracts were washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the coupling product.

rac-tetrahydro-2*H*,5*H*-4a,7a-propanocyclopenta[*b*]pyran-2-one (220)

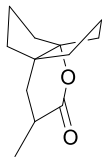


220

Following the general procedure, carboxylic acid **114** (32.6 mg, 0.192 mmol) was coupled with methyl acrylate to give the corresponding lactone. Purification of the crude mixture by flash chromatography (*n*-hexane:EtOAc = 15:1) afforded **220** (15.6 mg, 0.0865 mmol, 45%) as a white solid.

220: IR (neat) 2943, 2866, 1742, 1456, 1335, 1271, 1206, 1190, 1140, 1040, 1001, 976 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.39–2.35 (m, 2H), 1.87–1.81 (m, 4H), 1.77–1.70 (m, 4H), 1.70–1.62 (m, 2H), 1.61-1.51 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 100.1, 48.5, 41.8 (2C), 39.6 (2C), 31.4, 27.9, 22.6 (2C); HRMS (ESI) *m/z* 203.1043, calcd for $C_{11}H_{16}O_2$ $[M+Na]^+$ 203.1043.

rac-3-methyltetrahydro-2*H*,5*H*-4a,7a-propanocyclopenta[*b*]pyran-2-one (221)

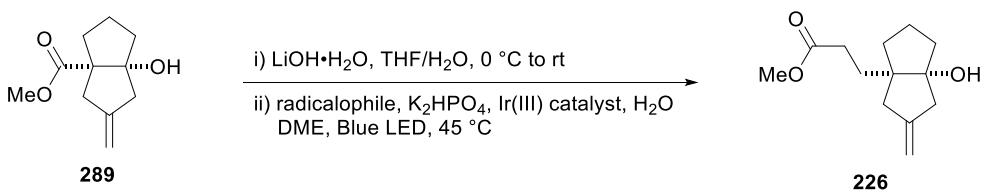


221

Following the general procedure, carboxylic acid **114** (37.7 mg, 0.221 mmol) was coupled with methyl methacrylate to give the corresponding lactone. Purification of the crude mixture by flash chromatography (*n*-hexane:EtOAc = 15:1) afforded **221** (36.6 mg, 0.188 mmol, 85%) as a white solid.

221: IR (neat) 2965, 2861, 1732, 1468, 1198, 1123, 1028, 993, 980, 754, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.36 (dqd, *J* = 13.8, 6.6, 4.2 Hz, 1H), 2.22–2.16 (m, 1H), 2.06 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.80 (dd, *J* = 13.8, 4.2 Hz, 1H), 1.77–1.44 (m, 11H), 1.21 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.4, 99.7, 49.5, 42.4, 42.3, 41.0, 40.4, 37.7, 32.3, 23.8, 21.4, 15.9; HRMS (ESI) *m/z* 217.1194, calcd for $C_{12}H_{18}O_2$ $[M+Na]^+$ 217.1199.

Hydrolysis and Decarboxylative Giese Reaction

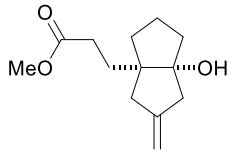


289 **226**

To the THF/ H_2O (1:1, 4.8 mL) solution of ester **289** (424 mg, 2.16 mmol) was added $LiOH \cdot H_2O$ (136 mg, 3.24 mmol) at 0 ºC. The reaction mixture was warmed to room temperature and stirred at the same temperature until the starting material was consumed. The reaction was quenched with 1 M HCl aqueous solution. The aqueous layer was extracted with EtOAc (9.0 mL × 3), and the combined organic extracts were dried over Na_2SO_4. After the filtration, the filtrate was concentrated in vacuo to afford carboxylic acid **225** (366 mg, 2.01 mmol, 93%) as a white form. Carboxylic acid **225** was used in the next reaction without purification. A portion of obtained carboxylic acid **225** (30.4 mg, 0.167 mmol, 8.3w/w%) was used in the next reaction without purification.

To a degassed DME (4.2 mL) solution of carboxylic acid **225** (30.4 mg, 0.167 mmol) was added H_2O (30.1 µL, 1.67 mmol), K_2HPO_4 (87.2 mg, 0.500 mmol), methyl acrylate (22.5 µL, 0.251 mmol), and $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (9.4 mg, 0.00838 mmol). The resulting suspension was stirred under the irradiation of blue LED for 24 hours (Aldrich SynLED Parallel Photoreactor was used. The reaction temperature reached 45 °C due to the irradiation). After the period of time, the reaction mixture was diluted with H_2O (17 mL), and the aqueous layer was extracted with EtOAc (17 mL × 3). Combined organic extracts were washed with brine (17 mL), dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane:EtOAc = 15:1) to afford **226** (9.70 mg, 0.0432 mmol, 26%) as a yellow oil.

rac-methyl 3-((3a*S*,6a*R*)-6a-hydroxy-2-methylenehexahydropentalen-3a(1*H*)-yl)propanoate (226)

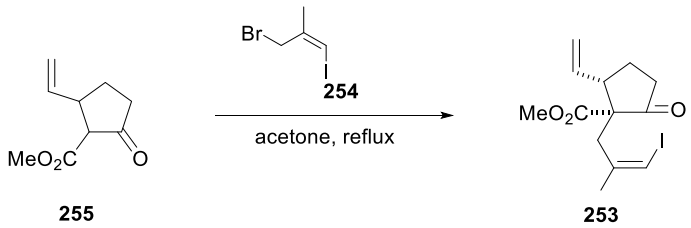


226

226: IR (neat) 3466, 2963, 1686, 1605, 1447, 1364, 1329, 1277, 1169, 1078, 1020, 849, 758, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.82 (app sextet, J = 1.8 Hz, 1H), 4.80 (app sextet, J = 1.8 Hz, 1H), 3.68 (s, 3H), 2.56 (ddd, J=16.0, 3.2, 1.4 Hz, 1H), 2.47 (d, J=16.0 Hz, 1H), 2.37–2.31 (m, 2H), 2.13 (ddd, J=15.6, 3.2, 1.8 Hz, 1H), 1.89 (ddd, J=13.5, 9.6, 4.5 Hz, 1H), 1.76–1.45 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8, 148.2, 107.3, 89.2, 53.5, 51.8, 47.7, 44.0, 40.5, 36.5, 30.9, 30.4, 21.7; HRMS (ESI) *m/z* 247.1302, calcd for $C_{13}H_{20}O_3$ $[M+Na]^+$ 247.1305.

Synthesis of Angular Triquinanes

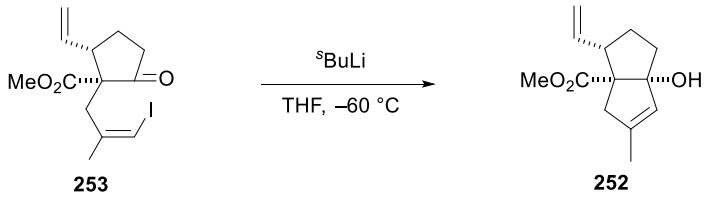
***rac*-methyl (1*R*,5*S*)-1-((*Z*)-3-iodo-2-methylallyl)-2-oxo-5-vinylcyclopentane-1-carboxylate (253)**



255 253

To an acetone (63.0 mL) solution of ketoester **255** (2.49 g, 14.8 mmol) was added allyl bromide **254** (4.63 g, 17.7 mmol) and potassium carbonate (6.13 g, 44.3 mmol) at room temperature. The reaction mixture was warmed to reflux and stirred for 12 hours. After the period of time, the mixture was cooled to room temperature and filtered through Celite (washed with EtOAc 20 mL). The filtrate was concentrated under reduced pressure, and the resulting crude material was purified by silica gel column chromatography (*n*-hexane:EtOAc = 15:1) to afford vinyl iodide **253** (5.11 g, 14.7 mmol, contains a small amount of inseparable impurity) as a pale yellow oil.

***rac*-methyl (3*S*,3a*R*,6a*R*)-6a-hydroxy-5-methyl-3-vinyl-2,3,4,6a-tetrahydropentalene-3a(1*H*)-carboxylate (252)**



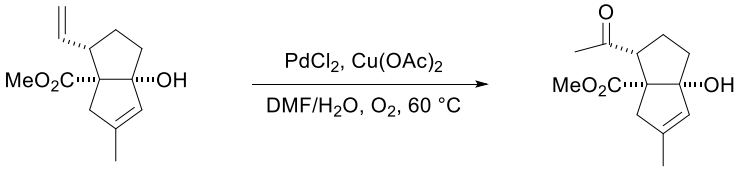
253 252

To a THF (280 mL) solution of vinyl iodide **253** (3.44 g, 9.88 mmol) was added *sec*-butyllithium (1.23 M solution in cyclohexane/*n*-hexane, 14.5 mL, 17.9 mmol) dropwise at –60 °C. After being stirred at the same temperature for 1 hour, the reaction was quenched by an addition of MeOH (4.10 mL, 101 mmol). The mixture was warmed to room temperature and diluted with saturated aqueous solution of NH_4Cl (180 mL). The aqueous layer was extracted with EtOAc (200 mL × 3). The combined organic extracts were washed with brine (125 mL) and dried over Na_2SO_4. After filtration, the extracts were concentrated under reduced pressure, and purified by silica gel chromatography (*n*-hexane:EtOAc = 10:1) to afford bicyclic compound **252** (1.11 g, 4.98 mmol, 50%) as a yellow oil.

252: IR (neat) 3497, 3077, 3013, 2951, 2916, 2857, 2355, 2251, 1717, 1655, 1640, 1437, 1379, 1337, 1317, 1242, 1217, 1180, 1152, 1078, 1009, 910, 822, 758, 735, 667, 648 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.2, 10.2, 7.8 Hz, 1H), 5.38–5.35 (m, 1H), 5.06 (ddd, *J* = 17.2, 1.7, 0.7 Hz, 1H), 5.01 (ddd, *J* = 10.3, 1.7, 0.7 Hz, 1H), 3.69 (s, 3H), 3.03 (ddd, *J* = 17.0,

2.4, 1.2 Hz, 1H), 2.56 (bs, 1H), 2.40 (app t, J = 9.6, 7.9 Hz, 1H), 2.19–2.10 (m, 3H), 2.08–2.01 (m, 1H), 1.78–1.72 (m, 1H), 1.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 141.7, 138.1, 130.2, 116.2, 95.9, 66.4, 55.9, 51.7, 43.2, 38.4. 29.6, 17.0; HRMS (ESI) *m/z* 245.1154, calcd for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1148.

rac-methyl (3*R*,3a*R*,6a*R*)-3-acetyl-6a-hydroxy-5-methyl-2,3,4,6a-tetrahydropentalene-3a(1*H*)-carboxylate (259)

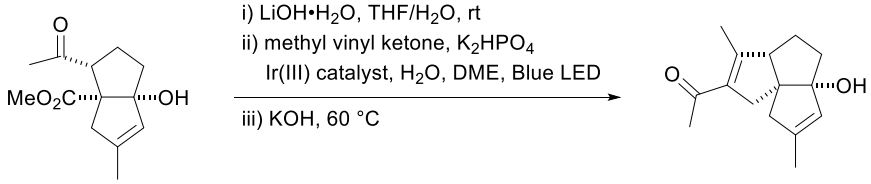


252 259

To a solution of bicyclic compound **252** (381 mg, 1.71 mmol) in DMF/H_2O (7:1, 20 mL) was added $PdCl_2$ (152 mg, 0.856 mmol) and $Cu(OAc)_2$ (218 mg, 1.20 mmol) at room temperature and stirred for 24 hours at 60 °C. After the period of time, the reaction mixture was filtered through Celite (washed with EtOAc (20 mL)). The filtrate was added brine (51 mL), and the resulting solution was extracted with EtOAc (3 × 170 mL). The combined organic extracts were dried over Na_2SO_4 and filtrated. The solvent was removed in vacuo at 40 °C, and obtained crude mixture was purified by silica gel chromatography (*n*-hexane:EtOAc = 5:1) to afford ketone **259** (191 mg, 0.853 mmol, 46%) as a yellow oil.

259: IR (neat) 3385, 2951, 2860, 1734, 1707, 1663, 1437, 1375, 1319, 1238, 1086, 1045, 1011, 939, 849, 821, 675 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.36–5.32 (m, 1H), 3.66 (s, 3H), 3.26 (ddd, J = 17.4, 1.8, 0.6 Hz, 1H), 2.77–2.73 (m, 1H), 2.41–2.34 (m, 1H), 2.27 (d, J = 17.4 Hz, 1H), 2.16 (s, 3H), 2.13–2.01 (m, 3H), 1.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5, 174.0, 141.8, 129.8, 96.5, 64.4, 63.7, 52.0, 46.2, 37.8, 28.8, 27.1, 16.7; HRMS (ESI) *m/z* 261.1098, calcd for $C_{13}H_{18}NaO_4$ $[M+Na]^+$ 261.1097.

rac-1-((3a*S*,5a*R*,8a*R*)-5a-hydroxy-3,7-dimethyl-1,3a,4,5,5a,8-hexahydrocyclopenta[*c*]pentalen-2-yl)ethan-1-one (263)



259 263

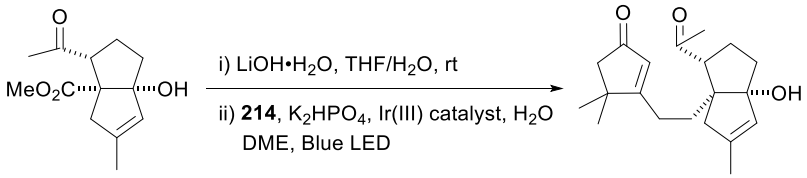
To a THF/ H_2O (1:1, 560 µL) solution of ketone **259** (44.2 mg, 185 µmol) was added $LiOH{\cdot}H_2O$ (11.7 mg, 278 µmol) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction was quenched with 1 M HCl aqueous solution, and the aqueous layer was extracted with EtOAc (1.0 mL × 3). Combined organic extracts were dried

over Na_2SO_4, filtrated, and concentrated in vacuo to afford carboxylic acid **251** (47.2 mg, quant.) as a brown form. Carboxylic acid **251** was used in the next reaction without purification.

To a degassed DME (2.9 mL) solution of carboxylic acid **251** (32.9 mg, 0.147 mmol) was added H_2O (26.4 μL, 1.47 mmol), K_2HPO_4 (78.4 mg, 0.440 mmol), methyl vinyl ketone (17.9 μL, 0.220 mmol), and $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (8.23 mg, 0.00734 mmol). The resulting suspension was stirred under the irradiation of blue LED for 24 hours (Aldrich SynLED Parallel Photoreactor was used. The reaction temperature reached 45 °C due to the irradiation). After the period of time, KOH (247 mg, 4.40 mmol) was added to the reaction mixture and further stirred for 6 hours at 60 ºC. The reaction mixture was diluted with H_2O (19 mL) and the aqueous layer was extracted with EtOAc (3 ×19 mL). Combined organic extracts were washed with brine (19 mL), dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane:EtOAc = 2:1) to afford the triquinane product **263** (18.2 mg, 0.0783 mmol, 53%) as a white solid.

160: IR (neat) 3466, 2963, 1686, 1605, 1447, 1364, 1329, 1277, 1169, 1078, 1020, 849, 758, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.19 (s, 1H), 3.28 (ddd, *J* = 16.4, 1.8, 1.8 Hz, 1H), 2.81 (d, *J* = 8.2 Hz, 1H), 2.59–2.54 (m, 2H), 2.39 (d, *J* = 17.0 Hz, 1H), 2.25 (s, 3H), 1.98 (m, 3H), 1.83 (dd, *J* = 11.7, 5.6 Hz, 1H), 1.75–1.73 (m, 3H), 1.70 (dd, *J* = 11.7, 5.6 Hz, 1H), 1.64–1.56 (m, 1H), 1.51 (ddd, *J* = 11.7, 6.6, 6.6 Hz, 1H), 1.34 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 153.6, 145.0, 135.2, 130.0, 94.1, 66.8, 55.6, 51.1, 41.0, 35.8, 30.6, 26.5, 16.9, 15.0; HRMS (ESI) *m/z* 255,1354 calcd for $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356.

rac-3-(2-((3*R*,3a*S*,6a*R*)-3-acetyl-6a-hydroxy-5-methyl-2,3,4,6a-tetrahydropentalen-3a(1*H*)-yl)ethyl)-4,4-dimethylcyclopent-2-en-1-one (268)



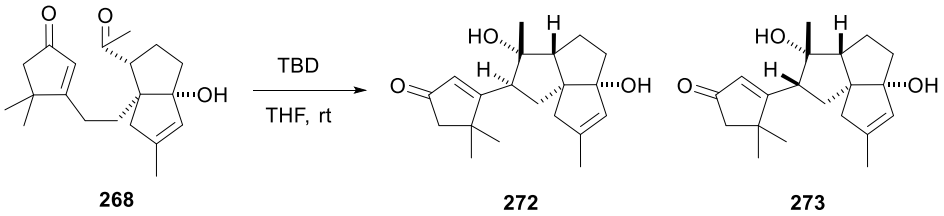
259 **268**

To a degassed DME (6.4 mL) solution of carboxylic acid **251** (36.5 mg, 0.163 mmol) was added H_2O (29.3 μL, 1.63 mmol), K_2HPO_4 (85.0 mg, 0.488 mmol), dienylketone **214** (33.2 mg, 0.244 mmol), and $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (9.13 mg, 0.00814 mmol). The resulting suspension was stirred under the irradiation of blue LED for 24 hours (Aldrich SynLED Parallel Photoreactor was used. The reaction temperature reached 45 °C due to the irradiation). During the reaction, additional dienylketone **214** was added at 3 hours (11.1 mg, 0.0815 mmol) and 6 hours (11.1 mg, 0.0815 mmol) time points after reaction initiation. After the period of time, the reaction mixture was diluted with H_2O (19 mL) and the aqueous phase was extracted with EtOAc (3 ×19 mL). Combined organic extracts were washed with brine (19 mL), dried over

Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane:EtOAc = 5:1 to 3:1) to afford the coupling product **268** (26.9 mg, 0.0850 mmol, 52%) as a pale yellow oil.

268: IR (neat) 3466, 2963, 1686, 1605, 1447, 1364, 1329, 1277, 1169, 1078, 1020, 849, 758, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.87 (t, *J* = 1.5 Hz, 1H), 5.19 (dd, *J* = 3.0, 1.2 Hz, 1H), 2.82 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.51–2.40 (m, 2H), 2.33 (d, *J* = 17.9 Hz, 1H), 2.29 (s, 2H), 2.17 (s, 3H), 2.14 (d, *J* = 17.9 Hz, 1H), 2.04 (dd, *J* = 12.0, 6.0 Hz, 1H), 1.89–1.84 (m, 3H), 1.73-1.66 (m, 2H), 1.69 (s, 3H), 1.61 (app dtd, *J* = 13.2, 12.6, 6.6 Hz, 1H), 1.21 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.3, 208.2, 190.7, 143.6, 129.5, 127.1, 94.8, 60.0, 55.0, 51.7, 45.7, 43.5, 39.6, 35.6, 31.0, 27.2 (2C), 26.2, 24.1, 16.6; HRMS (ESI) *m/z* 339.1939, calcd for $C_{20}H_{28}NaO_3$ $[M+Na]^+$ 339.1931.

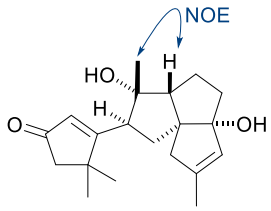
rac-3-((2*S*,3*S*,3a*R*,5a*R*,8a*S*)-3,5a-dihydroxy-3,7-dimethyl-1,2,3,3a,4,5,5a,8-octahydrocyclopenta[*c*]pentalen-2-yl)-4,4-dimethylcyclopent-2-en-1-one (272) and rac-3-((2*R*,3*S*,3a*R*,5a*R*,8a*S*)-3,5a-dihydroxy-3,7-dimethyl-1,2,3,3a,4,5,5a,8-octahydrocyclopenta[*c*]pentalen-2-yl)-4,4-dimethylcyclopent-2-en-1-one (273)



268 **272** **273**

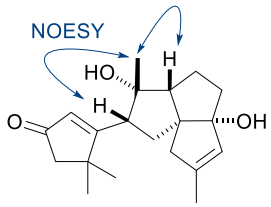
To a stirred solution of coupling product **268** (24.7 mg, 0.0781 mmol) in THF (2.3 mL) was added TBD (32.6 mg, 0.234 mmol) at room temperature and stirred for 18 hours. The reaction was quenched with saturated aqueous solution of NH_4Cl (2.0 mL), and the aqueous layer was extracted with ethyl acetate (3 ×2.9 mL). Combined organic extracts were washed with brine (2.0 mL), dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane:EtOAc = 2:1) to afford the tricyclic compound **272** and **273** (20.9 mg, 0.0660 mmol, **272**:**273** = 1:3, 85%) as a pale yellow oil.

272: IR (neat) 3422, 2957, 2924, 2853, 1684, 1601, 1466, 1445, 1364, 750 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.24 (s, 1H), 2.56–2.46 (m, 3H), 2.33 (dd, *J* = 12.0, 5.5 Hz, 1H), 2.28 (d, *J* = 4.8 Hz, 2H), 2.18 (dd, *J* = 8.3, 4.1 Hz, 1H), 1.90–1.82 (m, 2H), 1.77–1.72 (m, 2H), 1.71 (s, 3H), 1.61 (ddd, *J* = 8.3, 4.1, 2.4 Hz, 1H), 1.41–1.37 (m, 2H), 1.23 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8, 189.1, 144.4, 129.8, 129.3, 94.5, 83.5, 66.3, 59.8, 51.5, 50.7, 48.4, 44.1, 41.8, 38.6, 27.8, 26.9 (2C), 24.4, 16.9; HRMS (ESI) *m/z* 000.0000, calcd for $C_{20}H_{28}NaO_3$ $[M+Na]^+$ 339.1931.



272

273: IR (neat) 3437, 2963, 2359, 2342, 1690, 1603, 1462, 1443, 1410, 1366, 1277, 1258, 1171, 1090, 754 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.30 (s, 3H), 5.27 (s, 1H), 2.64 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.57 (d, *J* = 16.5 Hz, 1H), 2.43 (d, *J* = 16.5 Hz, 1H), 2.36 (app t, *J* = 13.2, 1H), 2.29 (d, *J* = 3.7 Hz, 2H), 2.05 (d, *J* = 9.2 Hz, 1H), 2.01 (ddd, *J* = 12.4, 7.3, 1.4 Hz, 1H), 1.90 (ddd, *J* = 12.6, 7.2, 1.8 Hz, 1H), 1.75 (s, 3H), 1.74–1.67 (m, 2H), 1.52–1.45 (m, 1H), 1.44 (s, 1H), 1.232 (s, 3H), 1.226 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 187.8, 143.5, 130.2, 129.7, 94.1, 82.2, 65.1, 59.8, 53.9, 50.7, 49.5, 43.9, 43.2, 38.9, 27.7, 27.2, 27.0, 23.0, 17.0; HRMS (ESI) *m/z* 339.1924, calcd for $C_{20}H_{28}NaO_3$ $[M+Na]^+$ 339.1931.

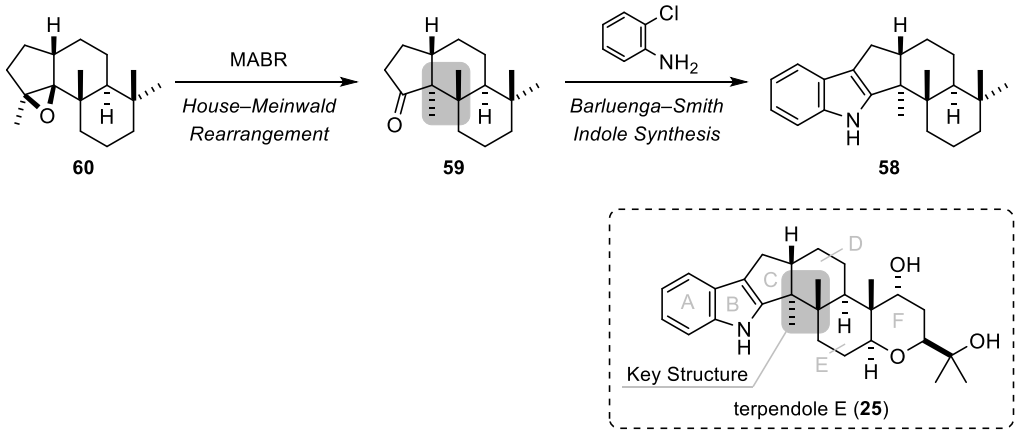


273

Chapter 5. Grand Summary

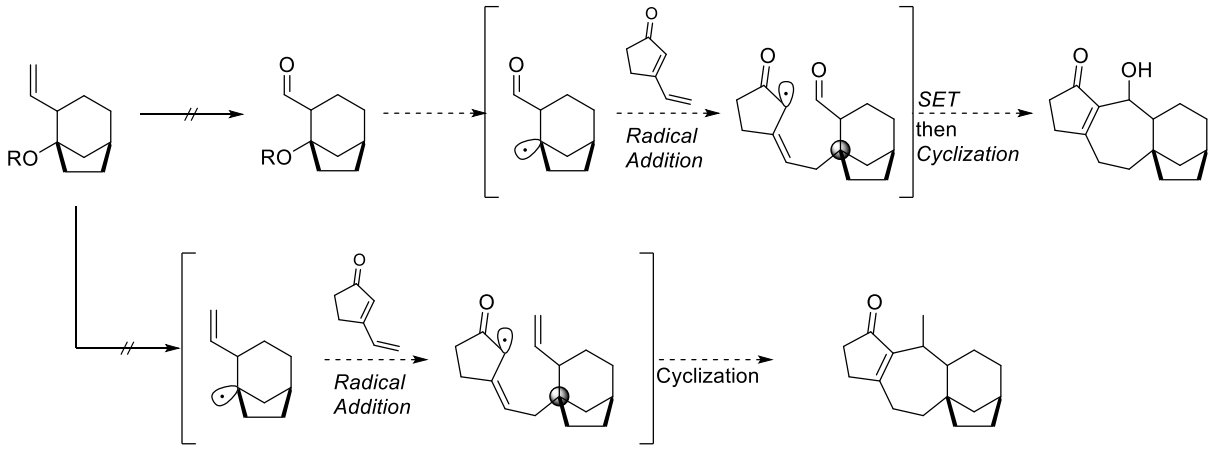
This study investigated methods for the stereoselective construction of quaternary carbons with potential applications in natural product synthesis. In Chapter 2, attention was focused on the contiguous asymmetric quaternary carbons, a structural feature of indole terpenes, and efforts were made to develop a construction method using the House–Meinwald rearrangement. In Chapter 3, the target was natural products with a bicyclo[3.2.1]octane framework. The study aimed to develop an annulation strategy that simultaneously induces the addition of two components followed by cyclization using the bridgehead position of the bicyclo[3.2.1]octane ring. In Chapter 4, the goal was to develop a strategy combining annulation using bicyclo[3.3.0]octane as a building block with a skeletal rearrangement that converts the bicyclo[3.3.0]octane framework to a bicyclo[3.3.0]octane framework.

In Chapter 2, I focused on developing a method for constructing contiguous asymmetric quaternary carbon centers, a key structural feature of indole terpenoids. By treating epoxide **60** with MABR as a super Lewis acid, the House–Meinwald rearrangement was successfully induced, enabling the construction of contiguous asymmetric quaternary carbon centers (Scheme 1). Furthermore, the introduction of an indole moiety into the resulting ketone **59** allowed the synthesis of the A–E ring system of terpendole E (**25**). This study provides a novel method for constructing a quaternary carbon center at a sterically congested position. Furthermore, ketone **59** is expected to serve as a valuable intermediate for the synthesis of various indole terpenoids through the application of C–H oxidation reactions.



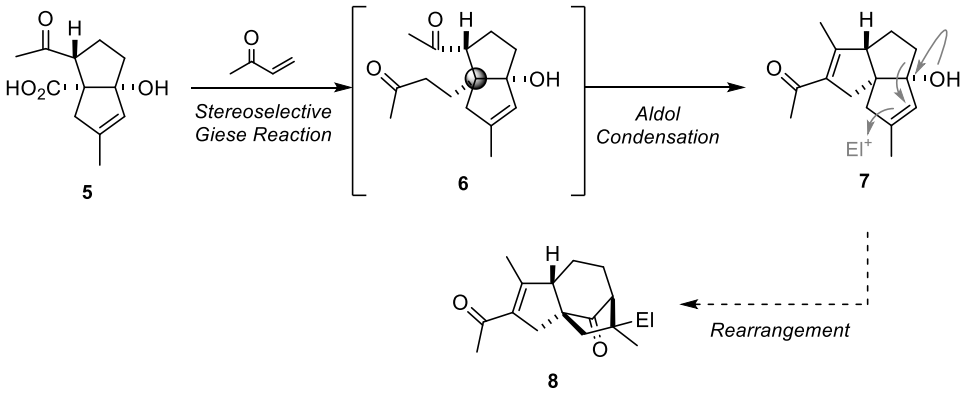
Scheme 1. Construction of contiguous quaternary carbon centers via House–Meinwald rearrangement and introduction of the indole moiety

In chapter 3, aiming to develop a novel annulation method utilizing a bicyclo[3.2.1]octane ring as a building block for constructing natural product frameworks, research was undertaken. Despite various attempts, generating a radical at the bridgehead position of the bicyclo[3.2.1]octane ring was unsuccessful. This difficulty is likely attributed to the rigidity of the bicyclo[3.2.1]octane ring and the high strength of the C–O bond.



Scheme 2. Annulation using bicyclo[3.2.1]octane core as a building block

In Chapter 4, I developed a method for stereoselective Giese reactions at the ring-junction position of bicyclo[3.3.0]octane and applied this approach to construct natural product frameworks (Scheme 3). By leveraging the properties of the bicyclo[3.3.0]octane system, I demonstrated that a quaternary carbon center can be constructed stereoselectively. Furthermore, by combining this approach with aldol reaction, I established a method for constructing angular triquinane frameworks. While there are limitations in the range of applicable substrates, this study proposes a novel and straightforward method for constructing cyclic structures from two components. Additionally, as the bicyclo[3.3.0]octane system is expected to rearrange into the bicyclo[3.2.1]octane framework, further developments and applications of this strategy are anticipated.



Scheme 3. Annulation using bicyclo[3.3.0]octane core as a building block

In conclusion, this study employed both intramolecular and intermolecular reactions to achieve the stereoselective construction of quaternary carbon center by leveraging the structural features of compounds, facilitating the synthesis of natural product frameworks. This strategy is expected to contribute significantly to the synthesis of complex organic molecules.

List of Publications

1) Toward the Synthesis of Paspaline-type Indole-terpenes: Stereoselective Construction of Core Scaffold with Contiguous Asymmetric Quaternary Carbon Centers
Ichiro Hayakawa, Naochika Matsumaru, Akira Sakakura
J. Org. Chem. **2021**, *86*, 9802–9810.
(*Chapter 2*)

2) Synthesis of an Angular Triquinane Structure Based on a Stereoselective Decarboxylative Giese Reaction at an Angular Position in a Diquinane Skeleton
Naochika Matsumaru, Takumu Nishitani, Haruki Mizoguchi, and Akira Sakakura

(*Chapter 4*)

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