DISSERTATION

Studies toward the Asymmetric Total Synthesis of Cyclocitrinol

(シクロシトリノールの不斉全合成研究)

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Contents

Introduction

Steroids are class of naturally occurring organic compounds with a basic structure consisting of a 6-6-6-5 tetracyclic carbon framework. These compounds are widely distributed in nature, including plants, animals, and bacteria. Steroids play a variety of roles in the cells of organisms, for example, testosterone and estrone are known as male and female hormones, and cholic acid and cholesterol are components of bile acids and biological membranes, respectively. The studies of steroid chemistry were initiated in the early 19th century, and the fundamental aspects were, as a result of intense researches, firmly laid in the early 20th century. Synthetic chemists were particularly interested in how to construct the polycyclic structure with contiguous stereogenic centers, that caused progress in developing new annulation methods. Scheme 1 shows a representative example, which is one of the most important annulation methods to date.

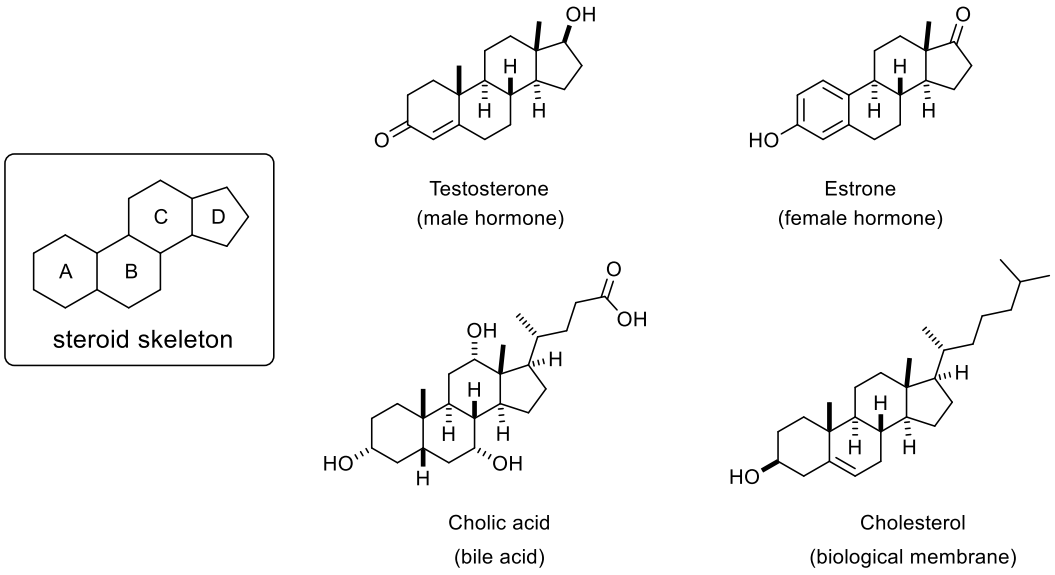
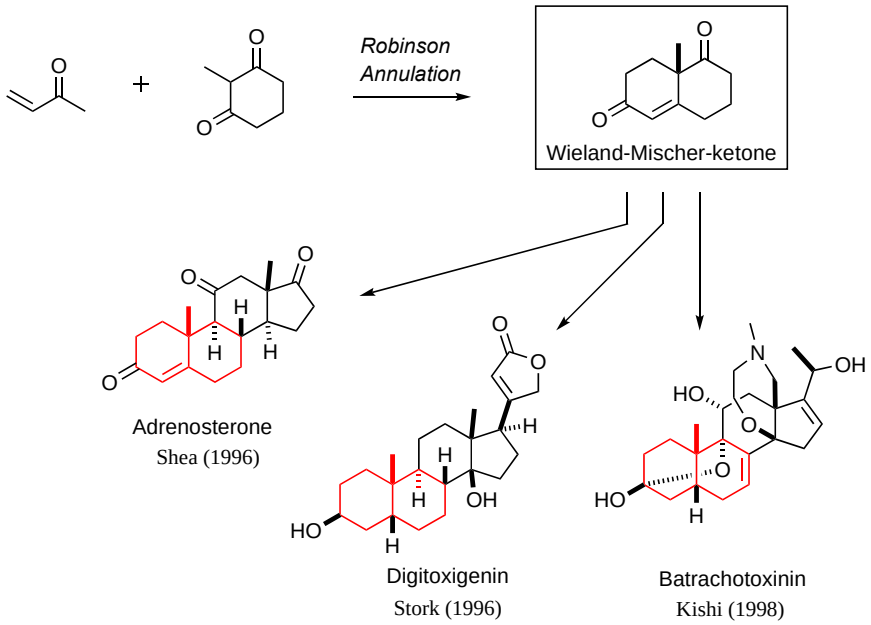


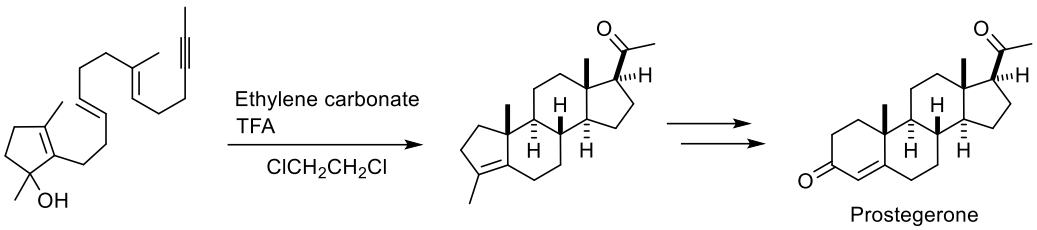
Figure 1. Structure of normal steroids



Scheme 1. Application of Robinson annulation

Robinson annulation has been considered as a powerful method for the construction of six-membered carbocycles, and the method has found widespread use in steroid synthesis. For example, Wieland-Miescher ketone, which was synthesized through Robinson annulation in 1950[1], was employed as the starting material in the total synthesis of several steroids, such as adrenosterone[2], digitoxigenin[3], and batrachotoxinin A[4]. The bicyclo ketone is advantageous as a precursor of the AB ring of steroids, because the B-ring ketone moiety is useful for constructing the CD ring system. In addition, Wieland-Miescher ketone can be obtained as an enantiopure form on a multi-gram scale by using a chiral organocatalyst. Thus, it has been used in the industrial production of several bioactive steroids, which led to the use of steroids as drugs.

Cation-π cyclization of polyene compounds has long been studied as an effective method of constructing steroid skeletons. This type of approach is based on the biosynthetic hypothesis, which is now widely recognized as one of the most promising approaches to natural product synthesis. In 1971, Johnson reported the total synthesis of prostegerone[5] in which the tetracyclic skeleton was constructed in one step by the polyene cyclization, proving the usefulness of this method for the construction of complex polycyclic molecules (Scheme 2).



Scheme 2. Application of poly-ene cyclization

On the other hand, a class of steroids, which have a carbon skeleton quite different from that of normal steroids such as, cortistatin A[6], aplysiasecosterol A[7], and swinhoeisterol A[8], have been isolated (Figure 2). These compounds are named as *seco*- and *aveo*-steroids, which means that cleavage of a ring structure or swapping of bonds has occurred.

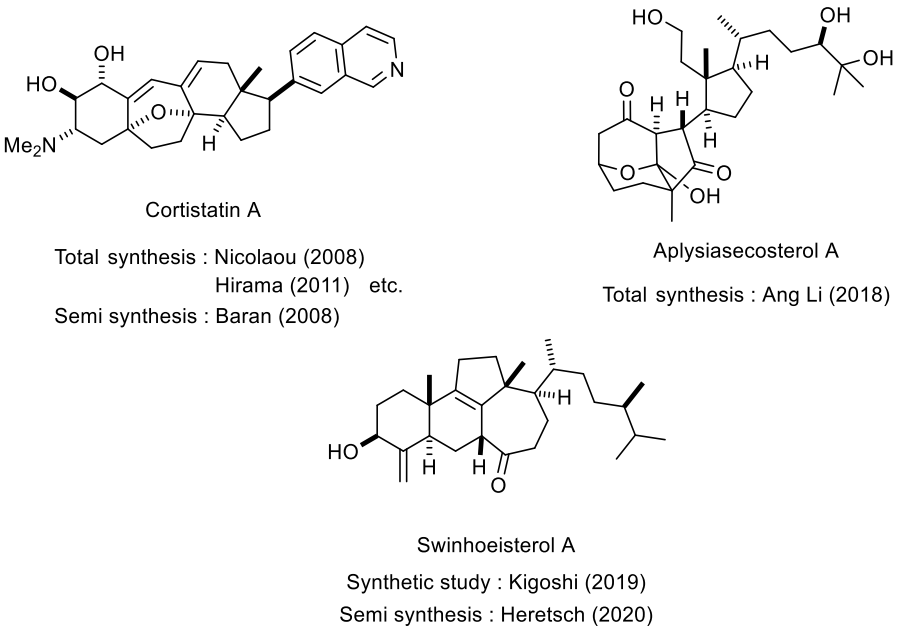


Figure 2. Structure of novel steroids having unusual carbon skeletons

The biological activities of these steroids have not been studied in detail because of the smaller supply of them from natural sources than that of the normal ones, but some of them have been found to exhibit interesting activity. In addition, the unusual structure of these steroids has attracted much attention from synthetic chemists as challenging target molecules. Since the conventional methods for normal steroid synthesis are not suitable, new strategies to construct the unique carbon skeleton should be provided.

Cyclocitrinol : a novel steroid with 7/7/6/5 tetra cyclic core

Cyclocitrinol (**1**), a unique steroid possessing a novel AB ring system, was isolated from a terrestrial *Penicillium citrinum* by Gräfe and co-workers in 2000 (Figure 3)[9]. They submitted the original structure of **1** as **2**, but it was revised by Crews and co-workers in 2003 based on structure determination of isocyclocitrinol (**3**) by X-ray crystallographic analysis.[10]

Structurally, cyclocitrinol has a 7/7/6/5 tetracyclic carbon framework containing a unique bicyclo [4.4.1] undecane skeleton with a characteristic bridgehead olefin moiety. To date, more than 25 derivatives such as isocyclocitrinol A (**3**), neocyclocitrinol A (**4**), and norcyclocitrinol A (**5**) were isolated. Most of them have the common AB ring and a side chain which is different with one another, while *erythro*-11α-hydroxyneocyclocitrinol (**6**) and (16R)-16-hydroxy-24-epi-cyclocitrinol (**7**) have oxygenated core skeletons.[11]

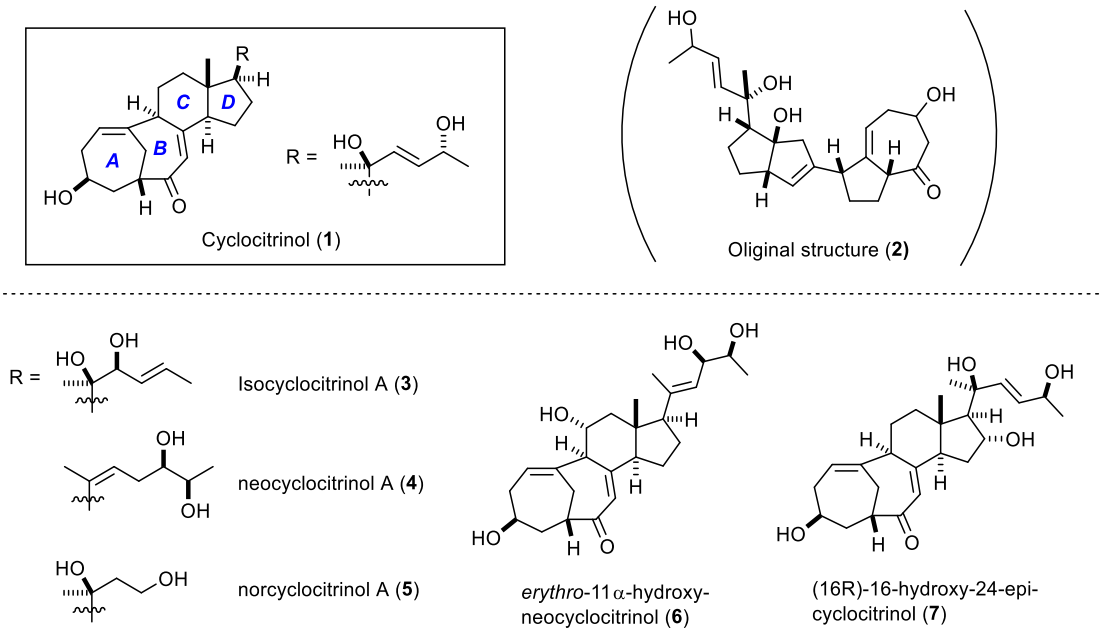
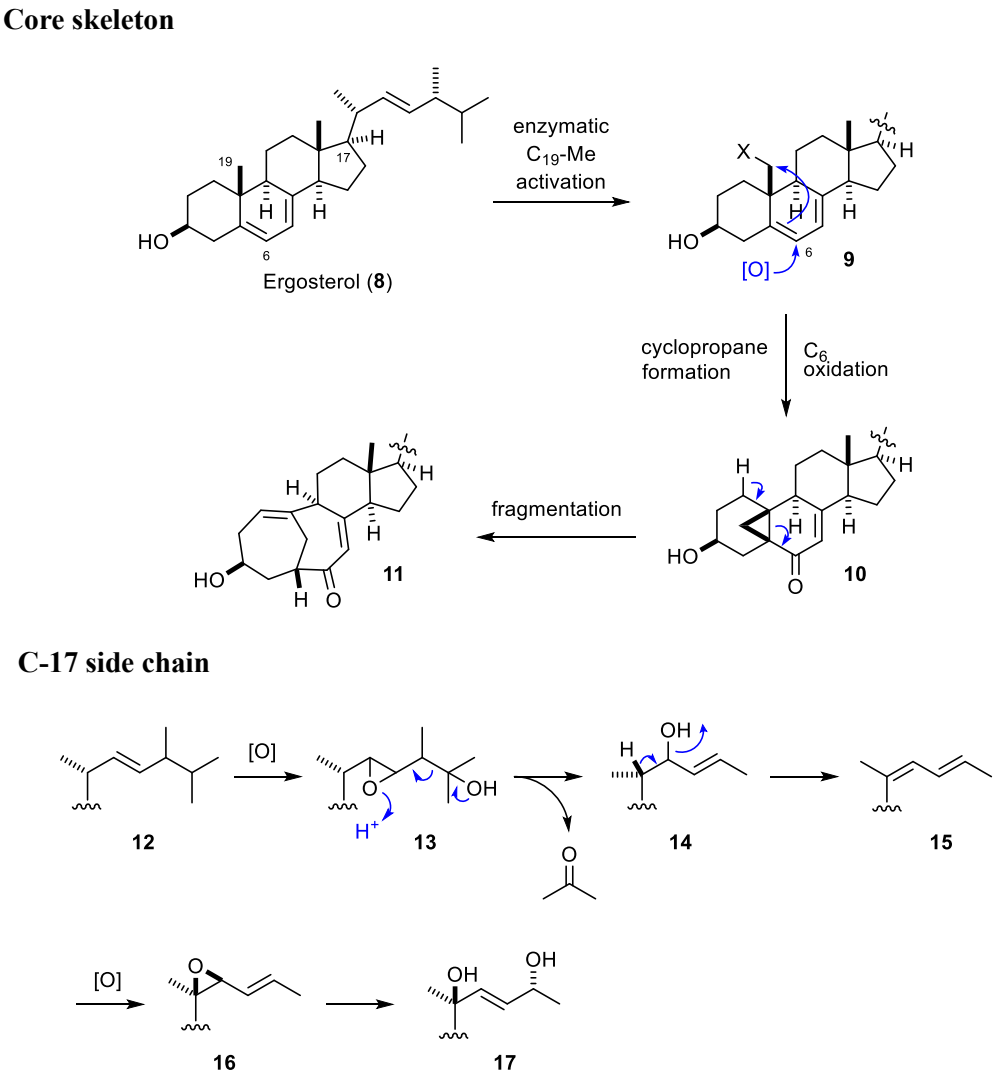


Figure 3. Structure of cyclocitrinol and derivative

Cyclocitrinol (**1**) was reported to exhibit an inducing effect on the production of cyclic adenosine monophosphate (cAMP) in GPR12-transfected CHO cells at 10μM. GPR12 is a protein receptor that is highly expressed in the central nervous system, and cAMPs are second messengers involved in a wide variety of processes in neurons, including differentiation, survival, polarity formation, process elongation, axonal guidance, axonal regeneration, synaptic transmission,

synaptic plasticity, and hormone secretion. Therefore, cyclocitrinol has shown promise as a treatment drug for a variety of neurological disorders, including spinal cord injury and stroke.

The biosynthetic hypothesis of **1** was advocated by Rodrigues-Filho as shown in Scheme 3.[11a]



Scheme 3. Presumed biogenesis of cyclocitrinol from ergosterol

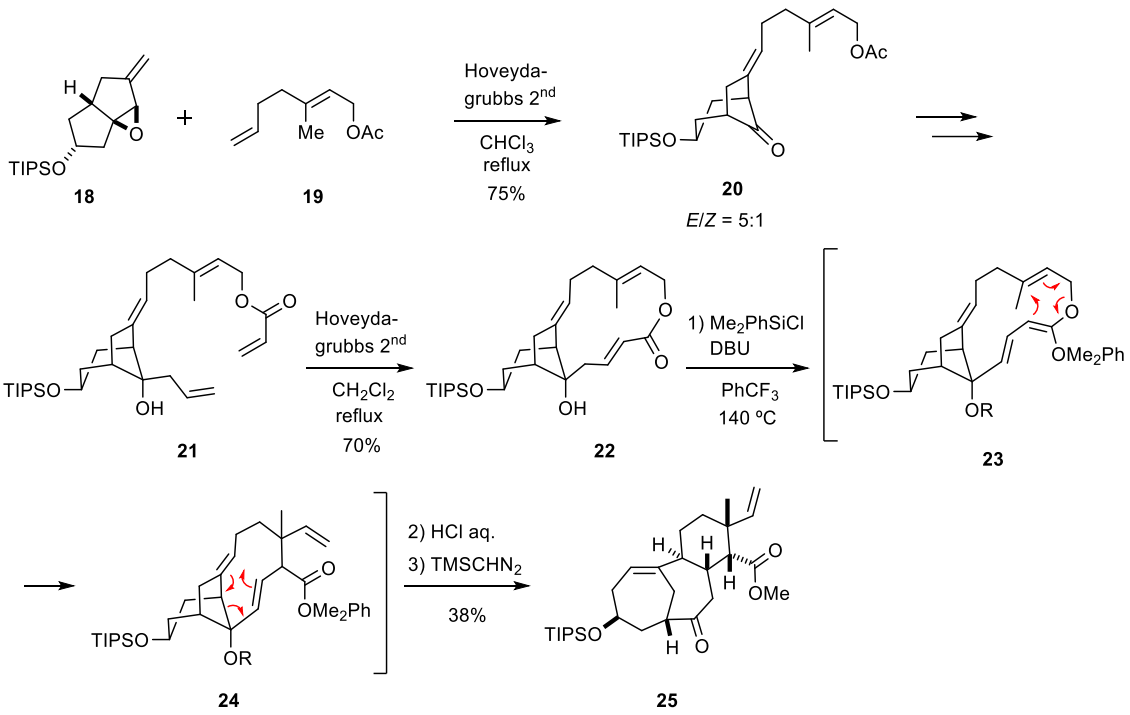
Cyclocitrinol was expected to arise from Ergosterol (**8**) due to the fact that cyclocitrinols and sterol are often co-isolated. The enzyme activates the C-19 methyl group for the generation of the electrophilic center, and subsequent nucleophilic oxidation causes the C-C bond formation between the C-5 and C-19 positions, giving rise to a cyclopropane intermediate (**8** to **10**). Finally, the cyclopropane ring is cleaved by deprotonation at the C-1 position, resulting in generation of

the bicyclo[4.4.1]undecane AB ring system. The side chain of ergosterol could be transformed into an allyl alcohol through oxidation to epoxy alcohol **13** and elimination of acetone (**12** to **14**). The resulting alcohol could undergo subsequent elimination process followed by oxidation/addition of H_2O to afford cyclocitrinol side chain **(14** to **17)**.

Synthetic studies by other groups

As mentioned above, cyclocitrinol (**1**) possesses a unique bicyclo[4.4.1]undecane AB ring system containing a highly strained bridgehead olefin, that makes it an attractive target for synthetic organic chemists. There have been several reports on the synthetic study of **1**.

In 2014, Leighton and co-workers succeeded in constructing the tricyclic skeleton of **1** using the tandem Ireland Claisen/Cope rearrangement reactions[12] (Scheme 4).

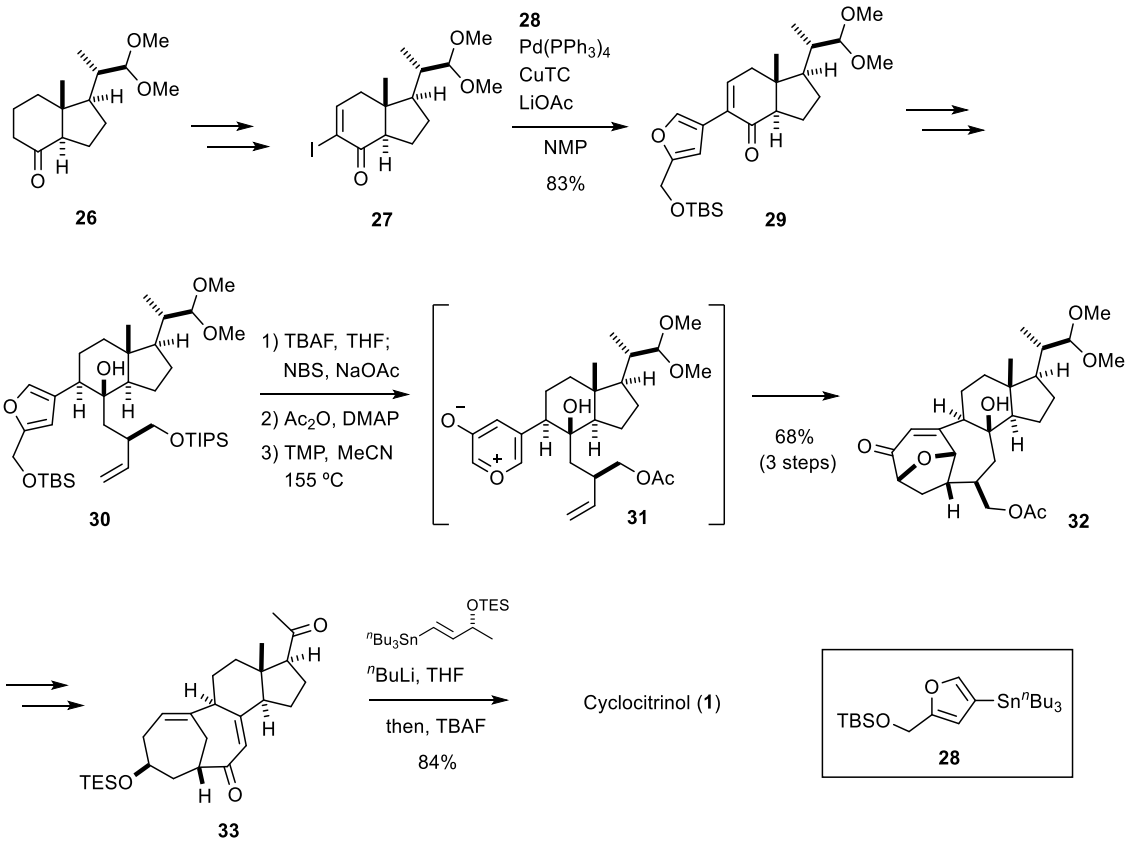


Scheme 4. Leighton's approach for construction tricyclic skeleton

Epoxide **18** and alkene **19** was subjected to a cross-metathesis reaction accompanied with semi-pinacol rearrangement, giving rise to bicyclic ketone **20**. After introduction of an allyl group and an acrylate moiety, the resulting hydroxy ester **21** was transformed into macrocyclic lactone **22** via a ring-closing-metathesis reaction. The key tandem reaction was initiated with conversion of

22 to silyl ketene acetal **23**, which underwent the Ireland-Claisen rearrangement followed by the Cope rearrangement at 140 °C. The product was obtained as ester **25** through one-pot methylation, the tricyclic skeleton of which corresponds to the ABC ring of cyclocitrinol.

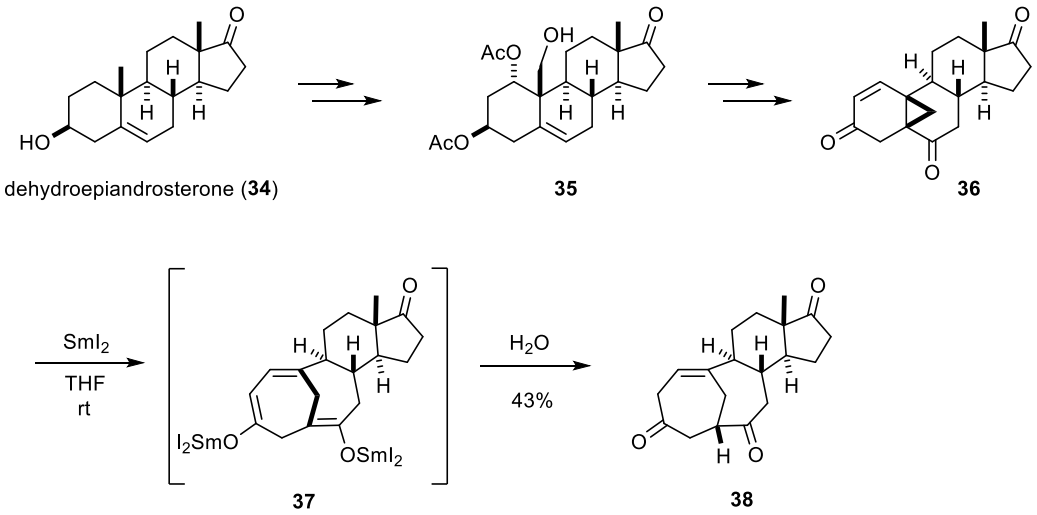
In 2018, Li and co-workers reported the first asymmetric total synthesis of **1** based on type II intramolecular [5+2] cycloaddition reaction developed by his own group[13] (Scheme 5). Initially, optically active bicyclic ketone **26**, which was prepared from vitamin D_2, was converted to iodo enone **27**. After connecting with the furan segment **28** by a Still coupling and introducing a homoallyl side chain, the furan moiety was converted to an oxidopyrylium ion **31** which underwent an intramolecular [5+2] cycloaddition reaction, affording tetracyclic ketone **32** in 68% yield for 3 steps. After several steps to complete the transformation of the AB ring moiety with the correct functionalities, the resulting diketone **33** was converted to cyclocitrinol (**1**) through installation of the side chain. Thus, they synthesized the desired natural product in 18 steps (Longest linear sequence) from vitamin D_2 analog.



Scheme 5. Li's work: first asymmetric total synthesis of 1

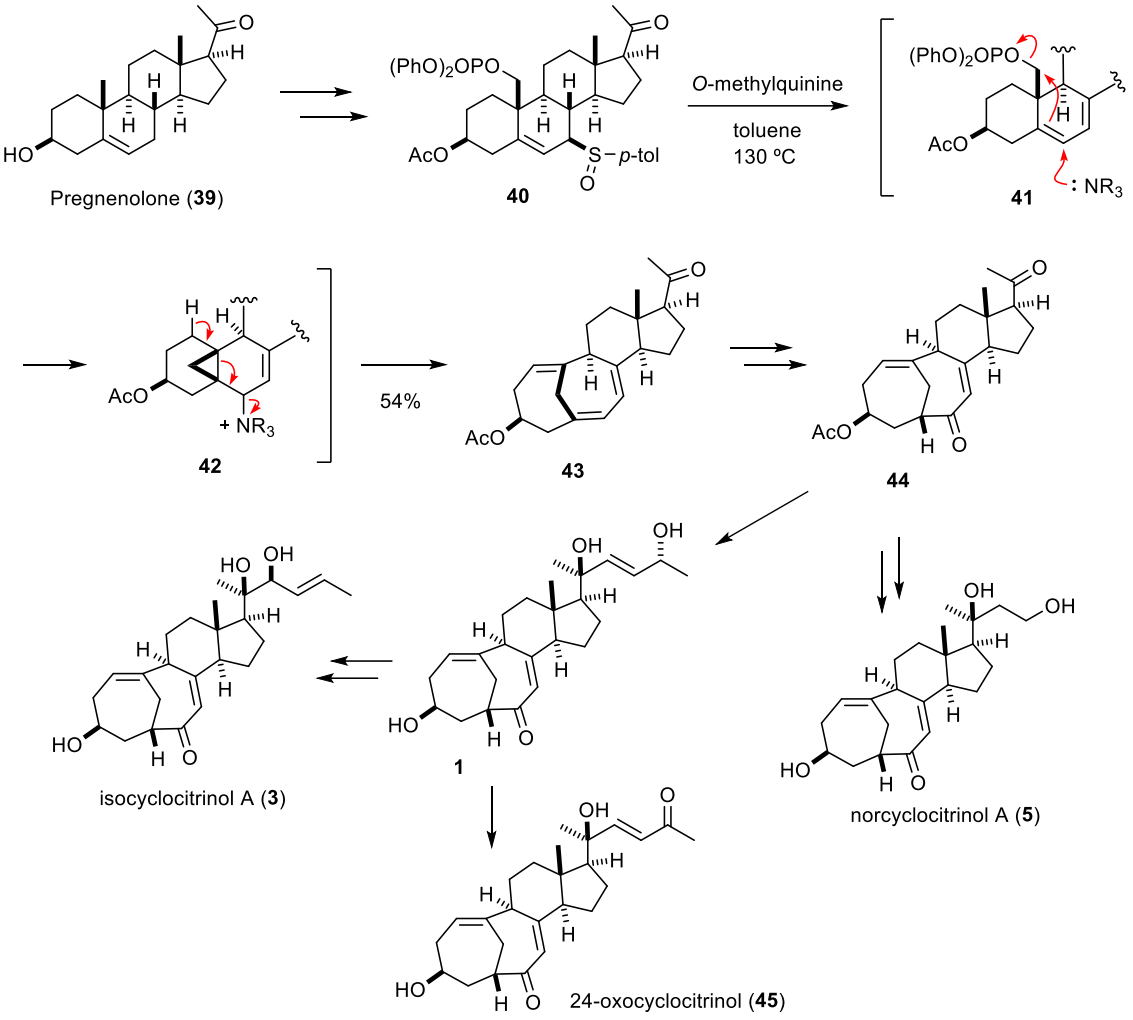
Studies of semi-synthesis from normal steroids

The synthesis of **1** by biomimetic strategy starting from commercially available steroids was explored by two groups. Schmalz demonstrated construction of the AB ring system using reductive fragmentation of a cyclopropyl ketone derivative as shown in Scheme 6[14]. They started the semi-synthesis from dehydroepiandrosterone (**34**) which was transformed into **35** through several oxidation steps. After conversion to triketone **36**, the cyclopropane moiety was cleaved by the treatment with SmI_2, generating enolate **37**. The intermediate was quenched with water to produce triketone **38** possessing the AB ring system with the highly strained alkene moiety.



Scheme 6. Synthesis of the core structure via SmI_2-mediated fragmentation

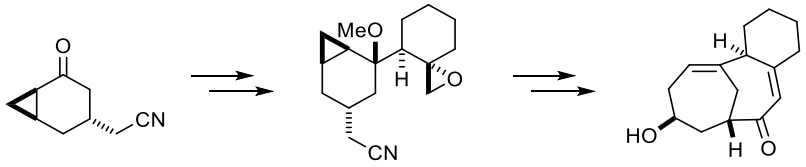
Recently, Gui and co-workers reported a scalable synthesis of cyclocitrinol starting with pregnenolone (**39**)[15] (Scheme 7). After transformation of **39** into sulfoxide **40**, the AB ring system was constructed simply by heating in toluene with an amine. This reaction consists of three stages: 1) syn-elimination of the sulfoxide group (**40** to **41**), 2) formation of a cyclopropane ring through π-cyclization accompanied with the nucleophilic attack of the bulky amine (**41** to **42**), 3) ring cleavage combined with deprotonation at the C-1 position and elimination of the amine. The resulting compound **43** was subjected to manipulation of the functional groups at the AB ring moiety to afford diketone **44** which was converted to totally ten derivatives of cyclocitrinol through installation of suitable side chain segments.



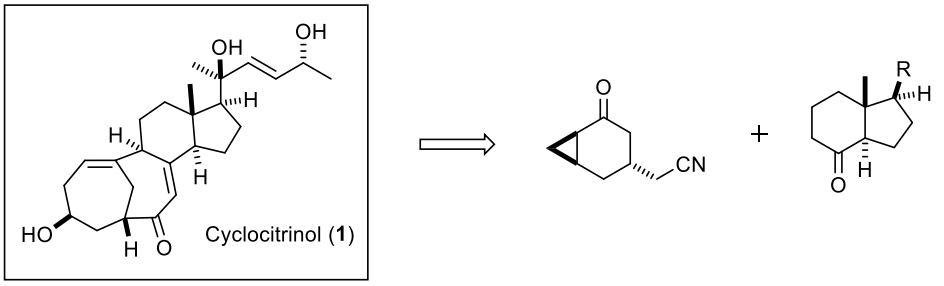
Scheme 7. Gui's work: divergent synthesis of cyclocitrinols

In this dissertation, synthetic studies on cyclocitrinol through a new approach will be described. In chapter I, the method for the construction of the AB ring system based on the epoxy-nitrile cyclization and cyclopropane ring opening is describe. In chapter II, efforts of toward the asymmetric total synthesis of cyclocitrinol is to be described.

Chapter I



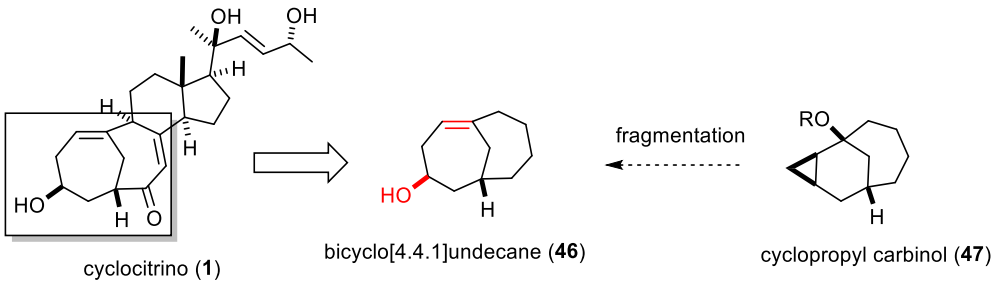
Chapter II



Chapter I.
Stereoselective synthesis of the ABC model compound of cyclocitrinol

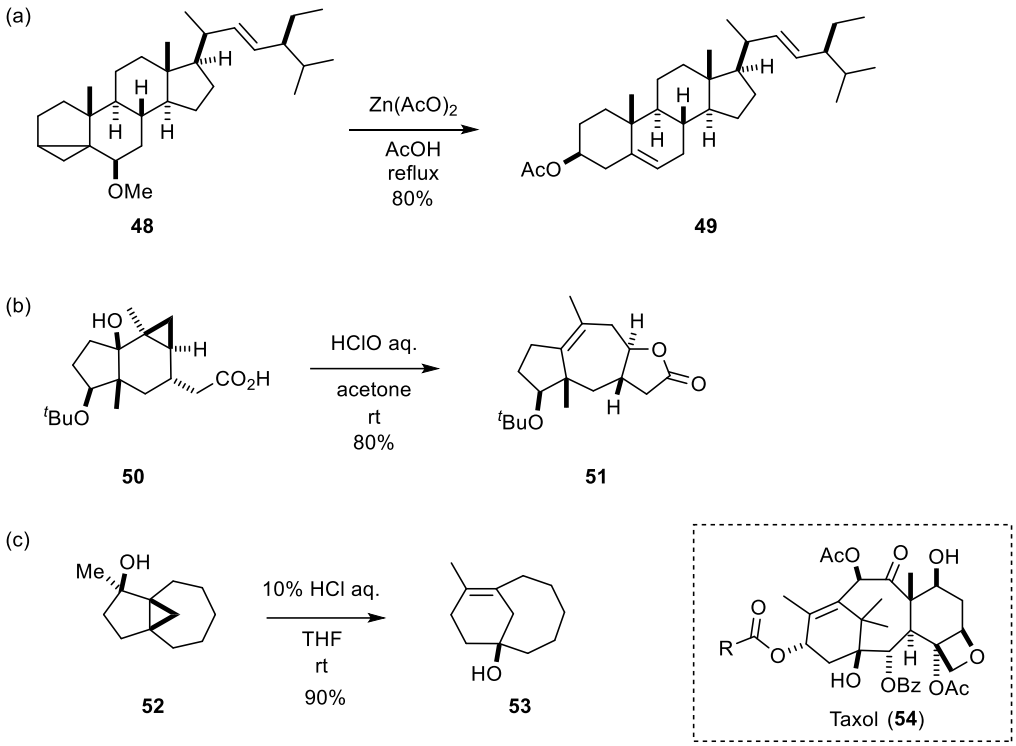
1-1. Introduction

To start study on the synthesis of cyclocitrinol, the author worked on the construction of bicyclo[4.4.1]undecane with an olefin in against of Bredt's rule. By the way, looking at the structure of the A ring, there is a hydroxyl group at the homo allyl position of the bridgehead olefin. The author employed the fragmentation reaction of cyclopropyl carbinol **47** as a method for the introduction of distorted double bond and hydroxyl group stereoselective.



Scheme 8. Bicyclo[4.4.1]undecane in cyclocitrinol

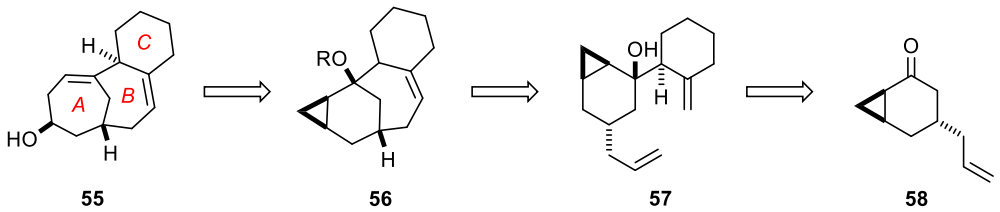
This reaction is well-known for an installation of double bond in steroid synthesis (Scheme 9a)[16]. Intramolecular reaction is also reported that enable to construct *trans* fused γ-lactone **51** (9b)[16]. Through the document research on this reaction, it became clear that Cosey and co-workers constructed bicyclo alkanol **53** with bridgehead olefin corresponding to taxol by this type reaction in 2002 (9c)[16]. With a view to these examples, it is clear that the nucleophilic attack proceeds in a stereoselective manner and led author to design the method for unique AB ring system of cyclocitrinol.



Scheme 9. Application of cyclopropyl methyl ether fragmentation

1-2. First generation approach toward tricyclic model compound of cyclocitrinol

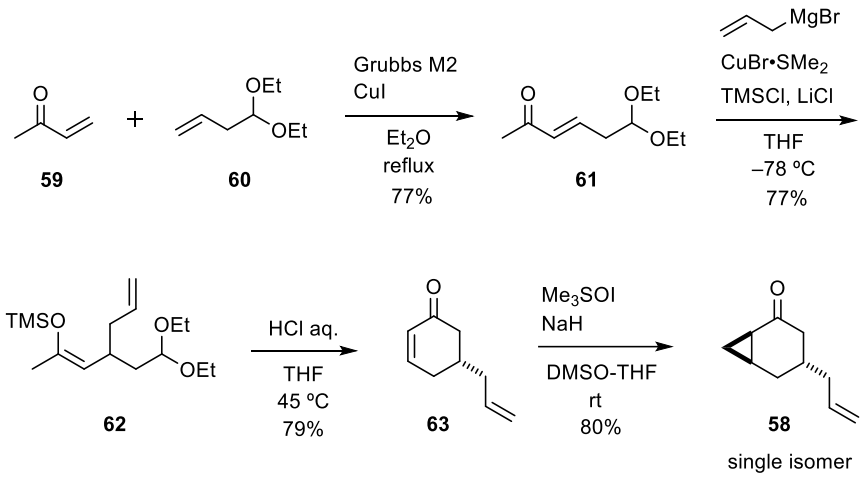
Scheme 10 shows the retrosynthetic analysis of the ABC model compound **55**. Target compound is to be synthesized above three membered ring opening reaction. It was envisioned that seven membered ring of **56** could construct from alkene **57** by ring-closing-metathesis reaction and homoallyl alcohol **57** would be obtained from ketone **58** by installation of C ring segment.



Scheme 10. Retrosynthetic analysis of tricyclic model compound

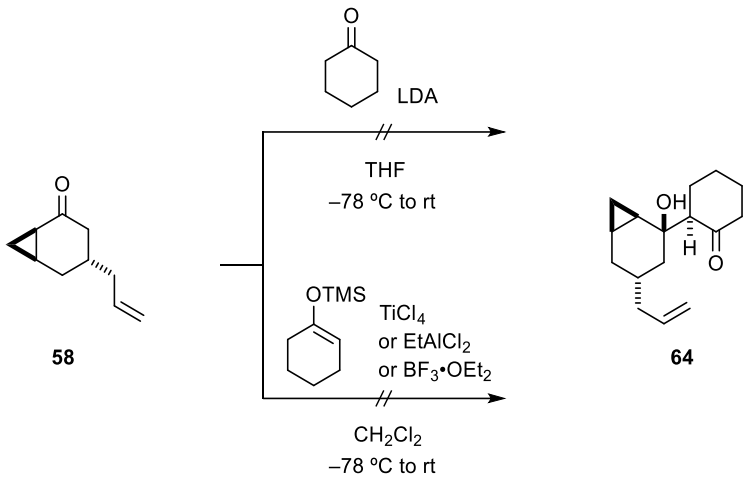
The model study was started with synthesis of ketone **58** (Scheme 11). Cross-metathesis reaction of metylvinyl ketone (**59)** and commercially available alkene **60** afforded enone **61**[17]. Resulting enone was subjected to 1.4-addition of allyl copper reagent in presence of TMSCl and LiCl due to get enol silyl ether **56**.

Ander acidic conditions, intramolecular aldol condensation of ketoaldehyde generated from **56** afforded cyclohexanone **57**. The desired bicyclo ketone **58** was obtained by Corey-Chaykovsky reaction[28] as a single diastereomer. In this case, sulfoxonium ylide approached from the axial direction and showed high selectively.



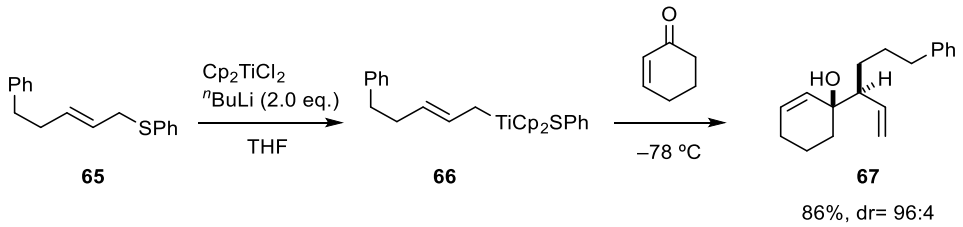
Scheme 11. Synthesis of ketone 58

With the ketone **58** in hand, connecting to the C-ring segment was examined. Initially, aldol type reaction was screened. Lithium enolate generated from cyclohexanone and LDA was not react with ketone **58**. Mukaiyama-aldol reaction also attempted that 1-(trimethylsilyloxy) cyclohexene and Lewis acids ($TiCl_4$ or Et_2AlCl or $BF_3•OEt_2$) added to **58**, however desired product **64** was not detected (Scheme 10). Since the aldol reaction between cyclic ketones is generally difficult and often results in low yields, it was decided to try other coupling methods.



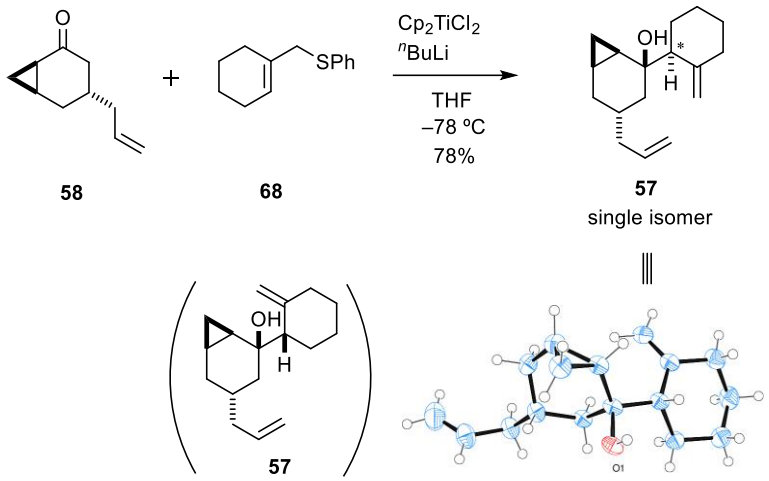
Scheme 12. Aldol reaction of ketone 58

Therefore, the author focused on the Takeda's protocol which was 1,2-addition of allyltitanocene generated from corresponding allylsulfide[19]. Shown in Scheme 13, allyltitanocene **66** was readily prepared by the sulfide **65** and titanocene(Ⅱ)-1-butene complex which was generated from Cp_2TiCl_2 and two equivalent ^{n}BuLi, following addition of cyclohexanone afforded homoallyl alcohol **67** in 86% yield and high diastereoselectivity.



Scheme 13. Takeda's protocol: diastreoselective addition of allyltitanocene to ketone

To implement this reaction, corresponding allylsulfide **68** was prepared as the C ring segment and addition reaction was conducted (Schem 14). As a result, homoallyl alcohol **51** was obtained in 78% yield as a single diastereomer and X-ray crystallographic analysis indicated that **51** has a desired configuration.



Scheme 14. Preparation of alcohol 57

The stereochemistry at the allylic position (asterisked carbon in Scheme 14) could be predicted by assuming a six-membered chair-like transition state model (Figure 4). Steric repulsion between the cyclopropane moiety and a ligand of the titanium atom would make TS-1 less favorable than TS-2. The remarkably high stereoselectivity in this case may arise from the bulkiness of the titanocene moiety.

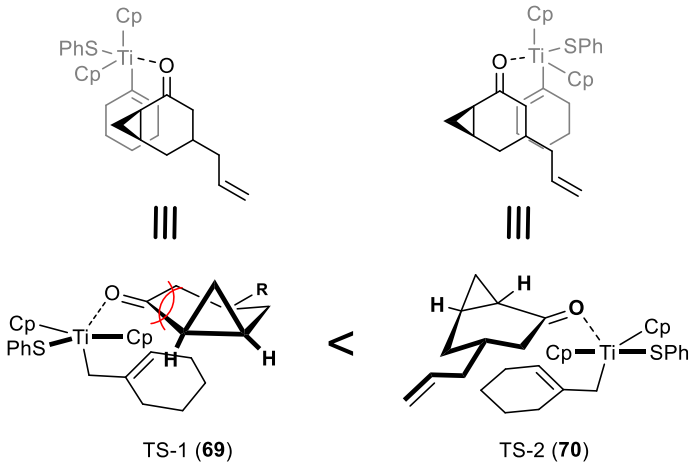
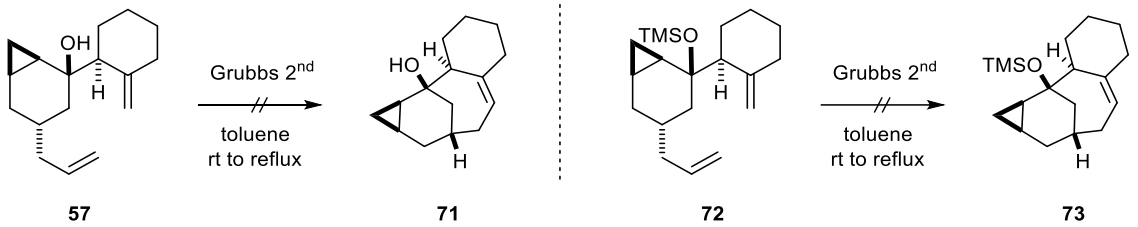


Figure 4. Stereoselectivity of addition of allyltitanocene

With the key intermediate **57** in hand, the stage was set for the construction of the B ring by ring-closing metathesis reaction (Scheme 15). However, no tetracycline compound **71** was

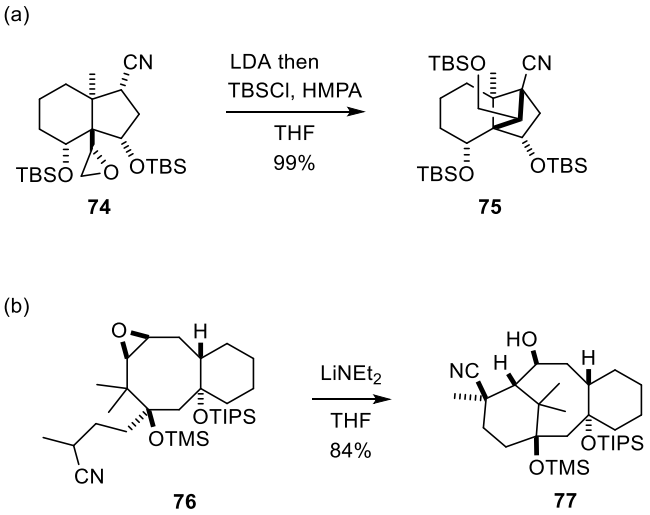
detected at all. Silylated substrate **72** was prepared and attempted for ring construction, but reaction was not proceeded. This method was found to be inappropriate for the construction of the B ring, probably because of the large distortions.



Scheme 15. Attempts for ring-closing metathesis reaction

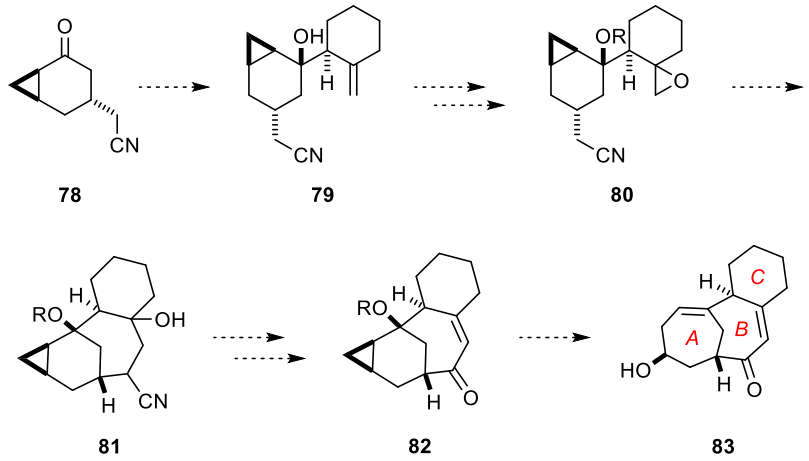
1-3. Second generation approach toward tricyclic model compound of cyclocitrinol

By the way the Tanino's research group, to which the author belongs, reported construction of polycyclic systems which have relatively high distortion by using an epoxy-nitrile intramolecular cyclization reaction (Scheme 16). In the total synthesis of solanoeclepin A, highly strained tricyclo[5.2.1.$0^{1,6}$]decane skeleton was constructed by this intramolecular cyclization (16a)[20a]. In addition, his group reported the successful formation of taxane core structure by same method (16b)[20b]. These results indicated that cyclization of epoxy-nitriles has powerful tool for various ring sizes carbocyclic construction.



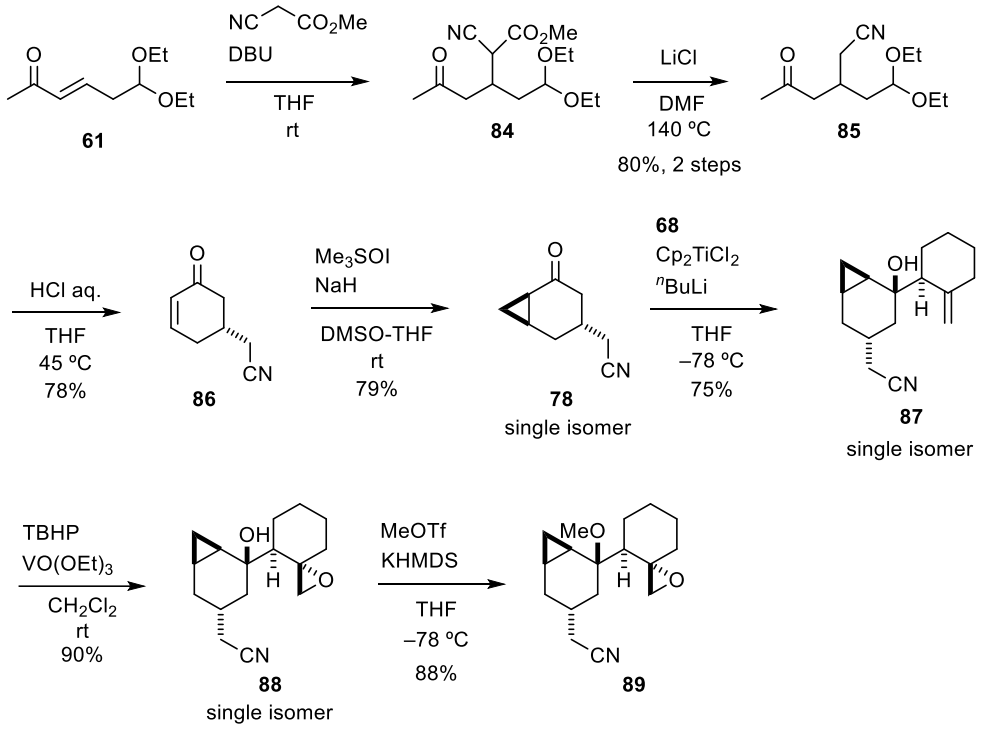
Scheme 16. Application of epoxy-nitrile cyclization in Tanino's group

The author designs an alternative to access the B ring structure by using this method (Scheme 17). The compound **80** which is converted from **78** using the titanocene reagent same as scheme 14 is assumed to be a cyclization precursor, and then resulting cyclization product **81** can expect to convert to the enone moiety. Lastly, fragmentation of **82** would yield a model compound **83** that is closer in structure to the natural product than the first generation.



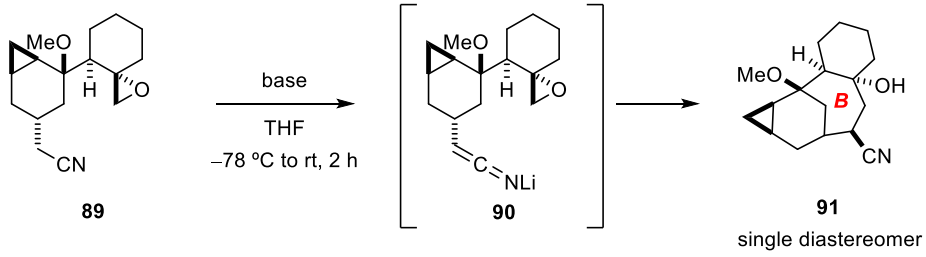
Scheme 17. Alternative pathway to construct tricyclic skeleton

To implement this strategy, the author first worked on the synthesis of cyclization precusor **80** (Scheme 18). The enone **61** was subjected to 1,4-addition of methylcyanoacetate and cleavage methylester by Krapco's protocol afforded methyl ketone **84**. Aldol condensation and Corey-Chaykovsky cyclopropanation was conducted same as Scheme 11 to obtain **78** in good yield as a single diastereomer. Next, the cyclization precursor was synthesized. Addition reaction of ketone **78** with titanocene reagent was also procced diastereoselective and alcohol **87** was obtained[21]. Epoxidation of **87** using TBHP in presence of vanadium catalyst gave **88** as a single diastereomer by directive effect of hydroxy group. The methylation of alcohol **88** by KHMDS and MeOTf afforded cyclization precursor **89**.



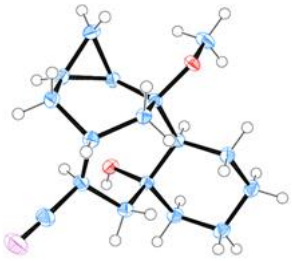
Scheme 18. Synthesis of epoxy nitrile 89

With the epoxy nitrile **89** in hand, optimization of the epoxy-nitrile intramolecular cyclization was conducted (Table 1). The reaction conditions were set for deprotonation at -78 °C and stirring for 2 h at room temperature. When LDA was used as the base, cyclization product **91** was obtained 65% yield (entry 1). The case of using $LiNEt_2$, it was no significant change in yield (entry 2). Moreover, reaction with LHMDS gave **91** in 51% and 18% of the starting material was recovered (entry 3). KHMDS and NaHMDS were also tested, but recover of **91** was increased in this case (entries 4 and 5). The lithium ion with a weak Lewis acidity probably acted as an activator of the epoxide since using a base with lithium as the counter ion promoted the consumption of **91** more quickly. The best result of this reaction system was using LTMP as a base and isolated yield of 73%. However, adding HMPA to this reaction decreased the product yield (entries 6 and 7). Under all reaction conditions investigated, the product **91** was obtained as a single diastereomer. The stereochemistry of **91** was confirmed via X-ray crystallography and nitrile group was directed to the *β*-side.



entry	Base (equiv.)	NMR yield (%)
1	LDA (2.5)	65
2	$LiNEt_2$ (2.5)	68
3	LHMDS (2.5)	51 (**89**: 18)
4	NaHMDS (2.5)	17 (**89**: 68)
5	KHMDS (2.5)	32 (**89**: 59)
6	LTMP (2.5)	73*
7	LTMP (2.5) HMPA (5.0)	60

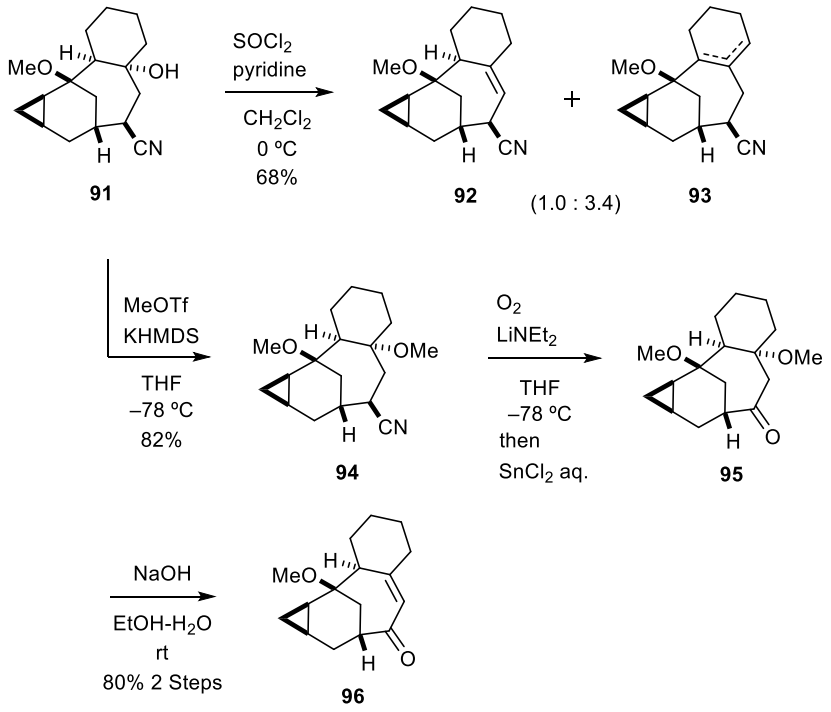
* Isolated yield.



X-ray crystal structure of **91**

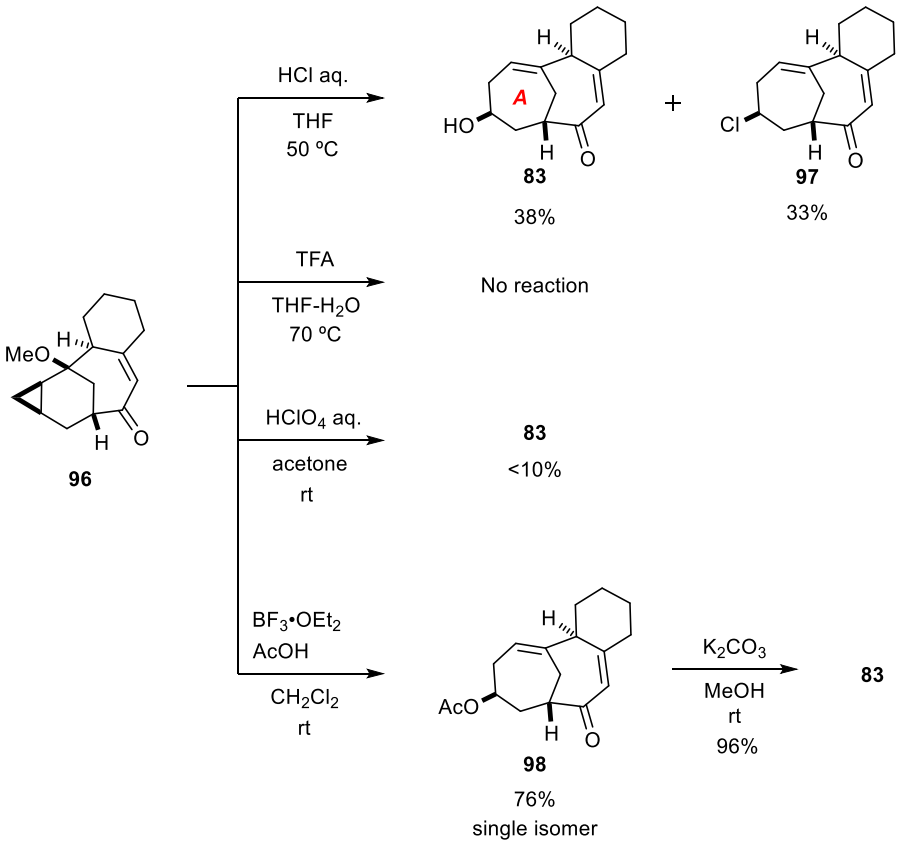
Table 1. Optimization of the cyclization reaction

Having successfully synthesized the tetracyclic core, the author focused on converting nitrile **91** to cycloheptenone motif (Scheme 19). At first, dehydrating **91** with thionyl chloride was tried to install doble bond. However, the products were obttained an inseparable mixture of the desired **92** and regioisomer **93**. Secondly, the hydroxy group of **91** was methylated by MeOTf and KHMDS and then resulting **94** was transformed ketone **95** via the oxidative decyanation reaction, involved peroxidation by treating **94** with $LiNEt_2$ under oxygen, followed by the addition of an aqueous tin [II]chloride solution[22]. Compound **95** was converted to enone **96** by eliminating the methoxide moiety using NaOH.

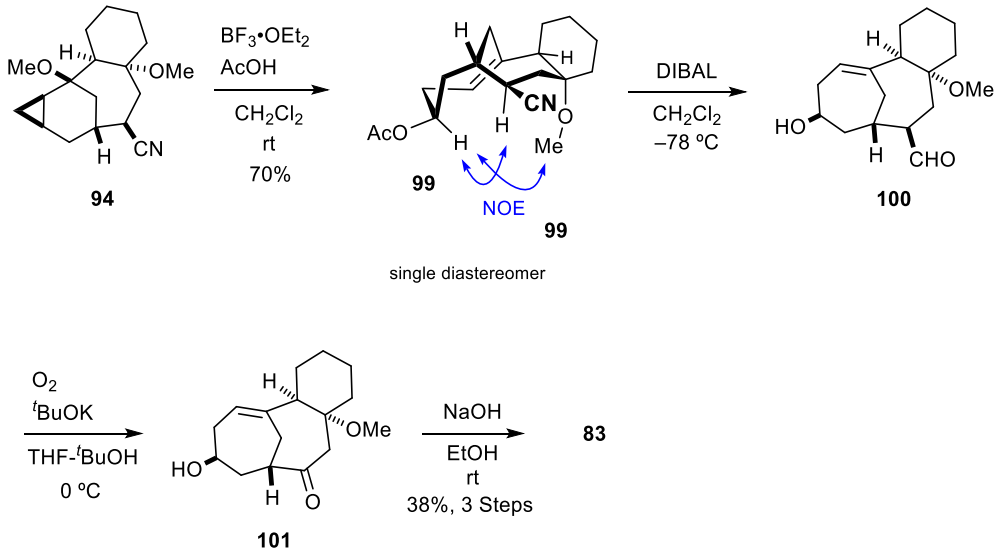


Scheme 19. Synthesis of enone 96

Finally, the cyclopropane ring-opening reaction for construction of the A ring was examined (Scheme 18). The desired reaction was proceeded when enone **96** was treated with hydrochloric acid to afford alcohol **83** with a bridgehead olefin.[@] Nevertheless, the yield was as low as 38% yield due to the presence of the chlorinated byproduct **97**, which was obtained 33% yield. Aqueous solutions of other acids were used. For example, TFA[@] was added to **96** and heated to 70 °C. However, the reaction was not occurred. The case of using aqueous solution of $HClO_4$[@], decomposition of the starting material occurred and the yield of the target compound was reduced, probably due to the strong acidity. Hence, **83** was prepared via a two steps conversion process. Firstly, adding acetic acid to **96** in the presence of BF_3•OEt_2[@]as a catalystresukted in the formation of acetate **98** in good yield as a single diastereomer. The acetyl group was then removed using K_2CO_3/MeOH to afford model compound **83**.



Scheme 20. Synthesis of the model compound 83



Scheme 21. Confirmation of stereochemistry

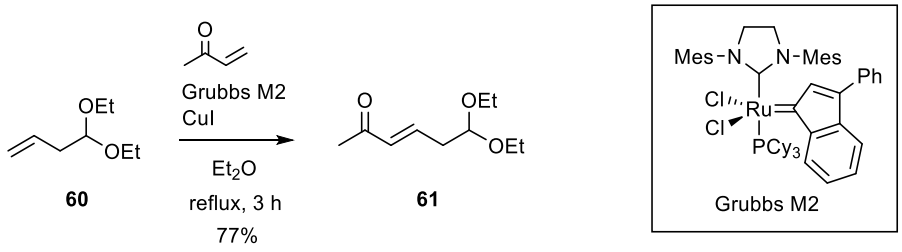
The stereochemistry of ring-opening product **83** was confirmed as Scheme 21. Compound **94** was transformed into **99** using BF_3•OEt_2 and AcOH and NOE experiment determined the relation ship between the protons in which were displayed above. Compound **83** was obtained from **99** by 3 steps transformation and then, model compound **83** correspond to ABC ring system of **1**

In summary, the author has achieved the stereoselective synthesis of the model compound, which corresponded to the ABC ring of cyclocitrinols. The key cyclization precursor was synthesized by linking the A and C ring segments in the addition reaction developed by Takeda. Following the synthesis of the B ring via an epoxy-nitrile intramolecular cyclization, the A ring formation and installation of the bridgehead double bond were conducted by a fragmentation of the cyclopropane ring.

Experimantal Section

General Experimental Details: All the reactions were carried out in a round-bottomed flask with an appropriate number of necks and side arms connected to a three-way stopcock and/or a rubber septum cap under an argon atmosphere. All vessels were first evacuated by a rotary pump and then flushed with argon prior to use. Solutions and solvents were introduced by a hypodermic syringe through a rubber septum. During the reaction, the vessel was kept under a positive pressure of argon. Dry tetrahydrofuran (THF) and diethyl ether were freshly prepared by distillation from benzophenone ketyl before use. Anhydrous CH_2Cl_2, 1,2-dichloroethane, methanol, ethanol, DMF and DMSO were purchased from Kanto Chemical Co. Inc. Most of the reagents were purchased from Tokyo Kasei Kogyo Co. Ltd., Wako Pure Chemicals Co. Ltd., Kanto Chemical Co. Inc. and Aldrich Chemicals Co. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Wavelengths of maximum absorbance are quoted in cm^{-1}. ^1H NMR spectra were recorded on a JEOL ECA-500 (500 MHz) in $CDCl_3$. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). ^{13}C NMR spectra were recorded on a JEOL ECA-500 (125 MHz) in $CDCl_3$. Chemical shifts are reported in part per million (ppm). High resolution mass (HRMS) spectra were recorded on a JEOL JMS-T-100GCV at the GC-MS & NMR Laboratory, Research Faculty of Agriculture, Hokkaido University. Optical rotation data was recorded on a JASCO P-2200. Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel (60F-254) plates. Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, or ceric ammonium molybdate in 10% sulfuric acid. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for column chromatography.

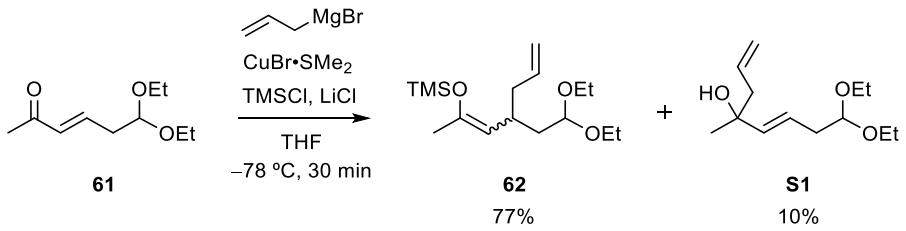
Compound 61



To a mixture of Grubbs Catalyst M2 (48 mg, 0.05 mmol), CuI (14 mg, 0.075 mmol) in Et_2O (10 mL) was added **60** (7.20 g, 50 mmol) and methyl vinyl ketone (4.9 mL, 60 mmol). After refluxing for 3 h, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=4:1) to give **61** as a yellow oil (7.17 g, 38.5 mmol, 77%).; IR (neat): ν 2976, 2930, 2880, 1698, 1676, 1631, 1360, 1254, 1118, 1057, 977 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.49 (1H, dt, *J* = 16.0, 7.2 Hz), 5.85 (1H, t, *J* = 12.6 Hz), 4.31 (1H, t, *J* = 5.7 Hz), 3.41-3.35 (2H, m), 3.27-3.21 (2H, m), 2.28 (2H, t, *J* = 6.3 Hz), 1.97 (3H, s), 1.21-1.12 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 198.29, 142.45, 133.27, 101.05, 61.38, 36.96, 26.50, 14.97; HRMS (FI): Calcd for $C_{10}H_{19}O_3$ $[M+H]^+$: 187.1334; found: 187.1332

Compound **60** is commercially available, but if you want to obtain **60** in large quantities, it can be synthesized by the self-condensation of ethyl vinyl ethers, see: Hoaglin, R. I.; Kubler, D. G.; Montagna, A. E. *J. Am. Chem. Sci.* **1958**, *80*, 5460.

Compound 62

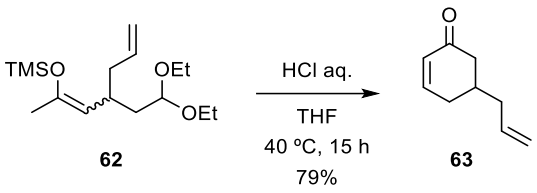


A mixture of CuBr•SMe_2 (2.40 g, 11.6 mmol) and LiCl (0.5M in THF, 23.0 ml, 11.5 mmol) in THF (20 ml) was added allylmagnesiumbromide (1.0 M in Et_2O, 11.5 ml, 11.5 mmol) and TMSCl (11.6 mmol, 1.45 ml) at -78 °C. After being stirred for 30 min, the reaction mixture was added Compound **61** (990 mg, 5.3 mmol) in THF (7.0 ml) and warmed up to 0 °C. The mixture was stirred for 30 min, then added saturated aqueous NH_4Cl solution and 30% aqueous NH_3 solution. The mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 9:1) to give enol sylilether **62** as a yellow oil (1.22 g, 4.08 mmol, 77%, dr=2:1) and alcohol **S1** as a colorless oil (120 mg, 0.53 mmol, 10 %).

Enolsylilether (diastereomixture) **62** ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.98-5.88 (2H, m), 5.81-5.73 (1H, m), 4.98 (3H, dd, *J* = 18.9, 13.7 Hz), 4.49 (2H, dq, *J* = 17.5, 4.7 Hz), 4.23 (3H, dd, *J* = 26.3, 6.3 Hz), 3.69-3.56 (4H, m), 3.54-3.38 (4H, m), 2.62 (1H, s), 2.43 (2H, t, *J* = 6.3 Hz), 2.32 (1H, s), 2.07 (3H, ddt, *J* = 48.0, 25.9, 10.5 Hz), 1.78 (2H, d, *J* = 12.0 Hz), 1.71 (1H, dd, *J* = 12.3, 7.7 Hz), 1.39 (1H, td, *J* = 13.9, 10.3 Hz), 1.23 (19H, tt, *J* = 22.1, 9.0 Hz), 0.88 (3H, t, *J* = 6.6 Hz), 0.22-0.08 (21H, m).

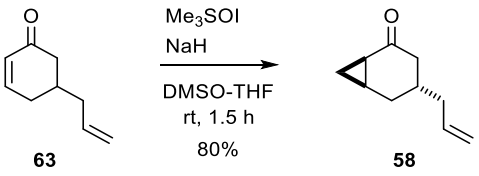
Alcohol **S1** ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.84-5.75 (1H, m), 5.65-5.60 (2H, m), 5.12 (2H, t, *J* = 11.5 Hz), 4.49 (1H, t, *J* = 6.0 Hz), 3.68-3.62 (2H, m), 3.53-3.47 (2H, m), 2.37 (2H, t, *J* = 5.7 Hz), 2.32-2.25 (2H, m), 1.58 (3H, s), 1.19 (6H, q, *J* = 8.4 Hz).

Compound 63



To a solution of enolsylilether **62** (655 mg, 2.18 mmol) in THF (8.0 ml) was added 4M HCl aq. (2.0 ml) at room temperature. After being stirred for 30 min, the mixture was heated to 45 °C. The reaction mixture was stirred for 15 h and then cooled to room temperature. The mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:Et_2O = 4:1) to give cyclohexanone **63** as a yellow oil (235 mg, 1.72 mmol, 79%).; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.96 (1H, d, *J* = 8.0 Hz), 6.03 (1H, d, *J* = 10.3 Hz), 5.75 (1H, td, *J* = 16.6, 6.9 Hz), 5.06 (2H, t, *J* = 8.6 Hz), 2.53 (1H, d, *J* = 13.7 Hz), 2.44 (1H, d, *J* = 18.3 Hz), 2.16-2.05 (5H, m).

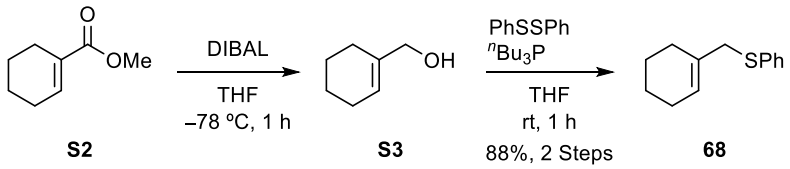
Compound 58



To a solution of NaH (45 mg, 1.03 mmol, after being briefly immersed in hexane to remove any mineral oil) in DMSO (2.3 ml) was added trimethyl sulfoxonium iodide (230 mg, 1,03 mmol) in water bath. After being sttired for 2 h, the mixture was added cyclohexanone **63** (130 mg, 0.94 mmol) in THF (2.3 ml) at room temperature. The reaction mixture was stirred for 1.5 h and added water at 0 °C. The reaction mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica chromatography

(hexane:Et_2O = 9:1) to give cyclopropane **58** as a pale yellow oil (112 mg, 0.752 mmol, 80%).; ^{1}H-NMR ($CDCl_3$): δ 5.71 (1H, dt, *J* = 26.0, 8.4 Hz), 5.03 (2H, t, *J* = 8.3 Hz), 2.38 (1H, d, *J* = 13.7 Hz), 2.09 (1H, d, *J* = 13.7 Hz), 2.03-1.98 (2H, m), 1.73 (4H, dd, *J* = 17.5, 11.2 Hz), 1.59-1.57 (1H, m), 1.18 (1H, q, *J* = 5.2 Hz), 1.06 (1H, dd, *J* = 14.0, 8.9 Hz).

Compound 68

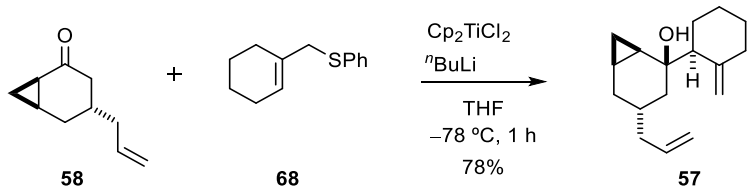


To a cooled (-78 °C) solution of **S2** (2.21 g,15.8 mmol) in THF (33 mL) was added DIBAL (1.03 M in hexane, 33 mL, 35.0 mmol). After being stirred for 1 h, a saturated aqueous Rochelle salt solution was added. The reaction mixture was stirred at room temperature for 3 h. The mixture was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude **S3** was used for the next step without purification.

To a solution of crude **S3** (1.56 g) and diphenyl disulfide (3.34 g, 15.3 mmol) in THF (65 mL) was added tri-butylphosphine (4.12 mL, 16.7 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was poured to a saturated aqueous $NaHCO_3$ solution. The mixture was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 99.5:0.5) to afford **S4** as a colorless oil (2.84 g, 13.9 mmol, 88%).

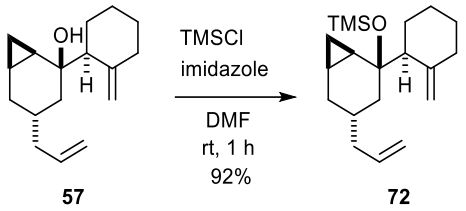
Ref) Nakagawa, I.; Hata, T. *Tetrahedron Lett*, **1975**, *17*, 1409.

Compound 57



To a cooled (-78 °C) suspension of Cp_2TiCl_2 (750 mg, 3.0 mmol) in THF (4.0 mL) was added *n*-BuLi (2.67 M in hexane, 2.2 mL, 6.0 mmol). After being stirred for 1 h, a THF solution (1.0 mL) of **68** (245 mg, 1.2 mmol) was added, and stirring was continued for 10 min at the same temperature and then at 0 °C for 1 h. After cooling to -78 °C, ketone **58** (150 mg, 1.0 mmol) in THF (1.0 mL) was added. After being stirred for 1 h, a 1M aqueous NaOH solution was added, and the mixture was filtered through a pad of celite. The insoluble materials were washed with EtOAc, and the filtrate was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=75:15) to afford **57** as a yellow oil (370 mg, 1.5 mmol, 75%, single isomer)..; ^{1}H-NMR ($CDCl_3$) δ: 5.75 (1H, td, *J* = 17.0, 7.3 Hz), 4.98 (2H, t, *J* = 9.2 Hz), 4.88 (2H, t, *J* = 13.5 Hz), 2.30 (1H, d, *J* = 12.6 Hz), 2.18 (1H, d, *J* = 9.2 Hz), 2.04 (2H, t, *J* = 12.0 Hz), 1.96 (3H, t, *J* = 10.9 Hz), 1.85 (1H, s), 1.76 (1H, s), 1.64 (1H, s), 1.43 (4H, d, *J* = 6.9 Hz), 1.29 (2H, m), 1.17 (2H, d, *J* = 13.2 Hz), 0.54 (1H, q, *J* = 5.0 Hz), 0.46 (1H, td, *J* = 8.9, 4.6 Hz).

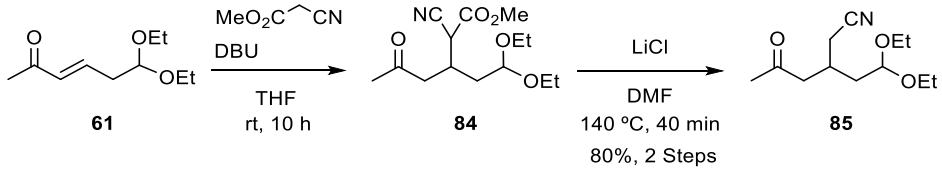
Conpound 72



57 **72**

To a mixture of alcohol **57** (25.0 mg, 0.1 mmol) and imidazole (20.0 mg, 0.3 mmol) in DMF (500 µl) was added TMSCl (25 µl, 0.2 mmol) at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was added a saturated aqueous $NaHCO_3$ solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc =98:2) to afford @ as a colorless oil (29.3 mg, 0.092 mmol, 92%). ^{1}H-NMR ($CDCl_3$): δ 5.80-5.71 (1H, m), 4.97 (2H, t, *J* = 8.3 Hz), 4.85 (2H, d, *J* = 17.2 Hz), 2.25-2.20 (2H, m), 2.09 (1H, d, *J* = 9.7 Hz), 1.99-1.88 (2H, m), 1.84 (2H, dd, *J* = 17.5, 8.3 Hz), , 1.39-1.11 (4H, m), 0.53 (1H, q, *J* = 5.0 Hz), 0.46 (1H, td, *J* = 8.9, 4.8 Hz), 0.14 (9H, t, *J* = 2.9 Hz).

Compound 85

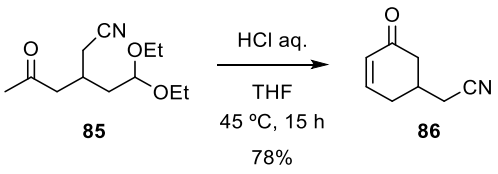


61 **84** **85**

To a mixture of **61** (2.79 g, 15 mmol) and methyl cyanoacetate (2.0 mL, 22.5 mmol) in THF (75 mL) was added DBU (670 µL, 4.5 mmol). After being stirred for 10 h, the mixture was poured to a saturated aqueous NH_4Cl solution. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product **84** was used for the next step without purification.

To a solution of crude **84** (5.2 g) in DMF (15 mL) was added LiCl (1.91 g, 45 mmol) at room temperature. After being stirred for 40 min at 140 °C, water was added. The mixture was separated, and the aqueous layer was extracted with a 1:1 mixture of hexane and EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=7:3) to afford **85** as a yellow oil (2.73 g, 12 mmol, 80%).; IR (neat): ν 2976, 2930, 2887, 2360, 1714, 1427, 1373, 1357, 1211, 1164, 1124, 1057, 1004 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.54 (1H, t, *J* = 5.2 Hz), 3.64 (2H, tt, *J* = 11.7, 5.2 Hz), 3.51-3.44 (2H, q, J = 3.1 Hz), 2.64 (2H, q, *J* = 3.1 Hz), 2.57 (2H, q, *J* = 2.7 Hz), 2.45 (1H, q, *J* = 6.3 Hz), 2.16 (3H, s), 1.72 (2H, td, *J* = 6.0, 3.1 Hz), 1.20 (6H, td, *J* = 7.0, 3.1 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.42, 118.19, 100.96, 61.61, 61.20, 46.52, 36.47, 30.16, 26.69, 21.64, 14.98; HRMS (FI): Calcd for $C_{12}H_{22}NO_3$ $[M+H]^+$: 228.1599; found: 228.1604.

Compound 86

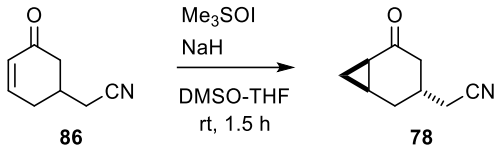


A mixture of **85** (2.73 g, 12 mmol), THF (45 mL), and a 4 M HCl (15 mL) was stirred at room temperature for 30 min and at 45 °C for 15 h. After cooling to room temperature, a saturated aqueous $NaHCO_3$ solution was added carefully. The mixture was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:Et_2O=1:2) to afford **86** as a white solid (1.26 g, 9.36 mmol, 78%).; mp. 54-55 °C; IR (neat): ν 2926, 2360, 2342, 1715, 1677, 1428, 1389, 1251, 419 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.98 (1H, dq, *J* = 10.2, 2.8 Hz), 6.10 (1H, dd, *J* = 9.7, 2.3 Hz), 2.63-2.55 (2H, m), 2.54-2.43 (3H, m), 2.33 (2H,m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 196.57, 147.53, 129.76, 116.97,

42.76, 31.66, 30.47, 23.00; HRMS (FD): Calcd for C_8H_9NO $[M]^+$: 135.0684; found: 135.0691.

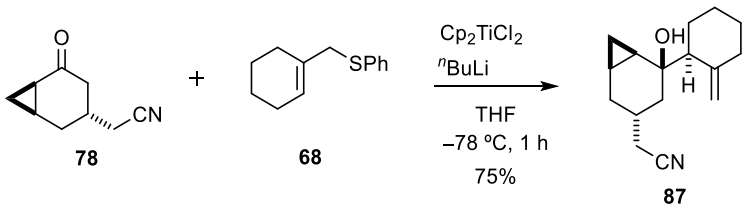
Compound **86** has already been reported to be synthesized by different route; Tristan A. Reekie, Martin G. Banwell,and Anthony C. Willis, *J. Org. Chem.* **2012**, *77*, 10773.

Compound 78



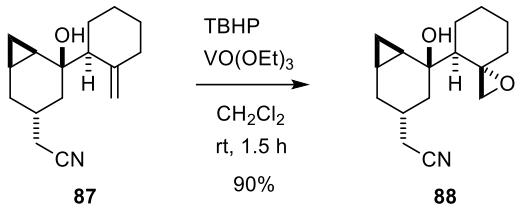
To a suspension of NaH (247 mg, 10.3 mmol, being briefly immersed in hexane to remove any mineral oil) in DMSO (23 mL) was added trimethylsulfoxonium iodide (2.27 g, 10.3 mmol). After being stirred for 2 h, **86** (1.26 g, 9.36 mmol) in THF (23 mL) was added at room temperature, and the reaction mixture was stirred for 1.5 h. After cooling to 0 °C, water was added, and the reaction mixture was separated. The aqueous layer was extracted with chloroform, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica chromatography (hexane:Et_2O=1:2) to afford **78** as a white solid (1.10 g, 7.39 mmol, 79%)..; mp. 55-57 °C; IR (neat): ν 2926, 2360, 2342, 1684 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.49 (1H, dd, *J* = 17.8, 5.2 Hz), 2.33 (2H, t, *J* = 6.0 Hz), 2.25 (1H, dd, *J* = 11.5, 3.4 Hz), 2.13 (1H, tt, *J* =16.9, 5.5 Hz), 1.85 (4H, m), 1.15 (2H, t, *J* = 6.9 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.04, 117.38, 42.19, 27.18, 26.31, 24.81, 23.83, 16.15, 9.96; HRMS (FD): Calcd for $C_9H_{11}NO$ $[M]^+$: 149.0841; found: 149.0844.

Compound 87



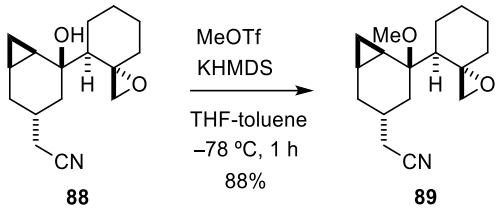
To a cooled (-78 °C) suspension of Cp_2TiCl_2 (1.50 g, 6.0 mmol) in THF (8.0 mL) was added *n*-BuLi (2.67 M in hexane, 4.5 mL, 12.0 mmol). After being stirred for 1 h, a THF solution (1.0 mL) of **68** (490 mg, 2.4 mmol) was added, and stirring was continued for 10 min at the same temperature and then at 0 °C for 1 h. After cooling to -78 °C, ketone **78** (300 mg, 2.0 mmol) in THF (1.0 mL) was added. After being stirred for 1 h, a 1M aqueous NaOH solution was added, and the mixture was filtered through a pad of celite. The insoluble materials were washed with EtOAc, and the filtrate was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=75:15) to afford **87** as a yellow oil (370 mg, 1.5 mmol, 75%, single isomer).; IR (neat): ν 2926, 2853, 2360, 2341, 1638, 1447, 1420, 1386, 1113, 1059, 995, 984, 953, 891cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.90 (1H, s), 4.83 (1H, s), 2.33 (1H, dd, *J* = 9.0, 6.0 Hz), 2.26 (1H, q, *J* = 6.5 Hz), 2.21 (1H, t, *J* = 4.6 Hz), 2.11 (1H, dd, *J* = 12.6, 4.0 Hz), 2.04 (2H, d, *J* = 5.2 Hz), 1.87 (1H, d, *J* = 10.3 Hz), 1.82-1.74 (3H, m), 1.53-1.40 (4H, m), 1.31-1.23 (4H, m), 0.55 (2H, dt, *J* = 17.9, 6.3 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 149.33, 118.37, 108.47, 71.97, 56.65, 38.97, 38.11, 29.41, 29.00, 28.94, 26.15, 24.38, 21.12, 13.79, 5.83; HRMS (FI): Calcd for C16H23NO $[M]^+$: 245.1780; found: 245.1773.

Compound 88



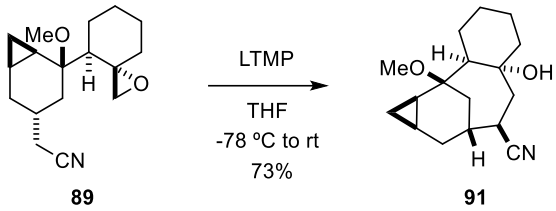
To a solution of alkene **87** (370 mg, 1.5 mmol) in CH_2Cl_2 (7.5 ml) were added TBHP (5.5 M in nonane, 545 μL, 3.0 mmol) and $VO(OEt)_3$ (27 μL, 0.15 mmol) at room temperature. After being stirred for 1.5 h, to the reaction mixture was added a saturated aqueous $NaHCO_3$ solution. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=4:1) to afford **88** as a white solid (353 mg, 1.35 mmol, 90%, single isomer).; mp. 88-90 °C; IR (neat): ν 3725, 2927, 2359, 2342, 1716, 1698, 1541 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.71 (1H, s), 3.54 (1H, s), 2.70 (1H,s), 2.25 (2H, t, *J* = 5.9 Hz), 2.04 (3H,m), 1.89 (3H, m), 1.44 (4H,m), 1.37-1.25 (3H, m), 1.14-1.03 (2H, m), 0.59 (1H, q, *J* = 5.5 Hz), 0.51 (1H, td, *J* = 9.2, 5.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 118.11, 71.48, 63.24, 53.22, 49.71, 42.38, 37.02, 29.17, 28.01, 25.56, 25.44, 24.23, 22.91, 18.11, 12.95, 5.33; HRMS (FI): Calcd for $C_{16}H_{23}NO_2$ $[M]^+$: 261.1729; found: 261.1740.

Compound 89



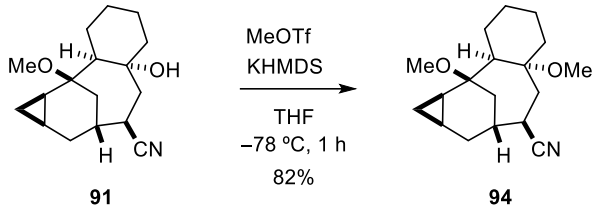
To a cooled (-78 °C) solution of **88** (353 mg, 1.35 mmol) in THF (6.7 mL) was added a solution of KHMDS (0.5 M in toluene, 2.97 mL, 1.49 mmol). After being stirred for 30 min, MeOTf (220 μL, 2.02 mmol) was added, and the reaction mixture was stirred for 1 h. To this was added a saturated aqueous NH_4Cl solution, and the mixture was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=75:15) to afford methyl ether **89** as a yellow oil (327 mg, 1.19 mmol, 88%).; IR (neat): ν 2932, 2856, 2361, 2342, 1456, 1382, 1069, 918, 818 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.20 (3H, s), 3.09 (1H, d, *J* = 4.6 Hz), 2.58 (1H, d, *J* = 4.0 Hz), 2.30-2.18 (3H, m), 2.01 (2H, d, *J* = 12.0 Hz), 1.82-1.68 (4H, m), 1.49-1.22 (8H, m), 1.15 (1H, t, *J* = 13.2 Hz), 0.65 (1H, td, *J* = 9.0, 4.8 Hz), 0.38 (1H, q, *J* = 5.3 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 118.21, 59.87, 53.13, 49.18, 44.81, 38.02, 37.47, 29.43, 26.03, 25.10, 25.04, 24.40, 24.23, 15.70, 13.30, 6.83; HRMS (FI): Calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885; found: 275.1879.

Compound 91



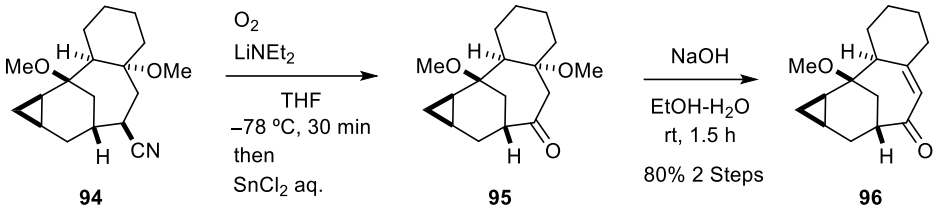
To a cooled (-78 °C) solution of LTMP, which was freshly prepared from tetramethylpiperidine (250 μL, 1.45 mmol) in THF (6.3 mL) and *n*-BuLi (2.67 M in hexane, 540 μL, 1.45 mmol), was added a solution of **89** (200 mg, 0.727 mmol) in THF (1.0 mL). After being stirred for 30 min, the reaction mixture was slowly warmed up to room temperature. After being stirred for 1 h, the reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=75:15) to afford **91** as a white solid (146 mg, 0.531 mmol, single isomer).; mp. 207-209 °C; IR (neat): ν 3381, 2960, 2939, 2919, 2872, 2359, 2225, 1496, 1296, 1237, 1061, 1036, 1004, 978 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.39 (1H, dd, *J* = 10.9, 7.4 Hz), 3.17 (3H, s), 2.36 (1H, dd, *J* = 14.0, 12.3 Hz), 2.12-2.08 (2H, m), 2.01 (2H, t, *J* = 14.9 Hz), 1.90 (1H, q, *J* = 4.4 Hz), 1.83 (1H, dd, 12.0, 6.3 Hz) 1.75-1.66 (2H, m), 1.58 (2H, m), 1.47 (1H, s), 1.41 (1H, dt, *J* = 14.1, 3.9 Hz), 1.33-1.22 (4H, m), 1.17 (1H, dd, *J* = 15.2, 8.9 Hz), 1.03 (1H, td, *J* = 8.9, 4.6 Hz), 0.85 (1H, d, *J* = 14.3 Hz), 0.29 (1H, q, *J* = 5.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 124.41, 74.74, 72.16, 50.72, 47.09, 46.26, 36.05, 34.52, 31.38, 30.97, 27.75, 25.69, 23.90, 23.39, 18.87, 13.91, 12.66; HRMS (FI): Calcd for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885; found: 275.1884.

Compound 94



To a cooled (-78 °C) solution of **91** (146 mg, 0.531 mmol) in THF (2.7 mL) was added KHMDS (0.5 M in toluene, 1.6 mL, 0.80 mmol). After being stirred for 30 min, the reaction mixture was stirred at 0 °C for 10 min. After cooling to -78 °C, MeOTf (88 μL, 0.80 mmol) was added, and the mixture was stirred for 1 h. A saturated aqueous NH_4Cl solution was added, and the mixture was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under deduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=9:1) to afford **94** as a yellow oil (126 mg, 0.435 mmol, 82%).; IR (neat): ν 2862, 2824, 2360, 2342, 2235, 1472, 1448, 1160, 1135, 1124, 1037, 975, 905, 874, 731 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.17-3.14 (7H, m), 2.25 (1H, dd, *J* = 15.2, 11.7 Hz), 2.15 (1H, d, *J* = 8.6 Hz), 2.08-2.05 (2H, m), 2.02 (1H, t, *J* = 8.6 Hz), 1.90 (2H, d, *J* = 13.7 Hz), 1.79 (2H, d, *J* = 14.9 Hz), 1.72 (1H, d, *J* = 3.4 Hz), 1.55 (1H, m), 1.38 (1H, d, *J* = 14.3 Hz), 1.24 (5H, m), 0.97 (1H, td, *J* = 8.9, 4.6 Hz), 0.81 (1H, d, *J* = 14.3 Hz), 0.23 (1H, q, *J* = 5.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 124.69, 76.42, 75.46, 47.79, 47.71, 47.25, 38.61, 34.96, 32.08, 31.61, 31.49, 27.14, 25.93, 24.12, 23.33, 18.69, 14.00, 12.79; HRMS (FI): Calcd for $C_{18}H_{27}NO_2$ $[M]^+$: 289.2041; found: 289.2029

Compound 96

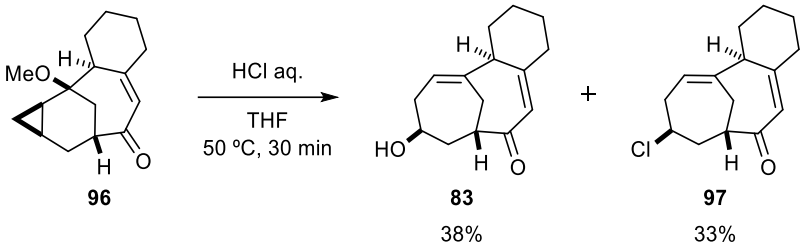


To a cooled (-78 °C) solution of $LiNEt_2$, which was freshly prepared from diethylamine (140 μL 1.32 mmol) in THF (3.4 mL) and *n*-BuLi (2.67 M in hexane, 495 μL, 1.32 mmol), was added a solution of **94** (126 mg, 0.435 mmol) in THF (1.0 mL). After being stirred for 30 min, the reaction mixture was warmed up to 0 °C. After being stirred for 10 min, the solution was cooled to -78 °C, and O_2 gas was bubbled for 30 min. To this was added $SnCl_2$ (250 mg, 1.32 mmol) and H_2O (4.4 mL), and the mixture was stirred at room temperature for 1 h. Water was added, and the mixture was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product **95** was used for the next step without purification.

To a solution of crude **95** (134 mg) in EtOH (1.1 mL) and H_2O (1.1 mL) was added NaOH (50 mg, 1.25 mmol) at room temperature. After being stirred for 1.5 h, the mixture was neutralized by a 1 M HCl. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=9:1) to afford **96** as a yellow oil (86 mg, 0.348 mmol, 80%).; IR (neat): ν 2931, 2858, 2364, 1632, 1458, 1141, 1075 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.97 (1H, s), 3.28 (3H, s), 2.83 (1H, d, *J* = 12.0 Hz), 2.50 (1H, d, *J* = 2.9 Hz), 2.41 (1H, dd, *J* = 12.9, 10.6 Hz), 2.36 (1H, d, *J* = 12.6 Hz), 2.28-2.22 (2H, m), 2.18 (1H, d, *J* = 12.0 Hz), 2.05 (1H, d, *J* = 12.0 Hz), 1.95 (1H, d, *J* = 12.0 Hz), 1.61 (1H, d, *J* = 8.6 Hz), 1.58-1.46 (2H, m), 1.42 (1H, td, *J* = 9.9, 4.6 Hz), 1.20 (1H, dq, *J* = 17.9, 4.4 Hz), 1.06 (1H, t, *J* = 7.4 Hz), 0.96 (1H, td, *J* = 8.9, 4.6 Hz), 0.71 (1H, dd, *J* = 14.6, 8.9 Hz), 0.26 (1H, q, *J* = 5.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 205.51, 160.56, 126.72, 73.70, 55.00, 47.55, 45.27, 42.51, 31.32,

31.22, 30.86, 29.41, 26.88, 18.05, 13.24, 12.91; HRMS (FD): Calcd for $C_{16}H_{22}O_2$ [M]$^+$: 246.2620; found: 246.1622.

Compound 83 and Coupound 97



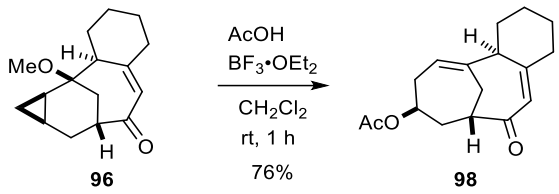
96 **83** 38% **97** 33%

To a mixture of **96** (25 mg, 0.10 mmol), THF (400 μL), and a 1 M HCl (100 μL) was stirred at 50 °C for 30 min. After cooling to 0 °C, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane:EtOAc=9:1 to 2:1) to afford **83** (8.8 mg, 38 μmmol, 38%) as a white solid along with **97** (8.2 mg) as a foam. Alcohol **83**; mp. 114-117 °C; IR (neat): ν 3298 (br), 2927, 2853, 2366, 2358, 2342, 1655, 1614, 1031 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.75 (1H, s), 5.57 (1H, t, *J* = 7.4 Hz), 3.50 (1H, t, *J* = 11.2 Hz), 2.86 (2H, m), 2.71 (1H, t, *J* = 6.0 Hz), 2.64 (1H, q, *J* = 6.7 Hz), 2.49 (2H, dt, *J* = 17.2, 8.3 Hz), 2.33-2.16 (3H, m), 1.88 (2H, t, *J* = 16.3 Hz), 1.70 (2H, m), 1.50-1.37 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 205.01, 157.10, 146.37, 125.82, 121.62, 64.68, 53.84, 48.58, 41.71, 37.34, 35.66, 31.11, 27.31, 27.30, 25.23; HRMS (FD): Calcd for $C_{15}H_{20}O_2$ [M]$^+$: 232.1463; found: 232.1458.

Chloride **97**; IR (neat): ν 2929, 2856, 1653, 1460, 1353, 1323,1297, 1262, 1213, 1163, 1099, 1001, 923, 909, 860, 850, 751 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.74 (1H, s), 5.59 (1H, t, *J* = 7.2 Hz), 3.79 (1H, t, *J* = 11.7 Hz), 3.15 (1H, t, *J* = 7.7 Hz), 2.82-2.77 (2H, m), 2.72-2.63 (2H, m), 2.58-2.49 (2H, m), 2.31 (1H, d, *J* = 13.7 Hz), 2.18 (1H, dd, *J* = 14.9, 12.6 Hz), 2.00 (1H, td, *J* = 12.6, 4.0 Hz), 1.87 (2H, t, *J* = 16.0 Hz), 1.59 (1H, dq, *J* = 12.5, 3.3 Hz), 1.51-1.34 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$, 500 MHz): δ 204.14, 156.71, 147.58, 125.66, 122.21, 54.68, 53.63, 49.64, 42.88, 37.26, 37.20, 30.91, 27.22, 27.23, 25.14; HRMS (FI): Calcd for $C_{15}H_{19}ClO$ [M]$^+$:

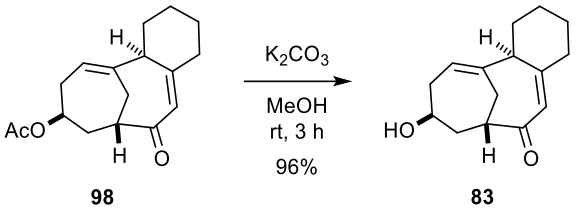
250.1124; found: 250.1125.

Compound 98



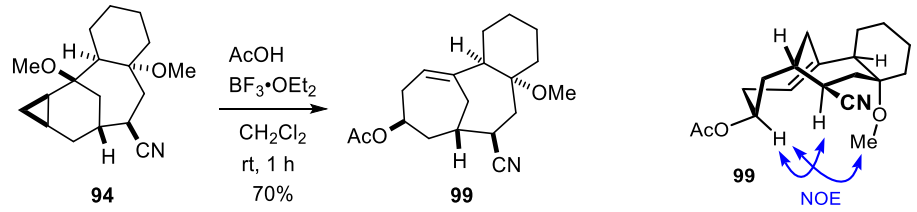
To a cooled (0 °C) mixture of **96** (40 mg, 0.162 mmol) and AcOH (200 μL) in CH_2Cl_2 (400 μL) was added BF_3•OEt_2 (2.0 μL, 0.016 mmol). The reaction mixture was warmed up to room temperature and was stirred for 1 h. After cooling to 0 °C, a saturated aqueous $NaHCO_3$ solution was added, and the mixture was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane:EtOAc = 9:1) to afford **98** as a yellow oil (34 mg, 0.123 mmol, 76%).; IR ($CHCl_3$): ν 2931, 2856, 2365, 2342, 1656, 1617, 1460, 1437, 1363, 1326, 1162, 1108, 1085, 1020, 970, 888, 867, 850, 751 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$): δ 5.76 (1H, s), 5.61 (1H, t, *J* = 7.4 Hz), 4.52-4.48 (1H, m), 2.87-2.80 (2H, m), 2.74 (1H, d, *J* = 5.2 Hz), 2.65 (1H, q, *J* = 6.7 Hz), 2.54-2.43 (2H, m), 2.33-2.29 (2H, m), 2.18 (1H, dd, *J* = 14.9, 12.6 Hz), 2.01 (3H, s), 1.91-1.77 (3H, m), 1.80 (1H, td, *J*= 12.2, 4.4 Hz) 1.73 (1H, d, *J* = 12.6 Hz), 1.43 (2H, dtd, *J* = 47.7, 15.3, 8.6 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 204.20, 169.97, 156.94, 146.84, 125.82, 121.11, 67.48, 53.75, 48.32, 37.62, 37.36, 32.65, 31.13, 27.32, 27.15, 25.22, 21.38; HRMS (FI): Calcd for $C_{17}H_{22}O_3$ $[M]^+$: 274.1569; found: 274.1572.

Compound 83



To a solution of acetate **98** (33 mg, 0.123 mmol) in MeOH (500 µl) was added K_2CO_3 (50 mg, 0.362 mmol) at room temperature. After being stirred for 3 h, EtOAc and brine was added and separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under deduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to afford alcohol **83** as a white solid (27.0 mg, 0.118 mmol, 96%).

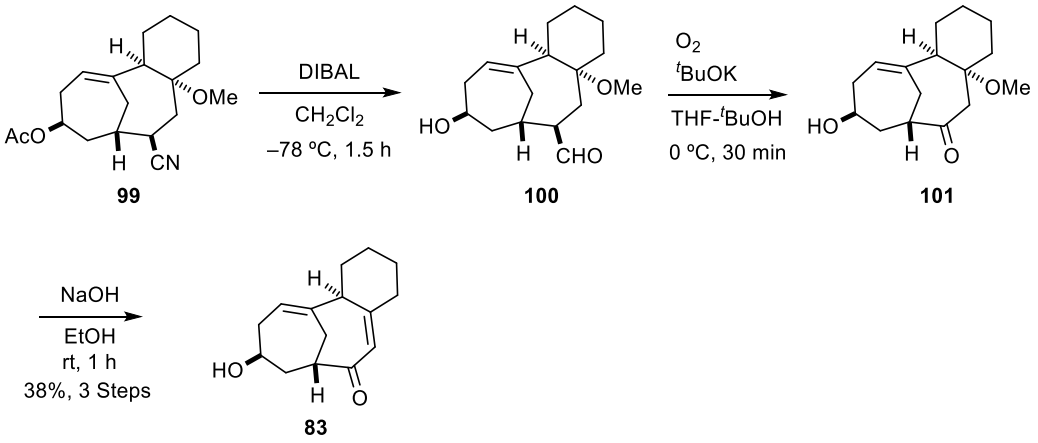
Compound 99



To a cooled (0 °C) mixture of **94** (30 mg, 0.104 mmol) and AcOH (120 µL) in CH_2Cl_2 (250 µL) was added BF_3•OEt_2 (2.0 µl, 0.016 mmol). The reaction mixture was warmed up to room temperature and was stirred for 1 h. After cooling to 0 °C, a saturated aqueous $NaHCO_3$ solution was added, and the mixture was separated. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=9:1) to afford **99** as a yellow oil (22 mg, 0.070 mmol, 70%).; IR ($CHCl_3$): ν 3488, 3017, 2860, 2364, 2343, 1732, 1475, 1367, 1151, 1072, 973, 863, 823, 615 cm^{-1}; ^{1}H-

NMR (500 MHz, $CDCl_3$): δ 5.51 (1H, t, *J* = 7.2 Hz), 4.76 (1H, td, *J* = 10.0, 6.5 Hz), 3.16 (3H, s), 2.49 (1H, td, J = 12.5, 6.1 Hz), 2.39-2.28 (4H, m), 2.22-2.15 (2H, m), 2.03 (3H, s), 1.93-1.87 (2H, m), 1.81 (2H, t, 15.2 Hz), 1.72 (2H, t, *J* = 10.6 Hz), 1.59-1.49 (3H, m), 1.25-1.12 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.00, 140.81, 124.02, 123.17, 74.44, 66.83, 50.95, 47.98, 40.39, 36.65, 36.14, 33.40, 33.01, 27.88, 27.78, 25.11, 24.98, 23.34, 21.36; HRMS (FD): Calcd for $C_{19}H_{27}NO_3$ $[M]^+$: 317.1991; found: 317.1988.

Compound 83



To a solution of nitrile **99** (32.0 mg, 0.10 mmol) in CH_2Cl_2 (500 μl) was added DIBAL (1.03 M in hexane, 240 μl, 0.25 mmol) at -78 °C. After being stirred for 1.5 h, the reaction mixture was added EtOAc, and sttired for 1 h at 0 °C. The mixture was added a solution of Rochelle salt and sttired for 3 h. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under deduced pressure. The crude compound **100** (30 mg) was used for the next step without purification.

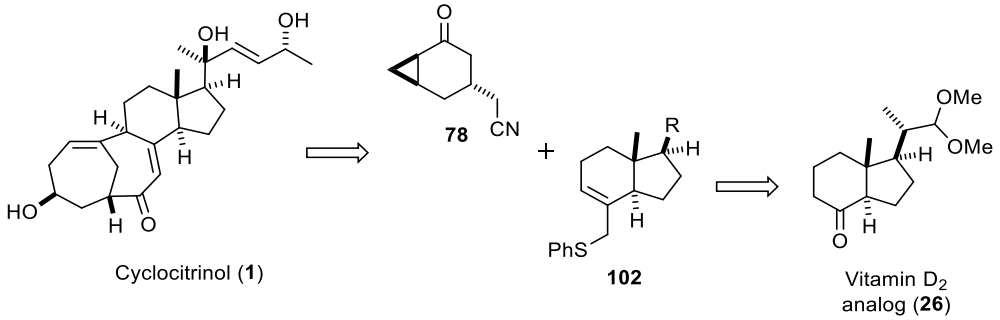
The mixture of crude **100** (30 mg) and ^{t}BuOK (45 mg, 0.4 mmol) in THF (500 μl) and ^{t}BuOH (500 μl) was bubbled O_2 gas for 30 min at 0 °C. A saturated aqueous NH_4Cl solution was added to the mixture and separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude **101** (17 mg) was used for the next step without purification.

To a solution of crude **101** (17 mg) in EtOH (500 μl) was added NaOH (8.0 mg, 0.2 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was added 1M HCl aqueous solution (200 μl) and diluted with water and Et_2O. The mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ((hexane:EtOAc = 2:1) to afford **83** as a white solid (8.8 mg, 0.038 mmol, 38% for 3 steps).

Chapter II.
Studies toward the asymmetric total synthesis of cyclocitrinol

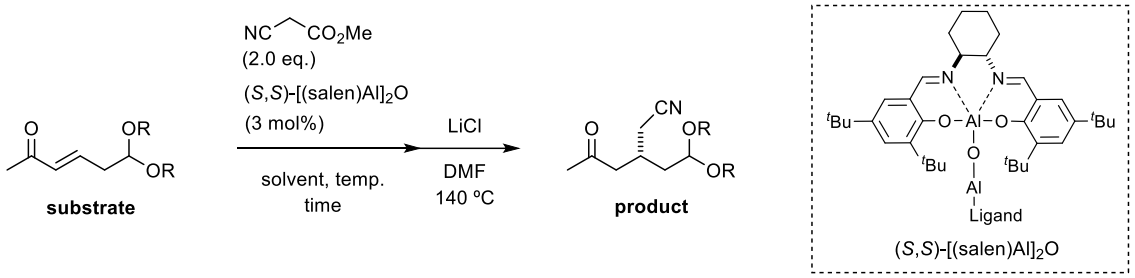
2-1. Synthesis of chiral segments

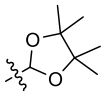
In chapter I, the synthesis of a model compound of cyclocitrinol, which corresponds to the ABC ring moiety, was described. Toward the asymmetric total synthesis of cyclocitrinol based on a similar strategy, the remaining issue is the construction of the D ring moiety. The author planned to use allylsulfide **102** having a hydrindane skeleton, which was expected to be prepared from ketone **26**[23] (Scheme 22). It was known that ketone **26** can be readily obtained from calciferol in an enantiomerically pure form. Therefore, it was required to prepare ketone **78** in an optically pure form as the coupling partner of the hydrindane segment.



Scheme 22. Synthetic plan toward cyclocitrinol

First, the author explored the asymmetric synthesis of ketone **78** for the asymmetric total synthesis of cyclocitrinol. After conducting a literature review, the author payed attention to the asymmetric conjugate addition reaction of methyl cyanoacetate with an enone catalyzed by a chiral aluminum complex (Table 2).



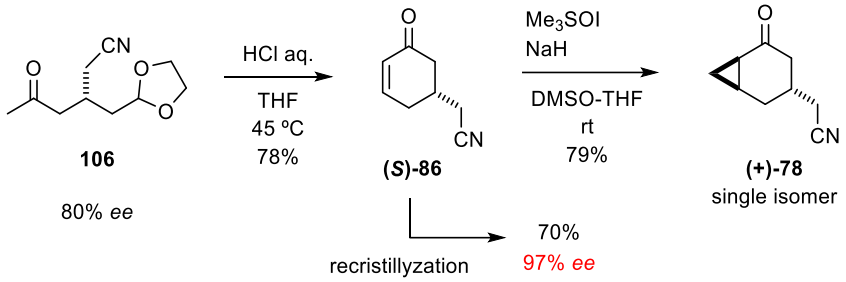
entry	substrate	solvent, temp, time	results*
1	 **61**	cyclohexane, rt 36 h	**85** 77%, er = 77:23
2	 **103**	cyclohexane, rt 36 h	**104** 82%, er = 80:20
3	 **105**	cyclohexane, rt 10 h	**106** 75%, er = 83:17
4		methyl cyclohexane, 0 ºC 24 h	**106** 75%, er = 90:10

* 2 steps yield

Table 2. Optimization of enantioselective conjugate addition[25]

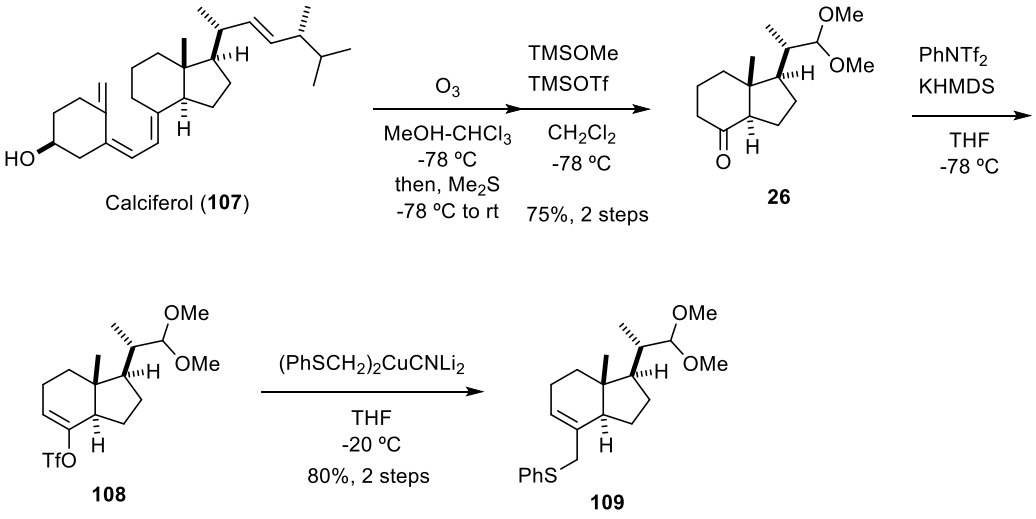
According to the protocol of Jacobsen[24], α,β-unsaturated ketones having an acetal moiety at the δ-position was reacted with methyl cyanoacetate. The product was then subjected to a decarboxylation reaction by heating with LiCl in DMF at 140 °C. The resulting ketone was treated with diluted hydrochloric acid in THF to afford cyclohexenone **78**, the enantiomeric purity of which was determined by an HPLC analysis using a chiral column. In the table showing the comparison of the acetal moiety, all substrates afforded the desired ketones in over 75% yields, respectively. The use of diethyl acetal **61** led to relatively low (73:17) enantiomeric ratio (entry 1), while sterically demanding pinacol derivative **103** afforded the adduct in slightly higher (80:20) ratio (entry 2). On the other hand, 1,3-dioxolane derivative **105** showed higher reactivity than substrates **61** and **103**, and the desired ketone was obtained in 83:17 enantiomeric ratio (entry 3). The enantioselectivity was increased to 90:10 by conducting the reaction in methylcyclohexane at 0 °C without reducing the chemical yield (entry 4), while substrates **61** and **103** failed to give the desired adduct under similar reaction conditions in entry 4.

As was mentioned above, the resulting ketone **106** was subjected to an intramolecular aldol reaction to afford enone **86** in 78% yield with 80%ee (Scheme 23). Fortunately, recrystallization of **86** from cooled ethanol at –78 °C gave enantiomerically enriched **(*S*)-86** in 70% yield with 97% ee. The enone was converted to the chiral segment **(+)-78** via the diastereoselective cyclopropanation reaction according to the same procedure described in Chapter I.



Scheme 23. Synthesis of (+)-78

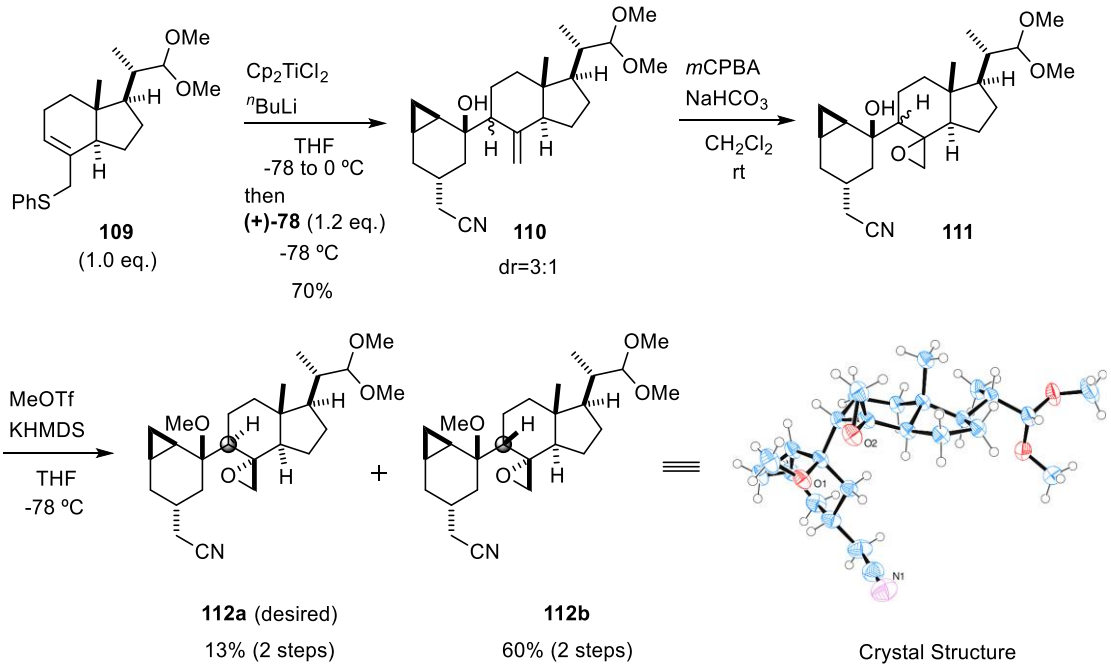
The CD ring segment was then prepared from calciferol (**107**) (Scheme 24). The alkene moieties of **107** were cleaved by ozonolysis, giving rise to a mixture of the expected keto aldehyde along with ketone **26**. Upon treatment with TMSOMe and TMSOTf, the mixture was fully converted to ketone **26** in 75% overall yield. Ketone **26** was transformed into allylsulfide **109** through the cross-coupling reaction of enol triflate **108** with a higher order organocuprate[25].



Scheme 24. Synthesis of CD ring segment

2-2. Synthesis of the key cyclization precursor

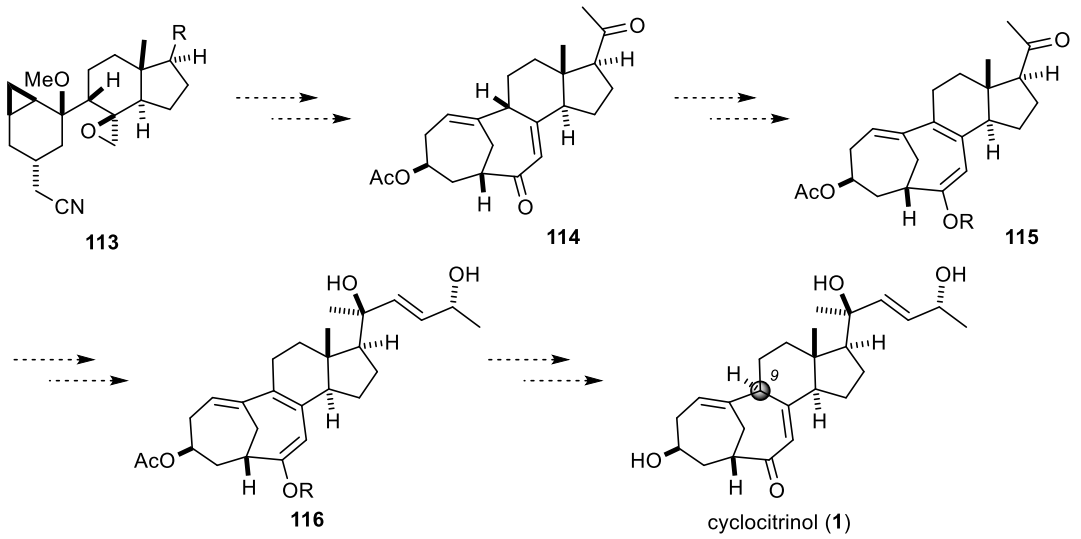
With the desired chiral segments in hand, coupling reaction of these segments was conducted (Scheme 25). The allyltitanium reagent, which was generated from allyl sulfide **109** by the combined use of Cp_2TiCl_2 and *n*-BuLi, was reacted with ketone **78** to afford adduct **110** in 70% yield as a 3:1 mixture of diastereomers. Oxidation of the mixture with *m*CPBA followed by methylation of the hydroxy group afforded a mixture of epoxide **112a** and **112b** which was found to be separable easily from each other by silica gel chromatography. The major isomer **112b** was obtained as a crystalline solid, and the X-ray crystallographic analysis of it was performed. The ORTEP drawing indicates that the configuration of the newly formed C9 (according to the steroid numbering system) stereogenic center is different from that of cyclocitrinol. Since the addition reaction of an achiral allyltitanium reagent and the racemate of ketone **78** in Chapter I mainly afforded the desired diastereomer, the favorable formation of **112b** would come from the requirement of the titanium reagent. Thus, formation of a new bond at the α-face of the bicyclic skeleton is preferred, because the reaction at the β-face suffers from the steric repulsion of the axial methyl group. It is noteworthy that stereoselective oxidation of the methylene group with *m*CPBA is also explained by the same effect.



Scheme 25. Accessing epoxy nitrile 112 and X-ray structure

Although the configuration at the C9 position was not consistent with that of cyclocitrinol (**1**),

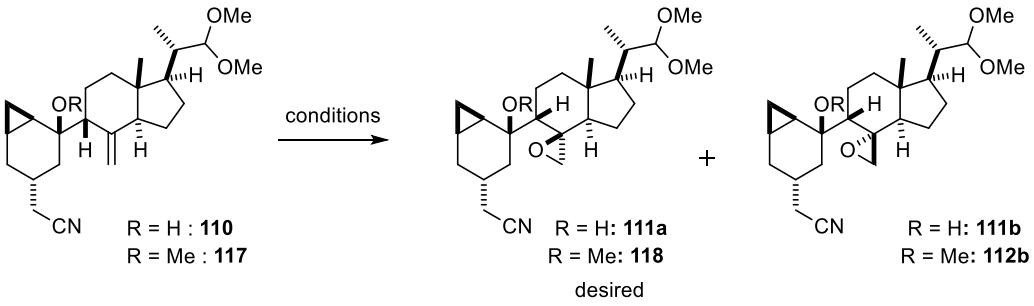
the author decided to use the major isomer as an intermediate of the total synthesis. It was expected that the configuration of the C9 position of the major isomer would be inverted after construction of the tetracyclic skeleton (Scheme 26). Since the C9 methine proton of **114** is at the γ-position of the B ring enone moiety, the wrong configuration might be inverted through formation of a dienol derivative **115** followed by protonation at the γ-position. This plan, however, suffered from the fact that the major isomer **112b** is not suitable for the intramolecular epoxy-nitrile cyclization, as was expected from the ORTEP drawing in Scheme 25. Therefore, preparation of **113**, the corresponding epimer of **112b** at the epoxide moiety, from adduct **110** was the first issue in achieving the epoxy-nitrile cyclization.



Scheme 26. Alternative plan toward total synthesis of 1

The efforts for obtaining the epoxide with β-configuration are summarized in Table 3. As was mentioned above, the reaction of alcohol **110** with *m*CPBA gave α-epoxide **111b** predominantly (entry 1), while *m*CPBA oxidation of the corresponding methyl ether **117** resulted in formation of a 1:1 mixture of **112b** and the desired β-epoxide **183** (entry 2). On the other hand, the use of DMDO generated in-situ effected preferential formation of β-epoxides. Thus, a 2:1 mixture of β-epoxide **111a** and α-epoxide **111b** was obtained from alcohol **110** (entry 3), and methyl ether **112b** afforded the β-epoxide **183** as a single diastereomer (entry 4). Finally, it was found that ozone is the oxidant of choice for obtaining the desired epoxide **118** (entry 5) [27]. It has been known that a

sterically demanding alkene can give epoxide rather than carbonyl compounds upon treatment with ozone.

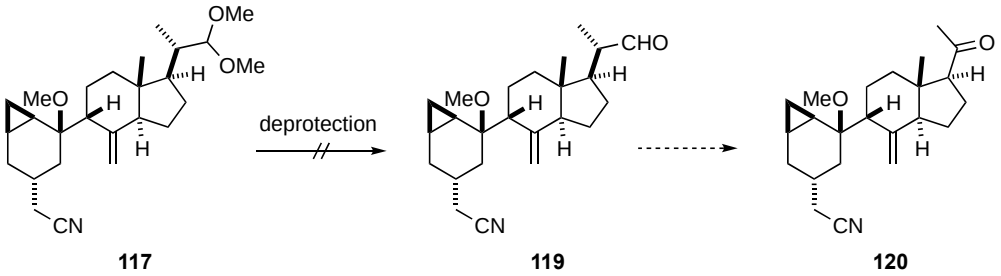


entry	substrate*	conditions	result
1	**110**	*m*CPBA, $NaHCO_3$ CH_2Cl_2, rt	80%, only **111b**
2	**117**	*m*CPBA, $NaHCO_3$ CH_2Cl_2, rt	78%, **118**:**112b** = 1:1
3	**110**	Oxone, $NaHCO_3$ CH_2Cl_2-acetone-H_2O, rt	65%, **111a**:**111b** = 2:1
4	**117**	Oxone, $NaHCO_3$ CH_2Cl_2-acetone-H_2O, rt	67%, only **118**
5	**117**	O_3, $NaHCO_3$ CH_2Cl_2-MeOH, -78 ºC	75%, only **118**

*substrate was used after removal of minor isomer

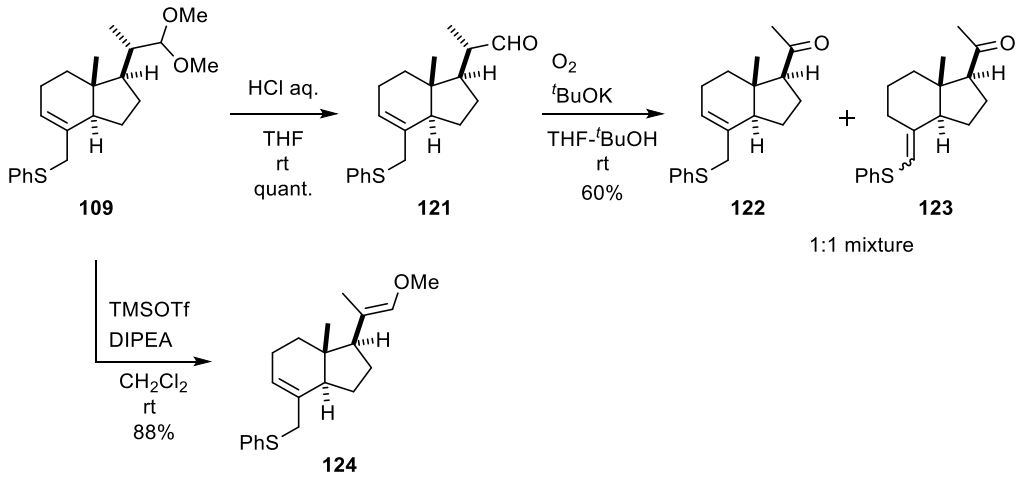
Table 3. Optimization of diastereoselective epoxidation

Although oxidation of methyl ether **117** with DMDO or ozone provided the desired epoxide **118**, it was found that these oxidants tend to oxidize the acetal moiety, leading to low reproducibility. The results led the author to manipulate the acetal moiety prior to the oxidation step. The attempts to hydrolyze the acetal group of **117** were fruitless, because the cyclopropyl methyl ether moiety was easily cleaved under acidic conditions (Scheme 27). Therefore, it was required that manipulation of the side chain should be done before the coupling reaction of the chiral segments.



Scheme 27. Attempts for manipulation of acetal moiety

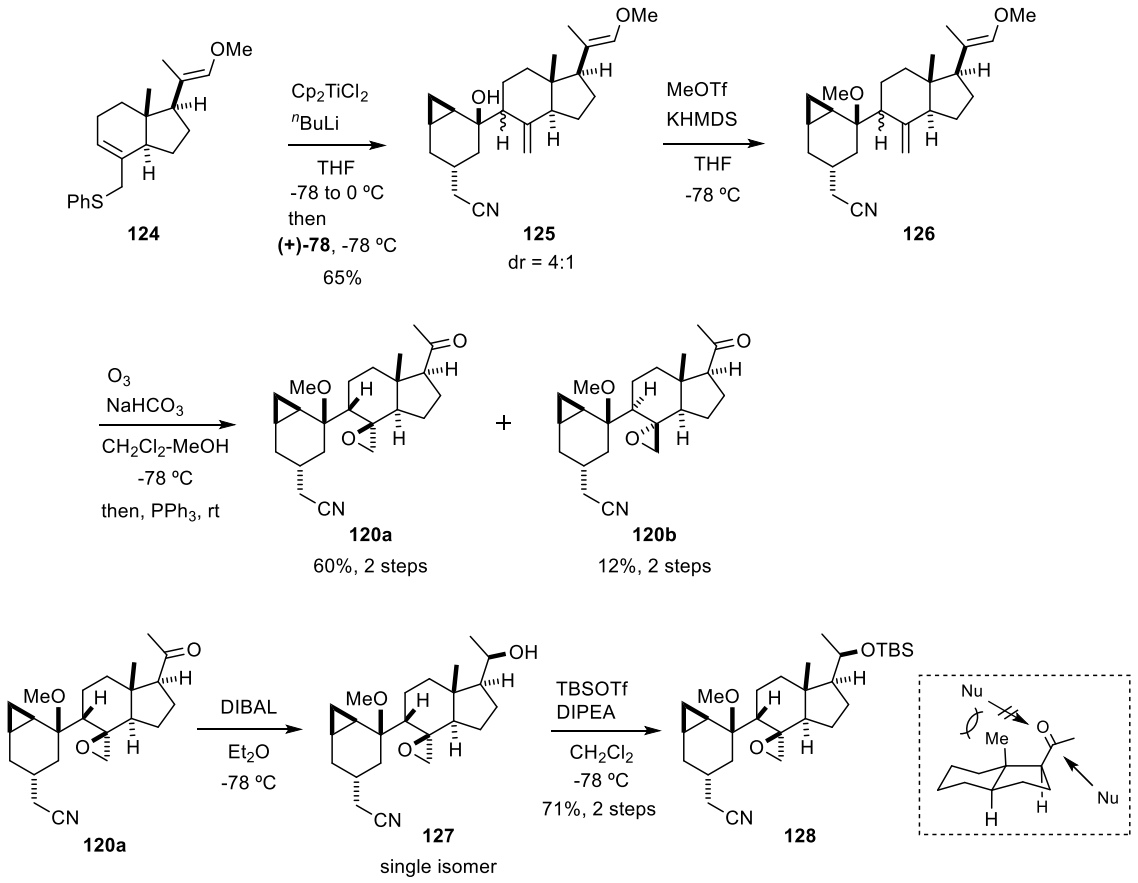
Transformation of acetal **109** was examined as shown in Scheme 28. Upon treatment with diluted hydrochloric acid in THF, acetal **109** was readily hydrolyzed to aldehyde **121** in quantitative yield. Under the influence of *t*-BuOK under O_2 atmosphere, **121** underwent an oxidative decarbonylation reaction to give the desired ketone **122**, but an equal amount of a side product **123** was also formed by isomerization of the allyl sulfide moiety. On the other hand, treatment of **109** with TMSOTf and DIPEA afforded enol ether **124** in high yield. It was expected that the enol ether moiety would be converted to the desired methyl ketone moiety at the epoxidation reaction by using ozone.



Scheme 28. Synthesis of other allylsulfides

The allyltitanium reagent prepared from **124** was reacted with ketone **78** to afford adduct **125** as a 4:1 mixture of isomers in 65% combined yield. After methylation of the hydroxy group, the products were treated with ozone to give the desired epoxy ketone **120a** along with epimer **120b**.

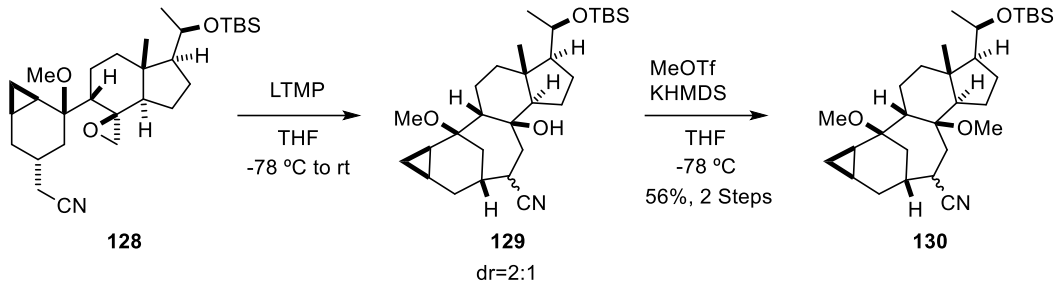
After removal of the minor isomer by silica gel chromatography[28], the ketone moiety of **120a** was transformed into secondary silyl ether **128** through stereoselective reduction with DIBAL and silylation of the resulting alcohol **127**. The configuration of the newly formed stereogenic center on the side chain was not determined but was expected from the well-known selectivity in steroid chemistry.



Scheme 29. Synthesis of cyclization precursor 128

2-3. Synthesis of the core skeleton of cyclocitrinol

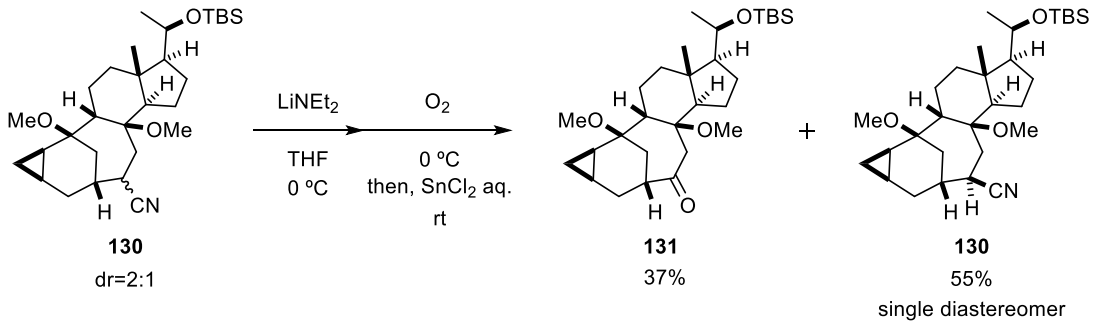
With the desired epoxy nitrile **128** in hand, the intramolecular cyclization reaction was conducted. Upon treatment with LTMP, which was found to be the best base in the model study, pentacyclic compound **129** was obtained as a 2:1 mixture of epimers at the nitrile moiety (Scheme 30). The alcohol was subjected to the methylation reaction with MeOTf and KHMDS, giving rise to compound **130** in 56% yield from **128**.



128 **129** dr=2:1 **130**

Scheme 30. Construction of B ring

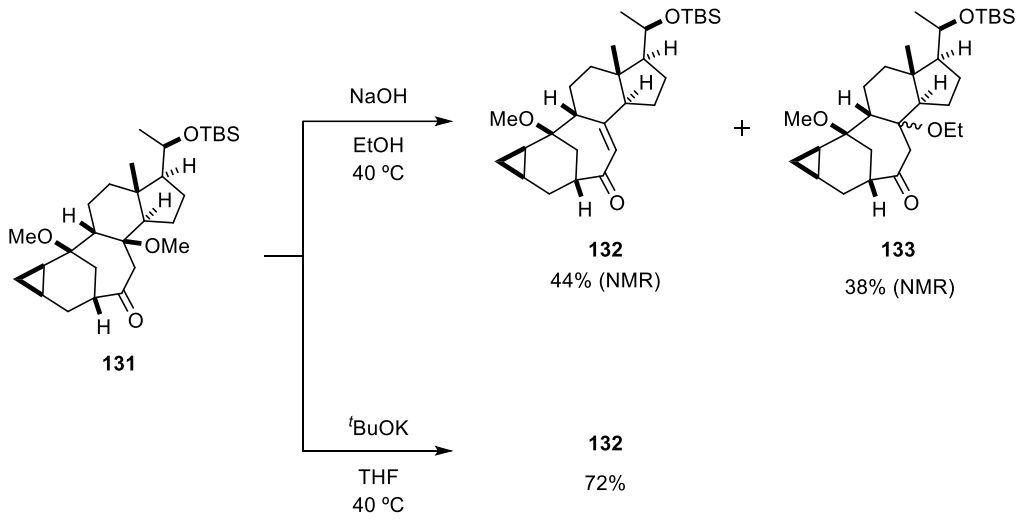
Upon treatment with $LiNEt_2$ under O_2 atmosphere followed by an aqueous solution of tin(II) chloride, nitrile **130** was converted to ketone **136** in 37% yield (Scheme 31). The low yield came from the recovery of substrate **135** as a single diastereomer in 55% yield, indicating that only the minor epimer of **130** at the nitrile moiety underwent the lithiation with $LiNEt_2$. The low reactivity of the major isomer can be explained by the steric hindrance around the α-proton of the nitrile moiety which is oriented to the concave face of the caged skeleton.



130 dr=2:1 **131** 37% **130** 55% single diastereomer

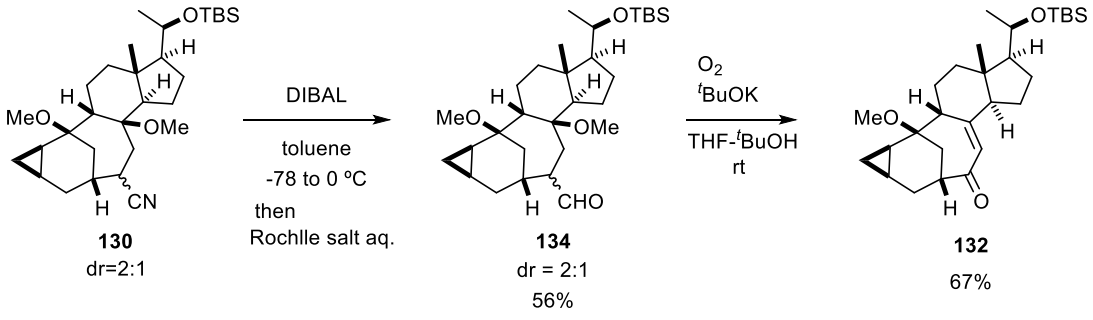
Scheme 31. Attempts for an oxidative decyanation

Although the low yield of ketone **131** remained as a problem to be solved, further transformation of **131** was explored (Scheme 32). Treatment of **131** with NaOH in ethanol effected elimination of the β-methoxy group to afford enone **132** in 44% NMR yield. The reaction, however, also produced ketone **133** in 38% NMR yield through incorporation of an ethoxy group under basic conditions. The side reaction was reduced by the use of more bulky ^{t}BuOK, resulting in formation of the desired enone **132** in 72% yield.



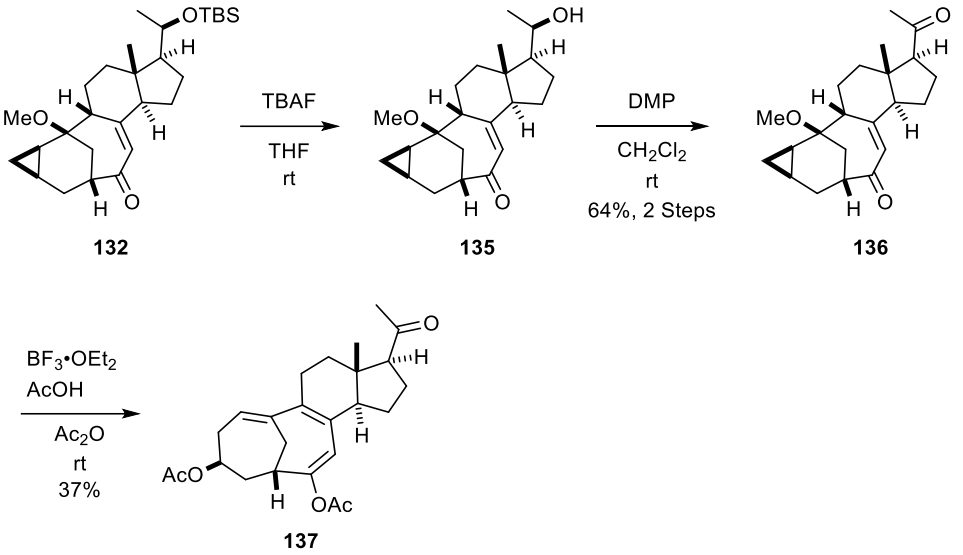
Scheme 32. Converts to enone 132

These results led the author to improve the protocol for the transformation of nitrile **130** into enone **132** (Scheme 33). Thus, DIBAL reduction of **130** afforded the corresponding aldehyde **134** which was expected to be enolizable under mild conditions. Upon treatment with *t*-BuOK under O_2 atmosphere, **134** underwent the oxidative decarbonylation reaction followed by β-elimination of the methoxy group to afford enone **132** in moderate overall yield.



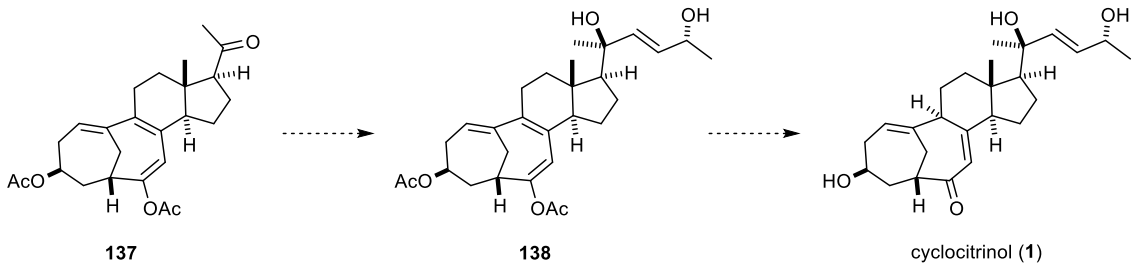
Scheme 33. Another protocol for conversion of 130 to enone 132

Silyl ether **132** was converted to methyl ketone **141** through removal of the TBS group by TBAF and Dess-Martin oxidation of the resulting alcohol **135** (Scheme 34). Finally, cleavage of the cyclopropane moiety of **141** was conducted by the treatment with $BF_3 \cdot OEt_2$ and acetic acid in acetic anhydride, giving rise to **142** possessing a linearly conjugated trienol acetate moiety in 37% yield.



Scheme 34. Construction of ABCD ring structure

Since the wrong configuration at the C9 position was lost by the final reaction, the remaining task for achieving the total synthesis of cyclocitrinol (**1**) is elongation of the side-chain and hydrolysis of the enol acetate moiety by the facial selective protonation at the C9 position (Scheme 35).



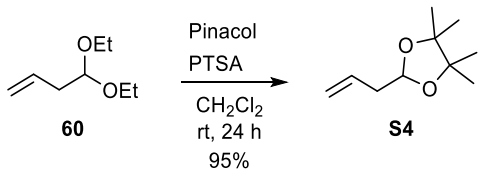
Scheme 35. Propose synthetic route toward cyclocitrinol

In summary, the author has achieved the construction of a tetracyclic skeleton that corresponds to the ABCD ring system of cyclocitrinol. The chiral segment of the A ring was synthesized through asymmetric conjugate addition of methyl cyanoacetate with an enone possessing an acetal moiety, intramolecular aldol condensation, and the Corey-Chaykovsky reaction. The chiral CD ring segment having an allyl sulfide moiety was prepared from calciferol. An allyltitanium reagent

generated from the CD ring segment was reacted with the A ring segment, and the resulting adduct was transformed into an epoxy nitrile. The B ring was constructed by the epoxy-nitrile intramolecular cyclization, and the ABCD ring system was formed through cleavage of the cyclopropane ring.

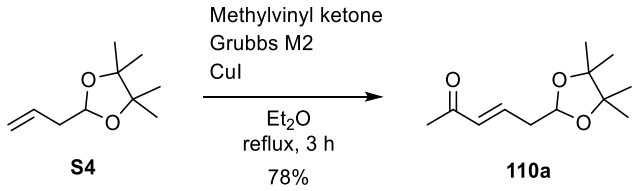
Experimental Section

Compound S4



To a mixture of diethylacetal **60** (1.44 g, 10.0 mmol) and pinacol (1.42 g, 12.0 mmol) in CH_2Cl_2 (10 ml) was added PTSA (19.0 mg, 0.10 mol) at room temperature. After being stirred for 24 h, the reaction mixture was added a saturated aqueous Na_2CO_3 solution. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 8:2) to afford acetate **S4** as a colorless oil (1.62 g, 9.5 mmol, 95%).; ^{1}H-NMR ($CDCl_3$): δ 5.87-5.79 (1H, m), 5.12 (3H, m), 2.37 (2H, q, *J* = 3.8 Hz), 1.21 (6H, s), 1.20 (6H, s).

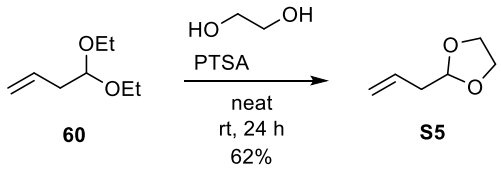
Compound 110a



A mixture of Grubbs M2 (5.0 mg, 50 μmol), CuI (1.5 mg, 75 μmol) in Et_2O (5 ml) was added acetal **S4** (850 mg, 5.0 mmol) and methyl vinyl ketone (490 μl, 6,0 mmol). The solution was heated to reflux for 3 h, the solution was removed under reduce pressure and residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) to give enone **110a** as a yellow oil 827 mg, 3.9 mmol, 78%).; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.82-6.76 (1H, m), 6.15 (1H, d, *J* = 16.0 Hz), 5.15 (1H, dd, *J* = 5.7, 4.0 Hz), 2.54 (2H, td, *J* = 6.0, 1.7 Hz), 2.26 (3H, d, *J* = 1.1 Hz),

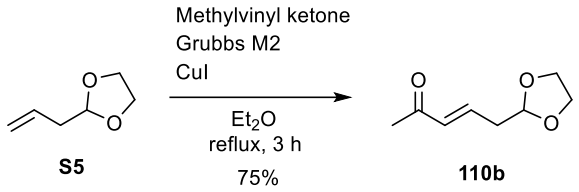
1.21 (12H, s).

Compound S5



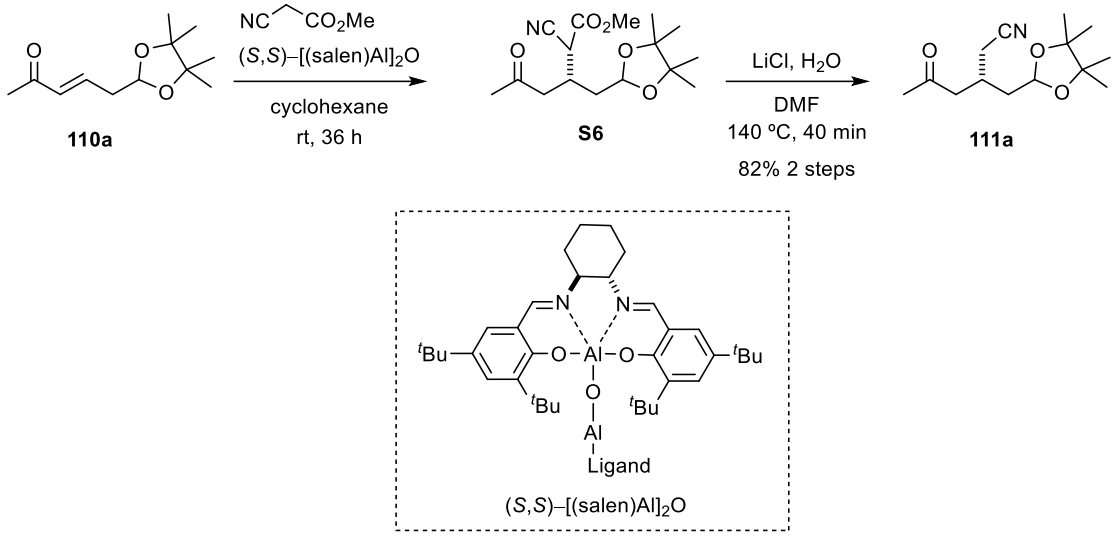
To a mixture of diethylacetal **60** (45 g, 312 mmol) and ethylene glycol (21 ml, 374 mmol) was added PTSA (570 mg, 3.0 mmol) at room temperature. After being stirred for 24 h, the reaction mixture was added a saturated aqueous Na_2CO_3 solution. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 and solvent was removed distillation at 70 °C. The residue was purified by distillation (bp. 70~72 °C, 90 torr) to afford acetal @ as a colorless oil (22 g, 193 mmol, 62 %)., ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.84 (1H, tt, *J* = 13.7, 5.2 Hz), 5.19-5.12 (2H, m), 4.91 (1H, t, *J* = 4.9 Hz), 3.99 (2H, q, *J* = 7.4 Hz), 3.86 (2H, q, *J* = 4.6 Hz), 2.44 (2H, q, *J* = 4.0 Hz).

Enone 110b



A mixture of Grubbs M2 (48 mg, 0.05 mmol), CuI (14 mg, 0.075 mmol) in Et_2O (10 ml) was added acetal **S5** (5.7 g, 50 mmol) and methyl vinyl ketone (4.9 ml, 60 mmol). The solution was heated to reflux for 3 h, the solution was removed under reduce pressure and residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to give enone **110b** as a yellow oil 5.88 g, 37.5 mmol, 75%).; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.78 (1H, td, *J* = 11.6, 5.5 Hz), 6.18 (1H, t, *J* = 8.6 Hz), 5.00 (1H, t, *J* = 4.3 Hz), 3.99 (2H, dt, *J* = 16.6, 7.3 Hz), 3.92-3.85 (2H, m), 2.61 (2H, dd, *J* = 6.3, 5.2 Hz), 2.24 (3H, s).

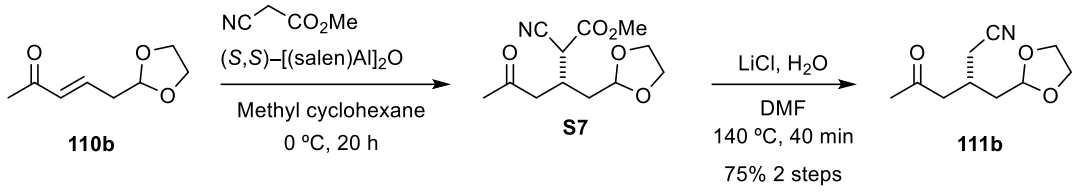
Methylketone 111a



To a mixture of enone **110a** (212 mg, 1.0 mmol) and Al-catalyst (35 mg, 0.03 mmol) in cyclohexane (5.0 ml) was added methyl cyanoacetate (200 µl, 2.3 mmol) at room temperature. After being stirring for 20 h, the organic solvent was concentrated under reduced pressure and the residue was filtrated through a pad of Celite. The crude product was used for the next step without additional purification.

To a solution of crude ketone **S6** (350 mg) in DMF (1.0 ml) was added LiCl (13.0 mg, 3.0 mmol) at room temperature. After being stirred for 40 min at 140 °C, water was added. The mixture was separated and the aqueous layer was extracted with hex/EtOAc (1:1) solution. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 7:3) to afford ketone **111a** as a yellow oil (207 mg, 0.82 mmol, 82% for 2 steps).; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.05 (1H, t, *J* = 5.4 Hz), 2.66 (2H, q, *J* = 5.7 Hz), 2.61 (2H, t, *J* = 5.7 Hz), 2.49-2.44 (1H, m), 2.16 (3H, s), 1.75-1.67 (2H, m), 1.19 (6H, s), 1.17 (6H, s).

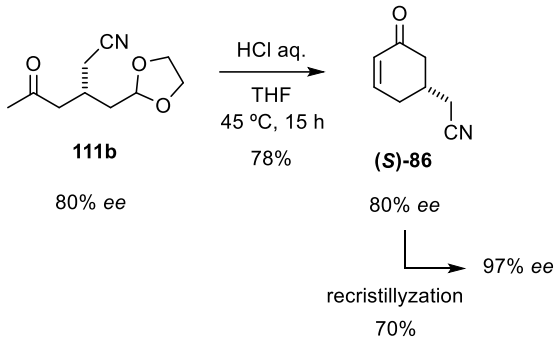
Methylketone 111b



To a mixture of enone **111b** (3.12 g, 20 mmol) and Al-catalyst (695 mg, 0.6 mmol) in methylcyclohexane (100 ml) was added methylcyanoacetate (4.0 ml, 46 mmol) at 0 ºC. After being stirring for 20 h, the organic solvent was concentrated under reduced pressure and the residue was filtrated through a pad of Celite. The crude product was used for the next step without additional purification.

To a solution of crude ketone **S7** (5.5 g) in DMF (20 ml) was added LiCl (2.54 g, 60 mmol) at room temperature. After being stirred for 40 min at 140 °C, water was added. The mixture was separated and the aqueous layer was extracted with hex/EtOAc (1:1) solution. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 7:3) to afford ketone **111b** as a yellow oil (2.96 g, 15 mmol, 75% for 2 steps).; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.89 (1H, t, *J* = 4.6 Hz), 3.96 (2H, dt, *J* = 14.1, 5.2 Hz), 3.84 (2H, td, *J* = 10.0, 4.4 Hz), 2.68 (1H, q, *J* = 6.1 Hz), 2.61 (2H, t, *J* = 6.0 Hz), 2.04 (0H, s), 1.84-1.75 (2H, m).

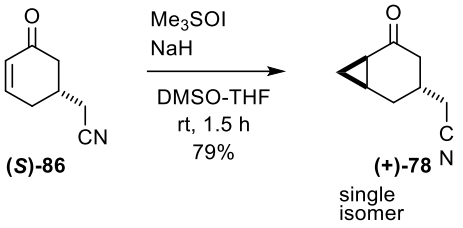
Compound (*S*)-86



According to the procedure described in chapter 1, enantioenriched **86** (1.58 g, 11.7 mmol) was obtained. The optically pure **(*S*)-86** was obtained by recrystallization from EtOH at -78 °C (2

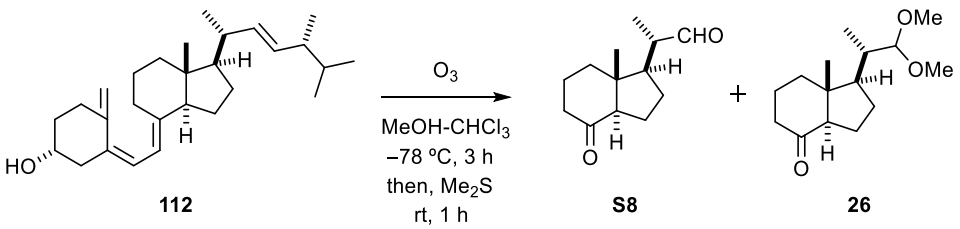
times). The crystalline of **(*S*)-86** was yield in 70% (1.11 g, 8.19 mmol, 97% ee). Enantiomeric excess was determineded by HPLC analysis (Chiralpak OB-H), eluted with n-hexane:isopropanol = 1:1, 1.0 ml/min)

Compound (+)-78



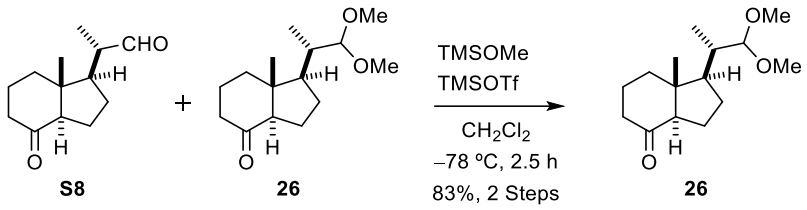
According to the procedure described in chapter 1, (+)-**78** (964 mg, 9.24 mmol) was obtained.; $[\alpha]_D^{25}$ +23.6 (*c*=1.0, $CHCl_3$)

Compound S8 and 26



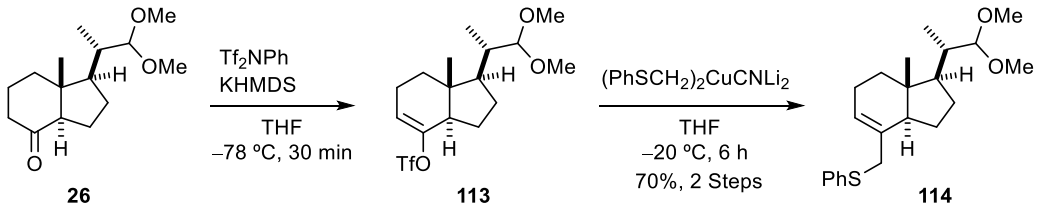
To a cooled (-78 °C) solution of calciferol (3.0 g, 7.56 mmol) in MeOH (60 ml) and $CHCl_3$ (7.2 ml) was bubbled ozone for 3 h. Argon was then passed through the mixture until the disappearance of the blue color. To the reaction mixture was added Me_2S (3.6 ml, 45.4 mmol) and stirred for 30 min at same temperature. The reaction mixture was warmed up to rt and stirred for 1 h. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to give aldehyde **S8** and acetal **26** (2:1) as a yellow oil (1.66 g).

Compound 26



To a cooled (-78 ℃) solution of aldehyde **S8** and acetal **26** (1.66 g) in CH_2Cl_2 (40 ml) was added TMSOMe (2.1 ml, 15.1 mmol). The mixture was added TMSOTf (70 μl, 0.38 mmol) and stirred for 2.5 h. The reaction mixture was added the solution of Et_3N (1.0 ml) in MeOH (10 mmol) at same temperature and stirred for 30 min. The reaction mixture was added H_2O and separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under deduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to give acetal **26** as a colorless oil (1.59 g, 6.27 mmol, 83% for 2 steps).

Compound 114

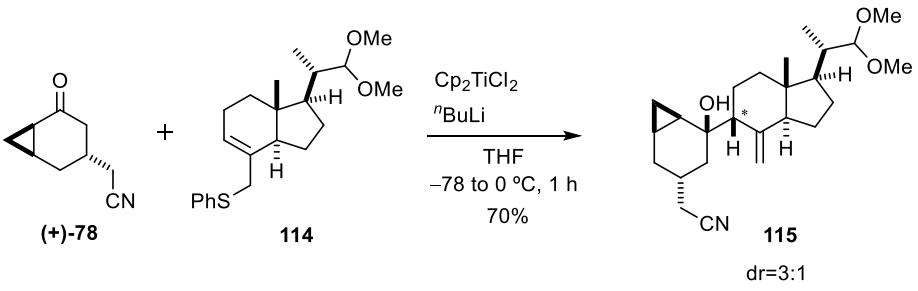


To a cooled (-78 ℃) solution of ketone **26** (1.59 g, 6.27 mmol) in THF (20 ml) was added KHMDS (0.5 M in toluene, 16.3 ml 8.15 mmol). After being stirred for 30 min, the reaction mixture was added a solution of Tf_2NPh (2.46 g, 6.90 mmol) in THF (5 ml). After being stirred for 30 min, the reaction mixture was added 1M NaOH aq. and stirred for 2 h at rt. The mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product **113** was used for the next step without purification.

To a cooled (0 ℃) mixture of thioanisole (3.67 ml, 31.3 mmol) and DABCO (3.50 g, 31.3

mmol) in THF (20 ml) was added ^{n}BuLi (2.67 M in hexane, 11.7 ml, 31.3 mmol), and stirred for 1 h at room temperature. To a mixture of CuCN (1.43 g, 16.0 mmol) in THF (5.0 ml) was added above lithium reagent at 0 ℃ and stirred for 15 min at same temperature. The reaction mixture was cooled into -20 ℃ and added the solution of crude triflate **113** (3.20 g) in THF (5 ml). After bring stirring for 6 h, the reaction mixture was added a saturated aqueous NH_4Cl solution. The mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under deduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 97:3) to afford allyl sulfide **114** as a yellow oil (1.58 g, 4.39 mmol, 70% for 2 steps).; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.32 (2H, t, *J* = 4.3 Hz), 7.26 (2H, dd, *J* = 10.6, 4.9 Hz), 7.19-7.16 (1H, m), 5.36 (1H, d, *J* = 2.9 Hz), 4.14 (1H, t, *J* = 6.6 Hz), 3.52-3.43 (5H, m), 3.39 (3H, s), 2.29 (1H, d, *J* = 10.3 Hz), 2.02 (2H, br-d), 1.93 (3H, tt, *J* = 12.6, 5.6 Hz), 1.73 (1H, td, *J* = 6.7, 3.4 Hz), 1.45 (4H, m), 0.98 (4H, d, *J* = 6.9 Hz), 0.68 (3H, s).

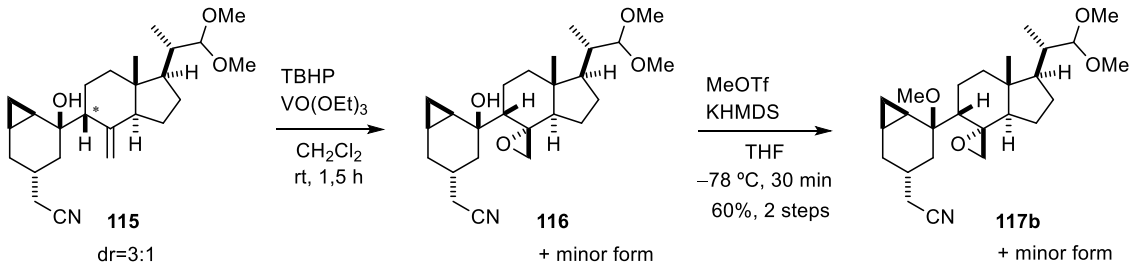
Compound 115



To a cooled (-78 °C) suspension of Cp_2TiCl_2 (620 mg, 2.5 mmol) in THF (4.0 ml) was added ^{n}BuLi (2.67 M in hexane, 1.90 ml, 5.0 mmol). After being stirred for 1 h, a THF solution (1.0 ml) of a **114** (360 mg, 1.0 mmol) was added, and stirring was continued for the 10 min same temperature and then at 0 °C for 1 h. After the reaction mixture had been stirred at -78 °C for 10 min, ketone **78** (180 mg, 1.2 mmol) in THF (1.0 ml) was added. The reaction mixture was stirred for 1 h and added a 1M aqueous NaOH solution. Insoluble materials were filtered off through celite and wased with EtOAc. The filtrate was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 75:15) to afford homoallyl alcohol **115** as a yellow oil (281 mg, 70%, 0.70 mmol, dr = 3:1).^{1}H-NMR (500 MHz, $CDCl_3$) δ: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.01 (1H, s), 4.90 (1H, s), 4.14 (1H, br-s), 3.45 (3H, s, *J* = 8.0 Hz), 3.39 (3H, s), 2.46 (1H, d, *J* = 7.4 Hz), 2.38 (1H, s), 2.26 (2H, t, *J* = 10.3 Hz), 2.17-2.05 (2H, m), 1.93 (5H, d, *J* = 10.3 Hz), 1.71 (2H, br-d), 1.37 (2H, t, *J* = 12.3 Hz), 1.25 (4H, br-s), 1.15 (1H, t, *J* = 12.9 Hz), 0.97 (3H, d, *J* = 6.9 Hz), 0.87 (3H, d, *J* = 6.9 Hz), 0.60 (3H, s), 0.55 (1H, t, *J* = 4.9 Hz) (described major isomer).

Compoud 117

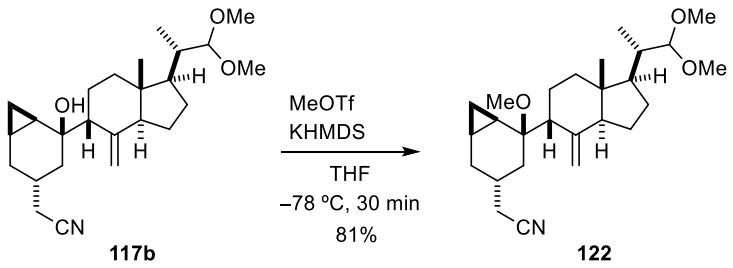


To a solution of homoallyl alcohol **115** (100 mg, 0.249 mmol) in CH_2Cl_2 (1.25 ml) was added TBHP (5.5 mmol in nonane, 70 µl, 0.374 mmol), $VO(OEt)_3$ (5.0 µl, 0.025 mmol) at room temperature. After being stirred for 1.5 h, the reaction mixture was added a saturated aqueous $NaHCO_3$ solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude epoxide **116** was used for the next step without purification.

To a cooled (-78 °C) solution of KHMDS (0.5 M in toluene, 1.25 ml 0.625 mmol) was added to a solution of crude **116** (118 mg) in THF (1.25 ml). After being stirred for 30 min at 0 °C, the reaction mixture was added MeOTf (55 µl, 0.5 mmol). The reaction mixture was stirred for 1 h and added a saturated aqueous NH_4Cl solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under deduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 75:15) to afford methyl ether **117** (65 mg, 0.15

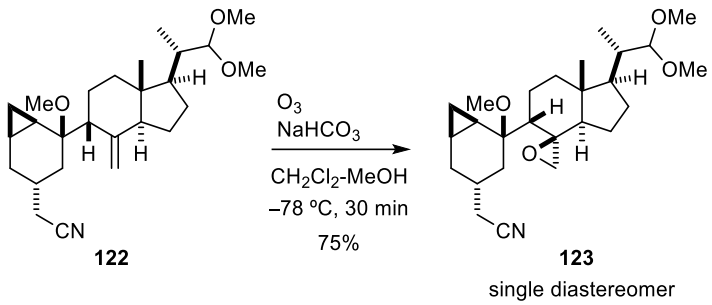
mmol, 60% for 2 steps, minor isomer was removed) as a yellow oil.; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.12 (1H, t, *J* = 6.3 Hz), 3.46-3.44 (3H, s), 3.38 (3H, s), 3.20 (3H, t, *J* = 12.3 Hz), 2.86 (1H, d, *J* = 5.2 Hz), 2.53 (1H, d, *J* = 4.6 Hz), 2.28-2.22 (2H, m), 2.07 (1H, t, *J* = 12.6 Hz), 2.00-1.66 (6H, m), 1.39-1.33 (2H, m), 1.28-1.22 (7H, m), 1.17-1.07 (3H, m), 0.96 (3H, d, *J* = 10.0 Hz), 0.80 (3H, s), 0.65 (1H, td, *J* = 9.0, 5.3 Hz), 0.44 (1H, d, *J* = 5.2 Hz). (described major isomer)

Compound 122



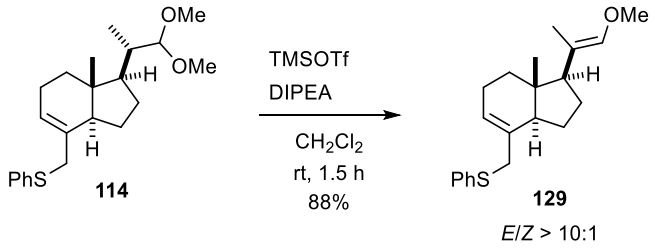
To a cooled (-78 °C) solution of KHMDS (0.5 M in toluene, 1.25 ml 0.625 mmol) was added to a solution of alcohol **117b** (100 mg, 0.25 mmol) in THF (1.25 ml). After being stirred for 30 min, the reaction mixture was added MeOTf (55 µl, 0.50 mmol). The reaction mixture was stirred for 1 h and added a saturated aqueous NH_4Cl solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under deduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 75:15) to afford methyl ether **122** (84.0 mg, 0.20 mmol 81%) as a yellow oil.; ^{1}H-NMR (500MHz, $CDCl_3$) δ: 5.03 (1H, s), 4.86 (1H, s), 4.14 (1H, d, *J* = 2.3 Hz), 3.45 (3H, s), 3.39 (3H, s), 3.30 (3H, s), 3.20 (1H, d, *J* = 6.9 Hz), 2.80 (1H, s), 2.26 (1H, dd, *J* = 16.6, 5.2 Hz), 2.16 (2H, q, *J* = 8.2 Hz), 2.09 (1H, d, *J* = 12.6 Hz), 1.85 (3H, d, br-s), 1.64-1.59 (4H,m), 1.49 (1H,m), 1.36 (1H, dd, *J* = 12.3, 8.3 Hz), 1.26-1.21 (5H, m), 1.18 (1H, t, *J* = 12.6 Hz), 0.96 (3H, d, *J* = 6.9 Hz), 0.71 (1H, d, *J* = 5.2 Hz), 0.59 (3H, s), 0.45 (1H, d, *J* = 5.2 Hz).

Compound 123



To a cooled (-78 °C) solution of **122** (21.0 mg, 0.05 mmol) in MeOH (250 µl) and CH_2Cl_2 (250 µl) was added $NaHCO_3$ (13.0 mg, 0.15 mmol) and bubbled ozone for 30 min. Argon was then passed through the mixture and concentrated under deduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to afford methyl ether **123** (16.2 mg, 0.0375 mmol) as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.12 (1H, t, *J* = 3.4 Hz), 3.44 (3H, s), 3.38 (3H, s), 3.18 (3H, s), 3.06 (1H, d, *J* = 4.6 Hz), 2.51 (1H, d, *J* = 4.6 Hz), 2.24 (2H, q, *J* = 5.9 Hz), 2.10-2.01 (4H, m), 1.96 (1H, dd, *J* = 11.7, 7.7 Hz), 1.87 (2H, t, *J* = 15.2 Hz), 1.67 (3H, t, *J* = 11.7 Hz), 1.46 (1H, q, *J* = 9.7 Hz), 1.39-1.27 (8H, m), 0.95 (3H, d, *J* = 6.9 Hz), 0.90 (1H, d, *J* = 4.0 Hz), 0.80 (1H, t, *J* = 8.6 Hz), 0.71 (1H, t, *J* = 7.2 Hz), 0.42 (1H, t, *J* = 5.2 Hz).

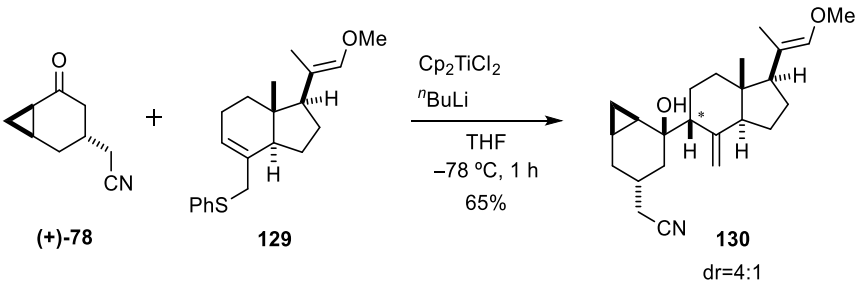
Compound 129



To a cooled (0 °C) solution of sulfide **114** (900 mg, 2.50 mmol) and DIPEA (1.30 ml, 7.50 mmol) in CH_2Cl_2 (12.5 ml) was added TMSOTf (680 µl, 3.75 mmol). The reaction mixture was warmed up to room temperature and stirred for 1.5 h. The reaction mixture was added a saturated aqueous $NaHCO_3$ solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 97:3) to afford methylvinylether **129** as a colorless oil (722 mg, 1.81 mmol, 88%, *E*/*Z* > 10:1).; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33 (2H, t, *J* = 4.6 Hz), 7.26 (2H, t, *J* = 7.7 Hz), 7.17 (1H, t, *J* = 7.4 Hz), 5.82 (1H, s), 5.36 (1H, s), 3.58 (3H, d, *J* = 6.9 Hz), 3.53 (2H, br-s), 3.47 (1H, t, *J* = 10.9 Hz), 2.29 (1H, d, *J* = 9.2 Hz), 2.06 (1H, t, *J* = 5.7 Hz), 2.02 (1H, t, *J* = 9.7 Hz), 1.99-1.92 (1H, m), 1.87-1.70 (3H, m), 1.63 (3H, s), 1.47 (1H, q, *J* =, 6.3 Hz), 1.29 (1H, dd, *J* = 12.5, 8.6 Hz), 0.58 (3H, s).

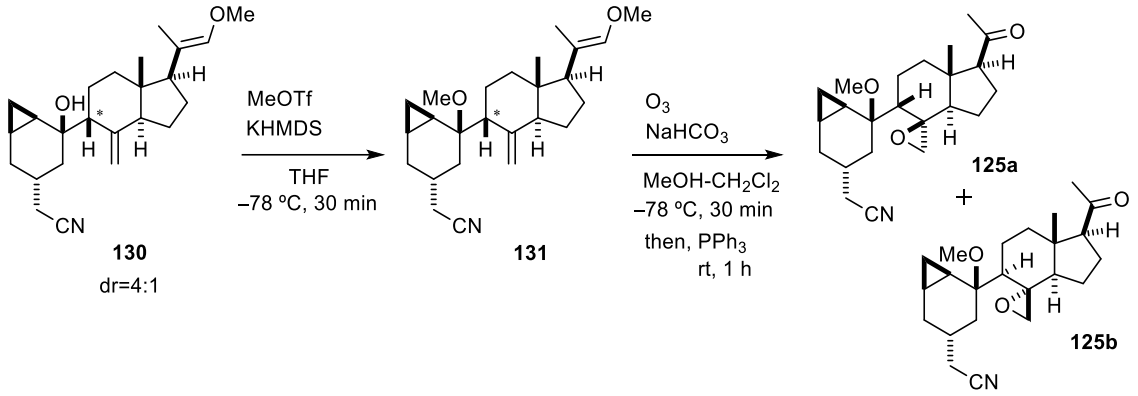
Compound 130



To a cooled (-78 °C) suspension of Cp_2TiCl_2 (1.13 g, 4.53 mmol) in THF (14 ml) was added ^{n}BuLi (2.67 M in hexane, 3.40 ml, 9.06 mmol). After being stirred for 1 h, a THF solution (2 ml) of a **129** (722 mg, 1.81 mmol) was added to the mixture. Stirring was continued for the 10 min same temperature and then at 0 °C for 1 h. After the reaction mixture had been stirred at -78 °C for 10 min, **(+)-78** (320 mg, 2.17 mmol) in THF (2 ml) was added. The reaction mixture was stirred for 1 h and added a 1M aqueous NaOH solution. Insoluble materials were filtered off through celite and wased with EtOAc. The filtrate was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 75:15) to afford homoallyl alcohol **130** (434 mg, 1.18 mmol, 65%, dr = 4:1) as a yellow oil.; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.81 (1H, d, *J* = 10.9 Hz), 4.99 (1H, s), 4.90 (1H, s), 3.56 (3H, d, *J* = 3.4 Hz), 2.46 (1H, d, *J* = 8.0 Hz), 2.27 (2H, d, *J* = 6.3 Hz), 2.18 (1H, dd, *J* = 10.8, 7.2 Hz), 2.07 (2H, dt, *J* = 10.8, 7.0 Hz), 2.00-1.85 (2H, m), 1.77-1.65 (6H, m), 1.61 (3H, s), 1.49-1.43 (1H, m), 1.37 (1H, d, *J* = 12.6 Hz), 1.26 (3H, d, *J* = 2.9

Hz), 1.19 (1H, q, *J* = 8.4 Hz), 0.88 (2H, t, *J* = 6.9 Hz), 0.54 (1H, q, *J* = 5.0 Hz), 0.50 (3H, s). (described major isomer)

Compond 125a and 125b



To a cooled (-78 °C) solution of KHMDS (0.5 M in toluene, 4.7 ml, 2.36 mmol) was added to a solution of alcohol **130** (434 mg, 1.18 mmol) in THF (6 ml). After being stirred for 30 min, the reaction mixture was added MeOTf (195 μl, 1.77 mmol). The reaction mixture was stirred for 1 h and added a saturated aqueous NH_4Cl solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under deduced pressure. The crude compound **131** was used for the next step without purification.

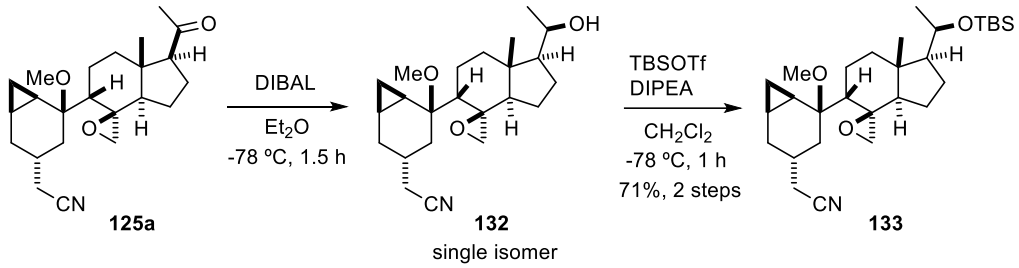
To a solution of **131** (460 mg) in MeOH (3.0 ml) and CH_2Cl_2 (3.0 ml) was added $NaHCO_3$ (300 mg, 3.54 mmol) and bubbled ozone for 30 min at -78 °C. Argon was then passed through the mixture until the disappearance of the blue color. To the reaction mixture was added PPh_3 (mmol) and stirred for 30 min at same temperature. The reaction mixture was warmed up to rt and stirred for 1 h. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:EtOAc = 85:15 to 70:30) to give compound **125a** (263 mg, 0.710 mmol, 60 % for 2 steps) as a yellow oil and **125b** (44.5 mg, 0.142 mmol, 12% for 2 steps)

132; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.19 (3H, s), 3.00 (1H, d, *J* = 4.6 Hz), 2.60 (1H, t, *J* = 9.5 Hz), 2.55 (1H, d, *J* = 4.6 Hz), 2.30 (2H, d, *J* = 5.7 Hz), 2.17-2.10 (5H, m), 2.08-2.00 (2H, m),

1.87-1.85 (2H, m), 1.75-1.70 (2H, s), 1.51-1.39 (5H, m), 0.86 (3H, s), 0.75 (1H, dt, *J* = 10.7, 5.2 Hz), 0.45 (1H, dt, 16.0, 5.2 Hz).

125b; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.31 (3H, s), 2.74 (1H, d, *J* = 4.0 Hz), 2.57 (3H, m), 2.31-2.14 (3H, m), 2.12 (3H, s), 2.06-1.97 (2H, m) 1.86 (2H, dd, *J* = 16.3, 10.6 Hz), 1.36-1.20 (9H, m), 1.13-1.09 (2H, m), 0.82 (3H, s), 0.64 (1H, dd, *J* = 9.2, 5.5 Hz), 0.01 (1H, q, *J* = 5.5 Hz).

Compound 133

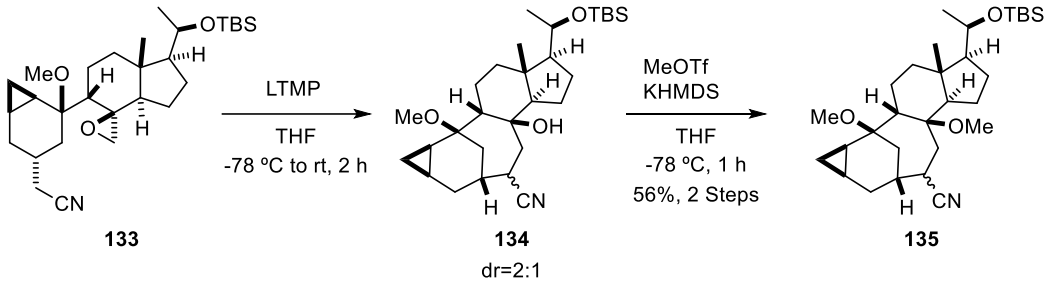


To a cooled (-78 °C) solution of ketone **125a** (263 mg, 0.710 mmol) in Et_2O (3.5 ml) was added DIBAL (1.03 M in hexane, 820 µl, 0.844 mmol). After being stirred for 1.5 h, the reaction mixture was added EtOAc, and sttired for 1 h at 0 °C. The mixture was added a solution of Rochelle salt and sttired for 3 h. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude compound **132** was used for the next step without purification.

To a solution of crude **132** (260 mg) and DIPEA (360 µl, 2.13 mmol) in CH_2Cl_2 (3.5 ml) was added TBSOTf (245 µl, 1.07 mmol) at -78 °C. After being stirred for 1 h, the reaction mixture was added a saturated aqueous $NaHCO_3$ solution. The mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 9:1) to afford silyl ether **133** (245 mg, 0.504 mmol 71% for 2 steps) as a colorless oil.; ^{1}H-NMR (500MHz, $CDCl_3$) δ: 3.73 (1H, dd, *J* = 9.5, 6.0 Hz), 3.19 (3H, d, *J* = 6.9 Hz), 3.05 (1H, d, *J* = 4.6 Hz), 2.49 (1H, d, *J* = 5.2 Hz), 2.29-2.19 (2H, m), 2.05 (4H, br-t, *J* = 7.2 Hz), 1.91 (1H, dd, *J* = 11.5, 8.0 Hz), 1.81 (1H, d, *J* = 13.2 Hz), 1.75-1.68 (1H, m) 1.51-1.40 (2H, m), 1.38-1.22 (4H, m), 1.08 (3H, d, *J* = 6.3 Hz), 0.92 (3H, s),

0.88 (11H, br-S), 0.84-0.79 (2H, m), 0.72-0.69 (2H, m), 0.41 (1H, t, *J* = 5.2 Hz), 0.08 (6H, d, *J* = 1.7 Hz).

Compound 135

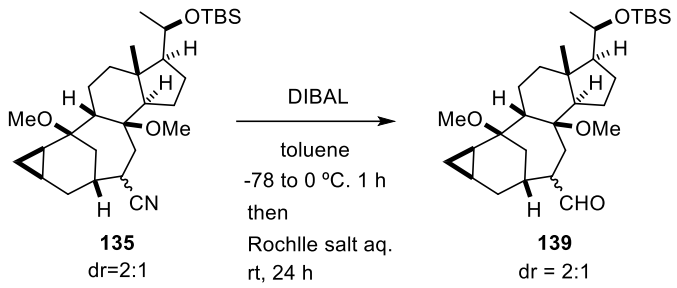


133 **134** dr=2:1 **135**

To a cooled (-78 °C) solution of LTMP which was freshly prepared from tetramethyl piperidine (170 µl, 1.01 mmol) in THF (1.5 ml) and ^{n}BuLi (2.67 M in hexane, 380 µl, 1.01 mmol), was added a solution of epoxide **133** (245 mg, 0.504 mmol) in THF (1.0 ml). After being stirred for 30 min, the reaction mixture was slowly warmed up to room temperature. After being stirred for 2 h, the reaction mixture quenched with a saturated aqueous NH_4Cl solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude compound **135** was used for the next step without purification.

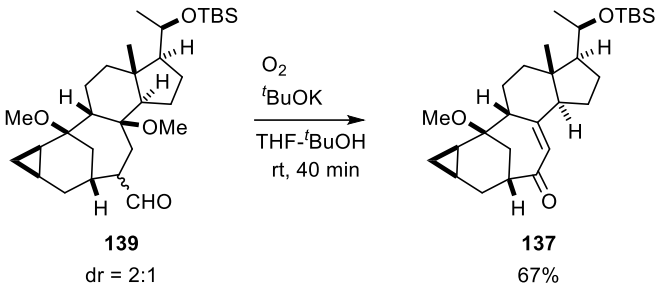
To a cooled (-78 °C) solution of KHMDS (0.5 M in toluene, 2.50 ml 1.26 mmol) was added to a solution of alcohol **134** (253 mg) in THF (2.5 ml). After being stirred for 30 min, the reaction mixture was added MeOTf (110 µl, 1.01 mmol). The reaction mixture was stirred for 1 h and added a saturated aqueous NH_4Cl solution. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 9:1) to afford methyl ether **135** (140 mg, 0.282 mmol, 56% for 2 steps) as a yellow oil.; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.74 (1H, dd, *J* = 9.5, 6.0 Hz), 3.28 (3H, d, *J* = 6.3 Hz), 3.25 (3H, d, *J* = 16.6 Hz), 2.87 (1H, d, *J* = 9.7 Hz), 2.30 (2H, d, *J* = 10.3 Hz), 2.17 (2H, t, *J* = 4.9 Hz), 1.89-1.78 (3H, m), 1.72-1.53 (9H, m), 1.20 (1H, dd, *J* = 12.4, 5.8 Hz), 1.15 (1H, dd, 12.4, 5.6 Hz), 1.12-1.05(5H, m), 1.01 (3H, d, *J* = 5.2 Hz), 0.94-0.87 (9H, m), 0.30 (1H, br-d, *J* = 5.2 Hz), 0.08- 0.05 (6H, br-s). (described major isomer)

Compound 139



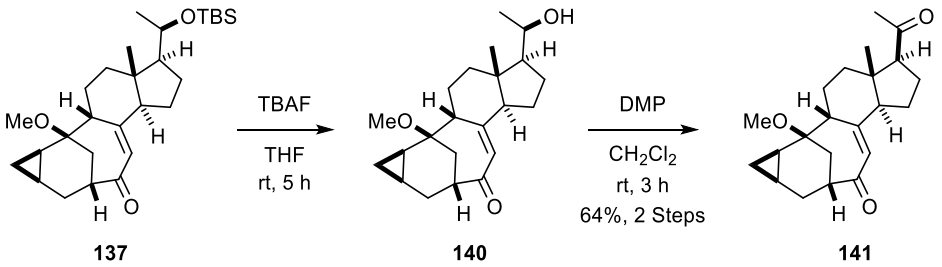
To a cooled (-78 °C) solution of nitrile **135a** (100 mg, 0.200 mmol) in toluene (1.0 ml) was added DIBAL (1.03 M in hexane, 580 µl, 0.600 mmol). After being stirred for 1.5 h, the reaction mixture was added Rochelle salt and sttired for 24 h at room temperature. Then, EtOAc was added and sttired for 1 h. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 9:1) to afford aldehyde **139** (56.5 mg, 0.112 mmol, 56%, dr = 2:1) as a yellow oil.; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.64 (1H, s), 3.74, (1H, dd, *J* = 9.3, 6.0 Hz), 3.28 (3H, s), 3.24 (3H, s), 3.18 (2H, d, *J* = 8.0 Hz), 2.44-2.55 (4H, m), 2.23 (1H, dd, *J* = 6.6, 2.0 Hz), 2.01-1.95 (3H, m), 1.90-1.77 (4H, m), 1.76-1.65 (6H, m), 1.01 (3H, s), 1.07 (3H, d, *J* = 5.2 Hz) 0.94-0.75 (12H, br-s), 0.31 (1H, dd, *J* = 9.1, 5.5 Hz), 0.05 (6H, br-s).

Compound 137



The mixture of crude aldehyde (56.5 mg, 0.112 mmol) and ^{t}BuOK (50 mg, 0.445 mmol) in THF (500 µl) and ^{t}BuOH (500 µl) was bubbled O_2 gas for 15 min at room teperature. After being stirred for 25 min, a saturated aqueous NH_4Cl solution was added to the mixture and separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 9:1) to afford enone **137** (34.4 mg, 0.075 mmol, 67%) as a yellow oil.; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.82 (1H, s), 3.72-3.70, (1H, m), 3.24 (3H, s) ,2.73-2.64 (2H, m), 2.55-2.44 (3H, m), 2.01-1.95 (3H, m), 1.88-1.76 (3H, m) 1.76-1.65 (5H, m), 1.00 (3H, s), 1.10 (3H, d, *J* = 5.2 Hz), 0.97-0.76 (12H, br-s), 0.23 (1H, dd, *J* = 9.1, 5.6 Hz), 0.08 (6H, br-s).

Compound 141

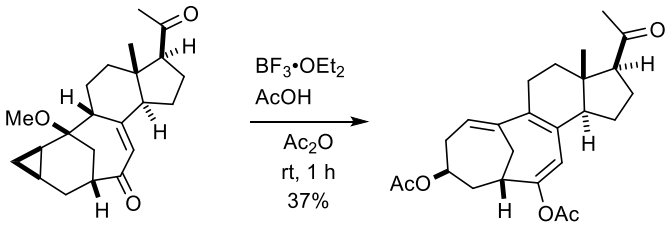


To a cooled (0 °C) solution of silylether **137** (34.4 mg, 0.075 mmol) in THF (350 µl) was added TBAF (1.0 M in THF, 150 µl, 0.15 mmol). After being sttired for 5 h at room temperature,

the reaction mixture was diluted with EtOAc, H_2O and separated. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to afford impure alcohol **140** (28.9 mg, reagent residure was mixed) as a yellow oil.

To a solution of impure **140** in CH_2Cl_2 (350 µl) was added Dess-Martin reagent (50 mg, 0.118 mmol) at 0 °C. After being stirred for 3 h, a saturated aqueous $Na_2S_2O_3$ solution and $NaHCO_3$ solution were added. After being stirred for 30 min, the mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to afford methyl ketone **141** (16.4 mg, 0.048 mmol, 64% for 2 steps) as a yellow oil.; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.78 (1H, s), 3.24 (3H, s) ,2.77-2.68 (2H, m), 2.45-2.29 (4H, m),2.17 (3H, s), 2.01-1.95 (3H, m), 1.90-1.80 (3H, m), 1.77-1.62 (5H, m), 0.88 (2H, t, *J* = 6.5 Hz), 0.78 (3H, s), 0.30 (1H, dd, *J* = 9.0, 5.2 Hz).

Compound 142



141 **142**

To a cooled (0 °C) mixture of methoxide **141** (16.4 mg, 0.048 mmol) and AcOH (30 µl, 0.524 mmol) in Ac_2O (240 µl) was added BF_3•OEt_2 (6.0 µl, 0.048 mmol). After being stirred for 1 h at room temperature, the reaction mixture was diluted with Et_2O and slowly added a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, developed by hexane:EtOAc = 4:1) to afford acetate **142** (7.3 mg, 0.018 mmol, 37%) as a yellow oil.; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.64 (1H, t, *J* = 7.4 Hz), 5.48 (1H,

s), 4.52 (1H, t, *J* = 10.9 Hz), 2.98 (1H, br-s), 2.73 (1H, d, *J* = 13.2 Hz), 2.47-2.26 (4H, m), 2.18 (3H, s), 2.16 (3H, s, *J* = 9.2 Hz), 2.03 (3H, s), 2.01-1.92 (3H, m), 1.84-1.79 (3H, m), 1.77-1.60 (5H, m), 0.69 (3H, s).

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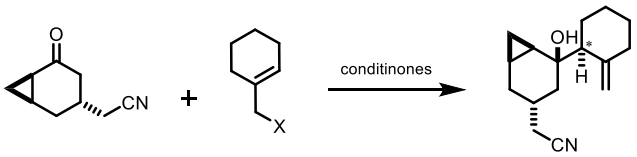
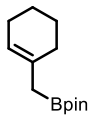
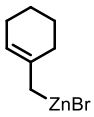
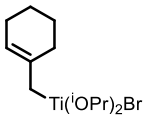
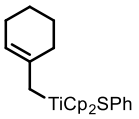
21) Addition of allyl metal nucleophile was examined shown in below.



Entry	nucleophile*	conditions	results
1		$ClCH_2CH_2Cl$ rt to 60 ºC	No reaction
2		THF 0 ºC to rt	No reaction
3		THF –78 to 0 ºC	44% dr = 5:2
4		THF –78 to 0 ºC	75% single diastereomer

* 1.2 eq.

Table Optimization of the 1,2-addition reaction

22) Selikson, S. J.; Watt, D. S. *J. Org. Chem*. **1975**, *40*, 267.

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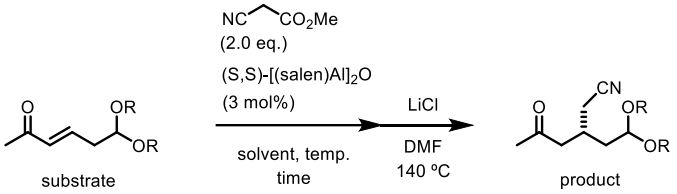
25)



entry	substrate	solvent, temp, time	results*
*	 105	methyl cyclohexane, 0 ºC 24 h	106 75%, er = 90:10
1	105	toluene, 0 ºC	106 74%, er = 88:12
2	105	hexane, 0 ºC, 12 h then, rt, 12 h	No reaction
3	105	methyl cyclohexane, –20 ºC 24 h	106 60%, er = 89:11 (32% SM recover)
4		methyl cyclohexane, 0 ºC 24 h	A 66%, er=85:15

* 2 steps yield

Table ; additional results of asymmetric reaction

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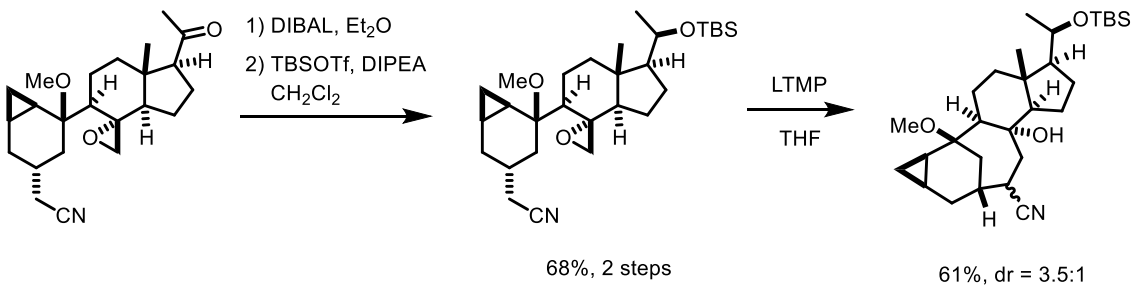
28) The construction of the B ring using the minor isomer was successful, but due to the small amount available, the author could not investigate the subsequent conversion.



Scheme : Cyclization using minor isomer

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Finally, the author would like to thank sincerely his family, Keishi, Toshie, and Taiga for their encouragement, understanding, and support.