DISSERTATION

Synthetic Studies toward Tubiferal A

(ツビフェラール A の合成研究)

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Contents

Introduction

Many natural organic compounds found in nature exhibit a wide range of biological activities and have long been used as pharmaceuticals, agrochemicals, and useful lead compounds for these purposes. A variety of natural chemical scaffolds, such as terpenes, alkaloids, polyethers, peptides are known as biologically active compounds. In terms of terpenes, Taxol, a diterpenoid isolated from the bark of *Taxus brevifolia*, has been used as a new drug for antineoplastic activity.[1)] Solanoeclepin A,[2)] a terpenoid isolated from the hydroponic solution of potato in 1986, is expected to be a natural pesticide because of its remarkable hatching-promoting activity against potato cyst nematodes. On the other hand, alkaloids also exhibit a wide range of biological activities. Strychnine is an indole alkaloid first discovered from *Strychnos ignatia* in 1818. Although it is no longer used in medicine due to its extremely high toxicity, it had been used in medicine as a convulsant inducing drug and ghrelin receptor antagonist.[3)] Morphine is an opium alkaloid found from the Opinium poppy *Papaver Somniferum*, and has strong analgesic and anesthetic properties.[4)] In polyether, halichondrin B, a huge molecule with molecular weight of over 1000 found from a marine sponge, *Halichondria okadai*, possesses a potent anticancer activity.[5)] Vancomycin, a cyclic peptide isolated from *Streptomyces Orientalis*, has a bactericidal effect on Gram-positive bacteria and bacteriostatic effect on enterococci. Vancomycin has such potent bioactivity that it has been called the last resort for infectious disease.[6)]

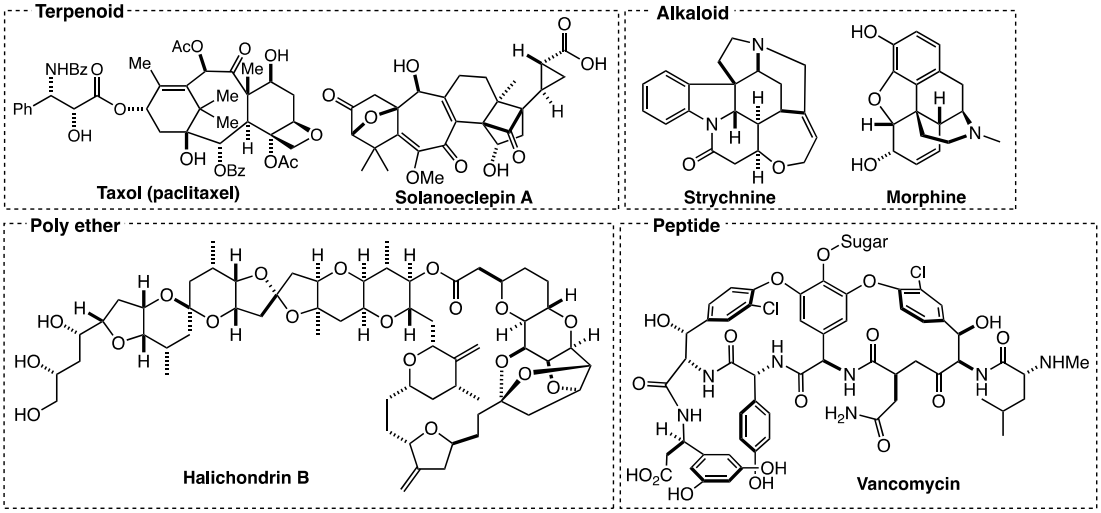
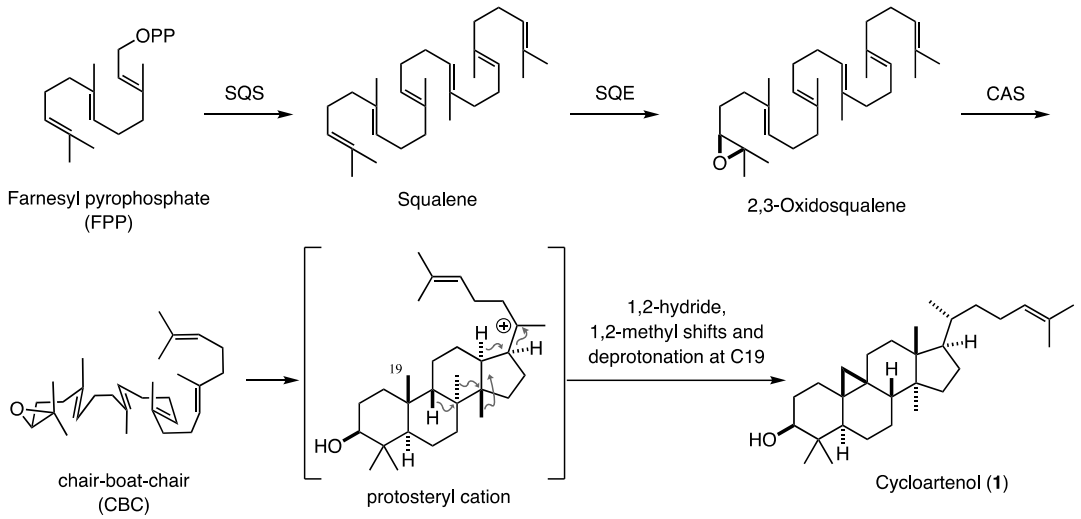


Figure 1 Example of natural products

Terpenes, which are widely found in plants, insects, and fungi, are a group of natural biological compounds consisting of C5 isoprene units. They are classified according to the number of isoprene units as monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), and triterpenes (C30). Triterpenes, which are composed of six isoprene units, include a large number of compounds that play an important role in biological activities, such as steroid hormones and components of cell membranes in plants and animals. Most of them possess tetracyclic or pentacyclic steroid skeletons. The diverse structures of triterpenes are derived from the mode of cyclization and functionalization of the common precursor, squalene (C30). Among the triterpenoids, members of cycloartane family possess a three-membered ring-fused structure on the B-ring of the steroid skeleton. One of the simplest compounds in this family is cycloartenol (**1**), which is an important intermediate in the biosynthesis.

The biosynthetic mechanism has been proposed as shown in Scheme 1.[7] Squalene, a dimer of farnesyl pyrophosphate (FPP) by squalene synthase (SQS), is epoxidized by squalene epoxy synthase (SQE) to form 2,3-oxidosqualene. Cycloartenol synthase (CAS) folds 2,3-oxidosqualene into a chair-boat-chair (CBC) conformation to provide the protosteryl cationic intermediate, which is a precursor of sterol and other steroids. Following a cascade reaction of 1,2-hydride shift and methyl shift, deprotonation at C19 provides a cyclopropane-containing terpene, namely cycloartenol (**1**).



Scheme 1 Biosynthetic pathway to cycloartenol

In recent years, a number of isolations of novel cycloartane analogues and their skeletal rearrangement products have been reported, and most of them exhibit potent biological activities (Figure 2). For example, compound **2,** a glycoside of a shengmanol analogue, was isolated from the plant of *Actaea helacleifolia* and was found to have antitumor activity against HL-60, A549, and MCF-7 cell lines.[8)] In addition, 3,4-*seco*-cycloartane compound **3**, isolated from the flower of *Gardenia jasminoides* in Zhejiang province of China, shows cytotoxic activity against HepG2 hepatocellular carcinoma cell lines (IC_{50} value: 9.3 μM).[9]

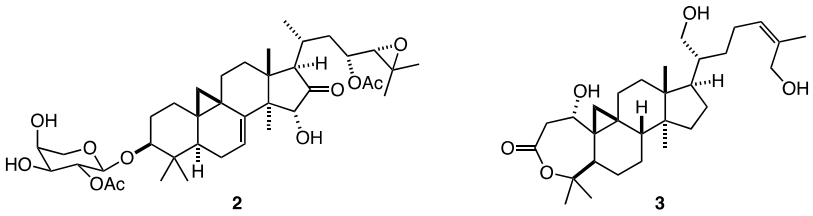


Figure 2 Examples of cycloartane analogue

Tubiferal A (**4**), one of the *seco*-cycloartane terpenoids cleaved at the C9-10 bond, is a novel terpenoid isolated from the fruiting body of the myxomycete, *Tubifera dimorphotheca*, in 2004 by Ishibashi and co-workers (Figure 3).[10] The skeleton of **4** is classified as 9,10-*seco*-cycloartane-16,21-olide. The complex 6-7-6-5 polycyclic hydrocarbon skeleton of **4** contains a 1,2-diol, a conjugated diene, an aldehyde, and a γ-lactone, and possesses nine stereocenters, including two quaternary carbons on the angular positions of the *trans*-hydrindane. The bioactivity is to overcome drug resistance in vincristine (VCR) resistant KB cell lines (IC_{50} value: 2.7μM in the presence of 100 ng/mL of VCR). Tubiferal B (**5**), a *seco*-acid of tubiferal A, was also isolated at the same time, but did not show any biological activity.

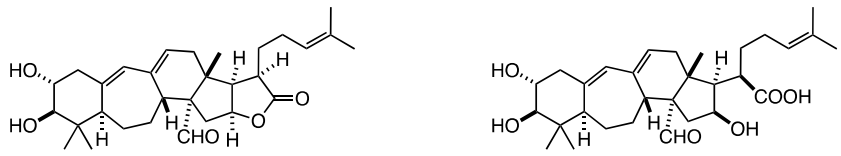


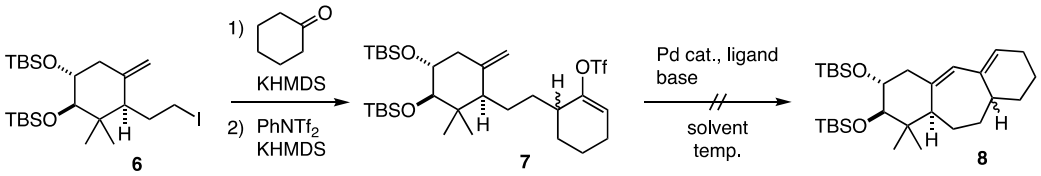
Figure 3 Structure of tubiferal A (**4**) and tubiferal B (**5**)

Although the total synthesis of **4** has not been achieved, there was only one synthetic study reported by Paquette and co-worker in their doctoral dissertation in 2014,[11] except the synthetic study of the model ABC-ring compound reported by the author's laboratory.[12] The following is a summary of the synthetic efforts of the ABC-ring model compound and the CDE-ring segment by Paquette's group.

Synthetic studies by Paquette' group

·ABC-ring system synthesis

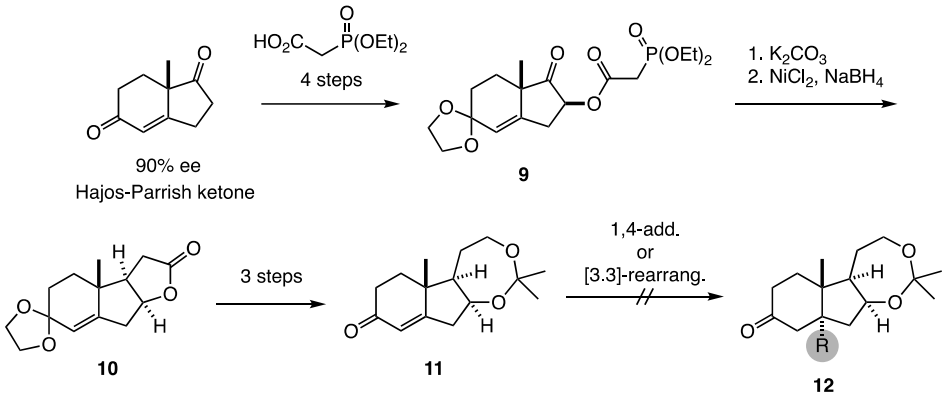
Scheme 2 shows attempts at an intramolecular Heck reaction to construct seven-membered B-ring part toward ABC-ring system. The precursor of cyclization **7** was prepared by the alkylation of A-ring segment **6** with cyclohexanone, the C-ring segment, followed by triflation with McMurry's reagent and KHMDS. However, the key intramolecular Heck reaction failed to afford cyclization product **8** under various conditions such as catalyst, ligand, base, solvent, additive, and temperature.



Scheme 2 Synthetic approach to model ABC-ring segment by Paquette's group

·CDE-ring segment synthesis

They also investigated the synthetic approach to *trans*-hydrindane framework for the construction of CDE-ring segment (Scheme 3). The intramolecular Horner-Wadsworth-Emmons reaction of phosphonate **9** prepared from Hajos-Parish ketone and phosphonocarboxylic acid gave an unsaturated lactone, which on treatment with $NiCl_2$ and $NaBH_4$ afforded lactone **10**. Lactone **10** was converted to acetonide **11** by reduction of the lactone and protection of resulting diol. Although the acetonide **11** was subjected to various reactions, including 1,4-addition and [3.3]-rearrangement, no *trans*-fused hydrindane **12** was detected.



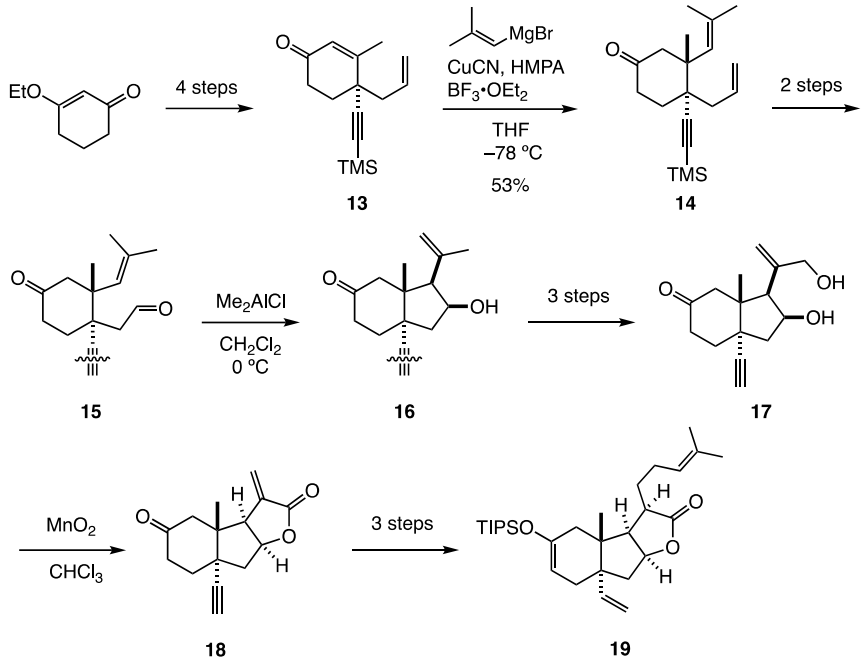
Scheme 3 Synthetic approach to CDE-ring segment by Paquette's group

Synthetic studies by Dr. Hiramatsu

These results suggest the difficulties in the construction of the seven-membered B-ring moiety and the bicyclic *trans*-fused hydrindane skeleton. On the other hand, Dr. Hiramatsu, who was a former member of the author's laboratory, developed synthetic methods for the CDE-ring segment and a model compound of the ABC-ring system[12] as shown below.

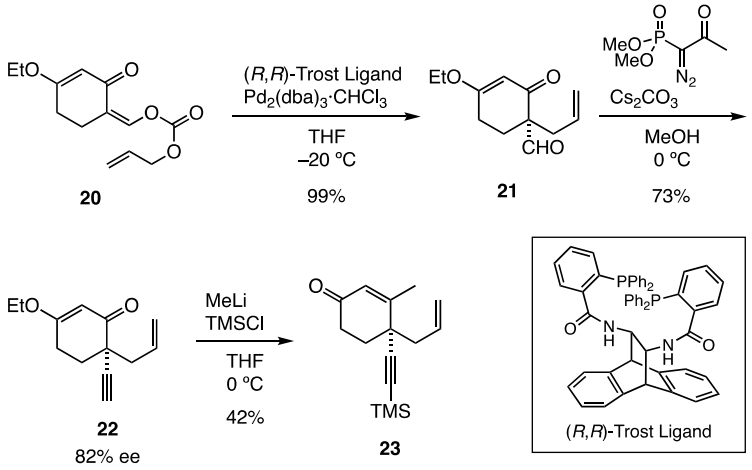
·Synthesis of CDE-ring segment

To cyclohexenone **13** with a quaternary carbon at γ-position, prepared in four steps from commercially available 3-ethoxy-2-cyclohexen-1-one, a diastereoselective 1,4-addition of 2-methyl-1-propenyl cupper reagent gave ketone **14** with continuous quaternary carbons. Treatment of aldehyde **15**, which was converted from the terminal alkene of **14**, with Me_2AlCl resulted in an intramolecular ene reaction affording *trans*-fused hydrindane **16** as a single isomer. The construction of the lactone moiety was achieved by oxidation of diol **17**, prepared by allylic oxidation of **16**, to afford lactone **18** with *exo*-methylene. After several steps, the synthesis of CDE-ring segment **19** was achieved in 15 steps.



Scheme 4 Synthetic route to CDE-ring segment established by Dr. Hiramatsu

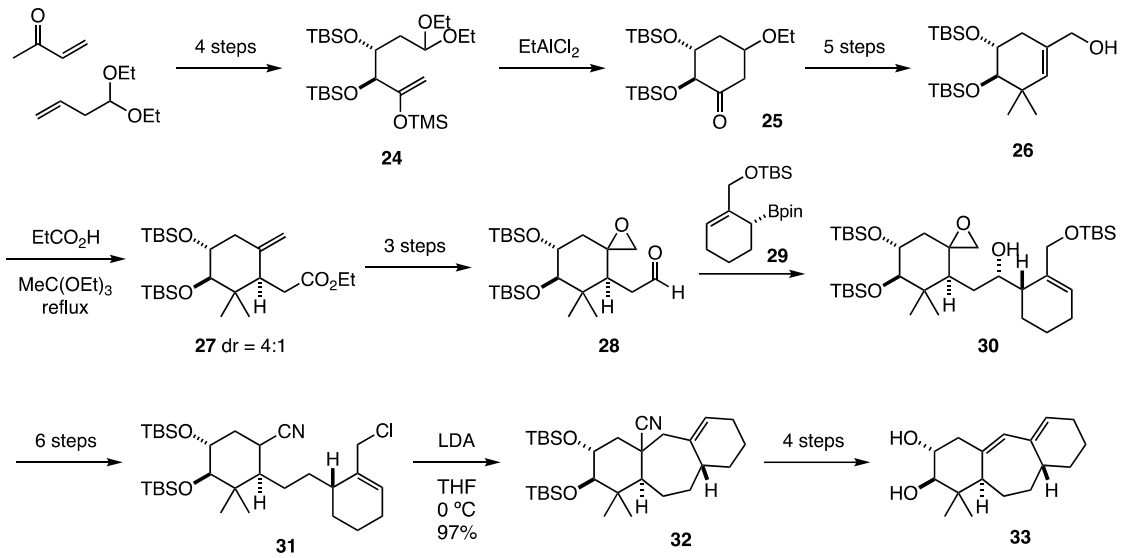
He also made efforts for the asymmetric synthesis of the CDE-ring segment as shown in Scheme 5. An enantioselective palladium-catalyzed decarboxylative allylation of allyl enol carbonate **20** with a chiral Trost ligand was employed to construct the chiral quaternary carbon. HPLC analysis of terminal alkyne **22** prepared by alkynylation of aldehyde **21** with Ohira-Bestmann reagent determined the enantiomeric purity of aldehyde **21** was 82% ee. Treatment of **22** with MeLi and TMSCl afforded optically active cyclohexenone **23**, which was corresponding to the key intermediate **13**.



Scheme 5 Synthesis of optically active enone **23**

·Synthesis of ABC-ring segment

The synthetic study of a model compound of the ABC-ring system is shown in Scheme 6. Starting from commercially available methyl vinyl ketone and 3-butenal diethyl acetal, silyl enol ether **24** was prepared via Sharpless asymmetric dihydroxylation. Exposure of **24** to $EtAlCl_2$ led to an intramolecular Mukaiyama aldol reaction to form cyclohexanone **25**. The Johnson-Claisen rearrangement of allylic alcohol **26** gave ester **27** as an inseparable mixture of two diastereomers (dr 4:1). After conversion to epoxyaldehyde **28**, the intermolecular addition reaction with allylboronate **29** afforded alcohol **30**. A six-step transformation including removal of the resulting hydroxyl group provided cyclization precursor **31**. Treatment of cyclization precursor **31** with LDA resulted in an intramolecular alkylation reaction to form tricyclic compound **32** in high yield. After several steps, the synthesis of ABC-ring model compound **33** was achieved.



Scheme 6 Synthetic route of model ABC-ring compound

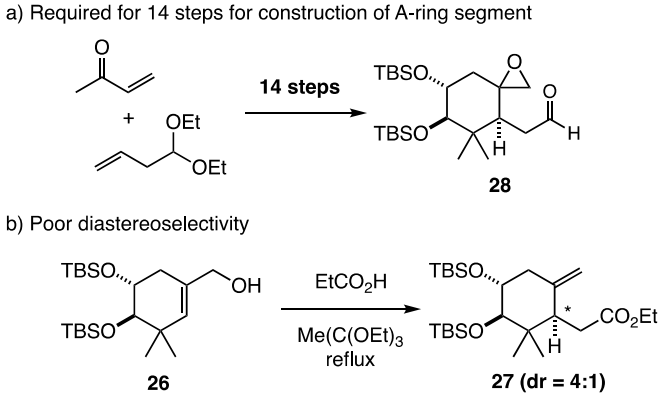
Previous synthetic studies on tubiferal A have successfully synthesized tricyclic model compounds, however, they required more than 26 steps from commercially available reagents. Therefore, the author decided to develop an alternative synthetic route toward an efficient total synthesis of **4**. In this dissertation, synthetic studies towards tubiferal A based on a convergent synthetic strategy are described. In Chapter 1, the stereoselective synthesis of a tricyclic model compound corresponding to the ABC-ring system of tubiferal A is described. In Chapter 2, the synthetic studies towards the total synthesis of tubiferal A based on the results obtained in Chapter 1 is described.

Chapter 1

Asymmetric Synthesis of a Model ABC-ring Compound

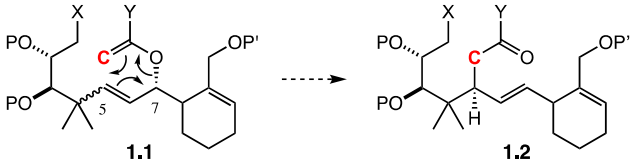
1-1. Introduction

In the previous section, the author described the synthetic method for model compound of the ABC-ring system of tubiferal A reported by Dr. Hiramatsu. Although the asymmetric synthesis of the model compounds was successfully achieved, there were still two serious problems to be resolved. First, a long synthetic route (14 steps) was required to establish the A-ring system (Scheme 1.1, a). Second, the stereoselectivity of the Johnson-Claisen rearrangement in the construction of A-ring was poor (4:1) (Scheme 1.1, b). In order to resolve these problems, new synthetic methodologies should be developed.



Scheme 1.1 The problems of the model compound synthesis developed by Dr. Hiramatsu

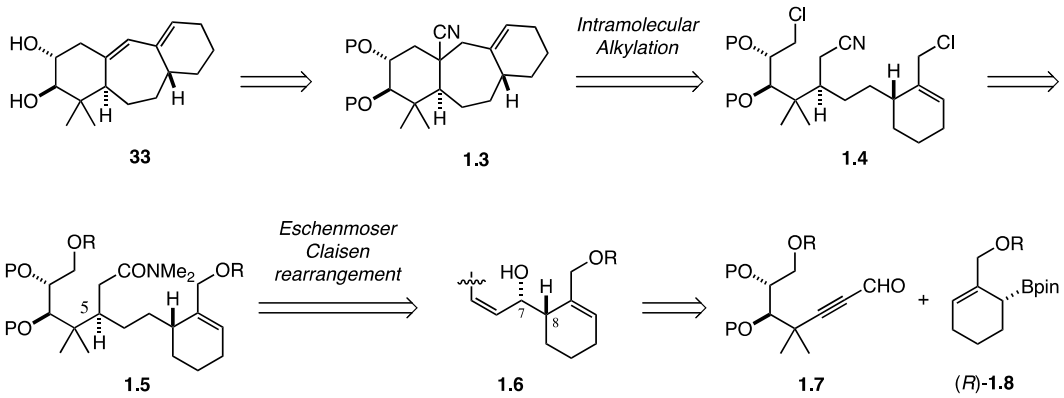
In order to solve the aforementioned problems, the author proposed a solution as shown in Scheme 1.2. Focusing on the high selectivity of the stereochemistry generated by the addition reaction of an allylboronate with an aldehyde, the author planned a synthetic strategy based on chirality transfer by Claisen rearrangement of **1.1**. Since the Claisen rearrangement is a highly robust reaction for which various methods have been reported[13], the asymmetric induction from the C7 position to the C5 position is highly reliable. In addition, the synthetic route should be shortened because the acyclic A-ring unit must be prepared. Furthermore, it was expected that the construction of the A-ring could be carried out by intramolecular alkylation in the same step as the B-ring construction.



Scheme 1.2 Construction of the stereogenic center at the C5 position

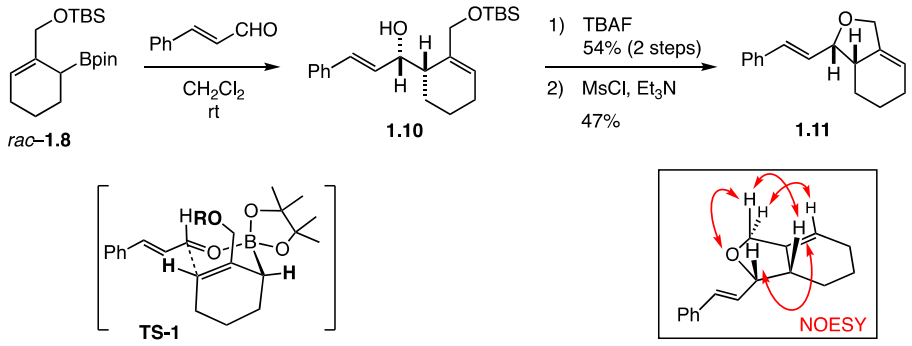
1-2. Retrosynthetic analysis of the tricyclic model compound

For the efficient synthesis of tricyclic model compound **33**, the author designed a new synthetic route as shown in Scheme 1.3. Namely, a stereoselective addition reaction between an aldehyde and an allylboronate was adopted to construct the desired stereochemistry at the two angular positions (C5 and C8) of the tricyclic skeleton. Tricyclic nitrile **1.3**, designed as a precursor to model compound **33** was expected to be obtained by intramolecular alkylation reactions of nitrile **1.4** bearing two terminal chloride moieties. The stereogenic center of C5, which corresponds to the angular position of the AB-ring system, was expected to be formed by a Claisen rearrangement of allyl alcohol **1.6** with chirality transfer. The stereogenic centers at the C7 and C8 positions would be controlled by the addition reaction of the optically active allylboronate (*R*)-**1.8** to aldehyde **1.7** in a stereoselective manner. Since the following preliminary experiments shows that the product of the addition reaction of an allylboronate with an aldehyde gives *syn*-isomer, the resulting alkyne could be converted to *cis*-alkene **1.6** by Lindlar reduction.



Scheme 1.3 Synthetic strategy for model ABC-ring system compound **33**

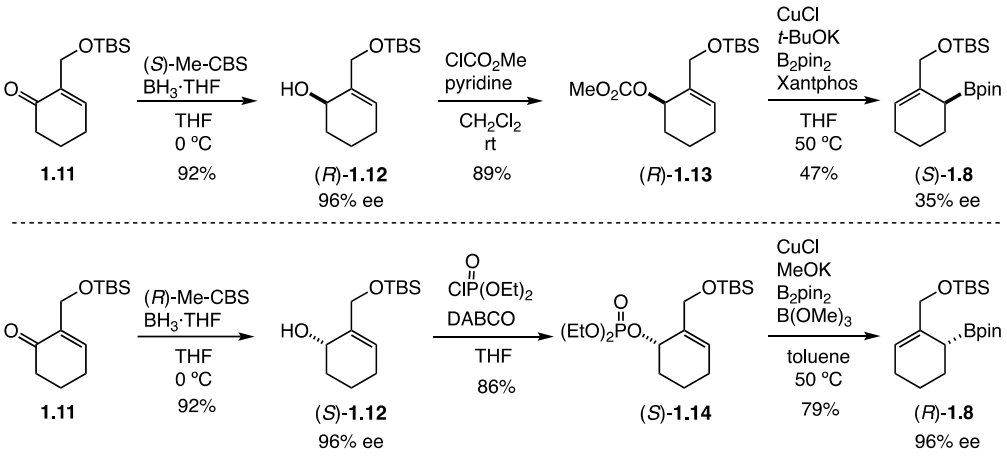
Preliminary experiments on the stereochemistry in the addition reaction of allylboronate **1.8** with aldehydes were carried out (Scheme 1.4). The reaction of *rac*-**1.8** and cinnamaldehyde in CH_2Cl_2 proceeded at room temperature to afford alcohol **1.9** as a single diastereomer. Removal of the TBS group followed by mesylation of the less hindered primary alcohol moiety gave cyclic ether **1.10**, the configuration of which was confirmed by NOE experiments. This result suggested that the *syn*-adduct was formed through a *chair*-like six-membered transition state **TS-1**.



Scheme 1.4 Determination of stereochemistry in the addition reaction of allylboronate **1.8**

1-3. Enantioselective synthesis of allylboronate

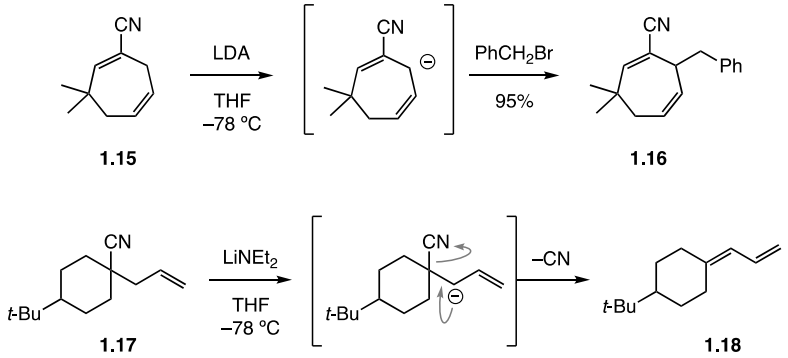
The enantioselective synthesis of the allylboronate corresponding to the C-ring moiety is shown in Scheme 1.5. Preparation of the known compound **1.11**,[14] cyclohexenone bearing a silyloxymethyl group, and the (*S*)-CBS reduction of **1.11** afforded the optically active alcohol (*R*)-**1.12**. The absolute configuration and enantiomeric excess of the resulting alcohol **1.12** were determined to be *R*-isomer and 96% ee by ^{1}H-NMR analysis of its Mosher ester.[15] Esterification of (*R*)-**1.12** with methyl chloroformate afforded carbonate (*R*)-**1.13**, which was subjected to the allylic borylation reaction proceeding at *anti*-S_N2' reaction according to the protocol reported by Ito, Sawamura and co-workers.[16] The resulting allylboronate was oxidized with alkaline hydrogen peroxide to give the corresponding alcohol, and the enantiomeric excess was determined. Unexpectedly, the absolute configuration was found to be the *S* form, with 35% ee.[15] This result indicated that carbonate (*R*)-**1.13** preferred the *syn*-S_N2' reaction rather than the expected *anti*-S_N2' reaction, albeit in low selectivity. The reason for this preference for *syn*-selectivity is that the silyloxymethyl group would cover the surface opposite to the leaving group, making it difficult for the reactant to approach from the *anti*-surface. After numerous attempts, the author found the optimized combination of the substrate, solvent, catalyst, and additives to give the desired allylboronate (*R*)-**1.8** (Scheme 1.5). Namely, a toluene solution of phosphonate (*S*)-**1.14**, which was prepared from CBS reductant (*S*)-**1.12** and chlorophosphate, B_2pin_2 and $B(OMe)_3$ was heated at 50 ºC in the presence of the catalytic amount of copper(I) chloride and KOMe, giving rise to allylboronate (*R*)-**1.8** (79% yield, 96% ee). This reaction condition was inspired by the copper-catalyzed *syn*-S_N2'reaction of allyl phosphonates with organoboranes reported by Sawamura, Ohmiya and co-workers.[17]



Scheme 1.5 Attempts on enantioselective synthesis of allylboronate **1.8**

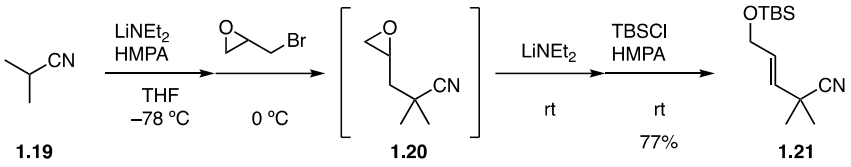
1-4. Construction of A-ring segment

Next, the author aimed at the preparation of the optically active acyclic A-ring aldehyde. Dr. Yamada and Mr. Nishida, former members of the author's laboratory, have reported that treatment of nitriles possessing no hydrogen at the α-position with a strong base results in the formation of β-cyanocarbanion.[18] For example, treatment of cycloheptadiene **1.15** with LDA resulted in the formation of a carbanion at β-position of the cyano group, followed by the reaction with alkyl halides as a electrophile, to afford alkylated nitrile **1.16** (Scheme 1.6, top).[18] Furthermore, treatment of nitrile **1.17** with a quaternary carbon at the α-position of the cyano group with $LiNEt_2$ in THF at 0 ºC, proceeded with the β-elimination of the resulting cyano-carbanion to undergo a decyanation reaction to afford conjugate diene **1.18** (Scheme 1.6, bottom).[18]



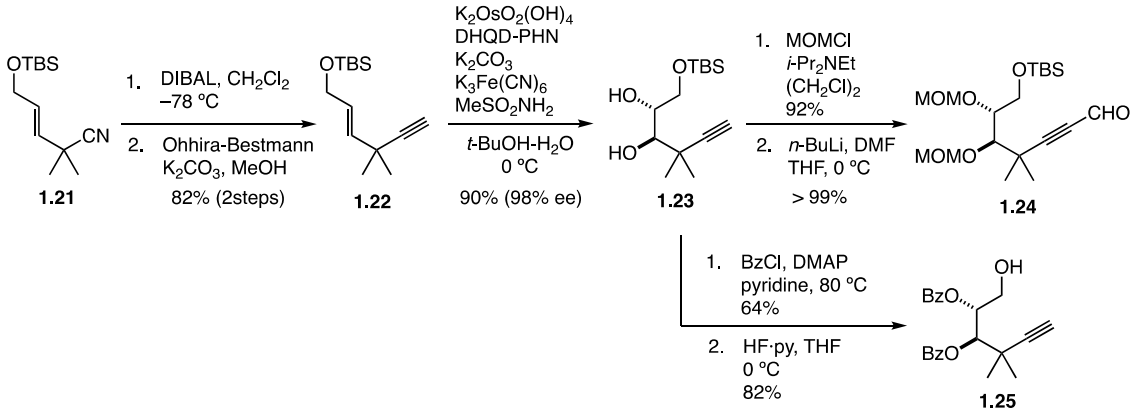
Scheme 1.6 Formation of a carbanion at β-position of cyano group

Based on these reports, the author developed an efficient synthesis of nitrile **1.21** in one-pot operation (Scheme 1.7). Successive treatment of isobutyronitrile (**1.19**) in THF with $LiNEt_2$ and epibromohydrin gave a solution of epoxy nitrile **1.20**, to which another equivalent of $LiNEt_2$ was added at 0 ºC. The epoxide underwent a ring-opening reaction induced by abstraction of the β-hydrogen atom of the nitrile and the resulting alkoxide was silylated by treatment with TBSCl and HMPA to give the desired nitrile **1.21** in 77% yield.



Scheme 1.7 One-pot synthesis of β,γ-unsaturated nitrile

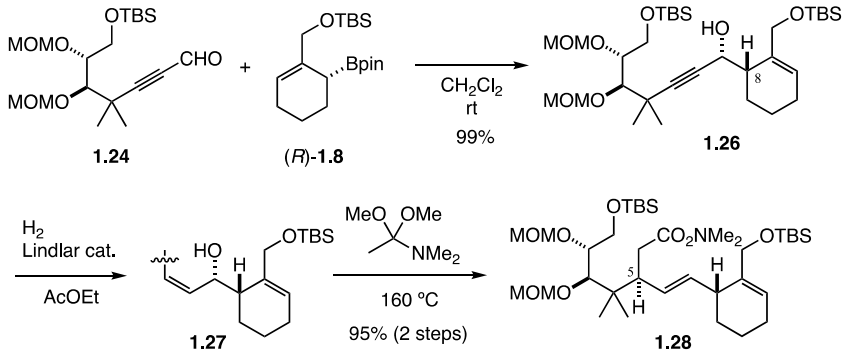
Reduction of nitrile **1.21** with DIBAL followed by Ohira-Bestmanm alkynylation[19] gave enyne **1.22**. Enyne **1.22** was subjected to Sharpless asymmetric dihydroxylation reaction using DHQD-PHN ligand[20] to give diol **1.23**. The enantiomeric excess of the resulting alcohol **1.23** was determined by a HPLC analysis of its bisbenzoate derivative **1.25** (98% ee). Protection of the optical active diol **1.23** with two MOM groups and treatment of the terminal alkyne with *n*-BuLi and DMF afforded aldehyde **1.24**.



Scheme 1.8 Preparation of optically active aldehyde **1.24**

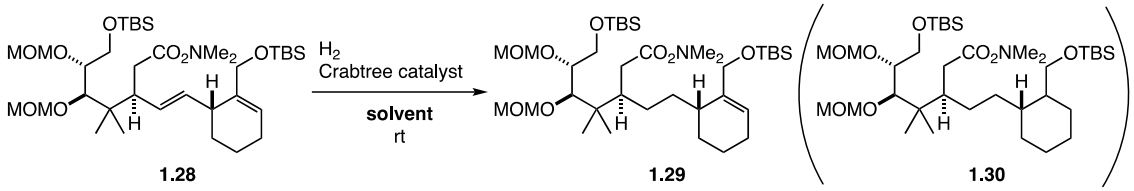
1-5. Construction of tricyclic skeleton

With the both optically active segments **1.24** and (*R*)-**1.8** in hand, the stage was set for the construction of the stereogenic centers at the C5 and the C8 positions (Scheme 1.9). The intermolecular addition reaction of allylboronate (*R*)-**1.8** with aldehyde **1.24** in CH_2Cl_2 proceeded quantitively at room temperature to afford alcohol **1.26** as a single diastereomer. After Lindlar reduction of the alkyne moiety, the resulting *cis*-alkene **1.27** was subjected to Eschenmoser-Claisen rearrangement. Heating *cis*-alkene **1.27** with *N*,*N*-dimethylacetamide dimethyl acetal at 160 ºC afforded amide **1.28** in 86% yield as a single diastereomer.



Scheme 1.9 Construction of two stereogenic centers at the C5 and the C8 positions

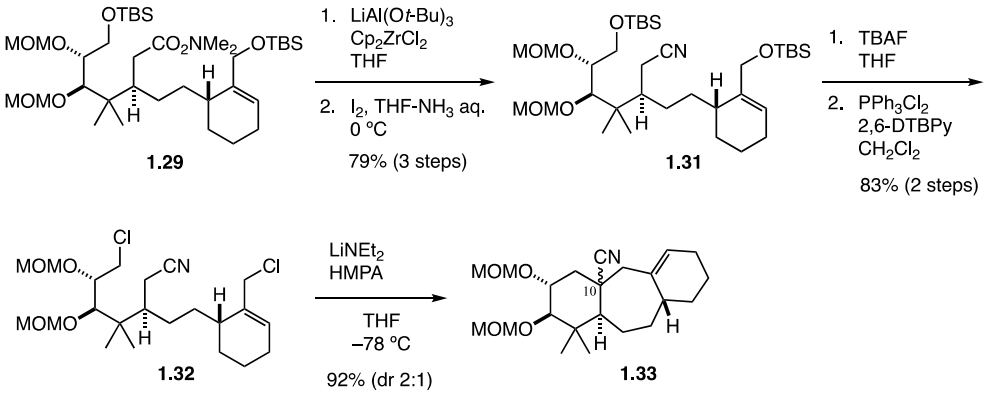
The next task was the selective reduction of the *trans*-alkene moiety of diene **1.28** while leaving the double bond on the cyclohexene ring intact. A survey of the literature on hydrogenation suggested that an amide group induces the Crabtree catalyst to hydrogenate the neighboring alkene.[21)] The author investigated the selective reduction of alkenes based on the directing effect of amide group of the Crabtree catalyst (Table 1). While the reaction in CH_2Cl_2 gave **1.30**, in which the cyclohexene moiety was also reduced (entry 1), the reaction in Et_2O was very sluggish to afford a trace amount of **1.29** (entry 2). Finally, the use of *t*-BuOMe as a solvent promoted the reduction at the neighboring site (entry 3). It is assumed that the reactivity and selectivity of the Ir catalyst became moderate by use of *t*-BuOMe, which is more coordinating than CH_2Cl_2.



entry	solvent	result
1	CH_2Cl_2	**1.30**: 83%
2	Et_2O	**1.29**: trace
3	*t*-BuOMe	**1.29**: 99%

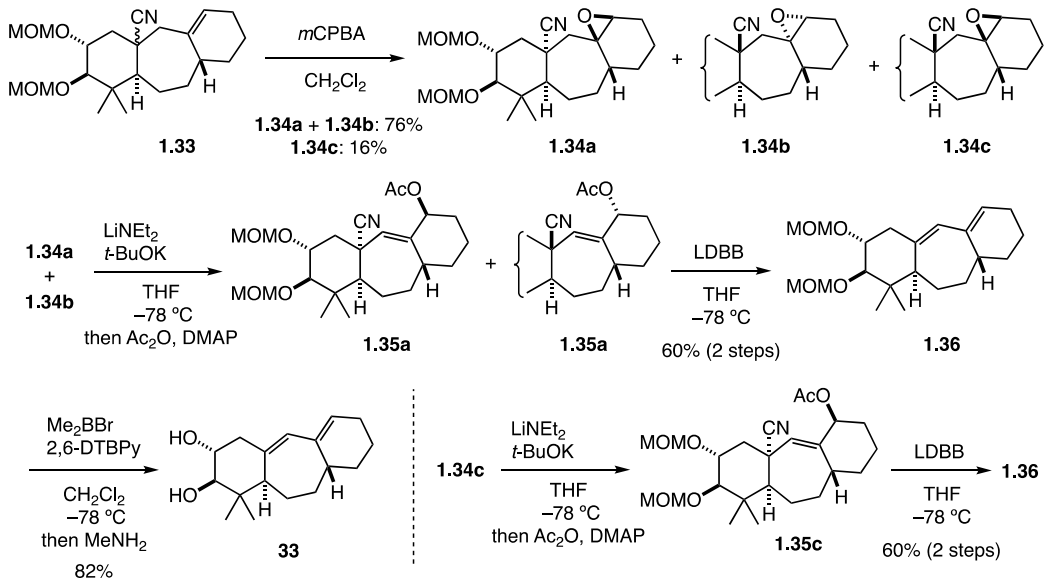
Table 1.1. Investigation of solvent for hydrogenation with Crabtree catalyst

Having succeeded in the selective reduction of diene **1.28**, the author subsequently set out to construct the AB-ring system. As shown in Scheme 1.10, the transformation of amide **1.29** to the cyclization precursor **1.32** was achieved by a routine four-step reaction sequence: (i) reduction with Schwartz reagent (Cp_2ZrClH),[22] (ii) oxidation to nitrile by treatment with iodine in an aqueous ammonia solution,[23] (iii) removal of the two TBS groups, and (iv) chlorination of the resulting diol with Ph_3PCl_2.[24] The key intramolecular double alkylation reaction of nitrile **1.32** was carried out by treatment with 2.5 equivalents of $LiNEt_2$ in the presence of HMPA to form the A- and B-ring at once, giving the tricyclic compound **1.33** in 92% yield. The product of **1.33** was an inseparable mixture of epimers (2:1) at C10 position.



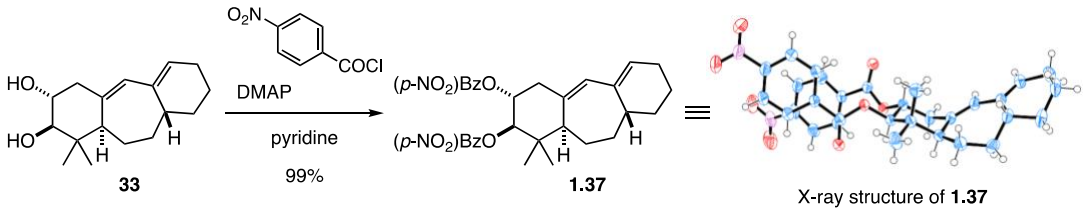
Scheme 1.10 Construction of AB-ring part via intramolecular alkylation reaction

Treatment of **1.33** with *m*CPBA gave a mixture of three diastereomers, which was separated to **1.34c** and a mixture of **1.34a** and **1.34b**.[25] The author noted that the γ,δ-epoxynitrile substructure of these compounds was similar to that of compound **1.20** in Scheme 1.7. Indeed, a mixture of epoxide **1.34a** and **1.34b** underwent a similar ring-opening reaction under the influence of $LiNEt_2$ assisted with potassium *t*-butoxide.[26] One-pot acetylation of the resulting alkoxides afforded a mixture of δ-acetoxynitriles **1.35a** and **1.35b**. A mixture of the products **1.35a** and **1.35b** was treated with LDBB in order to remove the cyano and acetoxy groups, resulting in moderate yield of the conjugated diene **1.36** as the common intermediate at this point. The same transformation also led epoxide **1.34c** to the common intermediate **1.36**. Removal of the two MOM groups by treatment with Me_2BBr followed by $MeNH_2$ at −78 °C afforded the formation of diol **33**, the ABC-ring model compound of tubiferal A.



Scheme 1.11 Synthesis of ABC-ring model compound

The entire structure of the final compound **33** was confirmed by the X-ray crystallographic analysis after conversion to the corresponding bis(*p*-nitrobenznoate) **1.37**.



Scheme 1.12 Formation of bis(*p*-nitrobenzoate) and its crystal structure

1-6. Conclusion

In summary, the author has developed a new method for the construction of the ABC-ring system of tubiferal A. The two stereogenic centers (C5 and C8) at the angular positions of the tricyclic skeleton were constructed by the stereoselective intermolecular addition reaction of optically-active cyclic allylboronate followed by the Eschenmoser-Claisen rearrangement. The construction of the AB-ring system was achieved by the double intramolecular alkylation reaction of a dichloro nitrile intermediate. The author could achieve the synthesis of model compound **33** in 19 steps, which was more efficient than that by Dr. Hiramatsu (26 steps).

1-7. Experimental Section

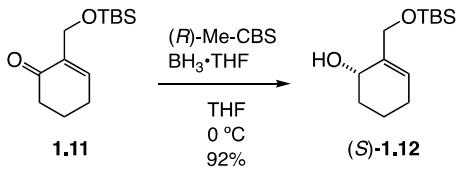
General Information

All reactions were conducted in oven- or flame-dried glassware under a positive pressure of argon. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous acetone, acetonitrile (MeCN), *tert*-butyl methy ether (*t*-BuOMe), 1,2-dichloroethane ($(CH_2Cl)_2$), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol (EtOH), methanol (MeOH), 2-propanol (*i*-PrOH), pyridine, and toluene were purchased from Kanto Chemical Co., Inc. Diethylamine (Et_2NH), diisopropylethylamine (*i*-Pr_2NEt) and triethylamine (Et_3N) was distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). Hexamethylphosphoric triamide (HMPA) and chlorotrimethylsilane (TMSCl) were distilled from CaH_2 under argon and stored in the presence of MS 4Å. 1,4-Diazabicyclo[2.2.2]octane (DABCO) was azeotropically dried with benzene. Copper(I) chloride (CuCl) was prepared as follows: (1) CuCl being dissolved in 12 M HCl (2) adding copper powder until colorless solution (3) supernatant solution being to water (white precipitate was deposited) (4) the precipitation being filtered through a glass filter and washed H_2O, EtOH and acetone in a sequence under argon atmosphere. Ph_3PCl_2 was prepared according to the literature.[24] All other reagents and solvents were used as received from commercial sources without further purification.

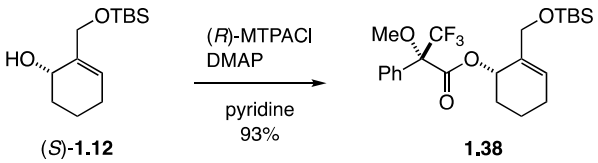
^{1}H-NMR spectra were recorded on a JEOL-JNM-ECA-500 (500 MHz) in $CDCl_3$ (δ_H 7.26), C_6D_6 (δ_H 7.16). Chemical shifts are reported in parts per million (ppm) from internal tetramethyl silane, and signals are expresses as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Coupling constants are reported in Hz. ^{13}C-NMR spectra were recorded on a JEOL-JNM- ECA-500 (125 MHz) in $CDCl_3$ (δ_C 77.0). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-T100GCV (GC-TOFMS) at GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University. Infrared (IR) spectra were recorded on a JASCO FT-IR 4100 spectrophotometer with an attenuated total reflection (ATR) unit. Optical rotations were determined using JASCO P-2200 digital polarimeter at the sodium D line (589 nm) in the solvent

and concentration indicated. Melting points (M.p.) are measured using ATM-024 melting point meter and are uncorrected. X-ray crystallographic data were recorded with a Rigaku XtaLAB Synergy Diffractometer at the Faculty of Science, Hokkaido University. High performance liquid chromatography (HPLC) was recorded on a Jasco PU-2089 *Plus* instrument with UV detection at 254 nm. 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 6% ethanolic *p*-anisaldehyde (includes 6% conc. sulfuric acid and 1% acetic acid), 8% ethanolic phosphomolybdic acid. Flash column chromatography were performed with Silica Gel 60N (neutral, particle size 40–50 μm) purchased form Kanto Chem. Co., Inc.

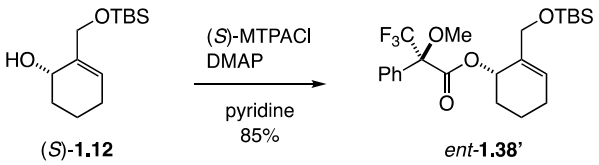
Experimental Section



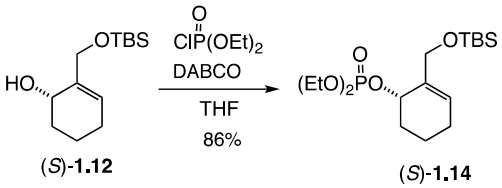
Optically active alcohol (*S*)-1.12: To a solution of (*R*)-Me-CBS catalyst (780 mg, 2.81 mmol) in THF (70 mL) was added BH_3·THF (0.91 M in THF, 14.4 mL, 13.1 mmol) at 0 ºC. After stirring for 5 min, to the mixture was added a solution of cyclohexenone **1.11**[14] (4.51 g, 18.8 mmol) in THF (20 mL). After 10 min, the reaction was carefully quenched with water at the same temperature. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded alcohol (*S*)-**1.12** (4.44 g, 18.3 mmol, 98%) as a colorless oil. The enantiomeric excess was determined to be 96% ee by ^{1}H-NMR analysis of the derivative (*R*)-MTPA ester **1.38**. The characterization data of (*S*)-**1.12** are identical to those of (*R*)-**1.12** reported in the literature[14] except for optical rotation: $[\alpha]_D^{26}$ −71.9 (*c* 1.02 $CHCl_3$).



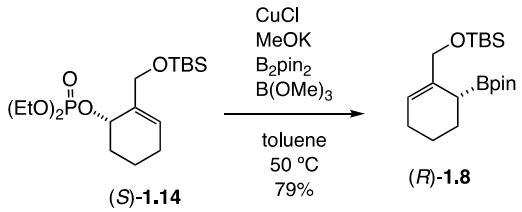
MTPA ester 1.38: To a solution of alcohol (*S*)-**1.12** (4.1 mg, 17 μmol) and DMAP (1 chip) in pyridine (100 μL) was added (*R*)-(−)-a-methoxy-a-(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPA-Cl) (3.8 μL, 20 μmol) at room temperature. After stirring for 1.5 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded (*S*)-MTPA ester **1.38** (7.2 mg, 16 μmol, 93%) as a colorless oil. The characterization data of **1.38** are identical to those of *ent*-**1.38** reported in the literature[14] except for optical rotation: $[\alpha]_D^{26}$ −59.1 (*c* 0.36 $CHCl_3$).



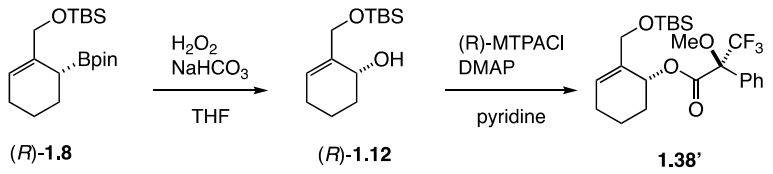
MTPA ester *ent*-1.38': Using the same procedure as above, (*R*)-MTPA ester *ent*-**1.38'** (7.9 mg, 17 μmol, 85%) was obtained from (*S*)-**1.12** (4.9 mg, 20 μmol) and (*S*)-MTPA-Cl (4.5 μL, 24 μmol). The characterization data of **1.38'** are identical to those of *ent*-**1.38'** reported in the literature[14] except for optical rotation: $[\alpha]_D^{26}$ −14.6 (*c* 0.40 $CHCl_3$).



Allyl Phosphate (*S*)-1.14: To a solution of alcohol (*S*)-**1.12** (4.44 g, 18.3 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (8.21 g, 73.2 mmol) in THF (60 mL) was added diethyl chlorophosphate (5.26 mL, 36.6 mmol) at room temperature. After stirring for 3 h, the reaction was quenched with brine at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography pre-treated by *N*,*N*-dimethylaniline (SiO_2, *n*-hexane/EtOAc = 1/1) afforded allyl phosphate (*S*)-**1.14** (5.94 g, 15.7 mmol, 86%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.95 (1H, s), 4.83 (1H, br), 4.16 (2H,s), 4.16–4.02 (4H, m), 2.16–2.07 (2H, m), 2.05–1.95 (1H, m), 1.80–1.67 (2H, m), 1.65–1.56 (1H, m), 1.32 (6H, t, *J* = 6.9 Hz), 0.90 (9H, s), 0.05 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.2 (d, *J* = 7.2 Hz), 127.3, 71.8 (d, *J* = 6.0 Hz), 63.8, 63.5 (d, *J* = 6.0 Hz), 63.4 (d, *J* = 6.0 Hz), 29.8, 25.9 (3C), 24.7, 18.3, 17.5, 16.13 (d, *J* = 7.2 Hz), 16.10 (d, *J* = 7.2 Hz), −5.3, −5.4; IR (ATR): ν 2952, 2931, 2857, 1257, 1066, 1034, 984, 836 cm^{-1}; HRMS (FD): Calcd for $C_{17}H_{36}O_5PSi$ $[M+H]^+$: 379.2070; found: 379.2051; $[\alpha]_D^{26}$ −35.1 (*c* 1.00 $CHCl_3$).

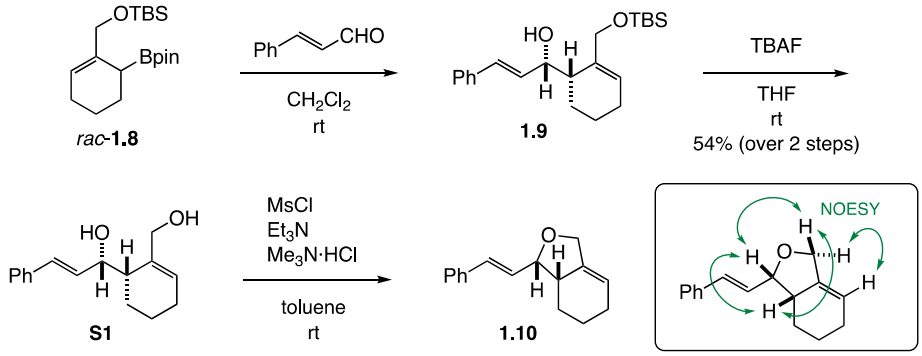


Allylboronate (*R*)-1.8: A flame-dried two-neck round bottom flask was charged with bis(pinacolato)diboron ($B_2(pin)_2$) (3.05 g, 12.0 mmol), copper(I) chloride (CuCl) (59.4 mg, 0.60 mmol) and potassium methoxide (MeOK) (1.26 g, 18.0 mmol) in an argon atmosphere. To the flask was added toluene (9.0 mL), and the resulting suspension was stirred for 10 min at 40 ºC. Then, trimethyl borate ($B(OMe)_3$) (1.0 mL, 9.0 mmol) followed by allyl phosphate (*S*)-**1.14** (2.27 g, 6.00 mmol) in toluene was added. After stirring for 12 h, the reaction mixture was passed through a pad of silica gel, which was rinsed with *n*-hexane/EtOAc = 1/1. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 15/1) afforded allylboronate (*R*)-**1.8** (1.87 g, 4.75 mmol, 79%) as a colorless oil. The enantiomeric excess of (*R*)-**1.8** was determined to be 96% ee by ^{1}H-NMR analysis of the derivative (*R*)-MTPA ester **1.38'** according to scheme S1: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.65 (1H, s), 4.07 (2H, s), 2.02 (2H, br), 1.84–1.75 (2H, m), 1.70–1.60 (2H, m), 1.58–1.51 (1H, m), 1.23 (12H, s), 0.90, (9H, s), 0.06 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 138.0, 119.6, 83.1 (2C), 67.0, 26.0 (3C), 24.9, 24.8, 24.6 (2C), 24.5 (2C), 22.1, 18.5, −5.2, −5.3 (one peak missing); IR (ATR): ν 2978, 2928, 2856, 1471, 1359, 1319, 1252, 1146, 1095, 1073, 836, 775 cm^{-1}; HRMS (FI): Calcd for $C_{19}H_{37}BO_3Si$ $[M]^+$: 351.2641; found: 351.2640; $[\alpha]_D^{26}$ +45.5 (*c* 1.01 $CHCl_3$).



MTPA ester 1.38': To a solution of allylboronate (*R*)-**1.8** (5.6 mg, 14 μmol) and $NaHCO_3$ (4.8 mg, 57 μmol) in THF (140 μL) was added 30% aqueous H_2O_2 solution (2.9 μL, 28 μmol) at 0 ºC. After completion of the reaction which was monitored by TLC, a saturated aqueous $NaHCO_3$ solution was added to the reaction mixture at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded allyl alcohol (*R*)-**1.12** (4.1 mg). The product (*R*)-**1.12** was used for next step without further purification.

Using the same Mosher esterification procedure as above, (*S*)-MTPA ester **1.38'** was obtained from the crude (*R*)-**1.12** and (*R*)-MTPA-Cl (3.1 μL, 17 μmol). The enantiomeric excess was determined to be 96% ee by ^{1}H-NMR analysis of crude product. The characterization data of **1.38'** are reported in the literature. [14)]

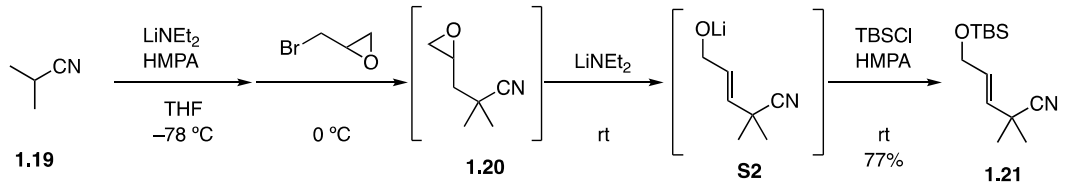


Bicyclic ether 1.10: To a solution of boronate *rac*-**1.8** (46.7 mg, 0.118 mmol) in CH_2Cl_2 (590 μL) was added cinnamaldehyde (17.9 μL, 0.142 mmol) at room temperature. After 1.5 h, sodium borohydride (9.0 mg, 0.24 mmol) and MeOH (400 μL) were added, effecting the selective quenching of aldehyde, before a saturated aqueous $NaHCO_3$ solution was added. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was roughly purified by silica

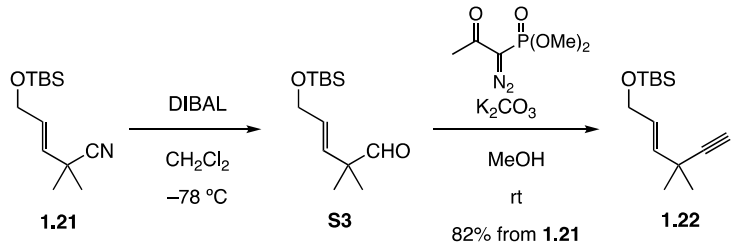
gel column chromatography, using eluent *n*-hexane/EtOAc = 15/1. The crude alcohol **1.9** was used for the next steps without further purification.

To a solution of alcohol **1.9** in THF (300 µL) was added tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 88.3 µL, 88.3 µmol) at 0 ºC. After stirred for 20 min at room temperature, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 1/1) afforded diol **S1** (15.6 mg, 63.8 µmol, 54% over 2 steps) as a colorless oil.

To a solution of diol **S1** (9.3 mg, 0.038 mmol), Et_3N (11 µL, 0.076 mmol), and $Me_3N{\cdot}HCl$ (0.4 mg, 4.1 µmol) in toluene (380 µL) was added methanesulfonyl chloride (MsCl) (5.9 µL, 0.076 mmol) at 0 ºC and the mixture was stirred at room temperature for 16 h. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 1/2) afforded bicyclic ether **1.10** (4.0 mg, 18 µmol, 47%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46–7.31 (5H, m), 6.66 (1H, d, *J* = 16.1 Hz), 6.30 (1H, dd, *J* = 16.1, 5.8 Hz), 6.07 (1H, s), 4.73 (1H, s), 4.41 (1H, d, *J* = 10.9 Hz), 4.05 (1H, d, *J* = 10.9 Hz), 2.67 (1H, s), 2.08 (2H, br), 1.82–1.72 (3H, m), 1.64–1.62 (1H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 136.7, 134.2, 133.0, 130.6, 130.5, 128.6 (2C), 127.6, 126.4 (2C), 72.3, 49.2, 40.4, 25.4, 22.7, 20.5; IR (ATR): ν 3425, 3058, 3026, 2930, 2860, 1716, 1495, 1448, 1259, 1069, 968, 750, 693 cm^{-1}; HRMS (FI): Calcd for $C_{16}H_{18}O$ $[M]^+$: 226.1358; found: 226.1355.

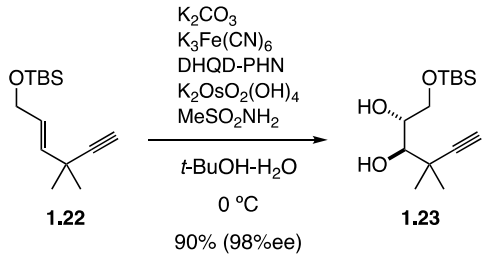


Nitrile 1.21: To a solution of Et_2NH (3.58 mL, 34.5 mmol) in THF (33 mL) was added *n*-BuLi (2.67 M in *n*-hexane, 12.4 mL, 33.0 mmol) at −78 ºC, and the solution was stirred for 20 min at 0 ºC. The solution was cooled down to −78 ºC, and to this was added HMPA (5.74 mL, 33.0 mmol) followed by isobutyronitrile (**1.19**) (2.69 mL, 30.0 mmol). After stirring for 30 min, epibromohydrin (2.95 mL, 36.0 mmol) was added, and the mixture was stirred at 0 ºC for 1 h. The mixture was cooled down to −78 ºC, and to this was added a solution of $LiNEt_2$ (1.0 M in THF, 60.0 mmol, 60.0 mL). The reaction mixture was stirred at room temperature for 10 min, at which time monitoring by TLC indicated the disappearance of intermediate **1.20**. After selective quenching of remaining $LiNEt_2$ by stirring with $(CH_2Cl)_2$ (7.12 mL, 90.0 mmol) for 30 min, the reaction mixture was cooled down to 0 ºC, and TBSCl (9.04 g, 60.0 mmol) followed by HMPA (11.0 mL, 60.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h at which time monitoring by TLC indicated the disappearance of intermediate **S2**. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the layers were separated. The aqueous layer was extracted with *n*-hexane, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 50/1 to 40/1) afforded nitrile **1.21** (5.53 g, 23.1 mmol, 77%) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, dt, *J* = 15.5, 4.5Hz), 5.58 (1H, d, *J* = 15.5 Hz), 4.20–4.19 (2H, m), 1.44, (6H, s), 0.91 (9H, s), 0.08 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 130.4, 129.7, 123.6, 62.5, 34.3 , 27.5 (2C), 25.9 (3C), 18.3, −5.3 (2C); IR (ATR): ν 2955, 2930, 2885, 2857, 1470, 1389, 1377, 1363, 1253, 1119, 1066, 966, 834, 775, 666 cm^{-1}; HRMS (FI): Calcd for $C_{13}H_{25}NOSi$ $[M]^+$: 239.1705; found: 239.1708

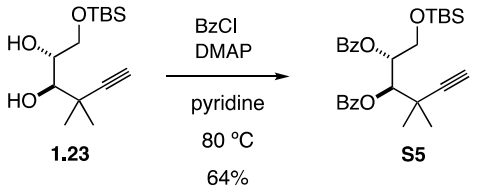


Alkyne 1.22: To a cooled (−78 ºC) solution of nitrile **1.21** (3.84 g, 16.0 mmol) in CH_2Cl_2 (80 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 20.2 mL, 20.8 mmol), and the mixture was stirred at the same temperature for 20 min. The resulting mixture was treated with ethyl acetate (3 mL) at −78 ºC, then stirred at room temperature, effecting quenching of the excess amount of DIBAL. A 10% aqueous tartaric acid solution was slowly added at 0 ºC, and the resulting solution was stirred vigorously at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was passed through a short pad of silica, using eluent *n*-hexane/EtOAc = 15/1. The crude aldehyde **S3** was used for the next step without further purification

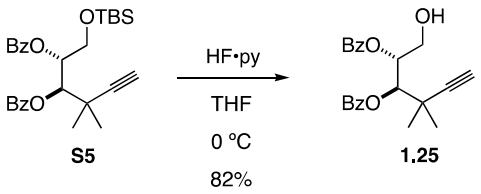
To a solution of the crude product and K_2CO_3 (4.06 g, 29.4 mmol) in MeOH (60 mL) was added Ohira-Bestmann reagent (3.38 g, 17.6 mmol) in MeOH (20 mL) at 0 ºC. After stirring at room temperature for 2 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded alkyne **1.22** (3.15 g, 13.2 mmol, 82% for 2 steps) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.83 (1H, dt, *J* = 15.5, 4.6 Hz), 5.61 (1H, d, *J* = 15.5 Hz), 4.18 (2H, d, *J* = 4.6 Hz), 2.24 (1H, s), 1.31 (6H, s), 0.91 (9H, s), 0.07 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.9, 127.0, 89.9, 69.4 63.4, 33.1, 29.7 (2C), 26.0 (3C), 18.4, −5.1 (2C); IR (ATR): ν 3312, 2956, 2929, 2886, 2857, 1464, 1362, 1254, 1110, 1063, 969, 834, 774, 631 cm^{-1}; HRMS (FI): Calcd for $C_{14}H_{26}OSi$ $[M]^+$: 238.1753; found: 238.1750.



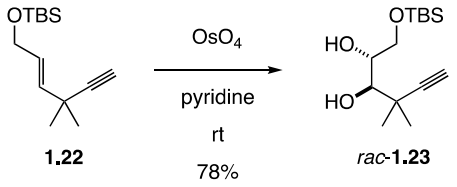
Diol 1.23: To a mixture of $K_3Fe(CN)_6$ (4.94 g, 15.0 mmol), K_2CO_3 (2.76 g, 20.0 mmol), $MeSO_2NH_2$ (476 mg, 5.00 mmol) and DHQD-PHN (101 mg, 0.200 mmol) in *t*-BuOH-H_2O (1:1, 50 mL) was added $K_2OsO_2(OH)_4$ (18.4 mg, 0.050 mmol) at room temperature. After stirring at the same temperature for 10 min, the mixture was cooled to 0 ºC, and a solution of alkyne **1.22** (1.19 g, 5.00 mmol) in *t*-BuOH (5 mL) was added. After stirring at 0 ºC for 24 h, $Na_2S_2O_3$ was added, and the mixture was stirred at 0 ºC for 1 h. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 15/1 to 6/1) afforded diol **1.23** (1.23 g, 4.51 mmol, 90%) as a pale yellow oil. The enantiomer excess (ee) of **1.23** was determined to be 98% ee by HPLC analysis of derivative **1.25**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.04 (1H, dd, *J* = 6.3, 4.6 Hz), 3.70 (1H, dd, *J* = 10.3, 4.6 Hz), 3.64 (1H, dd, *J* = 10.3, 6.3 Hz), 3.33 (1H, d, *J* = 6.9 Hz), 3.03 (1H, d, *J* = 6.9 Hz), 2.80 (1H, d, *J* = 4.0 Hz), 2.19 (1H, s), 1.27 (6H, s), 0.91 (9H, s), 0.09 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 89.8, 75.4, 70.1, 69.5, 65.9, 35.6, 26.4, 25.7 (3C), 24.2, 18.1, −5.5, −5.6; IR (ATR): ν 3309, 2955, 2930, 2858, 1472, 1389, 1255, 1112, 834, 776, 634 cm^{-1}; HRMS (FD): Calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$: 273.1886; found: 273.1891; $[\alpha]_D^{26}$ −2.9 (*c* 1.17 $CHCl_3$).



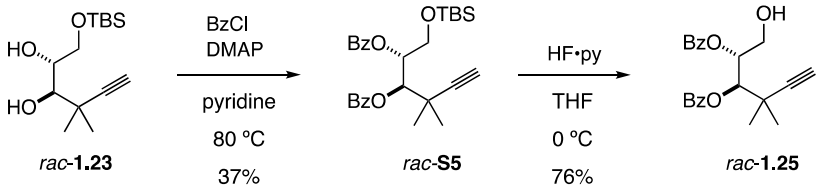
Bisbenzoate S5: To a mixture of **1.23** (22.2 mg, 81.5 µmol) and DMAP (9.9 mg, 82 µmol) in pyridine (410 µL) was added BzCl (47.3 µL, 0.41 mmol) at 0 ºC. After stirring at the same temperature for 10 min, the mixture was heated to 80 ºC. After stirring 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded bisbenzoate **S5** (25.0 mg, 0.052 mmol, 64%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.15 (2H, dd, *J* = 8.1, 1.1 Hz), 8.06 (2H, dd, *J* = 8.0, 1.1 Hz), 7.59 (1H, tt, *J* = 7.5, 1.1 Hz), 7.54 (1H, tt, *J* = 7.5, 1.1 Hz), 7.48 (2H, dd, *J* = 8.1, 7.5 Hz), 7.42 (2H, dd, *J* = 8.1, 7.5 Hz), 5.75 (1H, td, *J* = 6.3, 2.3 Hz), 5.44 (1H, d, *J* = 2.3 Hz), 3.77 (2H, dd, *J* = 5.7, 4.0 Hz), 2.06 (1H, s), 1.37 (3H, s), 1.34 (3H, s), 0.83 (9H, s), −0.01 (3H, s), −0.03 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.7, 165.6, 133.2, 132.9, 130.2, 129.9 (2C), 129.84 (2C), 129.81, 128.5 (2C), 128.3 (2C), 88.0, 75.3, 72.2, 70.3, 62.2, 34.8, 26.9, 25.9, 25.7 (3C), 18.1, –5.5, –5.6; IR (ATR): ν 2952, 2929, 2883, 2857, 1724, 1314, 1260, 1176, 1108, 1068, 1027, 838, 777, 710 cm^{-1}; HRMS (FI): Calcd for $C_{28}H_{37}O_5Si$ $[M+H]^+$: 481.2410; found: 481.2410; $[\alpha]_D^{23}$ +34.2 (*c* 1.23 $CHCl_3$).



Alcohol 1.25: To a mixture of **S5** (25.0 mg, 52.4 μmol) in THF (400 μL) in a polypropylene test tube was added hydrogen fluoride-pyridine complex (HF•pyridine) (0.3 mL) at 0 °C. After stirring at the same temperature for 0.5 h, methoxytrimethylsilane (TMSOMe) (0.1 mL) was added to the reaction mixture. The mixture was further stirred at room temperature for 1 h, and quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded alcohol **1.25** (15.6 mg, 42.5 μmol, 82%) as a colorless oil. The enantiomeric excess (ee) was determined by HPLC analysis (CIRALCEL OJ-H column, 5.0 μm, 250×4.6 mm, *n*-hexane/isopropanol (80:20 v/v as an eluent), flow rate = 1.0 mL/min, λ = 220 nm, major enantiomer t_R = 6.9 min, minor enantiomer t_R = 8.5 min): ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.16 (2H, dd, *J* = 8.6, 1.1 Hz), 8.05 (2H, dd, *J* = 8.6, 1.1 Hz), 7.63 (1H, tt, *J* = 7.5, 1.1 Hz), 7.55 (1H, tt, *J* = 7.5, 1.1 Hz), 7.51 (2H, dd, *J* = 8.6, 7.5 Hz), 7.42 (2H, dd, *J* = 8.6, 7.5 Hz), 5.79 (1H, td, *J* = 5.2, 2.3 Hz), 5.37 (1H, d, *J* = 1.7 Hz), 3.86–3.80 (1H, m), 3.70–3.65 (1H, m), 2.69 (1H, dd, *J* = 8.6, 6.3 Hz), 2.09 (1H, s), 1.39 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.0, 165.7, 133.7, 133.2, 133.0 (2C), 129.9 (2C), 129.7, 129.1, 128.6 (2C), 128.3 (2C), 87.7, 75.8, 72.0, 70.6, 61.3, 34.5, 26.8, 26.1; IR (ATR); ν 3566, 3503, 3298, 2979, 2939, 1719, 1602, 1452, 1333, 1315, 1262, 1177, 1109, 1068, 1027, 709, 686, 670 cm^{-1}; HRMS (FI): Calcd for $C_{22}H_{23}O_5$ $[M+H]^+$: 367.1546; found: 367.1548; $[\alpha]_D^{23}$ +41.3 (*c* 0.78 $CHCl_3$).

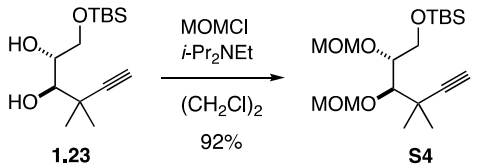


Racemic diol *rac*-1.23: To a solution of alkyne **1.22** (45.0 mg, 0.189 mmol) in pyridine (945 µL) was added OsO_4 (1.0 mg, 3.8 µmol) at room temperature. After stirring at the same temperature for 1 h, the reaction was quenched with an aqueous $NaHSO_3$ solution at 0 ºC, and the mixture was stirred at room temperature for 1 h. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 6/1) afforded diol *rac*-**1.23** (40.4 g, 0.148 mmol, 78%) as a colorless crystal. The characterization data of *rac*-**1.23** are identical to **1.23** except for melting point: 43-44 ºC.



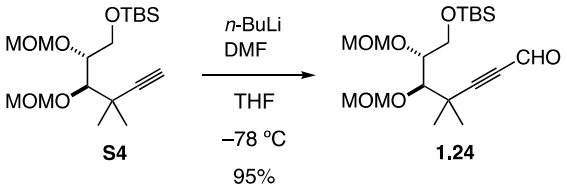
Racemic bisbenzoate *rac*-S5: Using the same procedure as above, bisbenzoate *rac*-**S5** (3.1 mg, 6.5 µmol, 37%) was obtained from *rac*-**1.23** (4.8 mg, 18 µmol). The characterization data of *rac*-**S5** are identical to those of **S5**.

Racemic alcohol *rac*-1.25: Using the same procedure as above, alcohol *rac*-**S5** (1.8 mg, 4.9 µmol, 85%) was obtained from *rac*-**S5** (3.1 mg, 6.5 µmol). The characterization data of *rac*-**1.25** are identical to those of **1.25**.

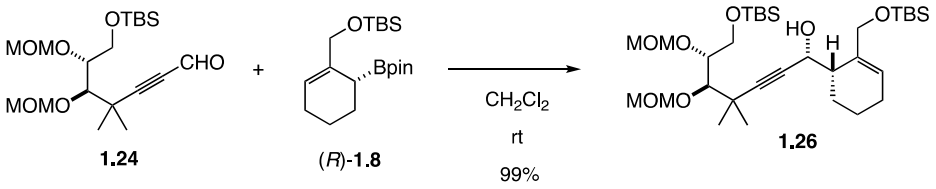


1.23 S4

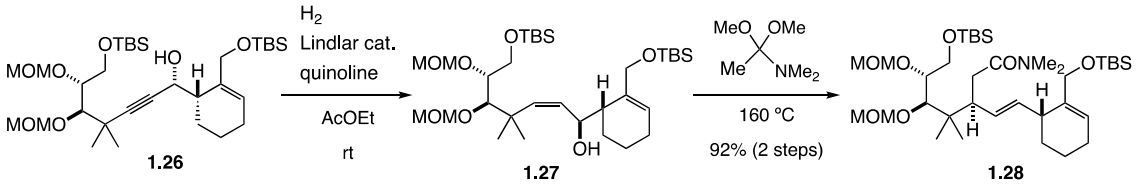
Alkyne S4: To a solution of diol **1.23** (2.81 g, 10.3 mmol) and *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) (10.5 mL, 61.8 mmol) in $(CH_2Cl)_2$ (10.3 mL) was added methoxymethyl chloride (MOMCl) (2.3 mL, 31 mmol) at 0 ºC. After stirring at room temperature for 18 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded alkyne **S4** (3.41 g, 9.46 mmol, 92%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.83 (1H, d, *J* = 6.9 Hz), 4.82 (1H, d, *J* = 6.9 Hz), 4.76 (1H, d, *J* = 6.9 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.02–3.98 (1H, m), 3.78 (1H, dd, *J* = 10.3, 6.3 Hz), 3.70 (1H, dd, *J* = 10.3, 6.9Hz), 3.55 (1H, d, *J* = 2.9 Hz), 3.43 (3H, s), 3.39 (3H, s), 2.17 (1H, s), 1.33 (6H, s), 0.89 (9H, s), 0.07 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 98.4, 97.3, 89.9, 81.7, 78.2, 69.8, 63.1, 56.0, 55.6, 35.0, 27.7, 25.7 (3C), 25.2, 18.0, −5.5, −5.7; IR (ATR): ν 3417, 2929, 2856, 2462, 1253, 1156, 1100, 1065, 1042, 1005, 982, 833, 774 cm^{-1}; HRMS (FD): Calcd for $C_{18}H_{37}O_5Si$ $[M+H]^+$: 361.2410; found: 361.2424; $[\alpha]_D^{26}$ +63.5 (*c* 0.96 $CHCl_3$).



Aldehyde 1.24: To a cooled (−78 ºC) solution of alkyne **S4** (412 mg, 1.14 mmol) in THF (5.7 mL) was added *n*-BuLi (2.76 M in *n*-hexane, 513 µL, 1.37 mmol). After stirring at the same temperature for 30 min, *N*,*N*-dimethylformamide (DMF) (177 µL, 2.28 mmol) was added to the mixture. After stirring at 0 ºC for 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 7/1 to 5/1) afforded aldehyde **1.24** (422 mg, 1.09 mmol, 95%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.20 (1H, s), 4.82 (1H, d, *J* = 6.9 Hz), 4.77–4.75 (3H, m), 3.89–3.86 (1H, m), 3.80 (1H, dd, *J* = 10.3, 5.7 Hz), 3.69 (1H, d, *J* = 8.6 Hz), 3.61 (1H, s), 3.44 (3H, s), 3.39 (3H, s), 1.41 (3H, s), 1.38 (3H, s), 0.89 (9H, s), 0.07 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 176.6, 103.0, 98.5, 97.2, 82.3, 81.8, 78.1, 62.3, 56.1, 55.7, 35.7, 26.3, 25.6 (3C), 25.4, 17.9, −5.6, −5.7; IR (ATR): ν 2932, 2894, 1716, 1663, 1471, 1219, 1149, 1102, 1025, 772 cm^{-1}; HRMS (FD): Calcd for $C_{19}H_{37}O_6Si$ $[M+H]^+$: 389.2359; found: 389.2359; $[\alpha]_D^{26}$ +41.0 (*c* 1.21 $CHCl_3$).

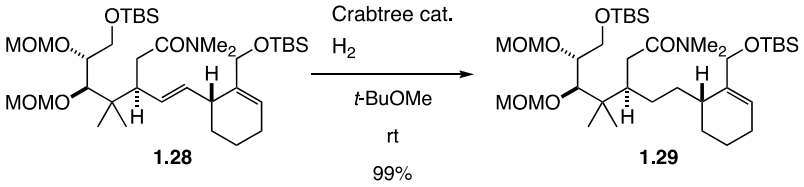


Propargyl Alcohol 1.26: To a solution of aldehyde **1.24** (1.28 g, 3.29 mmol) in CH_2Cl_2 (10 mL) was added a solution of allylboronate (*R*)-**1.8** (1.43 g, 3.62 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature. After completion of the reaction which was monitored by TLC, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 5/1) afforded alcohol **1.26** (1.99 g, 3.24 mmol, 99%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.84 (1H, s), 4.89 (1H, d, *J* = 6.9 Hz), 4.79 (1H, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.3 Hz), 4.69 (1H, d, *J* = 6.9 Hz), 4.62–4.60 (1H, m), 4.24 (1H, d, *J* =12.0 Hz), 4.09 (1H, *J* = 11.5 Hz), 4.04–4.01 (1H, m), 3.81 (1H, d, *J* = 5.8 Hz), 3.75 (1H, dd, *J* = 10.3, 6.3 Hz), 3.67 (1H, dd, *J* = 10.3, 6.9 Hz), 3.50 (1H, s), 3.42 (3H, s), 3.39 (3H, s), 2.44 (1H, br), 2.03 (2H, br), 1.90–1.80 (1H, m), 1.75–1.66 (1H, m), 1.51–1.45 (1H, m), 1.29 (6H, s), 0.89 (18H, s), 0.08 (6H, s), 0.07 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.9, 129.2, 98.4, 97.1, 90.9, 82.1, 82.0, 77.8, 67.5, 64.1, 63.8, 56.2, 55.7, 43.2, 35.5, 28.0, 25.9 (6C), 25.3, 25.2, 24.8, 21.0, 18.22, 18.19, −5.3, −5.4 (2C), −5.5; IR (ATR): ν 2952, 2929, 2887, 2853, 2335, 1471, 1253, 1102, 1030, 834, 775 cm^{-1}; HRMS (FD): Calcd for $C_{32}H_{63}O_7Si_2$ $[M+H]^+$: 615.4112; found: 615.4103; $[\alpha]_D^{26}$ +101 (*c* 1.03 $CHCl_3$).



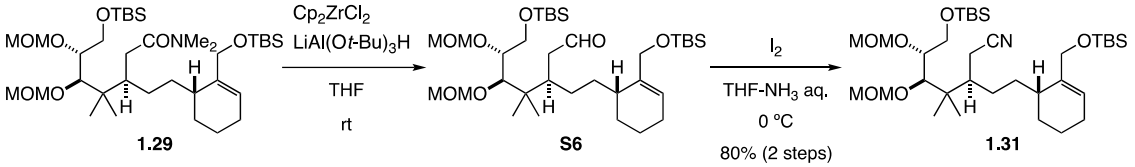
Amide 1.28: A mixture of alcohol **1.26** (104 mg, 0.168 mmol), quinoline (84 µL, 8.4 µmol) and Lindlar catalyst (51.8 mg, 50 wt%) in EtOAc (840 µL) was stirred at room temperature under H_2 atmosphere. After 0.5 h, the flask was purged with argon, and the reaction mixture was passes through a pad of Celite®, which was rinsed with EtOAc. The residue was used for the next step without further purification.

The above crude (*Z*)-allyl alcohol **1.27** was stirred in *N*,*N*-dimethylacetamide dimethyl acetal (420 µL) at 160 ºC for 0.5 h. After cooling to room temperature, the resulting mixture was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 1/1) affording amide **1.28** (108 mg, 0.154 mmol, 92% for 2 steps) as a yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.68 (1H, s), 5.34 (1H, dd, *J* = 14.9, 8.0 Hz), 5.22 (1H, dd, *J* = 14.9, 9.2 Hz), 4.76–4.67 (4H, m), 3.91 (2H, s), 3.78–3.72 (2H, m), 3.61–3.57 (1H, m), 3.50 (1H, d, *J* = 1.7 Hz), 3.40 (3H, s), 3.35 (3H, s), 2.97 (3H, s), 2.84 (3H, s), 2.83–2.79 (1H, m), 2.69 (1H, br), 2.52 (1H, dd, *J* = 14.3, 2.9 Hz), 2.33 (1H, dd, *J* =14.3, 10.9 Hz), 1.96 (2H, br), 1.64–1.59 (1H, m), 1.53–1.44 (3H, m), 0.91 (3H, s), 0.89 (3H, s), 0.86 (18H, s), 0.03 (6H, s), 0.01 (3H, s), 0.00 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.1, 138.0, 135.7, 129.7, 122.0, 98.9, 97.5, 81.7, 65.5, 63.7, 56.1, 55.9, 45.1, 40.1, 38.1, 37.3, 35.4, 33.3, 29.2, 25.9 (3C), 25.8 (3C), 24.9, 23.1, 20.7, 18.6, 18.3, 18.1, −5.3, −5.4, −5.5, −5.6 (one peak missing); IR (ATR): ν 2952, 2982, 2888, 2856, 1651, 1471, 1391, 1253, 1100, 1072, 1031, 919, 835, 775 cm^{-1}; HRMS (FD): Calcd for $C_{36}H_{71}NO_7Si_2$ $[M]^+$: 685.4769; found: 685.4767; $[\alpha]_D^{23}$ −29.1 (*c* 1.00 $CHCl_3$).



Amide 1.29: A mixture of amide **1.28** (233 mg, 0.332 mmol) and Crabtree's catalyst (13.3 mg, 16.6 µmol) in *tert*-butyl methyl ether (*t*-BuOMe) (6.7 mL, 0.05 M) was stirred at room temperature under H_2 atmosphere. After 1 h, the flask was purged with argon, and the solution was concentrated under reduce pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 1/1) afforded amide **1.29** (233 mg, 99%) as a yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.58 (1H, s), 4.83 (1H, d, *J* = 6.9 Hz), 4.77 (1H, d, *J* = 6.9 Hz), 4.72–4.68 (2H, m), 4.05 (1H, d, *J* = 13.2 Hz), 3.95 (1H, d, *J* = 12.6 Hz), 3.77–3.72 (2H, m), 3.65–3.58 (2H, m), 3.39 (3H, s), 3.34 (3H, s), 3.00 (3H, s), 2.90 (3H, s), 2.53 (1H, dd, *J* = 16.1, 4.0 Hz), 2.23–2.15 (1H, m), 2.04 (1H, dd, *J* = 16.6, 6.9 Hz), 1.94 (3H, br), 1.60–1.51 (3H, m), 1.50–1.42 (3H, m), 1.13–1.06 (1H, m), 0.99–0.94 (4H, m), 0.91 (3H, s), 0.87 (9H, s), 0.86 (9H, s), 0.04 (3H, s), 0.03 (3H, s),

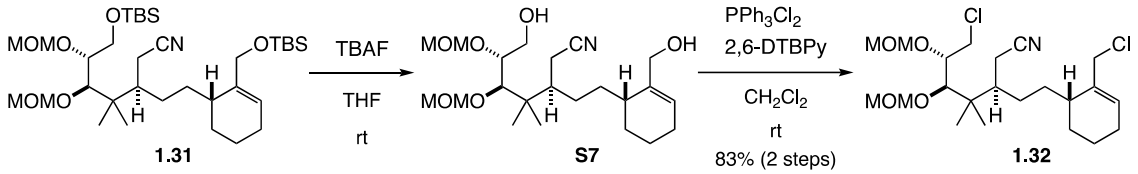
0.02 (3H, s), 0.01 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.0, 140.3, 121.6, 98.7, 97.4, 81.6, 77.5, 65.4, 62.6, 55.7, 55.3, 40.3, 40.1, 36.7, 35.3, 34.7, 34.2, 31.2, 28.8, 26.9, 25.5 (3C), 25.4, 24.7, 21.8, 21.0, 19.0, 17.9, 17.8, 14.9, −5.6, −5.7, −5.8, −5.9 (one peak missing); IR (ATR): ν 2928, 2856, 1653, 1472, 1395, 1254, 1150, 1033, 914, 836, 744, 669 cm^{-1}; HRMS (FD): Calcd for $C_{36}H_{73}NO_7Si_2$ $[M]^+$: 687.4926; found: 687.4918; $[\alpha]_D^{26}$ +17.2 (*c* 1.00 $CHCl_3$).



Nitrile 1.31: To a mixture of amide **1.29** (776.3 mg, 1.10 mmol) and zirconocene dichloride (Cp_2ZrCl_2) (419 mg, 1.43 mmol) in THF (5.5 mL) was added lithium tri-*tert*-butoxyaluminum hydride (LiAl(O*t*-Bu)$_3$H) (1.0 M in THF, 1.38 mL, 1.38 mmol) at 0 ºC. The reaction mixture was warmed up to room temperature and was stirred for 20 min. Then, an aqueous sodium potassium tartrate solution was added at 0 ºC, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography. The product **S6** was used for next step without further purification.

To a solution of crude aldehydes **S6** in THF–aq. NH_3 (1:1, 5.5 mL) was added iodine (840 mg, 3.30 mmol) at 0 ºC. After stirring for 20 min at the same temperature, the reaction was quenched with an aqueous $Na_2S_2O_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by open column chromatography (SiO_2, *n*-hexane/EtOAc = 7/1 to 5/1) afforded nitrile **1.31** (568 mg, 0.883 mmol, 80% for 2 steps) as a yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.68 (1H, s), 4.77 (1H, d, *J* = 6.9 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.3 Hz), 4.65 (1H, d, *J* = 6.3 Hz), 4.12 (1H, d, *J* = 12.6 Hz), 4.03 (1H, d, *J* = 12.6 Hz), 3.77–3.74 (2H, m), 3.62–3.58 (1H, m), 3.53–3.51 (1H, m), 3.41 (3H, s), 3.38 (3H, s), 2.69 (1H, dd, *J* = 17.8, 4.6 Hz), 2.60 (1H, dd, *J* = 17.8, 5.7 Hz), 2.11 (1H, br), 2.00 (2H, br), 1.77 (2H, m), 1.68–

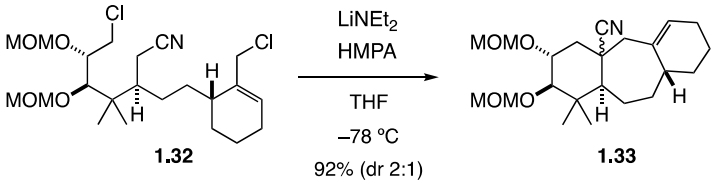
1.53 (4H, m), 1.30–1.16 (3H, m), 0.99 (6H, s), 0.89 (18H, s), 0.06 (12H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 140.0, 122.6, 120.6, 99.1, 97.2, 83.4, 77.0, 65.8, 63.0, 56.2, 56.1, 41.6, 41.1, 34.8, 31.9, 27.5, 27.1, 26.0 (3C), 25.9 (3C), 25.1, 24.0, 20.5, 19.4, 18.4, 18.3, 18.1, −5.2, −5.3, −5.4, −5.5; IR (ATR): ν 2949, 2930, 2886, 2858, 2357, 2337, 1732, 1458, 1252, 1160, 1049, 979, 946, 846, 776, 730, 648 cm^{-1}; HRMS (FD): Calcd for $C_{34}H_{67}NO_6Si_2$ $[M]^+$: 641.4507; found: 641.4511; $[\alpha]_D^{26}$ +6.81 (*c* 1.00 $CHCl_3$).



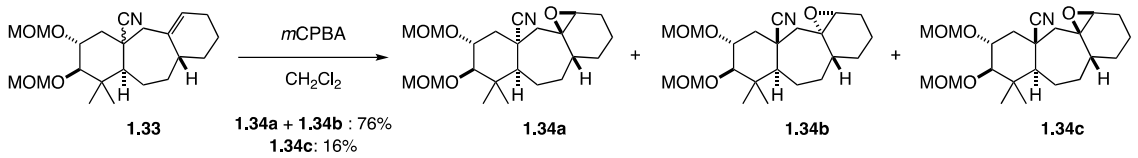
Dichloride 1.32: To a solution of **1.31** (532 mg, 0.828 mmol) in THF (4.2 mL) was added TBAF (1.0 M in THF, 2.5 mL, 0.25 mmol) at 0 ºC. After stirring at room temperature for 19 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through a short pad of silica, using eluent $CHCl_3$/MeOH = 40/1. The crude diol **S7** was used for next step without further purification.

A solution of triphenylphosphine dichloride (PPh_3Cl_2)[24] in CH_2Cl_2 (0.40 M, 6.2 mL, 2.5 mmol) was added to a mixture of diol **S7** and 2,6-di-*tert*-butylpyridine (2,6-DTBPy) (1.09 mL, 4.97 mmol) in CH_2Cl_2 (1.7 mL) at 0 ºC. After stirring at 0 ºC for 5 min, the mixture was warmed up to room temperature. After stirring at the same temperature for 1 h, water was slowly added to the reaction mixture. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 7/1 to 3/1) afforded dichloride **1.32** (311 mg, 0.690 mmol, 83% for 2 steps) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.85 (1H, s), 4.80 (1H, d, *J* = 6.9 Hz), 4.76 (2H, s), 4.66 (1H, d, *J* = 6.3 Hz), 4.20 (1H, d, *J* = 12.0 Hz), 3.85–3.82 (1H, m), 3.75 (2H, s), 3.61 (1H, s), 3.43 (3H, s), 3.41 (3H, s), 2.76 (1H, dd, *J* = 17.2, 4.6 Hz), 2.54 (1H, dd, *J* = 17.2, 6.9 Hz), 2.39–2.30 (1H, m), 2.04 (2H, br), 1.84–1.34

(8H, m) 1.33–1.19 (2H, m), 1.02 (3H, s), 0.99 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 137.1, 129.4, 120.5, 99.6, 97.5, 84.3, 77.3, 56.3, 56.2, 48.8, 43.2, 41.6, 41.3, 34.4, 31.3, 27.5, 26.9, 25.4, 23.8, 20.5, 19.1, 18.4; IR (ATR): ν 2924, 2827, 2359, 2326, 1218, 1148, 1098, 1077, 1025, 920, 772, 689 cm^{-1}; HRMS (FD): Calcd for $C_{22}H_{37}Cl_2NO_4$ $[M]^+$: 449.2100; found: 449.2089; $[\alpha]_D^{26}$ +9.02 (*c* 1.02 $CHCl_3$).



Tricyclic nitrile 1.33: To a cooled (−78 ºC) solution of dichloride **1.32** (292 mg, 0.648 mmol) and HMPA (248 µL, 1.43 mmol) in THF (3.2 mL) was added $LiNEt_2$ (1.0 M in THF, 1.43 mL, 1.43 mmol). After 30 min, the reaction was quenched with acetic acid in THF (ca. 1.0 M, 500 µL, 0.5 mmol) at −78 ºC, followed by a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 7/1) afforded tricyclic nitrile **1.33** (225 mg, 0.597 mmol, 92%, d.r. = 2:1) as a yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.81 (0.67H, s), 5.44 (0.33H, s), 4.90 (0.33H, d, *J* = 6.9 Hz), 4.75–4.66 (3H, m), 4.62 (0.67H, d, *J* = 6.9 Hz), 3.86–3.81 (1H, m), 3.50 (0.67H, d, *J* = 5.2 Hz), 3.41 (2H, s), 3.40 (1H, s), 3.374 (2H, s), 3.370 (1H, s), 2.95 (0.33H, d, *J* = 9.2 Hz), 2.51–2.39 (1.33H, m), 2.20 (0.33H, dd, *J* = 13.2, 4.6 Hz), 2.12–1.35 (13.01H, m), 1.27 (2H, s), 1.25–1.20 (1H, m), 1.11–1.08 (0.33H, m), 1.04 (1H, s), 1.03 (1H, s), 0.98 (2H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.5, 134.2, 127.5, 126.9, 126.7, 124.3, 99.0, 97.8, 96.7, 95.7, 87.3, 82.8, 75.6, 74.7, 56.3, 56.2, 55.6, 55.5, 52.4, 50.8, 49.5, 47.7, 41.9 40.7, 40.2, 39.9, 39.1, 38.4, 37.3, 37.1, 35.3. 34.7, 30.0, 29.5, 28.8, 27.3, 26.3, 25.8, 25.7, 24.4, 23.0, 19.7, 18.7, 15.5; IR (ATR): ν 2927, 2857, 1456, 1147, 1098, 1026, 917, 753 cm^{-1}; HRMS (FD): Calcd for $C_{22}H_{35}NO_4$ $[M]^+$: 377.2566; found: 377.2553; $[\alpha]_D^{26}$ −27.3 (*c* 0.87 $CHCl_3$).



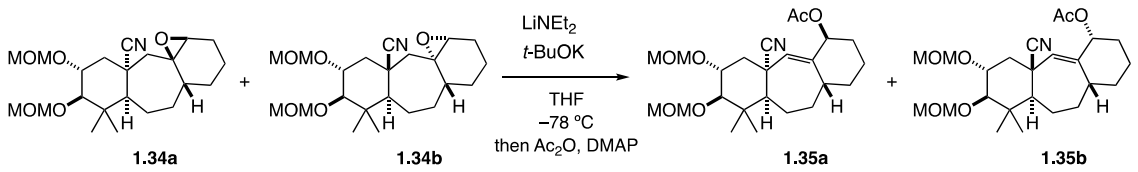
Epoxide 1.34: To a solution of tricyclic nitrile **1.33** (58.8 mg, 0.156 mmol) in CH_2Cl_2 (750 µL) was added *m*-chloroperoxybenzoic acid (*m*CPBA) (contains *ca*. 30% water, 62.0 mg, 0.233 mmol) at 0 ºC, and the mixture was vigorously stirred at room temperature for 1 h. The mixture was treated with 2-methyl-2-butene (330 µL, 3.11 mmol) at room temperature for 1 h, effecting quenching of *m*CPBA. After addition of $NaHCO_3$, the mixture was vigorously stirred for 1 h at room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4/1 to 1/1) afforded epoxide **1.34a** + **1.34b** (46.5 mg, 0.118 mmol, 76% for 2 steps) as a colorless oil along with the diastereomer **1.34c** (9.8 mg, 25 µmol, 16% for 2 steps) as a white powder.

1.34a + **1.34b**:

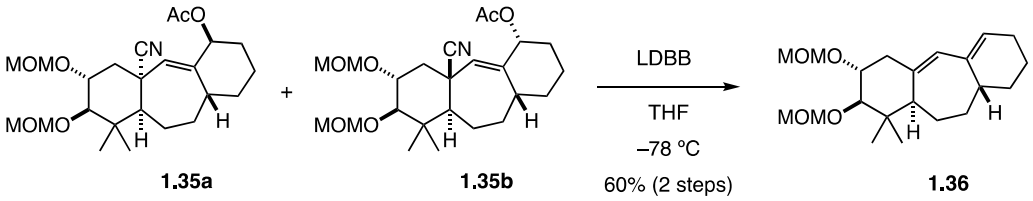
3:1 diastereomer mixture: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.87 (0.25H, d, *J* = 6.3 Hz), 4.83 (0.75H, d, *J* = 6.9 Hz), 4.74–4.65 (3H, m), 3.78–3.84 (0.25H, m), 3.74–3.68 (0.75H, m), 3.42 (3H, s), 3.38 (2.25H, s), 3.36 (0.75H, s), 3.27 (1H, d, *J* = 5.8 Hz), 3.23 (0.25H, br), 3.06 (0.25H, d, *J* = 9.2 Hz), 2.90 (0.25H, d, *J* = 4.6 Hz), 2.69 (0.75H, br), 2.50 (0.25H, d, *J* = 14.9 Hz), 2.19 (0.25H, dd, *J* = 13.2, 4.6 Hz), 2.11–2.06 (3H, m), 1.99–1.85 (5H, m), 1.79–1.72 (2H, m), 1.61–1.58 (2H, m), 1.47–1.15 (3H, m), 1.33 (3H, s), 1.06 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 124.8, 99.1, 97.9, 96.7, 95.6, 87.3, 75.8, 73.3, 61.9, 61.1, 60.8, 59.9, 56.3, 56.3, 55.6, 55.5, 51.3, 48.6, 48.3, 43.5, 41.0, 40.3, 40.1, 38.8, 36.9, 34.3, 29.0, 28.0, 27.4, 26.3, 24.6, 24.3, 19.7, 16.8, 15.4; HRMS (FD): Calcd for $C_{22}H_{35}NO_5$ $[M]^+$: 393.2515; found: 393.2513; $[\alpha]_D^{26}$ +40.3 (*c* 0.98 $CHCl_3$).

1.34c

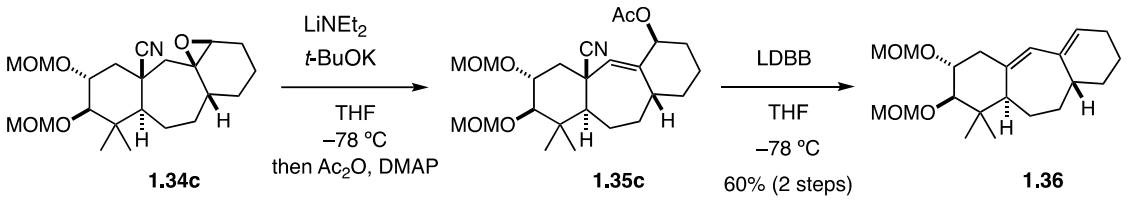
^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.92 (1H, d, *J* = 6.3 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.3 Hz), 4.67 (1H, d, 6.3 Hz), 3.88 (1H, td, *J* = 9.2, 4.0 Hz), 3.42 (3H, s), 3.35 (3H, s), 2.98 (1H, d, *J* = 9.7 Hz), 2.83 (1H, s), 2.32 (1H, dd, *J* = 13.8, 4.0 Hz), 2.30 (1H, d, *J* = 14.9 Hz), 2.19 (1H, dd, *J* = 14.3, 8.0 Hz), 2.04–2.11 (2H, m), 1.83–1.76 (2H, m), 1.66–1.53 (2H, m), 1.42–1.19 (6H, m), 1.09 (6H, s), 0.88–0.78 (1H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 122.2, 99.0, 96.7, 87.3, 74.8, 60.2, 58.0, 56.4, 55.6, 55.5, 50.9, 44.0, 41.0, 40.3, 38.4, 33.1, 30.6, 28.3, 27.8, 25.1, 17.8, 15.4; HRMS (FD): Calcd for $C_{22}H_{35}NO_5$ $[M]^+$: 393.2515; found: 393.2524; $[\alpha]_D^{26}$ +67.5 (*c* 1.09 $CHCl_3$); Recrystallization of this powder from *n*-hexane/EtOAc/Et_2O = 10:1:1 afforded colorless needles, which were analyzed by X-ray: M.p. 153–157 ºC.



Allyl Acetate 1.35a + **1.35b:** To a solution of epoxide **1.34a** + **1.34b** (122 mg, 0.311 mmol) in THF (1.5 mL) was added $LiNEt_2$ (1.0 M in THF, 778 µL, 0.778 mmol), followed by *t*-BuOK (1.0 M in THF, 1.56 mL, 1.56 mmol) at −78 ºC, and the mixture was vigorously stirred at the same temperature for 0.5 h. After selective quenching of the bases with acetic acid (1.0 M in THF solution, 3.1 mL), Ac_2O (293 µL, 3.1 mmol) followed by DMAP (1 chip) was added. After stirring at room temperature for 1.5 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through a short pad of silica, using eluent *n*-hexane/EtOAc = 2/1. The crude acetate **1.35a** and **1.35b** was used for the next step without further purification.

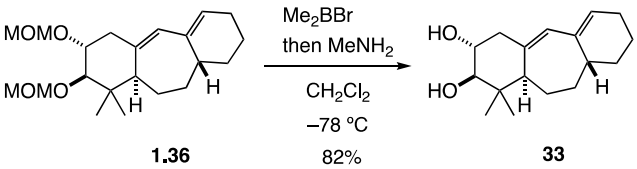


Diene 1.36: To a cooled (−78 ºC) solution of acetate **1.35a** + **1.35b** in THF (3.1 mL) was dropwise added lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)[27] (1.0 M in THF, 1.2 mL) until the mixture turned dark green. After 20 min, $(CH_2Cl)_2$ was added until the color of the mixture turned orange. A saturated aqueous NH_4Cl solution was added, and the mixture was warmed up to room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 50/1 to 10/1) afforded diene **1.36** (66.0 mg, 0.188 mmol, 60% for 2 steps) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.89 (1H, s), 5.60 (1H, s), 4.91 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.9 Hz), 4.69 (1H, d, *J* = 6.9 Hz), 3.57–3.62 (1H, m), 3.42 (3H, s), 3.38 (3H, s), 3.09 (1H, d, *J* = 9.2 Hz), 2.54 (1H, dd, *J* = 13.2, 5.7 Hz), 2.19–2.06 (5H, m), 2.00 (1H, t, *J* = 13.8 Hz), 1.73 (2H, d, *J* = 12.1 Hz), 1.43–1.48 (2H, m), 1.20–1.38 (3H, m), 1.03 (3H, s), 0.77 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 140.1, 132.8, 131.1, 129.8, 99.0, 96.3, 88.1, 78.6, 56.3, 55.4, 49.9, 46.0, 42.4, 41.0, 31.9, 31.8, 29.0, 26.1, 24.9, 22.0, 15.9; IR (ATR): ν 2925, 2851, 2826, 1441, 1148, 1103, 1026, 979, 915, 755 cm^{-1}; HRMS (FD): Calcd for $C_{21}H_{34}O_4$ $[M]^+$: 350.2457; found: 350.2463; $[\alpha]_D^{26}$ +46.7 (*c* 1.22 $CHCl_3$).



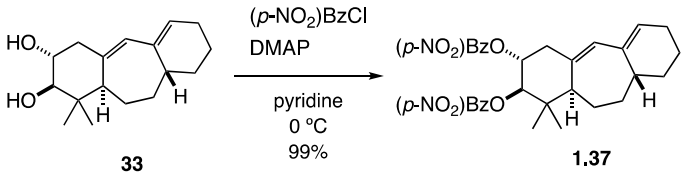
Diene 1.36 from **1.34c:** Using the same procedure as above, diene **1.36** (5.4 mg, 15 µmol, 60% for 2 steps) was obtained with following reagents: (1) **1.34** (9.8 mg, 25 µmol) and $LiNEt_2$ (1.0 M in THF, 63 µL, 63 µmol) and *t*-BuOK (1.0 M in THF, 125 µL, 125 µmol), (2) LDBB (1.0 M in

THF, 300 µL). The characterization data of synthesized compound are identical to those of above **1.36**.



1.36 **33**

Diol 33: To a cooled (−78 ºC) solution of diene **1.36** (24.3 mg, 69.3 µmol), 2,6-DTBPy (76.7 mL, 0.347 mmol) in CH_2Cl_2 (345 µL) was added Me_2BBr (1.07 M in CH_2Cl_2, 324 µL, 0.347 mmol). After completion of the reaction which was monitored by TLC, $MeNH_2$ aqueous solution (40% in water, 107 µL, 1.38 mmol) was added to the mixture, and the mixture was warmed up to 0 ºC. After stirring for 1.5 h, H_2O was added to the mixture. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 2/1) afforded diol **33** (14.9 mg, 56.8 µmol, 82%) as a colorless oil: ^{1}H-NMR (500MHz, $CDCl_3$): δ 5.92 (1H, s), 5.63 (1H, s), 3.60–3.55 (1H, m), 3.10 (1H, d, *J* = 9.2 Hz), 2.49 (1H, dd, *J* = 13.2, 5.8 Hz), 2.38 (1H, br), 2.20–1.99 (6H, m), 1.75–1.70 (3H, m), 1.62–1.58 (1H, m), 1.54–1.42 (2H, m), 1.33–1.18 (2H, m), 1.03 (3H, s), 0.76 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 140.0, 132.8, 131.5, 130.2, 82.8, 71.5, 50.1, 47.0, 42.4, 40.6, 31.9, 31.9, 28.8, 26.1, 24.7, 22.0, 15.1; IR (ATR): ν 3363, 2968, 2928, 1457, 1378, 1306, 1128, 1105, 1056, 950, 816 cm^{-1}; HRMS (FI): Calcd for $C_{17}H_{26}O_2$ $[M]^+$: 262.1933; found: 262.1926; $[\alpha]_D^{26}$ −20.2 (*c* 0.75 $CHCl_3$).



33 1.37

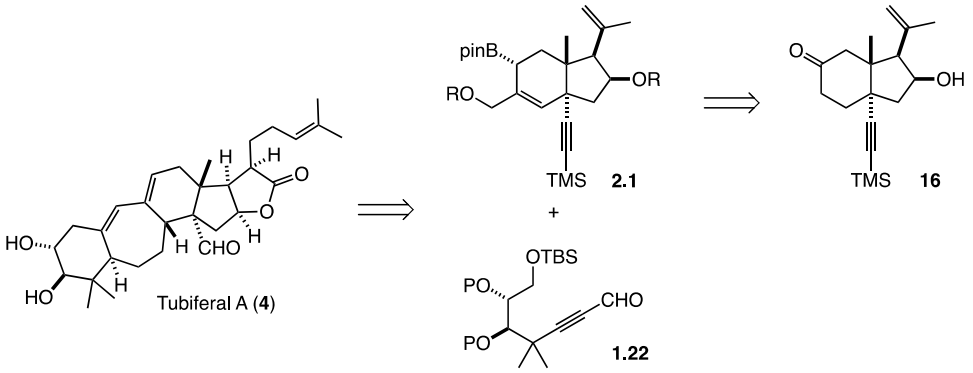
Bisbenzoate 1.37: To a solution of diol **33** (0.8 mg, 3.1 µmol) and DMAP (1 chip) in pyridine (100 µL) was added *p*-NO_2BzCl (2.8 mg, 15 µmol). After stirring for 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded bis-*p*-nitrobenzoate **1.37** (1.7 mg, 3.0 µmol, 99%) as a white powder. Recrystallization of this power from *n*-hexane/EtOAc = 10/1 afforded colorless needles, which were analyzed by X-ray: M.p. 195–199 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.23 (2H, d, *J* = 8.6 Hz), 8.19 (2H, d, *J* = 8.6 Hz), 8.13 (2H, d, *J* = 9.2 Hz), 8.06 (2H, d, *J* = 8.6 Hz), 6.05 (1H, s), 5.72 (1H, s), 5.36–5.32 (2H, m), 2.83–2.81 (1H, m), 2.51–2.47 (1H, m), 2.31–2.27 (1H, m), 2.21–2.15 (4H, m), 1.79–1.77 (2H, m), 1.66 (1H, dd, *J* = 13.2, 7.5 Hz), 1.39–1.32 (1H, m), 1.28–1.19 (2H, m), 1.07 (3H, m), 1.01 (3H, s), 0.88–0.83 (1H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.4, 164.0, 150.6, 150.5, 139.6, 135.1, 135.0, 133.5, 131.9, 130.7 (2C), 130.6 (2C), 129.4, 123.7 (2C), 123.5 (2C), 81.3, 73.8, 49.7, 43.9, 42.5, 40.9, 31.9, 29.7, 28.7, 26.2, 24.4, , 22.0, 16.2; IR (ATR): ν 2925, 2850, 1727, 1528, 1347, 1280, 1216, 1122, 1099, 771 cm^{-1}; HRMS (FD): Calcd for $C_{31}H_{32}N_2O_8$ $[M]^+$:560.2159; found: 560.2140; $[\alpha]_D^{26}$ −82.9 (*c* 0.12 $CHCl_3$).

Chapter 2

Synthetic studies toward the total synthesis of tubiferal A

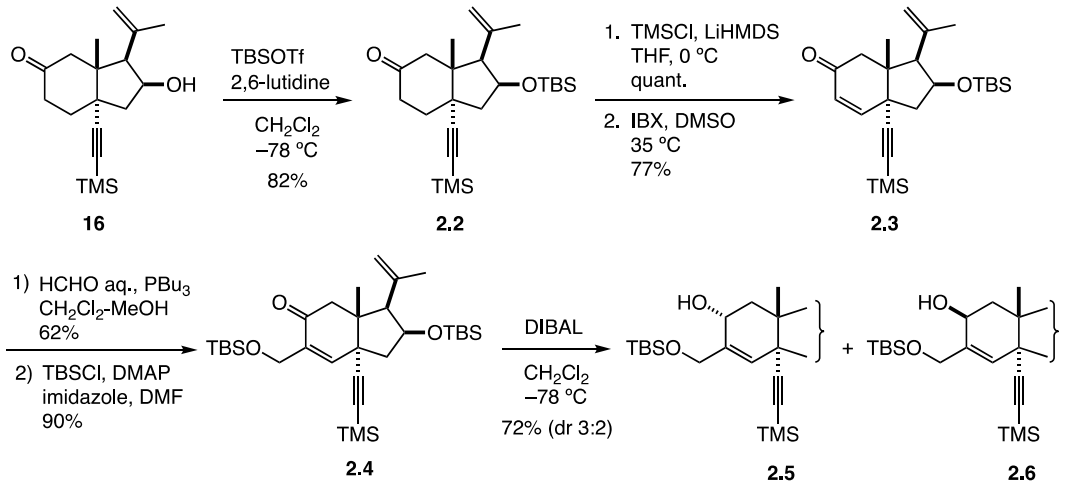
2-1. Attempts at synthesis of tubiferal A with acyclic A-ring segment and CD-ring segment

Since the efficient synthesis of the ABC ring segment of tubiferal A was achieved, the author aimed for the total synthesis of tubiferal A. Based on the methodology established in Chapter 1, the author believed that tubiferal A could be obtained from the acyclic A ring unit **1.25** and allylboronate **2.1** as a CD ring unit. The CD ring unit **2.1** was expected to be prepared from the *trans*-fused bicyclic alcohol **16** reported by Dr. Hiramatsu (Scheme 2.1).



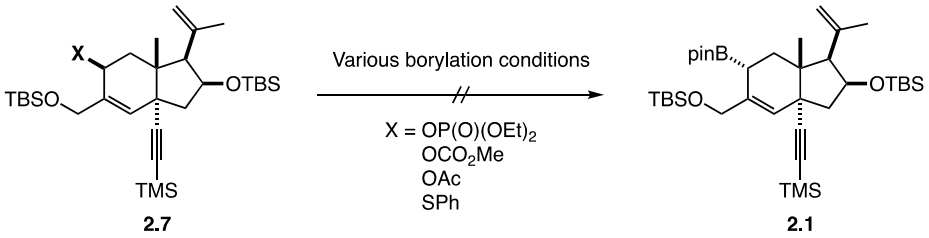
Scheme 2.1. Synthetic strategy for tubiferal A (**4**).

At first, allylic alcohols **2.5** and **2.6**, precursors of allylboronate **2.1**, were prepared as shown in Scheme 2.2. After protecting the optically active bicyclic alcohol **16** with a TBS group, the ketone **2.2** was converted to enone **2.3** over two steps by silyl-enol-etherification with TMSCl and LiHMDS and oxidation with IBX in DMSO at 35 ºC. Silyloxymethyl group of **2.4** was introduced by Morita-Baylis-Hillman reaction, and protection with a TBS group. Subsequently, DIBAL reduction of enone **2.4** afforded allylic alcohols **2.5** and **2.6** in a ratio of 3:2. With both isomer **2.5** and **2.6** in hand, allylic alcohols **2.5** or **2.6** were converted to precursors **2.7** with various leaving group for investigation of borylation.



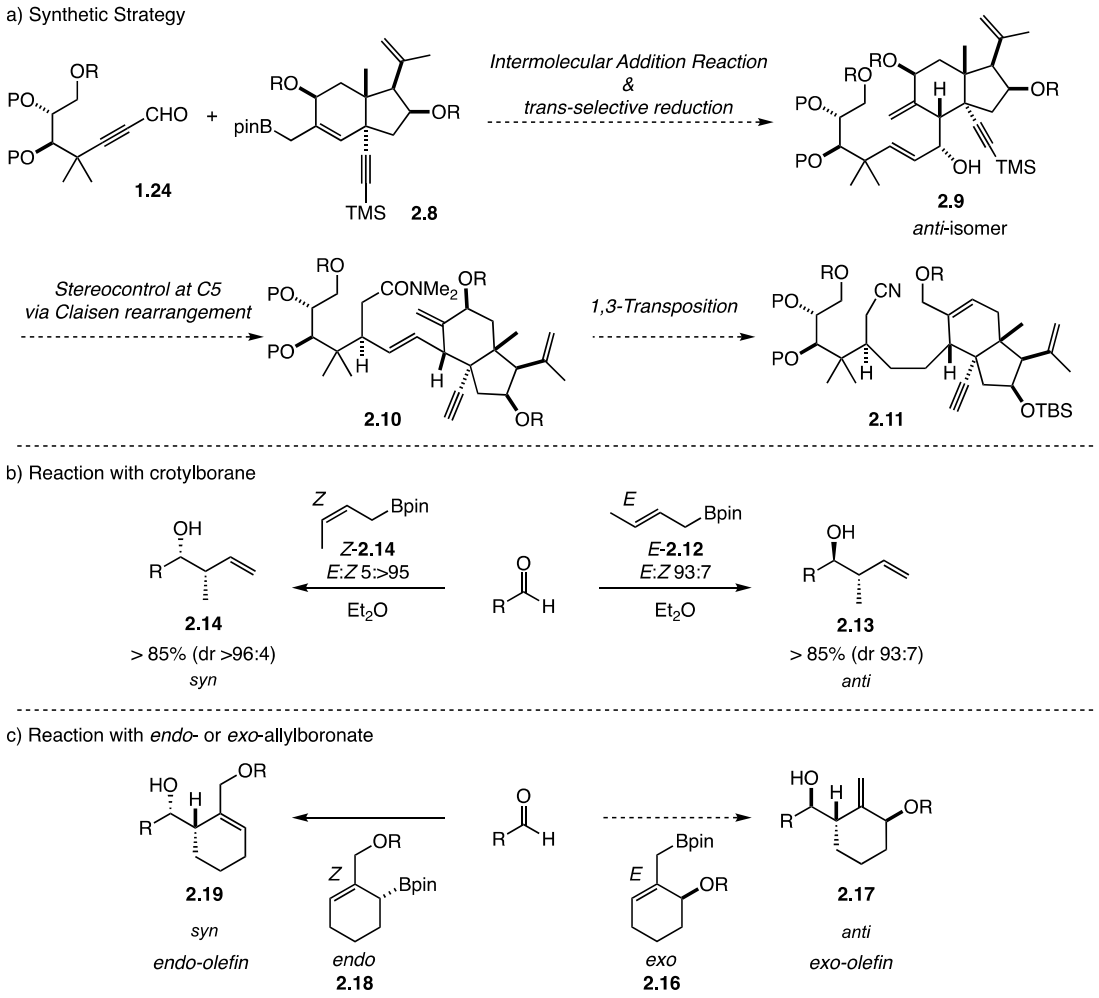
Scheme 2.2 Preparation of allyl alcohol **2.5** and **2.6**

The Diastereoselective introduction of a boryl group into allyl alcohol derivative **2.7** using various leaving groups (-OP(O)(OEt)$_2$, -OCO$_2$Me, -OAc, -SPh) were investigated (Scheme 2.3). However, none of these conditions provide a detectable amount of boronate **2.1**. Frist, the copper-catalyzed borylation could only recover the starting materials due to steric hindrance in the vicinity of the reactive site[28]. Then, attempts at borylations via π-allylpalladium and radial intermediates resulted in the decomposition of the substrate, probably due to reactions with the neighboring alkyne. The similar experiments were also carried out for *epi*-**2.7**, but with the same results.



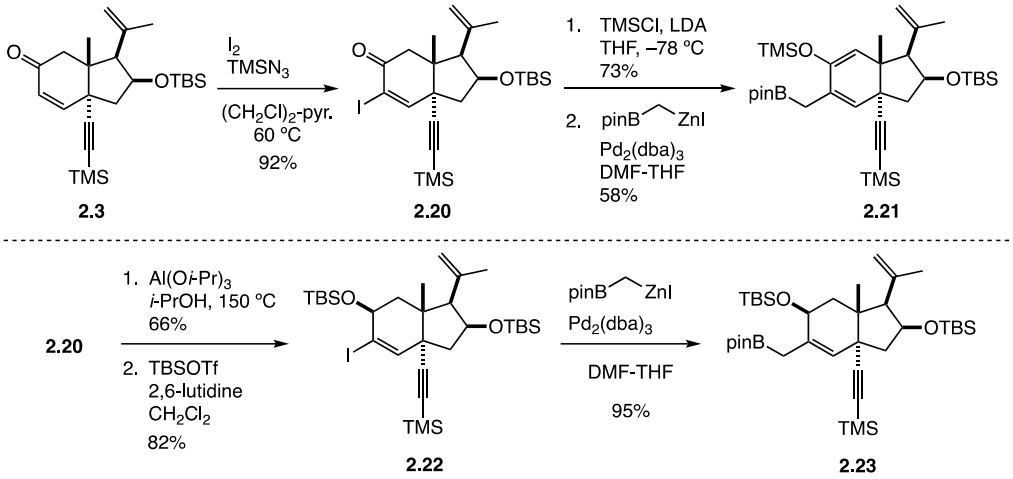
Scheme 2.3 Attempt at allylborylation

Due to the difficulty of the synthesis of *endo*-allylboronate such as **2.1**, the author investigated the synthesis of *exo*-allylboronate like **2.8** (Scheme2.4, a). The addition reaction of an allylboronate with an aldehyde is well known to exhibit high stereoselectivity due to the short B-O bond and the compact six-membered transition state. For example, Hoffmann and Zeiss reported the addition reactions of *E*- and *Z*-crotylboronate (**2.12** and **2.14**) with aldehydes afforded the *anti*- and *syn*-homoallylic alcohols (**2.13** and **2.15**), respectively (Scheme 2.4, b).[29] Based on these facts, an alternative to the *endo*-allylboronate reagent **2.18**, that is borylated inside of the cyclohexene ring as used in Chapter 1, is a boronate reagent that is borylated outside of the cyclohexene ring (*exo*-allylboronate). Using this *exo*-allylboronate reagent **2.16**, the adduct **2.17** with the desired stereochemistry at the C8 position could be obtained. However, the stereochemistry at the C7 position and the position of the double bond were different from the previous product **2.19**.[30] For the former, the *trans*-reduction of the alkyne and the Claisen rearrangement would converge to the same stereochemistry at the C5 position as that of **4**. The latter could be settled by 1,3-transposition of the oxygen functional group.



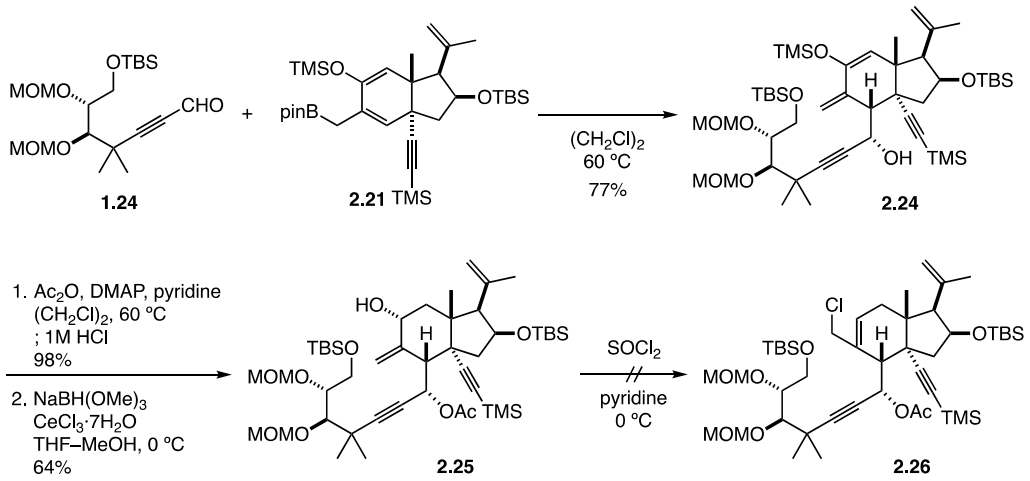
Scheme 2.4 New synthetic strategy and addition reaction with allylboronates with aldehydes

Iodination of enone **2.3** with I_2 and $TMSN_3$ in a mixed solvent of dichloroethane and pyridine at 60 ºC gave vinyl iodide **2.20** in 92% yield. The introduction of a borylmethyl group into iodide **2.20** was successfully achieved to give **2.21** in good yield by silyl-enol-etherification with LDA and TMSCl followed by Negishi coupling reaction with the zinc reagent[31] and $Pd_2(dba)_3$ (Scheme 2.5, top). On the other hand, TBS ether **2.23** was also synthesized by (i) Meerwein-Ponndorf-Verley reduction of **2.20** with $Al(O\textit{i}\text{-}Pr)_3$ in *i*-PrOH at 150 ºC, (ii) protection with a TBS group, (iii) Negishi coupling reaction under the same condition as described above (Scheme 2.5, bottom).



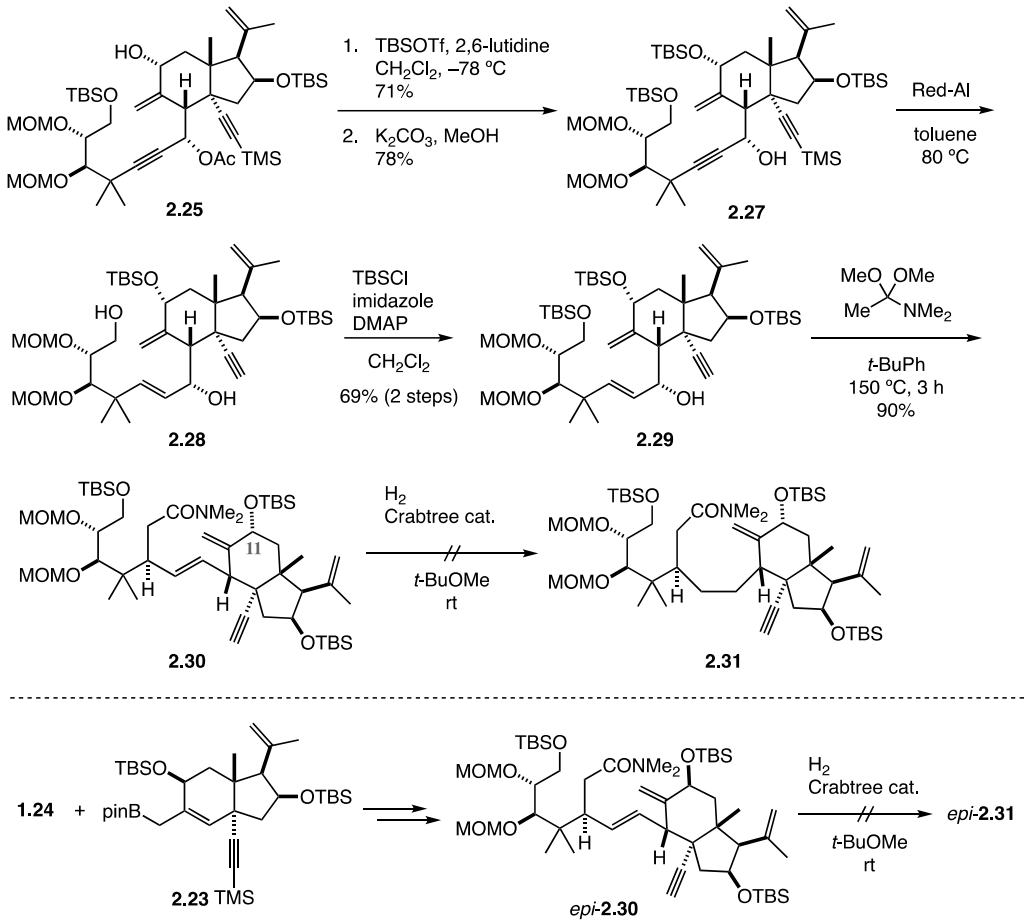
Scheme 2.5 Preparation of allylboronate **2.21** and **2.23**

Since the right-hand segment allylboronate **2.21** and **2.23** in hand, the author embarked on the intermolecular addition reaction with A-ring segment. Heating aldehyde **1.25** and allylboronate **2.21** in $(CH_2Cl)_2$ gave adduct **2.24** in 77% yield as s single diastereomer. Protection of the resulting alcohol with acetyl group at 60 ºC followed by hydrolysis with hydrochloric acid afforded *exo*-enone. The ketone moiety was reduced by $NaBH(OMe)_3$ with $CeCl_3$ at 0 ºC, and afforded allyl alcohol **2.25**. At this point, attempt at chlorination involving 1,3-transposition of allyl alcohol **2.25** failed to afford the desired product **2.26**. This synthetic route was expected to take long steps, as the sensitive allylic chloride had to transform into other functional groups.



Scheme 2.6 Attempt at synthesis of allylic chloride

Therefore, the author investigated the stereoselective introduction of an amide side chain by Claisen rearrangement prior to the 1,3-transposition of the allylic alcohol (Scheme 2.7). Propargyl alcohol **2.27**, obtained by protection with a TBS group of **2.25** and deprotection of the acetyl group, was reduced with Red-Al® in toluene at 80 ºC to afford a *trans*-alkene **2.28**. At the same time, the less hindered TBS group was removed, the resulting primary alcohol was reprotected using TBSCl to afford *trans*-allyl alcohol **2.29** in 69% yield over two steps. Eschenmoser-Claisen rearrangement with *N*,*N*-dimethylacetamide dimethyl acetal in *t*-BuPh proceeded smoothly at 150 ºC to give amide **2.30** as a single diastereomer. Although reduction of the resulting *trans*-alkene was attempted, the desired product **2.31** could not be obtained. Because of the high reactivity of *exo*-methylene, it was assumed that the *exo*-methylene moiety was also involved in Ir-catalyzed reactions, resulting in a number of unknown products. An attempt at hydrogenation with Crabtree catalyst of the epimer at C11 position, prepared from allylboronate **2.23**, gave the same result as for **2.30** (Scheme 2.7, bottom)

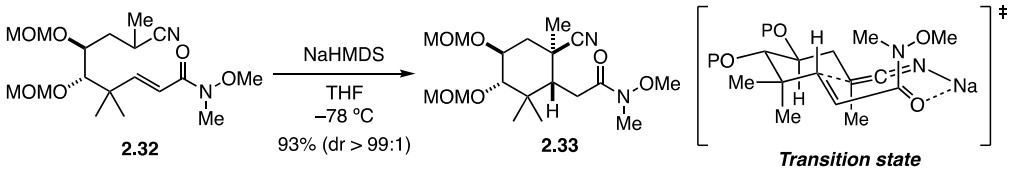


Scheme 2.7 Stereoselective introduction of amide side chain and reduction of alkene

2−2: Attempt at synthesis of tubiferal A with cyclic A-ring segment

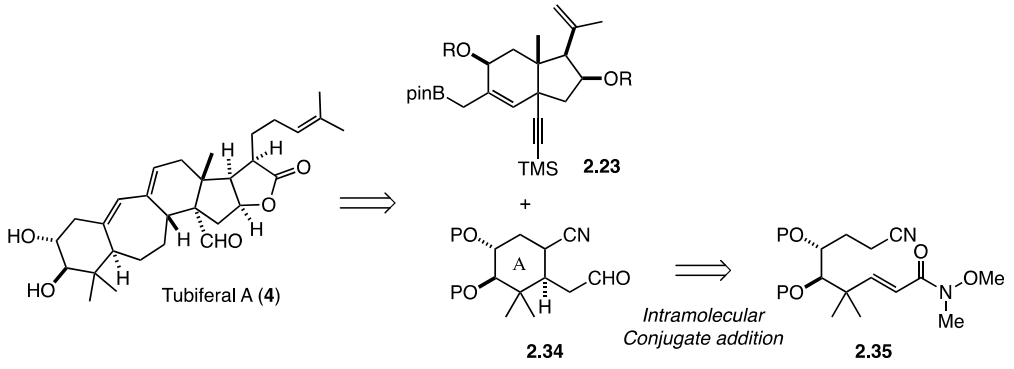
As mentioned in the previous section, the combination of *exo*-allylboronate and acyclic A-ring segment was not suitable for synthesis of tubiferal A (**4**) because of the difficulty in the selective reduction of the *trans*-alkene formed after Claisen rearrangement. Thus, it was decided to investigate the synthesis of **4** using a cyclic A-ring segment that was formed in advance.

In the meantime, Dr. Itoh, who was a former member of the author's laboratory, reported a synthetic method for stereoselective construction of six-membered ring system **2.33** by the intramolecular conjugate addition reaction of α,β-unsaturated Weinreb amide **2.32** possessing a nitrile moiety (Scheme 2.8)[32] Dr. Itoh postulated that the complete stereocontrol of **2.32** is due to chelation control, since both the keteniminate and α,β-unsaturated amide moieties are equatorially oriented in the transition state.



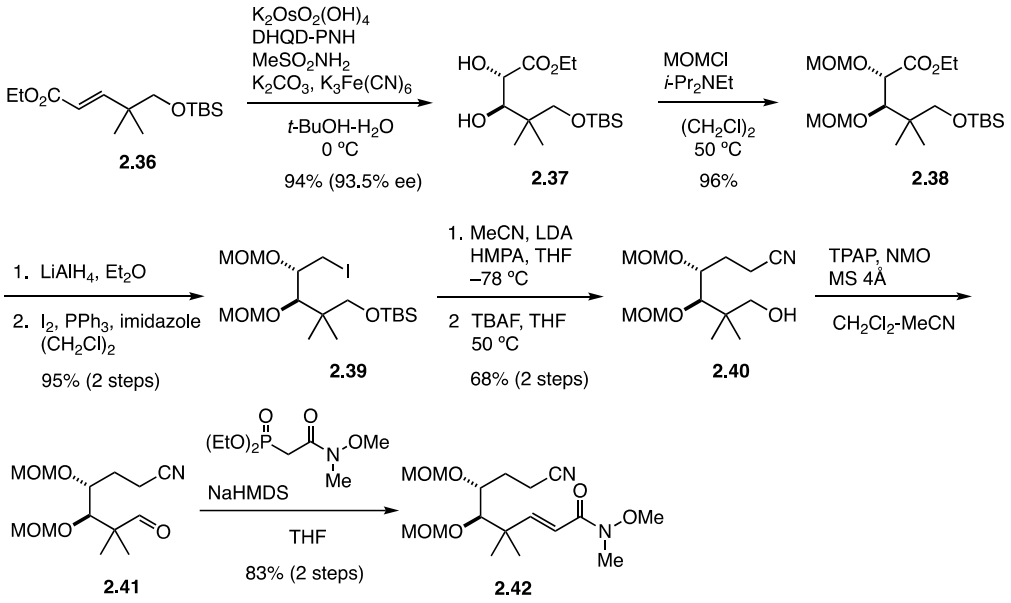
Scheme 2.8 Intramolecular conjugate addition reaction of α,β-unsaturated Weinreb amide **2.32**

An alternative synthetic strategy for tubiferal A (**4**) using the A-ring prepared by the intramolecular conjugate addition methodology described above is shown in Scheme 2.9. The intermolecular addition reaction of *exo*-allylboronate **2.23** with cyclic aldehyde **2.34** could be applicable for the synthesis of **4**. Aldehyde **2.34** would be prepared by the intramolecular conjugate addition reaction of Weinreb amide **2.35**.



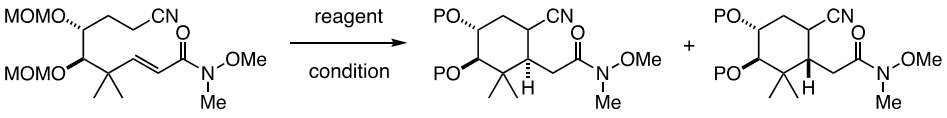
Scheme 2.9 New synthetic approach to tubiferal A with cyclic A-ring part

The precursor of **2.35** was synthesized from unsaturated ester **2.36** following the article on the total synthesis of Brasiricardins (Scheme 2.10). Ester **2.36** was subjected to the Sharpless asymmetric dihydroxylation reaction using DHQD-PHN as a chiral ligand to give the optically active diol **2.37** with 93.5% ee. Protection of the resulting diol with MOM groups, followed by reduction of the ester moiety with $LiAlH_4$ and iodination of the resulting primary alcohol afforded alkyl iodide **2.39**. Alkylation of **2.39** with α-cyanocarbanion prepared from acetonitrile and removal of the TBS group afforded alcohol **2.40**. Ley oxidation with TPAP/NMO and Horner-Wadsworth-Emmons olefination with phosphonoacetamide afforded (*E*)-α,β-unsaturated Weinreb amide **2.42** as the precursor for the intramolecular conjugate addition reaction.



Scheme 2.10 Preparation of intramolecular conjugate addition reaction precursor

With the α,β-unsaturated Weinreb amide **2.42** in hand, the intramolecular conjugate reaction was investigated as shown in Table 2.1. First, treatment of amide **2.42** with NaHMDS in THF at −78 ºC (entry 1) afforded a mixture of cycloadducts **2.43** and **2.44** in good yield and high diastereoselectivity. Determination of the stereochemistry of major cycloadduct **2.44** by NOESY experiments revealed that major isomer **2.44** possessed the undesired stereochemistry (Figure 2.1). To investigate the effect of the counter cation on the selectivity, LiHMDS and KHMDS were used (entry 2 and 3); LiHMDS showed no significant change, while KHMDS showed an increased in the ratio of isomer **2.43**. The steric configuration of **2.43** was determined by NOESY experiments. When the reaction was carried out under the condition of addition of TIPSCl and HMPA,[32b)] an inversion of the selectivity was observed (entry 4). Furthermore, when toluene was used instead of THF as a solvent (entry 5), the selectivity was increased (dr 75:25) and resulted in the selective formation of **2.43** as the major product.



2.42 **2.43** **desired** **2.44** **undesired**

entry	reagent	condition	**2.43** : **2.44** [a]
1	NaHMDS	THF, –78 ºC	17 : 83
2	LiHMDS	THF, –78 ºC	12 : 88
3	KHMMDS	THF, –78 to 0 ºC	40 : 60
4	KHMDS, TIPSCl, HMPA; TBAF	THF, –78 ºC	63 : 37
5	same as above	toluene, –78 ºC	75 : 25

[a] The ratio related to C5 position was determined by ^{1}H-NMR analysis

Table 2.1 Attempts to intramolecular addition reaction

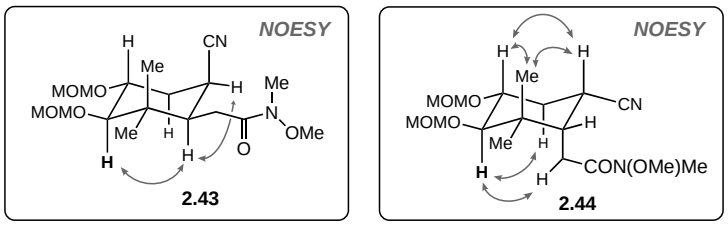


Figure 2.1 NOESY experiments of **2.43** and **2.44**

Figure 2.2 shows the proposed transition state models for the intramolecular conjugate addition reaction. The desired isomer **2.43**, in which the amide side chain occupies the equatorial position, is likely to be generated from **TS-2** because it is produced under conditions where there is no chelating effect of metal ions[33]. This is probably because the MOM group prefers an axial coordination to avoid Gaucher repulsion, and the anionic sites of the keteniminate and the amide group prefer to face opposite directions, resulting in an antiperiplanar relationship. It is also expected that if the metal coordinates with the keteniminate and the amide group and the reaction proceeds, **2.44** will be obtained via **TS-3**.

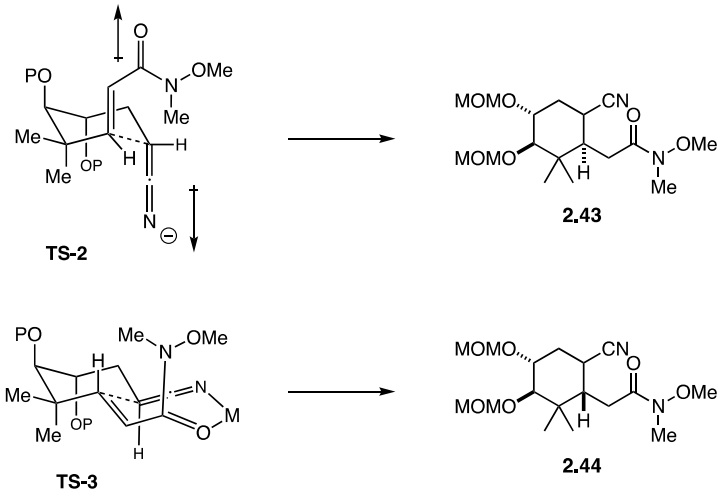
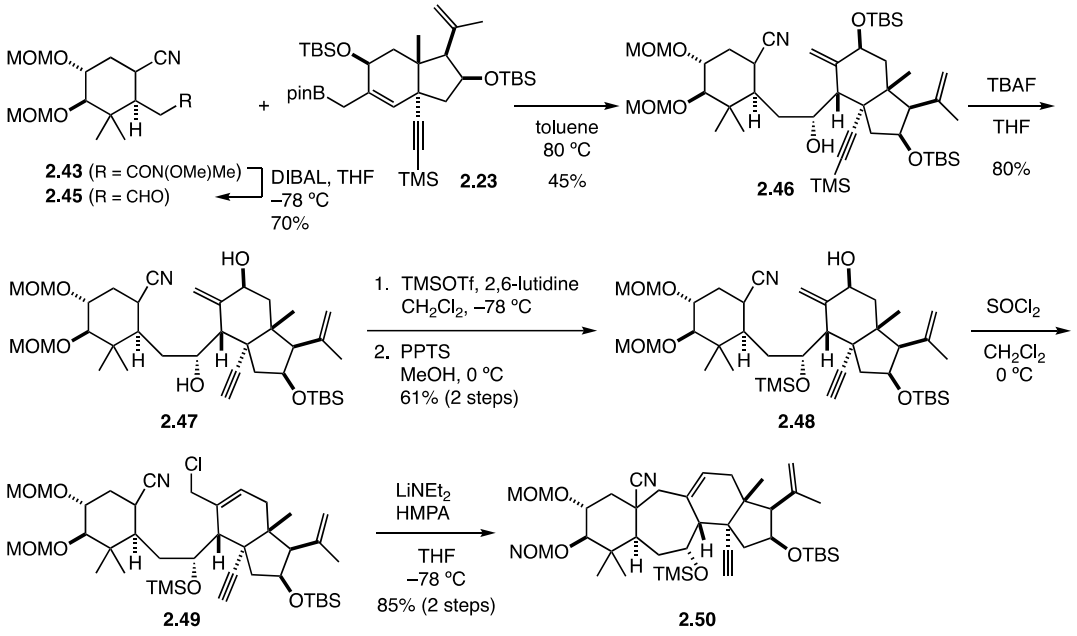


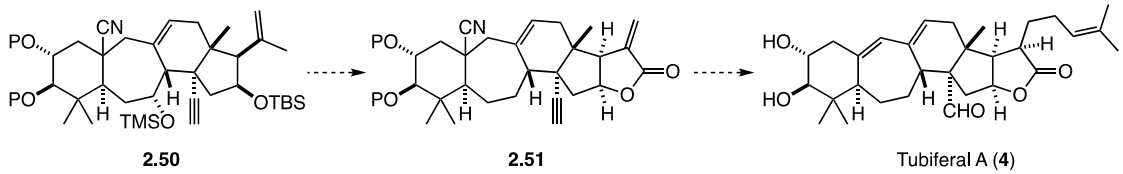
Figure 2.2 Proposed transition state models of the conjugate reaction of **2.42**

Using the desired isomer **2.43**, the A-ring segment, the author moved on to the coupling stage with the CD segment. Reduction of amide group of **2.43** with DIBAL afforded aldehyde **2.45**. The intermolecular addition reaction of aldehyde **2.45** with allylborane **2.23** gave the desired adduct **2.46** as a single isomer in moderate yield. The rest of compounds in this reaction were the decomposition products of allylboronate **2.23** and recovered a small amount of aldehyde **2.45**. The adduct **2.46** was subjected to the condition of desilylation using TBAF to give diol **2.47**, leaving the OTBS group on the D-ring intact. After protection of the diol with TMS groups, only less hindered TMS group on C-ring was removed under acidic conditions using PPTS in MeOH to give allylic alcohol **2.48**. Chlorination including 1,3-transposition using $SOCl_2$ transformed allylic alcohol **2.48** to allylic chloride **2.49**, the precursor for the cyclization. The cyclization of **2.49** proceeded smoothly by treatment with $LiNEt_2$ in the presence of HMPA to give tetracyclic compound **2.50**.



Scheme 2.11 Construction of tetracyclic framework

Having succeeded in constructing tetracyclic framework, the remaining tasks for achieving the total synthesis of tubiferal A (**4**) are the deoxygenation on B-ring, the construction of E-ring lactone, and introduction of conjugate diene and aldehyde (Scheme 2.12).

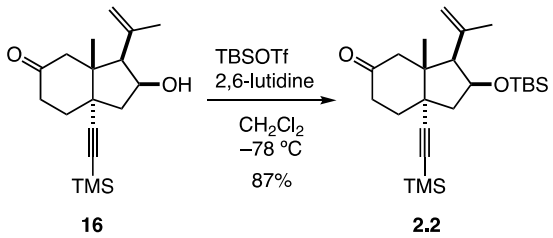


Scheme 2.12 Proposed synthetic plan toward tubiferalA (**4**)

In summary, the author has established the methodology of the construction of the tetracyclic framework that corresponds to the ABCD-ring skeleton of tubiferal A. The chiral A-ring segment was synthesized by the stereoselective intramolecular conjugate addition reaction of the α-cyano carbanion with the α,β-unsaturated Weinreb amide moiety, which allows simultaneous ring formation and construction of the stereogenic center at C5.

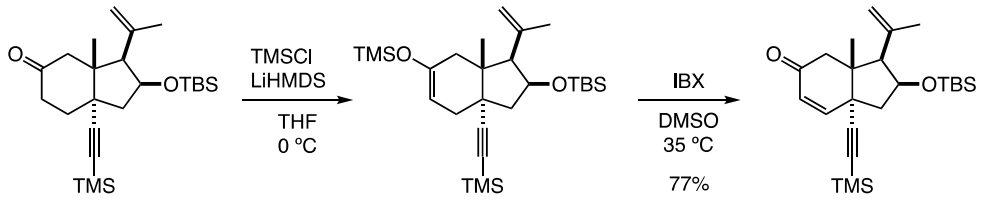
The chiral CD-ring segment was prepared as allylboronate by oxidation and coupling reaction with borylmethyl zinc reagent from the bicyclic alcohol reported by Dr. Hiramatsu. The intermolecular addition reaction of the allylboronate with the A-ring aldehyde afforded the desired adduct as a single diastereomer, albeit in moderate yield. The construction of the ABCD skeleton of tubiferal A was accomplished by cyclization of the B-ring moiety using intramolecular alkylation of chloro nitrile.

2-3. Experimental Section



16 **2.2**

Ketone 2.2: To a solution of alcohol **16** (6.16 g, 20.3 mmol) and 2,6-lutidine (3.52 mL, 30.1 mmol) in CH_2Cl_2 (50 mL) was added TBSOTf (4.89 mL, 21.3 mmol) at −78 ºC. After stirring for 0.5 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 40/1) afforded ketone **2.2** (7.39 g, 17.7 mmol, 87%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.98 (1H, s), 4.90 (1H, s), 4.58 (1H, ddd, *J* = 11.5, 6.9, 4.6 Hz), 2.96 (1H, d, *J* = 6.9 Hz), 2.80 (1H, d, *J* =14.9 Hz), 2.71 (1H, dddd, *J* = 20.0, 16.6, 12.0, 8.0 Hz), 2.52 (1H, dd, *J* = 13.2, 8.0 Hz), 2.37–2.33 (1H, m), 2.29 (1H, d, *J* = 14.9 Hz), 2.02–1.90 (2H, m), 1.79 (3H, s), 1.64 (1H, dd, *J* = 13.2, 4.6 Hz), 1.04 (3H, s), 0.86 (9H, s), 0.15 (9H, s), 0.03 (3H, s), 0.02 (3H, s).

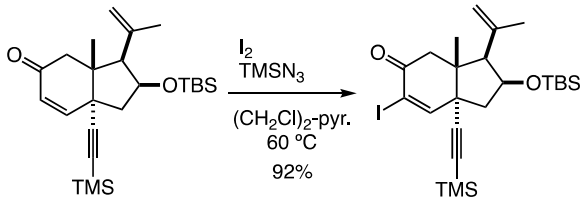


2.2 **S8** **2.3**

Enone 2.3: To a cooled (−78 ºC) solution of ketone **2.2** (7.39 g, 17.7 mmol) in THF (60 mL) was added LiHMDS (1.0 M in toluene, 21.2 mL, 21.2 mmol). After stirring for 0.5 h, TMSCl (2.69 mL, 21.2 mmol) was added to the mixture. After stirring at 0 ºC for 1 h, Et_3N and a saturated aqueous $NaHCO_3$ solution were added to the reaction mixture at the same temperature. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers

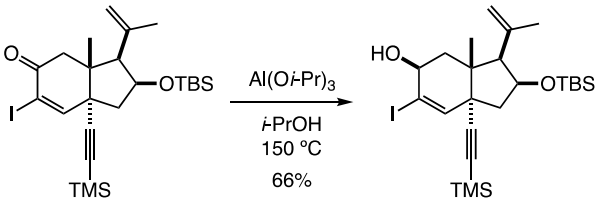
were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was used for the next step without further purification.

To the above crude enol silyl ether in DMSO (44 mL) was added IBX (0.4 M in DMSO, 221 mL, 88.5 mmol). After stirring at 35 ºC for 24 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 50/1) afforded enone **2.3** (5.35 g, 12.8 mmol, 72% for 2 steps) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.89 (1H, d, *J* = 9.2 Hz), 5.93 (1H, d, *J* = 9.2 Hz), 4.97 (1H, s), 4.89 (1H, s), 4.63 (1H, ddd, *J* = 13.2, 5.7, 4.6 Hz), 3.13 (1H, d, *J* = 6.9 Hz), 2.92 (1H, d, *J* = 16.6 Hz), 2.57 (1H, d, *J* = 13.2, 7.5 Hz), 2.53 (1H, d, *J* =16.6 Hz), 1.84–1.81 (4H, m), 1.23 (3H, s), 0.86 (9H, s), 0.11 (9H, s), 0.05 (6H, s).



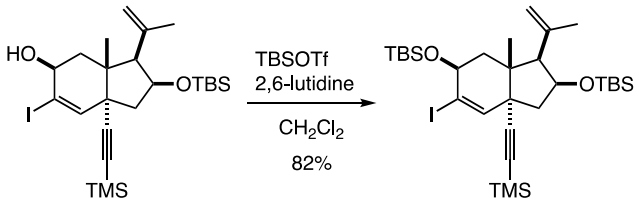
2.3 **2.20**

Iodide 2.20: To a mixture of enone **2.3** (3.17 g, 7.6 mmol) and $TMSN_3$ (1.99 mL, 15.2 mmol) in $(CH_2Cl)_2$-pyridine (2:1 38 mL) was added iodine (3.85 g, 15.2 mmol) at 0 ºC in two portions. After stirring at 60 ºC for 15 h, the reaction was quenched with an aqueous $Na_2S_2O_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 50/1) afforded iodide **2.8** (3.80 g, 7.01 mmol, 92%) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, s), 4.98 (1H, s), 4.88 (1H, s), 4.63–4.59 (1H, s), 3.10 (1H, d, *J* = 6.3 Hz), 3.07 (1H, d, *J* = 16.6 Hz), 2.88 (1H, d, *J* = 16.6 Hz), 2.57 (1H, dd, *J* = 12.6, 7.5 Hz), 1.86 (1H, dd, *J* = 12.6, 4.6 Hz), 1.79 (3H, s), 1.24 (3H, s), 0.85 (9H, s), 0.12 (9H, s), 0.04 (6H, s).



2.20 **S9**

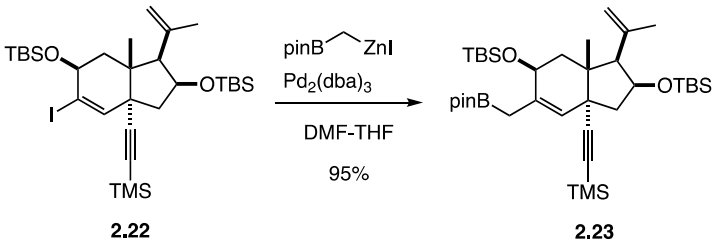
Allyl alcohol S9: To a solution of enone **2.20** (898 mg, 1.65 mmol) in *i*-PrOH (8.3 mL) was added Al(O*i*-Pr)$_3$ (101 mg, 0.50 mmol). After stirring at 150 ºC for 6 h, the reaction mixture was cooled to room temperature, and concentrated under reduce pressure. After 1M HCl (5 mL) was added to the residue, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 50/1 to 40/1) afforded enone **2.20** (555 mg, 1.02 mmol) along with alcohol **S9** (245 mg, 0.45 mmol, 27%) as a colorless oil. The recovered **2.20** was subjected to the same condition with Al(O*i*-Pr)$_3$ (100 mg, 0.49 mmol) in *i*-PrOH (5.0 mL) at 150 ºC for 5 h. The same work up procedure of the reaction mixture as described above afforded the alcohol **S9** (349 mg, 0.641 mmol, 66% for 2 cycles) as a colorless oil along with enone **2.20** (66.4 mg, 0.122 mmol, 11%): ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.56 (1H, s), 4.59 (1H, s), 4.93 (1H, s), 4.55 (1H, ddd, *J* = 12.1, 7.5, 4.6 Hz), 4.26 (1H, t, *J* = 5.7 Hz), 2.85 (1H, d, *J* = 7.5 Hz), 2.47 (1H, dd, *J* = 13.8, 7.5 Hz), 2.43 (1H, dd, *J* =12.6, 7.5 Hz), 2.13 (1H, d, *J* = 13.8 Hz), 2.05 (1H, d, *J* = 4.6 Hz), 1.80 (3H, s), 1.73 (1H, dd, *J* = 12.6, 5.2 Hz), 1.24 (3H, s), 0.85 (9H, s), 0.12 (9H, s), 0.02 (3H, s), 0.01 (3H, s).



S9 **2.22**

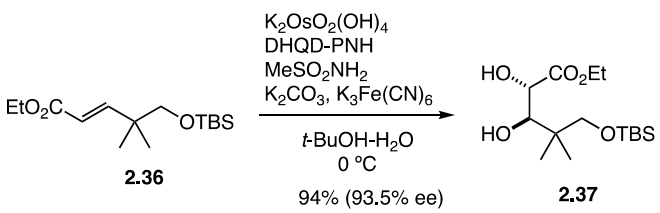
Iodide 2.22: To a solution of alcohol **S9** (594 g, 1.09 mmol) and 2,6-lutidine (404 µL, 2.24 mmol) in CH_2Cl_2 (5.6 mL) was added TBSOTf (309 µL, 1.34 mmol) at −78 ºC. After stirring at room temperature for 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic

layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 50/1) afforded iodide **2.22** (589 mg, 0.895 mmol, 82%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.52 (1H, d, *J* = 1.2 Hz), 4.93 (1H, s), 4.89 (1H, s), 4.55 (1H, ddd, *J* = 12.1, 7.4, 5.2 Hz), 4.27 (1H, d, *J* = 6.3 Hz), 2.84 (1H, d, *J* = 7.4 Hz), 2.44–2.37 (2H, m), 1.98 (1H, d, *J* = 13.8 Hz), 1.79 (3H, s), 1.72 (1H, dd, *J* = 12.6, 4.6 Hz), 1.24 (3H, s), 0.94 (9H, s), 0.84 (9H, s), 0.20 (3H, s), 0.12 (9H, s), 0.09 (3H, s), 0.02 (3H, s), 0.01 (3H, s).



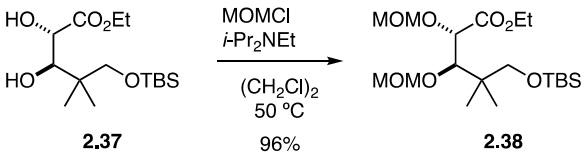
2.22 **2.23**

Allylboronate 2.23: To a mixture of iodide **2.22** (492 mg, 0.800 mmol) and borylmethyl zinc iodide (1.0 M in THF, 1.2 mL, 1.2 mmol), which was separately prepared by treatment of zinc (196 mg, 3.00 mmol) in THF (1.5 mL) with boryl methyl iodide (402 mg, 1.50 mmol) at room temperature for 10 min, was added $Pd_2(dba)_3$ (73.2 mg, 0.080 mmol). After stirring 0.5 h, the mixture was directly filtered through a short pad of silica, using eluent *n*-hexane/EtOAc = 10/1. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 40/1) affording boronate **2.23** (514 mg, 0.763 mmol, 95%) as a brown oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.51 (1H, s), 4.90 (2H, s), 4.56 (1H, ddd, *J* = 12.0, 7.4, 4.6 Hz), 4.34 (1H, d, *J* = 6.9 Hz), 2.86 (1H, d, *J* = 7.4 Hz), 2.38–2.30 (2H, m), 1.85–1.75 (5H, m), 1.69–1.65 (2H, m), 1.23 (6H, s), 1.22 (6H, s), 1.19 (3H, s), 0.89 (9H, s), 0.84 (9H, s), 0.09 (15H, s), 0.01 (6H, s).



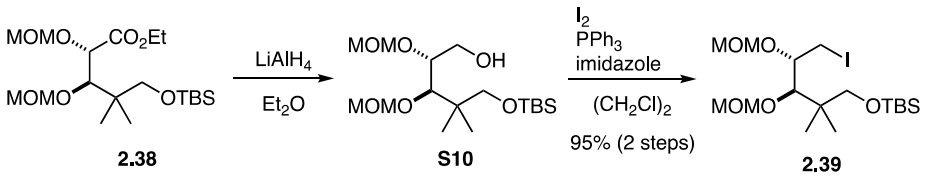
2.36 **2.37**

Diol 2.37: To a mixture of $K_3Fe(CN)_6$ (24.4 g, 74.1 mmol), K_2CO_3 (10.2 g, 74.1 mmol), $MeSO_2NH_2$ (2.35 g, 24.7 mmol) and DHQD-PHN (620 mg, 1.24 mmol) in *t*-BuOH-H_2O (1:1, 250 mL) was added $K_2OsO_2(OH)_4$ (91 mg, 0.25 mmol) at room temperature. After stirring at the same temperature for 10 min, the mixture was cooled to 0 ºC, and a solution of (*E*)-unsaturated ester **236** (7.07 g, 24.7 mmol) in *t*-BuOH (20 mL) was added. After stirring at 0 ºC for 24 h, $Na_2S_2O_3$ was added, and the mixture was stirred at 0 ºC for 1 h. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 3/1) afforded optical active diol **2.37** (7.43 g, 23.2 mmol, 94%) as a yellow oil. The enantiomer excess (ee) of **2.37** was determined to be 93.5% ee by HPLC analysis (CHIRALCEL AD-H column, 5 μm, 250×4.6 mm, *n*-hexane/*i*-propanol (98:2 v/v as an eluent), flow rate = 1.0 mL/min, λ = 220 nm, major enantiomer t_R = 12.9 min, minor enantiomer t_R = 16.3 min). The characterization data of **2.37** are identical to those of *ent*-**2.37** reported in the literature[32].



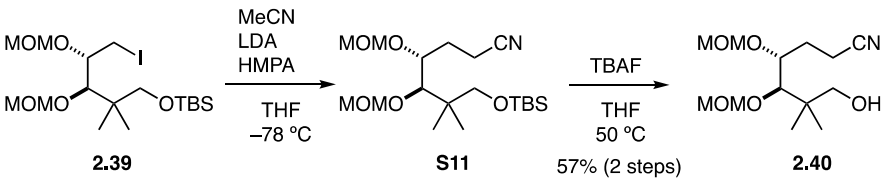
2.37 96% **2.38**

Ester 2.38: To a solution of diol **2.37** (859 mg, 2.68 mmol) and *i*-Pr_2NEt (2.73 mL, 16.1 mmol) in $(CH_2Cl)_2$ (2.7 mL) was added MOMCl (604 μL, 8.03 mmol) at 0 ºC. After stirring at 50 ºC for 7 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4/1) afforded ester **2.38** (1.05 g, 2.56 mmol, 96%) as a colorless oil. The characterization data of **2.38** are identical to those of *ent*-**2.38** reported in the literature[32].



Iodide 2.39: To a mixture of $LiAlH_4$ (243 mg, 6.40 mmol) in Et_2O (5.0 mL) was added dropwise a solution of ester **2.38** (1.05 g, 2.56 mmol) in Et_2O (3.5 mL) at 0 ºC. After stirring at 0 ºC for 1.5 h, H_2O (0.25 mL), 15% aqueous NaOH solution (0.25 mL), and H_2O (0.75 mL) was sequentially added to the reaction mixture at 0 ºC. Then, the resulting suspension was stirred room temperature for 1 h, dried over $MgSO_4$ for 1 h with stirring, and filtered through a pad of Celite®, which was rinsed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was used for the next step without further purification.

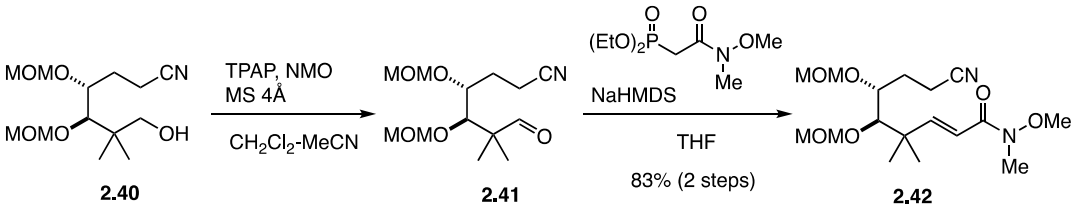
To a mixture of the above crude alcohol **S10** in $(CH_2Cl)_2$ (5.2 mL) was added I_2 (844 mg, 3.33 mmol), PPh_3 (873 mg, 3.33 mmol), and imidazole (244 mg, 3.58 mmol) at 0 ºC. After stirring at room temperature for 1.5 h, the reaction was quenched with a saturated aqueous $Na_2S_2O_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded iodide **2.39** (1.16 mg, 2.43 mmol, 95% for 2 steps) as a colorless oil. The characterization data of **2.39** are identical to those of *ent*-**2.39** reported in the literature[32].



Alcohol 2.40: To a 1.0 M in THF solution of CH_2LiCN (16.7 mmol), which was prepared by treatment of MeCN (872 µL, 16.7 mmol) with LDA (1.0 M in THF solution, 16.7 mL, 16.7 mmol) at −78 ºC for 0.5 h, was added HMPA (5.8 mL, 33.4 mmol) at −78 ºC. After stirring at −78 ºC for 10 min, a solution of iodide **2.39** (3.18 g, 6.68 mmol) in THF (10 mL) was added at −78 ºC. After stirring at the same temperature for 1 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was

extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was used for the next step without further purification.

To a solution of the above crude nitrile **S11** in THF (16 mL) was added TBAF (1.0 M in THF, 13.3 mL, 13.3 mmol) at 0 ºC. After stirring at 50 ºC for 17 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 2/3) afforded alcohol **2.40** (1.04 g, 3.79 mmol, 57% for 2 steps) as an orange oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.75–4.73 (2H, m), 4.67 (2H, d, *J* =6.9 Hz), 3.81 (1H, td, *J* = 9.2, 4.6 Hz), 3.57 (1H, dd, *J* = 11.5, 6.3 Hz), 3.46 (1H, d, *J* = 5.2 Hz), 3.44 (3H, s), 3.43 (3H, s), 3.26–3.21 (1H, s), 2.86–2.84 (1H, m), 2.51 (2H, t, *J* = 7.5 Hz), 2.04–1.94 (2H, m), 1.00 (3H, s), 0.91 (3H, s).

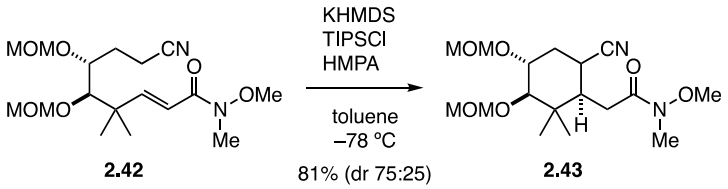


2.40 **2.41** **2.42**

Weinreb amide 2.42: To a mixture of alcohol **2.40** (601 mg, 2.18 mmol), freshly activated and powdered molecular sieves 4Å (MS 4Å) (1.10 g), and NMO (383 mg, 3.27 mmol) in CH_2Cl_2–MeCN (10:1, 11 mL) was added TPAP (38.3 mg, 0.109 mmol) at 0 ºC, and the mixture was stirred at room temperature for 1 h. Further TPAP (38.3 mg, 0.109 mmol) was added at 0 ºC, and the mixture was stirring at room temperature for additional 1 h. The reaction mixture was filtered through a pad of Celite®, which was rinsed EtOAc. The filtrate was concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography, using eluent *n*-hexane/EtOAc = 1/1. The residue was used for the next step without further purification

To a solution of diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (584 µL, 2.83 mmol) in THF (2.8 mL) was slowly added NaHMDS (1.16 M in THF, 2.35 mL, 2.72 mmol) at 0 ºC. After mixture was stirred at 0 ºC for 30 min, a solution of the above crude aldehyde **2.41** in

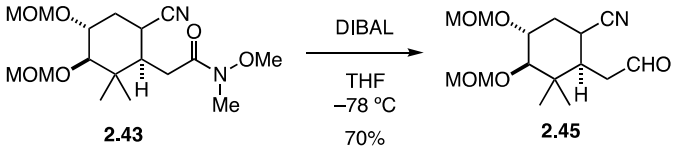
THF (10 mL) was added at 0 ºC. After stirring at room temperature for 2 h, the reaction mixture was quenched with a saturated NH_4Cl solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 1/3) afforded Weinreb amide **2.42** (648 mg, 1.81 mmol, 83% for 2 steps) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.09 (1H, d, *J* = 15.5 Hz), 6.37 (1H, d, *J* = 16.1 Hz), 4.75 (1H, d, *J* = 6.9 Hz), 4.68 (1H, d, *J* = 6.9 Hz), 4.66 (1H, d, *J* = 6.9 Hz), 4.61 (1H, d, *J* = 6.9 Hz), 3.72–3.70 (4H, m), 3.43 (3H, s), 3.39 (3H, s), 3.35 (1H, d, *J* = 4.6 Hz), 2.25 (1H, s), 2.48–2.45 (2H, m), 1.95–1.90 (1H, m), 1.86–1.80 (1H, m), 1.19 (3H, s), 1.17 (3H, s).



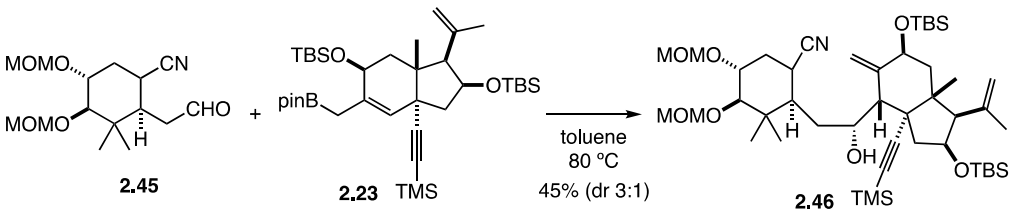
2.42 **2.43**

Cyclic Weinreb amide 2.43: To a mixture of (*E*)-unsaturated Weinreb amide **2.42** (90.4 mg, 0.252 mmol) in toluene (2.5 mL), TIPSCl (80.9 µL, 0.378 mmol) and HMPA (131.6 µL, 0.757 mmol) was slowly added KHMDS (0.5 M in toluene, 1.0 mL, 0.50 mmol) at −78 ºC, and the reaction mixture was stirried at the same temperature for 30 min. Then, to the mixture was added TBAF (1.0 M in THF, 1.3 mL, 1.3 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution at −78 ºC. The mixture was allowed to warm up to room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 20/1 to 1/2) afforded Weinreb amide **2.43** (73.0 mg, 0.204 mmol, 81%, d.r. 38:37:24:1) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.90 (0.38H, d, *J* = 6.9 Hz), 4.86 (0.38H, d, *J* = 6.3 Hz), 4.75 (0.62H, d, *J* = 6.9 Hz), 4.73–4.68 (2H, m), 4.65 (0.38H, d, *J* = 6.9 Hz), 4.60 (0.24H, d, *J* = 6.3 Hz), 3.89–3.82 (0.38H, m), 3.37–3.74 (3.24H, m), 3.52 (0.38H, td, *J* = 10.6, 4.7 Hz), 3.42 (1.2H, s), 3.40 (1.8H, s), 3.38 (1.8H, s), 3.37 (1.2H, s), 3.29–3.26 (0.62H, m), 3.21 (3H, s), 3.15–3.13 (0.24H, m), 3.09 (0.38H, d, *J* = 9.2 Hz), 3.06 (0.38H, d, *J* = 9.7 Hz), 2.76–2.67 (1.14H, m),

2.62–2.50 (1.24H, m), 2.43–2.33 (1.14H, m), 2.22 (0.24H, td, *J* = 13.2, 4.6 Hz), 2.08–2.04 (0.76H, m), 1.96–1.90 (0.24H, m), 1.76–1.63 (0.62H, m), 1.09 (1.14H, s), 1.07 (1.14H, s), 1.04 (1.14H, s), 1.01 (0.72H, s), 0.88 (0.72H, s), 0.82 (1.14H, s).

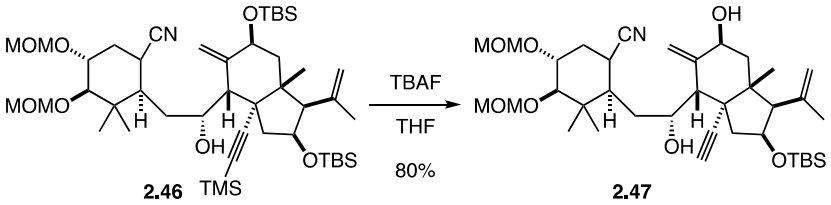


Aldehyde 2.45: To a solution of Weinreb amide **2.43** (73.0 mg, 0.204 mmol) in THF (1.0 mL) was DIBAL (1.02 M in *n*-hexane, 300 μL, 0.305 mmol) at −78 ºC. After stirring at the same temperature for 1 h, the reaction was quenched with a aqueous sodium potassium tartrate solution at −78 ºC, and the mixture was vigorously stirred at room temperature until both phase became clear. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 3/2) afforded aldehyde **2.45** (58.2 mg, 0.150 mmol, 73%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.85 (1H, s), 4.89–4.59 (4H, m), 3.85 (0.38H, td, *J* = 10.9, 4.0 Hz), 3.75–3.72 (0.24H, m), 3.59 (0.38H, d, *J* = 4.6 Hz), 3.56–3.51 (0.38H, m), 3.42–3.37 (6H, m), 3.25 (0.24H, d, *J* = 7.4 Hz), 3.21–3.19 (0.38H, m), 3.11–3.03 (0.76H, m), 2.92–2.87 (0.38H, m), 2.82 (0.38H, d, *J* = 9.2 Hz), 2.79–2.77 (0.62H, m), 2.75–2.65 (0.72H, m), 2.59–2.54 (0.76H, m), 2.46–2.42 (0.38H, m), 2.36–2.32 (0.62H, m), 2.27–2.23 (0.24H, m), 2.15–2.11 (0.38H, m), 1.75–1.67 (0.76H, m), 1.08 (0.72H, s), 1.06 (1.14H, s), 1.05 (1.14H, s), 1.01 (1.14H, s), 1.00 (1.14H, s), 0.80 (0.72H, s).



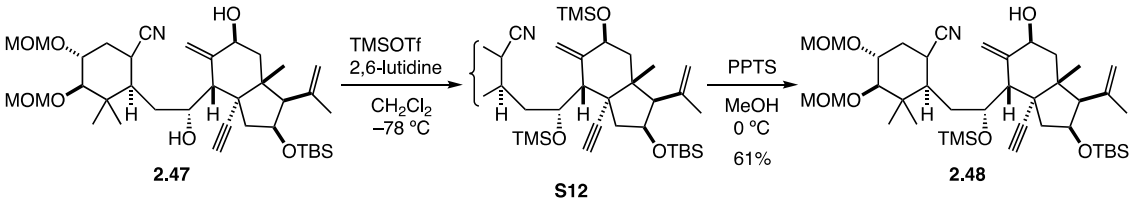
Alcohol 2.46: To a solution of aldehyde **2.45** (58.2 mg, 0.149 mmol) in toluene (500 μL) was added a solution of allylboronate **2.23** (77.3 g, 0.115 mmol) in toluene (150 μL). After stirring

for 18 h 80 ºC, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1) afforded alcohol **2.46** (43.5 g, 0.0514 mmol, 45% d.r. 75:25) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.42 (0.75H, s), 5.36 (0.25H, s), 5.10 (1H, s), 4.95–4.84 (4H, m), 4.78–4.70 (2H, m), 4.52–4.49 (1H, m), 4.08–4.05 (0.25H, m), 3.90–3.84 (0.75H, m), 3.78–3.75 (0.75H, m), 3.63–3.60 (0.75H, m), 3.43 (2.25H, s), 3.41 (0.75H, s), 3.38 (3H, s), 3.27 (0.25H, d, *J* = 5.2 Hz), 3.10–3.06 (0.5H, m), 3.03 (1H, d, *J* = 9.2 Hz), 2.90 (1H, d, *J* = 6.9 Hz), 2.85 (0.75H, s), 2.63 (0.25H, q, *J* = 6.9 Hz), 2.57–2.47 (2H, m), 2.37 (0.75H, ddd, *J* = 13.8, 4.6, 2.9 Hz), 2.27–2.05 (2.25H, m), 1.97 (0.75H, d, *J* = 14.9 Hz), 1.80 (3H, s), 1.74–1.66 (2H, m), 1.64–1.59 (1H, m), 1.51–1.46 (1.25H, m), 1.27 (3H, s), 1.20 (0.75H, s), 1.12 (2.25H, s), 1.08 (2.25H, s), 1.01 (0.75H, s), 0.90 (9H, s), 0.86 (6.75H, s), 0.84 (2.25H, s), 0.15 (2.25H, s), 0.13 (6.75H, s), 0.04 (6H, s), 0.02 (6H, s).



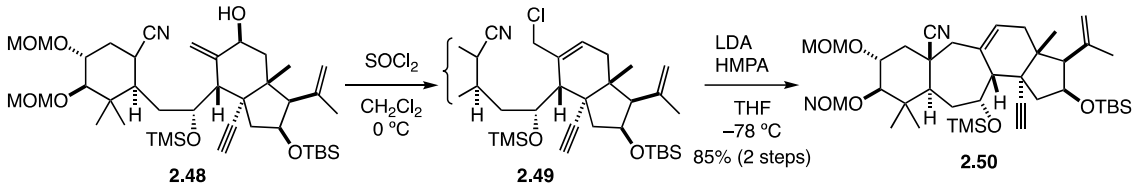
Diol 2.47: To a solution of the alcohol **2.46** (12.4 mg, 0.0146 mmol) in THF (150 µL) was added TBAF (1.0 M in THF, 44 µL, 0.044 mmol) at 0 ºC. After stirring at room temperature for 5 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution at 0 ºC. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 1/1) afforded diol **2.47** (6.9 mg, 0.0117 mmol, 80%, d.r. 3:1) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.44 (1H, s), 5.25 (0.25H, s), 5.19 (0.75H, s), 5.00 (1H, s), 4.93–4.85 (2.75H, m), 4.76 (0.75H, d, *J* = 6.3 Hz), 4.72–4.69 (2.25H, m), 4.62 (0.25H, d, *J* = 6.3 Hz), 4.56 (1H, td, *J* = 11.5, 6.9, 2.9 Hz), 3.90–3.78 (2H, m), 3.62–3.60 (0.75H, m), 3.43 (3H, s), 3.38 (3H, s), 3.29 (0.25H, d, *J* = 5.7 Hz), 3.09–3.06 (0.25H, m), 3.03 (075H, d, *J* = 9.8 Hz), 2.90 (1H, d, *J* = 6.9 Hz), 2.72 (1H, s), 2.67–2.55 (3H, m), 2.44–2.35 (2H,

m), 2.31 (1H, s), 2.01 (1H, d, *J* = 14.9 Hz), 1.81 (3H, s), 1.78–1.70 (2H, m), 1.48–1.43 (1H, m), 1.32–1.24 (4H, m), 1.11 (3H, s), 1.09 (3.25H, s), 1.02 (0.75H, s), 0.86 (9H, s), 0.02 (6H, s).



Alcohol 2.48: To a mixture of diol **2.47** (6.9 mg, 11.7 μmol) and 2,6-lutidine (6.8 μL, 58.5 μmol) in CH_2Cl_2 (117 μL) was added TMSOTf (5.3 μL, 29.3 μmol) at −78 ºC. After stirring at the same temperature for 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was used for the next step without further purification.

To a mixture of the above crude product **S12** in MeOH (100 μL) was added PPTS (0.01 M in MeOH, 21 μL, 0.2 μmol) at 0 ºC. After stirring at the same temperature for 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 3/1) afforded alcohol **2.48** (5.2 g, 7.1 μmol, 61% for 2 steps, d.r. 3:1) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.32 (0.25H, s), 5.26 (0.75H, s), 4.96–4.92 (2.75H, m), 4.85 (0.75H, s), 4.76–4.69 (4H, m), 4.62 (0.25H, d, *J* = 6.9 Hz), 4.54–4.51 (1.25H, m), 4.10–4.07 (1H, m), 3.89–3.84 (1H, m), 3.43 (2.25H, s), 3.40 (0.75H, s), 3.38 (3H, s), 3.33–3.31 (1H, m), 3.01 (1H, d, *J* = 9.2 Hz), 2.93–2.91 (2H, m), 2.68 (1H, dd, *J* = 13.7, 7.4 Hz), 2.40–2.37 (1H, m), 2.32 (1H, dd, *J* = 13.7, 7.4 Hz), 2.26 (1H, s), 2.14–2.00 (2H, m), 1.94–1.86 (2H, m), 1.81 (3H, s), 1.61 (1H, dd, *J* = 13.7, 3.5 Hz), 1.54–1.52 (1H, m), 1.35–1.26 (6H, m), 1.05 (5.25H, s), 1.00 (0.75H, s), 0.88 (9H, s), 0.13 (9H, s), 0.04 (3H, s), 0.02 (3H, s).



Tetracyclic nitrile 2.50: To a solution of **2.48** (5.2 mg, 7.1 μmol) in CH_2Cl_2 (70 μL) was added $SOCl_2$ (0.2 M in CH_2Cl_2, 71 μL, 14 μmol) at 0 ºC. After stirring at the same temperature for 10 min, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was used for the next step without further purification.

To a mixture of the above crude chloride **2.49** and HMPA (6.2 μL, 35.5 μmol) in THF (100 μL) was added $LiNEt_2$ (0.5 M in THF, 35.5 μL, 17.8 μmol) at −78 ºC. After stirring at the same temperature for 10 min, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 6/1) afforded tetracyclic nitrile **2.50** (4.3 g, 6.0 μmol, 85% for 2 steps, d.r. 3:1) as a pale yellow oil: ^{1}H-NMR (500 MHz, C_6D_6): δ 5.50 (0.75H, s), 5.24 (0.25H, s), 5.21 (0.75H, s), 5.15 (1H, s), 5.08 (0.25H, d, *J* = 6.9 Hz), 5.05 (0.75H, d, *J* =6.3 Hz), 4.69–4.66 (1.5H, m), 4.63 (0.25H, d, *J* = 6.3 Hz), 4.59 (1.25H, d, *J* = 6.3 Hz), 4.49 (1H, d, *J* = 6.9 Hz), 4.32 (1H, d, *J* = 6.9 Hz), 4.10–4.04 (1H, m), 3.46 (0.25H, d, *J* = 9.8 Hz), 3.27 (3H, s), 3.20 (1.5H, d, *J* = 5.2 Hz), 3.17 (3H, s), 3.15–3.05 (1.5H, m), 2.98 (0.75H, d, *J* = 9.8 Hz), 2.90 (0.25H, d, *J* = 7.5 Hz), 2.83–2.79 (1.5H, m), 2.65–2.42 (1.5H, m), 2.31–2.24 (2H, m), 2.06–1.94 (2H, m), 1.90 (3H, s), 1.84 (1H, s), 1.62 (1H, t, *J* = 13.8 Hz), 1.50 (3H, s), 1.38 (1H, s), 1.24 (3H, s), 1.12 (3H, s), 0.98 (9H, s), 0.19 (9H, s), 0.09 (3H, s), 0.05 (3H, s).

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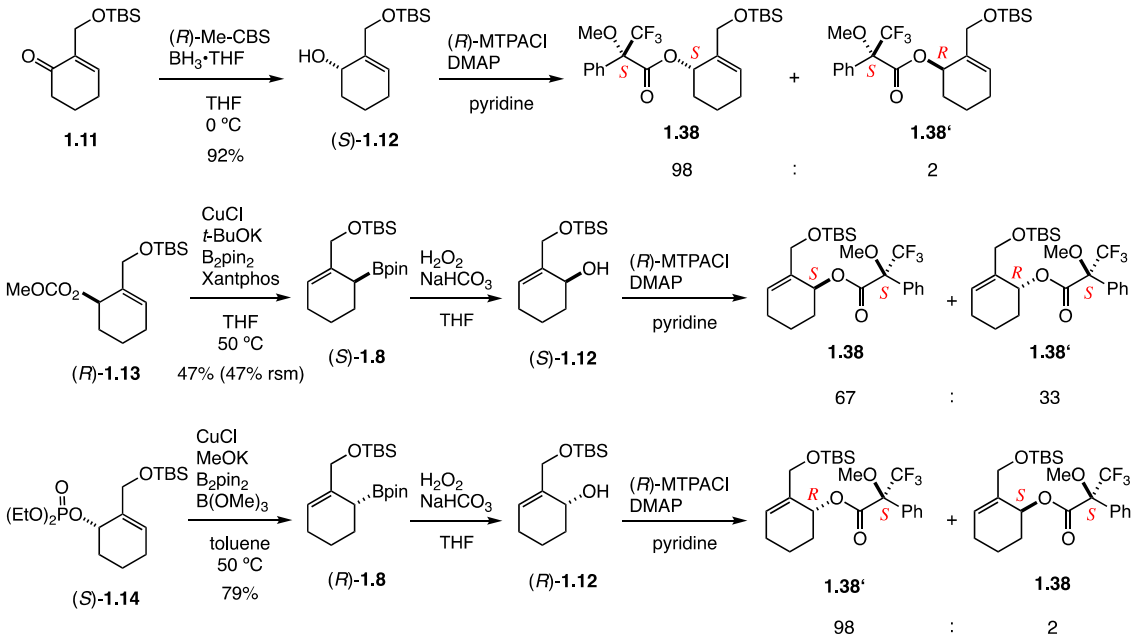

Scheme S1. Determination of enantiomeric purity of alcohol (*S*)-**1.12** and allylborane (*R*)- and (*S*)-**1.8**.

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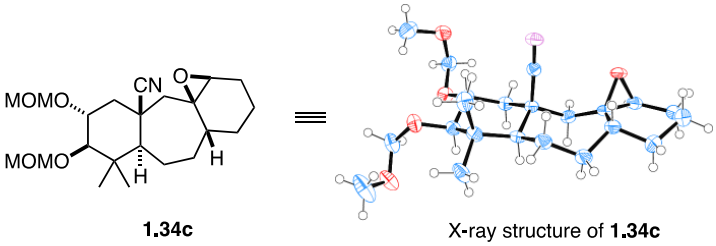
25. A small amount of each diastereomer in pure form was obtained through incomplete separation of the isomeric mixture of **1.33** by silica gel chromatography. Upon treatment with *m*CPBA, the major isomer of **1.33** was selectively converted to epoxide **1.34a**, and the minor diastereomer of **1.33** afforded a mixture of epoxides **1.34b** and **1.34c**. Since the stereochemistry of **1.34c** was determined by X-ray crystallography (see below), the author could assign the configuration of epoxide **1.34b** having the same AB ring moiety with **1.34c**. The configuration of epoxide **1.34a** was expected by assuming the oxidation of the major isomer of **1.33** from the convex face.



1.34c ≡ X-ray structure of **1.34c**

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