DISSERTATION

Synthetic Studies on Taxane Diterpenoids

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Contents

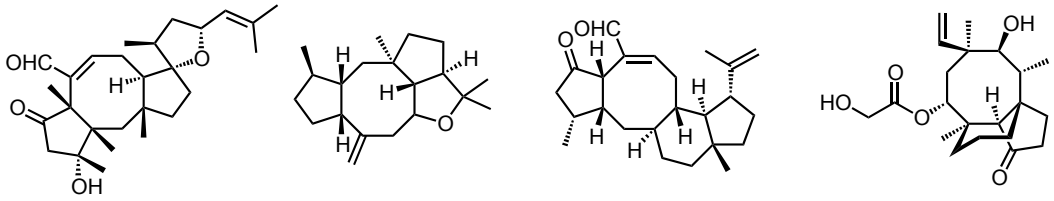
Abbreviations

Ac	:	acetyl
AIBN	:	azobisisobutyronitrile
Bn	:	benzyl
BOM	:	benzyloxymethyl
Bu	:	butyl
Bz	:	benzoyl
Cp	:	cyclopentyl
DABCO	:	1,4-diazabicyclo[2.2.2]octane
DBB	:	4,4'-di-*tert*-butylbiphenyl
DEAD	:	diethyl azodicarboxylate
DIBAL	:	diisobutylaluminium hydride
DMAP	:	*N,N*-4-dimethylaminopyridine
DME	:	1,2-dimethoxyethane
DMF	:	*N,N*-dimethylformamide
DMSO	:	dimethylsulfoxide
d.r.	:	diastereomeric ratio
EE	:	ethoxyethyl
ee	:	enantiomeric excess
Et	:	ethyl
HFIP	:	1,1,1,3,3,3-hexafluoro-2-isopropanol
KHMDS	:	potassium bis(trimethylsilyl)amide
LDA	:	lithium diisopropylamide
LHMDS	:	lithium bis(trimethylsilyl)amide
*m*CPBA	:	3-chloroperbenzoic acid
Me	:	methyl
MPM (PMB)	:	*p*-methoxylbenzyl
Ms	:	methanesulfonyl
NaHMDS	:	sodium bis(trimethylsilyl)amide
NBS	:	*N*-bromosuccinimide
NIS	:	*N*-iodosuccinimide
NMO	:	*N*-methylmorpholine oxide

Ns	:	2-nitrobenzenesulfonyl
Ph	:	phenyl
Pr	:	propyl
r.s.m.	:	recovered starting material
TBAF	:	tetra-*n*-butylammonium fluoride
TBAI	:	tetra-*n*-butylammonium iodide
TBDPS	:	*tert*-butyldiphenylsilyl
TBHP	:	*tert*-butylhydroperoxide
TBS	:	*tert*-butyldimethylsilyl
TES	:	triethylsilyl
Tf	:	trifluoromethanesulfonyl
THF	:	tetrahydrofurane
TIPS	:	triisopropylsilyl
TMEDA	:	*N,N,N',N'*-tetramethylethylenediamine
TMS	:	trimethylsilyl
Troc	:	2,2,2-trichloroethoxycarbonyl
Ts	:	*p*-toluenesulfonyl

Introduction

The medium-sized ring architecture, namely, eight- to eleven-membered carbocycles has been one of the most important motifs in aspects of synthetic organic chemistry.[1] Such rings are notoriously difficult to be formed because of both transannular interaction and substantial entropic cost in the transition state with smaller entropic costs in the product cycle.[2] In the meanwhile, these ring systems, especially an eight-membered ring, have widely been found in natural products.[1] For example, Figure 1 shows selected natural products containing eight-membered carbocycles. Even if the natural products are found to exhibit important biological activities, chemical synthesis of these compounds usually suffered from the complex structure containing the medium-sized ring.



Ophiobolin A Epoxydictymene Kalmanol Pleuromutilin

Figure 1. Natural products containing an eight-membered carbocycle

Taxol, one of the world's best selling anti-cancer drug in the 20th century, also contains an eight-membered ring. This natural product was procured in 1960s from samples of the Pacific Yew Trees (*Taxus brevifolia*) through the plant products-screening program by National Cancer Institute (NCI) and United States Department of Agriculture (USDA), to discover new drugs for antineoplastic activity. A decade later, Monroe E. Wall and Mansukh C. Wani isolated a pure sample and determined the chemical structure of taxol by X-ray crystallographic analysis.[3] The structure, as shown in Figure 2, consists of a 6-8-6 (A-B-C rings) intricate tricyclic ring system and oxetane ring on the C ring. Especially, the transannular strain of the eight-membered B ring is increased by the presence of the geminal dimethyl group and angular methyl group at the C-8 position. In addition, the '1,3 bridged' A ring contains a highly distorted bridgehead double bond.

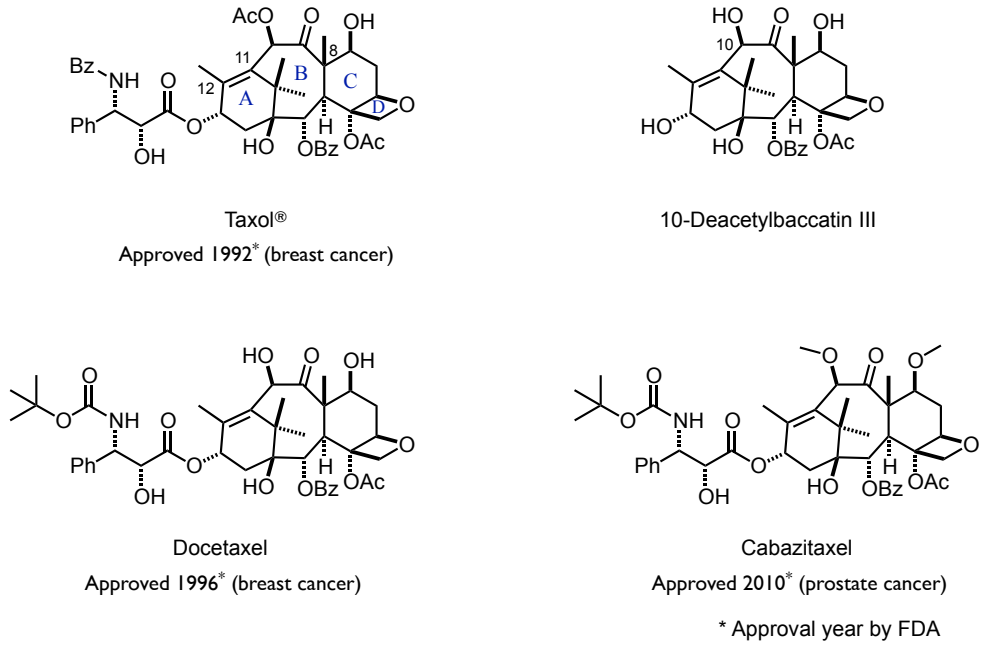


Figure 2. Taxol and several anti-cancer drugs

Early clinical trials revealed remarkable response with ovarian and breast cancer. However, only 10 g of taxol, which can treat only 5 patients, could be obtained from 1,200 kg amount of bark. The scarcity of resources in combination with the unique structure of taxol attracted attention from both chemists and biologists.[4]

Main mechanism of taxol action is stabilizing microtubules and as a result, interferes with the normal breakdown of microtubules during cell division.[4,5] Meanwhile, the industrial production of toxoids including taxol, docetaxel and cabazitaxel are currently conducted by the semi-synthesis from 10-deacetylbaccatin III, which is provided in bulk by the plant cell fermentation of the yew.

Synthetic studies by other groups

As mentioned above, taxol has been one of the most challenging targets for synthetic chemists still today.[6] The first total synthesis of taxol was achieved by R. A. Holton in 1994,[7] and K. C. Nicolaou also reported the total synthesis almost at the same time.[8] Since their initial syntheses, four total syntheses (S. J. Danishefsky in 1996, P. A. Wender in 1997, T. Mukaiyama in 1998, and I. Kuwajima in 1998) and one formal total synthesis (T. Takahashi in 2006) have appeared.[9–13] These studies can be classified according to the different strategies for constructing the fully substituted eight-membered B ring (Figure 3), namely, intramolecular

cyclization (Strategy 1), fragmentation of bicyclic framework (Strategy 2), and ring expansion of a smaller carbocycle (Strategy 3).

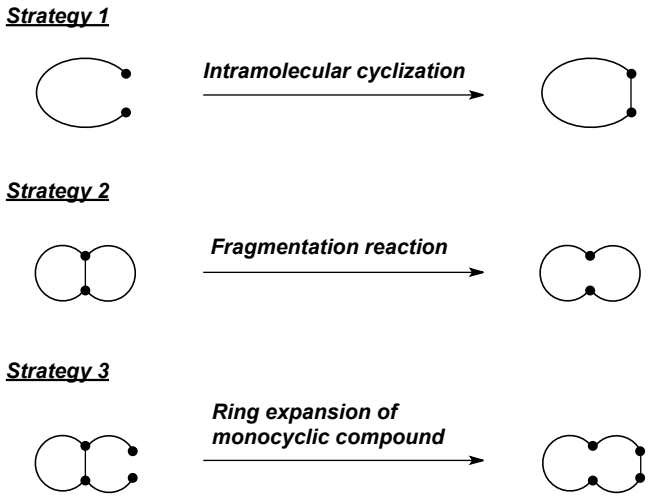
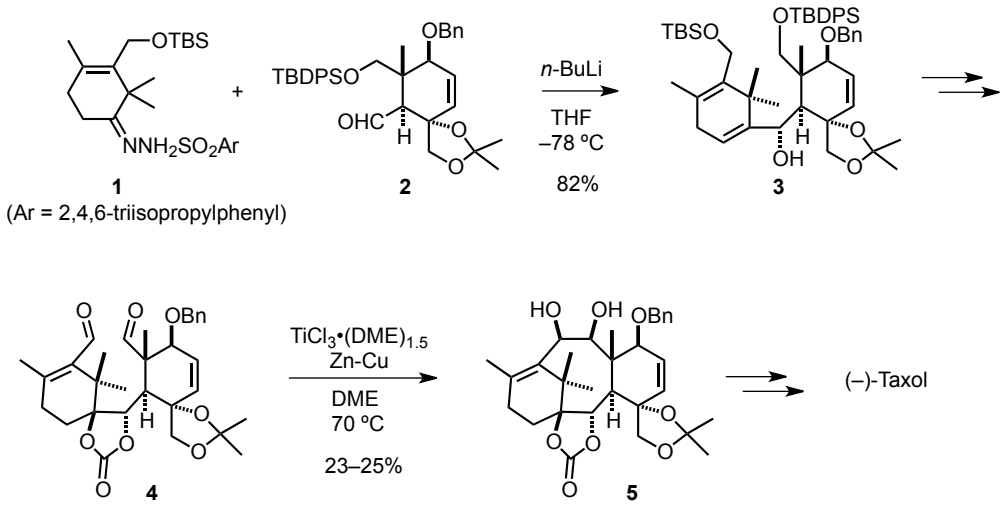


Figure 3. Three types of strategies for constructing the eight-membered ring

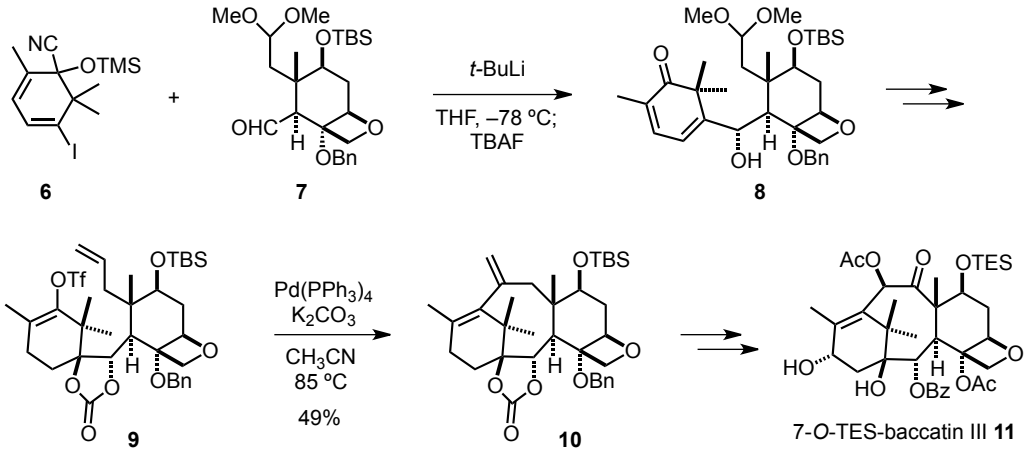
Strategy 1: Intramolecular cyclization

This type of approach is most frequently employed, because the convergent synthesis starting from the A ring segment **1** and the C ring segment **2** usually involves connection of the two segments followed by intramolecular cyclization. Nicolaou and co-workers succeeded in constructing the B ring through the intramolecular McMurry coupling reaction of dialdehyde **4**, albeit in low yield (Scheme 1).[8]



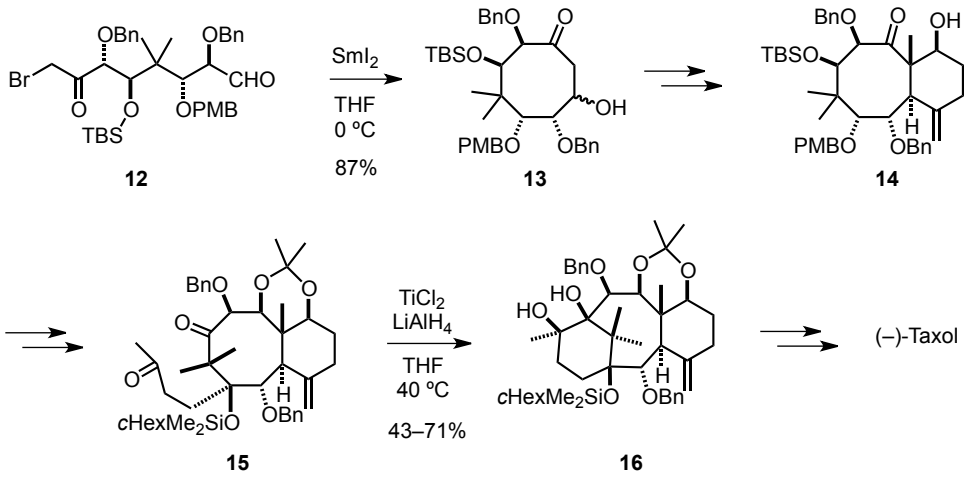
Scheme 1. Nicolaou's strategy for constructing the B ring of (–)-taxol

Danishefsky and co-workers adopted the coupling reaction of the C/D ring segment **7** with the A ring segment **6**, and subsequent intramolecular Heck reaction of compound **9** between the C10 and C11 positions led to formation of the eight-membered ring (Scheme 2).[9]



Scheme 2. Danishefsky's strategy for constructing the B ring of (–)-taxol

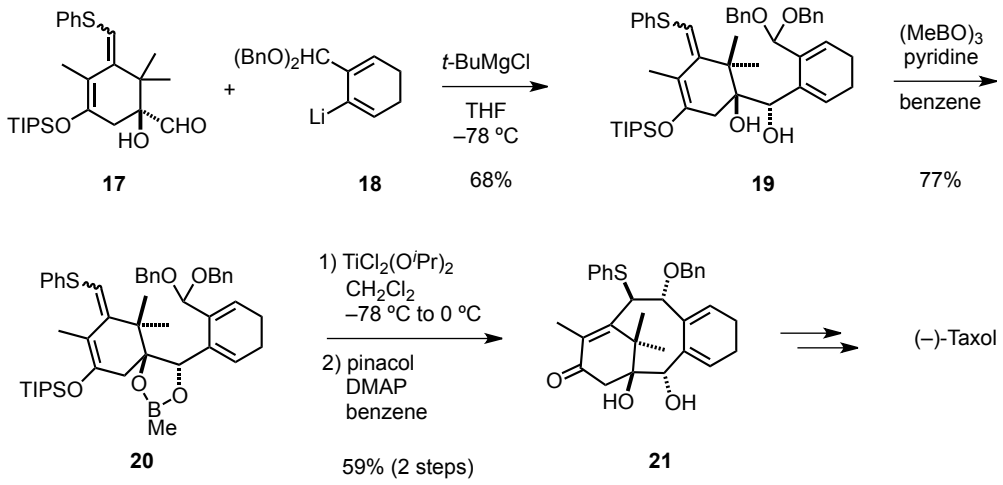
Mukaiyama and co-workers synthesized the B ring segment as a monocyclic compound **13** by the intramolecular Barbier-type aldol reaction of ketoaldehyde **12** mediated by samarium(II) iodide. The tricyclic skeleton **16** was then constructed by annulation of the C ring moiety **14** followed by the intramolecular McMurry coupling reaction of diketone **15** (Scheme 3).[11]



Scheme 3. Mukaiyama's strategy for constructing the B ring of (–)-taxol

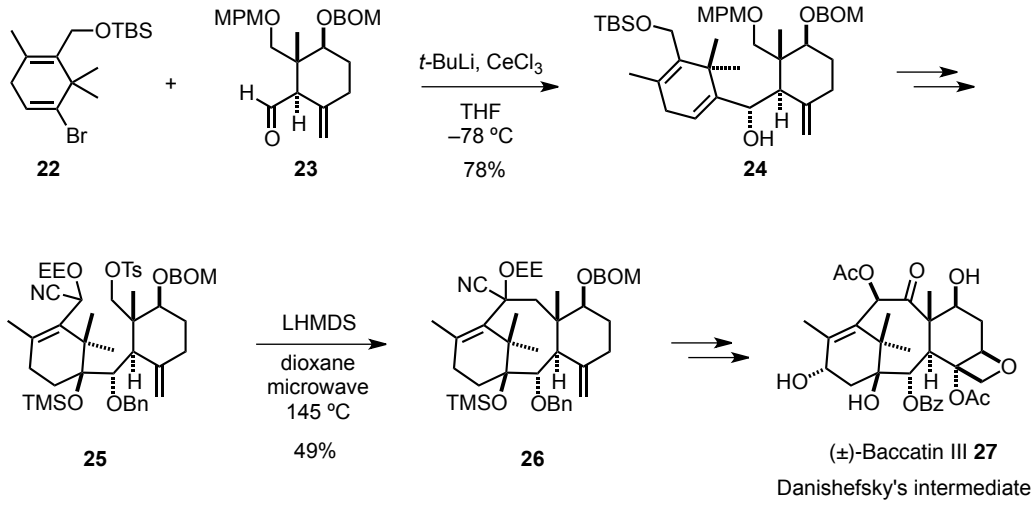
Kuwajima and co-workers constructed the eight-membered ring **21** via the intramolecular

vinylogous Mukaiyama aldol reaction of compound **20** possessing the A ring with an enol silyl ether moiety and the C ring with an acetal moiety (Scheme 4).[12]



Scheme 4. Kuwajima's strategy for constructing the B ring of (–)-taxol

Takahashi and co-workers employed the intramolecular alkylation reaction of nitrile derivative **25** under basic conditions. The cyclization precursor **25** was prepared by the addition reaction of the A ring vinylanion to the C ring aldehyde **23** (Scheme 5).[13]



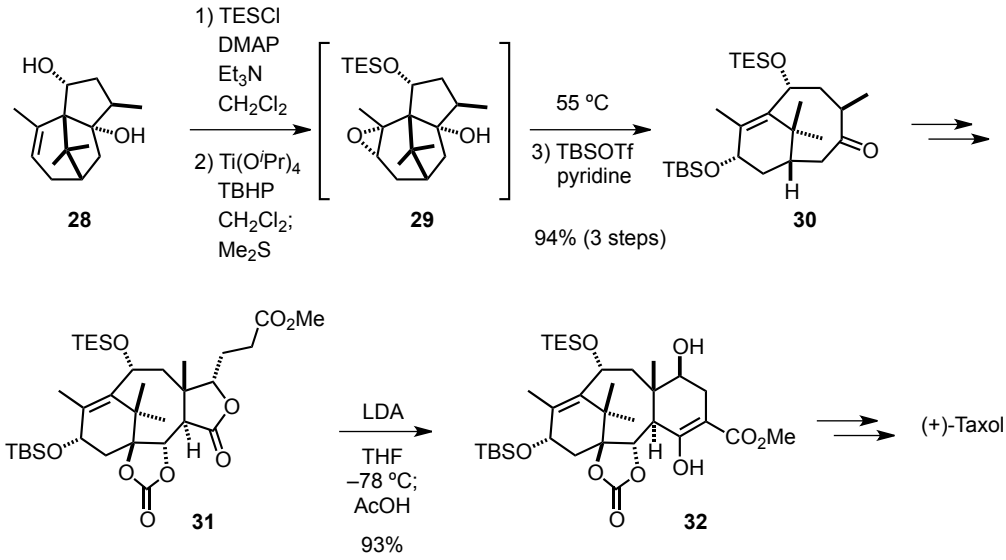
Scheme 5. Takahashi's strategy for constructing the B ring

Strategy 2: Fragmentation reaction of bicyclic compound

This type of approach is advantageous for avoiding the direct formation of an

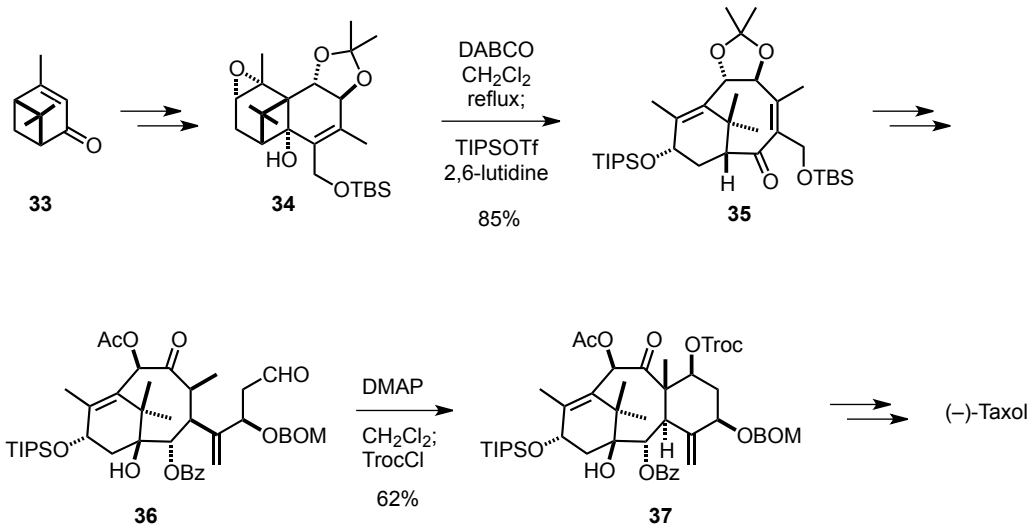
eight-membered carbocycle, while stereoselective synthesis of the fragmentation precursor with a polycyclic skeleton may also be difficult.

Holton and co-workers performed the Grob fragmentation reaction of tricyclic compound **29**, which was synthesized from (–)-patchoulene oxide, and the AB ring segment was obtained in high yield. Construction of the C ring **32** was then achieved through Dieckmann condensation of lactone **31** (Scheme 6).[7] This is the first synthesis of taxol, albeit it as the unnatural antipode. They also described correct enantiomer would be given from unnatural (–)-camphor.



Scheme 6. Holton's strategy for constructing the B ring of (+)-taxol

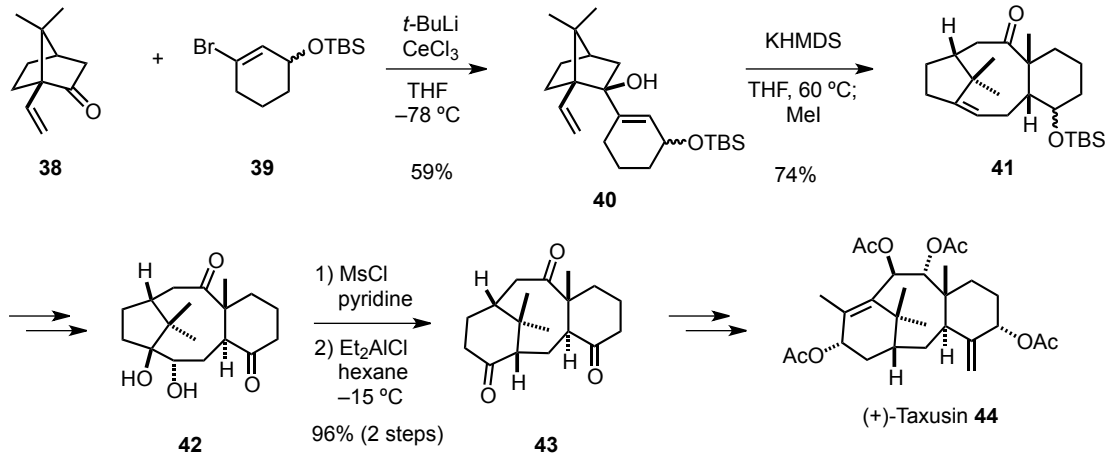
Wender and co-workers also applied Grob fragmentation of epoxy alcohol **34**, which was prepared from (–)-verbenone **33**, for constructing the AB ring framework **35**. The C ring moiety **37** was constructed by the aldol reaction of keto aldehyde **36** (Scheme 7).[10]



Scheme 7. Wender's strategy for constructing the B ring of (–)-taxol

Strategy 3: Ring expansion reaction

This strategy was adopted for the total synthesis of (+)-taxusin by L. A. Paquette. The oxy-Cope rearrangement of alcohol **40** under basic conditions afforded 5-9-6 tricyclic compound **41**, which was transformed into triketone **43** with the 6-8-6 skeleton through the second rearrangement step (Scheme 8).[14]



Scheme 8. Paquette's strategy for constructing the B ring of (+)-taxusin

Strategy 4: Cycloaddition approach for constructing an eight-membered carbocycle

There remains another strategy in construction of an eight-membered carbocycle, that is, a cycloaddition reaction between two acyclic compounds (Figure 4).

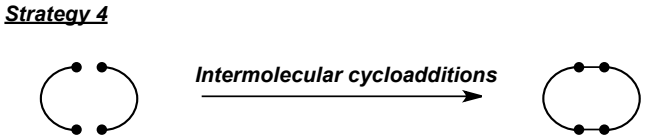


Figure 4. Intermolecular cycloaddition strategy

It should be noted that a cycloaddition reaction which produces two C-C bonds in one-stage is advantageous from the viewpoint of efficiency.[15] For example, the Diels-Alder reaction is known as one of the most important method for constructing a six-membered ring, and the [4+3] cycloaddition reaction of a conjugated diene and a 2-oxyallyl cation species is widely used for the synthesis of cycloheptanone derivatives (Figure 5).[16]

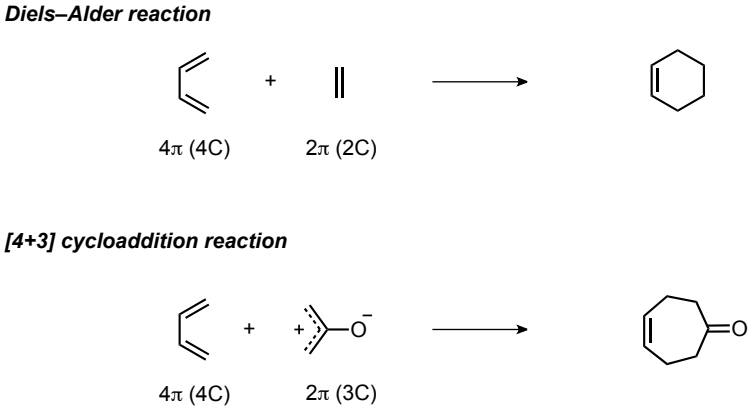
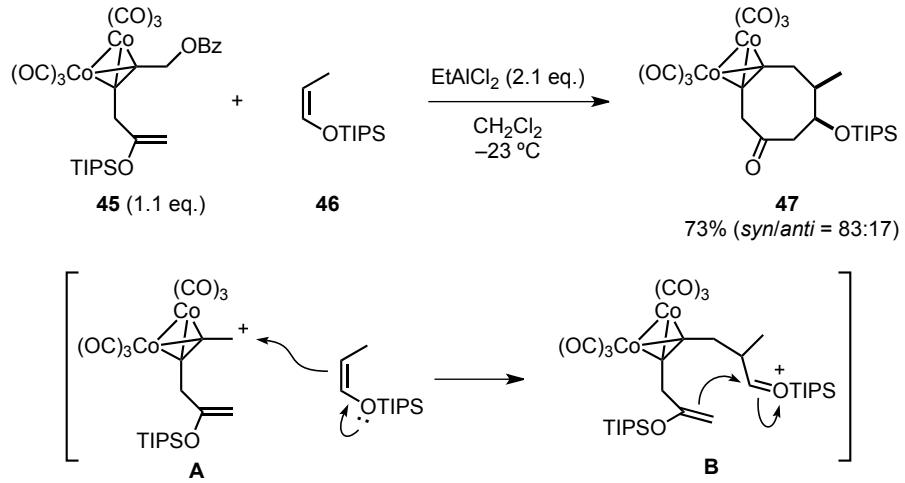


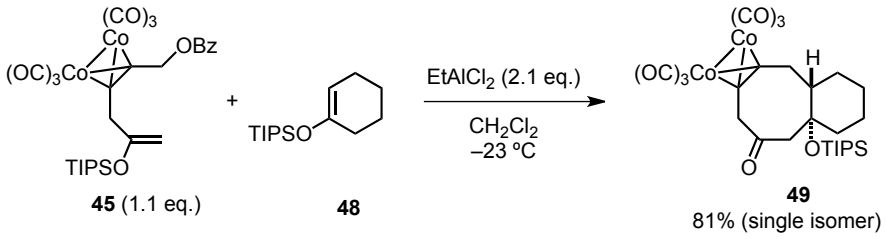
Figure 5. Diels-Alder reaction and [4+3] cycloaddition reaction

On the other hand, there are few methods for the construction of an eight-membered ring by cycloaddition approaches. Dr. Katsuhiko Mitachi, who was working on the development of higher order cycloaddition reactions in the same laboratory of the author, reported the formal [6+2] cycloaddition reaction using a dicobalt acetylene complex **45** having an enol silyl ether moiety as a new six-carbon unit (Scheme 9).[17] In the presence of $EtAlCl_2$, enol silyl ether **46** reacted with the six-carbon unit **45** to give a cyclooctanone derivative in good yield with high diastereoselectivity. The reaction proceeds through intermolecular addition of an enol triisopropylsilyl ether with the dicobalt propargyl cation **A** giving rise to the silyloxonium ion **B** which in turn undergoes an intramolecular addition reaction.



Scheme 9. Formal [6+2] cycloaddition reaction of **45** with an enol silyl ether

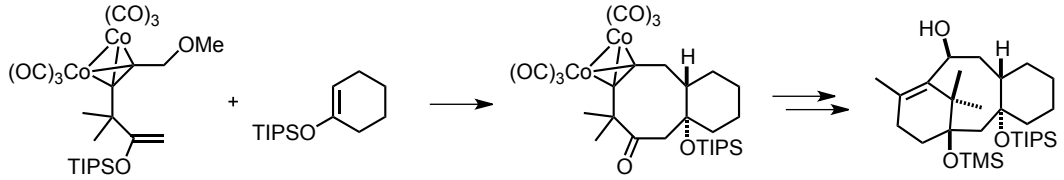
While concerted cycloaddition like the Diels-Alder reaction usually affords a *cis*-fused bicyclic compound from a cycloalkene derivative, the stepwise mechanism of the [6+2] cycloaddition reaction allowed the formation of a *trans*-fused bicyclic compound **49** from 1-(triisopropylsilyl-oxy)cyclohexene **48** (Scheme 10).



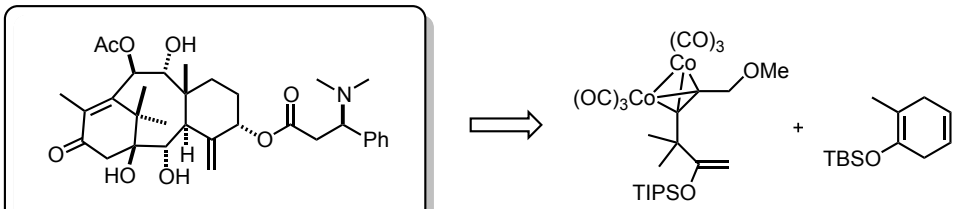
Scheme 10. The [6+2] cycloaddition reaction of cycloalkane derivative

The structure of the cycloadduct **49** is similar with the BC ring skeleton of taxane diterpenoids, and the result led the author to design a new route for the taxane diterpenoids. In this dissertation, synthetic studies of taxane diterpenoids through completely new approach will be described. In chapter I, construction of the taxane skeleton on the basis of the [6+2] cycloaddition reaction is described. In chapter II, synthetic studies on taxine B is to be described.

Chapter I



Chapter II

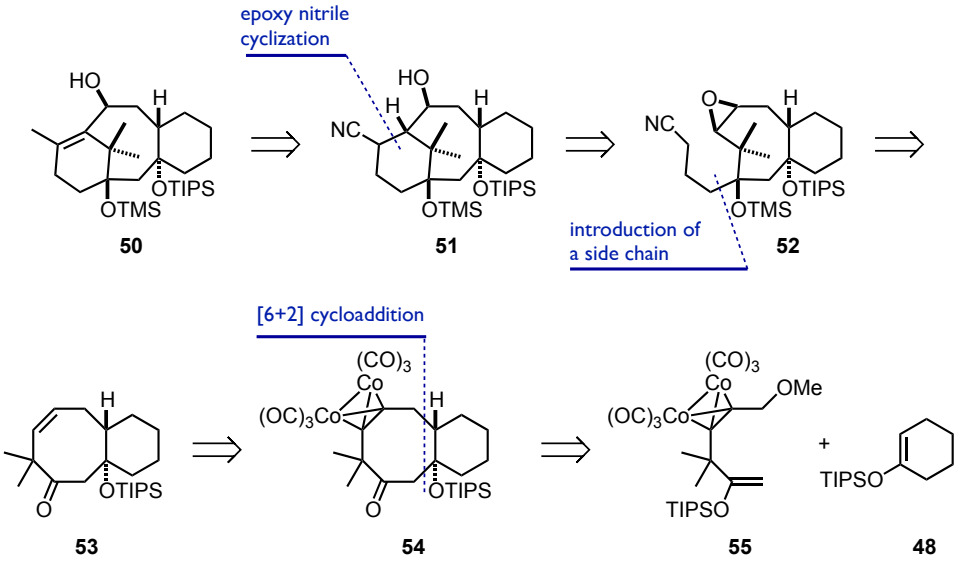


Chapter I

Construction of the Taxane Skeleton on the Basis of the [6+2] Cycloaddition Reaction

1-1. Previous work by Dr. Mitachi[18]

Dr. Katsuhiko Mitachi, who was working on the development of higher order cycloaddition reactions in the same laboratory of the author, initiated a study toward the total synthesis of taxane diterpenoids on the basis of the [6+2] cycloaddition reaction. The initial synthetic plan for the taxane model compound **50** is shown in Scheme 1. The bridgehead double bond in the A ring, that is well known as a highly strained *anti*-Bredt's rule olefin, is expected to be installed from cyano alcohol **51**. The A ring would be constructed by the intramolecular cyclization reaction of epoxy nitrile **52** under basic conditions.[19] The cyclization precursor **52** is to be synthesized through reductive decomplexation of dicobalt acetylene complex **54**, stereoselective introduction of the side chain, and oxidation of the olefin moiety. The key *trans*-fused bicyclic ketone **54** would be constructed by the [6+2] cycloaddition reaction of dicobalt acetylene complex **55** possessing the *gem*-dimethyl group with six-membered enol silyl ether **48**.



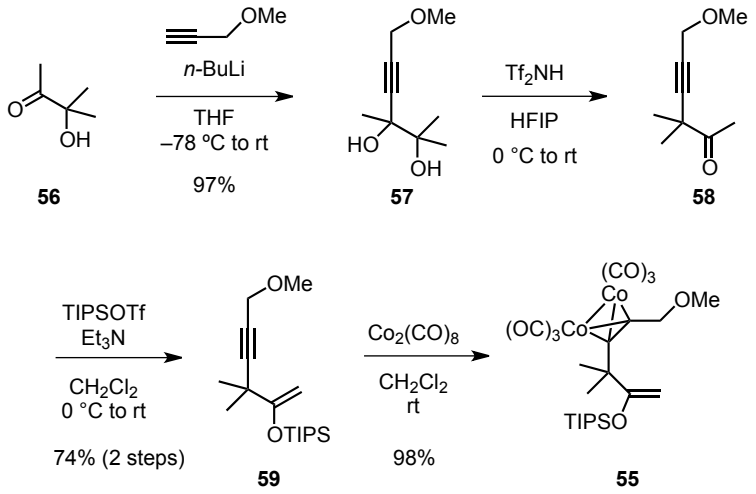
Scheme 1. Retrosynthetic analysis of taxane model compound

Dr. Mitachi succeeded in synthesizing tricyclic compound **51** so far, but there remained several problems in efficiency of the multistep transformations. In addition, the most challenging issue, the installation of the bridgehead double bond in the A ring, was not explored

at all. Therefore, the author undertook the research toward the synthesis of the ABC ring system of taxane diterpenoids through an improved route and new method for installation of the *anti*-Bredt's rule olefin.

1-2. Improved synthesis of tricyclic compound

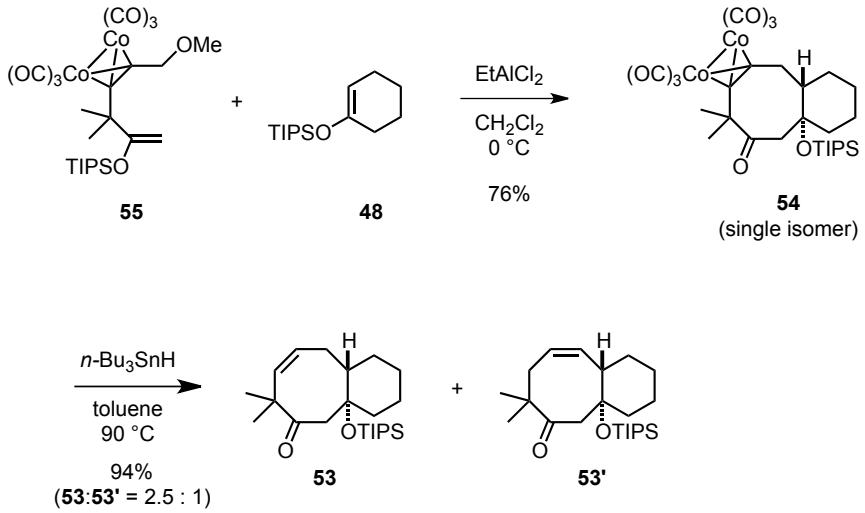
Firstly, the synthesis of dicobalt acetylene complex **55** was explored (Scheme 2). The reaction of a lithium acetylide generated from methyl propargyl ether and butyllithium with 3-hydroxy-3-methyl-2-butanone **56** afforded 1,2-diol **57** in quantitative yield. Treatment of the diol with trifluoromethanesulfonimide in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) effected the pinacol rearrangement reaction, giving rise to ketone **58**. The desired six-carbon unit **55** was obtained in high overall yield through conversion to enol triisopropylsilyl ether **59** followed by the reaction with $Co_2(CO)_8$.



Scheme 2. Synthesis of six-carbon unit having a quaternary carbon atom

The six-carbon unit having a *gem*-dimethyl group in hand, construction of the BC ring system by a [6+2] cycloaddition reaction was explored (Scheme 3). Under the influence of $EtAlCl_2$, cobalt complex **55** underwent the cycloaddition reaction with 1-(triisopropylsilyloxy)cyclohexene **48** to give the desired bicyclic ketone **54** as a single diastereomer in good yield. Transformation of the cyclic cobalt complex into an olefin was examined using the decomplexation protocol of Isobe.[20] Unfortunately, heating of ketone **54** with tributyltin hydride resulted in formation of an inseparable mixture of enones **53** and **53'** through partial isomerization of the double bond. To suppress the production of isomer **53'**,

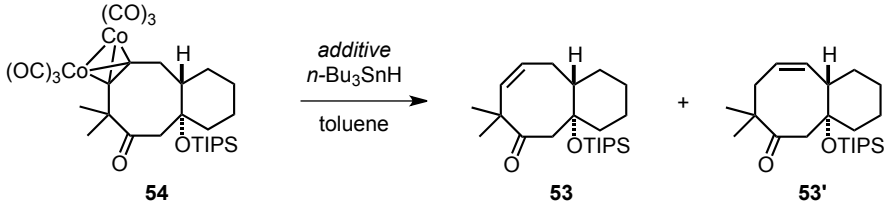
several reaction conditions were examined.



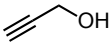
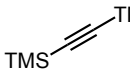
Scheme 3. Formal [6+2] cycloaddition reaction of dicobalt acetylene complex **55** with enol silyl ether **48**

Isobe et al. observed similar isomerization of a double bond in the reductive decomplexation reaction of dicobalt acetylene complex promoted by a trialkylsilane,[21] and they reported that the use of some type of alkyne as an additive prohibited the isomerization pathway. The report let the author to explore the decomplexation reaction of **54** in the presence of some additives as shown in Table 1. Although the use of propargyl alcohol led to formation of the desired product in higher ratio, the chemical yield was decreased to 70% (entry 2). On the other hand, the reaction in the presence of bis(trimethylsilyl)acetylene proceeded quantitatively, but the product ratio was only 3.5:1 (entry 3). Finally, 1,4-cyclohexadiene was found to be the best additive, and the product was obtained as a 5:1 mixture in 97% yield (entry 4).

Table 1. Decomplexation of dicobalt acetylene complex into olefins

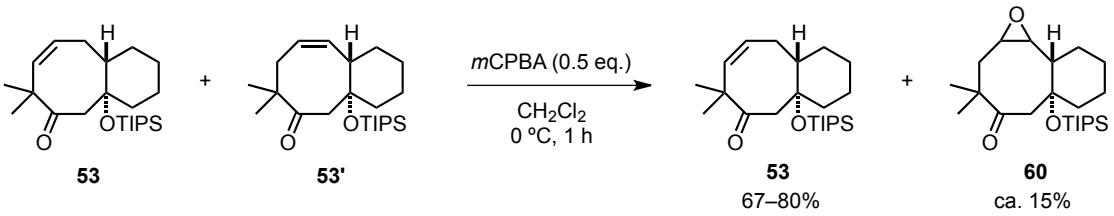


54 **53** **53'**

entry	*n*-Bu_3SnH (eq.)	*additive*	temp., time	yield (%)	ratio (**53:53'**)[a]
1	5	none	90 ºC, 15 min	94	2.5 : 1
2	10	 (5.0 eq.)	100 ºC, 30 min	70	4.2 : 1
3	5	 (5.0 eq.)	100 ºC, 15 min	quant.	3.5 : 1
4	4	 (3.0 eq.)	80 ºC, 5 min	97	5.0 : 1

a) Determined by ^{1}H NMR analysis

While separation of the desired product **53** from its isomer **53'** by silica gel chromatography was difficult, the author found a practical method for removing **53'**. Thus, treatment of the mixture with *m*CPBA resulted in selective oxidation of the minor isomer, and the resulting epoxide **60** was easily removed from olefin **53** by silica gel chromatography (Scheme 4).

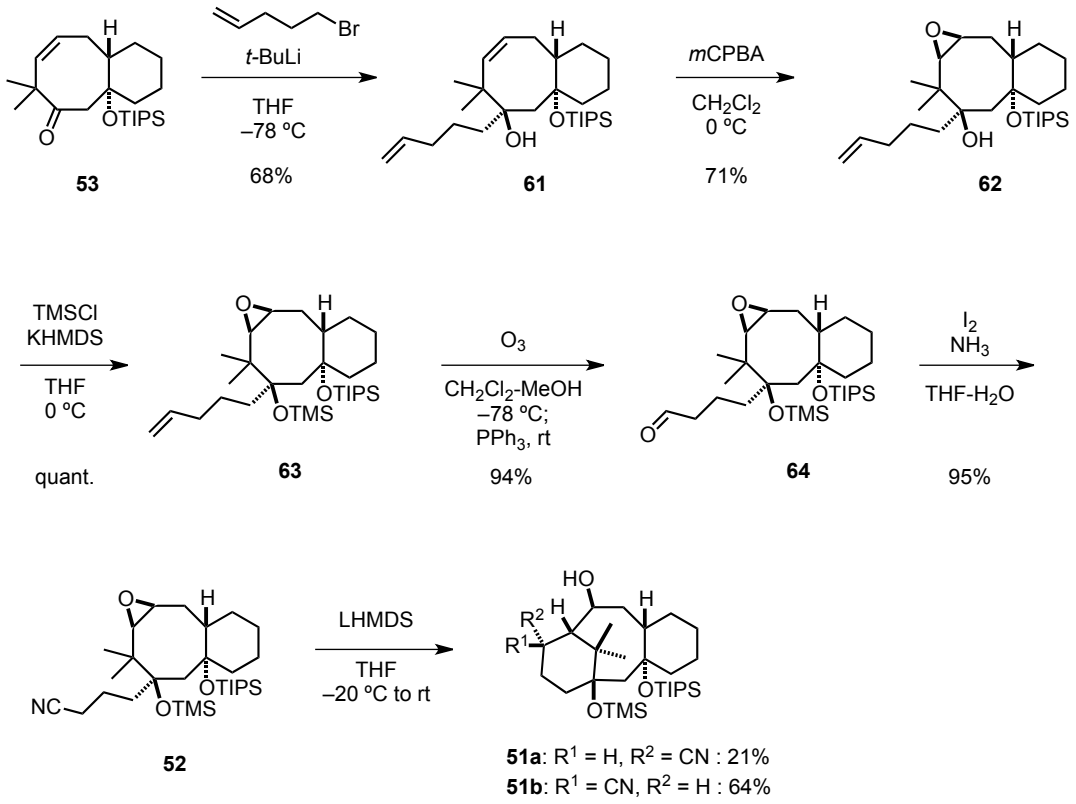


53 **53'** **53** 67–80% **60** ca. 15%

Scheme 4. Selective oxidation of the minor olefin

According to the Mitachi's procedure,[18] bicyclic ketone **53** was transformed into the tricyclic compound **51** as shown in Scheme 5. Introduction of the side chain was achieved by the reaction of ketone **53** with 4-pentenyllithium which was prepared from 5-bromo-1-pentene and *tert*-butyllithium. The reaction proceeded in a stereoselective manner to afford the desired alcohol **61** as a single diastereomer. On treatment with *m*CPBA, diene **61** underwent the oxidation reaction selectively at the internal olefin moiety, and epoxide **62** was obtained as a single isomer after silylation of the hydroxyl group. Terminal olefin **63** was then subjected to

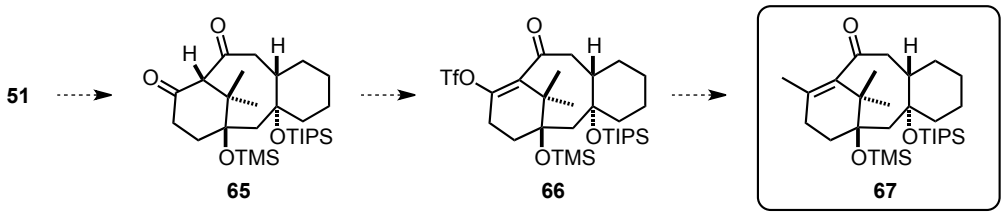
ozonolysis to afford aldehyde **64** which was converted to nitrile **52** by treating with aqueous ammonia and iodine. Finally, epoxy nitrile **52** was reacted with LHMDS to afford the desired tricyclic compounds **51a** and **51b** in acceptable yield (Scheme 5).



Scheme 5. Construction of the tricyclic compound

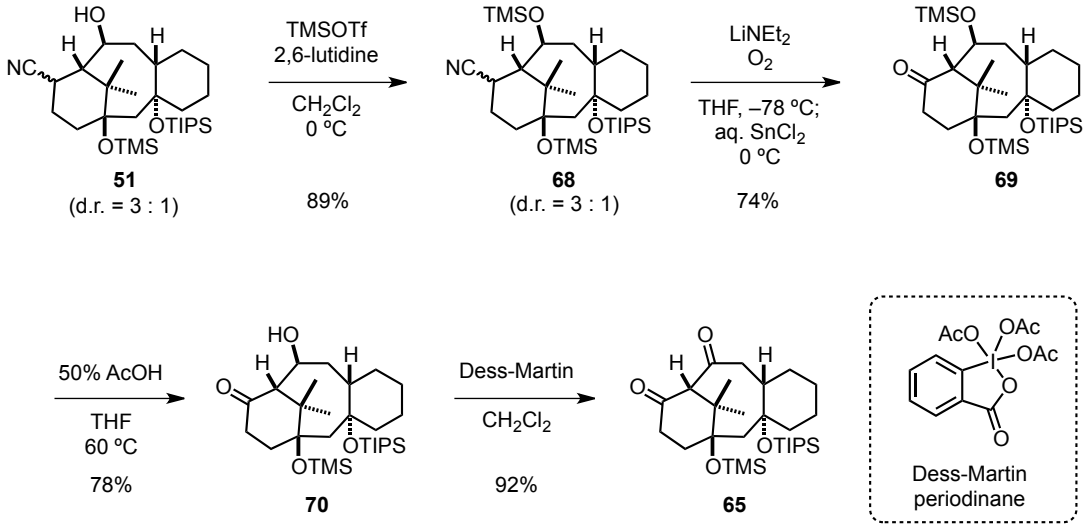
1-3. Attempts for introducing the bridgehead double bond

The tricyclic key compound **51** in hand, the author planed installation of the highly strained bridgehead double bond in the A ring as shown in Scheme 6. Oxidative cleavage of the nitrile moiety of **51** followed by oxidation of the secondary alcohol moiety would afford 1,3-diketone **65**. After conversion to enol triflate **66**, the allylic methyl group is to be introduced by a palladium-catalyzed coupling reaction to afford taxane model compound **67**.



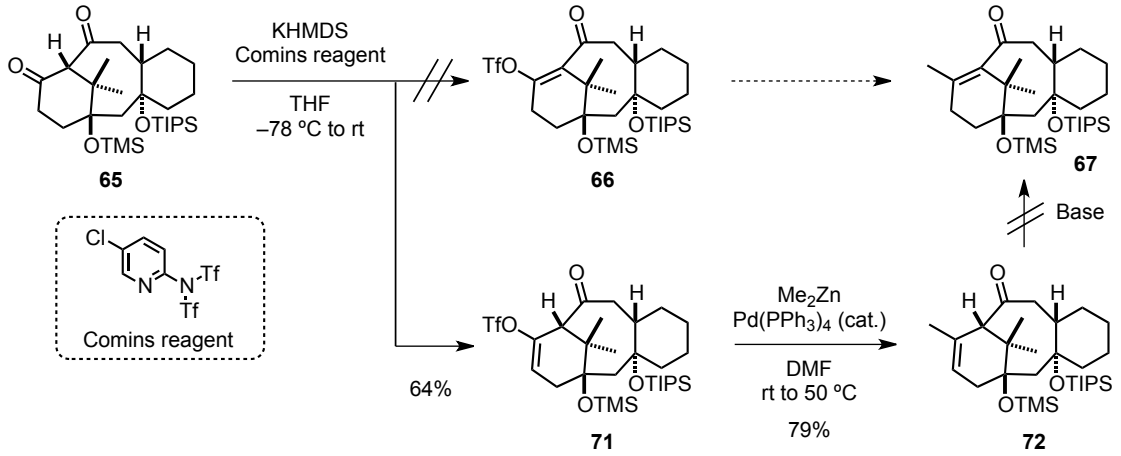
Scheme 6. A plan for installation the bridgehead double bond

Secondary alcohol **51** was protected with a trimethylsilyl group, and the resulting nitrile **68** was successively treated with $LiNEt_2$, oxygen gas, and $SnCl_2$ to afford ketone **69**. Selective removal of the secondary silyl group was effected by treatment with aqueous acetic acid, and 1,3-diketone **65** was obtained through Dess-Martin oxidation (Scheme 7).



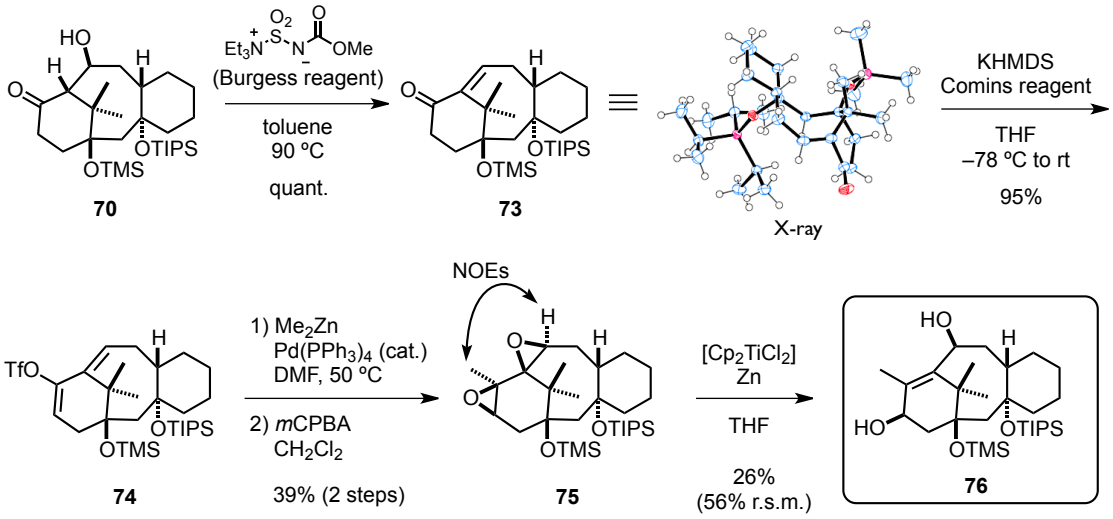
Scheme 7. Synthesis of 1,3-diketone **65**

Although abstraction of the bridgehead methyne proton of 1,3-diketone **65** was expected to occur readily, treatment of **65** with KHMDS followed by Comins' reagent gave enol triflate **71** in 64% yield (Scheme 8). Methylation of the product through the Negishi coupling reaction with Me_2Zn afforded β,γ-unsaturated ketone **72** which was subjected to isomerization of the double bond. The desired α,β-unsaturated ketone **67** was, however, not obtained in the presence of various types of bases.



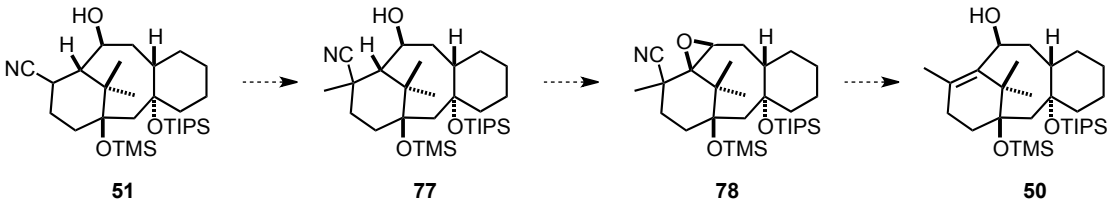
Scheme 8. The reaction of 1,3-diketone **65**

These results indicate the difficulty in introducing the highly strained C9-C10 bridgehead double bond in the A ring even by enolization of the 1,3-diketone **65**. On the other hand, installation of the C9-C10 bridgehead double bond in the B ring was easily achieved as shown in Scheme 9. Thus, ketone **70** underwent dehydration by treating with Burgess reagent to afford α,β-unsaturated ketone **73**, the structure of which was confirmed by X-ray crystallographic analysis. The product was then transformed into bisepoxide **75** through the Negishi coupling reaction of enol triflate **74** with Me_2Zn followed by treatment with an excess amount of *m*CPBA. The stereochemistry of **75** was determined by the NOE experiments, indicating that the oxidation reactions of the two olefin moieties occurred both from the convex face of the AB ring system. As was reported by Granja et al.,[6a] reduction of bisepoxide **75** with trivalent titanium reagent generated from titanocene dichloride and activated zinc dust resulted in cleavage of the epoxides, giving rise to diol **76** with the bridgehead double bond.



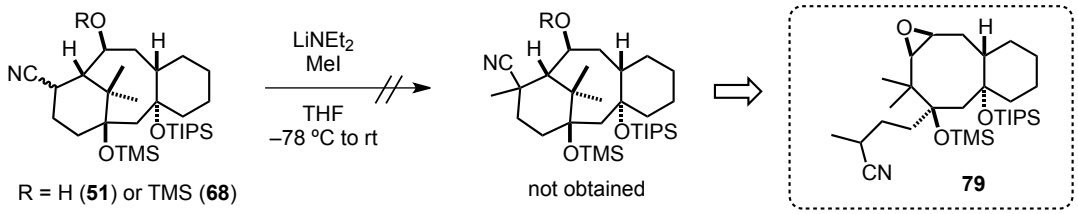
Scheme 9. Synthesis and cleavage of bisepoxide **75**

While the ABC ring skeleton possessing the bridgehead double bond **76** was successfully constructed through the present route, there remains inefficiency due to the requirement for many steps. With a view to achieving installation of the bridgehead double bond in shorter steps, the author planed to use the cyano group for introduction of the C-18 methyl group (Scheme 10). After methylation of nitrile **51** under basic conditions, secondary alcohol **77** is to be converted to β,γ-epoxy nitrile **78** through dehydration and oxidation. Finally, cleavage of the cyano group accompanied with the epoxide opening would be achieved by the single electron reduction of nitrile **50**.[22]



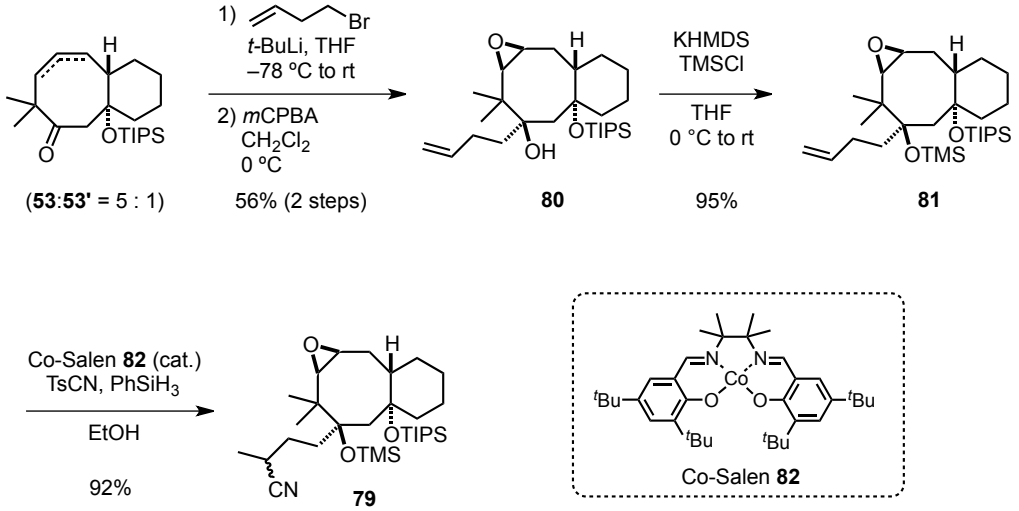
Scheme 10. Alternative plan for installation of the bridgehead double bond

Successive treatment of nitrile **51** with LDA and methyl iodide resulted in recovery of the starting material, and the use of $LiNEt_2$, a less bulky base, also failed to give the desired product (Scheme 11). The reaction of the corresponding trimethylsilyl ether **68**, which was prepared with a view to avoiding the formation of dianion, did not proceed at all. These results prompted the author to introduce the methyl group prior to the construction of the A ring.



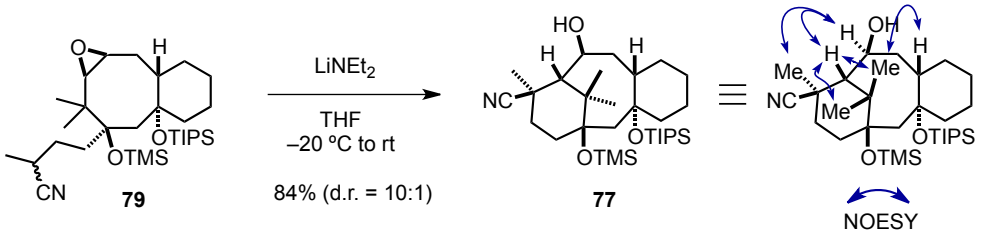
Scheme 11. Attempted methylation on the C12 position

The newly designed epoxy nitrile **79** was synthesized through a similar synthetic pathway to Scheme 5. Enone **53**, which was obtained by decomplexation of cobalt complex **54** as a 5:1 mixture with isomer **53'**, was subjected to the reaction with 3-butenyllithium followed by epoxidation of the internal olefin moiety to give **80** in 56% yield after removing the impurities arising from **53'**. The side chain of **81** with a terminal olefin moiety was converted to 3-cyanobutyl group through the hydrocyanation reaction catalyzed by a cobalt complex **82** according to the Carreira's protocol,[23] and nitrile **79** was obtained as a mixture of diastereomers (Scheme 12).



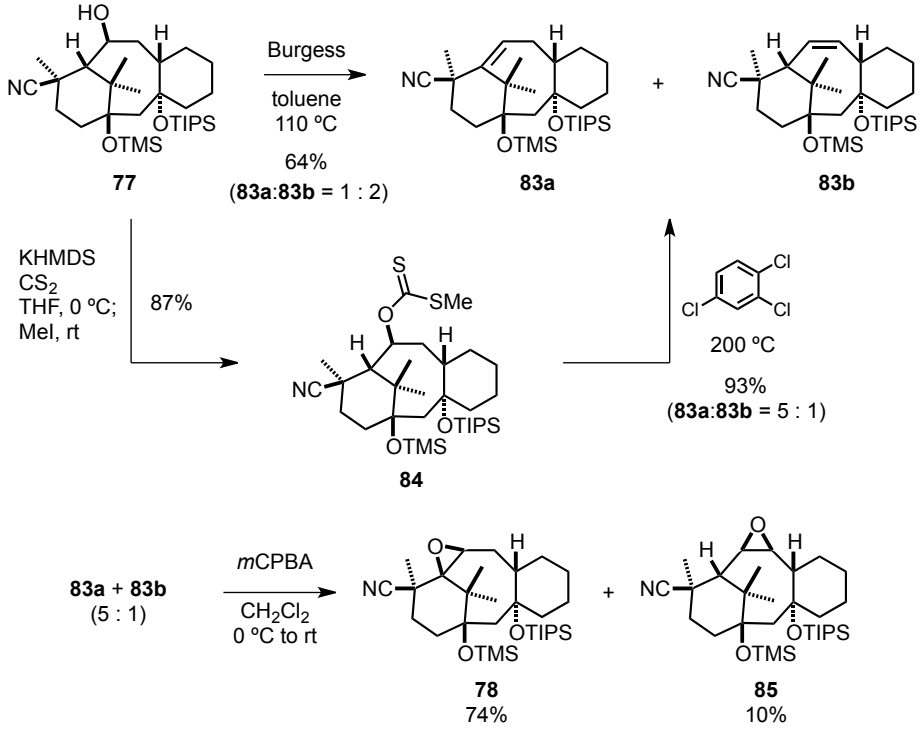
Scheme 12. Synthesis of a new cyclization precursor **79**

The new cyclization precursor in hand, the stage was set for construction of the A ring (Scheme 13). Under the influence of $LiNEt_2$, nitrile **79** underwent a smooth cyclization reaction, giving rise to the tricyclic compound **77** in 84% yield. The relative configuration of the major isomer was determined by the NOE experiment.



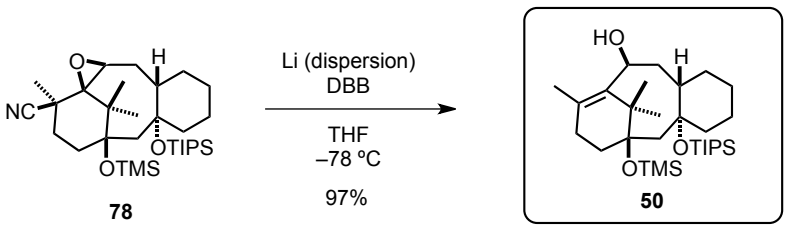
Scheme 13. Epoxy nitrile cyclization

In contrast with the previous reaction of alcohol **70**, the dehydration reaction of **77** promoted by Burgess reagent gave the wrong isomer **83b** as a major product (Scheme 14). On the other hand, Chugaev elimination of xanthate **84** was found to afford the desired olefin **83a** accompanied with a small amount of **83b**. The resulting 5:1 mixture of the olefins was oxidized with *m*CPBA, and the desired epoxide **78** was separated from isomer **85** arising from **83b** by silica gel column chromatography.



Scheme 14. Examinations on dehydration of alcohol **77**

Finally, epoxy nitrile **78** was converted to the desired alcohol **50** possessing the bridgehead olefin via the reductive cleavage reaction induced by lithium di(*tert*-butyl)biphenylide (LDBB).[22]



Scheme 15. Installation of the bridgehead double bond by reductive cleavage of **78**

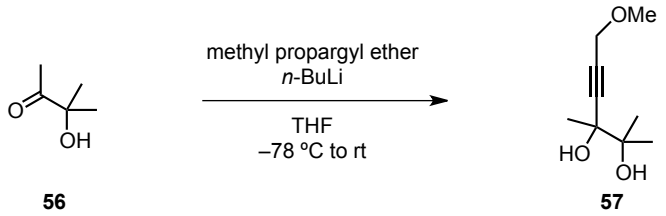
In summary, the author has achieved the stereoselective synthesis of a model compound of taxane diterpenoids. The BC ring system was constructed on the basis of a [6+2] cycloaddition reaction of a dicobalt acetylene complex with an enol silyl ether. The A ring was formed via an intramolecular substitution reaction of an epoxy nitrile. Finally, installation of the bridgehead double bond in the A ring was achieved through reductive cleavage of a nitrile having an epoxide moiety.

Experimental Section

General. All the reactions were carried out in a round-bottomed flask with an appropriate number of necks and side arms connected to a three-way stopcock and/or a rubber septum cap under an argon atmosphere. All vessels were first evacuated by a rotary pump and then flushed with argon prior to use. Solutions and solvents were introduced by a hypodermic syringe through a rubber septum. During the reaction, the vessel was kept under a positive pressure of argon. Dry THF and diethyl ether were freshly prepared by distillation from benzophenone ketyl before use. Triethylamine (Et_3N), tetramethylenediamine (TMEDA), trimethylsilylchloride (TMSCl) were distilled from CaH under argon atmosphere. Anhydrous CH_2Cl_2, methanol, ethanol, dimethoxyethane (DME), DMF, DMSO, benzene, toluene, *m*-xylene and pyridine were purchased from Kanto Chemical Co. Inc. and Wako Pure Chemicals Co. Ltd. 1,2,4-trichlorobenzene (TCB) were purchased from Sigma-Aldrich Co. Most of the reagents were purchased from Tokyo Chemical Industry Co. Ltd., Kanto Chemical Co. Inc., Wako Pure Chemicals Co. Ltd. and Sigma-Aldrich Co.

Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer using 5 mm NaCl plates. ^{1}H-NMR spectra were recorded on a JEOL ECA-500 (500 MHz) in $CDCl_3$ (δ: 7.26). Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). ^{13}C-NMR spectra were recorded on a JEOL ECA-500 (125.7 MHz) in $CDCl_3$ (δ: 77.0). Chemical shifts are reported in part per million (ppm). High resolution mass (HRMS) spectra were recorded on a JEOL JMS AX-500, JEOL JMS-SX102A or JEOL JMS-T-100GCV at the S1GC-MS & NMR Laboratory, Graduate School of Agriculture, Hokkaido University. 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, or ceric ammonium molybdate in 10% sulfuric acid. Kanto Chem. Co. Inc. Silica Gel 60N (particle size 0.040–0.050 mm) was used for column chromatography.

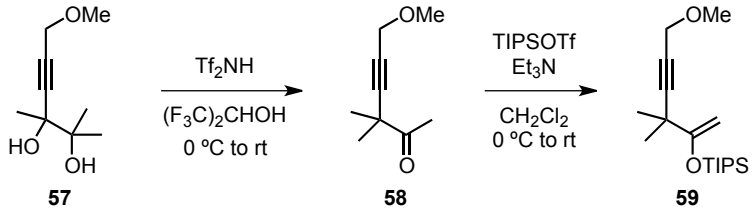
Compound 57



56 **57**

To a solution of methylpropargyl ether (8.3 mL, 101 mmol) in THF (50 mL) was slowly added a 2.65 M hexane solution of butyllithium (39 mL, 103 mmol) at –78 °C. After being stirred for 30 min at 0 °C, 3-hydroxy-3-methyl-2-butanone **56** (5.2 mL, 49.0 mmol) was added at –78 ºC. The reaction mixture was warmed up to room temperature and stirred for 3 h. After addition of saturated aqueous NH_4Cl, the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 1:1) to give diol **57 (**8.20 g, 97%) as a white solid. mp 44.3–48.0 °C. IR ($CHCl_3$) *v* 3420, 2986, 2940, 2904, 2847, 2824, 1455, 1371, 1281, 1172, 1153, 1100, 1022, 1000, 962, 918, 903 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.13 (s, 2H), 3.37 (s, 3H), 2.80 (brs, 1H), 2.17 (brs, 1H), 1.47 (s, 3H), 1.38 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 88.91, 80.07, 76.74, 73.69, 59.76, 57.49, 25.46, 24.22, 22.00; HRMS (FD+) calcd for $C_9H_{17}O_3$ $[M+H]^+$: 173.1178, found: 173.1179.

Compound 59



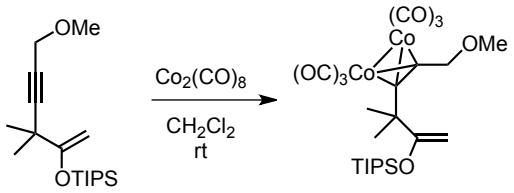
57 **58** **59**

To a solution of diol **57** (1.81 g, 10.5 mmol) in 1,1,1,3,3,3-hexafluoroisopropanol (5.2 mL) was added trifluoromethanesulfonimide (2.96 g, 10.5 mmol) at 0 °C. After being stirred at 0 ºC for 1 h, ether and a saturated aqueous $NaHSO_4$ solution were added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered

through a silica gel plug, which was rinsed with pentane/ether (10:1). The crude ketone **58** was used for the next step without further purification.

To a solution of the crude ketone **58** in CH_2Cl_2 (35 mL) were added triethylamine (5.2 mL, 37.8 mmol) and triisopropylsilyl trifluoromethanesulfonate (5.1 mL, 18.9 mmol) at 0 °C. After stirred at room temperature for 17 h, EtOAc and a saturated aqueous $NaHCO_3$ were added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1) to give silyl enol ether **59** (2.40 g, 74% from diol **57**) as a pale yellow oil. IR (neat) *v* 2965, 2945, 2894, 2868, 2819, 1996, 1657, 1622, 1466, 1378, 1356, 1288, 1231, 1187, 1164, 1105, 1022, 950, 926, 905, 882, 822, 737, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.50 (d, *J* = 1.0 Hz, 1H), 4.10 (s, 2H), 3.98 (s, 1H), 3.36 (d, *J* = 1.0 Hz, 3H), 1.39 (s, 6H), 1.23 (sep, *J* = 7.5 Hz, 3H), 1.09 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 161.8, 92.56, 86.22, 60.13, 57.26, 37.62, 27.95, 18.05, 12.69; HRMS (EI+) calcd for $C_{18}H_{34}O_2Si$ $[M]^+$: 310.2328, found: 310.2313.

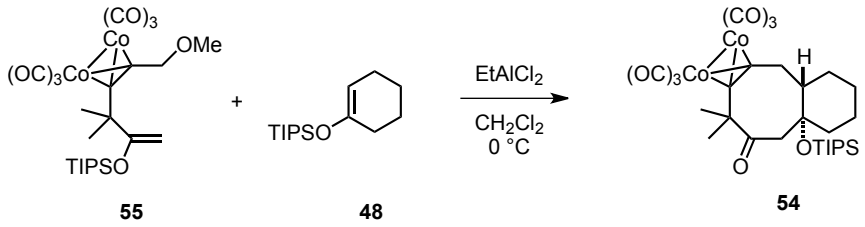
Compound 55



59 **55**

To a solution of a silyl enol ether **59** (1.00 g, 3.22 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (1.67 g, 4.88 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was filtered through a celite pad. The filtrate was concentrated and purified by silica gel column chromatography (hexane:EtOAc = 100:1) to give cobalt complex **55** (1.88 g, 98%) as a deep red solid. mp 57.2–59.4 °C. IR ($CHCl_3$) *v* 2964, 2948, 2931, 2895, 2870, 2821, 2089, 2047, 2008, 1973, 1620, 1466, 1383, 1352, 1269, 1195, 1159, 1117, 1058, 1011, 921, 884, 827, 680, 655 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.63 (s, 2H), 4.32 (d, *J* = 1.5 Hz, 1H), 4.17 (d, *J* = 1.5 Hz, 1H), 3.51 (s, 3H), 1.45 (s, 6H), 1.30 (sep, *J* = 7.5 Hz, 3H), 1.14 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 200.2, 163.9, 107.4, 94.98, 89.64, 73.23, 58.86, 44.06, 30.31, 18.34, 12.85; HRMS (EI+) calcd for $C_{22}H_{34}Co_2O_6Si$ $[M–(CO)_2]^+$: 540.0789, found: 540.0793.

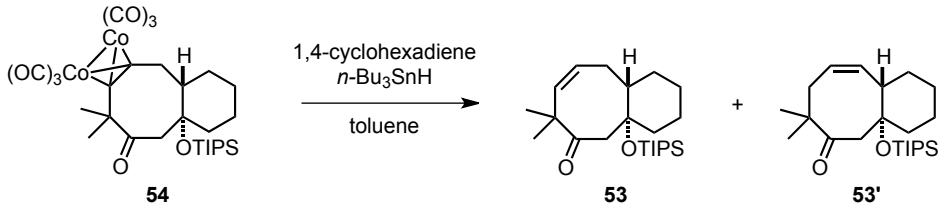
Compound 54



55 **48** **54**

To a mixture of 1-(triisopropylsiloxy)cyclohexene **48** (1.20 g, 4.50 mmol) and acetylene dicobalt complex **55** (1.80 g, 3.00 mmol) in CH_2Cl_2 (7.5 mL) was added a 1.04 M hexane solution of $EtAlCl_2$ (5.8 mL, 6.00 mmol) at 0 °C. After being stirred for 30 min, the reaction was quenched with a saturated aqueous Rochelle salt solution. The mixture was stirred vigorously at room temperature under argon atmosphere for 30 min and separated. The aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Concentration under reduced pressure followed by purification by silica gel column chromatography (hexane then hexane:ether = 100:1) afforded 1.53 g (76%) of cycloadduct **54** as a deep brown crystal. mp 112 °C (dec.). IR ($CHCl_3$) *v* 2942, 2868, 2089, 2048, 2022, 1974, 1709, 1465, 1446, 1383, 1364, 1326, 1313, 1124, 1063, 1034, 996, 883, 828, 678, 658 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.48 (d, *J* = 13.0 Hz, 1H), 3.42 (dd, *J* = 17.0, 8.5 Hz, 1H), 2.56 (d, *J* = 16.5 Hz, 1H), 2.38 (d, *J* = 13.0 Hz, 1H), 2.20 (td, *J* = 13.7, 4.6 Hz, 1H), 1.82–1.73 (m, 2H), 1.64–1.72 (m, 2H), 1.51–1.49 (m, 1H), 1.42–1.39 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H), 1.25–1.17 (m, 2H), 1.12 (d, *J* = 4.6 Hz, 21H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 206.0, 199.6, 102.7, 97.99, 75.93, 50.82, 49.38, 48.78, 38.12, 37.23, 30.63, 30.42, 27.53, 26.19, 21.42, 18.72, 18.60, 13.96; HRMS (EI+) calcd for $C_{26}H_{40}Co_2O_5Si$ $[M–(CO)_3]^+$: 578.1309, found: 578.1290.

Compound 53



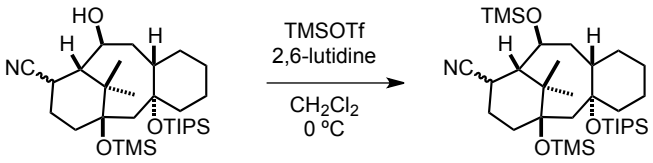
54 **53** **53'**

To a solution of ketone **54** (1.53 g, 2.31 mmol) in toluene (20 mL) was added

1,4-cyclohexadiene (645 μL, 6.93 mmol). The mixture was heated at 80 °C, and then was slowly added tributyltin hydride (2.4 mL, 9.24 mmol). After being stirred for 5 min, the mixture was concentrated and purified by silica gel column chromatography (hexane:EtOAc = 100:1) to give mixture of enones **53** and **53'** (848 mg, 97%, **53**:**53'**=5:1) as a pale yellow oil.

Corresponding to major isomer **53** data: IR (neat) *v* 2929, 2866, 1702, 1465, 1444, 1414, 1388, 1370, 1356, 1301, 1245, 1183, 1152, 1129, 1085, 1043, 1013, 1006, 918, 882, 824, 795, 766, 733, 710, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.51 (ddd, *J* = 13.0, 4.5, 4.0 Hz, 1H), 5.29 (ddd, *J* = 13.5, 2.0, 1.5 Hz, 1H), 3.65 (brs, 1H), 2.66 (brs, 1H), 2.21 (d, *J* = 5.5 Hz, 1H), 2.00–1.93 (m, 1H), 1.81 (d, *J* = 19.0 Hz, 1H), 1.66 (d, *J* = 14.5 Hz, 1H), 1.62–1.53 (m, 2H), 1.43 (d, *J* = 12.0 Hz, 2H), 1.36 (dd, *J* = 23.5, 12.0 Hz, 1H), 1.25–1.21 (m, 1H), 1.23 (s, 3H), 1.16 (dt, *J* = 13.5, 3.5 Hz, 1H), 1.13–1.05 (m, 3H), 1.11 (s, 3H), 1.09 (d, *J* = 3.5 Hz, 18H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 214.3, 134.0, 129.1, 76.04, 50.74, 49.85, 42.18, 37.70, 34.52, 30.62, 30.19, 25.69, 21.06, 18.57, 18.47, 14.11, 13.82; HRMS (EI+) calcd for $C_{23}H_{42}O_2Si$ $[M]^+$: 378.2954, found: 378.2934.

Compound 68



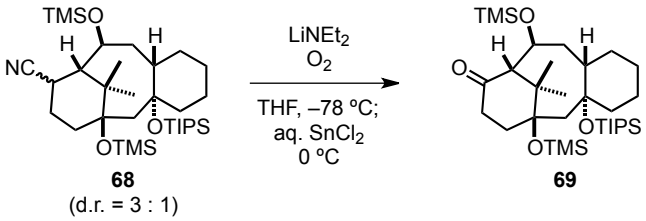
51
(d.r. = 3 : 1)

68
(d.r. = 3 : 1)

To a solution of alcohol **51** (108 mg, 0.201 mmol, d.r. = 3:1) in CH_2Cl_2 (1.0 mL) were added 2,6-lutidine (70 μL, 0.604 mmol) and trimethylsilyl trifluoromethanesulfonate (81 μL, 0.302 mmol) at 0 ºC. After being stirred for 1 h, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether = 100:1) to give silyl ether **68** (109 mg, 89%, d.r. = 3:1) as a colorless oil.

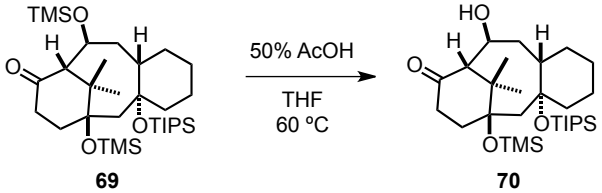
Corresponding to major isomer data: ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.94 (t, *J* = 4.0 Hz, 1H), 2.58 (dt, *J* = 12.0, 8.0 Hz, 1H), 2.54–2.48 (m, 1H), 2.21 (dd, *J* = 9.0, 4.0 Hz, 1H), 2.14–1.94 (m, 3H), 1.88–1.58 (m, 8H), 1.47–1.42 (m, 1H), 1.39 (s, 3H), 1.34–1.17 (m, 3H), 1.15 (m, 3H), 1.14–1.06 (m, 22H), 0.13 (s, 9H), 0.12 (s, 9H).

Compound 69



To a solution of **68** (297 mg, 0.488 mmol, d.r.= 3:1) in THF (2.4 mL) was added a 0.5 M THF solution of lithium diethylamide (2.90 mL, 1.47 mmol) at 0 ºC. The mixture was stirred at –78 °C followed by treated with oxygen gas. After being bubbled for 10 min, the reaction was warmed up to 0 ºC and quenched with addition of 1.0 M aqueous solution of HCl and 0.5 M aqueous solution of $SnCl_2$. After being stirred for 15 min, the mixture was neutralization with saturated aqueous $NaHCO_3$. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1) to give **69** (215 mg, 74%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.68 (td, *J* = 4.5, 1.0 Hz, 1H), 2.60 (ddd, *J* = 20.0, 11.0, 1.5 Hz, 1H), 2.55–2.46 (m, 3H), 2.25 (ddd, *J* = 11.0, 10.5, 6.5 Hz, 1H), 1.96 (d, *J* = 15.0 Hz, 1H), 1.89 (td, *J* = 12.5, 3.5 Hz, 1H), 1.82 (dd, *J* = 15.0, 5.0 Hz, 1H), 1.78 (d, *J* = 15.0 Hz, 1H), 1.77–1.68 (m, 2H), 1.64 (d, *J* = 13.0 Hz, 2H), 1.48–1.42 (m, 1H), 1.44 (s, 3H), 1.39–1.24 (m, 3H), 1.21–1.15 (m, 1H), 1.13 (s, 3H), 1.09–1.04 (m, 21H), 0.15 (s, 9H), 0.10 (s, 9H).

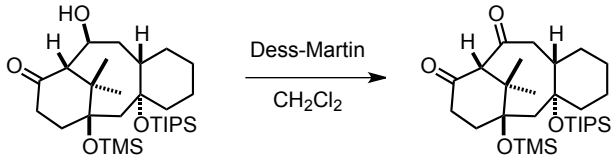
Compound 70



The solution of **69** (160 mg, 0.268 mmol) in THF (1.2 mL) was stirred with a 50% aqueous acetic acid (1.2 mL) at 60 ºC for 6 h. The mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether = 100:1 then 10:1 then 2:1) to give alcohol **70** (110 mg, 78%) as

a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.71 (td, *J* = 4.5, 1.5 Hz, 1H), 2.67 (d, *J* = 4.5 Hz, 1H), 2.65–2.60 (m, 1H), 2.54–2.42 (m, 2H), 2.27 (ddd, *J* = 12.5, 10.5, 6.5 Hz, 1H), 1.98 (d, *J* = 15.0 Hz, 1H), 1.96 (ddd, *J* = 16.0, 7.5, 1.5 Hz, 1H), 1.90 (td, *J* = 13.0, 4.0 Hz, 1H), 1.82 (d, *J* = 15.0 Hz, 1H), 1.85–1.71 (m, 2H), 1.67 (d, *J* = 15.0 Hz, 2H), 1.53–1.45 (m, 4H), 1.40–1.21 (m, 3H), 1.18 (s, 3H), 1.20–1.15 (m, 1H), 1.07 (brs, 22H), 0.16 (s, 9H).

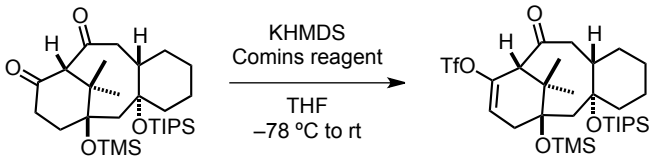
Compound 65



70 **65**

To a solution of alcohol **70** (70 mg, 0.133 mmol) in CH_2Cl_2 (1.1 mL) was added Dess-Martin periodinane (170 mg, 0.401 mmol). After being stirred at room temperature for 2 h, an aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution were added. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether = 10:1) to give diketone **65** (64.2 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.17 (s, 1H), 2.90 (dd, *J* = 12.5, 8.5 Hz, 1H), 2.68–2.64 (m, 2H), 2.40–2.33 (m, 1H), 2.23–2.16 (m, 1H), 2.14 (d, *J* = 15.5 Hz, 1H), 2.02 (d, *J* = 15.5 Hz, 1H), 1.92–1.78 (m, 4H), 1.77–1.65 (m, 3H), 1.50–1.45 (m, 1H), 1.42–1.36 (m, 1H), 1.29 (s, 3H), 1.29–1.23 (m, 1H), 1.24 (s, 3H), 1.10 (s, 21H), 0.18 (s, 9H).

Compound 71

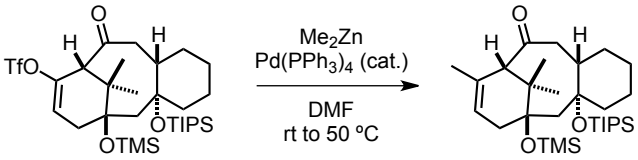


65 **71**

To a solution of diketone **65** (10 mg, 19.1 μmol) in THF (0.2 mL) was added a 0.5 M toluene solution of KHMDS (57 μL, 28.7 μmol) at –78 ºC. After being stirred for 10 min, Comins' reagent (11.3 mg, 28.7 μmol) was added at same temperature. The mixture was warmed up to room temperature and stirred for 30 min. After addition of saturated aqueous NH_4Cl, the

mixture was extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether = 100:1) to give enol triflate **71 (**8.0 mg, 64%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.92 (d, *J* = 5.0 Hz, 1H), 3.21 (brs, 1H), 3.11 (dd, *J* = 12.5, 7.5 Hz, 1H), 2.69 (d, *J* = 15.5 Hz, 1H), 2.58 (d, *J* = 17.0 Hz, 1H), 2.38 (dd, *J* = 17.0, 6.5 Hz, 1H), 2.08–2.02 (m, 1H), 2.00 (d, *J* = 15.5 Hz, 1H), 1.92–1.83 (m, 2H), 1.74–1.65 (m, 4H), 1.48–1.42 (m, 2H), 1.30–1.23 (m, 2H), 1.21 (s, 3H), 1.15 (s, 3H), 1.11 (s, 21H), 0.16 (s, 9H).

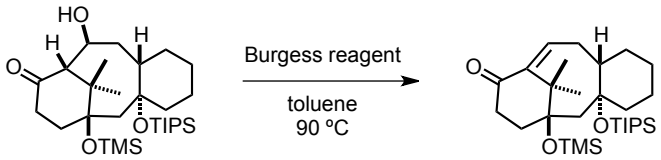
Compound 72



71 **72**

To a solution of enol triflate **71** (8.0 mg, 12.2 μmol) in DMF (0.2 mL) were added $Pd(PPh_3)_4$ (1.4 mg, 1.22 μmol) followed by a 2.0 M toluene solution of Me_2Zn (31 μL, 61.1 μmol), and the resulting mixture was heated to 50 ºC. After being stirred for 20 min, the reaction mixture was cooled to room temperature and quenched with water. The mixture was extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether = 100:1) to give β,γ-unsaturated ketone **72 (**5.0 mg, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.55–5.52 (m, 1H), 2.93 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.88 (d, *J* = 15.5 Hz, 1H), 2.80 (s, 1H), 2.41 (d, *J* = 18.0 Hz, 1H), 2.16–2.02 (m, 2H), 1.90 (d, *J* = 15.5 Hz, 1H), 1.91–1.83 (m, 1H), 1.77–1.63 (m, 5H), 1.56 (s, 3H), 1.47–1.37 (m, 2H), 1.31–1.21 (m, 1H), 1.18 (s, 3H), 1.09 (s, 21H), 1.05 (s, 3H), 0.15 (s, 9H).

Compound 73

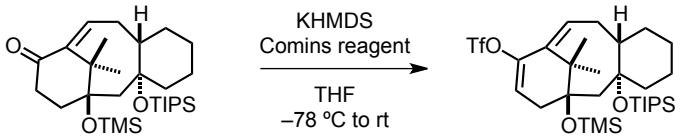


70 **73**

To a solution of alcohol **70** (53 mg, 0.100 mmol) in toluene (1.0 mL) was added Burgess

reagent (71.5 mg, 0.300 mmol), and the resulting mixture was heated to 90 ºC. After being stirred at this temperature for 2 h, the reaction mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether = 50:1) afforded **73** (51.0 mg, quant.) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.83 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.94–2.86 (m, 1H), 2.68 (d, *J* = 15.0 Hz, 1H), 2.51 (dd, *J* = 18.0, 8.0 Hz, 1H), 2.32 (ddd, *J* = 19.0, 12.5, 9.0 Hz, 1H), 2.24–2.09 (m, 3H), 1.94 (td, *J* = 14.0, 4.0 Hz, 1H), 1.80–1.56 (m, 4H), 1.73 (d, *J* = 15.0 Hz, 1H), 1.53 (s, 3H), 1.48–1.42 (m, 1H), 1.34–1.19 (m, 2H), 1.10 (s, 3H), 1.09–1.03 (brs, 22H), 0.17 (s, 9H).

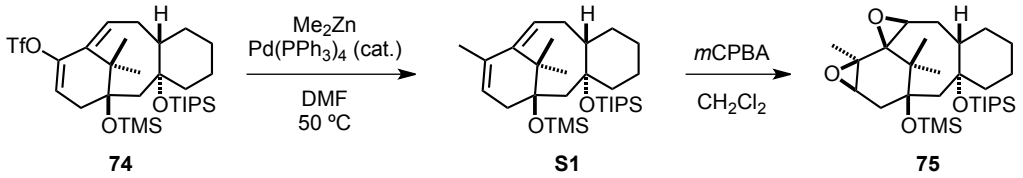
Compound 74



73 **74**

To a solution of enone **73** (47 mg, 92.7 μmol) in THF (0.46 mL) was added a 0.5 M toluene solution of KHMDS (0.56 mL, 278 μmol) at –78 ºC. After being stirred for 15 min, 0.6 M THF solution of Comins' reagent (0.46 mL, 278 μmol) was added at same temperature. The mixture was warmed to room temperature and stirred for 30 min. 10 min after addition of 1 N aqueous solution of NaOH, the mixture was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% hexane) afforded enol triflate **74** (37.6 mg, 63%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.07 (dd, *J* = 10.5, 4.0 Hz, 1H), 5.27 (dd, *J* = 5.0, 3.0 Hz, 1H), 2.88–2.80 (m, 1H), 2.48 (d, *J* = 16.5 Hz, 1H), 2.38 (ddd, *J* = 18.5, 6.5, 3.5 Hz, 1H), 2.30 (d, *J* = 14.5 Hz, 1H), 2.19 (ddd, *J* = 18.5, 12.0, 10.5 Hz, 1H), 2.05 (dd, *J* = 17.0, 5.0 Hz, 1H), 1.82 (td, *J* = 14.0, 4.0 Hz, 1H), 1.76–1.52 (m, 8H), 1.46–1.40 (m, 1H), 1.30–1.23 (m, 2H), 1.24 (s, 3H), 1.08–1.00 (m, 21H), 0.16 (s, 9H).

Compound 75

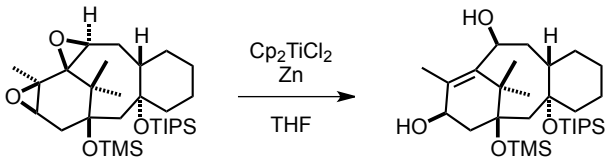


74 **S1** **75**

To a solution of enol triflate **74** (37 mg, 57.9 μmol) in DMF (0.3 mL) were added $Pd(PPh_3)_4$ (6.7 mg, 5.79 μmol) followed by a 2.0 M toluene solution of Me_2Zn (87 μL, 174 μmol), and the resulting mixture was heated to 50 ºC. After being stirred at this temperature for 45 min, the reaction mixture was cooled to room temperature and quenched with water and 1.0 M aqueous solution of HCl. The mixture was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a silica gel plug, which was rinsed with hexane. The crude diene **S1** was used for the next step without further purification.

To a solution of crude **S1** in CH_2Cl_2 (0.15 mL) was added *m*CPBA (100 mg, 0.436 mmol). After being stirred for 16 h, aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution were added. The mixture was extracted with ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane:acetone = 10:1) afforded **75** (12.0 mg, 39%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.22 (d, J = 7.5 Hz, 1H), 3.19 (d, J = 1.5 Hz, 1H), 2.74 (d, J = 15.5 Hz, 1H), 2.36–2.27 (m, 1H), 2.25–2.17 (m, 3H), 1.82–1.65 (m, 3H), 1.64–1.49 (m, 6H), 1.41–1.36 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.12–1.07 (s, 24H), 0.17 (s, 9H).

Compound 76

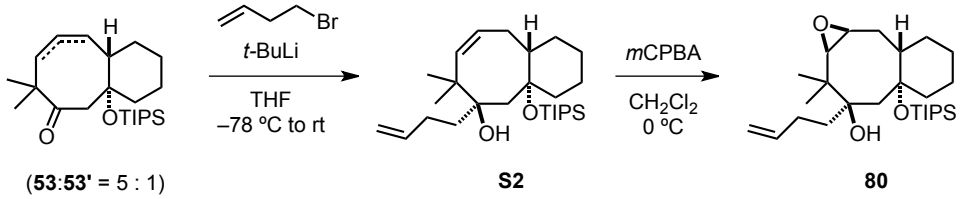


75 **76**

Zinc dust (196 mg, 3 mmol) was added to a solution of titanocene dichloride (249 mg, 1 mmol) in THF (2.5 mL) and the suspension was vigorously stirred for 1 h. This freshly prepared 0.2 M solution of [{$TiClCp_2$}$_2$] (335 μL, 66.9 μmol) was added dropwise to a solution of **75** (12 mg, 22.3 μmol) in THF (1.2 mL) at 0 °C, and the mixture was warmed up to rt. After stirred for 3 h,

saturated aqueous NH_4Cl was added and the aqueous layer was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1 then 5:1) afforded starting material **75** (6.7 mg, 56%) and diol **76** (3.1 mg, 26%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.20 (brs, 1H), 4.49 (d, *J* = 8.5 Hz, 1H), 2.76–2.70 (m, 1H), 2.66 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.26 (d, *J* = 15.0 Hz, 1H), 1.96–1.82 (m, 3H), 1.71 (s, 3H), 1.72–1.62 (m, 2H), 1.60 (s, 3H), 1.47–1.20 (m, 6H), 1.10–1.04 (s, 24H), 1.00 (s, 3H), 0.14 (s, 9H).

Compound 80



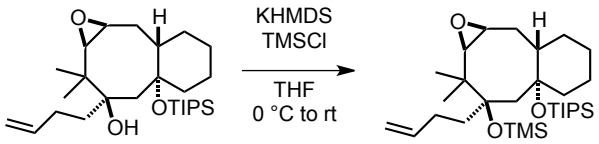
(**53**:**53'** = 5 : 1) **S2** **80**

To a 1.54 M pentane solution of *tert*-butyllithium (5.5 mL, 8.40 mmol) in THF (5.0 mL) was slowly added 4-bromo-1-butene (426 μL, 4.20 mmol) at –78 °C. After being stirred for 45 min, cyclooctenones **53** and **53'** (1.06 g, 2.80 mmol, **53**:**53'** = 5:1) in THF (9.0 mL) were added via cannula. After being stirred at room temperature for 1.5 h, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **S2** was used for the next step without further purification.

To a solution of a crude **S2** in CH_2Cl_2 (9.3 mL) was added *m*CPBA (967 mg, 4.20 mmol) at 0 °C. After being stirred 15 min, 2-methyl-2-butene and saturated aqueous Na_2HCO_3 solution were added. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1) afforded epoxide **80** (708 mg, 56%) as a white solid. mp 87–89 °C. IR (neat) *v* 3495, 3075, 2941, 2865, 1639, 1460, 1412, 1387, 1343, 1254, 1207, 1146, 1109, 1095, 1057, 1029, 915, 882, 714, 672, 654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.83 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.02 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.94 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.36 (br s, 1H), 3.31 (dd, *J* = 7.0, 4.5 Hz, 1H), 2.74 (d, *J* = 4.5 Hz, 1H), 2.64 (dd, *J* = 16.5, 10.5 Hz, 1H), 2.29–2.13 (m, 2H), 2.03 (d, *J* = 14.5 Hz, 1H), 1.98–1.90 (m, 2H), 1.81 (dd, *J* = 16.5, 7.5 Hz, 1H), 1.78–1.58 (m, 4H), 1.58 (d, *J* = 14.5 Hz, 1H), 1.46–1.40 (m, 1H), 1.35 (s, 3H), 1.32–1.21

(m, 3H), 1.14–1.07 (m, 22H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 139.4, 114.3, 77.46, 76.74, 74.45, 70.93, 62.53, 44.56, 43.47, 40.23, 37.93, 37.53, 30.87, 29.69, 27.87, 26.12, 24.20, 22.08, 21.77, 18.73, 14.19; HRMS (FD+) calcd for $C_{27}H_{50}O_3Si$ $[M]^+$: 450.3529, found: 450.3515.

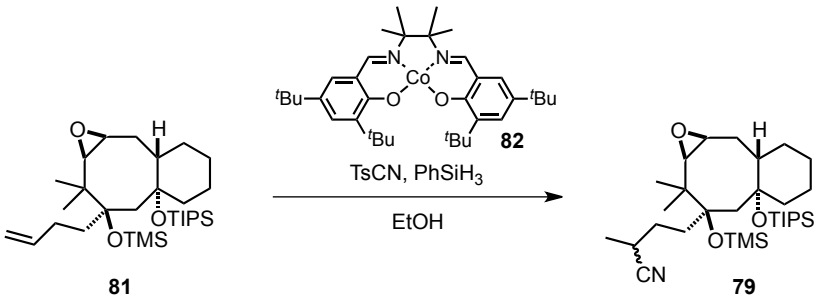
Compound 81



80 **81**

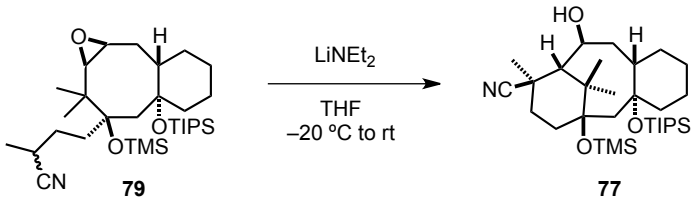
To a mixture of **80** (708 mg, 1.57 mmol) and TMSCl (0.40 mL, 3.14 mmol) in THF (8.0 mL) was added a 0.5 M toluene solution of KHMDS (6.3 mL, 3.14 mmol) at 0 °C. After being stirred for 30 min at room temperature, a saturated aqueous $NaHCO_3$ was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1) afforded **81** (784 mg, 95%) as a colorless oil. IR (neat) *v* 3584, 2942, 2866, 1640, 1461, 1388, 1252, 1211, 1159, 1101, 1030, 993, 911, 880, 857, 837, 753, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.80 (ddt, *J* = 16.5, 10.5, 7.0 Hz, 1H), 5.03 (dd, *J* = 16.5, 1.0 Hz, 1H), 4.99 (dd, *J* = 10.5, 1.0 Hz, 1H), 3.10 (td, *J* = 4.0, 1.0 Hz, 1H), 2.62 (d, *J* = 4.5 Hz, 1H), 2.51 (ddd, *J* = 16.5, 10.5, 2.0 Hz, 1H), 2.25–2.05 (m, 3H), 2.15 (d, *J* = 14.5 Hz, 1H), 1.91 (td, *J* = 13.0, 4.0 Hz, 1H), 1.77–1.69 (m, 2H), 1.68–1.47 (m, 5H), 1.54 (d, *J* = 14.5 Hz, 1H), 1.43–1.37 (br d, 1H), 1.29 (s, 3H), 1.28–1.21 (m, 1H), 1.14–1.08 (m, 25H), 0.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 138.3, 114.8, 81.14, 77.87, 68.70, 60.58, 47.93, 44.14, 41.06, 37.44, 35.51, 30.80, 30.60, 28.97, 26.03, 24.98, 21.72, 18.79, 18.76, 14.23, 3.21; HRMS (EI+) calcd for $C_{30}H_{58}O_3Si_2$ $[M]^+$: 522.3924, found: 522.3922.

Compound 79



To a mixture of olefin **81** (705 mg, 1.35 mmol) and cobalt catalyst **82** (8.0 mg, 13.5 μmol) in ethanol (6.8 mL) were added TsCN (366 mg, 2.02 mmol) and $PhSiH_3$ (166 μL, 1.35 mmol). After being stirred for 2 h, a saturated aqueous $NaHCO_3$ solution and EtOAc were added. The resulting mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1 then 20:1) afforded cyanide **79** (680 mg, 92%, d.r. = 1:1) as a pale yellow oil. IR (neat) *v* 2943, 2866, 2240, 1463, 1415, 1383, 1366, 1355, 1337, 1308, 1252, 1213, 1158, 1127, 1099, 1081, 1029, 997, 966, 930, 917, 880, 857, 838, 755, 734, 673, 649 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.10 (br s, 1H), 2.62–2.48 (m, 3H), 2.22–2.14 (m, 2H), 1.97–1.83 (m, 1.5H), 1.78–1.69 (m, 3.5H), 1.68–1.38 (m, 6H), 1.36 (d, *J* = 7.0 Hz, 1.5H), 1.35 (d, *J* = 7.0 Hz, 1.5H), 1.313 (s, 1.5H), 1.309 (s, 1.5H), 1.30–1.20 (m, 2H), 1.14–1.07 (m, 25H), 0.24 (s, 4.5H), 0.21 (s, 4.5H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 122.32, 122.26, 80.91, 80.85, 77.66, 77.60, 68.52, 68.47, 60.47, 48.09, 47.77, 44.25, 44.18, 39.47, 39.33, 37.47, 37.38, 35.43, 35.41, 31.54, 30.65, 30.51, 29.28, 29.12, 26.99, 26.84, 25.99, 25.94, 24.99, 24.97, 21.64, 18.75, 18.73, 18.69, 18.49, 18.20, 14.17, 3.33, 3.29; HRMS (FD+) calcd for $C_{31}H_{59}NO_3Si_2$ $[M]^+$: 549.4033, found: 549.4007.

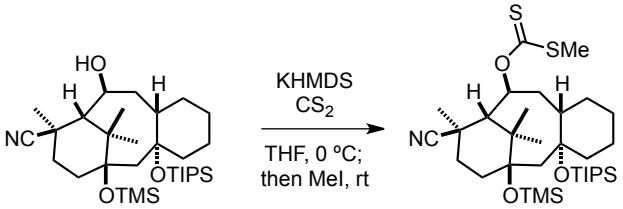
Compound 77



To a solution of diethylamine (0.34 mL, 3.44 mmol) in THF (5.2 mL) was added a 2.64 M hexane solution of butyllithium (1.3 mL, 3.44 mmol) at –78 °C. After stirring for 15 min at 0 °C,

it was added to a solution of nitrile **79** (630 mg, 1.15 mmol) in THF (5.8 mL) at –20 °C. After being stirred for 1 h at room temperature, a saturated aqueous NH_4Cl solution was added and the mixture was separated. The aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ether = 10:1 then 5:1 then 2:1) to give **77** (528 mg, 84%, d.r.=10:1) as a white solid. mp 56–58 °C. IR (neat) *v* 3450, 2945, 2866, 2228, 1654, 1542, 1459, 1388, 1250, 1162, 1107, 1072, 1035, 915, 883, 856, 838, 734, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.46 (br s, 0.1H), 4.28 (br s, 1H), 2.79 (dd, *J* = 16.5, 7.0 Hz, 0.1H), 2.43 (d, *J* = 3.5 Hz, 1H), 2.40–2.33 (m, 1H), 2.29 (td, *J* = 13.0, 5.0 Hz, 1H), 2.15 (d, *J* = 15.5 Hz, 1H), 2.18–1.97 (m, 3.4H), 1.94 (d, *J* = 15.5 Hz, 1H), 1.87–1.80 (m, 0.3H), 1.74–1.58 (m, 7H), 1.49–1.42 (m, 9.9H), 1.38–1.21 (m, 4.2H), 1.16–1.08 (m, 24H), 0.12 (s, 9H), 0.11 (s, 0.9 H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 128.4, 79.90, 78.71, 71.10, 56.68, 56.33, 42.81, 40.37, 37.25, 35.97, 35.94, 35.09, 33.72, 33.08, 32.34, 28.26, 26.82, 25.81, 22.63, 21.64, 18.94, 18.91, 14.62, 2.86; HRMS (EI+) calcd for $C_{31}H_{59}NO_3Si_2$ $[M]^+$: 549.4033, found: 549.4010.

Compound 84

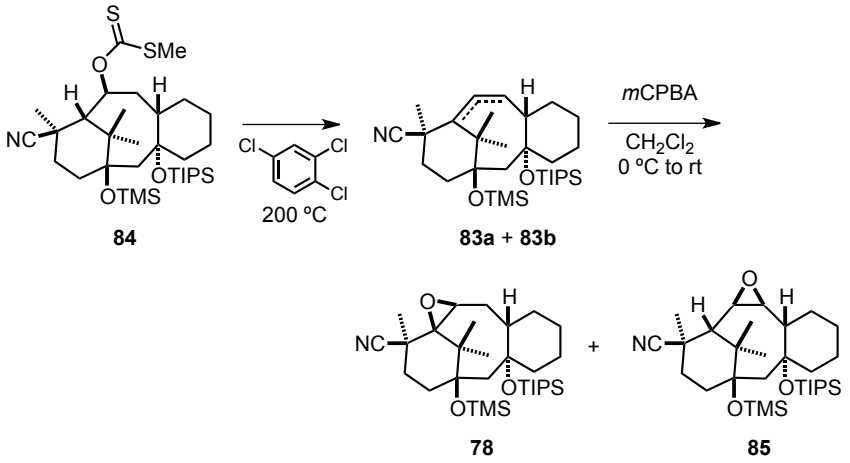


77 **84**

To a solution of **77** (527 mg, 0.960 mmol) in THF (5.0 mL) was added a 0.5 M toluene solution of KHMDS (2.9 mL, 1.44 mmol) at 0 °C. After being stirred for 5 min, CS_2 (116 μL, 1.92 mmol) was added. After being stirred for 15 min at the same temperature, iodomethane (300 μL, 4.80 mmol) was added and stirred for 10 min at room temperature. Then a saturated aqueous NH_4Cl solution was added to the solution. The mixture was separated, and aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1) to give **84** (532 mg, 87%) as a amorphous solid. IR (neat) *v* 2946, 2867, 2229, 1460, 1402, 1383, 1339, 1315, 1249, 1210, 1163, 1110, 1055, 957, 906, 882, 855, 839, 752, 734, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.29 (dd, *J* = 7.0, 4.0 Hz, 0.1H), 6.24 (t, *J* = 4.5 Hz, 1H), 2.87 (dd, *J* = 17.0, 7.0 Hz, 0.1H), 2.76 (s, 0.2H), 2.66 (d, *J* = 3.5

Hz, 1H), 2.57 (s, 3H), 2.56 (s, 0.3H), 2.45–2.39 (m, 1H), 2.37 (d, J = 4.0 Hz, 0.1H), 2.31 (td, J = 14.0, 5.0 Hz, 1H), 2.23–2.08 (m, 2.2H), 2.19 (d, J = 15.0 Hz, 1H), 2.06–1.99 (m, 1H), 2.01 (d, J = 15.0 Hz, 1H), 1.89–1.83 (m, 0.2H), 1.81–1.75 (m, 1H), 1.74–1.61 (m, 5.2H), 1.60 (s, 3H), 1.58 (s, 0.3H), 1.53 (dd, J = 16.0 6.5 Hz, 1H), 1.48–1.42 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 1.36–1.10 (m, 27H), 0.13 (s, 9H), 0.12 (s, 0.9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 214.6, 127.6, 83.16, 79.84, 78.44, 56.87, 52.28, 42.60, 40.35, 38.60, 35.78, 35.18, 33.47, 33.30, 32.95, 31.76, 31.56, 27.82, 26.84, 25.81, 21.56, 19.05, 18.94, 18.90, 18.71, 14.99, 14.61, 14.09, 2.84, 2.73; HRMS (FD+) calcd for $C_{33}H_{61}NO_3S_2Si_2$ $[M]^+$: 639.3631, found: 639.3638.

Compound 78



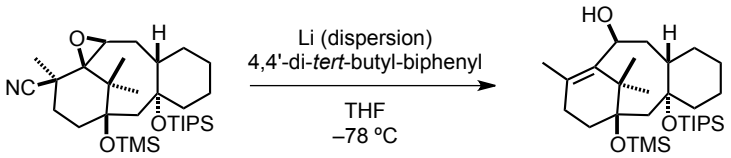
A solution of xanthate **84** (532 mg, 0.831 mmol) in 1,2,4-trichlorobenzene (4.2 mL) was placed in 200 °C of oil bath. After being stirred for 5 min, the reaction mixture was cooled to room temperature. The mixture was filtered through a silica gel plug, which was rinsed with hexane then hexane/EtOAc (50:1). The crude olefins **83a**,**b** was used for the next step without further purification.

To a solution of crude olefins **83a**,**b** in CH_2Cl_2 (2.6 mL) was added *m*CPBA (532 mg, 2.31 mmol) at 0 °C. After being stirred for 3 h at room temperature, the mixture was quenched with an aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1 to 20:1) afforded epoxide **78** (311 mg, 68% over 2 steps) as a colorless oil and **85** (43.4 mg, 10% over 2 steps).

Corresponding to **78** data: IR (neat) v 2944, 2866, 2231, 1464, 1445, 1388, 1251, 1218, 1162,

1147, 1120, 1037, 1000, 969, 920, 895, 841, 753, 734, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.23 (d, *J* = 8.0 Hz, 1H), 2.43 (d, *J* = 15.0 Hz, 1H), 2.48–2.32 (m, 3H), 2.17 (ddd, *J* = 16.5, 13.0, 8.5 Hz, 1H), 1.85–1.76 (m, 2H), 1.76 (d, *J* = 15.0 Hz, 1H), 1.72–1.50 (m, 5H), 1.59 (s, 3H), 1.45–1.39 (m, 1H), 1.30 (s, 3H), 1.16 (s, 3H), 1.28–1.04 (m, 24H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 125.0, 81.43, 78.50, 65.74, 57.41, 54.26, 43.15, 42.72, 40.53, 38.86, 37.30, 34.43, 31.83, 29.59, 29.22, 26.68, 25.90, 23.72, 21.67, 18.78, 18.73, 14.30, 2.79; HRMS (EI+) calcd for $C_{31}H_{57}NO_3Si_2$ $[M]^+$: 547.3877, found: 547.3867.

Compound 50



78 **50**

To a suspension of a Li metal (39.3 mg, after being briefly immersed in hexanes to remove any mineral oil) in THF (2.8 mL) was added a 4,4'-di-*tert*-butylbiphenyl (151 mg, 0.568 mmol) at 0 °C. After being stirred for 1 h, the mixture was cooled to –78 °C. A solution of epoxide **78** (311 mg, 0.568 mmol) in THF (2.0 mL) was added to the mixture. After being stirred for 10 min, 1,2-dichloroethane followed by a saturated aqueous NH_4Cl solution were added. The mixture was separated, and aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1 then 10:1) afforded allyl alcohol **50** (288 mg, 97%) as a amorphous solid. IR (neat) *v* 3398, 2944, 2866, 1463, 1445, 1249, 1170, 1145, 1119, 1069, 1042, 960, 912, 882, 859, 838, 749, 735, 720, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.13 (br s, 1H), 2.74–2.67 (m, 1H), 2.45 (dd, *J* = 19.0, 10.5 Hz, 1H), 2.00 (d, *J* =14.5 Hz, 1H), 2.01–1.79 (m, 5H), 1.75–1.54 (m, 4H), 1.58 (s, 3H), 1.57 (s, 3H), 1.46 (d, *J* = 14.5 Hz, 1H), 1.45–1.20 (m, 4H), 1.09–1.05 (m, 25H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 142.6, 127.5, 81.84, 78.90, 72.29, 56.25, 43.34, 40.51, 39.17, 37.85, 35.47, 32.89, 31.73, 31.04, 26.53, 24.87, 21.93, 19.96, 18.90, 18.83, 14.29, 2.72; HRMS (EI+) calcd for $C_{30}H_{58}O_3Si_2$ $[M]^+$: 522.3924, found: 522.3911.

Chapter II

Synthetic Studies on Taxine B and 2-Deoxytaxine B Derivatives

2-1. Introduction

Taxine B (**86**) was isolated from English yew leaves (the genes *T. baccata* L.) in 1958 by Graf and Baxter, respectively.[24,25] Similarly with this compound, 2-deoxytaxine B derivative (**87**) (formal nomenclature: 9α,13α-diacetoxy-5α-[(*R*)-30-dimethylamino-30-phenylpropanoyloxy]taxa-4(20),11-diene- 1β,10β-diol) has also been isolated from seeds of the Chinese yew (the genes *T. mairei*) in 1999.[26] Although these compounds do not have antitumor activity like taxol, it is reported that taxine B has cardiovascular action similar to verapamil which is a Ca^{2+} channel blocker.[27] Since these natural products have not been synthesized so far, the author planed to apply the synthetic strategy described in Chapter I to these natural products.

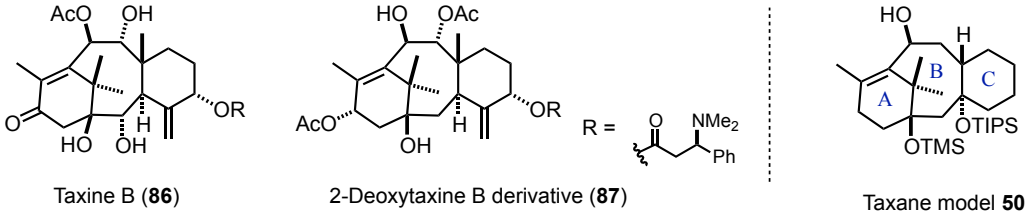
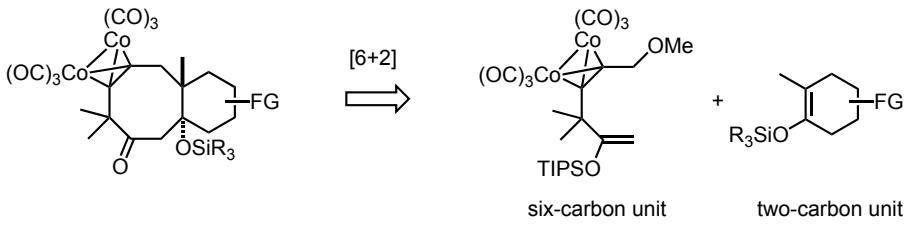


Figure 1. Natural taxane diterpenoids and taxane model compound

The large structural differences between the model compound and these natural products are the substituents on the C ring. With a view to constructing the angular quaternary carbon atom, the [6+2] cycloaddition reactions of enol silyl ethers possessing a methyl group ware explored.



Scheme 1. Synthetic plan toward taxine B

2-2. Synthesis of the BC ring system

In order to obtain the [6+2] cycloaddition products possessing the angular C-19 methyl group, several six-membered enol silyl ethers with suitable substituents were newly synthesized (Figure 2). The known enol silyl ethers **88a** and **88b** were synthesized according to literatures.[28,29]

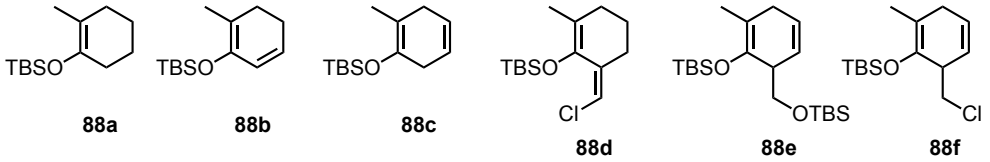
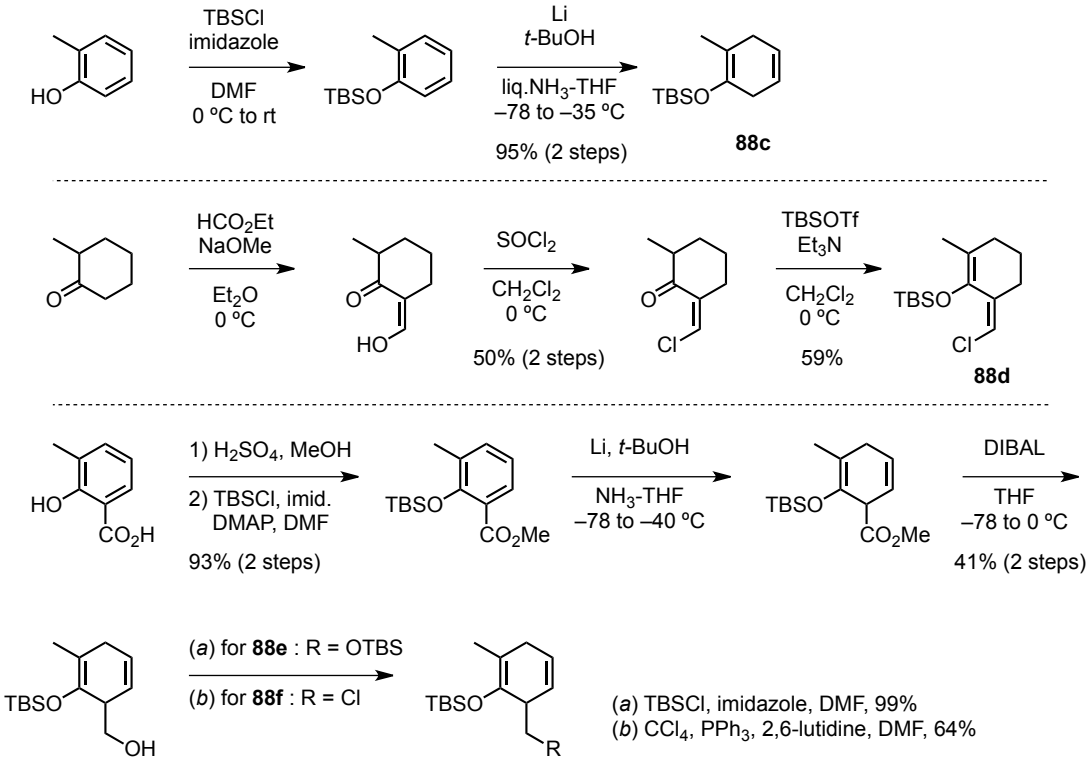


Figure 2. New substrates for the [6+2] cycloaddition reactions

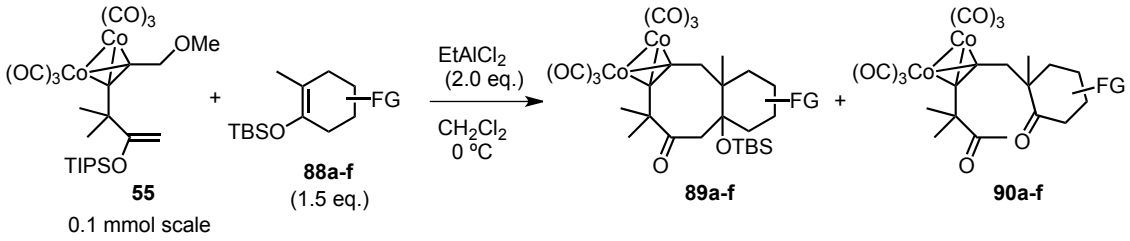


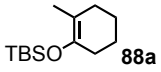
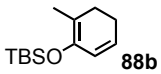
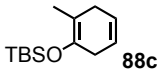
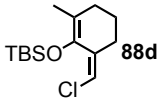
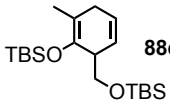
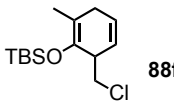
Scheme 2. Preparation of the enol silyl ethers

With the new enol silyl ethers in hand, the [6+2] cycloaddition reactions with dicobalt acetylene complex **55** were explored (Table 1). Generally, the methyl group of the enol silyl ethers was found to affect the intramolecular cyclization step of the [6+2] cycloaddition reaction. Thus, the desired product **89a** was obtained in only 20% yield from enol silyl ether **88a**, and

diketone **90a** arising from desilylation of the silyloxonium ion intermediate was formed in 76% yield (entry 1). Enol silyl ethers **88b** and **88f** having a conjugated diene moiety failed to undergo the cycloaddition reaction, resulting in formation of a complex mixture (entries 2 and 6). On the other hand, 1,4-cyclohexadiene derivative **88c** gave the cycloadduct **89c** in 77% yield as a single diastereomer, the stereochemistry of which was not determined at this stage (entry 3). Since an additional substituent on the six-membered ring of **88d-e** inhibited the cyclization step (entries 4 and 5), bicyclic ketone **89c** was chosen as the key intermediate of the total synthesis.

Table 1. The [6+2] cycloaddition reaction with various enol silyl ethers

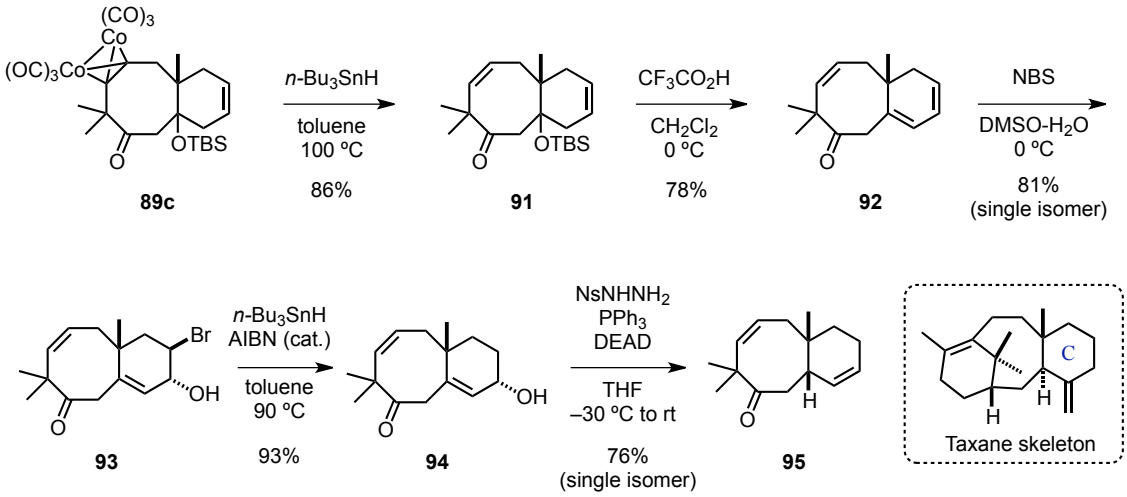


entry	two-carbon unit	yield: **89**	**90**
1	 **88a**	20%	76%
2	 **88b**	complex mixture	
3[a]	 **88c**	77%	13%
4	 **88d**	0%	trace
5	 **88e**	0%	59%
6	 **88f**	complex mixture	

a) Conducted at 20 mmol scale.

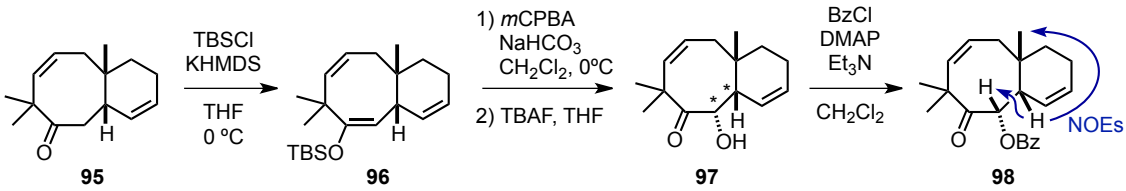
Cobalt complex **89c** was heated with tributyltin hydride to afford the corresponding olefin **91** which was subjected to various transformations. Treatment of silyl ether **91** with trifluoroacetic acid promoted elimination of the tertiary silyloxy group, and conjugated olefin **92** was obtained in good yield. Several attempts to introduce an oxygen functionality to the conjugated diene

moiety were fruitless, but the reaction with NBS in wet DMSO yielded bromohydrin **93** as a single isomer. While the configuration of the substituents could not be determined at this point, radical reduction of the bromide moiety gave allyl alcohol **94** which was subjected to the Myers' Mitsunobu reduction condition,[30] giving rise to the C ring moiety of the taxane skeleton (Scheme 3).



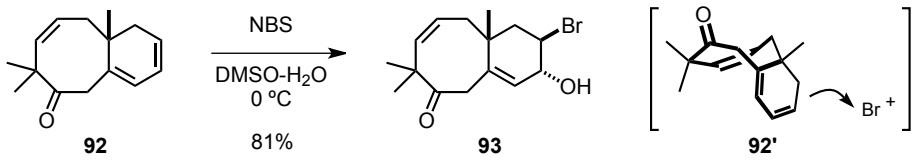
Scheme 3. First attempts for construction of the BC ring system

The stereochemistry of the bicyclic skeleton of **95** was, however, found to be cis after transformation of ketone **98** (Scheme 4). Thus, enol silyl ether **96** derived from ketone **95** was oxidized with *m*CPBA to give an α-silyloxy ketone. Removal of the silyl group followed by benzoylation of the resulting ketol **97** gave ester **98** in which the cis relationship between the angular methyl group and the methyne proton was established by the NOE experiments.



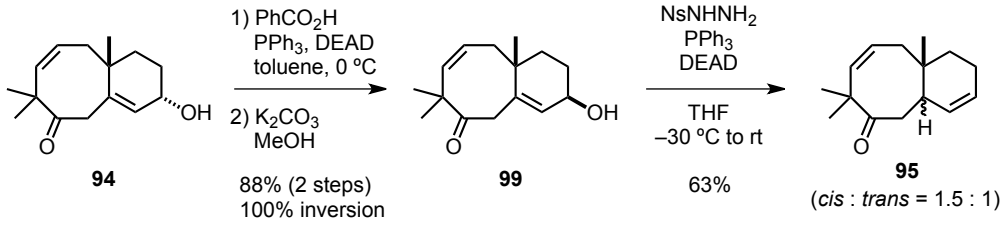
Scheme 4. Confirmation the stereochemistry of **98**

Therefore, the stereochemistry of bromohydrin intermediate **93** was supposed as depicted in Scheme 3, which is consistent with the reaction pathway through bromonium ion formation at the convex-face followed by attack of water on the allylic carbon atom (Scheme 5).



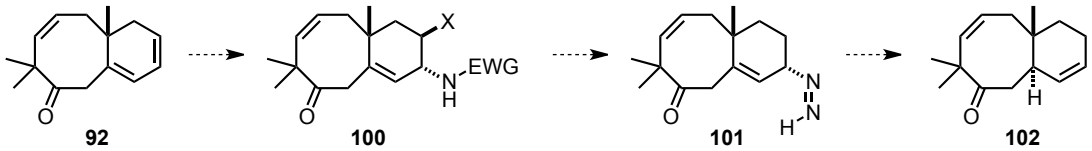
Scheme 5. Stereochemistry of bromohydrin formation

With a view to constructing the *trans*-fused BC ring system, allyl alcohol **94** was subjected to Mitsunobu inversion reaction followed by hydrolysis of the resulting benzoate to afford the epimeric alcohol **99** (Scheme 6). The Myers' Mitsunobu reduction of **99**, however, led to formation of a 1.5:1 mixture of *cis*- and *trans*-fused compounds, indicating that introduction of the nitrogen atom from the concave-face of the bicyclic skeleton is very difficult.



Scheme 6. Reductive Mitsunobu reaction with β-alcohol **99**

These results prompted the author to develop a new method for constructing the *trans*-fused BC ring system as shown in Scheme 7. Similarly with the bromohydrin formation from **92**, a haloamination reaction of **92** would afford the adduct with a 5α-amino group and a 6β-halogen substituent **100**. After removal of the halogen atom, amination of the allylic nitrogen atom would lead to formation of the desired *trans*-fused product **102** through allyldiazene rearrangement of **101**.[31]

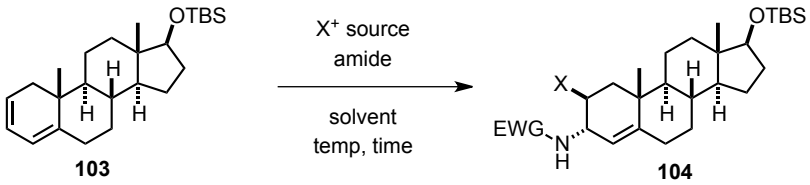


Scheme 7. Alternative plan for the stereoselective synthesis of trans-fused ketone **102**

The new idea was explored by using steroid derivative **103** as a model compound, and the haloamination reaction with a halogenation reagent and a sulfonamide derivative were

examined (Table 2).

Table 2. Bromoamination reaction of steroid derivative **103**



103 **104**

entry	X^+ source	(eq.)	amide	(eq.)	solvent	temp. (ºC)	time (min)	NMR yield[a]
1	NBS	(1.2)	$MsNH_2$	(1.2)	CH_2Cl_2	0	15	31%
2	NIS	(1.2)	$MsNH_2$	(1.2)	CH_2Cl_2	0	5	20%
3	NBS	(1.2)	$TsNH_2$	(1.2)	CH_2Cl_2	0	5	44%
4	NIS	(1.2)	$TsNH_2$	(1.2)	CH_2Cl_2	0	20	36%
5	I_2	(1.0)	Chloramine T	(1.0)	H_2O-CH_2Cl_2	rt	15	54%
6	I_2	(1.0)	Chloramine M	(1.0)	H_2O-CH_2Cl_2	rt	15	complex mixture
7	$TsNBr_2$	(1.2)	—		CH_2Cl_2	0	5	59%

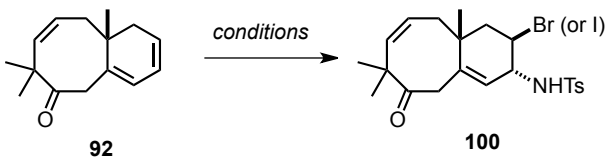
a) Pyrazine was used as an internal standard.

chloramine T chloramine M

The combined use of NBS or NIS with methanesulfonamide ($MsNH_2$) or *p*-toluenesulfonamide ($TsNH_2$) effected the desired transformation of diene **103**, albeit in low yield (entries 1–4). The haloamination reaction with I_2 and chloramine T in aqueous two-phase system afforded the desired product **104** in 54% yield (entry 5).[32] On the other hand, dibromoamine T ($TsNBr_2$) was found to act as both a bromination reagent and the nitrogen source, giving rise to the adduct **104** in 59% yield (entry 7).[33]

These results led the author to apply the conditions of entries 3,5 and 7 to the real substrate **92** (Table 3). The reaction with $TsNH_2$ and NBS gave the desired product **100** in 46% yield (entry 1), and a similar result was obtained by applying

Table 3. Bromoamination to the real substrate



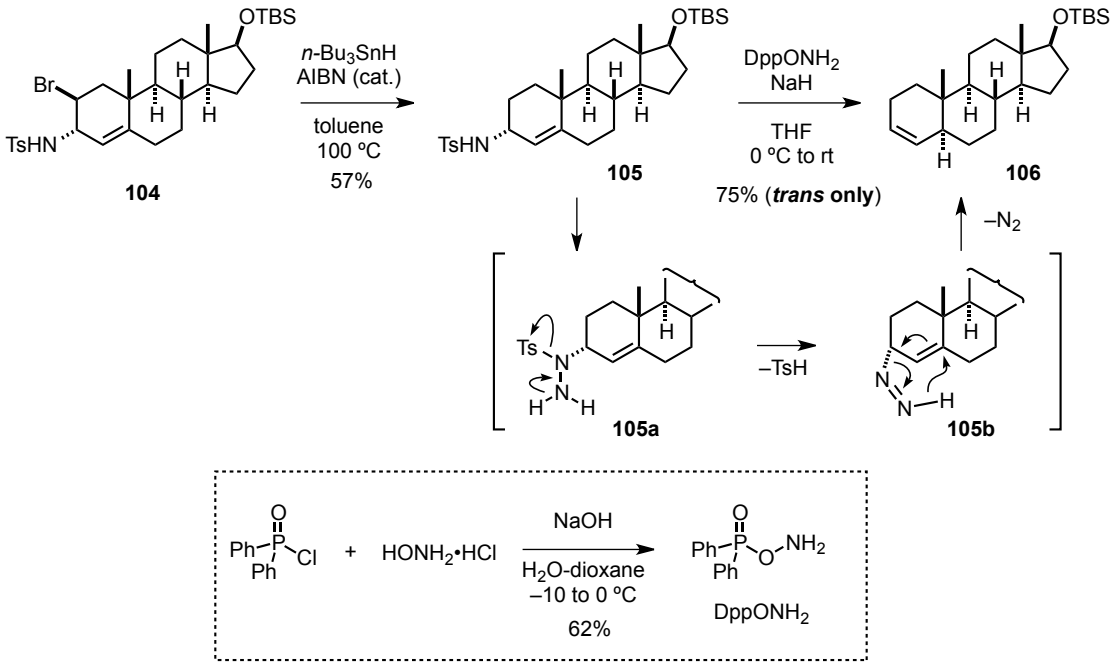
92 **100**

entry	*conditions*	**Table 2**	NMR yield[a]
1	$TsNH_2$, NBS CH_2Cl_2, 0 ºC	*same as entry 3*	46%
2	Chloramine T, I_2 H_2O-CH_2Cl_2, rt	*same as entry 5*	46%
3	$TsNBr_2$ CH_2Cl_2, 0 ºC	*same as entry 7*	84%[b]

a) Pyrazine was used as an internal standard. *b*) Isolated yield

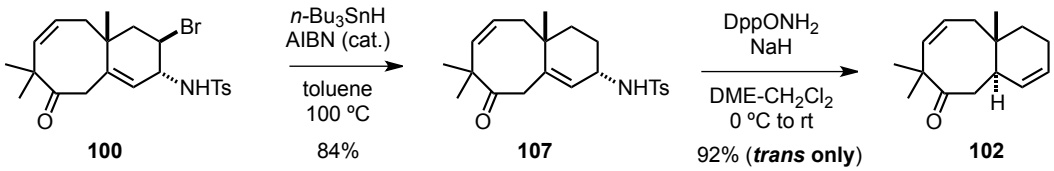
the same reaction conditions of entry 5 in Table 2. Gratifyingly, use of $TsNBr_2$ led to the desired product **100** in 84% isolated yield (Table 3, entry 3).

With the desired haloamides in hand, the stage was set for construction of the *trans*-fused bicyclic system. A preliminary experiment was again conducted by using steroid analog **105** which was prepared by radical reduction of bromoamination product **104** (Scheme 8). Successive treatment of amide **105** with sodium hydride and *O*-diphenylphosphinyl hydroxylamine ($DppONH_2$), which was reported as a useful NH_2^+ equivalent,[34] effected the desired transformation into olefin **106** with the *trans*-AB ring system. This reaction proceeds through *N*-amination to give a *N*-tosylhydrazine derivative **105a**, detosylation to form the allyldiazene derivative **105b**, followed by rearrangement to yield the desired product.



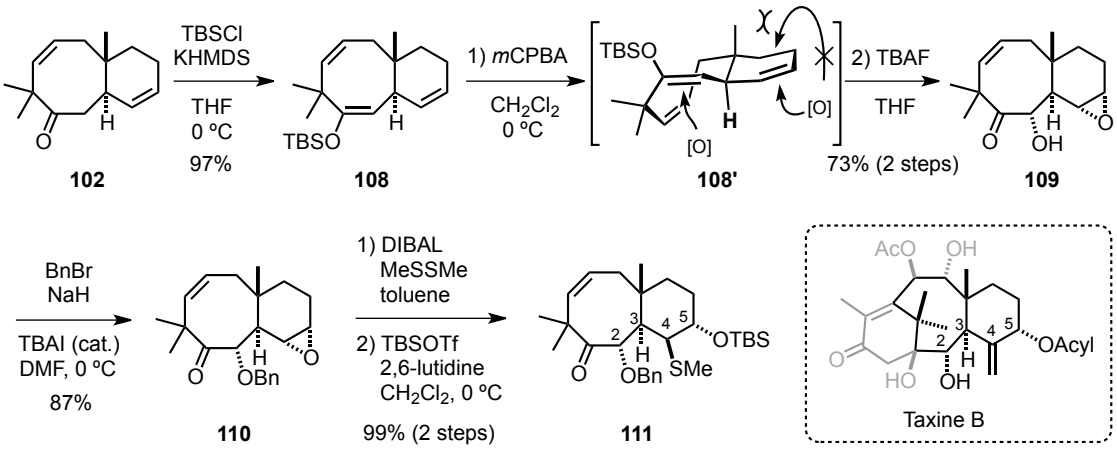
Scheme 8. Reductive deamination via allyldiazene rearrangement

The procedure was successfully applied to the transformation of bromide **100** into *trans*-fused BC ring segment **102** as shown in Scheme 9.



Scheme 9. Construction of the *trans*-fused BC ring system

The key intermediate **102** was then submitted to functional manipulation on the B and C rings (Scheme 10). The *m*CPBA oxidation of enol silyl ether **105** derived from ketone **102** followed by desilylation gave epoxy ketol **109** as a single diastereomer. Protection of the hydroxyl group with a benzyl group afforded epoxide **110** which was reacted with diisobutylaluminum methylthiolate prepared from DIBAL and dimethyl disulfide. The methylthio group was introduced at the C4 position via axial attack from the β-face, and the resulting alcohol was protected with a TBS group to afford **111** in quantitative yield.

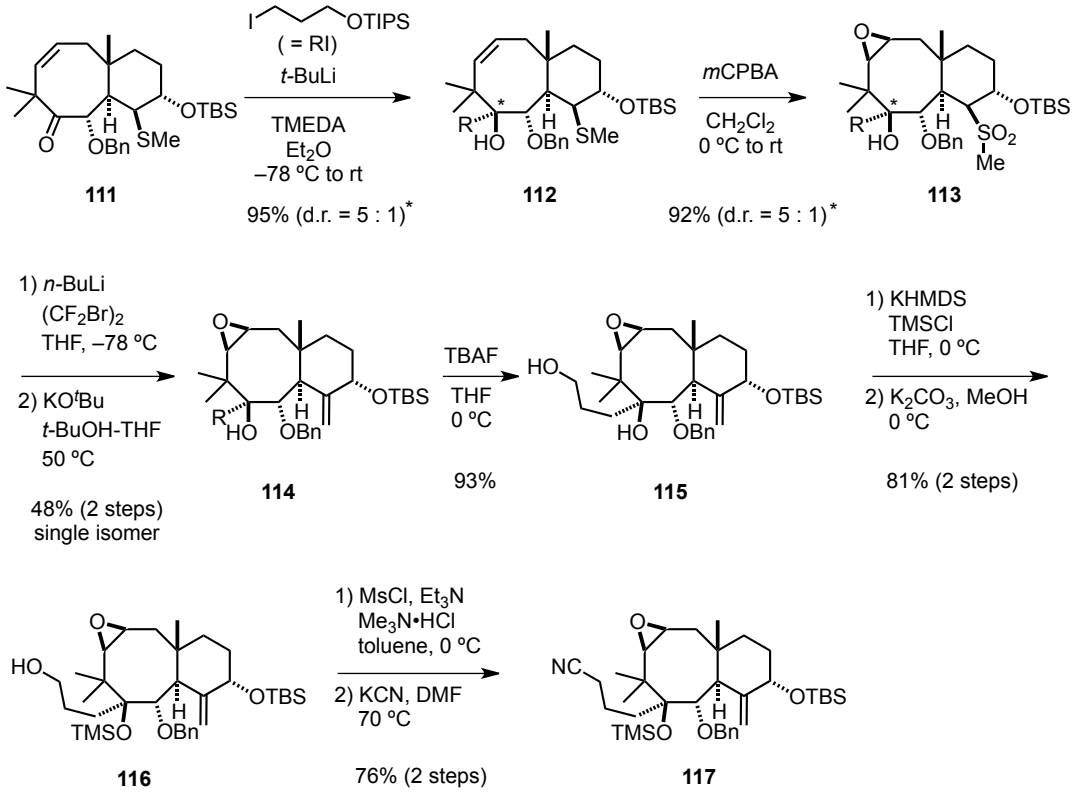


Scheme 10. Synthesis of BC ring system of taxine B

2-3. Construction of the A ring

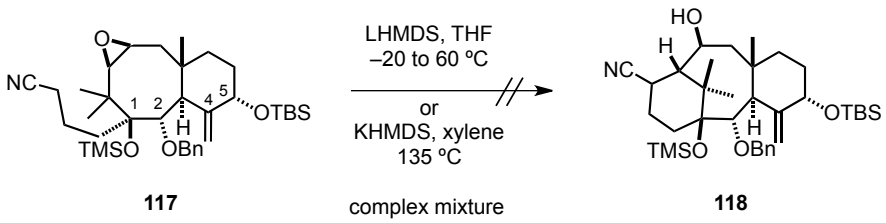
Synthesis of the cyclization precursor with an epoxide moiety and an alkanenitrile side chain was accomplished as shown in Scheme 11. The side chain was introduced by the reaction of ketone **111** with the organolithium prepared from 3-silyloxy-1-iodopropane, and alcohol **112** was obtained as a 5:1 mixture with its diastereomer. Treatment of **112** with an excess amount of *m*CPBA afforded epoxy sulfone **113** that was subjected to Ramberg-Bäcklund rearrangement,[35] giving rise to *exo*-olefin **114** in moderate yield. Removal of the terminal silyl group and protection of the tertiary alcohol moiety with a TMS group afforded primary alcohol **116**, and

the cyano group was introduced through a substitution reaction of the corresponding methansulfonate.



Scheme 11. Synthesis of a cyclization precursor

With epoxy nitrile **117** in hand, construction of the A ring under basic conditions was examined (Scheme 12). Treatment of **117** with LHMDS at –20 ºC to room temperature produced no product other than the starting material, and heating of the reaction mixture up to 60 ºC or 135 ºC merely led to decomposition of **117**.



Scheme 12. Attempted cyclization of epoxy nitrile **117**

These results suggested that the steric repulsion between the C-1 silyloxy group and the C-2

benzyloxy groups might restrict the conformation of the eight-membered B ring to prevent the cyclization reaction. Since the allyl silyl ether moiety on the C ring also seemed to be labile under basic conditions, a new cyclization precursor **119** having the protected 1,2-diol moiety was designed (Figure 3). Since epoxy nitrile **119** lacks the C2 oxygen functionality, the target natural compound should be 2-deoxytaxine B derivative isolated from seeds of the Chinese yew.[26] It is also noteworthy that oxidation of the C2 methylene group of taxusin derivative **120** has been achieved on the basis of an intramolecular C-H insertion reaction using the White's iron catalyst **121** (Scheme 13).[36]

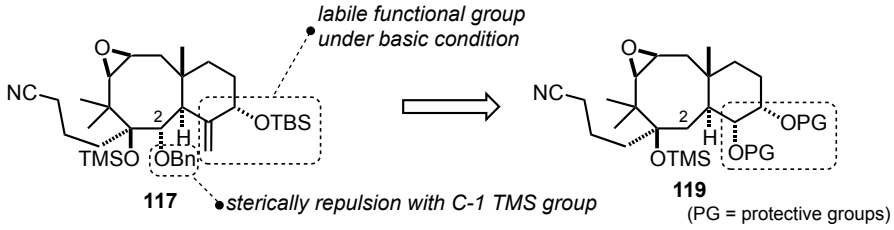
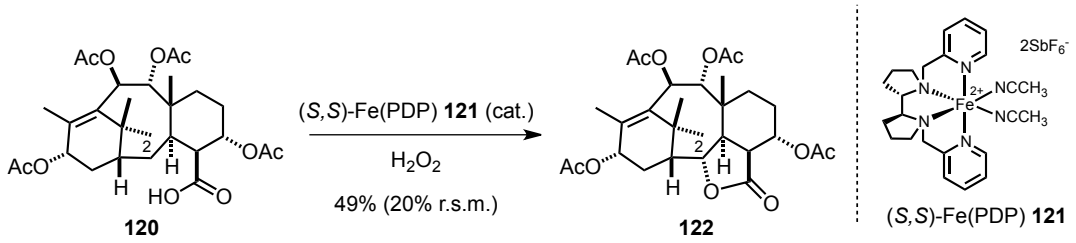
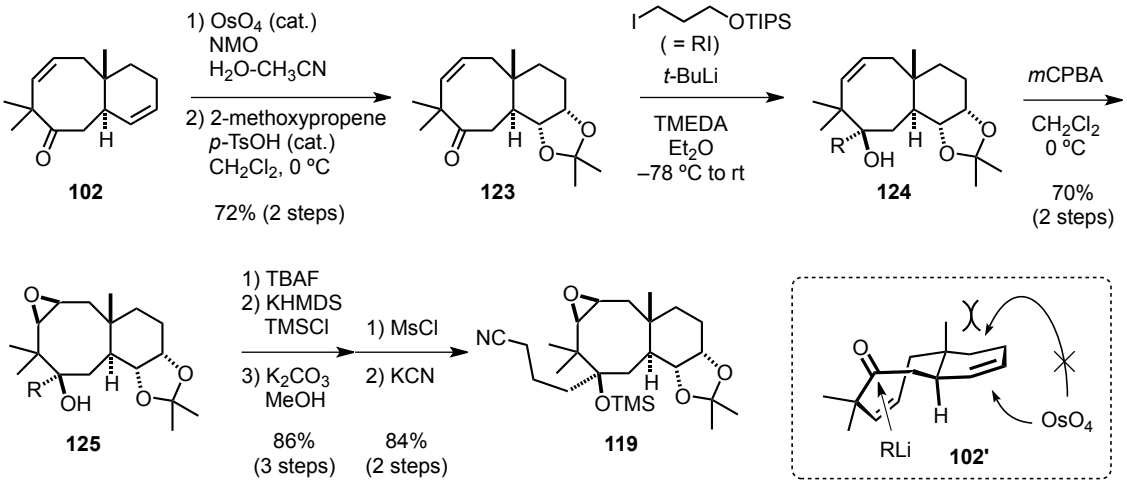


Figure 3. Design of the new cyclization precursor



Scheme 13. Directed oxidation of the C-2 C–H bond of taxusin derivative (M. Christina White et al.[36])

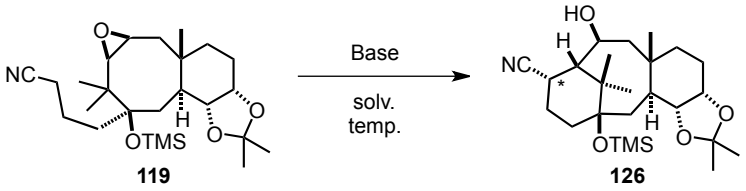
The new cyclization precursor **119** was prepared in a similar manner to the synthesis of **117** (Scheme 14). The sterically less hindered C4-C5 double bond of diene **102** was selectively oxidized with osmium tetroxide from the opposite face of the angular methyl group. Protection of the resulting diol as an acetonide **123**, stereoselective introduction of the side chain, and *m*CPBA oxidation of the remaining olefin moiety afforded epoxide **125** which was transformed into nitrile **119** through five-step transformation.



Scheme 14. Synthesis of the cyclization precursor

With the epoxy nitrile in hand, cyclization reactions under basic conditions were explored as shown in Table 4. The reaction with LHMDS at 60 ºC failed to yield the desired product, resulting in formation of a complex mixture (entry 1). On the other hand, heating at higher temperature facilitated the cyclization reaction of **119** to afford **126** in moderate yields. Thus, **126** was obtained in 33% yield as a single diastereomer by the reaction with KHMDS in toluene at 110 ºC (entry 2). While the yield of **126** was increased up to 48% by performing the reaction at 140 ºC in xylene (entry 3), refluxing in mesitylene at 165 °C led to decreased yield of **126**.

Table 4. Cyclization reactions of epoxy nitrile **119**

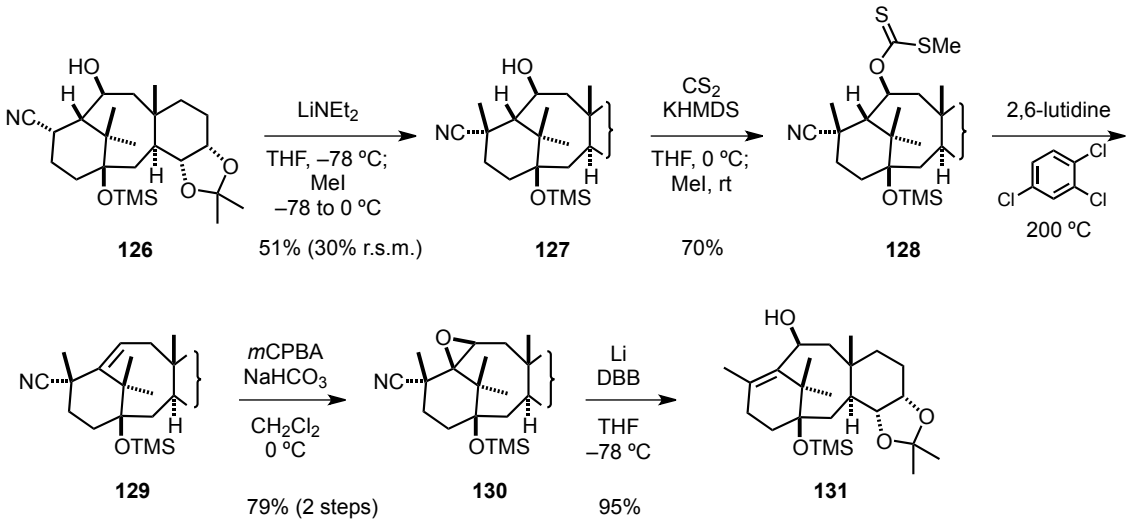


* single isomer

entry	Base	(eq.)	solv.	temp. (ºC)	yield
1	LHMDS	(3.0)	THF	–20 to 60	complex mixtures
2	KHMDS	(3.0)	toluene	110	33%
3	KHMDS	(3.0)	xylene	140	40–48%
4	KHMDS	(3.0)	mesitylene	165	34%
5	LHMDS	(3.0)	xylene	140	39%
6	NaHMDS	(3.0)	xylene	140	40%

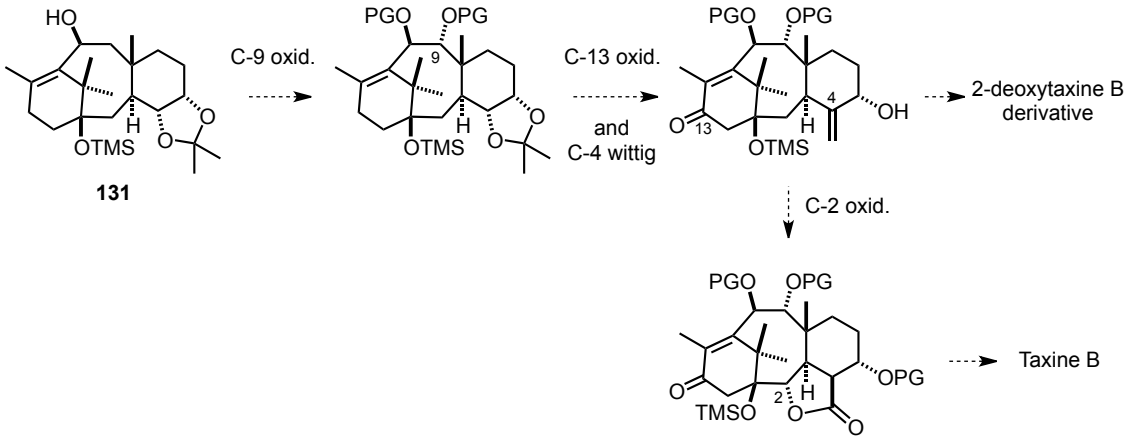
Other amide bases (LHMDS and NaHMDS) also effected the cyclization reaction at 140 ºC, giving rise to **126** in slightly lower yield (entries 5 and 6).

With a view to applying the similar method for installation of the bridgehead double bond in the A ring described in Chapter I, the C-12 methyl group was introduced through successive treatment with $LiNEt_2$ and methyl iodide. In contrast to the model study, the reaction of α-cyano carbanion generated by $LiNEt_2$ proceeded at the concave-face of the AB ring system (see; Chapter I, scheme 11). Alcohol **127** was then transformed into epoxide **130** through the Chugaev elimination of xanthate **128** followed by *m*CPBA oxidation. It is noteworthy that formation of the strained C10-C11 olefin was exclusively observed in this reaction. Epoxy nitrile **130** was reduced with LDBB to generate an anionic species which underwent β-elimination of the epoxide, and the desired allyl alcohol **131** was obtained in excellent yield (Scheme 15).



Scheme 15. Installation of the bridgehead double bond

Since the basic skeleton of taxine B has been synthesized, the remaining task toward the total synthesis is functional group manipulation. Oxidation of the C9 and C13 methylene group would lead to 2-deoxytaxine B derivative, and further oxidation of the C2 methylene group is needed to accomplish the total synthesis of taxine B. These transformations are to be examined in the future work (Scheme 16).

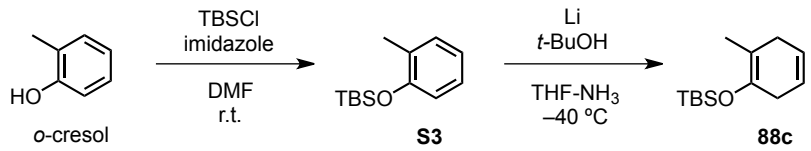


Scheme 16. Oxidation of the taxane skeleton **131**

In conclusion, the stereoselective construction of the core skeleton of 2-deoxytaxine B derivative was achieved through the [6+2] cycloaddition reaction using an acetylene dicobalt complex. The bicyclo[6.4.0]dodecane skeleton, which corresponds to the BC ring of taxane diterpenoids, was constructed by the cycloaddition reaction of an enol silyl ether possessing a six-membered ring. The angular silyloxy group was replaced with a hydrogen atom through an allyldiazene rearrangement reaction. After construction of the six-membered A ring by the epoxy nitrile cyclization, the bridgehead double bond of the A ring was introduced by reductive cleavage of an epoxy nitrile leading to the ABC tricyclic system of taxanes.

Experimental Section

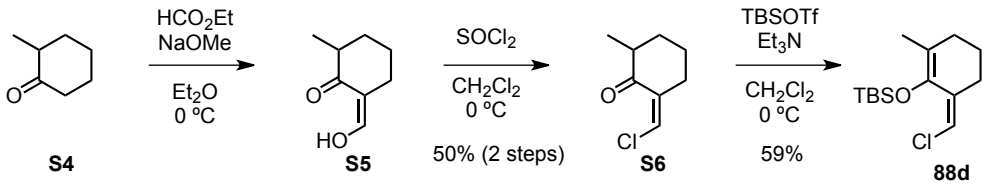
Compound 88c



To a mixture of *o*-cresol (9.5 mL, 92.5 mmol) and imidazole (12.6 g, 185 mmol) in DMF (185 mL) was added TBSCl (13.9 g, 92.5 mmol) at 0 °C. After being stirred for 3 h at room temperature, water was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S3** was used for the next step without purification.

To a mixture of crude **S3** and *t*-BuOH (44 mL, 450 mmol) in THF (120 mL) and liq.NH_3 (120 mL) was added lithium metal (1.87 g, 270 mmol) at –78 ºC. After being stirred for 2.5 h at –40 ºC, methanol and solid NH_4Cl were successively added, and NH_3 was removed by standing at room temperature. After addition of water, the mixture was separated. The aqueous layer was extracted with hexane. The combined organic layer was washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography (100% hexane) afforded diene **88c** (19.7 g, 98%) as a colorless oil. IR (neat) *v* 3030, 2929, 2857, 2819, 1703, 1472, 1254, 1192 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.67–5.59 (m, 2H), 2.68 (s, 4H), 1.60 (s, 3H), 0.95 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 140.5, 124.6, 123.6, 108.8, 32.83, 31.58, 31.34, 25.82, 15.63, –3.78; HRMS (FI+) calcd for $C_{13}H_{24}OSi$ $[M]^+$: 224.1596, found: 224.1582.

Compound 88d



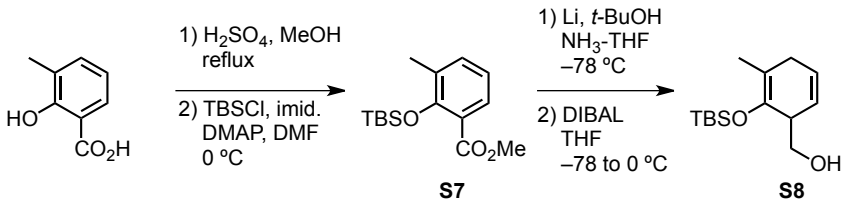
To a solution of NaOMe (540 mg, 10.0 mmol) in ether (20 mL) was added a solution of 2-methylcyclohexanone **S4** (1.34 mL, 11.0 mmol) in ethyl formate (0.88 mL, 11.0 mmol). The

mixture was stirred at 0 ºC for 15 min, then warmed to room temperature and stirred for 18 h. The thick suspension is filtered by suction, and the filter cake is washed with anhydrous ether. The solid salt was dissolved in water, and the mixture was acidified to pH = 1 with 1M HCl and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield **S5** (951 mg, 68%).

To a solution of hydroxymethylene ketone **S5** (300 mg, 2.14 mmol) in CH_2Cl_2 (10 mL) were added a thionyl chloride (0.31 mL, 4.28 mmol) and DMF (10 μL) at 0 ºC. After being stirred for 1 h, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% hexane) afforded **S6** (251 mg, 74%) as a colorless oil. ^{1}H NMR data was identical with the reported literature.[37] ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.07–7.05 (m, 1H), 2.93–2.86 (m, 1H), 2.43–2.33 (m, 2H), 2.08–2.01 (m, 1H), 1.98–1.90 (m, 1H), 1.74–1.64 (m, 1H), 1.59–1.50 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H).

To a mixture of **S6** (250 mg, 1.58 mmol) and Et_3N (0.65 mL, 4.72 mmol) in CH_2Cl_2 was added TBSOTf (0.54 mL, 2.36 mmol) at 0 ºC. After being stirred for 1 h at room temperature, water was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% hexane) afforded enol silyl ether **88d** (259 mg, 59%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.15 (s, 1H), 2.47 (t, J = 7.5 Hz, 2H), 2.11 (t, J = 6.5 Hz, 2H), 1.69 (s, 3H), 1.69–1.61 (m, 2H), 0.99 (s, 9H), 0.10 (s, 6H).

Compound S8



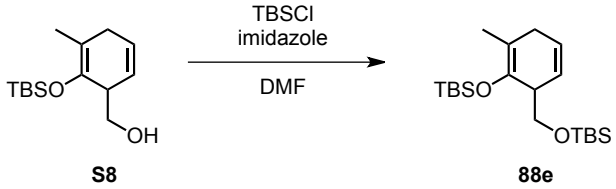
To a solution of 3-methylsalicylic acid (10.0 g, 65.7 mmol) in methanol (200 mL) was added H_2SO_4 (40 mL) and the mixture was stirred at 65 ºC. After being stirred at this temperature for 2 days, the mixture was concentrated under reduced pressure, and the residue was poured into ice cold saturated aqueous $NaHCO_3$. The organic materials were extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was used for the next step without purification.

To a mixture of crude methyl ester and imidazole (10.8 g, 159 mmol) in DMF (130 mL) was added TBSCl (12.0 g, 79.4 mmol) at 0 °C. After being stirred for 1 day at room temperature, DMAP (809 mg, 6.62 mmol) and TBSCl (5.98 g, 39.7 mmol) were added to the mixture. After being stirred for 2 days, water was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1) afforded silyl ether **S7** (17.3 g, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.29–7.25 (m, 2H), 6.92 (t, *J* = 7.5 Hz), 3.85 (s, 3H), 2.25 (s, 3H), 1.05 (s, 9H), 0.08 (s, 6H).

To a mixture of silyl ether **S7** (500 mg, 1.78 mmol) and *t*-BuOH (0.85 mL, 8.92 mmol) in THF (5.0 mL) and liq.NH_3 (10 mL) was added lithium metal (124 mg, 17.8 mmol) at –78 ºC. After being stirred for 2.5 h, methanol and solid NH_4Cl were successively added, and NH_3 was removed by standing at room temperature. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with brine, and dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was used for the next step without purification.

To a mixture of crude diene in THF (6.3 mL) was added a 1.0 M toluene solution of DIBAL (5.7 mL, 5.67 mmol) at –78 ºC. The reaction mixture was allowed to warm to 0 ºC. After being stirred for 1 h at 0 ºC, a saturated aqueous Rochelle salt solution was added. The mixture was stirred vigorously at room temperature for 30 min and then filtered through celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexane:EtOAc = 20:1 then 10:1) to give **S8** (199 mg, 41%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.86–5.82 (m, 1H), 5.61–5.56 (m, 1H), 3.83 (ddd, *J* = 10.0, 6.5, 3.5 Hz, 1H), 3.56 (ddd, *J* = 10.0, 6.5, 4.0 Hz, 1H), 2.90–2.84 (m, 1H), 2.73–2.68 (m, 2H), 1.66 (dd, *J* = 6.5, 5.5 Hz, 1H), 1.64 (d, *J* = 1.0 Hz, 3H), 0.96 (s, 9H), 0.13 (s, 6H).

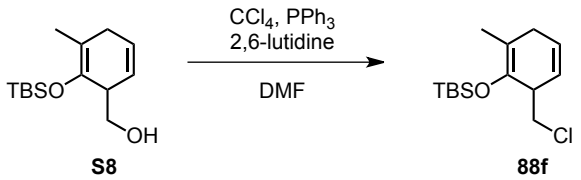
Compound 88e



S8 **88e**

To a mixture of alcohol **S8** (283 mg, 1.11 mmol) and imidazole (181 mg, 2.66 mmol) in DMF (3.7 mL) was added TBSCl (201 mg, 1.33 mmol) at 0 °C. After being stirred for 11 h at room temperature, water was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1) afforded **88e** (406 mg, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.79 (ddt, *J* = 7.5, 4.0, 2.0 Hz, 1H), 5.70 (dtd, *J* = 10.0, 3.0, 1.5 Hz, 1H), 3.92 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.48 (t, *J* = 10.0 Hz, 1H), 2.83–2.76 (m, 1H), 2.72–2.58 (m, 2H), 1.59 (s, 3H), 0.96 (s, 9H), 0.87 (s, 9H), 0.13 (s, 6H), 0.021 (s, 3H), 0.016 (s, 3H).

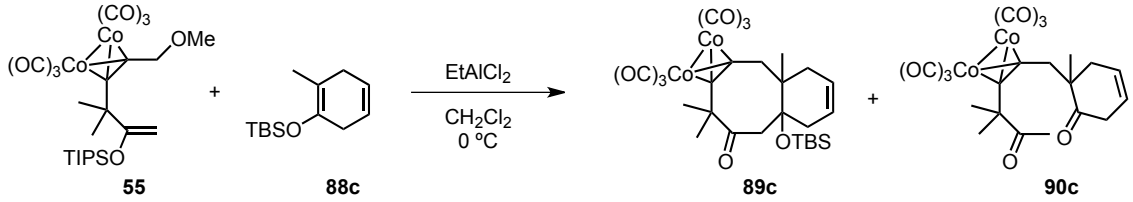
Compound 88f



S8 **88f**

To a mixture of **S8** (174 mg, 0.684 mmol) and PPh_3 (359 mg, 1.37 mmol) in DMF (3.4 mL) were added a 2,6-lutidine (0.47 mL, 4.10 mmol) and CCl_4 (0.20 mL, 2.05 mmol) at 0 ºC. After being stirred for 30 min at same temperature, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. After being added water, the mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with brine, and dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (100% hexane) afforded **88f** (119 mg, 64%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.83–5.75 (m, 2H), 3.80 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.51 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.06–2.99 (m, 1H), 2.76–2.62 (m, 2H), 1.62 (brs, 3H), 0.97 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H).

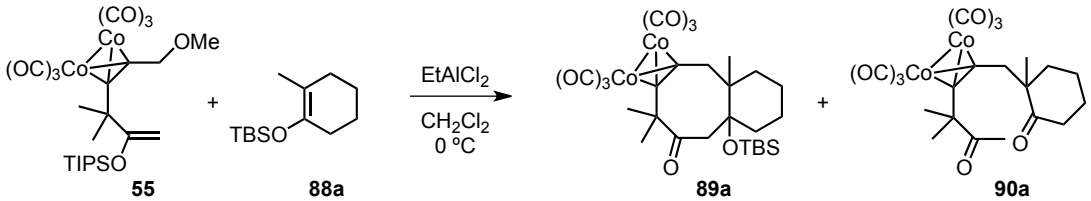
Compound 89c: Typical procedure for the [6+2]cycloaddition reaction



To a 1.07 M hexane solution of $EtAlCl_2$ (39 mL, 41.9 mmol) in CH_2Cl_2 (30 mL) was added a mixture of cobalt complex **55** (12.4 g, 20.8 mmol) and enol silyl ether **88c** (7.0 g, 31.2 mmol) in CH_2Cl_2 (40 mL) at 0 ºC. After being stirred for 5 min, a saturated aqueous Rochelle salt solution was added. After being stirred vigorously for 1 h under argon atmosphere at room temperature, the mixture was separated. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc=100:1 then 10:1) afforded **89c** (10.6 g, 77%) as a deep red solid, and **90c** as a deep-red oil which contains silanol as an inseparable mixture (c.a. 1.4 g, 13%, this yield was estimated by ^1H NMR).

For **89c** data: IR (neat) *v* 3020, 2957, 2930, 2857, 2087, 2048, 2024, 1703, 1464, 1257, 1216, 1061, 978, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.65–5.49 (m, 2H), 3.78–3.70 (m, 1H), 3.21–3.14 (m, 1H), 3.02–2.94 (m, 1H), 2.86–2.78 (m, 1H), 2.48–2.31 (m, 2H), 2.18–2.10 (m, 1H), 1.58–1.50 (m, 1H), 1.46–1.36 (m, 5H), 1.32–1.24 (m, 1H), 0.92–0.74 (m, 12H), 0.07 (brs, 6H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 209.5, 199.8, 125.8, 124.0, 78.10, 50.49, 49.82, 44.04, 43.92, 39.79, 35.77, 33.10, 29.20, 25.96, 22.53, 18.55, 17.67, –1.91, –2.75; HRMS (ESI+) calcd for $C_{27}H_{34}Co_2NaO_8Si$ $[M+Na]^+$: 655.0585, found: 655.0573.

Compounds 89a and 90a

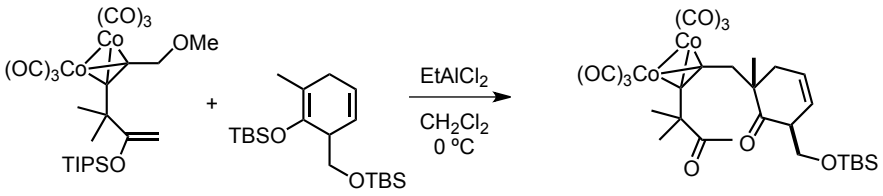


By the typical procedure for the [6+2] cycloaddition reaction of cobalt complex **55** (100 mg, 0.168 mmol) and enol silyl ether **88a** (57 mg, 0.252 mmol) afforded **89a** (21.3 mg, 20%) and **90a** (68.1 mg, 76%).

For **89a** data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.80 (d, *J* = 18.0 Hz, 1H), 3.18 (d, *J* = 12.0 Hz, 1H), 2.74 (d, *J* = 18.0 Hz, 1H), 2.38 (d, *J* = 12.0 Hz, 1H), 2.40–2.27 (m, 1H), 2.04 (td, *J* = 13.0, 4.5 Hz, 1H), 1.80–1.68 (m, 1H), 1.65–1.15 (m, 11H), 0.94 (s, 9H), 0.85 (s, 3H), 0.18 (s, 3H), 0.05 (s, 3H).

For **90a** data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.33–3.10 (m, 2H), 2.54–2.06 (m, 6H), 1.98–0.85 (m, 14H).

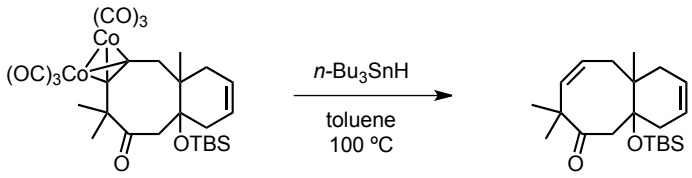
Compound 90e



55 **88e** **90e**

By the typical procedure for the [6+2] cycloaddition reaction of cobalt complex **55** (50 mg, 0.0838 mmol) and enol silyl ether **88e** (47 mg, 0.126 mmol) afforded **90e** (33.0 mg, 59%) as a deep-red oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.97–5.81 (m, 2H), 4.00–3.78 (m, 2H), 3.38–3.15 (m, 2H), 3.10–2.97 (m, 1H), 2.85–2.73 (m, 1H), 2.39–2.20 (m, 4H), 1.65–0.78 (m, 18H), 0.03 (brs, 6H).

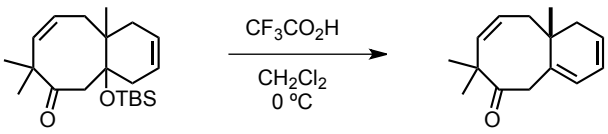
Compound 91



89c **91**

To a solution of cobalt complex **89c** (10.5 g, 15.8 mmol) in toluene (53 mL) was slowly added tributyltin hydride (21 mL, 79.2 mmol) at 100 °C. After being stirred for 10 min, a mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 500:1 then 100:1 then 30:1) afforded **91** (4.75 g, 86%) as a pale yellow oil. IR (neat) *v* 3023, 2967, 2927, 2856, 1704, 1470, 1254, 1101, 1080, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.63–5.58 (m, 1H), 5.53 (td, *J* = 11.0, 8.5 Hz, 1H), 5.47–5.42 (m, 1H), 5.41 (d, *J* = 11.0 Hz, 1H), 3.07 (d, *J* = 11.5 Hz, 1H), 2.35–2.30 (brs, 1H), 2.29 (dd, *J* = 14.0, 10.5 Hz, 1H), 2.15 (d, *J* = 20.0 Hz, 1H), 2.04 (d, *J* = 11.5 Hz, 1H), 2.04–1.99 (m, 1H), 1.54 (dd, *J* = 17.0, 5.0 Hz, 1H), 1.41 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.35 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 209.9, 136.4, 127.3, 126.8, 124.5, 77.54, 49.41, 44.59, 40.59, 38.98, 38.44, 32.91, 28.38, 26.78, 25.24, 19.42, 18.95, –1.00, –1.65; HRMS (FI+) calcd for $C_{21}H_{36}O_2Si$ $[M]^+$: 348.2485, found: 348.2466.

Compound 92

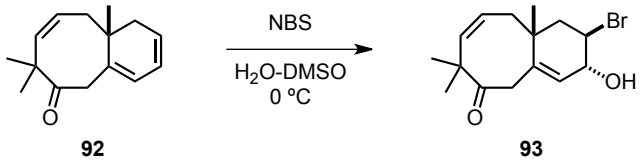


91 **92**

To a solution of **91** (4.75 g, 13.6 mmol) in CH_2Cl_2 (45 mL) was added trifloroacetic acid (3.0 mL, 40.9 mmol) at 0 °C. After being stirred for 1.5 h at 0 °C, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 30:1) afforded **92** (2.30 g, 78%) as a pale yellow oil. IR (neat) *v* 2966, 2925, 1709, 1463, 1372, 1298, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.81–5.75 (m, 1H), 5.68–

5.57 (m, 4H), 4.02 (d, J = 12.0 Hz, 1H), 2.62 (d, J = 12.0 Hz, 1H), 2.22 (d, J = 17.0 Hz, 1H), 2.01 (dd, J = 14.5, 8.5 Hz, 1H), 1.84 (dd, J = 17.0, 6.0 Hz, 1H), 1.74–1.68 (m, 1H), 1.24 (s, 3H), 1.17 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 215.9, 141.5, 138.8, 127.2, 124.6, 123.5, 123.4, 49.89, 44.23, 39.31, 37.98, 26.10, 23.86, 20.08, 14.16.; HRMS (EI+) calcd for $C_{15}H_{20}O$ $[M]^+$: 216.1514, found: 216.1538.

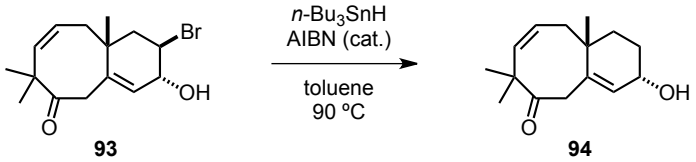
Compound 93



92 **93**

To a solution of **92** (68.0 mg, 0.314 mmol) in H_2O-DMSO (1:5, 1.2 mL) was slowly added NBS (67.2 mg, 0.377 mmol) at 0 °C. After being stirred for 45 min at 0 °C, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 3:1) afforded **93** (79.8 mg, 81%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.67 (s, 1H), 5.49–5.38 (m, 2H), 4.28 (d, J = 8.5 Hz, 1H), 4.12 (ddd, J = 14.0, 8.5, 4.0 Hz, 1H), 3.41 (d, J = 14.5 Hz, 1H), 3.19 (brd, J = 14.5 Hz, 1H), 2.25 (dd, J = 14.5, 4.0 Hz, 1H), 2.20–2.08 (m, 2H), 1.88 (dd, J = 14.0, 8.0 Hz, 1H), 1.31 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H).

Compound 94

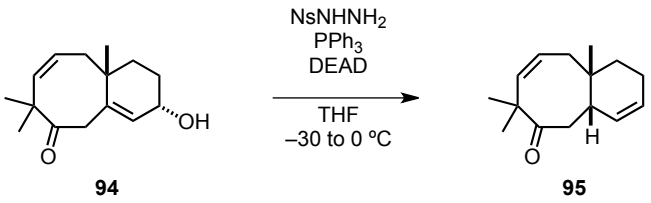


93 **94**

To a solution of **93** (105 mg, 0.335 mmol) in toluene (1.1 mL) were added AIBN (5.5 mg, 33.5 μmol) and tributyltin hydride (177 μL, 0.670 mmol) at 90 °C. After being stirred for 15 min at same temperature, a mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 then 3:1) afforded **94** (72.8 mg, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.69 (brs, 1H), 5.53 (brs, 1H), 4.08 (brs, 1H), 3.74 (brs,

1H), 2.76 (brs, 1H), 2.00–1.66 (m, 6H), 1.32–1.27 (m, 1H), 1.25 (brs, 3H), 1.15 (s, 3H), 1.05 (s, 3H).

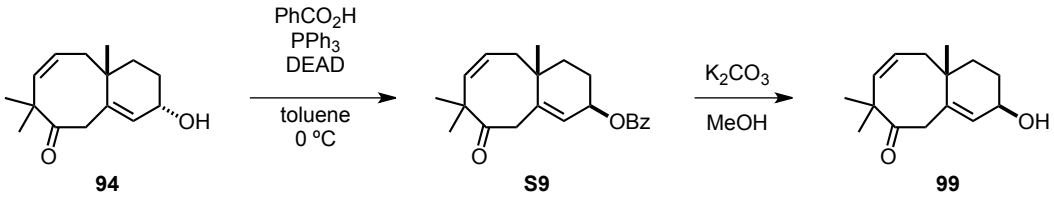
Compound 95



94 **95**

To a solution of **94** (10.0 mg, 42.7 μmol) in THF (0.2 mL) were added PPh_3 (22 mg, 85.4 μmol) and diethyl azodicarboxylate (39 μL, 85.4 μmol) at –30 °C. After being stirred for 30 min at same temperature, a solution of $NsNHNH_2$ (28 mg, 128 μmol) in THF (0.2 mL) was added to the mixture. After being stirred for 1 h at –30 ºC, the reaction mixture was allowed to warm to room temperature. After being stirred for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (hexane:EtOAc = 20:1 then 5:1 then 2:1) afforded **95** (7.1 mg, 76%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.66–5.60 (m, 1H), 5.60–5.47 (m, 3H), 2.99 (brs, 1H), 2.35 (brd, *J* = 11.0 Hz, 1H), 2.08–1.88 (m, 4H), 1.76–1.58 (m, 2H), 1.20 (s, 3H), 1.21–1.16 (m, 1H), 1.13 (s, 3H), 0.90 (s, 3H).

Compound 99



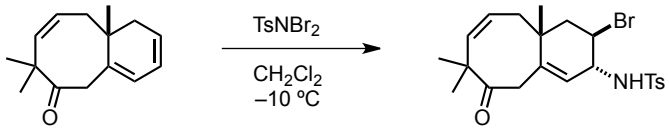
94 **S9** **99**

To a solution of **94** (10.0 mg, 42.7 μmol) in THF (0.3 mL) were added benzoic acid (10.4 mg, 85.4 μmol), PPh_3 (22 mg, 85.4 μmol) and diethyl azodicarboxylate (39 μL, 85.4 μmol) at 0 °C. After being stirred for 10 min, the reaction mixture was concentrated under reduced pressure. The residue was filtered through a silica gel plug, which was rinsed with hexane/EtOAc (20:1). The crude benzoate **S9** was used for the next step without further purification.

To a solution of crude benzoate **S9** in methanol (0.5 mL) was added K_2CO_3 (30 mg, 0.214 mmol) at room temperature. After being stirred for 3.5 h, a saturated aqueous NH_4Cl solution and ether were added. The mixture was separated, and the aqueous layer was extracted with

ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 then 3:1) afforded **99** (8.8 mg, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.57–5.44 (m, 3H), 4.26 (brs, 1H), 3.70 (brs, 1H), 2.72 (brs, 1H), 2.00–1.92 (m, 1H), 1.90–1.70 (m, 1H), 1.64–1.39 (m, 4H), 1.24 (brs, 3H), 1.15 (s, 3H), 1.12 (s, 3H).

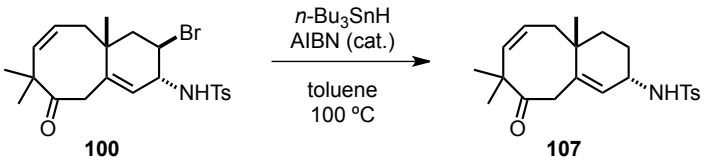
Compound 100



92 **100**

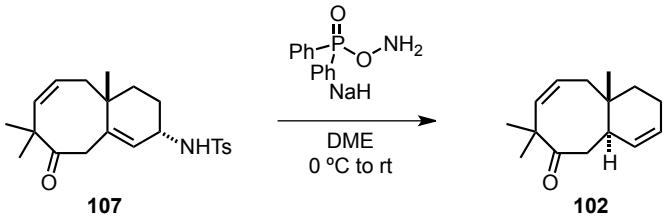
To a solution of diene **92** (2.30 g, 10.6 mmol) in CH_2Cl_2 (27 mL) was slowly added a solution of $TsNBr_2$ (4.20 g, 12.8 mmol) in CH_2Cl_2 (8 mL) at –10 °C. After being stirred for 5 min at –10 °C, an aqueous $Na_2S_2O_3$ solution was added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 then CH_2Cl_2:EtOAc = 30:1) afforded **100** (4.15 g, 84%) as a amorphous solid. IR (neat) *v* 3268, 2970, 2929, 2871, 1694, 1442, 1330, 1161, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.80 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.56 (brs, 1H), 5.47 (d, *J* = 11.0 Hz, 1H), 5.41–5.33 (m, 1H), 4.80 (brs, 1H), 4.05 (ddd, *J* = 10.5, 8.0, 4.0 Hz, 1H), 3.89–3.83 (m, 1H), 3.48–3.36 (m, 1H), 3.04 (brs, 1H), 2.43 (s, 3H), 2.21 (dd, *J* = 14.5, 3.5 Hz, 1H), 2.10–1.98 (m, 2H), 1.81 (dd, *J* = 14.5, 8.0 Hz), 1.67 (brs, 1H), 1.25 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 213.4, 143.8, 141.9, 139.7, 136.7, 129.7, 127.5, 126.6, 123.3, 57.24, 50.65, 49.34, 47.02, 45.70, 41.69, 39.39, 27.46, 26.98, 26.07, 21.58; HRMS (FD+) calcd for $C_{22}H_{28}BrNO_3S$ $[M]^+$: 465.0973, found: 465.0980.

Compound 107



To a solution of **100** (4.15 g, 8.92 mmol) in toluene (30 mL) were added AIBN (146 mg, 0.892 mmol) and tributyltin hydride (7.1 mL, 26.8 mmol) at 100 °C. After being stirred for 30 min at same temperature, a mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 then CH_2Cl_2:EtOAc = 30:1) afforded **107** (2.90 g, 84%) as a amorphous solid. IR (neat) *v* 3268, 2967, 2928, 2868, 1694, 1598, 1464, 1327, 1159, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.77 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.47 (brs, 2H), 5.22 (brs, 1H), 4.97 (brs, 1H), 3.70 (brs, 1H), 2.40 (s, 3H), 1.75–1.50 (m, 3H), 1.26–1.21 (m, 1H), 1.16 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), other peak cannot detected; ^{13}C NMR ($CDCl_3$, 125.8 MHz): very broadened spectra; HRMS (FD+) calcd for $C_{22}H_{29}NO_3S$ $[M]^+$: 387.1868, found: 387.1886.

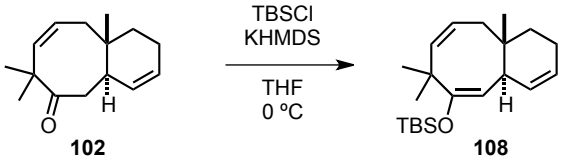
Compound 102



To a solution of NaH (362 mg, 15.1 mmol, after being briefly immersed in hexanes to remove any mineral oil) in DME (5 mL) was slowly added a solution of **107** (1.17 g, 3.02 mmol) in DME (30 mL) at 0 °C. After being stirred for 30 min at 0 °C, *O*-diphenylphosphinyl hydroxylamine (1.40 g, 6.04 mmol) was added to the mixture. After stirred for 1.5 h with ultrasonic waves, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1) afforded **102** (607 mg, 92%) as a colorless oil. IR (neat) *v* 3014, 2968, 2923, 1692, 1467 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ:

5.60–5.55 (m, 1H), 5.50 (d, J = 11.0 Hz, 1H), 5.36 (q, J = 11.0 Hz, 1H), 5.30 (brd, J = 8.5 Hz, 1H), 3.02 (brs, 1H), 2.50 (brs, 2H), 2.13–1.98 (m, 3H), 1.70 (dd, J = 14.5, 8.0 Hz, 1H), 1.54 (td, J = 12.0, 7.0 Hz, 1H), 1.28 (s, 3H), 1.29–1.23 (m, 1H), 1.14 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 216.1, 139.5, 129.9, 126.2, 122.8, 49.91, 44.62, 39.44, 35.29, 35.13, 29.64, 27.12, 26.10, 23.48, 17.68; HRMS (EI+) calcd for $C_{15}H_{22}O$ $[M]^+$: 218.1671, found: 218.1682.

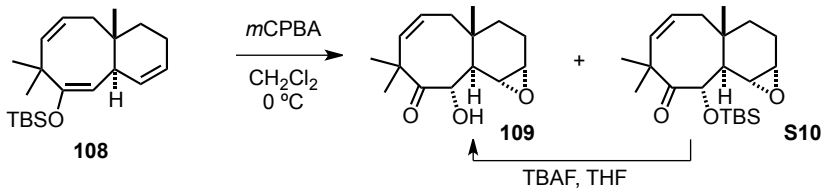
Compound 108



102 **108**

To a solution of **102** (366 mg, 1.68 mmol) in THF (5.5 mL) were added TBSCl (506 mg, 3.36 mmol) and a 0.5 M toluene solution of KHMDS (6.7 mL, 3.36 mmol) at 0 ºC. After being stirred for 20 min, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was washed with brine, and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% hexane) afforded enol silyl ether **108** (545 mg, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.57–5.50 (m, 2H), 5.46 (brd, J = 11.5 Hz, 1H), 5.26 (td, J = 10.5, 8.0 Hz, 1H), 4.30 (d, J = 10.5 Hz, 1H), 3.48–3.42 (m, 1H), 2.47 (t, J = 10.5 Hz, 1H), 2.13–1.96 (m, 2H), 1.60 (dd, J = 12.5, 7.5 Hz, 1H), 1.49 (td, J = 12.5, 7.0 Hz, 1H), 1.35–1.25 (m, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 0.94 (s, 9H), 0.75 (s, 3H), 0.19 (s, 6H).

Compound 109



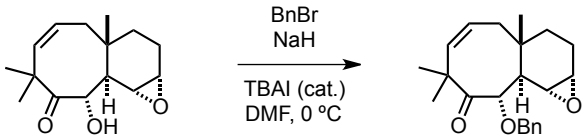
108 **109** **S10**

To a solution of **108** (523 mg, 1.57 mmol) in CH_2Cl_2 (7.9 mL) was added *m*CPBA (1.09 g, 4.72 mmol) at 0 ºC. After being stirred for 2 h at same temperature, 2-methyl-2-butene and a saturated aqueous $NaHCO_3$ solution were added. The mixture was separated, and the aqueous

layer was extracted with hexane. The combined organic layer was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography (hexane:EtOAc = 20:1 then 5:1) afforded silyl ether **S10** and alcohol **109** (211 mg, 53%).

To a solution of silyl ether **S10** in THF (2.5 mL) was added a 1.0 M THF solution of TBAF (2.3 mL, 2.25 mmol) at room temperature. After being stirred for 20 min, a saturated aqueous NH_4Cl was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 then 5:1) afforded alcohol **109** (80.4 mg, 20% from **108**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.51 (d, *J* = 10.5 Hz, 1H), 5.44 (q, *J* = 10.5 Hz, 1H), 4.45 (t, *J* = 11.0 Hz, 1H), 3.45 (brs, 1H), 3.21 (t, *J* = 3.5 Hz, 1H), 2.54 (d, *J* = 11.0 Hz, 1H), 2.06 (dd, *J* = 16.0, 6.5 Hz, 1H), 1.97–1.88 (m, 1H), 1.80 (brd, 10.5 Hz, 1H), 1.71 (dd, *J* = 14.5, 8.0 Hz, 1H), 1.60 (dd, *J* = 14.5, 10.0 Hz, 1H), 1.27 (s, 3H), 1.25 (s, 3H), 1.27–1.19 (m, 1H), 1.12 (dd, *J* = 13.0, 7.5 Hz, 1H), 0.92 (s, 3H).

Compound 110

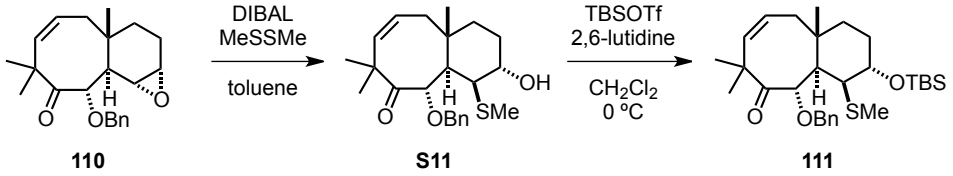


109 **110**

To a solution of NaH (108 mg, 4.50 mmol, after being briefly immersed in hexanes to remove any mineral oil) in DMF (2.5 mL) was slowly added a solution of **109** (376 mg, 1.50 mmol) in DMF (5.0 mL) at 0 ºC. After being stirred for 20 min at same temperature, benzyl bromide (0.27 mL, 2.25 mmol) and TBAI (55 mg, 0.15 mmol) were successively added, and the mixture was stirred for 30 min at 0 ºC. After addition of methanol and saturated aqueous NH_4Cl solution, the mixture was separated. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1 then 10:1) afforded alcohol **110** (444 mg, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.36–7.25 (m, 5H), 5.62 (d, *J* = 10.5 Hz, 1H), 5.35 (td, *J* = 10.5, 7.0 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 3.90–3.78 (m, 1H), 3.11 (brs, 1H), 2.99 (brs, 1H), 2.53 (d, *J* = 12.0 Hz, 1H), 2.00 (dd, *J* = 15.0, 6.0 Hz, 1H), 1.96 (dd, *J* = 15.0, 11.0 Hz, 1H), 1.88–1.79 (m, 1H), 1.70 (dd, *J* = 14.5, 7.0

Hz, 1H), 1.46 (s, 3H), 1.40 (td, *J* = 13.5, 5.5 Hz, 1H), 1.20 (s, 3H), 0.96 (dd, *J* = 13.5, 7.0 Hz, 1H), 0.85 (s, 3H).

Compound 111

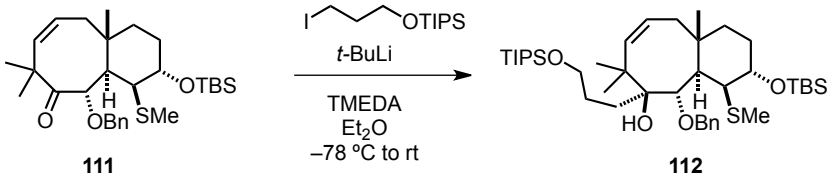


110 **S11** **111**

To a 1.0 M toluene solution of DIBAL (2.6 mL, 2.61 mmol) was added dimethyldisulfide (0.23 mL, 2.61 mmol) at room temperature. After being stirred for 30 min, a solution of **110** (444 mg, 1.30 mmol) in toluene (7.0 mL) was added at 0 ºC. After being stirred for 30 min at room temperature, a saturated aqueous Rochelle salt solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude **S11** was used for the next step without purification.

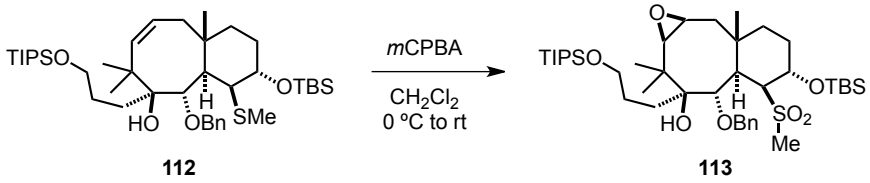
To a solution of crude **S11** in CH_2Cl_2 (4.3 mL) were added 2,6-lutidine (0.6 mL, 5.20 mmol) and TBSOTf (0.6 mL, 2.60 mmol) at 0 ºC. After being stirred for 5 min at the same temperature, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1) afforded **111** (648 mg, 99%) as a pale red solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.33–7.22 (m, 5H), 5.55 (d, *J* = 10.0 Hz, 1H), 5.42 (td, *J* = 10.0, 7.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.23 (d, *J* = 11.5 Hz, 1H), 4.00 (brs, 1H), 3.19–3.12 (m, 2H), 2.10 (tq, *J* = 14.5, 1.5 Hz, 1H), 1.98 (dd, *J* = 14.5, 10.0 Hz, 1H), 1.91–1.81 (m, 1H), 1.86 (s, 3H), 1.53 (s, 1H), 1.51 (dd, *J* = 14.5, 7.5 Hz, 1H), 1.43–1.37 (m, 1H), 1.39 (s, 3H), 1.17 (s, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

Compound 112



To a solution of 3-siloxy-1-iodopropane (147 mg, 0.430 mmol) in ether (2.2 mL) was added a 1.65 M pentane solution of *tert*-butyllithium (0.52 mL, 0.860 mmol) at –78 ºC. After being stirred for 1 h at the same temperature, a mixture of **111** (72 mg, 0.143 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.64 mL, 4.29 mmol) in ether (1.4 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After addition of a saturated aqueous NH_4Cl solution, the mixture was separated. The aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1) afforded **112** (98 mg, 95%, d.r.=5:1) as a colorless oil. Representative peaks: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.36–7.23 (m, 5H), 5.58–5.49 (m, 1H), 5.49 (d, *J* = 12.0 Hz, 1H), 5.24 (d, *J* = 11.0 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 3.92–3.87 (m, 1H), 3.70–3.56 (m, 3H), 2.69 (t, *J* = 3.5 Hz, 1H), 2.53 (brs, 1H), 2.40 (dd, *J* = 13.0, 10.5 Hz, 1H), 2.23–2.18 (m, 1H), 1.89–1.80 (m, 2H), 1.77 (s, 3H), 1.74–1.46 (m, 6H), 1.36–1.29 (m, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.13–0.94 (m, 24H), 0.88 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

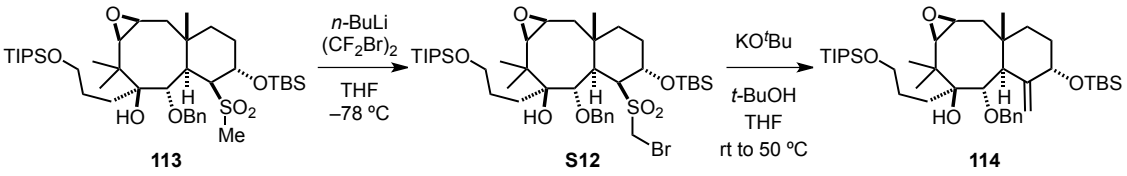
Compound 113



To a solution of **112** (98 mg, 0.136 mmol) in CH_2Cl_2 (0.7 mL) was added *m*CPBA (168 mg, 0.681 mmol) at 0 ºC. After being stirred for 4 h at room temperature, an aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution were added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography (hexane:EtOAc = 10:1) afforded **113** (96 mg, 92%, d.r.=5:1) as a

colorless oil. Representative peaks: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.49–7.46 (m, 2H), 7.33–7.25 (m, 3H), 4.90 (d, *J* = 9.0 Hz, 1H), 4.74 (d, *J* = 9.0 Hz, 1H), 4.61 (brs, 1H), 3.79 (d, *J* = 3.0 Hz, 1H), 3.76–3.70 (m, 1H), 3.69–3.56 (m, 1H), 3.40 (s, 1H), 3.31 (brs, 1H), 3.09 (t, *J* = 3.5 Hz, 1H), 3.04 (dt, *J* = 12.0, 4.0 Hz, 1H), 2.70 (d, *J* = 4.0 Hz, 1H), 2.47 (s, 3H), 2.20–2.02 (m, 3H), 1.95–1.85 (m, 2H), 1.79 (dd, *J* = 14.0, 4.0 Hz, 1H), 1.71–1.54 (m, 3H), 1.36 (s, 3H), 1.25 (s, 3H), 1.21 (brd, 12.5 Hz, 1H), 1.14 (s, 3H), 1.13–1.02 (m, 21H), 0.88 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H).

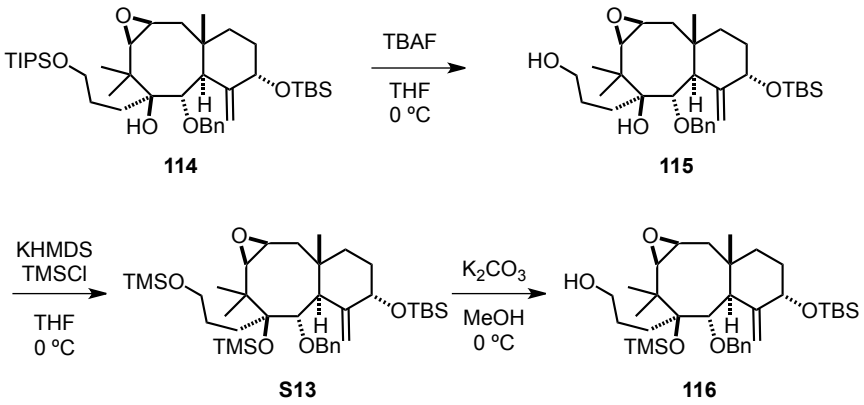
Compound 114



To a solution of **113** (43 mg, 56.0 μmol) in THF (0.5 mL) was slowly added a 1.65 M hexane solution of butyllithium (170 μL, 280 μmol) at –78 ºC. After being stirred for 15 min at the same temperature, 1,1,2,2-tetrafluoro-1,2-dibromoethane (34 μL, 280 μmol) was added at once. After being stirred for 5 min, methanol followed by a saturated aqueous NH_4Cl solution were added. The mixture was separated and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude **S12** was used for the next step without purification.

To a solution of crude **S12** in THF (0.1 mL) and *t*-BuOH (0.5 mL) was added potassium *tert*-butoxide (40 mg, 0.353 mmol) at room temperature. After being stirred at 50 ºC for 1 h, a saturated aqueous NH_4Cl solution was added at room temperature. The mixture was separated and the aqueous layer was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 30:1) afforded **114** (23.7 mg, 48%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.36–7.28 (m, 5H), 5.67 (s, 1H), 5.04 (s, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.11 (brs, 1H), 3.82 (d, *J* = 2.5 Hz, 1H), 3.68–3.63 (m, 1H), 3.57 (s, 1H), 3.55–3.49 (m, 1H), 3.24 (brs, 1H), 3.12 (dt, *J* = 11.5, 4.0 Hz, 1H), 2.76 (d, *J* = 4.0 Hz, 1H), 2.39 (td, *J* = 13.0, 4.0 Hz, 1H), 1.89 (dd, *J* = 14.5, 4.0 Hz, 1H), 1.85–1.71 (m, 4H), 1.64–1.58 (m, 1H), 1.53 (dd, *J* = 13.5, 11.5 Hz, 1H), 1.34 (s, 3H), 1.27–1.15 (m, 2H), 1.09 (s, 3H), 1.08 (s, 3H), 1.03–0.99 (s, 21H), 0.88 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).

Compound 116

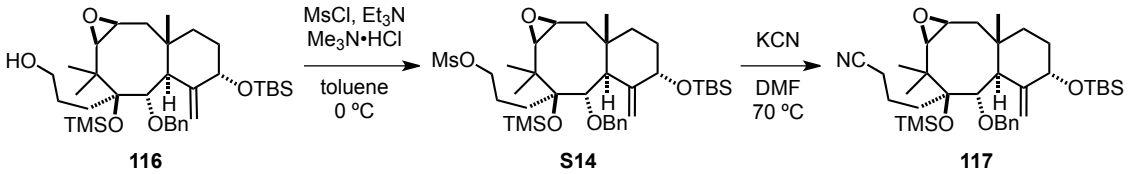


To a solution of **114** (23.7 mg, 33.8 μmol) in THF (0.3 mL) was added a 1.0 M THF solution of TBAF (56 μL, 56.0 μmol) at 0 ºC. After being stirred for 10 min at the same temperature, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude **115** was used for the next step without purification.

To a solution of crude **115** in THF (0.3 mL) were added TMSCl (12 μL, 94.2 μmol) and a 0.5 M toluene solution of KHMDS (188 μL, 94.2 μmol) at 0 ºC. After being stirred for 10 min at the same temperature, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S13** was used for the next step without purification.

To a solution of crude **S13** in methanol (0.5 mL) was added K_2CO_3 (22 mg, 157 μmol) at 0 ºC. After being stirred for 10 min at the same temperature, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) afforded **116** (15.6 mg, 75%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.34–7.21 (m, 5H), 5.91 (s, 1H), 5.07 (s, 1H), 4.98 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.13 (s, 1H), 3.89 (s, 1H), 3.62 (brs, 1H), 3.52 (brs, 1H), 3.17–3.10 (m, 2H), 2.71 (d, J = 4.5 Hz, 1H), 2.38–2.24 (m, 2H), 1.90–1.78 (m, 3H), 1.76–1.65 (m, 2H), 1.64–1.52 (m, 2H), 1.30 (s, 3H), 1.29–1.24 (m, 1H), 1.16–1.06 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.15 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

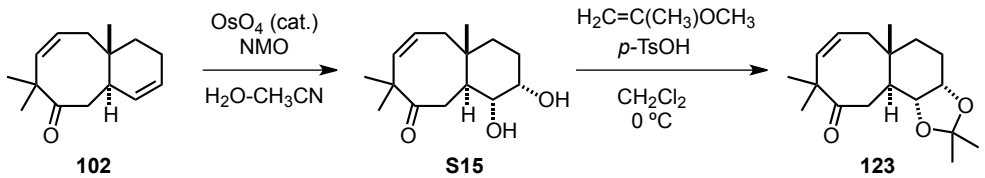
Compound 117



To a solution of **116** (15.6 mg, 25.3 μmol) in toluene (0.2 mL) were added triethylamine (21 μL, 152 μmol), Me_3N•HCl (2.4 mg, 25.3 μmol) and methanesulfonyl chloride (5.9 μL, 75.9 μmol) at 0 ºC. After being stirred for 5 min at the same temperature, water was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S14** was used for the next step without purification.

To a solution of crude **S14** in DMF (0.3 mL) was added potassium cyanide (27 mg, 415 μmol). The mixture was stirred at 70 ºC for 14 h and then cooled to room temperature. After addition of a saturated aqueous $NaHCO_3$ solution, the mixture was separated. The aqueous layer was extracted with ether, and the combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) afforded **117** (12.1 mg, 76%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.34–7.24 (m, 5H), 5.90 (s, 1H), 5.10 (s, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.15 (s, 1H), 3.90 (s, 1H), 3.16–3.09 (m, 2H), 2.66 (d, *J* = 4.0 Hz, 1H), 2.56–2.46 (m, 1H), 2.37–2.27 (m, 2H), 2.20–2.12 (m, 1H), 2.00–1.80 (m, 3H), 1.74–1.65 (m, 2H), 1.65–1.55 (m, 1H), 1.30 (s, 3H), 1.30–1.24 (m, 1H), 1.18–1.11 (m, 1H), 1.09 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.16 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

Compound 123

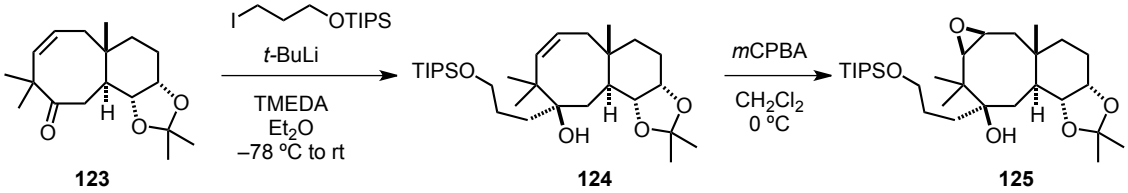


To a solution of **102** (727 mg, 3.33 mmol) in H_2O (6.0 mL) and acetonitrile (11 mL) were added *N*-methylmorpholine oxide (410 mg, 3.50 mmol) and a 0.157 M *t*-BuOH solution of osmium tetroxide (2.1 mL, 0.333 mmol). After being stirred for 1.5 h, a saturated aqueous Na_2SO_3

solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S15** was used for the next step without purification.

To a solution of crude **S15** in CH_2Cl_2 (17 mL) were added 2-methoxypropene (0.62 mL, 6.66 mmol) and *p*-toluenesulfonic acid monohydrate (119 mg, 0.333 mmol) at 0 ºC. After being stirred for 20 min at the same temperature, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:7 then 10:1) afforded **123** (700 mg, 72%) as a pale yellow oil. IR (neat) *v* 2969, 2933, 2873, 1703, 1468, 1380, 1244, 1218, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 5.49 (d, *J* = 11.0 Hz, 1H), 5.36 (brs, 1H), 4.20 (brs, 1H), 3.66 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.13–2.14 (m, 2H), 2.07–1.97 (m, 1H), 1.89 (brs, 1H), 1.73–1.47 (m, 6H), 1.35 (s, 3H), 1.31–0.98 (m, 8H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) very broadened spectra; HRMS (FD+) calcd for $C_{18}H_{28}O_3$ $[M]^+$: 292.2038, found: 292.2020.

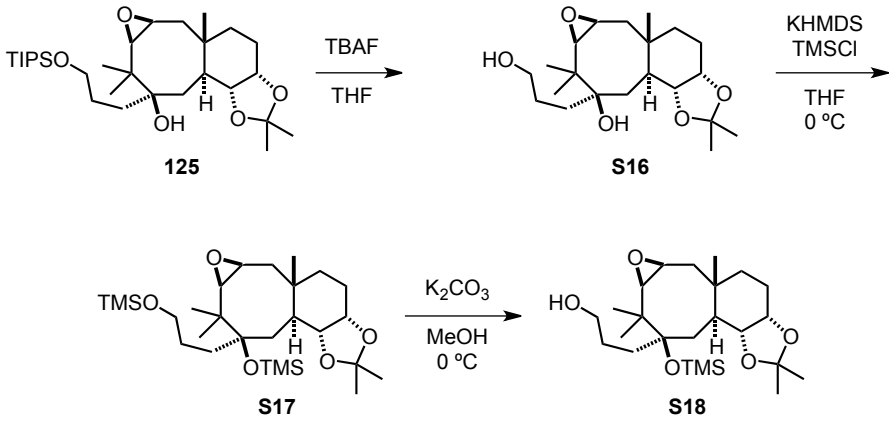
Compound 125



To a solution of 3-siloxy-1-iodopropane (240 mg, 0.702 mmol) in ether (3.5 mL) was added a 1.65 M pentane solution of *tert*-butyllithium (0.85 mL, 1.40 mmol) at –78 ºC. After being stirred for 1 h at the same temperature, a mixture of **123** (68.4 mg, 0.234 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.70 mL, 4.68 mmol) in ether (1.5 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After addition of a saturated aqueous NH_4Cl solution, the mixture was separated. The aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a silica gel plug, which was rinsed with hexane/EtOAc (5:1). The crude **124** was used for the next step without further purification.

To a solution of crude **124** in CH_2Cl_2 (1.0 mL) was added *m*CPBA (108 mg, 0.436 mmol) at 0 ºC. After being stirred for 1 h at the same temperature, an aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution were added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography (hexane:EtOAc = 10:1 then 5:1 then 2:1) afforded **125** (85.7 mg, 70%) as a white solid. mp 104–109 °C; IR (neat) *v* 3423, 2942, 2866, 1463, 1379, 1366, 1247, 1214, 1167, 1101, 1070, 1026, 882, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.20 (brs, 1H), 3.88–3.83 (m, 1H), 3.78 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.68–3.62 (m, 1H), 2.93 (dt, *J* = 12.0, 4.5 Hz, 1H), 2.70 (d, *J* = 4.5 Hz, 1H), 2.05–1.88 (m, 7H), 1.74 (dd, *J* = 14.5 Hz, 1H), 1.63–1.50 (m, 2H), 1.49 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.24–1.18 (m, 1H), 1.16–1.05 (m, 21H), 1.04 (s, 3H), 1.02 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 106.8, 81.24, 76.50, 72.53, 64.76, 61.16, 54.85, 42.77, 41.77, 39.41, 37.47, 36.63, 33.55, 29.50, 27.99, 26.93, 25.99, 25.86, 23.33, 20.50, 20.06, 17.93, 17.89, 11.82; HRMS (FD+) calcd for $C_{30}H_{57}O_5Si$ $[M+H]^+$: 525.3975, found: 525.3947.

Compound S18



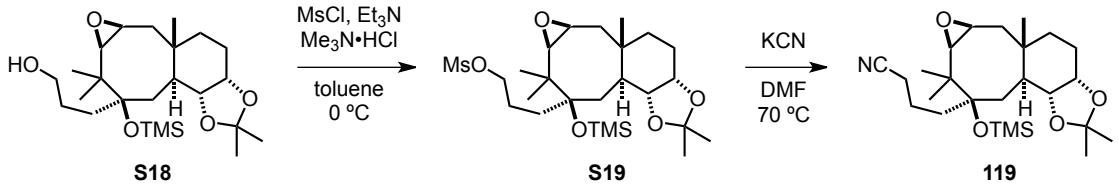
To a solution of **125** (724 mg, 1.38 mmol) in THF (7.0 mL) was added a 0.5 M THF solution of TBAF (2.1 mL, 2.07 mmol). After being stirred for 20 min, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S16** was used for the next step without purification.

To a solution of crude **S16** in THF (7.0 mL) was added a 0.5 M toluene solution of KHMDS (11 mL, 5.52 mmol) at 0 ºC. After being stirred for 10 min at the same temperature, TMSCl (697 µL,

5.52 mmol) was added. After being stirred for 10 min, a saturated aqueous $NaHCO_3$ solution was added. The mixture was separated, and the aqueous layer was extracted with hexane. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S17** was used for the next step without purification.

To a solution of crude **S17** in methanol (7.0 mL) was added K_2CO_3 (572 mg, 4.15 mmol) at 0 ºC. After being stirred for 20 min at the same temperature, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1 then 2:1) afforded **S18** (524 mg, 86%) as a colorless oil. IR (neat) *v* 3446, 2954, 2873, 1455, 1379, 1366, 1249, 1213, 1167, 1107, 1053, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.24–4.19 (m, 1H), 3.78 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.68–3.60 (m, 2H), 2.91 (dt, *J* = 12.0, 4.0 Hz, 1H), 2.71 (d, *J* = 4.0 Hz, 1H), 2.08–1.68 (m, 9H), 1.64–1.50 (m, 3H), 1.48 (s, 3H), 1.33 (s, 3H), 1.26–1.18 (m, 1H), 1.21 (s, 3H), 0.93 (s, 3H), 0.83 (s, 3H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 107.0, 82.26, 81.22, 72.58, 63.68, 61.26, 54.70, 43.61, 41.57, 39.49, 38.73, 36.41, 33.50, 30.55, 28.22, 27.86, 27.52, 25.87, 23.61, 21.15, 21.05, 2.96; HRMS (FD+) calcd for $C_{24}H_{45}O_5Si$ $[M+H]^+$: 441.3036, found: 441.3051.

Compound 119

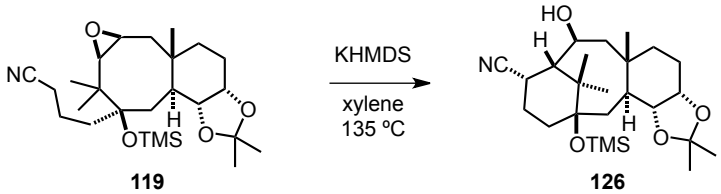


To a solution of **S18** (524 mg, 1.19 mmol) in toluene (6.0 mL) were added triethylamine (0.5 mL, 3.57 mmol), Me_3N•HCl (11 mg, 0.119 mmol) and methanesulfonyl chloride (184 μL, 2.38 mmol) at 0 ºC. After being stirred for 15 min at the same temperature, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S19** was used for the next step without purification.

To a solution of crude **S19** in DMF (4.0 mL) was added potassium cyanide (387 mg, 5.95 mmol). The mixture was stirred at 70 ºC for 5 h and then cooled to room temperature. After

addition of a saturated aqueous $NaHCO_3$ solution, the mixture was separated. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) afforded **119** (447 mg, 84%) as a colorless oil. IR (neat) *v* 2954, 2878, 2244, 1463, 1379, 1250, 1213, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.22 (dd, *J* = 9.0, 4.0 Hz, 1H), 3.79 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.91 (dt, *J* = 12.0, 4.5 Hz, 1H), 2.68 (d, *J* = 4.5 Hz, 1H), 2.39–2.25 (m, 2H), 2.19–2.10 (m, 1H), 2.06 (dd, *J* = 15.0, 6.5 Hz, 1H), 1.96–1.74 (m, 7H), 1.62–1.51 (m, 3H), 1.48 (s, 3H), 1.34 (s, 3H), 1.27–1.32 (m, 1H), 1.21 (s, 3H), 0.94 (s, 3H), 0.84 (s, 3H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 120.0, 107.0, 82.41, 81.24, 72.59, 60.95, 54.68, 43.66, 41.68, 39.45, 38.17, 36.41, 33.51, 33.48, 28.44, 27.37, 25.74, 23.70, 21.35, 21.02, 20.69, 17.76, 3.06; HRMS (FD+) calcd for $C_{25}H_{43}NO_4Si$ $[M]^+$: 449.2961, found: 449.2968.

Compound 126

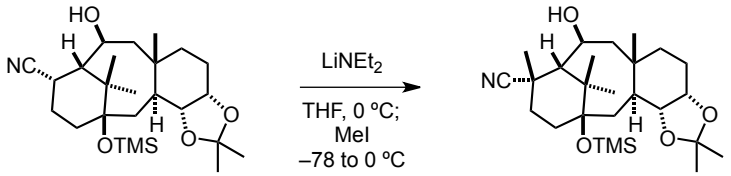


119 **126**

To a solution of **119** (121 mg, 0.269 mmol) in xylene (1.6 mL) was slowly added a 0.5 M toluene solution of KHMDS (1.61 mL, 0.807 mmol) at 135 ºC. After being stirred for 15 min at the same temperature, the reaction mixture was cool to room temperature and quenched with a saturated aqueous NH_4Cl solution. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1 then 4:1) afforded **126** (57.1 mg, 47%) as a pale yellow oil. IR (neat) *v* 2939, 2237, 1468, 1250, 1213, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.24 (brs, 1H), 3.97 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.63 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.36 (dt, *J* = 13.0, 4.5 Hz, 1H), 2.70 (dd, *J* = 15.5, 9.5 Hz, 1H), 2.47 (m, 1H), 2.22–1.86 (m, 9H), 1.76 (d, *J* = 15.0 Hz, 1H), 1.63 (t, *J* = 9.0 Hz, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.29 (d, *J* = 15.5 Hz, 1H), 1.15–1.11 (m, 1H), 1.13 (s, 3H), 0.80 (s, 3H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 123.8, 106.7, 79.28, 78.17, 72.13, 68.75, 57.16, 47.54, 42.67, 39.53, 39.49, 36.06, 33.80, 33.14, 31.37, 28.09, 27.73, 26.59, 25.85, 25.52, 23.21, 19.45, 2.61; HRMS (FD+) calcd for $C_{25}H_{43}NO_4Si$ $[M]^+$:

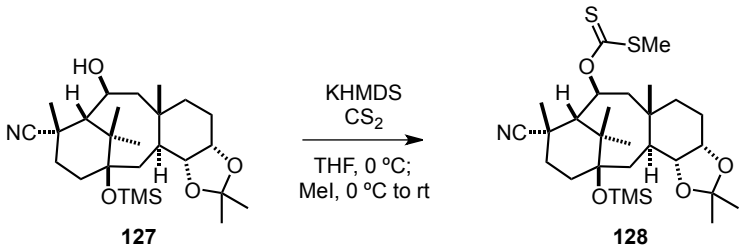
449.2961, found: 449.2970.

Compound 127



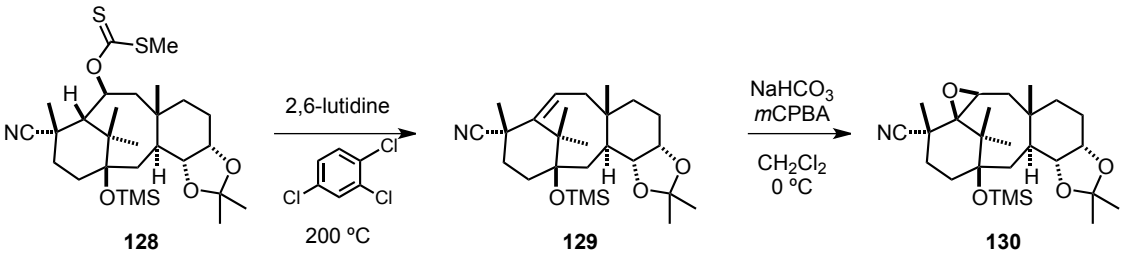
To a solution of **126** (22.0 mg, 48.9 μmol) in THF (0.24 mL) was slowly added a 0.5 M THF solution of $LiNEt_2$ (489 μL, 245 μmol) at –78 ºC. After being stirred for 15 min at 0 ºC, the mixture was cooled to –78 ºC and added iodomethane (30 μL, 489 μmol). After being stirred for 20 min at 0 ºC, a saturated aqueous NH_4Cl solution was added. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1 then 4:1 then 2:1) afforded **127** (11.6 mg, 51%) as a colorless oil and recovered starting material (6.7 mg, 30%). IR (neat) *ν* 2947, 1685, 1451, 1379, 1250, 1216, 1168, 1063, 953, 839, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.22–4.18 (m, 1H), 4.06 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.67 (dd, *J* = 9.5, 4.5 Hz, 1H), 2.25–2.17 (m, 1H), 2.19 (d, *J* = 14.5 Hz, 1H), 2.13–1.83 (m, 7H), 1.75 (d, *J* = 16.5 Hz, 1H), 1.69 (t, *J* = 9.5 Hz, 1H), 1.60 (dd, *J* = 14.5, 12.0 Hz, 1H), 1.55 (d, *J* = 11.5 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.28–1.19 (m, 1H), 1.14 (s, 3H), 1.13 (s, 3H), 0.95 (s, 3H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 118.5, 106.7, 80.20, 78.81, 75.30, 72.41, 58.35, 45.22, 45.16, 41.87, 40.01, 39.19, 38.54, 36.75, 32.68, 31.73, 29.09, 28.83, 28.68, 26.19, 25.85, 23.56, 19.66, 2.37; HRMS (FD+) calcd for $C_{26}H_{46}NO_4Si$ $[M+H]^+$: 464.3196, found: 464.3186.

Compound 128



To a solution of **127** (4.9 mg, 10.5 μmol) in THF (0.1 mL) was added KHMDS (105 μL, 52.4 μmol, 0.5 M solution in toluene) at 0 °C. After being stirred for 5 min, CS_2 (3.2 μL, 52.4 μmol) was added and stirred for 15 min at the same temperature. After iodomethane (6.5 μL, 105 μmol) was added to it, and the mixture was stirred for 10 min at room temperature. The reaction was quenched with a saturated aqueous NH_4Cl, and the mixture was separated. The aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) afforded xanthate **128** (4.1 mg, 70%) as a pale yellow oil. IR (neat) *ν* 2937, 1450, 1378, 1250, 1214, 1057, 969, 907, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.62–6.56 (m, 1H), 4.21–4.17 (m, 1H), 3.57–3.52 (m, 1H), 2.58 (s, 3H), 2.50–2.43 (m, 2H), 2.17–1.91 (m, 9H), 1.90–1.75 (m, 3H), 1.78 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H), 0.98 (s, 3H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 214.3, 125.4, 107.1, 85.43, 80.05, 77.91, 72.70, 45.67, 41.16, 40.54, 36.52, 34.86, 33.70, 33.47, 31.58, 30.59, 28.29, 21.17, 25.72, 25.66, 22.64, 22.58, 19.11, 14.12, 2.54; HRMS (FD+) calcd for $C_{28}H_{47}NO_4S_2Si$ $[M]^+$: 553.2716, found: 553.2709.

Compound 130

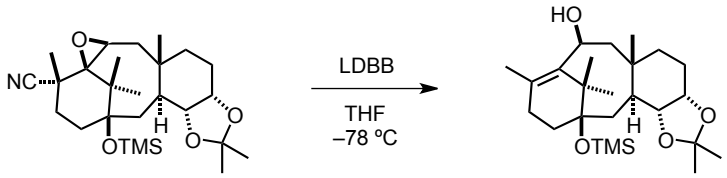


A mixture of xanthate **128** (4.1 mg, 7.40 μmol) and 2,6-lutidine (4.3 μL, 37.0 μmol) in 1,2,4-trichlorobenzene (0.1 mL) was placed in 200 °C of oil bath. After being stirred for 5 min, the reaction mixture was cooled to room temperature. The mixture was filtered through a silica

gel plug, which was rinsed with hexane then hexane/EtOAc (10:1). The crude olefin **129** was used for the next step without further purification.

To a solution of the crude olefin **129** in CH_2Cl_2 (0.1 mL) were added $NaHCO_3$ (2.3 mg, 26.9 μmol) and *m*-chloroperoxybenzoic acid (4.0 mg, 16.1 μmol) at 0 °C. After being stirred for 40 min at the same temperature, an aqueous $Na_2S_2O_3$ solution was added. The resulting mixture was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) afforded epoxide **130** (2.7 mg, 79% over 2 steps) as a white solid. IR (neat) *v* 2937, 1451, 1379, 1250, 1212, 1168, 1109, 1037, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.26–4.23 (m, 1H), 3.70 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.62 (dd, *J* = 12.0, 5.5 Hz, 1H), 2.57–2.49 (m, 1H), 2.41–2.27 (m, 2H), 2.13–1.92 (m, 6H), 1.85–1.76 (m, 3H), 1.64 (s, 3H), 1.34 (s, 3H), 1.35–1.28 (m, 1H), 1.28 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H), 0.87 (s, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 125.6, 107.0, 80.49, 80.22, 71.12, 64.51, 63.75, 44.78, 42.82, 41.22, 40.79, 40.20, 36.72, 35.49, 34.13, 32.37, 27.93, 27.17, 25.82, 24.70, 23.53, 23.38, 20.28, 2.60; HRMS (FD+) calcd for $C_{26}H_{43}NO_4Si$ $[M]^+$: 461.2961, found: 461.2963.

Compound 131



130 **131**

To a suspension of a Li metal (6.3 mg, after being briefly immersed in hexanes to remove any mineral oil) in THF (0.3 mL) was added a 4,4'-di-*tert*-butylbiphenyl (9.1 mg, 34.0 μmol) at 0 °C. After being stirred for 30 min, the mixture was cooled to –78 °C. A solution of epoxide **130** (15.7 mg, 34.0 μmol) in THF (0.5 mL) was added to the mixture. After being stirred for 10 min, 1,2-dichloroethane followed by a saturated aqueous NH_4Cl solution were added. The mixture was separated, and aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 then 4:1) afforded allyl alcohol **131** (14.1 mg, 95%) as a colorless oil. IR (neat) *v* 3398, 2941, 1458, 1379, 1364, 1249, 1211, 1167, 1065, 1039, 990, 878, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.94 (dd, *J* = 12.0,

5.5 Hz, 1H), 4.23–4.19 (m, 1H), 3.67 (dd, *J* = 10.5, 6.5 Hz, 1H), 2.60–2.51 (m, 1H), 2.32 (dd, *J* = 14.0, 12.5 Hz, 1H), 2.20–2.13 (m, 1H), 1.96–1.82 (m, 4H), 1.77 (s, 3H), 1.77–1.68 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.37–1.25 (m, 7H), 1.18–1.11 (m, 1H), 1.08 (s, 3H), 0.75 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 138.8, 134.8, 106.3, 81.94, 80.14, 72.47, 68.08, 47.41, 43.47, 41.41, 40.81, 36.58, 33.95, 31.98, 31.40, 28.31, 27.35, 25.53, 24.45, 22.51, 21.03, 20.86, 2.72; HRMS (FD+) calcd for $C_{25}H_{44}O_4Si$ $[M]^+$: 436.3009, found: 436.3009.

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