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Synthesis of the ABCDEF-Ring of Ciguatoxin 3C

（シガトキシン3CのABCDEF環の合成）

Takuto Sato

Dissertation
Hokkaido University
2017

Contents

Abbreviations

Ac	acetyl
AuNPs	gold nanoparticles
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	cerium(IV) diammonium nitrate
m-CPBA	*m*-chloroperoxybenzoic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPI	Dess-Martin-periodinane
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EE	ethoxyethyl
epi	epimer
equiv	equivalent
Et	ethyl
IPNBSH	*N*-isopropylidene-*N'*-2-nitrobenzenesulfonyl hydrazine
KHMDS	potassium hexamethyldisilazide
LHMDS	lithium hexamethyldisilazide
Me	methyl
MOM	methoxymethyl
NAP	2-naphthylmethyl
NHK	Nozaki-Hiyama-Kishi
NHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Np	2-naphthyl
Nph	neophyl
PBB	4-bromobenzyl
PCP	4-chlorophenyl
PDC	pyridinium dichromate

Ph	phenyl
Piv	pivaloyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
PMPAB	4-(*N*-methyl-*N*-phenylamino)benzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTS	*p*-toluenesulfonic acid
RCM	ring-closing olefin metathesis
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TC	thiophene-2-carboxylate
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPDS	1,3-(1,1,3,3-tetraisopropyldisiloxanylidene)
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tr	trityl

1. Introduction

1-1. Ciguatoxins

Ciguatera fish poisoning, which often breaks out in tropical coral reef regions, originates from naturally occurring toxins.[1] People develop ciguatera symptoms by eating poisoned fish. The typical symptoms are nausea, emesis, fatigue, arthralgia, and reversal of temperature sensation. Sometimes, the patients need a few months or a year to recover from these symptoms. However, ciguatera toxins are not produced by fish. The original producer of the toxins is dinoflagellate, *Gambierdiscus toxicus*. The toxins are first transformed into herbivorous fish and then into carnivorous fish by food chain.[2]

In 1967, the Scheuer group first isolated a causative agent of ciguatera from the moray eel, *Gymnothorax javanicus*, and named the compound ciguatoxin (CTX), which was later classified as ciguatoxin 1B (CTX1B).[3] However, they could not determine the structure of ciguatoxin due to the complexity and scarce material available. After 23 years, Yasumoto and co-workers isolated 0.35 mg of CTX1B from 4000 kg of the moray eels, and its relative stereostructure was determined by extensive NMR analysis.[4] In 1997, the absolute configuration of CTX1B was finally confirmed by the collaboration of Yasumoto and Hirama.[5] CTX1B possesses a ladder-shaped framework, which consists of *trans*-fused twelve ether rings with ring sizes ranging from six to nine memberes, a terminal five-membered spirocyclic acetal, and 33 chiral centers. On the other hand, ciguatoxin 3C (CTX3C) was isolated from cultured dinoflagellate, *Gambierdiscus toxicus,* by the Yasumoto group in 1993 (0.7 mg of CTX3C from 1100 L of the culture), thereby providing strong evidence that ciguatoxins are produced by the dinoflagellate.[6] The Yasumoto group also determined the relative structure of CTX3C by NMR analysis using only 0.7 mg of the sample, obtained from 1100 L of the culture. The absolute structure of CTX3C was determined by the total synthesis achieved by the Hirama group in 2001.[7] To date, over 20 congeners of CTXs were isolated.[8,9]

Although the causative toxin has been determined, the problem of how to prevent suffering from ciguatera fish poisoning, which causes about 20,000 ciguatera patients every year,[1] is remained to be solved. Because CTXs are transferred to various fish, the discrimination of the fish poisoned by CTXs is difficult. Furthermore, because of the stability of CTXs, they cannot be destroyed by heating during cooking of the poisoned fish. Therefore, numerous researchers study new methods for the detection of CTXs from fish.[10]

Biological studies revealed that the potent toxicity of CTX3C (MLD = 1.3 μg/kg, ip, in mice) and other ciguatoxin congeners was attributed to strong activation of voltage-gated sodium channels in nerve cells by their firm binding to site 5 of the channels (CTX3C: $Ki = 0.81 \times 10^{-4}$ μM).[11] This strong effect on sodium channels has potential for the application of ciguatoxins as biological tools.

However, due to scarce of natural source, the sufficient amount of CTXs does not supply to meet the demand of the above described biological studies aiming at prevention of ciguatera poisoning and development of new biological tools. Therefore, a synthetic supply of CTXs is a practical solution.

In the total synthesis of ciguatoxins, the large molecular size and complexity of the

structure are challenges that have been tackled by many research groups since the first publication of the structure of ciguatoxin 1B by Yasumoto. Thus, the author has also been interested in the synthesis of CTX3C, which has the simplest structure and comparable bioactivity among CTX congeners.

In this thesis, the author describes the completion of the synthesis of the ABCDEF-ring of CTX3C as a part of the total synthesis and an investigation toward the development of new convergent strategy for the formation of the FGHI-ring.

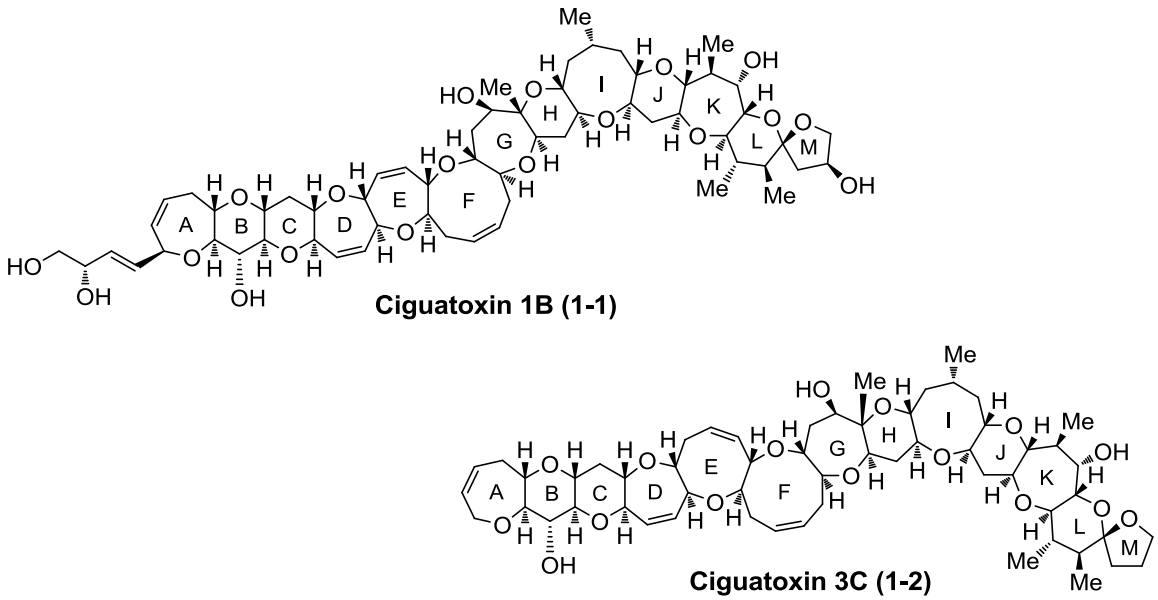


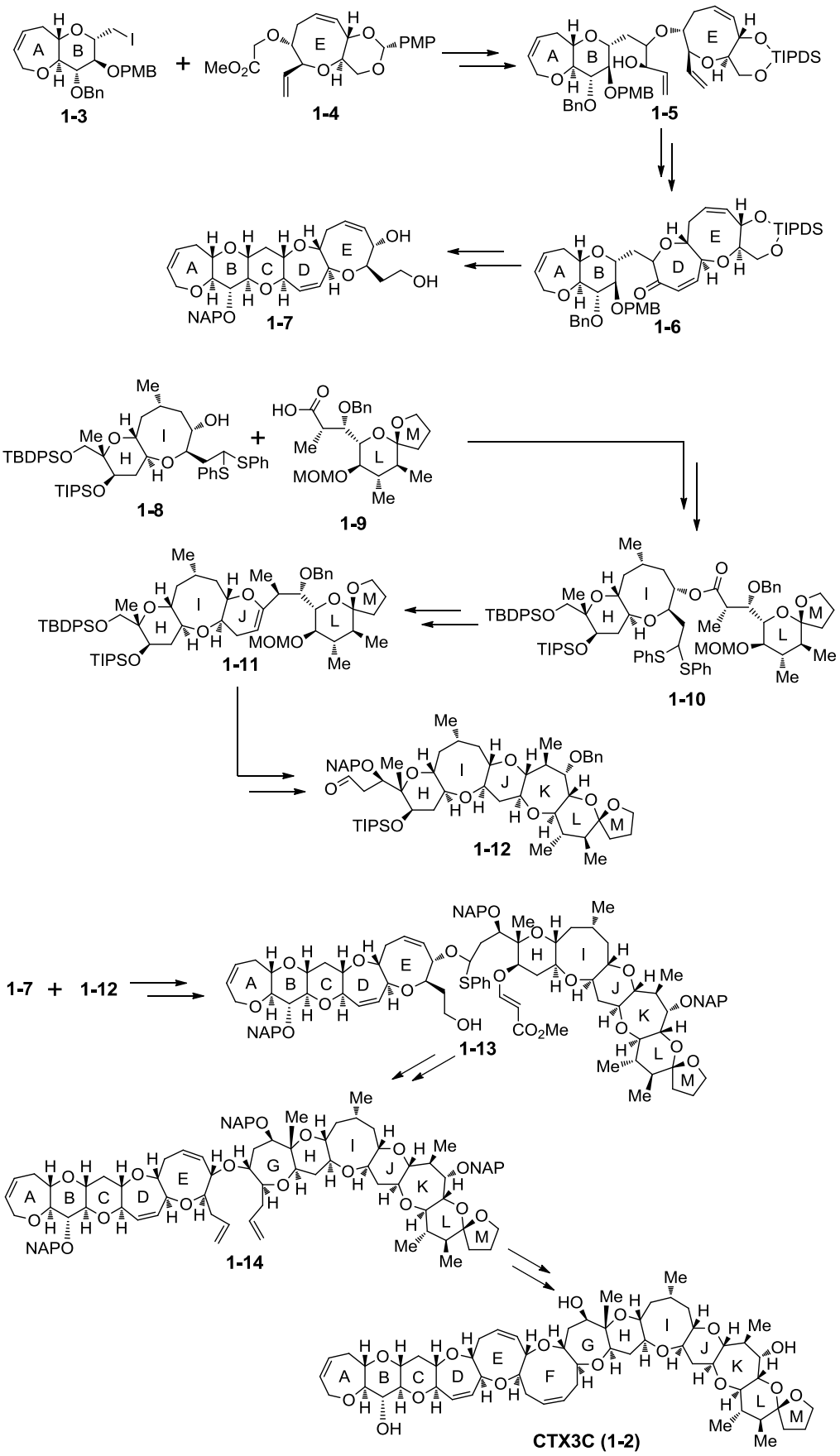
Figure 1-1. Structures of ciguatoxin-1B (**1-1**) and ciguatoxin-3C (**1-2**)

1-2. Synthetic studies on CTXs by other groups

In this section, the total synthesis and the synthetic studies of CTXs by other groups are outlined.

1-2-1. Total synthesis of CTX3C by Hirama Group

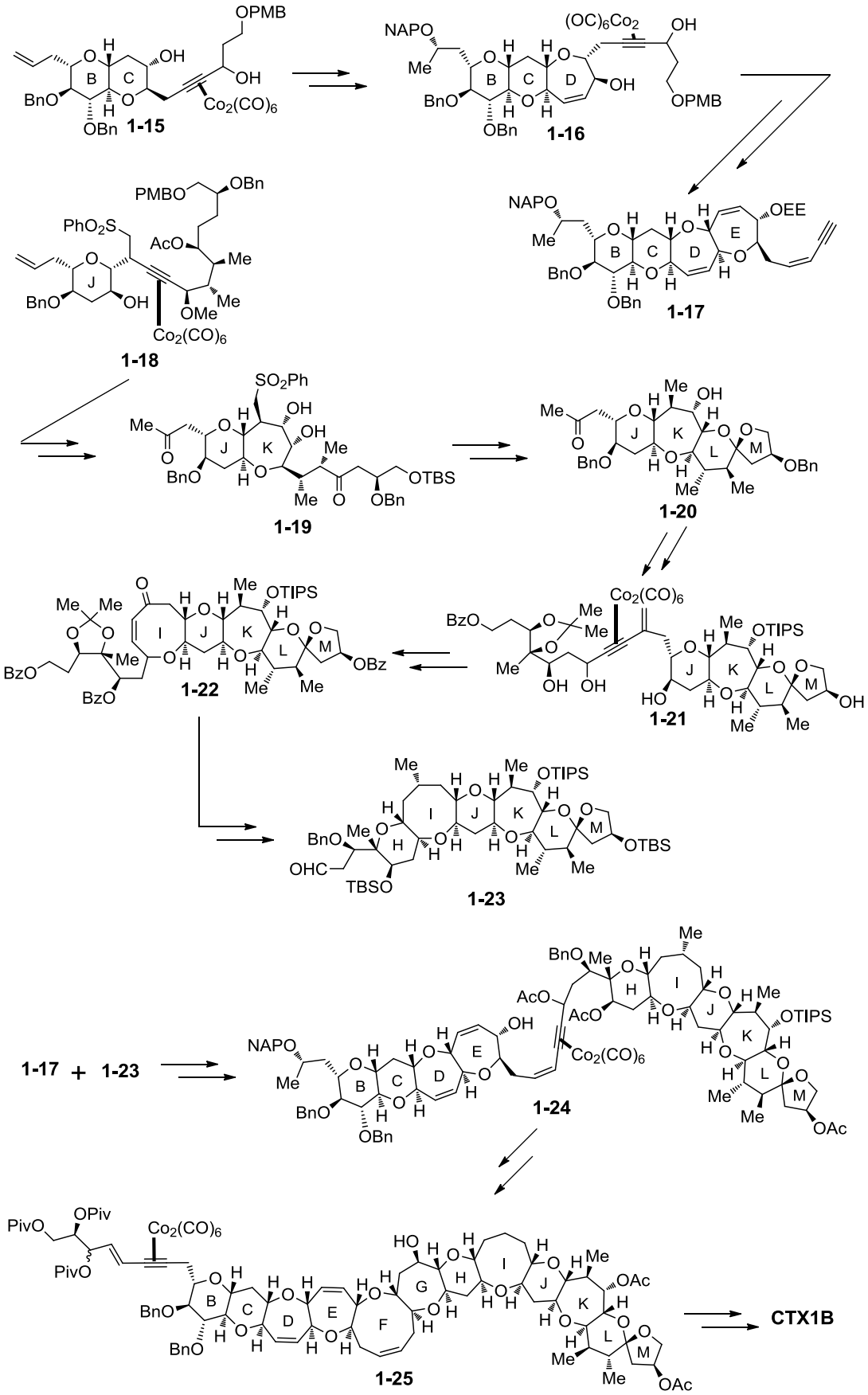
The Hirama group has achieved the first total synthesis of CTX3C using ring-closing olefin metathesis (RCM) as a key reaction (Scheme 1-1).[7,12] As a left half segment of CTX3C, ABCDE-ring **1-7** was prepared from AB-ring **1-3** and E-ring **1-4**. The coupling reaction of AB-ring **1-3** with E-ring **1-4** followed by a vinylation reaction afforded alcohol **1-5**. RCM of alkene **1-5** followed by oxidation of the alcohol produced ketone **1-6**. The C-ring was cyclized by reductive etherification to give ABCDE-ring **1-7**. As a right half segment of CTX3C, HIJKLM-ring **1-12** was synthesized from HI-ring **1-8** and LM-ring **1-9**. Condensation of alcohol **1-8** with carboxylic acid **1-9** furnished ester **1-10**. Intramolecular carbonyl olefination of ester **1-10** was accomplished by low-valent titanium complex to construct J-ring **1-11**. After hydroboration of the olefin of **1-11**, a sequence of reactions, involving intramolecular acetalization and reductive etherification, afforded HIJKLM-ring **1-12**. Finally, diol **1-7** and aldehyde **1-12** were reacted with $Sc(OTf)_3$, and the resulting *O,O*-acetal was converted to *O,S*-acetal **1-13**, which was cyclized under radical conditions to form G-ring. Each of the hydroxy group and the methyl ester moiety of the resulting dodecacyclic compound were transformed into a terminal olefin to give divinyl compound **1-14**. The synthesis of CTX3C was completed by the RCM reaction of divinyl compound **1-14** followed by deprotection of the tri-NAP group. Furthermore, they achieved total synthesis of CTX1B and 51-hydroxy CTX3C via a similar methodology.



Scheme 1-1. Total synthesis of CTX3C by Hirama group

1-2-2. Total synthesis of CTX1B by Isobe group

The Isobe group has achieved the total synthesis of CTX1B using Nicholas reaction as a key reaction (Scheme 1-2).[13] They synthesized CTX1B from BCDE-ring **1-17** and HIJKLM-ring **1-23**. Perparation of BCDE-ring **1-17** was performed from BC-ring **1-15** via a route including stepwise double Nicholas reaction. HIJKLM-ring **1-23** was obtained from J-ring **1-18**. The Nicholas reaction of J-ring **1-18** gave JK-ring **1-19**, which was subjected to acetalization to produce JKLM-ring **1-20**. After the I-ring was formed by Nicholas reaction, H-ring cyclization via a process involving intramolecular conjugate addition furnished HIJKLM-ring **1-23**. Then, deprotonated terminal alkyne **1-17** was reacted with aldehyde **1-23** to afford a coupling adduct, which was complexed with cobalt octacabonyl to give **1-24**. The cyclization of alkyne cobalt complex **1-24** using Nicholas reaction and reductive etherification produced dodecacyclic **1-25**, which was also cyclized by Nicolas reaction to give CTX1B.

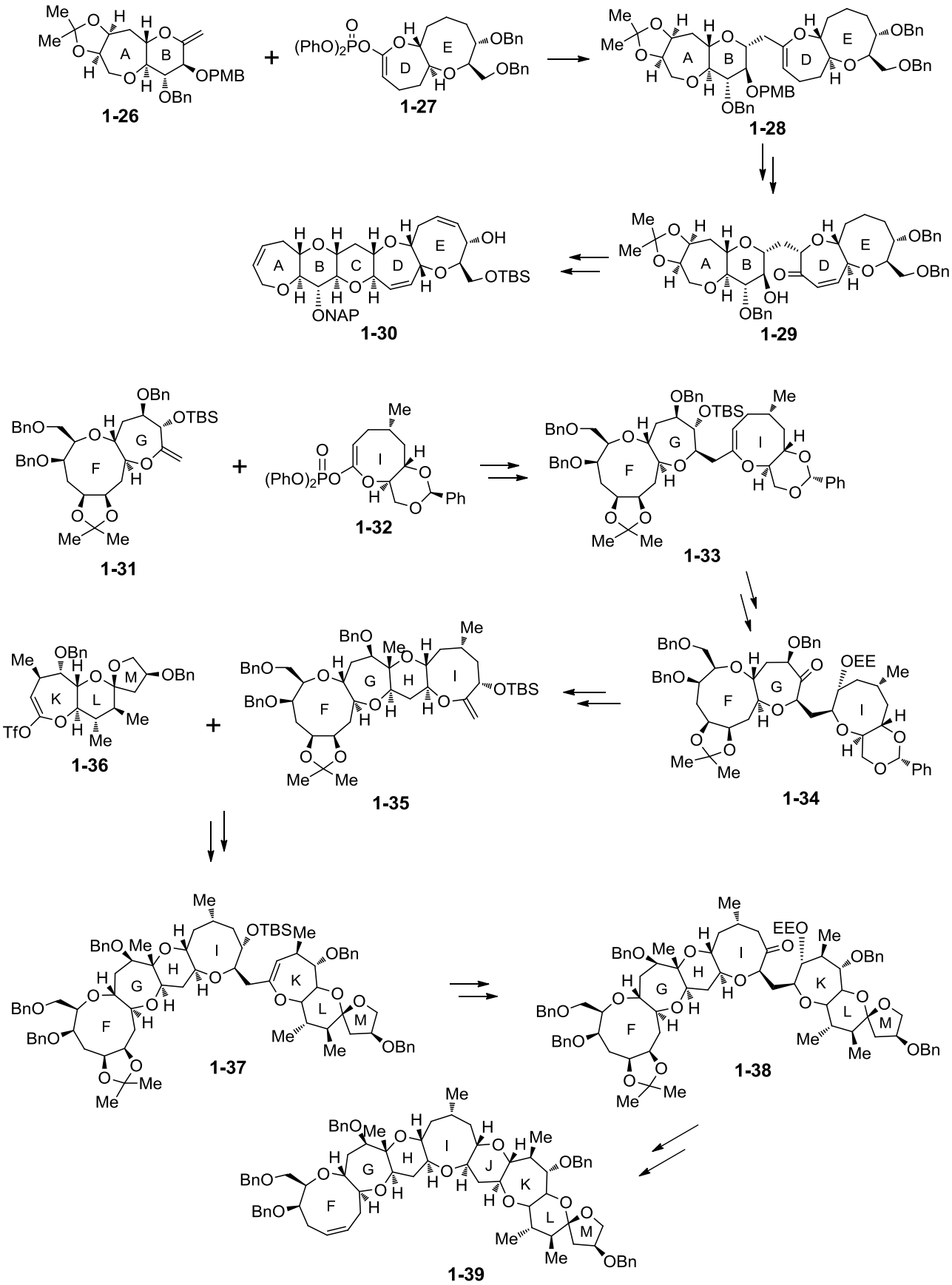


Scheme 1-2. Total synthesis of CTX1B by Isobe group

1-2-3. Synthetic studies on CTX3C by Tachibana, Sasaki, and co-workers

Sasaki, Tachibana, and co-workers have established the syntheses of ABCDE-ring **1-30** and FGHIJKLM-ring **1-27** of CTX3C using Suzuki-Miyaura cross coupling as a key reaction (Scheme 1-3).[14] The ABCDE-ring **1-30** was constructed from AB-ring **1-26** and DE-ring **1-27**. Initially, hydroboration of AB-ring **1-26** followed by Suzuki-Miyaura coupling with enol phosphate **1-27** gave **1-28**. Cyclic enol ether **1-28** was transformed to ketone **1-29**, which was subjected to reductive etherification to produce ABCDEF-ring **1-30**.

The FGHIJKLM-ring was prepared from FG-ring **1-31**, I-ring **1-32**, and KL-ring **1-36**. After hydroboration of alkene **1-31**, the resulting alkylborane was coupled with enol phosphate **1-32** under Suzuki-Miyaura's consitions to furnish coupling adduct **1-33**. Alkene **1-33** was converted to ketone **1-34** by a 5 step-process involving epoxidation, reductive cleavage of the resulting epoxide, protection of the resulting alcohol as an ethoxyethyl ether, removal of the TBS group, oxidation of the resulting alcohol. Treatment of ketone **1-34** with ethanedithiol and $Zn(OTf)_2$ afforded a thioketal, which was subjected to oxidation to a sulfone, methylation with $AlMe_3$, and further functional group interconversion to afford FGHI-ring **1-35**. After hydroboration of alkene **1-35**, Suzuki-Miyaura coupling of the resulting alkylborane with enol triflate **1-36** produced **1-37**. Hydroboration-oxidation of olefin **1-37** followed by protection of the alcohol as an ethoxyethyl ether, deprotection of the TBS group, and oxidation of the resulting alcohol gave ketone **1-38**. Finally, the synthesis of FGHIJKLM-ring **1-39** was completed by a sequence of intramolecular thioketalization, radical reduction to form the J-ring, and the introduction of a double bond to the F-ring.



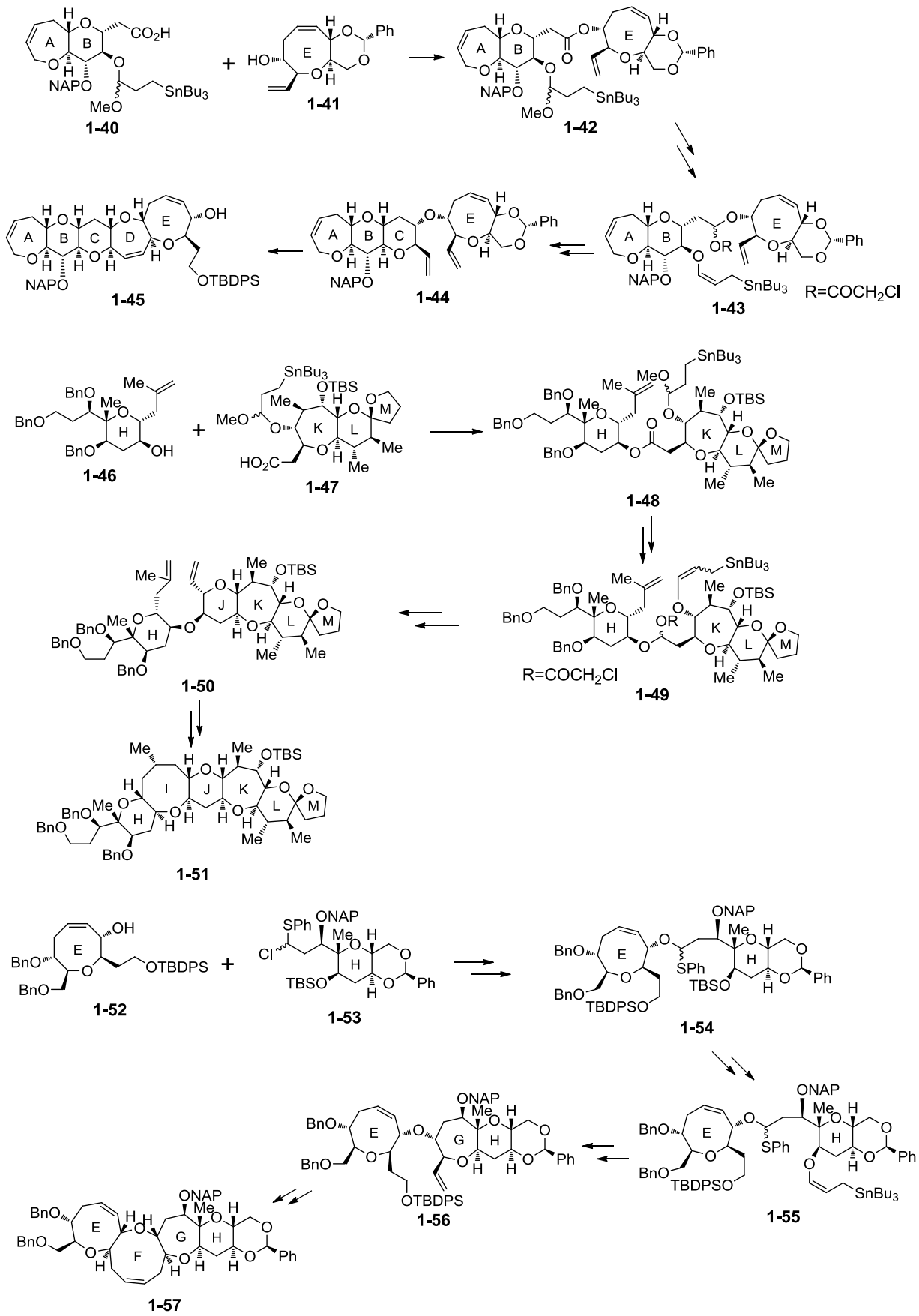
Scheme 1-3. Synthetic studies of CTX3C by Tachibana, Sasaki, and co-workers

1-2-4. Synthetic studies of CTX3C by Kadota group

Kadota and co-workers have synthesized ABCDE-ring **1-45**, HIJKLM-ring **1-51**, and EFGH-ring **1-57** of CTX3C using Lewis acid catalyzed intramolecular allyl stannation as a key cyclization reaction as shown in Scheme 1-4.[15] After condensation of AB-ring **1-40** with E-ring **1-41**, elimination of the methoxy group of the resulting **1-42** followed by the formation of an acyl acetal produced **1-43**, which was subjected to intramolecular allyl stannation with $MgBr_2 \cdot OEt_2$ and cyclization of the resulting **1-44** by RCM to furnish ABCDE-ring **1-45**.

The synthesis of HIJKLM-ring **1-51** was commenced with H-ring **1-46** and KLM-ring **1-47**. Alcohol **1-46** was condensed with carboxylic acid **1-47** to furnish **1-48**, which was converted to **1-49** by a 2-step process. Exposure of **1-49** to $MgBr_2 \cdot OEt_2$ induced cyclization to afford pentacyclic **1-50**. The synthesis of HIJKLM-ring **1-51** was completed by the following 2 steps: RCM, and stereoselective hydrogenation of the olefin with Crabtree's catalyst.

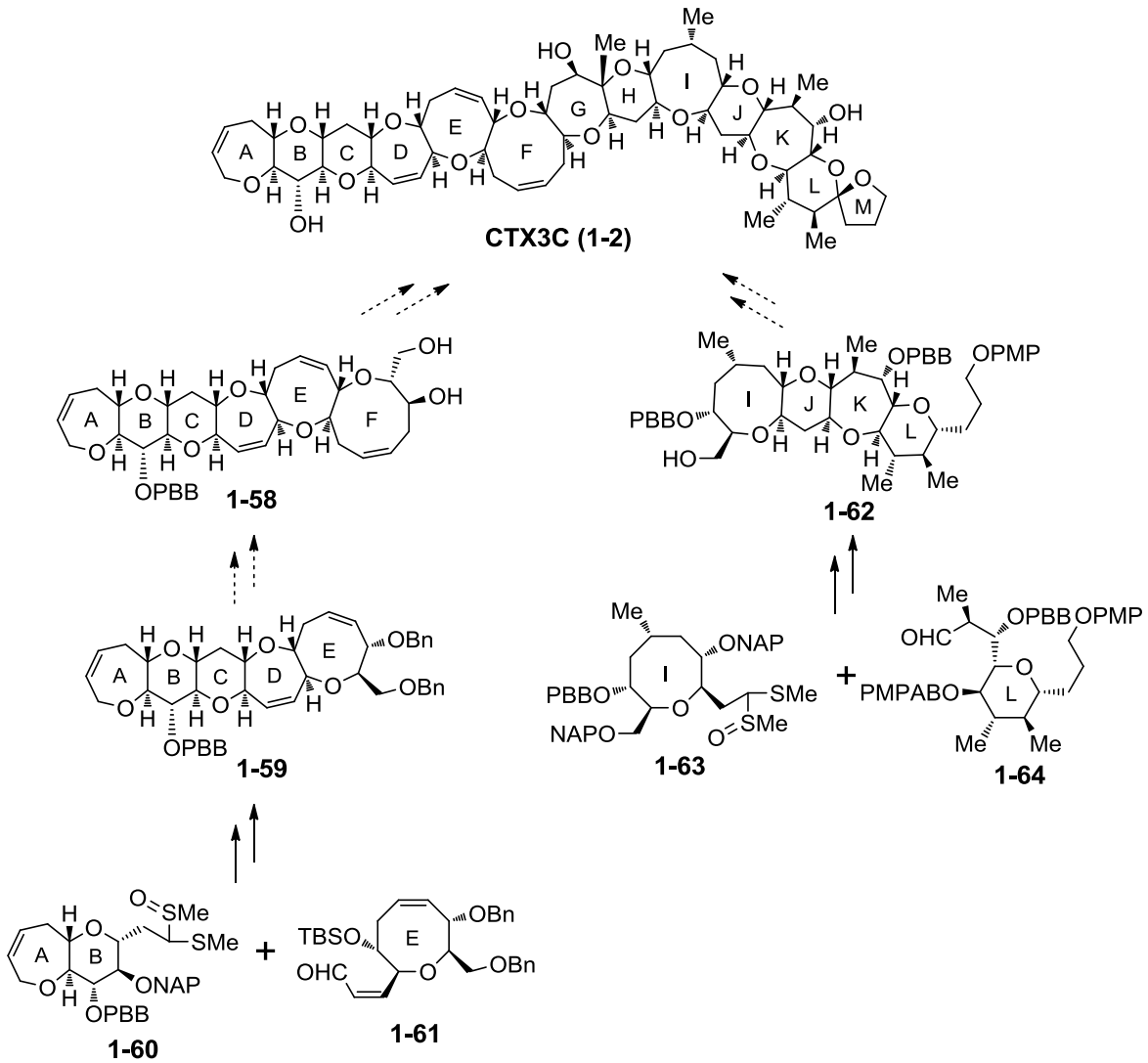
The EFGH-ring **1-57** was formed by allyl stannation of an *O,S*–acetal. Treatment of **1-52** and **1-53** with AgOTf gave *O,S*–acetal **1-54**. Organotin compound **1-55** was prepared from **1-54** by a 4-step protocol. After intramolecular allyl stannation of **1-55**, the F-ring was formed via RCM to complete the synthesis of EFGH-ring **1-57**.



Scheme 1-4. Synthetic studies of CTX3C by Kadota group

1-3. Preceding synthetic studies of CTX3C by the author's group

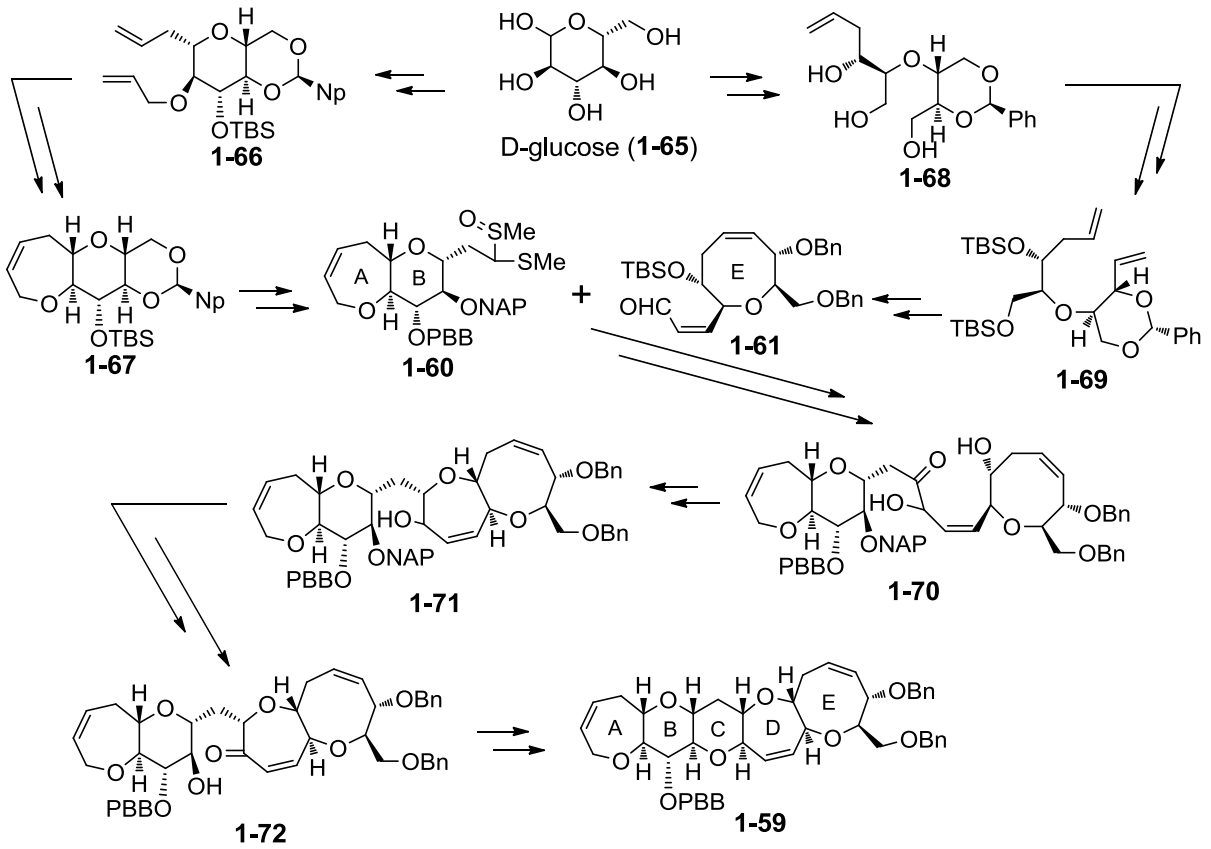
In the synthesis of CTX3C, convergent strategy is more efficient than liner strategy due to the large molecular size of CTX3C. The author's group planned to synthesize CTX3C from ABCDEF-ring **1-58** and IJKL-ring **1-62** (Scheme 1-5). So far, a methodology for connecting F- and I-ring to afford FGHI-ring has been established by Takizawa and Doi.[16] Furthermore, the author's group has developed a convergent method for constructing X/6/7/X polycyclic *trans*-fused ethers via a coupling reaction between a dimethyldithioacetal mono-*S*-oxide and an aldehyde.[17,18] Using this strategy, preparation of IJKL-ring **1-62** has achieved by Domon, Sano, and Saito,[19] and preparation of ABCDE-ring **1-59** has been achieved by Goto.[20] Additionally, construction of the ABCDEF-ring **1-58** from ABCDE-ring **1-59** was studied by Nogoshi.[21] In this section, the syntheses of each segment are illustrated.



Scheme 1-5. Previous synthetic plan of CTX3C by the author's group

1-3-1. Synthesis of the ABCDE-ring

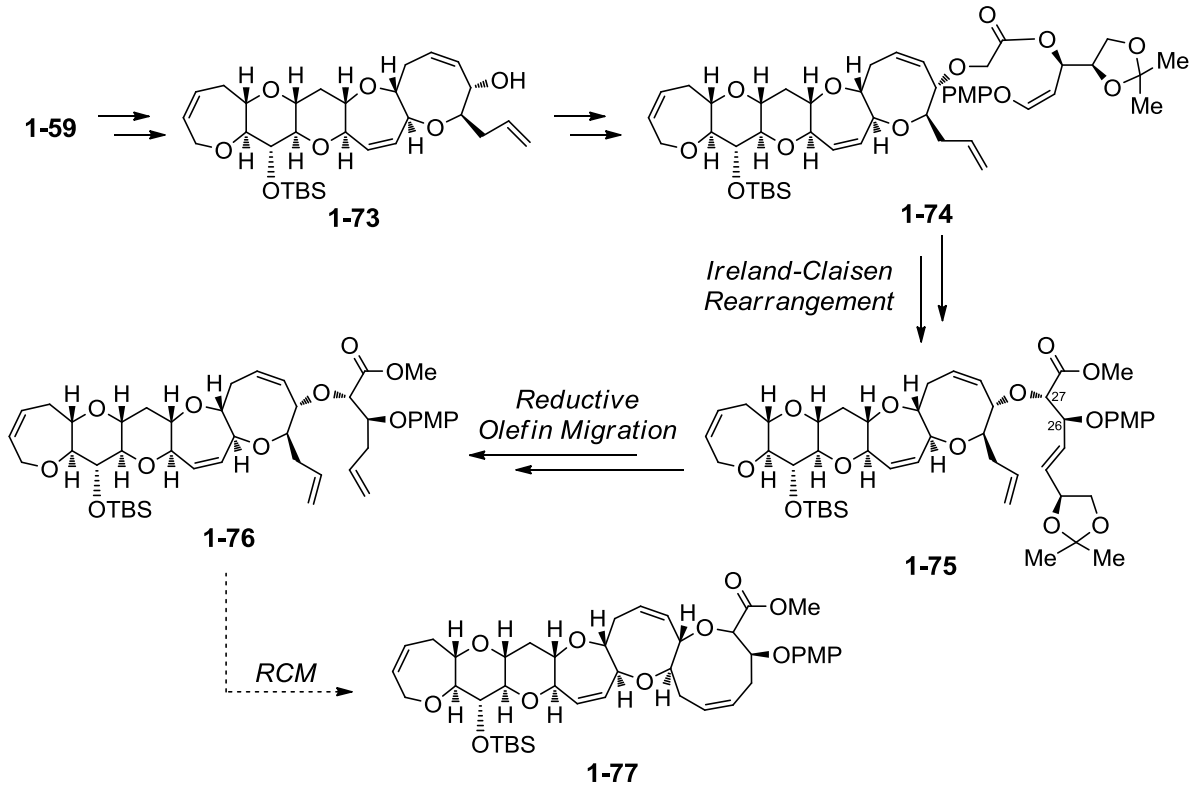
Goto has synthesized ABCDE-ring **1-59** from AB-ring **1-60** and E-ring **1-61** (Scheme 1-6).[20] First, diene **1-66** was prepared from D-glucose (**1-65**), and diene **1-66** was cyclized by RCM to afford 7- and 6-membered bicyclic ether **1-67**. Reduction of the 2-naphthylmethyliden acetal and attachment of a dimethyldithioacetal mono-*S*-oxide moiety gave AB-ring **1-60**. The synthesis of E-ring **1-61** was also commenced with D-glucose (**1-65**), which was initially transformed into triol **1-68**. After toriol **1-68** was converted to diene **1-69**, RCM of **1-69** followed by introduction of an aldehyde side chain produced E-ring **1-61**. The connection of the E-ring and the AB-ring segments was performed under anionic conditions. After deprotonation of dithioacetal moiety of **1-60**, the resulting acyl anion equivalent was reacted with aldehyde **1-61** in situ to furnish an adduct alcohol, which was then hydrolyzed under acidic conditions to afford α,ε-diol **1-70**. The reductive cyclization of ketone **1-70** constructed the D-ring. The resulting alcohol **1-71** was oxidized, and the NAP group was removed to produce ketone **1-72**. Finally, reductive etherification of ketone **1-72** synthesized ABCDE-ring **1-59**.



Scheme 1-6. Synthesis of ABCDE-ring **1-59** by Goto

1-3-2. Studies toward the synthesis of the ABCDEF-ring by Nogoshi

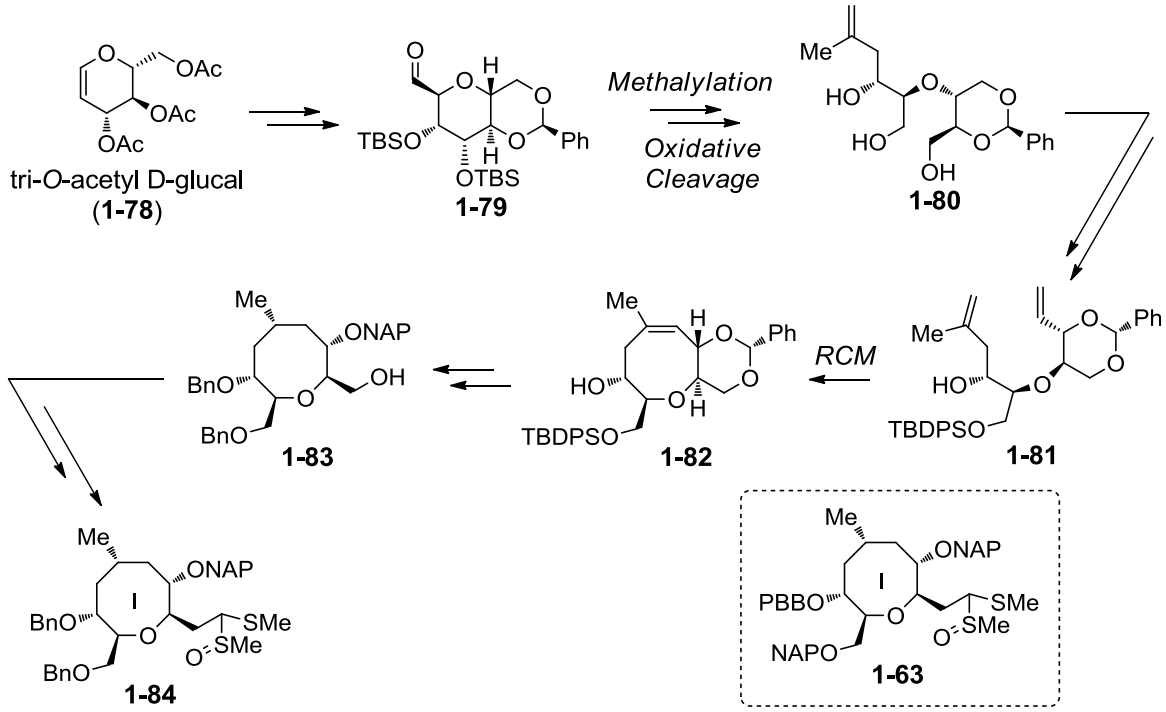
Nogoshi and Domon have developed a method for medium ring ethers based on chirality transferring Ireland-Claisen rearrangement and RCM. The method was applied to the synthesis of the EF-ring moiety of CTX3C (the details are described in Chapter 3). Nogoshi also attempted the synthesis of ABCDEF-ring **1-58** from ABCDE-ring **1-59** using the method (Scheme 1-7).[21] First, **1-59** was converted to alkene **1-73** via the manipulation of the protecting groups, triflation, and vinylation. However, the manipulation of the protecting groups was difficult and resulted in quite low yield. Alcohol **1-73** was transformed to ester **1-74** by the following 3 steps: etherification with *tert*-butyl bromoacetate, hydrolysis of the *tert*-butyl ester, and condensation of the carboxylic acid with a chiral 3-(4-methoxyphenoxy) allyl alcohol. Then, Ireland-Claisen rearrangement of ester **1-74** followed by methyl esterification selectively produced methyl ester **1-75**, of which the stereochemistry at C27 and C26 were anticipated to be proper but were not confirmed. After removal of the acetonide of **1-75**, oxidative cleavage of the resulting 1,2-diol followed by 1,2-reduction of the aldehyde furnished an allyl alcohol, which was then subjected to reductive olefin migration to produce terminal alkene **1-76**. Subsequently, RCM of diene **1-76** afforded a compound, which showed the same molecular weight as the expected ABCDEF-ring **1-77**. However, the certain structure of the compound could not be confirmed due to the small amount of the compound. The low production of the expected ABCDEF-ring segment was attributed to the difficulty of the manipulation of the protecting groups of **1-59**. To solve this problem, the author designed new synthetic strategy for the ABCDEF-ring of CTX3C. The details are outlined in section 1-4.



Scheme 1-7. Attempted synthesis of ABCDEF-ring **1-77** by Nogoshi.

1-3-3. Synthesis of the I-ring

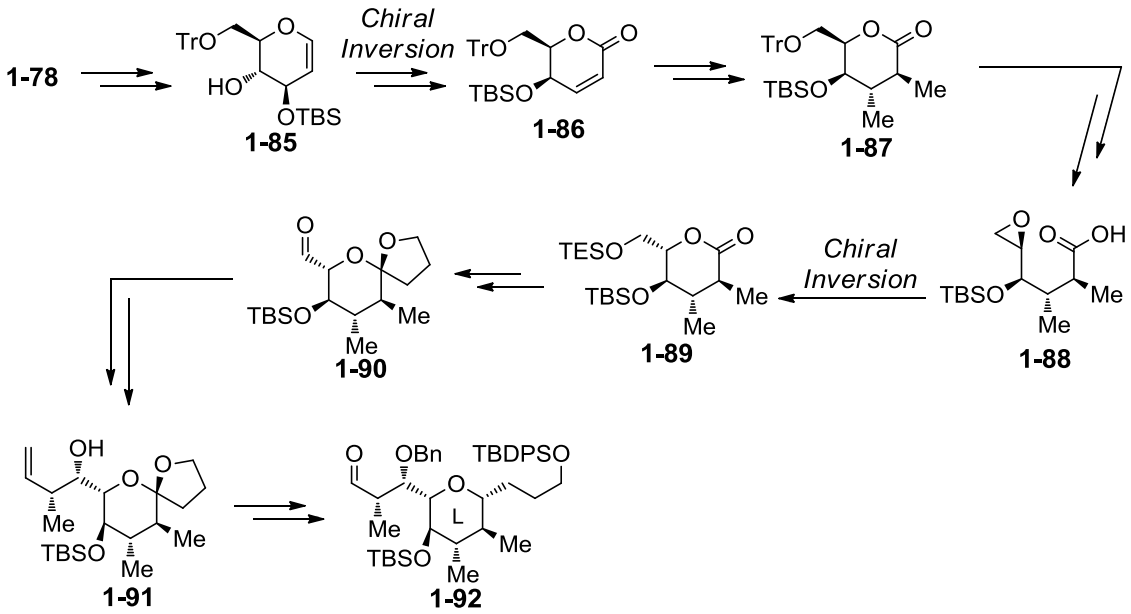
Synthesis of the I-ring **1-84** has been established by Domon (Scheme 1-8).[22] The preparation was commenced with tri-*O*-acetyl D-glucal (**1-78**), which was transformed to **1-79** by a 6-steps process. After stereoselective methalylation of **1-79**, the removal of the TBS group followed by oxidative cleavage gave triol **1-80**. The 4-step conversion of **1-80** provided diene **1-81**. RCM of diene **1-81** gave 8-membered cyclic ether **1-82**, which was transformed to **1-83** via stereoselective hydrogenation of the olefin with Crabtree's catalyst. Finally, alcohol **1-83** was subjected to triflation followed by the installation of a dimethyldithioacetal mono-*S*-oxide moiety to produce I-ring **1-84**. Recently, according to the same method, Saito synthesized modified I-ring **1-63**, of which the left side protecting groups were changed from those of **1-84** in expecting the selective removal of them at a later stage in the total synthesis of CTX3C.[19c]



Scheme 1-8. Synthesis of the I-ring by Domon and Saito

1-3-4. Synthesis of the L-ring

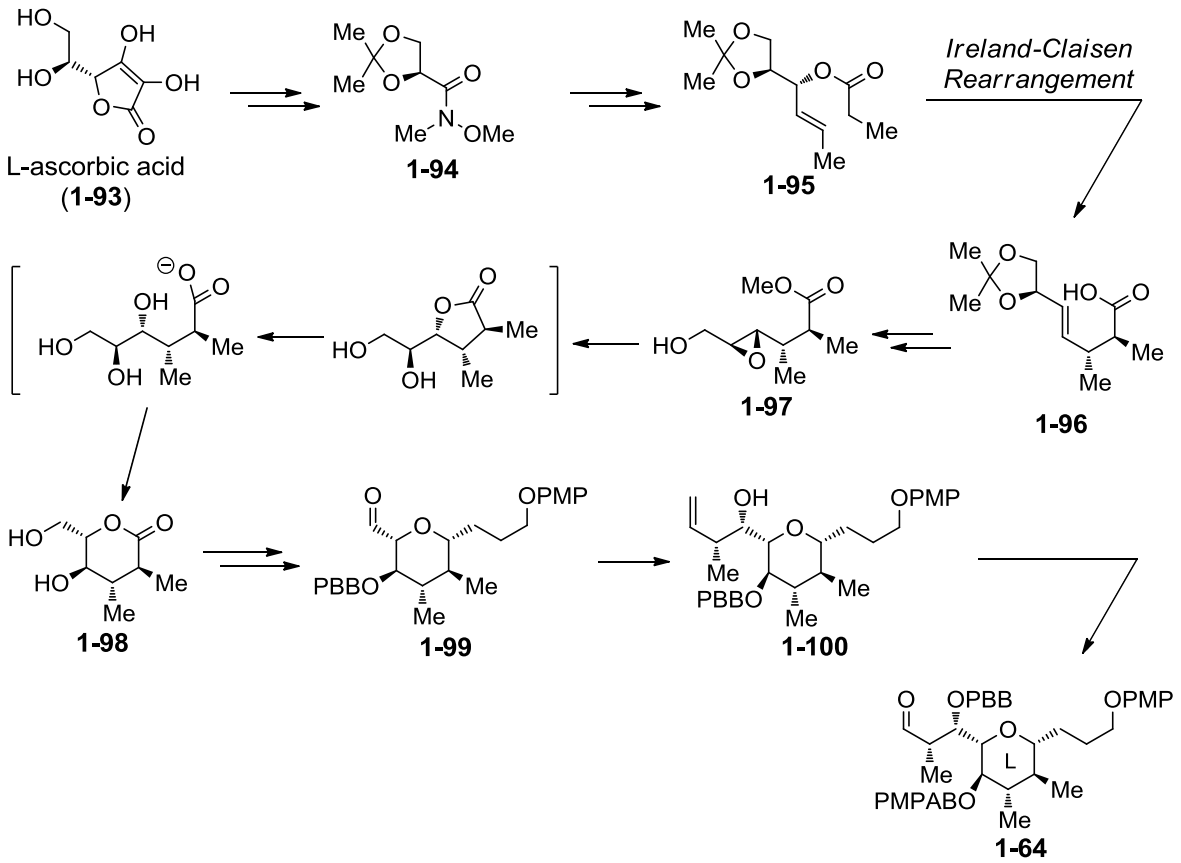
Domon achieved the first generation synthesis of L-ring **1-92** (Scheme 1-9).[23] First, alcohol **1-85** was prepared from tri-*O*-acetyl D-glucal **1-78** by a 3-step process. The stereochemistry at C4 of **1-85** was inverted via an epoxide intermediate to furnish unsaturated lactone **1-86**, which was methylated to afford **1-87**. After lactone **1-87** was transformed to **1-88**, the epoxy carboxylic acid was cyclized into lactone **1-89** with inversion of stereochemistry at C5. Conversion of lactone **1-89** to spirocyclic acetal **1-90** and the subsequent asymmetric crotylboration gave alcohol **1-91**. Finally, synthesis of L-ring **1-92** was completed by the following 4 steps: protection of the alcohol as a benzyl ether, reductive cleavage of the acetal, protection of the resulting alcohol as a TBDPS ether, and the oxidative cleavage of the double bond. Although the synthesis of the L-ring was achieved, the route was somewhat lengthy due to inclusion of two stereoinversion steps and several protection/deprotection steps.



Scheme 1-9. First generation synthesis of the L-ring by Domon

Sano and Saito developed improved synthetic route for the L-ring (Scheme 1-10).[19b,19c] The synthesis was started with L-ascorbic acid **1-93**, which was transformed into Weinreb amide **1-94**. Transformation of **1-94** into ester **1-95** was performed by a route including the formation of an ynone from **1-94**, Noyori asymmetric transfer hydrogenation of the ynone, (*E*)-selective reduction of the resulting propargyl alcohol, and esterification. The chirality-transferring Ireland-Claisen rearrangement of **1-95** stereoselectively produced vicinal dimethyl compound **1-96**, which was then converted to epoxide **1-97** by the following 5 steps: methylation of the carboxylic acid, removal of the acetonide, oxidative cleavage of the vicinal diol, Luche reduction, and Sharpless asymmetric epoxidation. The conversion of epoxide **1-97** to lactone **1-98** was performed in water. When the suspension of **1-97** in water was heated to reflux, 5-*exo*-cylization selectively occurred to give a

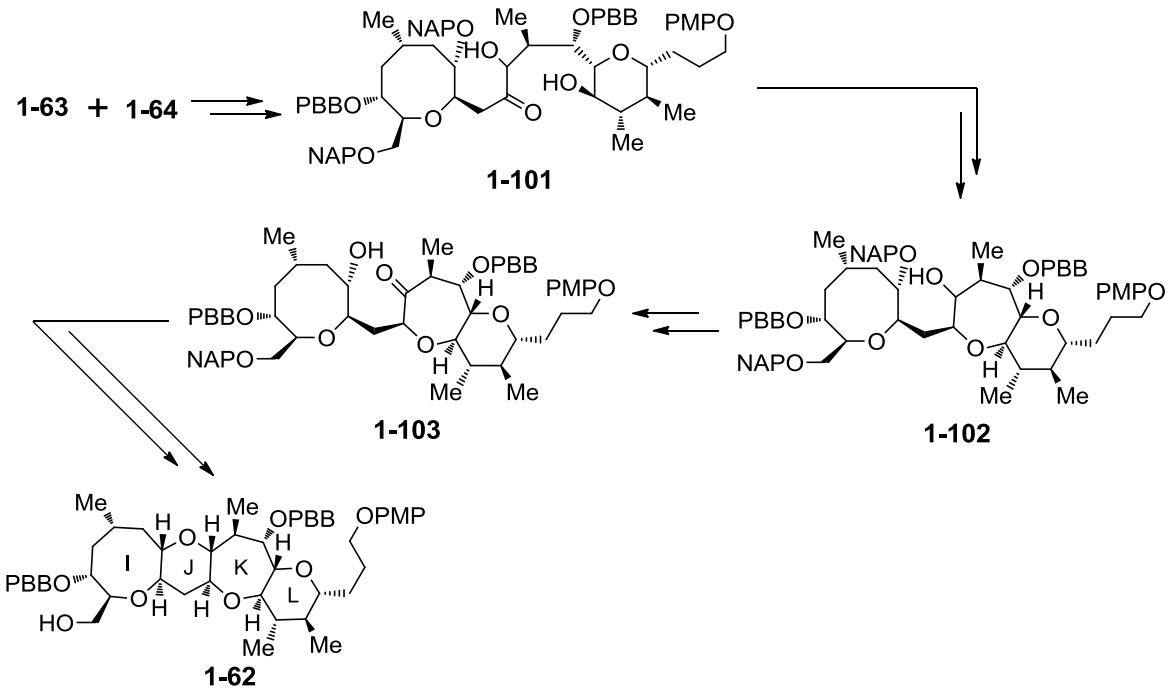
5-membered lactone. Then, the lactone ring was opened in situ by the addition of a hydroxide base, and the resulting secoic acid was recyclized by the acidification of the reaction solution to produce 6-membered lactone **1-98**. Transformation of **1-98** into aldehyde **1-99** was achieved by a process including the formation of a 4-bromobenziliden acetal, introduction of a PMP ether side chain, selective reductive cleavage of 4-bromobenziliden acetal, reductive etherification, and oxidation of the alcohol. After asymmetric crotylboration of aldehyde **1-99**, the synthesis of L-ring **1-64** was completed by the protection of the alcohol, and oxidative cleavage of the double bond.



Scheme 1-10. Second generation synthesis of the L-ring by Sano and Saito

1-3-5. Synthesis of the IJKL-ring

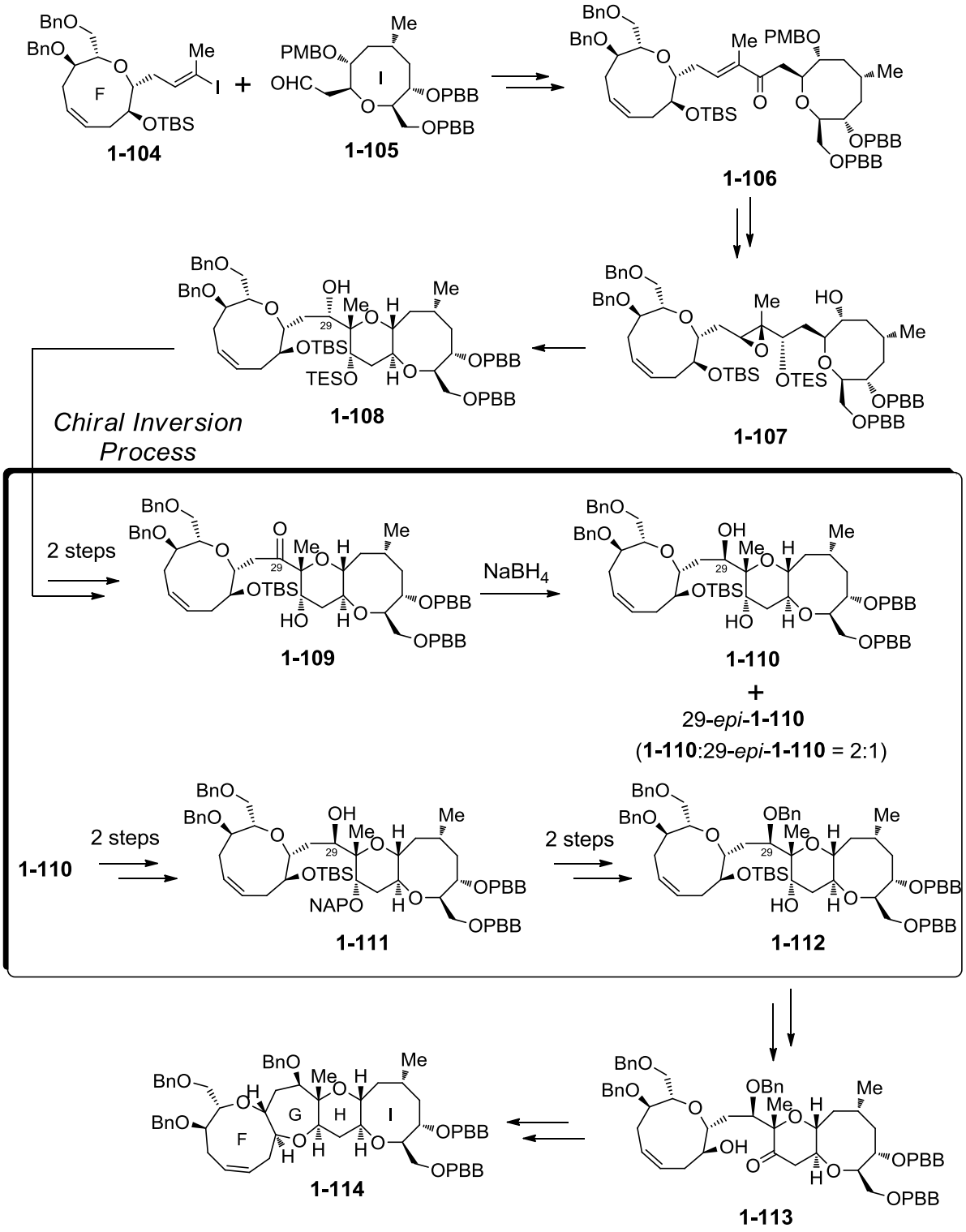
Saito, Sano, and Domon have established the synthetic route to the IJKL-ring (Scheme 1-11).[19] The deprotonated dimethyldithioacetal mono-*S*-oxide **1-63**, corresponding to the I ring, was reacted with aldehyde **1-64**, corresponding to the L-ring, to give an alcohol, which was hydrolyzed under acidic conditions to give ketone **1-101**. After reductive cyclization of ketone **1-101** into **1-102**, oxidation of the alcohol followed by the removal of the NAP group afforded ketone **1-103**. Finally, IJKL-ring **1-62** was synthesized by reductive etherification of ketone **1-103**.



Scheme 1-11. Synthesis of the IJKL-ring by Domon, Sano, and Saito.

1-3-6. Synthesis of the FGHI-ring

Takizawa and Doi have achieved the convergent synthesis of FGHI-ring **1-114** from F-ring **1-104** and I-ring **1-105** (Scheme 1-12).[16] Iodoalkene **1-104** was coupled with aldehyde **1-105** under Nozaki-Hiyama-Kishi conditions, and the resulting alcohol was oxidized to give ketone **1-106**, which was transformed to epoxide **1-107** by several steps including stereoselective reduction of ketone**1-106**. Cyclization of **1-107** with CSA followed by inversion of stereochemistry at C29 of the resulting oxane **1-108** via a route including oxidation of **1-108** and reduction of the resulting **1-109** afforded **1-112**, which was converted to ketone **1-113**. Finally, reductive cyclization of **1-113** completed the synthesis of FGHI-ring **1-114**. However, the steroinversion process required seven reaction steps including protection and deprotection steps, and the reduction of ketone **1-109** produced the desired **1-110** only with low selectivity (**1-110**:29-*epi*-**1-110** = 2:1). Therefore, more efficient method for the convergent construction of the GH-ring is required.

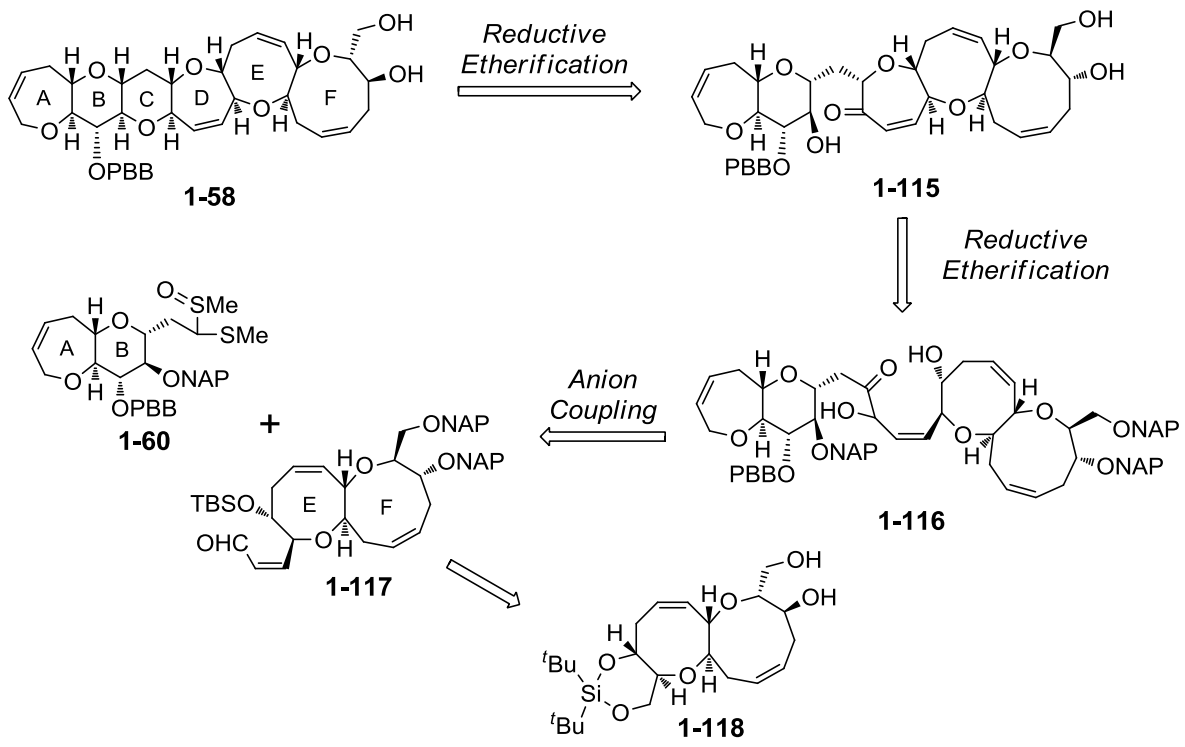


Scheme 1-12. Synthesis of the FGHI-ring by Doi and Takizawa

1-4. The objective of this work

As shown in chapter 1-3-2, the previous synthetic route to the ABCDEF-ring, which included the attachment of the F-ring to the ABCDE-ring, was ineffective, because the difficulty in manipulating protective groups of ABCDE-ring **1-59** prevented the attachment of the F-ring. Therefore, the author intended to construct the ABCDEF-ring convergently from the AB-ring and the EF-ring in expecting an improvement in efficiency. Furthermore, since the convergent route to the ABCDEF-ring includes the early-stage preparation of the EF-ring, which involves synthetically difficult medium ring ethers, the synthesis of the CD-ring at a later stage is expected to become simple and facile. Thus, the author proposed a new synthetic plan for the ABCDEF-ring (Scheme 1-13). The ABCDEF-ring **1-58** was envisioned to be synthesized from AB-ring **1-60** and EF-ring **1-117** applying Goto's procedure.[20] The construction of the C- and D-rings of **1-58** employed a stepwise process, including intramolecular reductive etherification reactions,[24] via α,ε-dihydroxy ketone **1-116**, which would be constructed by a coupling reaction of an acyl anion equivalent, generated from dimethyldithioacetal mono-*S*-oxide **1-60**, with aldehyde **1-117** followed by hydrolysis.[17,18] The preparation of AB-ring **1-60** has developed by Goto[20], and EF-ring **1-117** was anticipated to be transformed from **1-118**, which has been synthesized by Nogoshi.[25] In this dissertation, the author describes the improvement of the synthesis of AB-ring **1-60** for practical scale preparation as shown in chapter 2, the construction of EF-ring **1-117** with the improvement of the preparation of intermediate **118** as explained in chapter 3, and the completion of the synthesis of ABCDEF-ring as depicted in chapter 4.

Additionally, the author investigated a new strategy for the connection of the ABCDEF- and IJKLM-ring segments. The previous strategy developed by this laboratory for this purpose includes a very slow reaction step and a stereoinversion step, which caused the strategy less efficient. Therefore, the author planned a new strategy without stereoinversion and investigated the strategy through the synthesis toward the FGHI-ring as a model system. The investigation is illustrated in chapter 5.



Scheme 1-13. New synthetic plan for the ABCDEF-ring

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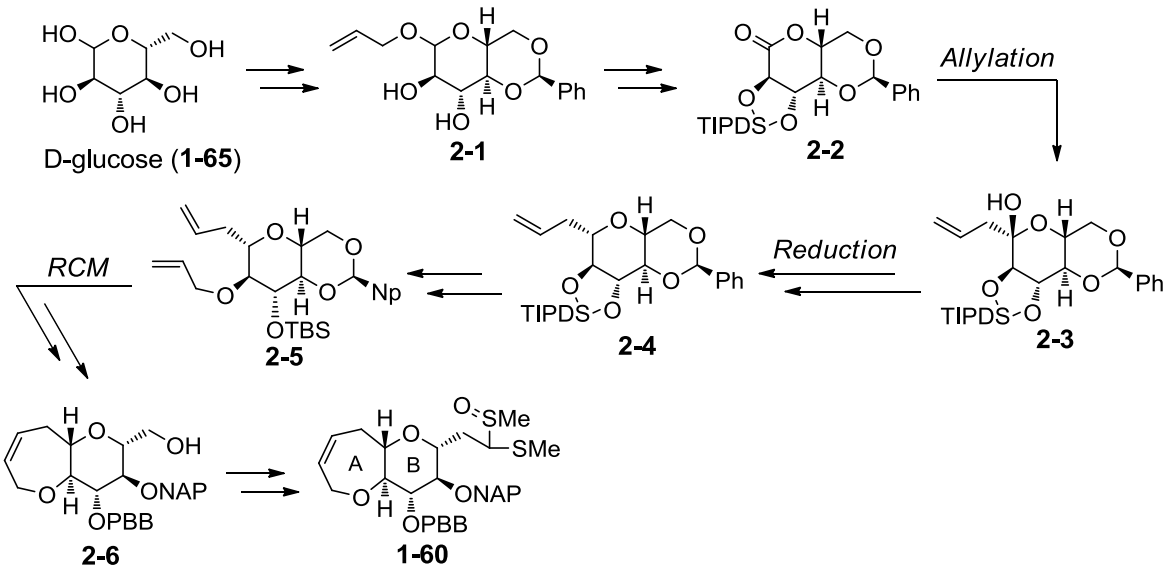
2. Synthesis of the AB-ring

2-1. Synthetic strategy of AB-ring 1-60

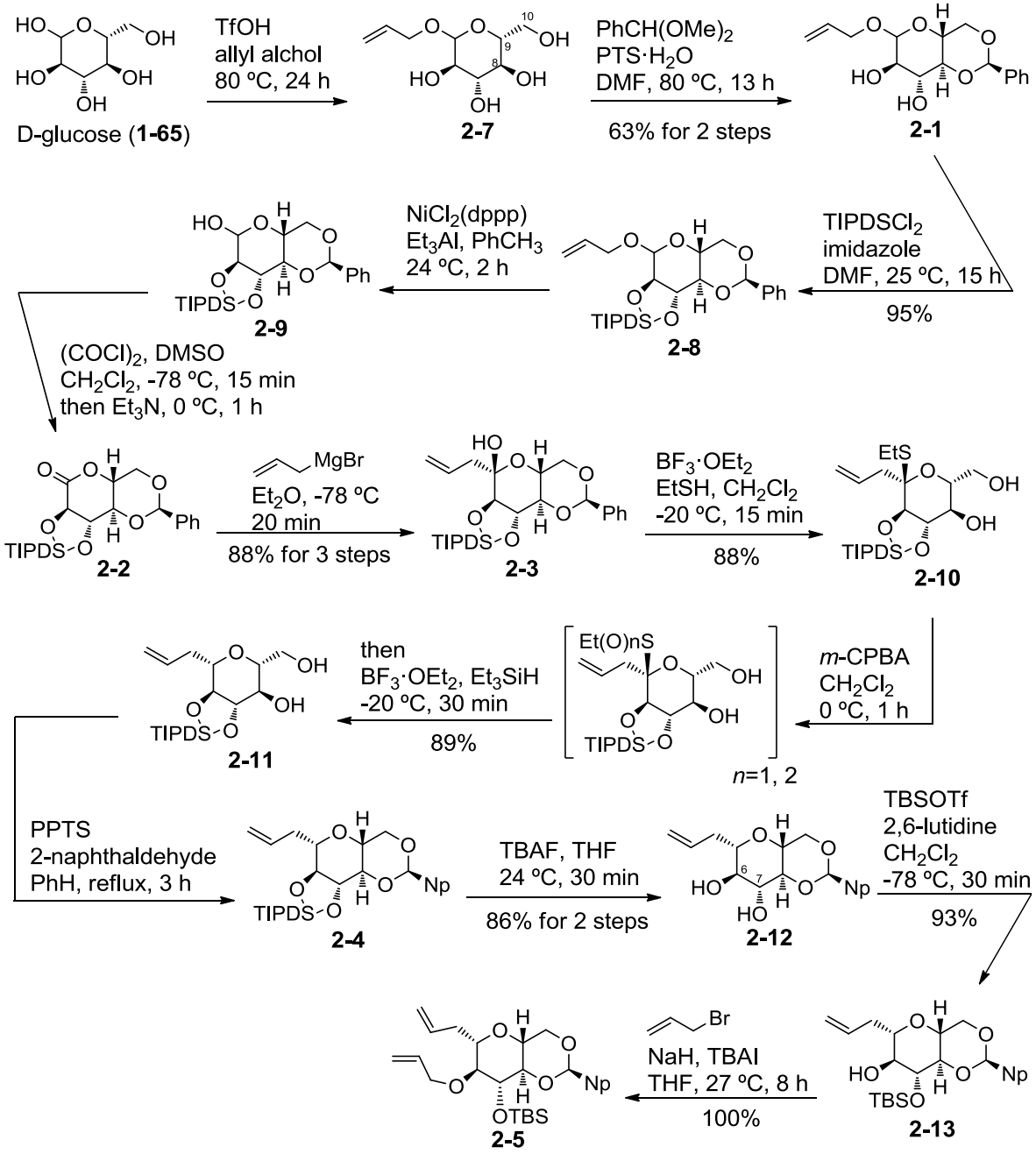
The synthesis of AB-ring **1-60** was conducted according to Goto's method.[1] The route is outlined in Scheme 2-1. Because the framework of the B-ring is similar to that of D-glucose (**1-65**), the B-ring was constructed from known D-glucose derivative **2-1**.[2] Diol **2-1** was transformed into lactone **2-2**, which was treated with allylmagnesium bromide to afford alkene **2-3**. The reductive etherification of **2-3** afforded tetrahydropyrane **2-4**. After conversion of **2-4** to diene **2-5**, RCM of **2-5** gave 7- and 6-membered bicyclic ether **2-6**.[3] Finally, introduction of a dimethylacetal mono-*S*-oxide moiety to **2-6** completed the synthesis of AB-ring **1-60**. The author optimized the synthetic route to achieve gram scale synthesis.



Scheme 2-1. Synthetic strategy for AB-ring **1-60**

2-2. Synthesis of allyl ether 2-5

First, diene **2-5**, a substrate for A-ring formation, was prepared from D-glucose (Scheme 2-2) according to Goto's procedure.[1] Treatment of **1-65** with allyl alcohol in the presence of TfOH produced allyl glucoside **2-7**. Then, the hydroxyl groups at C8 and C10 of **2-7** were protected as a benzylidene acetal to give known diol **2-1** (63% for 2 steps),[2] which was transformed into 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) derivative **2-8** (95%). After removal of the allyl group of **2-8**,[4] Swern oxidation of the resulting alcohol **2-9** followed by addition of allylmagnesium bromide produced adduct **2-3** (88% for 3 steps).[5] Hemiacetal **2-3** was reacted with EtSH and $BF_3 \cdot OEt_2$ to form *S,O*-acetal **2-10** (88%). Under the condition, the benzylidene acetal was removed simultaneously. The ethylthio group of **2-10** was oxidized with *m*-CPBA, and the resulting mixture of sulfoxide and sulfone derivatives was reduced with Et_3SiH and $BF_3 \cdot OEt_2$ in situ to furnish tetrahydropyran **2-11** (89%). After protection of 1,3-diol **2-11** as a 2-naphthylmethyliden acetal, the resulting TIPDS derivative was deprotected with TBAF to afford diol **2-12** (86% for 2 steps). Selective protection of the hydroxy group at C7 of **2-12** was successfully accomplished with TBSOTf and 2,6-lutidine at –78 °C to give silyl ether **2-13** (93%). The subsequent treatment of **2-13** with allyl bromide under basic conditions produced diene **2-5** (100%). Thus, the author demonstrated that the synthetic route from D-glucose to diene intermediate **2-5** showed good total yield (33%) and excellent reproducibility.

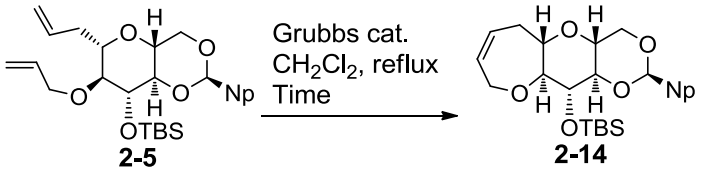


Scheme 2-2. Synthesis of Diene **2-5**

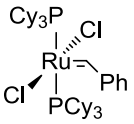
2-3. Modification of ring-closing olefin metathesis of 2-5

Next, the RCM of diene **2-5** was investigated. Since medium-ring construction by RCM usually needs high dilution conditions to avoid undesired intermolecular reactions, the use of a large amount of solvent becomes a problem in view of cost and handling. Furthermore, it is also important to reduce the amount of the expensive Grubbs catalyst (1st generation: ¥23,500/g; 2nd generation: ¥58,250/g). Therefore, the author examined the possibility of reducing the amounts of solvent and catalyst in this step (Table 2-1).

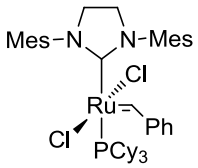
Goto performed the reaction with 10 mol% of the first generation Grubbs catalyst (**2-15**)[6] in CH_2Cl_2 (5 mM) to furnish the desired bicyclic ether **2-14** in 80% yield (Entry 1). When the amount of catalyst **2-15** was reduced to 5 mol%, the catalyst was deactivated before completion of the reaction, and the yield was decreased (Entry 2, 58%). Therefore, higher concentration was next examined. Treatment of a solution of **2-5** in CH_2Cl_2 (20 mM) with 5 mol% of catalyst **2-15** afforded **2-14** in 82% yield (Entry 3). Under the conditions, no byproduct caused by intermolecular reaction was detected. When the second generation Grubbs catalyst (**2-16**)[7] was used, the reaction was smoothly completed with only 1 mol% of the catalyst to produce **2-14** in 78% yield (Entry 4). These conditions are also effective in the gram-scale synthesis of **2-14** (82%; Entry 5). Thus, the author achieved the reduction of the amounts of solvent and catalyst in the RCM of **2-5**.



Entry	Substrate	Grubbs cat. (Equivalent)	Concentration	Time	Yield
1	393.3 mg	**2-15** (10 mol%)	5 mM	3 h	80%
2	397.5 mg	**2-15** (5 mol%)	5 mM	6 h	58%
3	471.0 mg	**2-15** (5 mol%)	20 mM	4 h	82%
4	414.8 mg	**2-16** (1 mol%)	20 mM	3 h	78%
5	16.28 g	**2-16** (1 mol%)	20 mM	2 h	82%



Grubbs' first generation catalyst (**2-15**)

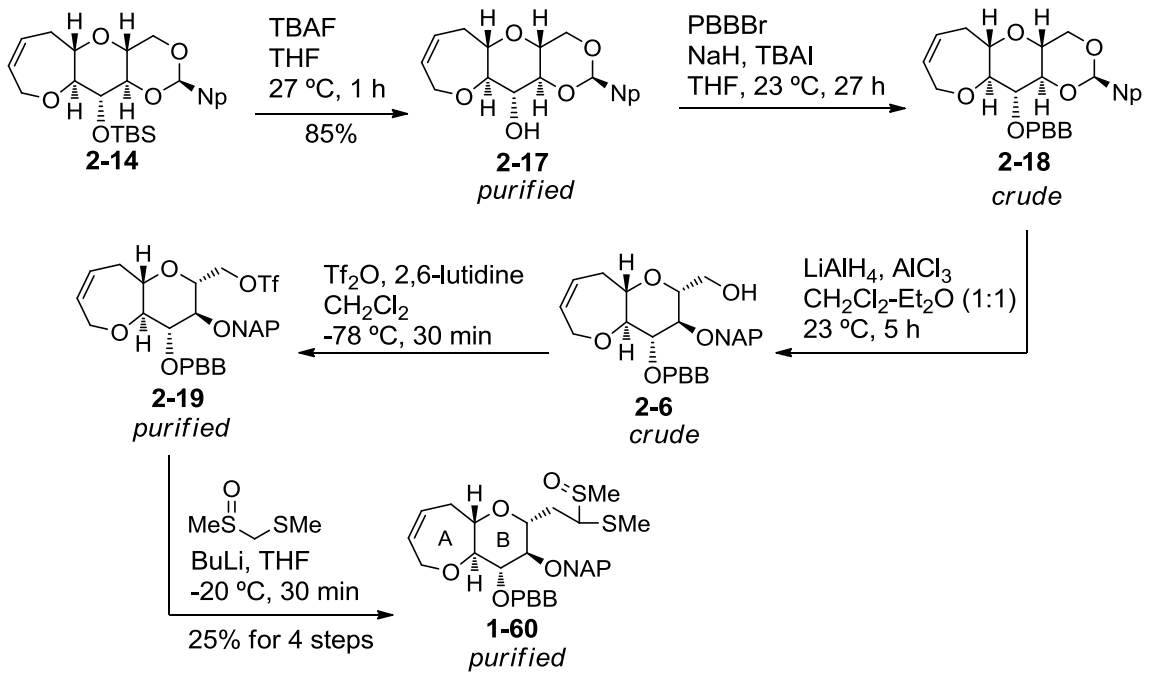


Grubbs' second generation catalyst (**2-16**)

Table 2-1. RCM of **2-5**

2-4. Synthesis of the AB-ring

AB-ring **1-60** was then synthesized from **2-14** according to Goto's method (Scheme 2-3). TBS group of **2-14** was removed with TBAF to give alcohol **2-17** (85%), which was purified by recrystallization. After protection of alcohol **2-17** as a PBB ether, reductive cleavage of 2-naphthylmethyliden acetal **2-18** followed by triflation of the resulting alcohol **2-6** produced **2-19**,[8] which was purified by silica gel column chromatography. Formaldehyde dimethyl dithioacetal mono-*S*-oxide was deprotonated by BuLi, and the resulting anion was reacted with **2-19** in situ to produce AB-ring **1-60**. However, the preparation of **1-60** from **2-17** resulted in low yield on large scale preparation (25% over 4 steps). The author found that the yield of **2-19** decreased with increasing time that was required for the purification of **2-19** by silica gel column chromatography. Thus, instability of triflate **2-19** to silica gel was found to affect the overall yield of **1-60**. Therefore, triflate **2-19** should be used immediately in the next reaction without purification. The author, then, readjusted the purification protocol for the process from **2-17** to **1-60**.

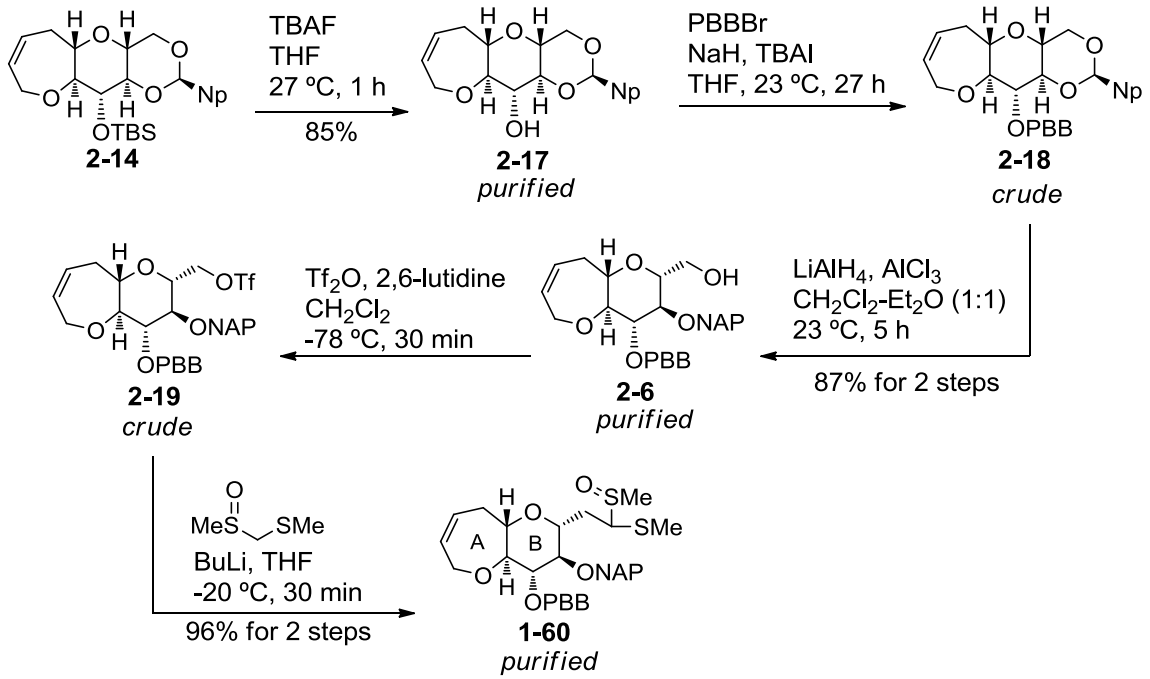


Scheme 2-3. Synthesis of AB-ring **1-60** according to Goto's procedure

The optimized construction of AB-ring **1-60** is shown in Scheme 2-4. Alcohol **2-17** was obtained according to previous process. Protection of alcohol **2-17** as a PBB ether followed by reductive cleavage of 2-naphthylmethyliden acetal **2-18** furnished alcohol **2-6** (87% for 2 steps), which was purified by silica gel column chromatography at this stage. After triflation of **2-6**, triflate **2-19** was immediately used in the next reaction without purification. Finally, the reaction of **2-19** with deprotonated dithioacetal mono-*S*-oxide afforded AB-ring **1-60** in good yield (96% for 2 steps).

All the above reactions were available on decagram scale preparation. Thus, the synthesis of

AB-ring **1-60** was achieved from D-glucose (**1-65**) in 18 steps in 19% overall yield.



Scheme 2-4. Optimized synthesis of AB-ring **1-60**

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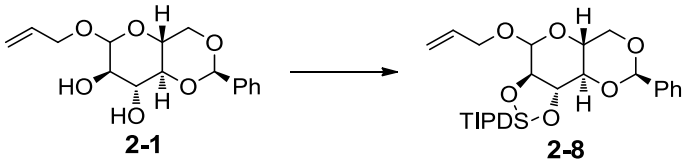
Experimental sections

General methods

All air sensitive reactions were carried out under argon in oven-dried glassware using standard syringe, cannula and septa techniques. Anhydrous tetrahydrofuran (THF) was prepared by Glass Contour Solvent Dispensing System (Nikko Hansen & Co., Ltd.). Other dry solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F_{254}). Plates were visualized by ultraviolet light and by treatment with acidic anisaldehyde or phosphomolybdic acid stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63-40 μm for flash column chromatography, 230-63 μm for gravity column chromatography) as a stationary phase. Melting points were measured on a YAMATO apparatus model MP-21 without calibration. Optical rotations were recorded on a JASCO P-1020 digital polarimeter at 589 nm. Infrared spectra (IR) were measured on a JEOL JIR-WINSPEC100 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-AL300 (^{1}H at 300 MHz, ^{13}C at 75 MHz), a JEOL JNM-α-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), a JEOL JNM-ECA500 (^{1}H at 500 MHz, ^{13}C at 125 MHz), or a Bruker AVANCE III 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of the residual solvent (^{1}H NMR: 7.15 ppm in C_6D_6, ^{13}C NMR: 128.0 ppm in C_6D_6) as the internal standard. The following abbreviations are used to describe spin multiplicity: s= singlet, d= doublet, t= triplet, q= quartet, qn= quintet, m= multiplet, br= broad, dd= double doublets, dt= double triplets, td= triple doublets, qd= quartet doublets, and ddd= double double doublets; other combination is derived from those listed. Coupling constants (*J*) are reported in Hz. High resolution mass spectra (HRMS) were measured on a JEOL JMS-600H (under electron impact ionization [EI] conditions), a JEOL JMS-SX102A (under field desorption [FD] conditions), or a JEOL JMS-T100GCV (under field desorption [FD] conditions) double focusing magnetic sector mass spectrometer.

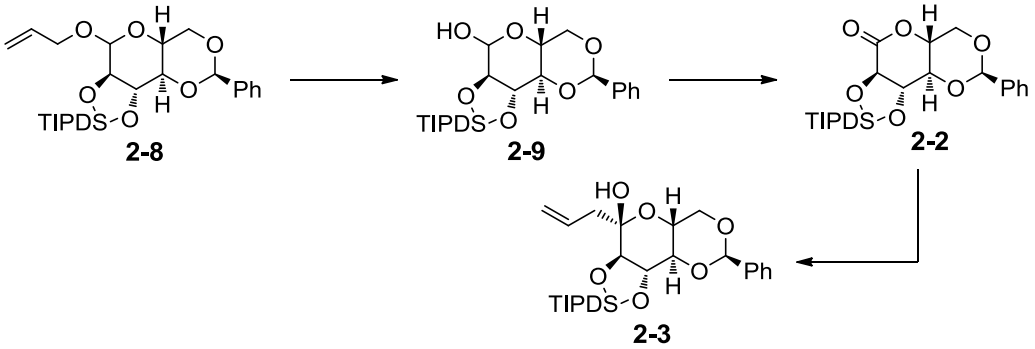
Compound 2-8.



To a solution of **2-1** (43.23 g, 0.1402 mol) in DMF (280 ml) were added imidazole (22.91 g, 0.3365 mol) and $ClSi(^iPr)_2O(^iPr)_2SiCl$ (55.0 mL, 0.172 mol) at 25 °C, and the mixture was stirred for 13 h. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 20 → 10) to give **2-8** (73.12 g, 0.1327 mol, 95%, α-anomer:β-anomer = 2:1) as a colorless oil.

2-8: The IR and HRMS data were already measured by H. Tanaka. IR (film) ν 2944, 2867, 1464, 1382, 1248, 1212, 1176, 1142, 1091, 1048, 990, 923, 886, 847, 746, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90-1.17 (28H, m), 3.39 (1/3H, dt, *J* = 4.5, 9.5 Hz), 3.49 (2/3H, t, *J* = 9.5 Hz), 3.54 (1/3H, t, *J* = 9.5 Hz), 3.63 (1/3H, t, *J* = 7.8 Hz), 3.73 (2/3H, t, *J* = 10.2 Hz), 3.76-3.83 (1H, m), 3.85-3.93 (1H, m), 4.06 (2/3H, tdd, *J* = 1.5, 5.6, 13.5 Hz), 4.13-4.18 (4/3H, m), 4.21 (1/3H, tdd, *J* = 1.7, 4.9, 13.6 Hz), 4.28 (2/3H, dd, *J* = 4.7, 10.0 Hz), 4.32-4.39 (2/3H, m), 4.45 (1/3H, d, *J* = 7.5 Hz), 4.86 (2/3H, d, *J* = 3.8 Hz), 5.18 (1H, qd, *J* = 1.4, 10.5 Hz), 5.35 (1/3H, qd, *J* = 1.7, 17.3 Hz), 5.36 (2/3H, qd, *J* = 1.7, 17.3 Hz), 5.55 (1H, s), 5.85-5.94 (1H, m), 7.30-7.37 (3H, m), 7.46-7.51 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3 (CH), 12.46 (CH×2/3), 12.53 (CH×1/3), 12.9 (CH×1/3), 13.0 (CH), 13.2 (CH×2/3), 17.18 (CH_3×2/3), 17.21 (CH_3×1/3), 17.23 (CH_3×1/3), 17.28 (CH_3), 17.33 (CH_3), 17.35 (CH_3×2/3), 17.37 (CH_3×1/3), 17.40 (CH_3×2/3H), 17.42 (CH_3×1/3), 17.45 (CH_3), 17.47 (CH_3×1/3), 17.6 (CH_3×2/3), 17.7 (CH_3×2/3), 62.5 (CH×2/3), 66.3 (CH×1/3), 68.8 (CH_2×2/3), 68.9 (CH_2×1/3), 69.3 (CH_2×2/3), 70.9 (CH_2×1/3), 73.3 (CH×2/3), 76.0 (CH×2/3), 76.8 (CH×1/3), 77.9 (CH×1/3), 80.6 (CH×1/3), 81.7 (CH×2/3), 98.9 (CH×2/3), 101.1 (CH×1/3), 101.2 (CH×2/3), 103.1 (CH×1/3), 117.0 (CH_2×2/3), 117.1 (CH_2×1/3), 126.0 (CH×2), 128.2 (CH×2), 128.78 (CH×2/3), 128.83 (CH×1/3), 134.11 (CH×1/3), 134.13 (CH×2/3), 137.2 (C×1/3), 137.9 (C×2/3); EI-HRMS (m/z) calcd for $C_{25}H_{39}O_7Si_2$ $[M - {}^iPr]^+$: 507.2234, found: 507.2232.

Compound 2-3.



To a solution of **2-8** (50.90 g, 92.41 mmol) and $NiCl_2$(dppp) (1.0076 g, 1.8589 mmol) in $PhCH_3$ (500 mL) was added Et_3Al (0.92 mol/L in $PhCH_3$, 200 mL, 0.184 mol) at 0 °C, and the mixture was stirred for 3 h at 28 °C. Then, the reaction was quenched with saturated aq. potassium sodium tartrate, and the mixture was stirred for 13 h at 28 °C. The mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **2-9**, which was used in the next reaction without purification.

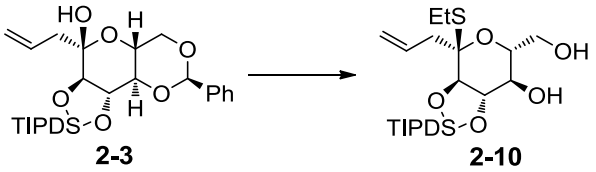
To a solution of $(COCl)_2$ (25.0 mL, 0.291 mol) in CH_2Cl_2 (240 mL) was added a solution of DMSO (33.0 mL, 0.465 mol) in CH_2Cl_2 (240 mL) dropwise at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added a solution of the above crude **2-9** in CH_2Cl_2 (50 mL) at –78 °C, and the mixture was stirred for 30 min. To the mixture was added Et_3N (130 mL, 0.925 mol) at –78 °C, and the mixture was warmed to 0 °C. After being stirred for 30 min, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with 0.2 mol/L aq. HCl, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **2-2**, which was used in the next reaction without purification.

To a solution of the above crude **2-2** in Et_2O (1.9 L) was added dropwise allylmagnesium bromide (1.0 mol/L in Et_2O, 186 mL, 186 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 15) to give **2-3** (44.83 g, 81.39 mmol, 88% from **2-8**) as a colorless oil.

2-3: All data were already measured by A. Goto. $[\alpha]_D^{30}$ –17.3 (c 1.50, $CHCl_3$); IR (neat) ν 3552, 3075, 3036, 2945, 2894, 2867, 1464, 1386, 1247, 1179, 1137, 1092, 991, 919, 886, 861, 817, 749, 698, 653, 520 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (28H, m), 2.43 (1H, dd, J = 5.5, 14.2 Hz), 2.56 (1H, dd, J = 7.2, 14.2 Hz), 3.12 (1H, s), 3.49 (1H, t, J = 9.6 Hz), 3.69 (1H, d, J = 8.3 Hz), 3.71 (1H, t, J = 10.2 Hz), 3.97-4.02 (1H, m), 4.05 (1H, dd, J = 8.3, 9.6 Hz), 4.31 (1H, dd, J = 4.9, 10.2 Hz), 5.16 (1H, dd, J = 1.7, 17.2 Hz), 5.20 (1H, dd, J = 1.7, 10.2 Hz), 5.55 (1H, s), 5.89 (1H, tdd, J = 7.2, 10.2, 17.2 Hz), 7.29-7.37

(3H, m), 7.48 (2H, dd, J = 2.8, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1 (CH), 12.3 (CH), 12.7 (CH), 13.0 (CH), 17.0 (CH_3), 17.1 (CH_3), 17.2 (CH_3), 17.26 (CH_3), 17.34 (CH_3), 17.4 (CH_3), 17.46 (CH_3), 17.51 (CH_3), 43.2 (CH_2), 63.1 (CH), 69.0 (CH_2), 74.2 (CH), 78.2 (CH), 80.7 (CH), 98.5 (C), 101.0 (CH), 119.6 (CH_2), 125.9 (CH×2), 128.0 (CH×2), 128.6 (CH), 131.9 (CH), 137.6 (C); EI-HRMS (m/z) calcd for $C_{25}H_{39}O_7Si_2$ [M – ^{i}Pr]$^+$: 507.2234, found: 507.2281.

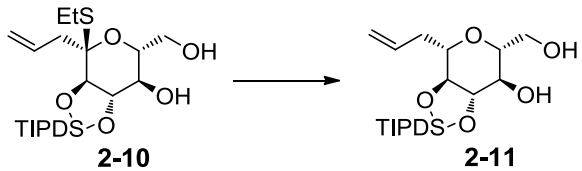
Compound 2-10.



To a solution of **2-3** (55.61 g, 100.9 mmol) and EtSH (37.4 mL, 505 mmol) in CH_2Cl_2 (500 mL) was added $BF_3 \cdot OEt_2$ (25.3 mL, 202 mmol) at –20 °C, and the mixture was stirred for 20 min. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 3) to give **2-10** (45.12 g, 89.02 mmol, 88%) as a colorless solid.

2-10: All data were already measured by A. Goto. mp 69-71 °C; $[\alpha]_D^{30}$ +56.0 (c 0.980, $CHCl_3$); IR (KBr) ν 3576, 3431, 2943, 2886, 1465, 1378, 1250, 1165, 1120, 1086, 1051, 1003, 986, 931, 885, 855, 823, 693, 632, 620, 586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (30H, m), 1.23 (3H, t, J = 7.5 Hz), 1.94 (1H, dd, J =5.5, 7.9 Hz), 2.34-2.55 (3H, m), 2.78 (2H, brd, J = 6.6 Hz), 3.49 (1H, dt, J = 2.2, 9.4 Hz), 3.75-3.92 (4H, m), 4.11 (1H, t, J = 8.5 Hz), 5.10 (1H, brs), 5.14 (1H, brdd, J = 1.6, 3.4 Hz), 5.82-5.93 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.20 (CH), 12.22 (CH), 12.6 (CH), 12.9 (CH), 14.3 (CH_3), 17.0 (CH_3), 17.1 (CH_3), 17.3 (CH_3), 17.40 (CH_3), 17.41 (CH_3), 17.5 (CH_3), 17.57 (CH_3), 17.59 (CH_3), 19.9 (CH_2), 43.6 (CH_2), 62.8 (CH_2), 71.3 (CH), 72.5 (CH), 76.8 (CH), 77.9 (CH), 91.5 (C), 118.4 (CH_2), 133.0 (CH); EI-HRMS (m/z) calcd for $C_{21}H_{41}O_6Si_2$ [M – SEt]$^+$: 445.2441, found: 445.2446.

Compound 2-11.

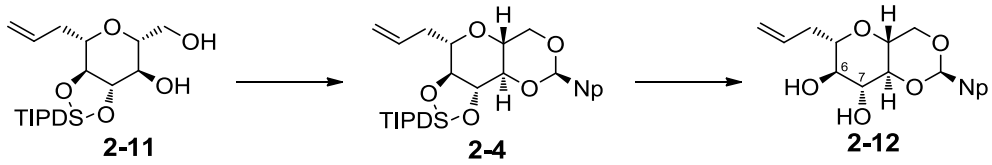


To a solution of **2-10** (44.27 g, 87.35 mmol) in CH_2Cl_2 (440 mL) was added mCPBA (30.16 g, 174.5 mmol) at 0 °C, and the mixture was stirred for 1 h. Then, to the mixture were added Et_3SiH (84.0 mL, 526 mmol) and $BF_3 \cdot OEt_2$ (66.0 mL, 525 mmol) at –20 °C, and the mixture was stirred for

30 min. Then, the reaction was quenched with 2.0 mol/L aq. NaOH and saturated aq. $Na_2S_2O_3$, and the mixture was filtered through a Celite pad. The filtrate was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **2-11** (34.86 g, 78.03 mmol, 89%) as a colorless oil.

2-11: All data were already measured by A. Goto. $[\alpha]_D^{30}$ –21.8 (*c* 1.67, $CHCl_3$); IR (neat) ν 3418, 3076, 2944, 2867, 2758, 2725, 1643, 1464, 1432, 1413, 1387, 1366, 1287, 1248, 1140, 990, 915, 886, 841, 701, 606, 564, 444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (28H, m), 2.14-2.23 (1H, m), 2.41 (1H, brs), 2.63 (1H, brdd, *J* = 1.4, 6.5 Hz), 3.28-3.38 (2H, m), 3.40 (1H, t, *J* = 9.4 Hz), 3.48 (1H, t, *J* = 9.4 Hz), 3.61 (1H, t, *J* = 8.4 Hz), 3.73 (1H, dd, *J* = 5.4, 11.6 Hz), 3.89 (1H, brdd, *J* = 3.2, 11.6 Hz), 5.08 (2H, dt, *J* = 1.8, 17.2 Hz), 5.88 (1H, tdd, *J* = 6.8, 10.2, 17.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1 (CH), 12.2 (CH), 12.79 (CH), 12.82 (CH), 17.2 (CH_3), 17.25 (CH_3), 17.31 (CH_3), 17.32 (CH_3), 17.36 (CH_3), 17.43 (CH_3×3), 36.1 (CH_2), 63.0 (CH_2), 71.6 (CH), 76.1 (CH), 78.1 (CH), 79.5 (CH), 81.4 (CH), 116.9 (CH_2), 134.8 (CH); EI-HRMS (m/z) calcd for $C_{18}H_{35}O_6Si_2$ [M – *i*Pr]$^+$: 403.1972, found: 403.1961.

Compound 2-12.



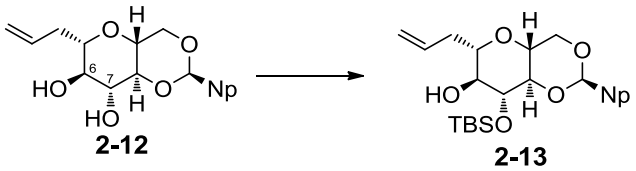
To a solution of **2-11** (23.08 g, 51.66 g) in PhH (300 mL) were added 2-naphthaldehyde (16.16 g, 103.4 mmol) and PPTS (1.2999 g, 5.1725 mmol) at 24 °C, and the mixture was stirred and heated to reflux with removal of water by a Dean-Stark apparatus. After being stirred for 3 h, the mixture was cooled to 24 °C, and the reaction was quenched with saturated aq. $NaHCO_3$. Then, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **2-4**, which was used in the next reaction without purification.

To a solution of the above crude **2-4** in THF (260 mL) was added TBAF (1.0 mol/L in THF, 130 mL, 130 mmol) at 0 °C, and the mixture was stirred for 40 min at 24 °C. Then, the reaction was quenched with water, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 2 → 1) to give **2-12** (15.18 g, 44.34 mmol, 86% from **2-11**) as a colorless solid.

2-12: All data were already measured by A. Goro. mp 144-146 °C; $[\alpha]_D^{19}$ –27.8 (*c* 0.270, $CHCl_3$); IR (KBr) ν 3447, 3071, 2976, 2867, 1641, 1476, 1435, 1377, 1345, 1328, 1272, 1213, 1179, 1128, 1094, 1078, 1009, 982, 951, 922, 900, 861, 823, 809, 798, 748, 608, 561, 502, 477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (1H, brtd, *J* = 6.0, 13.5 Hz), 2.57 (1H, brdd, *J* = 6.6, 14.6 Hz), 2.72 (1H, brs), 3.07 (1H,

brs), 3.35-3.51 (4H, m), 3.68-3.76 (2H, m), 4.34 (1H, dd, J = 5.0, 10.9 Hz), 5.11 (2H, dt, J = 1.4, 17.1 Hz), 5.65 (1H, s), 5.87 (1H, tdd, J=7.0, 10.2, 17.2 Hz), 7.47-7.52 (2H, m), 7.59 (1H, dd, J = 1.5, 8.5 Hz), 7.81-7.87 (3H, m), 7.96 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0 (CH_2), 68.9 (CH_2), 70.2 (CH), 73.9 (CH), 75.3 (CH), 79.2 (CH), 81.1 (CH), 101.9 (CH), 117.5 (CH_2), 123.7 (CH), 125.8 (CH), 126.3 (CH), 126.5 (CH), 127.7 (CH), 128.29 (CH), 128.33 (CH), 132.9 (C), 133.7 (C), 134.0 (CH), 134.3 (C); EI-HRMS (m/z) calcd for $C_{20}H_{22}O_5$ $[M]^+$: 342.1467, found: 342.1460.

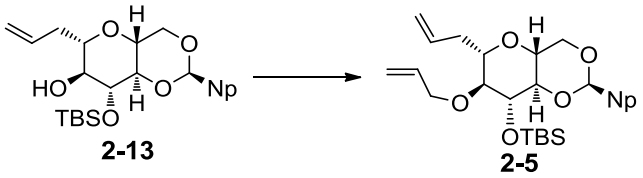
Compound 2-13.



To a solution of **2-12** (318.0 mg, 0.9288 mmol) and 2,6-lutidine (0.325 mL, 2.81 mmol) in CH_2Cl_2 (5 mL) was added TBSOTf (0.320 mL, 1.39 mmol) at –78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **2-13** (392.6 mg, 0.8597 mmol, 93%) as a colorless solid.

2-13: All data were already measured by A. Goto. mp 87-88 °C; $[\alpha]_D^{20}$ –65.9 (c 0.210, $CHCl_3$); IR (KBr) ν 3573, 3064, 2951, 2931, 2901, 2855, 1640, 1472, 1388, 1248, 1174, 1128, 1101, 1075, 1020, 911, 857, 778, 670, 473 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.11 (3H, s), 0.88 (9H, s), 2.27 (1H, d, J = 2.5 Hz), 2.32 (1H, qn, J = 7.5 Hz), 2.64 (1H, brd, J = 14.2 Hz), 3.35-3.51 (4H, m), 3.71-3.78 (2H, m), 4.36 (1H, dd, J = 4.4, 13.2 Hz), 5.11 (1H, dd, J = 1.0, 10.2 Hz), 5.16 (1H, dd, J = 1.7, 17.3 Hz), 5.65 (1H, s), 5.92 (1H, tdd, J = 6.8, 10.2, 17.3 Hz), 7.47-7.52 (2H, m), 7.59 (1H, dd, J = 1.6, 8.6 Hz), 7.85 (3H, brd, J = 8.6 Hz), 7.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8 (CH_3), -4.0 (CH_3), 18.2 (C), 25.9 (CH_3×3), 36.2 (CH_2), 69.0 (CH_2), 70.7 (CH), 75.0 (CH), 76.7 (CH), 79.2 (CH), 81.5 (CH), 101.7 (CH), 117.3 (CH_2), 123.9 (CH), 125.7 (CH), 126.1 (CH), 126.3 (CH), 127.7 (CH), 128.0 (CH), 128.3 (CH), 132.9 (C), 133.6 (C), 134.2 (CH), 134.7 (C); EI-HRMS (m/z) calcd for $C_{22}H_{27}O_5Si$ $[M - {}^tBu]^+$: 399.1628, found: 399.1637.

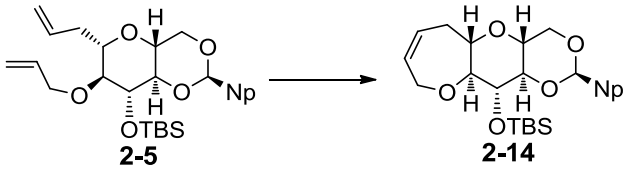
Compound 2-5.



To a solution of **2-13** (17.77 g, 38.91 mmol), TBAI (1.4696 g, 3.9787 mmol), and allylbromide (6.7 mL, 78 mmol) in THF (200 mL) was added NaH (60% in mineral oil, 7.7619 g, 194.13 mmol) at 0 °C, and the mixture was stirred for 10 h. Then, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **2-5** (19.15 g, 38.55 mmol, 100%) as a colorless solid.

2-5: All data were already measured by A. Goto. mp 65-67 °C; $[\alpha]_D^{21}$ –65.6 (*c* 0.390, $CHCl_3$); IR (KBr) ν 3075, 2924, 2854, 1644, 1472, 1388, 1256, 1176, 1081, 1031, 856, 776, 671, 473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 2.29 (1H, qn, *J* = 7.9 Hz), 2.60 (1H, brd, *J* = 13.9 Hz), 3.12 (1H, t, *J* = 8.5 Hz), 3.38-3.47 (3H, m), 3.72 (1H, t, *J* = 9.6 Hz), 3.86 (1H, t, *J* = 8.5 Hz), 4.10 (1H, dd, *J* = 6.0, 11.9 Hz), 4.34 (1H, dd, *J* = 4.6, 10.4 Hz), 4.41 (1H, dd, *J* = 6.0, 11.9 Hz), 5.09-5.20 (3H, m), 5.28 (1H, dd, *J* = 1.5, 17.2 Hz), 5.62 (1H, s), 5.86-5.98 (2H, m), 7.47-7.51 (2H, m), 7.59 (1H, dd, *J* = 1.8, 8.7 Hz), 7.81-7.87 (3H, m), 7.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.4 (CH_3), -4.1 (CH_3), 18.2 (C), 25.9 (CH_3×3), 36.0 (CH_2), 69.1 (CH_2), 70.4 (CH), 74.5 (CH_2), 76.3 (CH), 79.3 (CH), 82.2 (CH), 82.4 (CH), 101.9 (CH), 117.2 (CH_2), 117.3 (CH_2), 124.0 (CH), 125.8 (CH), 126.0 (CH), 126.3 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 132.8 (C), 133.6 (C), 134.49 (CH), 134.52 (CH), 134.7 (C); EI-HRMS (m/z) calcd for $C_{25}H_{31}O_5Si$ $[M - {}^tBu]^+$: 439.1941, found: 439.1940.

Compound 2-14.

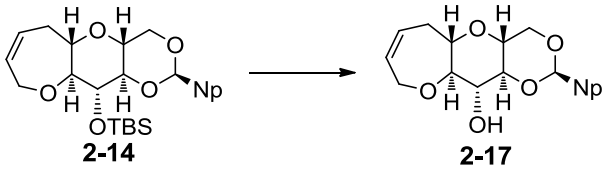


To a solution of **2-5** (1.0062 g, 2.0257 mmol) in degassed CH_2Cl_2 (100 mL) was added a solution of Grubbs' second generation catalyst (**2-16**) (18.3 mg, 0.0216 mmol) in degassed CH_2Cl_2 (1 mL) at 24 °C, and the mixture was refluxed with stirring. After 2 h from the start of the reaction, the mixture was cooled to 24 °C and stirred for 1 h under O_2 atmosphere. Then, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel + Florisil®, PhH) to give **2-14** (767.8 mg, 1.638 mmol, 82%) as a colorless solid.

2-14: Optical rotation, IR, and HRMS data were already measured by A. Goto. mp 133-136 °C; $[\alpha]_D^{22}$ –96.9 (*c* 0.0350, $CHCl_3$); IR (neat) ν 3481, 3023, 2927, 2855, 1725, 1510, 1472, 1387, 1247, 1175, 1108,

1011, 970, 855, 770, 740, 669, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 2.29-2.38 (1H, m), 2.67 (1H, ddd, *J* = 4.4, 8.0, 16.4 Hz), 3.24 (1H, t, *J* = 8.4 Hz), 3.40 (1H, dt, *J* = 4.4, 9.8 Hz), 3.47 (1H, dd, *J* = 5.1, 9.8 Hz), 3.55 (1H, t, *J* = 9.3 Hz), 3.74 (1H, t, *J* = 10.1 Hz), 3.82 (1H, t, *J* = 7.7 Hz), 3.99 (1H, brddd, *J* = 2.7, 5.7, 15.8 Hz), 4.31 (1H, dd, *J* = 5.7, 15.8 Hz), 4.36 (1H, dd, *J* = 5.1, 10.1 Hz), 5.70 (1H, s), 5.73-5.80 (1H, m), 5.85-5.90 (1H, m), 7.47-7.51 (1H, m), 7.60 (1H, dd, *J* = 1.7, 8.7 Hz), 7.82-7.85 (3H, m), 8.01 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.53 (CH_3), -4.46 (CH_3), 18.4 (C), 25.9 (CH_3×3), 34.8 (CH_2), 68.8 (CH_2), 69.0 (CH_2), 69.9 (CH), 74.9 (CH), 77.2 (CH), 82.0 (CH), 88.3 (CH), 101.4 (CH), 123.9 (CH), 125.5 (CH), 126.0 (CH), 126.2 (CH), 126.3 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 131.3 (CH), 132.9 (C), 133.6 (C), 134.9 (C); EI-HRMS (m/z) calcd for $C_{25}H_{31}O_5Si$ $[M]^+$: 411.1628, found: 411.1653.

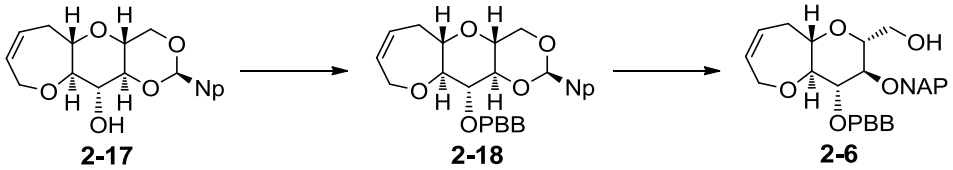
Compound 2-17.



To a solution of **2-14** (10.5 g, 22.4 mmol) in THF (120 mL) was added TBAF (1.0 mol/L in THF, 90 mL, 90 mmol) at 20 °C, and the mixture was stirred for 5 h. Then, the mixture was concentrated under reduced pressure, and the residue was purified by recrystallization (PhH + water) to give **2-17** (7.50 g, 21.2 mmol, 95%) as colorless needles.

2-17: All data were already measured by A. Goto. mp 217-219 °C; $[\alpha]_D^{24}$ –39.7 (*c* 0.0350, $CHCl_3$); IR (KBr) ν 3484, 3054, 3026, 2891, 1436, 1380, 1265, 1103, 1031, 861, 828, 801, 744, 678, 549, 476 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36-2.45 (1H, m), 2.66 (1H, ddd, *J* = 3.6, 8.3, 15.9 Hz), 2.80 (1H, s), 3.34 (1H, t, *J* = 8.5 Hz), 3.39 (1H, ddd, *J* = 4.0, 9.7, 19.4 Hz), 3.53 (1H, dt, *J* = 5.2, 9.7 Hz), 3.65 (1H, t, *J* = 9.3 Hz), 3.77 (1H, t, *J* = 10.5 Hz), 3.89 (1H, t, *J* = 8.8 Hz), 4.07 (1H, brqd, *J* = 2.9, 15.3 Hz), 4.35-4.40 (2H, m), 5.73 (1H, s), 5.82-5.88 (1H, m), 5.92-5.98 (1H, m), 7.46-7.50 (2H, m), 7.62 (1H, d, *J* = 8.5 Hz), 7.82-7.88 (3H, m), 7.99 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3 (CH_2), 68.5 (CH_2), 68.9 (CH_2), 69.9 (CH), 73.6 (CH), 76.4 (CH), 80.9 (CH), 87.8 (CH), 101.9 (CH), 123.8 (CH), 125.8 (CH), 126.1 (CH), 126.4 (CH), 127.3 (CH), 127.7 (CH), 128.2 (CH), 128.4 (CH), 131.7 (CH), 132.9 (C), 133.7 (C), 134.4 (C); EI-HRMS (m/z) calcd for $C_{21}H_{22}O_5$ $[M]^+$: 354.1467, found: 354.1464.

Compound 2-6.

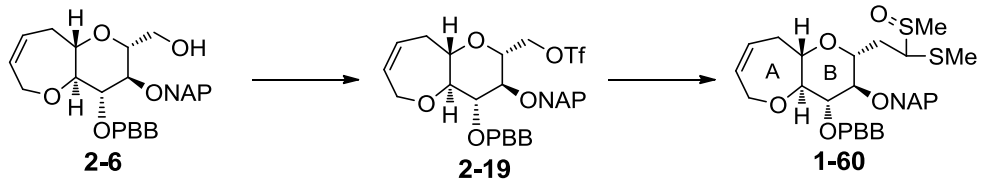


To a solution of **2-17** (11.98 g, 33.80 mmol), PBBBr (14.4566 g, 57.8426 mmol), and TBAI (1.2552 g, 3.3982 mmol) in THF (350 mL) was added NaH (60% in mineral oil, 4.9954 g, 124.94 mmol) at 0 ºC, and the mixture was stirred for 27 h at 23 ºC. Then, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **2-18**, which was used immediately in the next reaction.

To a solution of the above crude **2-18** in CH_2Cl_2-Et_2O (240 mL : 240 mL) were added $LiAlH_4$ (7.7686 g, 204.65 mmol) and a solution of $AlCl_3$ (9.0295 g, 67.718 mmol) in Et_2O (70 mL) at 23 ºC, and the mixture was stirred for 3 h. Then, to the mixture was added saturated aq. potassium sodium tartrate, and the mixture was stirred for 20 h at 23 ºC. Then, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 2) to give **2-6** (15.44 g, 29.39 mmol, 87% from **2-17**) as a colorless solid.

2-6: mp 101-103 ºC; $[\alpha]_D^{24}$ –32.4 (*c* 1.30, $CHCl_3$); IR (KBr) ν 3587, 3438, 3059, 3020, 2959, 2899, 2861, 2827, 1595, 1484, 1402, 1352, 1237, 1160, 1121, 1071, 1011, 813, 746, 620, 482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (1H, t, *J* = 6.0 Hz), 2.30-2.41 (1H, m), 2.65 (1H, ddd, *J* = 4.0, 8.0, 16.1 Hz), 3.28 (1H, td, *J* = 4.0, 9.2 Hz), 3.36-3.41 (1H, m), 3.37 (1H, t, *J* = 9.2 Hz), 3.55 (1H, t, *J* = 9.2 Hz), 3.65-3.71 (1H, m), 3.66 (1H, t, *J* = 9.2 Hz), 3.87 (1H, ddd, *J* = 2.8, 6.0, 11.6 Hz), 3.99 (1H, ddd, *J* = 2.4, 6.0, 15.4 Hz), 4.27 (1H, dd, *J* = 6.0, 15.4 Hz), 4.76 (1H, d, *J* = 11.5 Hz), 4.80 (1H, d, *J* = 11.5 Hz), 4.91 (1H, d, *J* = 11.5 Hz), 4.98 (1H, d, *J* = 11.5 Hz), 5.76-5.83 (1H, m), 5.87-5.94 (1H, m), 7.22 (2H, d, *J* = 8.5 Hz), 7.38 (1H, dd, *J* = 1.6, 8.5 Hz), 7.42 (2H, dt, *J* = 2.4, 8.5 Hz), 7.45-7.50 (2H, m), 7.69 (1H, s), 7.80 (3H, dd, *J* = 7.4, 15.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5 (CH_2), 62.4 (CH_2), 67.9 (CH_2), 74.7 (CH_2), 75.1 (CH_2), 75.8 (CH), 77.6 (CH), 78.5 (CH), 85.6 (CH), 88.2 (CH), 121.3 (C), 125.9 (CH), 126.0 (CH), 126.2 (CH), 126.7 (CH), 127.1 (CH), 127.7 (CH), 128.0 (CH), 128.3 (CH), 129.5 (CH×2), 131.4 (CH×2), 131.6 (CH), 133.0 (C), 133.3 (C), 135.6 (C), 138.1 (C); FD-HRMS (m/z) calcd for $C_{28}H_{29}O_5Br$ $[M]^+$: 524.1198, found: 524.1206.

Compound 1-60.



To a solution of **2-6** (14.21 g, 27.04 mmol) and 2,6-lutidine (9.40 mL, 81.1 mmol) in CH_2Cl_2 (150 mL) was added Tf_2O (9.20 mL, 54.8 mmol) at –78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with 0.5 mol/L aq. HCl, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **2-19**, which was used immediately in the next reaction.

To a solution of $MeSCH_2S(O)Me$ (8.80 mL, 86.5 mmol) in THF (170 mL) was added BuLi (1.60 mol/L in hexane, 51.0 mL, 81.6 mmol) at –20 °C, and the mixture was stirred for 20 min. Then, to the mixture was added a solution of the above crude **2-19** in THF (100 mL), and the mixture was stirred for 40 min. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1 → 0.5) to give **1-60** (brown oil, 16.3448 g, 25.88 mmol, 96% from **2-6**) as an inseparable mixture of 4 diastereomers.

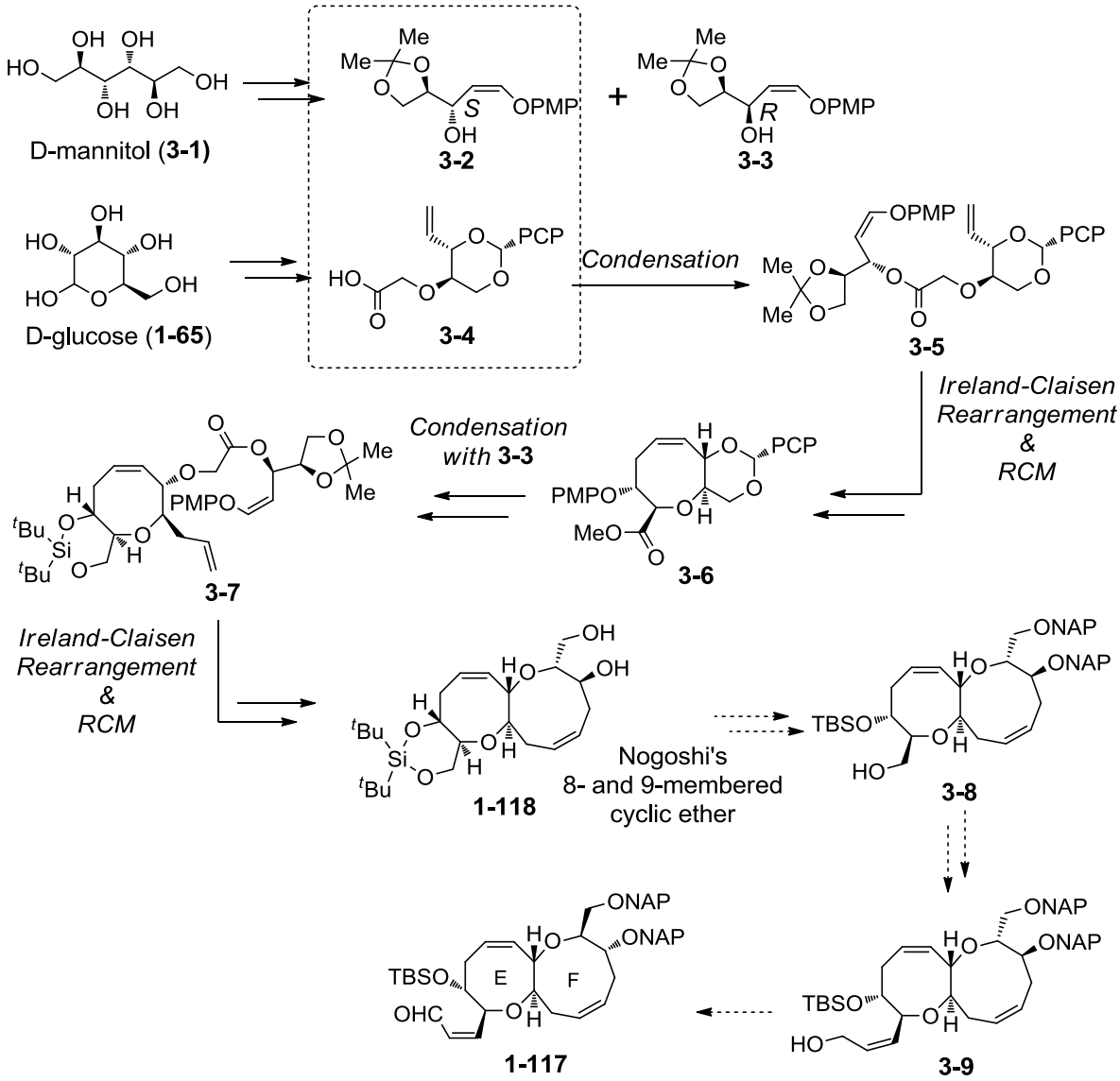
2-6: IR and HRMS were already measured by A. Goto. IR (neat) ν 3034, 2888, 1593, 1479, 1091, 815, 678 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.74-1.78 (2H, m), 1.89 (1H, s), 1.95 (1H, s), 2.13 (2H, s), 2.15-2.29 (2H, m), 2.34-2.52 (2H, m), 3.14-3.38 (4H, m), 3.57-3.67 (2H, m), 3.74-3.82 (1H, m), 3.94 (1H, dd, J = 5.1, 14.9 Hz), 4.54 (1/2H, d, J = 11.9 Hz), 4.61-4.66 (1H, m), 4.81-4.87 (1H, m), 4.90 (1/4H, d, J = 11.8 Hz), 4.93 (1/4H, d, J = 11.5 Hz), 5.46-5.59 (2H, m), 6.98-7.06 (2H, m), 7.20-7.35 (5H, m), 7.57-7.68 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 11.7 (CH_3×1/2), 14.1 (CH_3×1/4), 15.1 (CH_3×1/4), 28.8 (CH_2×1/2), 29.2 (CH_2×1/2), 32.9 (CH_3×1/4), 34.5 (CH_2), 35.4 (CH_3×1/4), 36.4 (CH_3×1/2), 61.2 (CH×1/2), 63.2 (CH×1/2), 65.5 (CH_2×1/4), 67.5 (CH_2×3/4), 71.9 (CH×1/4), 74.27 (CH_2×1/2), 74.32 (CH_2×1/2), 74.4 (CH×1/2), 74.9 (CH×1/4), 74.95 (CH_2×1/2), 75.02 (CH_2×1/2), 75.8 (CH), 81.5 (CH×1/2), 81.6 (CH×1/2), 85.69 (CH×1/2), 85.74 (CH×1/2), 88.1 (CH), 121.13 (C×1/2), 121.14 (C×1/2), 125.7 (CH×1/2), 125.83 (CH×1/2), 125.84 (CH×1/2), 125.9 (CH×1/2), 126.1 (CH×1/2), 126.3 (CH×1/2), 126.5 (CH×1/4), 126.56 (CH×1/2), 126.58 (CH×1/4), 127.7 (CH), 127.86 (CH×1/2), 127.89 (CH×1/2), 127.97 (CH×2), 128.04 (CH×1/2), 128.1 (CH×1/2), 129.17 (CH), 129.19 (CH), 131.3 (CH), 131.5 (CH), 133.1 (C×1/2), 133.16 (C×1/4), 133.18 (C×1/4), 133.5 (C), 136.08 (C×1/2), 136.12 (C×1/2), 138.5 (C×1/2), 138.6 (C×1/2); FD-HRMS (m/z) calcd for $C_{31}H_{35}O_5{}^{79}BrS_2Si$ $[M]^+$: 630.1091, found: 630.1100.

3. Synthesis of the EF-ring

3-1. Synthetic plan of EF-ring 1-117

The outline of the synthesis of bicyclic ether **1-118** and synthetic plan for EF-ring **1-117** from **118** are shown in Scheme 3-1. The author initially planned to synthesize EF-ring **1-117** from bicyclic ether **1-118** according to the method previously developed for E-ring **1-61** (Scheme 1-6) by Goto.[1] Bicyclic ether **1-118** would be transformed into primary alcohol **3-8** by manipulation of protecting groups, and the attachment of (*Z*)-olefin to **3-8** would afford precursor alcohol **3-9**, which would be oxidized to give EF-ring aldehyde **1-117**. Bicyclic ether **1-118** was envisioned to be prepared according to Nogoshi's Ireland-Claisen rearrangement[2,3]/RCM process.[4]

The author first optimized the synthesis of bicyclic ether **1-118** from **3-2** and **3-4** to achieve the practical supply of **1-118**. Then, the synthesis of EF-ring **1-117** from **1-118** was achieved with solving problems arose during the synthesis.

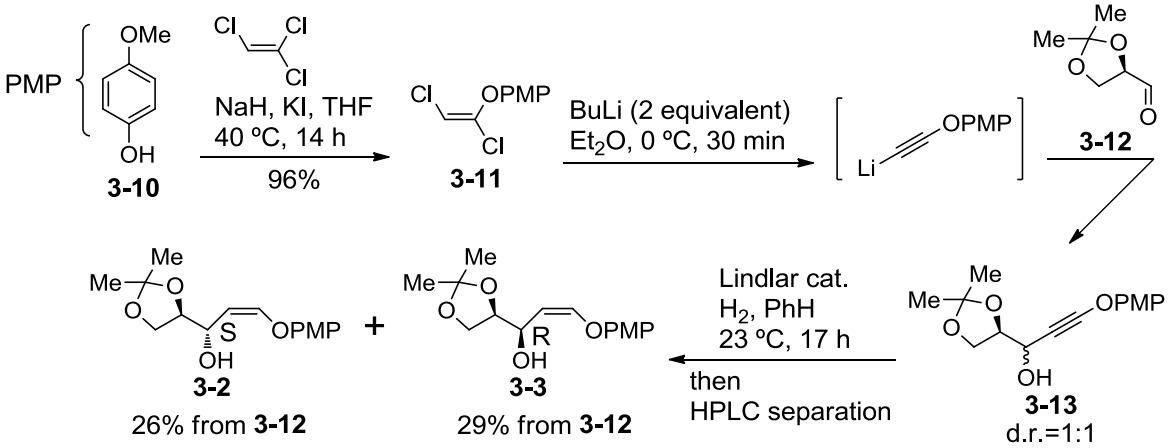


Scheme 3-1. Outline of the synthesis of **1-118** and plan for EF-ring **1-117**

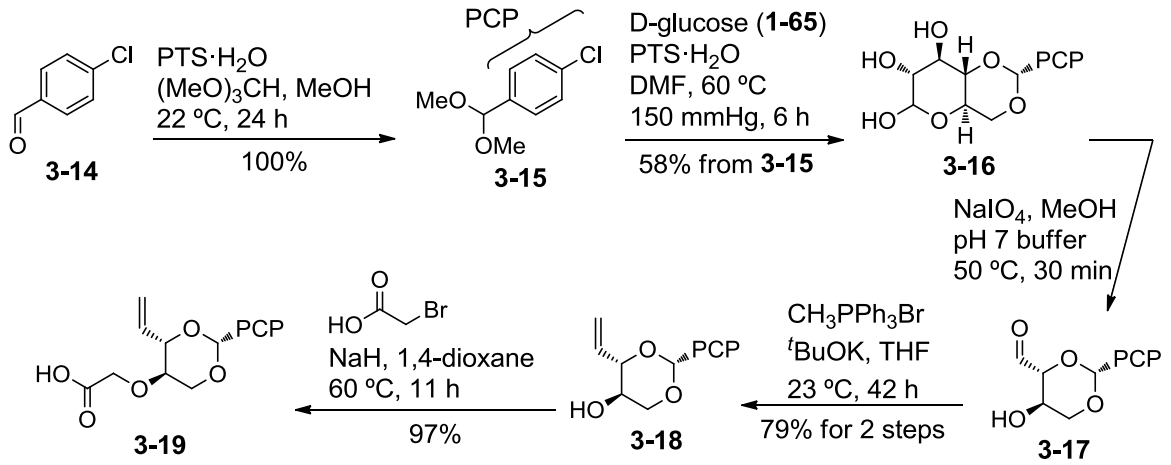
3-2. Preparation of the Nogoshi's bicyclic ether 1-118

The synthesis of bicyclic ether **1-118** was undertaken according to Nogoshi's procedure.[4] The synthesis was commenced with (*Z*)-3-aryloxyallyl alcohol **3-2** and carboxylic acid **3-4**.

The preparation of (*Z*)-aryloxyallyl alcohols **3-2** and **3-3** is shown in Scheme 3-2. 4-Methoxyphenol (**3-10**) was treated with NaH, KI, and trichloroethylene to afford PMP ether **3-11** (96%). Exposure of **3-11** with BuLi generated a lithium acetylide, which was reacted with (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**3-12**)[5] in situ to give alcohol **3-13** as a 1:1 mixture of diastereomers. Lindlar hydrogenation of **3-13** produced a 1:1 mixture of **3-2** (26% from **3-10**) and **3-3** (29% from **3-10**), which were separated by HPLC. The stereochemistry of **3-2** and **3-3** was confirmed by X-ray crystallographic analysis by Nogoshi.



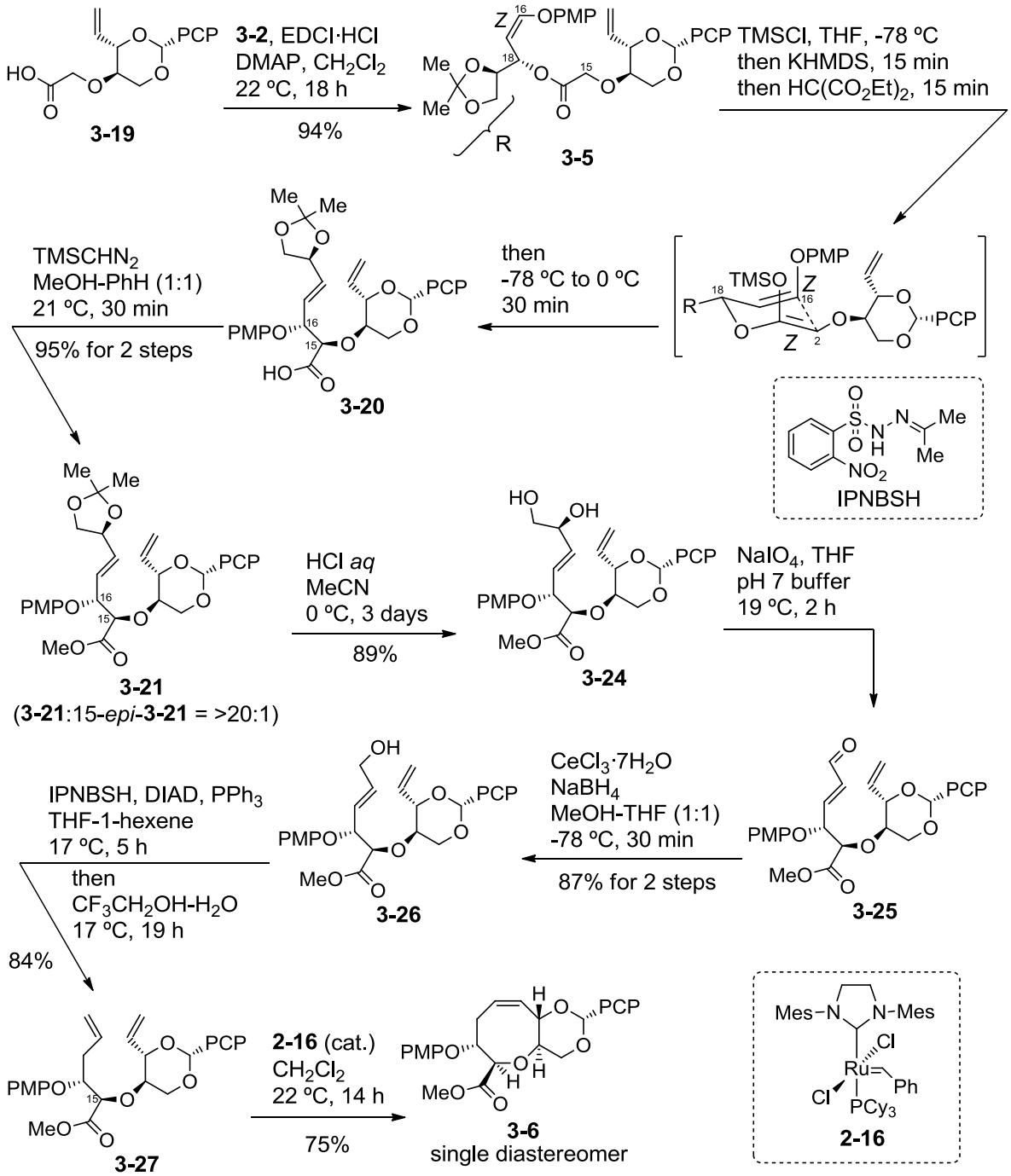
Scheme 3-2. Synthesis of (*Z*)-aryloxyallyl alcohol **3-2** and **3-3**



Scheme 3-3. Synthesis of carboxylic acid **3-19**

Carboxylic acid **3-19** was synthesized from 4-chlorobenzylidene dimethyl acetal (**3-15**), prepared from 4-chlorobenzaldehyde (**3-14**), and D-glucose via a 4-step process similar to the previously reported procedure (44% from **3-14**) (Scheme 3-3).[6] Thus, selective protection of the

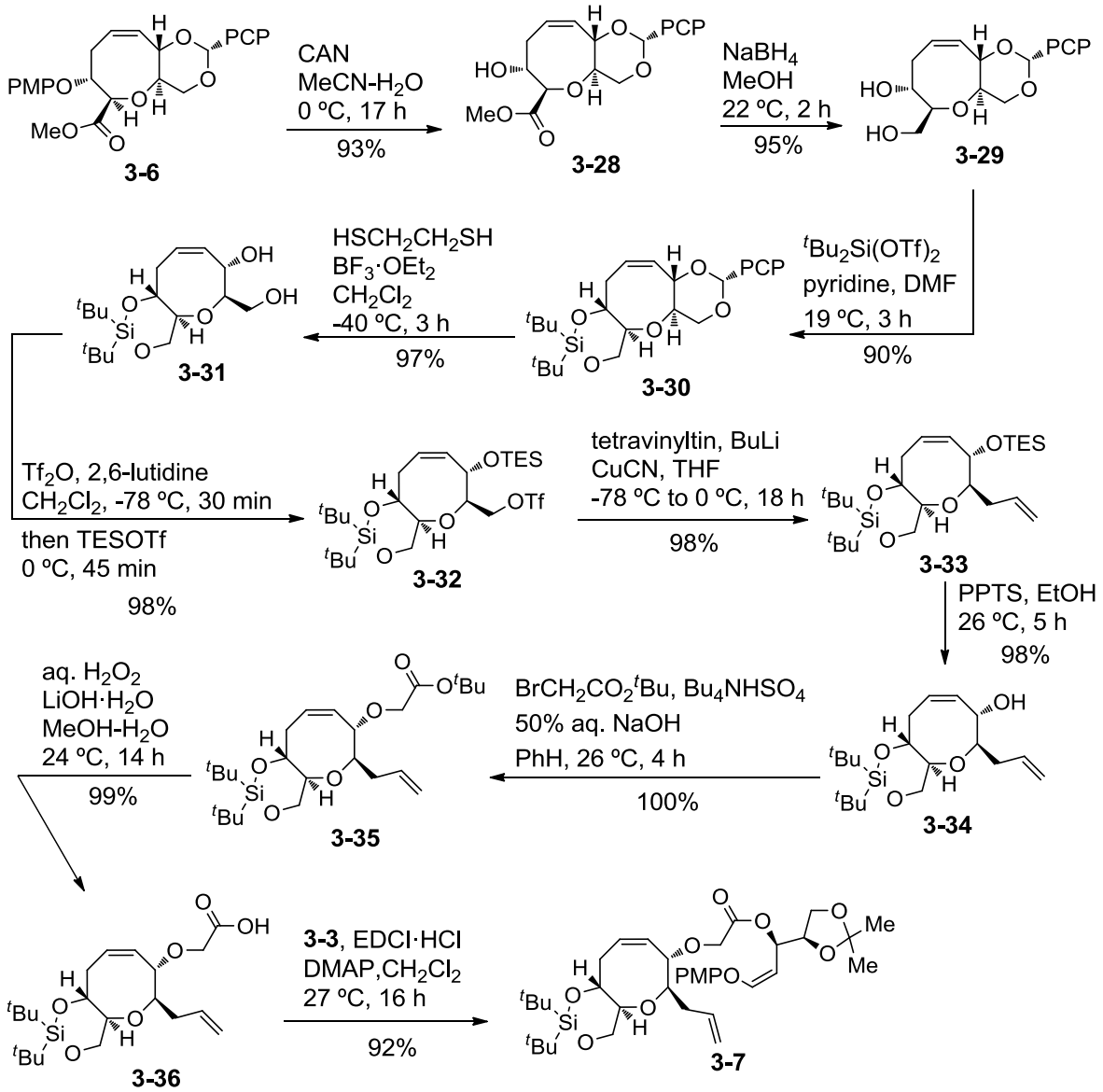
1,3-diol at C4 and C6 of D-glucose as a 4-chlorobenzylidene acetal, oxidative cleavage by $NaIO_4$, Wittig methylenation, and formation of a carboxymethyl ether constructed **3-19**.



Scheme 3-4. Formation of E-ring **3-6**

With alcohol **3-2** and carboxylic acid **3-19** in hand, cyclization of the E-ring was performed (Scheme 3-4). Carboxylic acid **3-19** was then condensed with **3-2** using EDCI·HCl and DMAP to afford ester **3-5** (94% from **3-2**). Ireland-Claisen rearrangement of **3-5** followed by methylation produced methyl ester **3-21** stereoselectively (95% from **3-5**). Although ester **3-21** was obtained as an

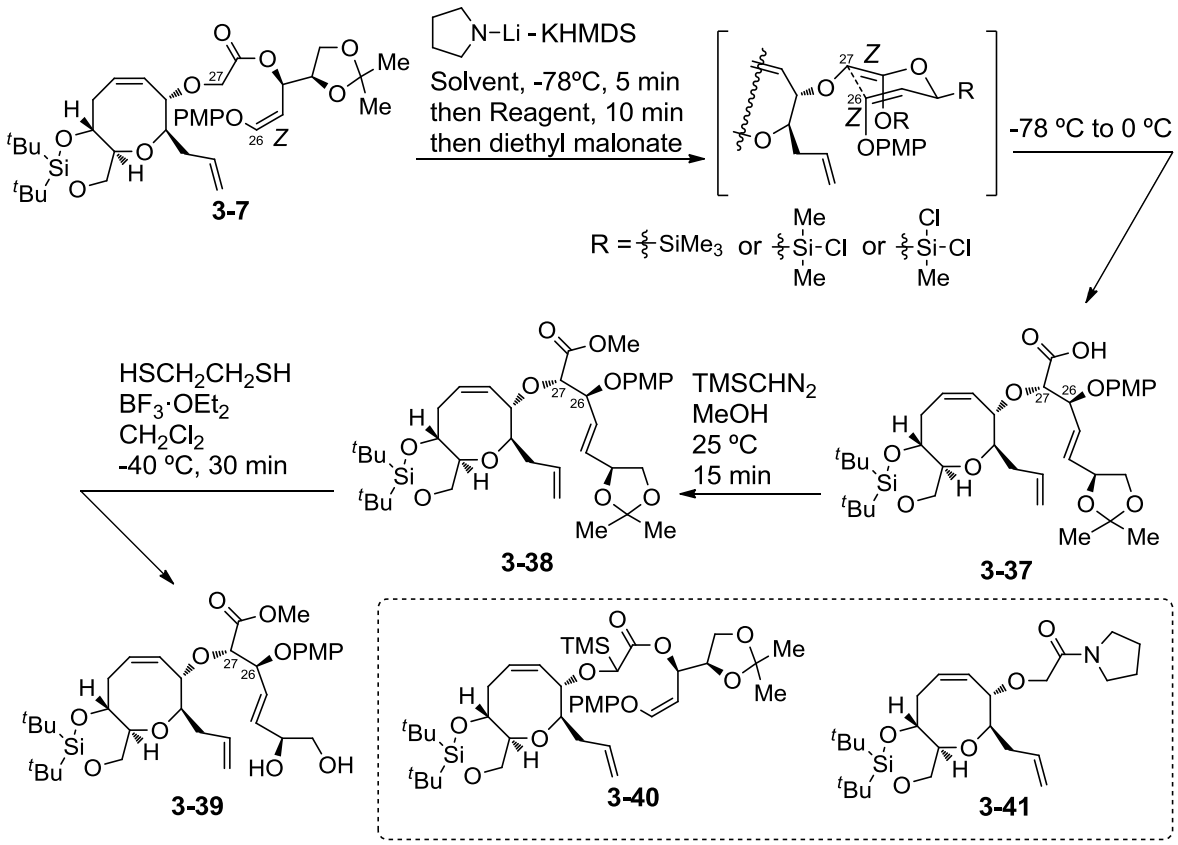
inseparable mixture with 15-*epi*-**3-21** (**3-21**:15-*epi*-**3-21** = > 20:1), the author found that the undesired 15-epimer was able to be separated at the later stage. The isopropylidene acetal of **3-21** was selectively hydrolyzed under acidic conditions without removal of the 4-chlorobenzylidene acetal to afford diol **3-24** (89%), which was subjected to oxidative cleavage followed by Luche reduction to give allyl alcohol **3-26** (87% from **3-24**).[7] Reductive rearrangement of allyl alcohol **3-26** was performed according to Movassaghi's procedure[8] with a slight modification to furnish diene **3-27** (84%), which was then transformed to eight-membered ring ether **3-6** (75%) by RCM using the second generation Grubbs catalyst (**2-16**). Although diene **3-27** included a trace amount of 15-*epi*-**3-27**, the RCM reaction gave no cyclized product from 15-*epi*-**3-27**, which was easily separated from **3-6** by column chromatography.



Scheme 3-5. Preparation of ester **3-7**

Toward the F-ring formation, protected cyclic ether **3-6** was converted to ester **3-7** (Scheme 3-5). After removal of the PMP group of **3-6** with CAN (93%),[9] the resulting β-hydroxy ester **3-28** was reduced with $NaBH_4$ to produce 1,3-diol **3-29** (95%), which was converted to 1,3,2-dioxasilinane **3-30** (90%). The 4-chlorobenzylidene acetal group of **3-30** was removed with 1,2-ethanedithiol and $BF_3 \cdot OEt_2$ to afford diol **3-31** (97%).[10] One-pot selective triflation/TES protection of **3-31** (98%) followed by vinylation of the triflate ester gave alkene **3-33** (98%),[11] which was treated with PPTS in EtOH to produce alcohol **3-34** (98%). Etherification of **3-34** with *tert*-butyl bromoacetate under phase-transfer conditions afforded **3-35** (100%), which was then hydrolyzed with H_2O_2/LiOH to produce glycolic acid **3-36** (99%).[12] Although Nogoshi performed the hydrolysis of *tert*-butyl ester **3-35** with hydroxide/methoxide, the reaction was associated with significant removal of the silylene group. Therefore, the author conducted the hydrolysis under milder conditions to give **3-36** successfully. Condensation of **3-36** with alcohol **3-3** afforded (*Z*)-3-aryloxyallyl ester **3-7** (92%).

Next, the asymmetric center of C26 and C27 was constructed by Ireland-Claisen rearrangement of (*Z*)-3-aryloxyallyl ester **3-7**. Nogoshi found that the treatment of **3-7** with a mixture of lithium pyrrolidinide and KHMDS selectively produced (*Z*)-ketene silyl acetal, which afforded the desired carboxylic acid **3-37** by rearrangement. However, the author found that the reaction showed poor reproducibility. Therefore, the author decided to modify/optimize the reaction conditions (Table 3-1). According to Nogoshi's method, treatment of **3-7** with the combination of KHMDS (6 equiv) and lithium pyrrolidinide (6 equiv) as a base for 5 min and then with TMSCl for 10 min in THF-PhMe (1:3), which was followed by scavenging of the excess base with diethyl malonate and warming the resulting ketene silyl acetal to 0 °C, induced the rearrangement to afford **3-37**, which was converted to methyl ester **3-38** (55% for 2 steps, Entry 1) on treatment with $TMSCHN_2$. The low yield of **3-38** was attributed to the formation of α-silyl ester **3-40**. When only PhMe was used as solvent, no rearrangement product was obtained, and amide **3-41** was only detected (Entry 2). When the ketene silyl acetal was generated in THF-$PhCH_3$ (5:1), rearranged product **3-38** was obtained in 58% yield along with α-silyl ester **3-40** (Entry 3). However, production of amide **3-41** was suppressed. Despite the good stereoselectivity (**3-39**:27-*epi*-**3-39** = 10:1), low yield of **3-39** due to byproduction of α-silyl ester **3-40** was a significant problem. Next, several silylation reagents were examined in THF-$PhCH_3$ (5:1). The use of Me_2SiCl_2 instead of TMSCl cleanly formed (*Z*)-ketene silyl acetal without formation of α-silyl ester and gave good result. However, a polysiloxane was generated from excess Me_2SiCl_2 under the conditions and was difficult to be separated from **3-38**. Therefore, the mixture of **3-38** and the polysiloxane was treated with $BF_3 \cdot OEt_2$ and $HSCH_2CH_2SH$, and the acetonide group was removed to afford diol **3-39**, which could be separated from the polysiloxane, in 65% over 3 steps (Entry 4).[13] When $MeSiCl_3$ was used, the recovery of **3-7** was increased, and the yield of **3-39** was decreased (Entry 5). The use of TMSOTf resulted in decomposition of the substrate (Entry 6). Thus, Me_2SiCl_2 was found to be good silylation reagent, which constructed the chiral centers at C26 and C27 in relatively good yield (65% over 3 steps) with high stereoselectivity (**3-39**:27-*epi*-**3-39** = 10:1).



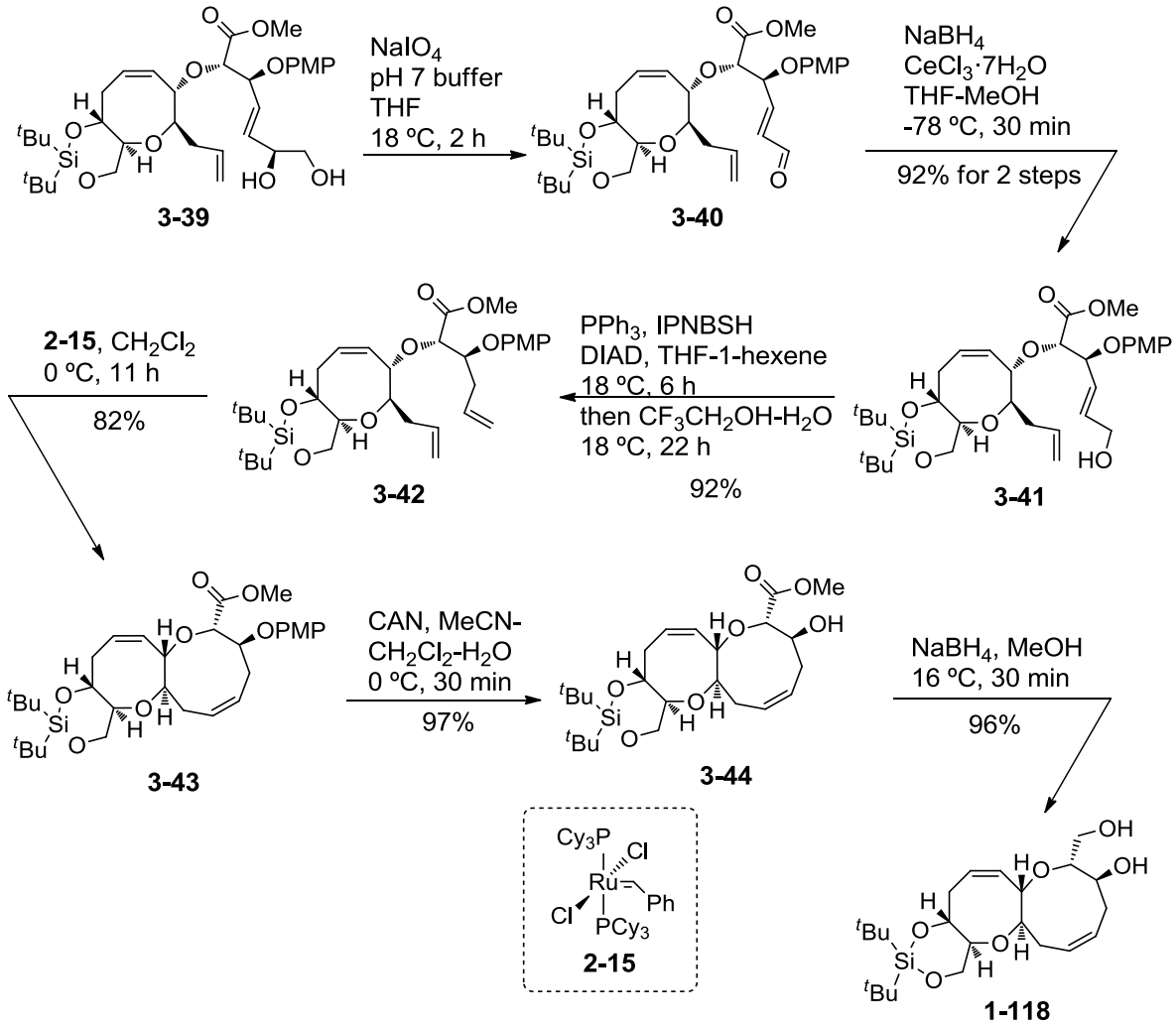
Entry	Solvent	Reagent	Yield of **3-38** or **3-39**[a]	**3-38**:27-*epi*-**3-38** [b] or **3-39**:27-*epi*-**3-39**
1	THF-PhMe (1:3)	TMSCl	**3-38** 55% (2 steps)	10:1
2	PhMe	TMSCl	not detected	———
3	THF-PhMe (5:1)	TMSCl	**3-38** 58% (2 steps)	10:1
4	THF-PhMe (5:1)	Me_2SiCl_2	**3-39** 65% (3 steps)	10:1
5	THF-PhMe (5:1)	$MeSiCl_3$	**3-39** 33% (3 steps)	10:1
6	THF-PhMe (5:1)	TMSOTf	not detected	———

[a] The yield was culculated as a mixture of the epimer
[b] The ratio was determined by the ^{1}H NMR spectra

Table 3-1. Ireland-Claisen rearrangement of (*Z*)-3-aryloxyallyl ester **3-7**

Synthesis of EF-ring diol **1-118** is outlined in Scheme 3-6. The second ring was constructed using a procedure similar to that described above. The oxidative cleavage of 1,2-diol **3-39** followed by Luche reduction gave allyl alcohol **3-41** (92% from **3-39**), which was transformed to **3-42** by reductive rearrangement (92%). The divinyl compound **3-42** was cyclized by RCM with the first generation Grubbs catalyst (**2-15**) at 0 °C to produce bicyclic ether **3-43** in good yield (82%). Although Nogoshi conducted RCM of diene **3-42** under reflux condition using CH_2Cl_2 as a solvent, the reaction shows poor reproducibility. When the RCM was conducted at higher temperature (> room temperature), significant production of byproducts was observed. Therefore, the author performed the RCM step at 0 °C to obtain a satisfactory result. The PMP group of **3-43** was removed with CAN to afford alcohol **3-44** (97%), which was reduced with $NaBH_4$ to give EF-ring diol **1-118** (96%).

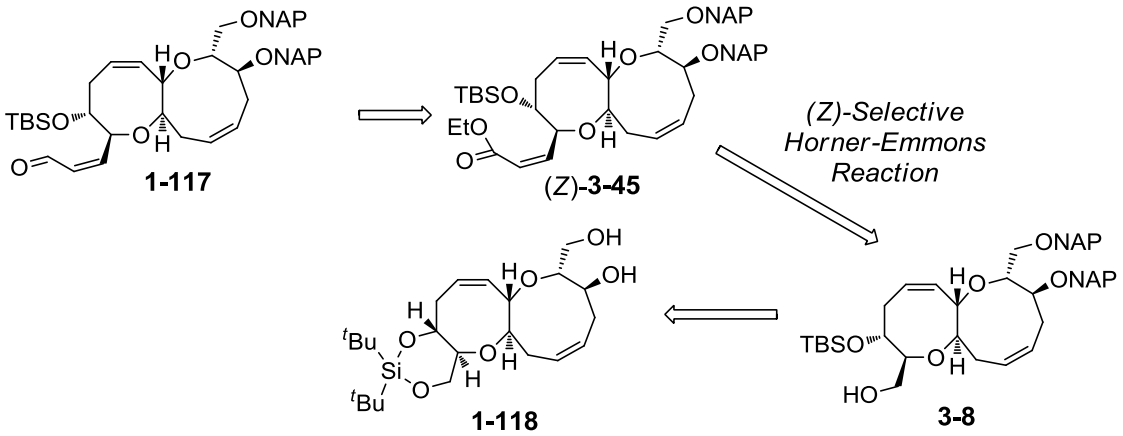
Thus, the author improved the reproducibility of Nogoshi's synthetic method for bicyclic ether **1-118** and synthesized **1-118** from 4-chlorobenzaldehyde over 32 steps in 5.4% overall yield.



Scheme 3-6. Synthesis of Nogoshi's bicyclic ether **1-118**

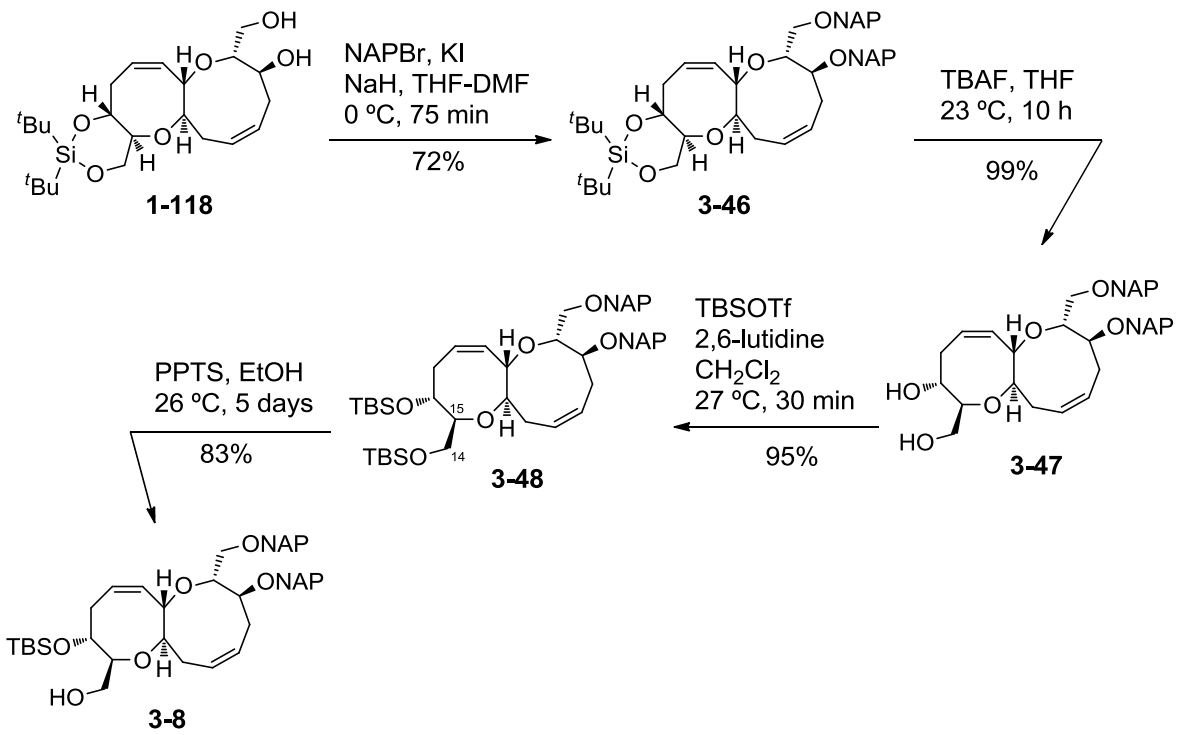
3-3. The first approach for the construction of EF-ring 1-117 via (*Z*)-selective Horner-Emmons reaction

Initially, EF-ring **1-117** was envisioned to be synthesized by a route including (*Z*)-selective Horner-Emmons reaction (Scheme 3-7). EF-ring **1-117** would be converted from (*Z*)-α,β-unsaturated ester **3-45**, which was expected to be constructed by (*Z*)-selective Horner-Emmons reaction of an aldehyde prepared from **3-8**. Alcohol **3-8** would be prepared from diol **1-118**.



Scheme 3-7. Synthetic plan for EF-ring **1-117** via (*Z*)-selective Horner-Emmons reaction

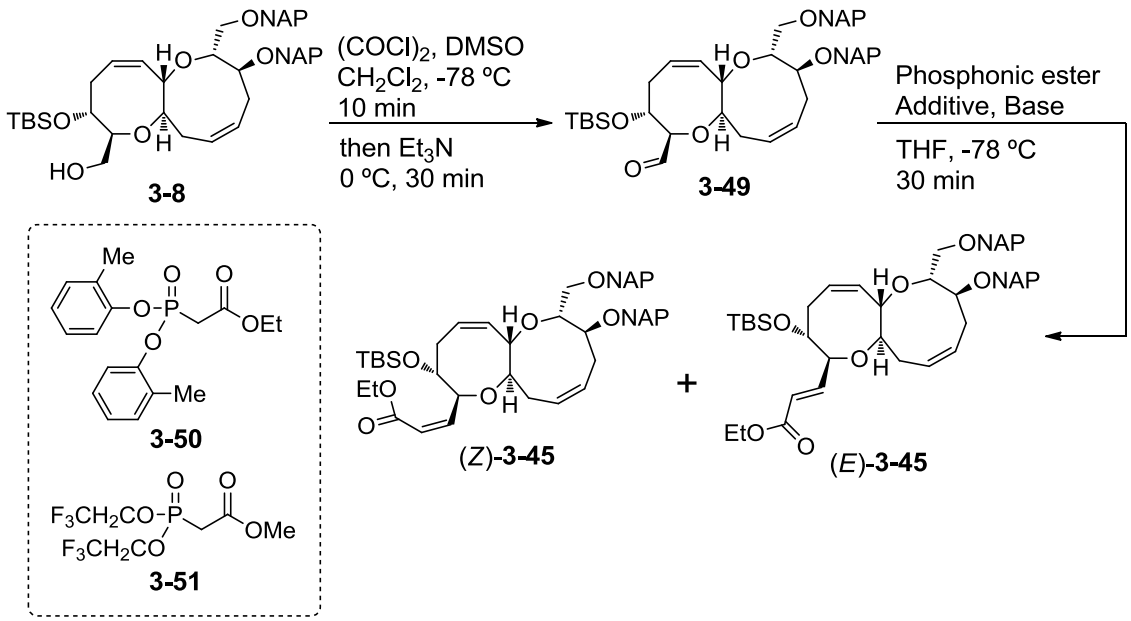
Alcohol **3-8** was constructed from diol **1-118** by a 4-step process as shown in Scheme 3-8. Diol **1-118** was protected as a bis-NAP ether to furnish **3-46** (72%), of which the silylene group was removed with TBAF to afford diol **3-47** in 99% yield. Diol **3-47** was reacted with TBSOTf to give bis-TBS ether **3-48** (95%), which was subjected to selective detachment of the primary TBS ether to give primary alcohol **3-8** (83%).



Scheme 3-8. Synthesis of alcohol **3-8**

Next, (*Z*)-selective Horner-Emmons reaction of aldehyde **3-49** was investigated (Table 3-2). Swern oxidation of alcohol **3-8** cleanly produced aldehyde **3-49**, which was immediately used in the next Horner-Emmons reaction without purification. Initially, according to Ando's report, [14] phosphonic ester **3-50** was used. Treatment of **3-50** with KHMDS followed by the addition of aldehyde **3-49** produced a 3:1 mixture of α,β-unsaturated esters (*Z*)-**3-45** and (*E*)-**3-45** in 11% yield over 2 steps (Entry 1). Because the yield and selectivity were unsatisfactory, the author decided to examine various bases. When NHMDS was used as base, the yield was improved (34%), but the ratio was unaffected (Entry 2). The use of NaH produced (*Z*)- and (*E*)-ester **3-45** in moderate yield (67% for 2 steps), and the selectivity was slightly increased (4:1) (Entry 3). When the combination of DBU and NaI was used as base, only trace amount of **3-45** was obtained along with the decomposition of most of the substrate (Entry 4). Then, Still-Gennari olefination was undertaken.[15] After the treatment of phosphonic ester **3-51** with KHMDS in the presence of 18-crown-6, the resulting anion was reacted with aldehyde **3-49** to give methyl ester in 55% yield for 2 steps with moderate selectivity (4:1) (Entry 5). As a consequence, it was found that highly selective formation of (*Z*)-ester **3-45** was difficult in

Ando and Still-Gennari modified Horner-Emmons reactions. Furthermore, it was difficult to separate (*Z*)-**3-45** from (*E*)-**3-45**. Thus, the author decided to develop another synthetic process for constructing the (*Z*)-olefin.



Entry	Phosphonic ester	Additive	Base	Yield (2 steps) ((*Z*)-**3-45** + (*E*)-**3-45**)	(*Z*)-**3-45** : (*E*)-**3-45** [a]
1	**3-50**	——	KHMDS	11%	3:1
2	**3-50**	——	NHMDS	34%	3:1
3	**3-50**	——	NaH	67%	4:1
4	**3-50**	NaI	DBU	trace	2:1
5	**3-51**	18-crown-6	KHMDS	55% [b]	4:1 [b]

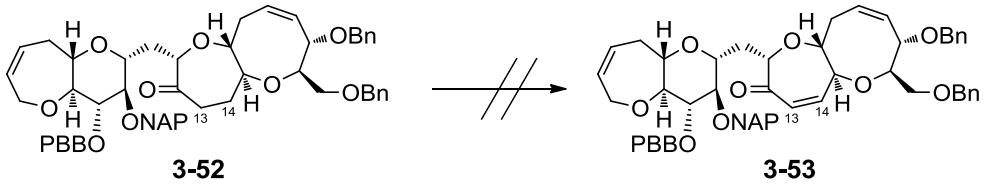
[a] The ratio was determined by ^{1}H NMR spectra

[b] Methyl ester was obtained in this condition

Table 3-2. (*Z*)-selective Horner-Emmons reaction of aldehyde **3-45**

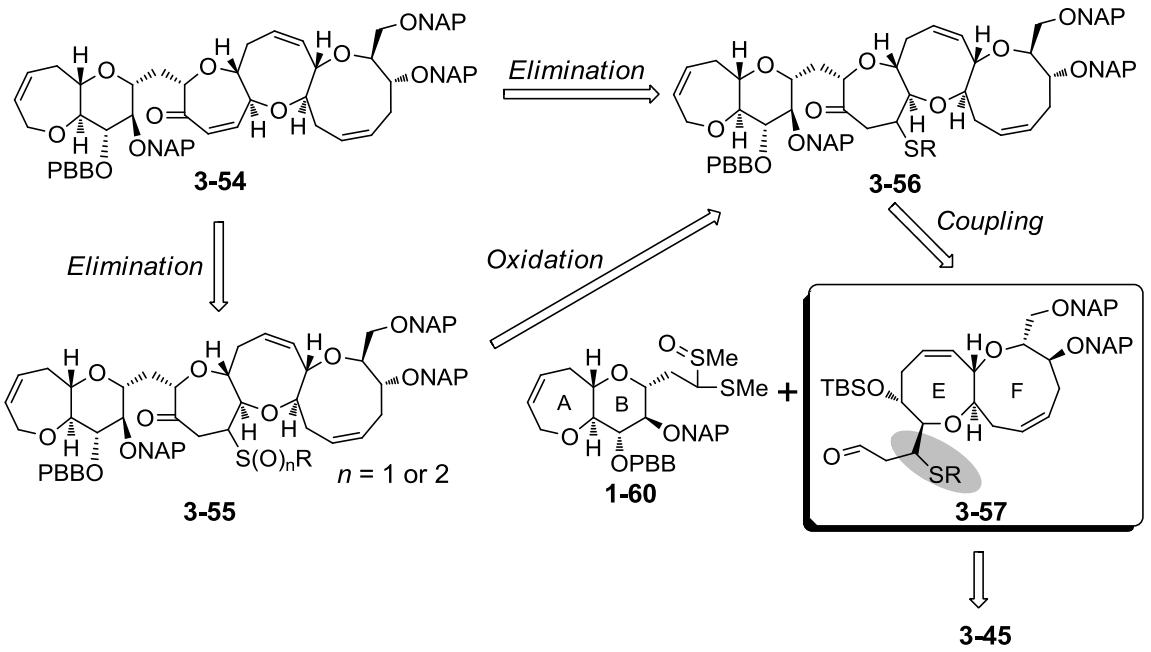
3-4. The second approach to the construction of (*Z*)-olefin via elimination of the sulfide of the D-ring

Considering the difficulty of (*Z*)-selective olefination of EF-ring aldehyde **3-49**, the author next planned to construct the olefin at C13-C14 after coupling between the AB- and EF-rings followed by D-ring formation. However, Goto found that the introduction of an olefin to the D-ring by Saegusa oxidation of saturated cyclic ketone **3-52** resulted in decomposition of the substrate (Scheme 3-9).[16]



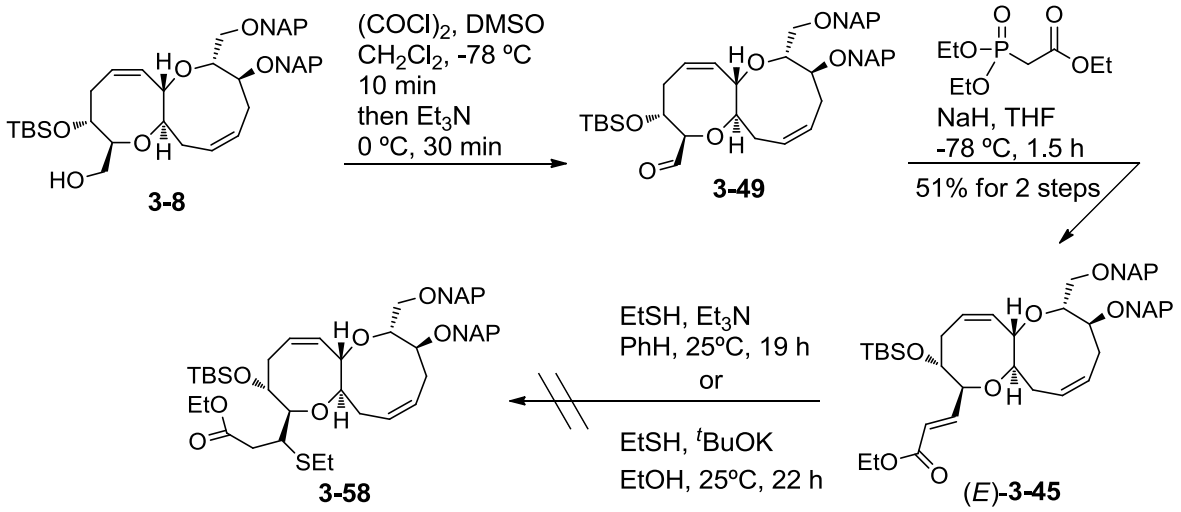
Scheme 3-9. Attempted introduction of an olefin to the D-ring by Goto

Therefore, the author planned to construct the olefin at C13-C14 from a cyclic ketone possessing leaving group at β-position (**3-55** or **3-56**), which would be converted to α,β-unsaturated ketone **3-54** via elimination process (Scheme 3-10). In the plan, a sulfide group was selected as a precursory leaving group, because a sulfide group would be easily installed to α,β-unsaturated ester **3-45** by Michael addition. Thus, α,β-unsaturated ester **3-45** would be converted to sulfide **3-57**, which would be coupled with AB-ring **1-60** to give **3-56**. The sulfide group of **3-56** itself or the sulfoxide/sulfone group of **3-55**, prepared by oxidation of the sulfide group of **3-56**, would be facilely eliminated to give **3-54**.



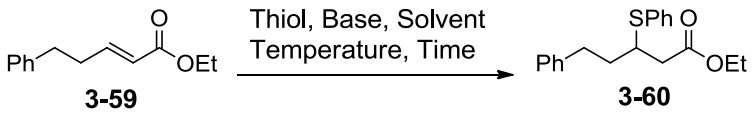
Scheme 3-10. The second approach to the construction of (*Z*)-olefin via elimination of the sulfide, sulfoxide, or sulfone group of the D-ring

First, the Michael addition of ethanethiol to α,β-unsaturated ester **3-45** was examined (Scheme 3-11). Alcohol **3-8** was oxidized to give aldehyde **3-49** by Swern method. Horner-Emmons reaction of aldehyde **3-49** was conducted according to general procedure[17] to produce only (*E*)-**3-45** in 51% yield over 2 steps. Treatment of (*E*)-**3-45** with EtSH in the presence of Et_3N or ^{t}BuOK, however, resulted in no reaction.



Scheme 3-11. Attempting construction of α,β-unsaturated ester **3-45**

To optimize the Michael addition conditions, simple α,β-unsaturated ester **3-59** was used as a model compound (Table 3-3).[18] Treatment of **3-59** with EtSH and $^{i}Pr_2NEt$ resulted in no reaction (Entry 1). On the other hand, the use of PhSH slowly gave a 1:1 mixture of the desired thioether **3-60** and ester **3-59** (50% conversion for 2 days) (Entry 2). When the reaction mixture was heated to 50 °C to accelerate the reaction, the starting material was decomposed (Entry 3). When base was changed to DBU, the result was almost same as that of $^{i}Pr_2NEt$ (Entry 4). Phase-transfer conditions using aq. NaOH and Bu_4NHSO_4 caused decomposition (Entry 5). Treatment of **3-59** with PhSLi, generated from BuLi and PhSH, for 14 h furnished only **3-60** in 74% yield (Entry 6). Thus, optimized conditions for the Michael addition of phenylthio group to an α,β-unsaturated ester was found.

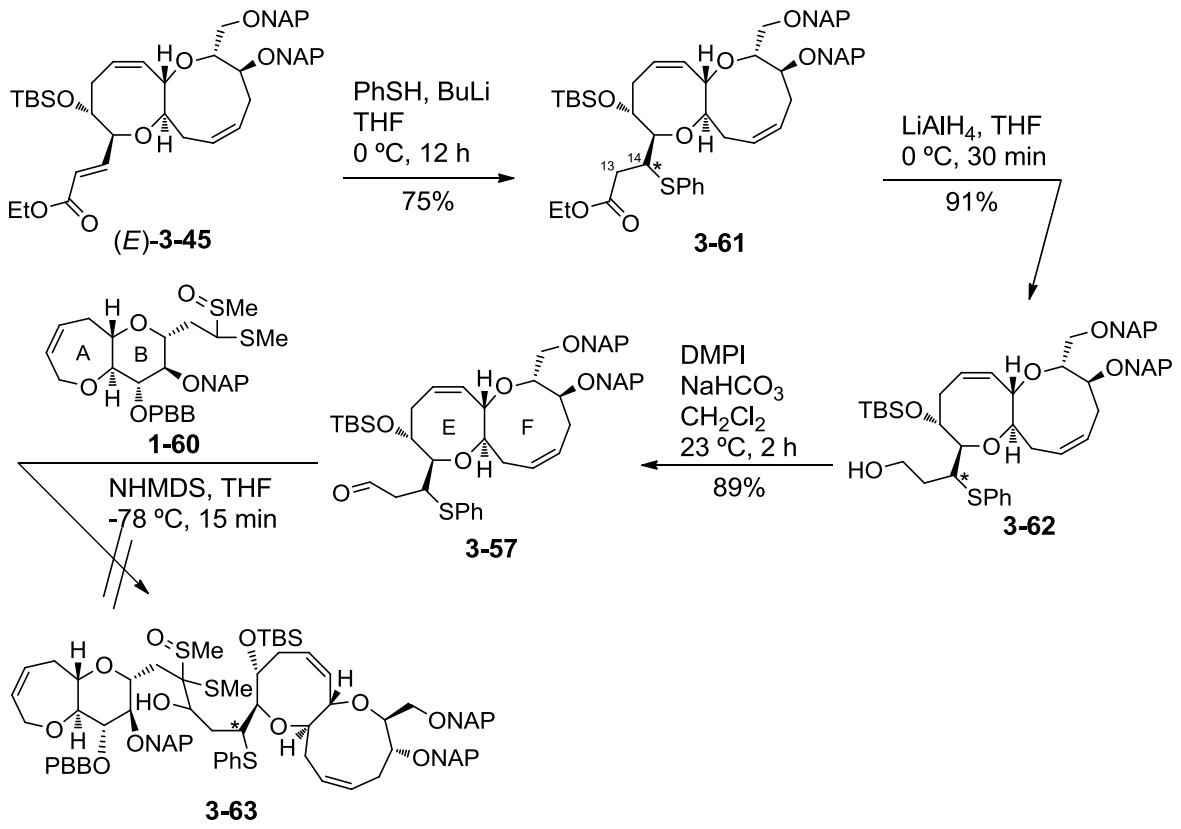


Entry	Thiol	Base	Solvent	Temperature	Time	**3-59**:**3-60** [a]
1 [b]	EtSH	$^{i}Pr_2NEt$	PhH	26 °C	2 days	only **3-59**
2	PhSH	$^{i}Pr_2NEt$	PhH	26 °C	2 days	1:1
3	PhSH	$^{i}Pr_2NEt$	PhMe	50 °C	1 days	——— [c]
4	PhSH	DBU	PhH	24 °C	2 days	1:1
5 [d]	PhSH	50% aq. NaOH	PhH	24 °C	2 days	——— [c]
6	PhSH	BuLi	THF	0 °C	14 h	only **3-60** [e]

[a] Since separation of **3-59** and **3-60** was difficult, the ratio of **3-59** and **3-60** was confirmed by ^{1}H NMR sptectra.
[b] This reaction condition would produce ethylthioether.
[c] The substrate was decomposed.
[d] This reaction was undertook under phase-transfer condition using Bu_4NHSO_4 as a catalyst.
[e] Sulfide **3-60** was obtained in 74% yield.

Table 3-3. Michael addition of model compound **3-59**

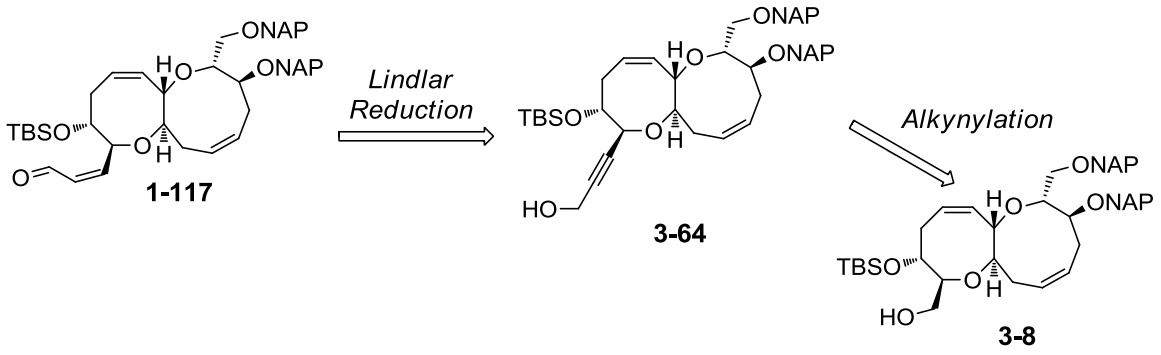
Then, aldehyde **3-57** was prepared from (*E*)-**3-45** (Scheme 3-12). Exposure of (*E*)-**3-45** to PhSLi smoothly produced sulfide **3-61** (75%), which was obtained as a single diastereomer at C14 with unknown stereochemistry. The ester was reduced by $LiAlH_4$ to furnish alcohol **3-62** (91%), which was subjected to Dess-Martin oxidation to produce aldehyde **3-57** (89%).[19] However, the anion coupling between **1-60** and **3-57** resulted in decomposition of the substrates. Thus, the attempt to introduce the double bond at C13-C14 of the D-ring by elimination was failed due to the instability of aldehyde **3-57** under the conditions of coupling with **1-60**.



Scheme 3-12. Synthesis of EF-ring **3-57** and its attempting coupling with AB-ring **1-60**

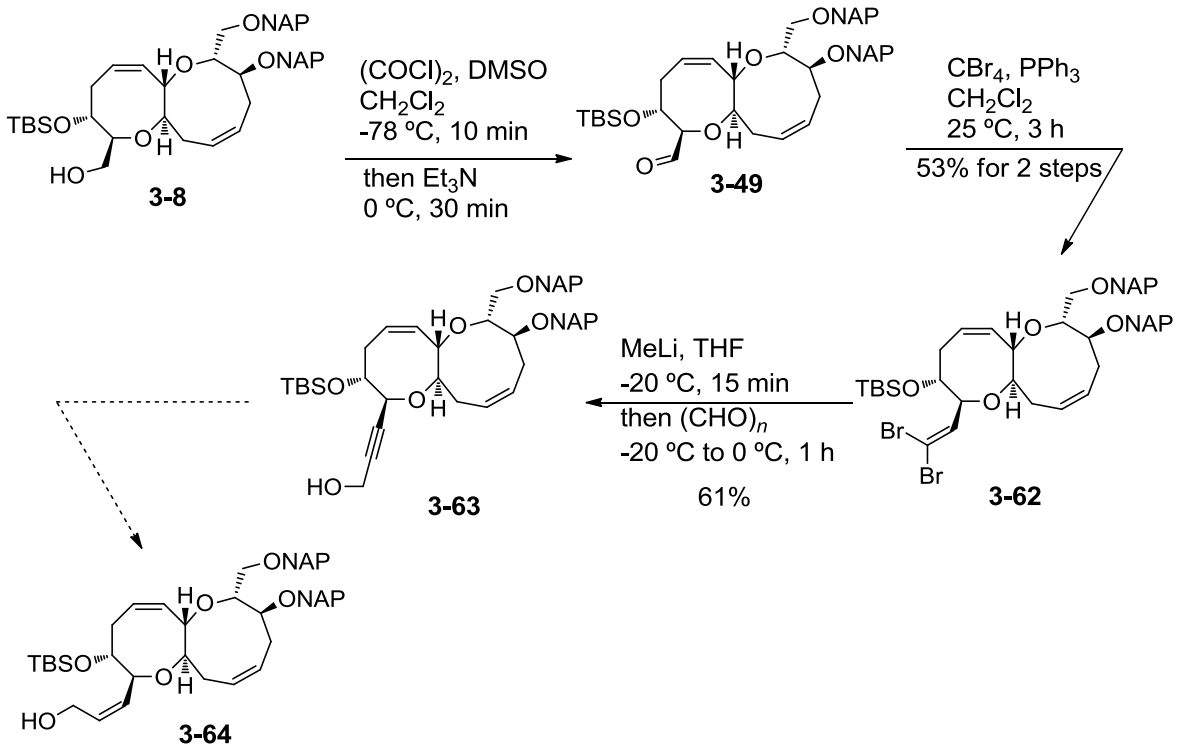
3-5. The third approach to the construction of (Z)-olefin via hydrogenation of alkyne

The author next planned the synthesis of (Z)-α,β-unsaturated aldehyde **1-117** by partial hydrogenation, such as Lindlar hydrogenation,[20] of alkyne **3-64**, which would be prepared from alcohol **3-8** (Scheme 3-13).



Scheme 3-13. The third approach to the construction of (Z)-olefin via hydrogenation of alkyne

Alkyne **3-63** was prepared from alcohol **3-8** by a 3-step process (Scheme 3-14). After Swern oxidation of **3-8**, the resulting aldehyde was subjected to dibromoolefination to afford dibromoolefin **3-62** (53% for 2 steps). Then, dibromoolefin **3-62** was treated with MeLi to give a lithium acetylide, which was reacted with paraformaldehyde in situ to produce alcohol **3-63** (61%).[21] However, hydrogenation of **3-63** by Lindlar catalyst was sluggish, and only ca. 60% of **3-63** was converted to **3-64** for a month.



Scheme 3-14. Attempting of construction of EF-ring **3-64**

To accelerate the partial hydrogenation, the author designed another substrate (Figure 3-1). It was assumed that the low reactivity of **3-63** was attributable to the steric repulsion of the bulky TBS ether. Therefore, the author expected that alkyne **3-65** having a smaller TES ether would relieve the steric repulsion and accelerate the hydrogenation. Accordingly, (*Z*)-α,β-unsaturated aldehyde **3-66** was planned to be synthesized as a new EF-ring.

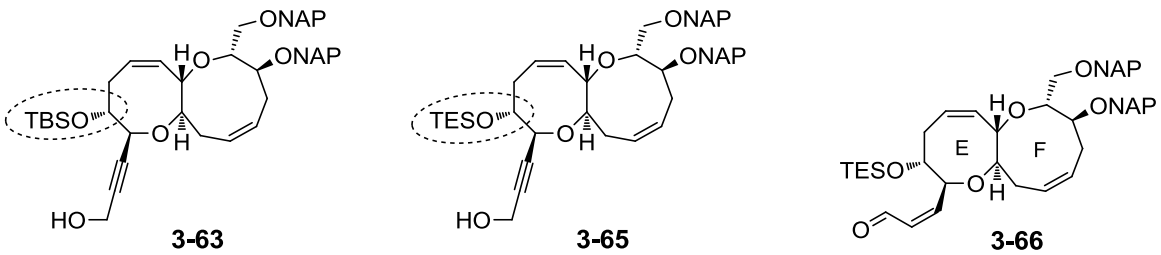
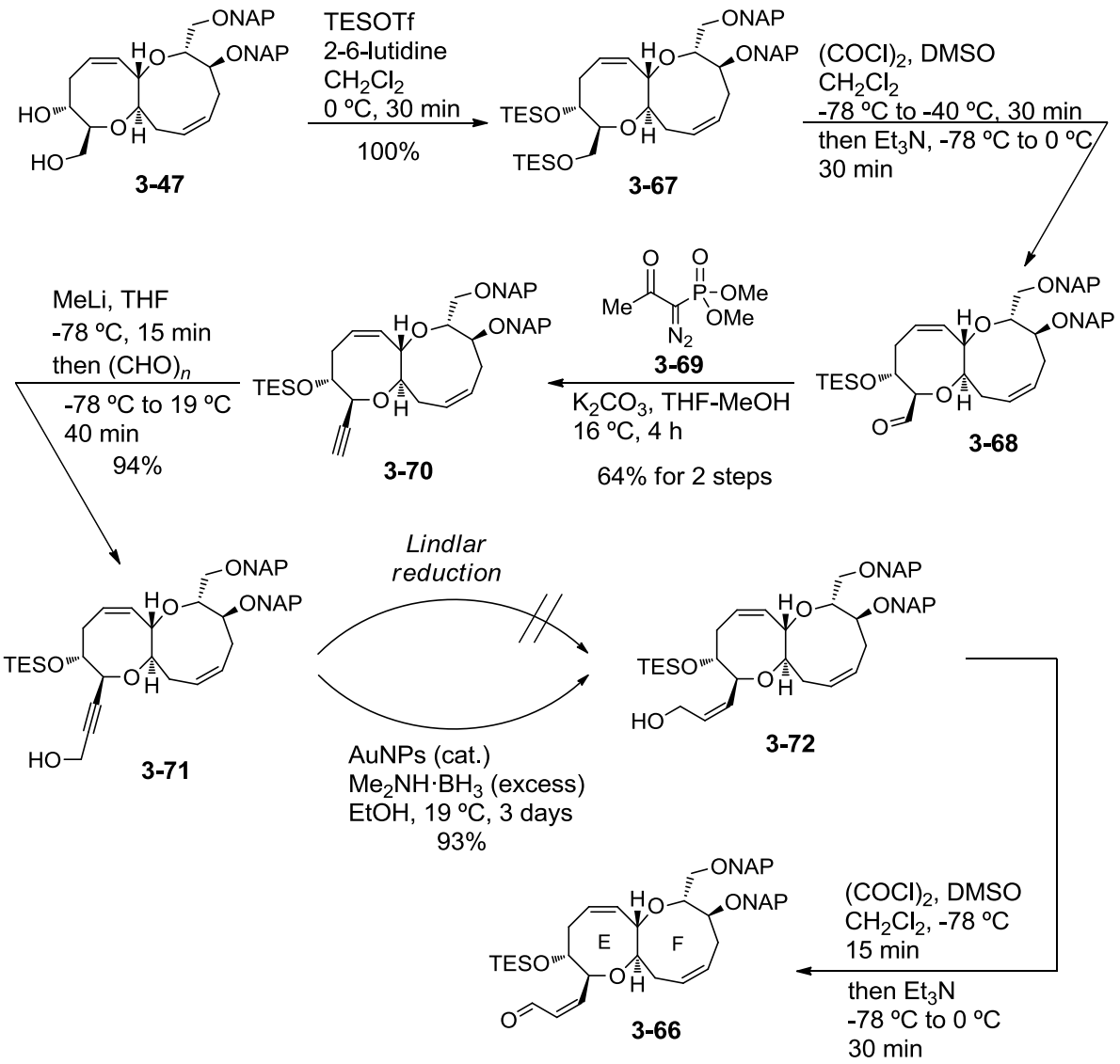


Figure 3-1. Structure of **3-63**, **3-65**, and **3-66**

Synthesis of the EF-ring **3-66**, which was commenced with diol **3-47**, is outlined in Scheme 3-15. Diol **3-47** was protected with TESOTf and 2,6-lutidine to furnish bis-TES ether **3-67** (100%). Then, direct oxidation of silyl ether **3-67** under Swern conditions selectively formed aldehyde **3-68**,[22] and the subsequent alkynylation with Ohira-Bestmann reagent (**3-69**) afforded terminal alkyne **3-70** (64% over 2 steps).[23] When aldehyde **3-68** was subjected to dibromoolefination using PPh_3 and CBr_4, the substrate was decomposed. Terminal alkyne **3-70** was deprotonated with MeLi, and the resulting lithium acetylide was reacted with paraformaldehyde to give alcohol **3-71** (94%). Lindlar hydrogenation of **3-71** was sluggish, and only trace amount of (*Z*)-alkene **3-72** was obtained. However, when alkyne 3-31 was subjected to Stratakis' hydrogenation conditions using gold nanoparticles as catalyst, (*Z*)-olefin **3-72** was smoothly produced in good yield (93%). For comparison, alkyne **3-63** having TBS ether was hydrogenated under the same conditions to give only trace amount of the corresponding alkene. Finally, the hydroxy group of **3-72** was oxidized by Swern oxidation to complete the synthesis of EF-ring **3-66** (almost quantitative yield). Since EF-ring **3-66** was suspected of instability, the oxidation of **3-72** was performed just before the coupling reaction of **3-66** with **1-60** (experimental procedure for **3-66** is described in Chapter 4).

Thus, the author achieved the preparation of the EF-ring possessing (*Z*)-α,β-unsaturated aldehyde.



Scheme 3-15. Synthesis of new EF-ring **3-66**

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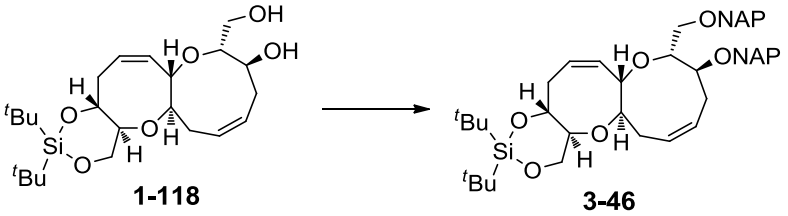
Experimental sections

General methods

All air sensitive reactions were carried out under argon or nitrogen in oven-dried glassware using standard syringe, cannula and septa techniques. Anhydrous tetrahydrofuran (THF) was prepared by Glass Contour Solvent Dispensing System (Nikko Hansen & Co., Ltd.) or purchased from commercial sources. Other dry solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F_{254}). Plates were visualized by ultraviolet light and by treatment with acidic anisaldehyde or phosphomolybdic acid stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63-40 μm for flash chromatography, 230-63 μm for gravity chromatography) as a stationary phase. Melting points were measured on a YAMATO apparatus model MP-21 without calibration. Optical rotations were recorded on a JASCO P-1020 digital polarimeter at 589 nm. Infrared spectra (IR) were measured on a JEOL JIR-WINSPEC100 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-AL300 (^{1}H at 300 MHz, ^{13}C at 75 MHz), a JEOL JNM-α-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), a JEOL JNM-ECA500 (^{1}H at 500 MHz, ^{13}C at 125 MHz), or a Bruker AVANCE III 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of the residual solvent (^{1}H NMR: 7.15 ppm in C_6D_6, ^{13}C NMR: 128.0 ppm in C_6D_6) as the internal standard. The following abbreviations are used to describe spin multiplicity: s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad, dd= double doublets, dt= double triplets, dq= double quartets, td= triple doublets, ddd= double double doublets, and ddt= double double triplets; other combination is derived from those listed. Coupling constants (*J*) are reported in Hz. High resolution mass spectra (HRMS) were measured on a JEOL JMS-T100GCV (under field desorption [FD] conditions) double focusing magnetic sector mass spectrometer.

The preparation of **1-118** was according to the dissertation of Keisuke Nogoshi, Hokkaido University, 2013. The experimental procedures and spectral data of **1-118** and the synthetic intermediates for **1-118** are described in the dissertation of Nogoshi.

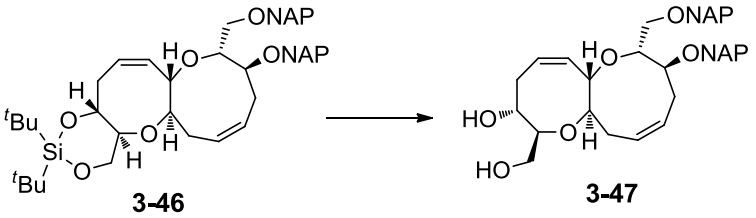
Compound 3-46.



To a solution of **1-118** (388.1 mg, 0.8807 mmol) in THF-DMF (8.0 mL: 16 mL) were added KI (17.5 mg, 0.105 mmol), NAPBr (589.2 mg, 2.665 mmol), and NaH (60% in mineral oil, 297.9 mg, 7.448 mmol) at 0 °C, and the mixture was stirred for 75 min. Then, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 20) to give **3-46** (459.5 mg, 0.6373 mmol, 72%) as a colorless oil.

3-46: $[\alpha]_D^{21}$ –28.5 (*c* 1.12, $CHCl_3$); IR (neat) ν 3059, 3020, 2971, 2932, 2861, 2806, 1953, 1914, 1853, 1743, 1633, 1605, 1512, 1473, 1445, 1390, 1365, 1351, 1308, 1295, 1274, 1249, 1214, 1196, 1168, 1097, 1014, 947, 902, 855, 821, 796, 750, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (9H, s), 1.00 (9H, s), 2.08 (1H, brd, *J* = 13.0 Hz), 2.26 (1H, ddd, *J* = 2.1, 6.7, 13.5 Hz), 2.34 (1H, brtd, *J* = 3.1, 13.5 Hz), 2.56 (1H, ddd, *J* = 3.8, 10.5, 13.5 Hz), 2.70 (1H, ddd, *J* = 2.9, 10.0, 13.5 Hz), 2.93 (1H, brt, *J* = 10.5 Hz), 3.20 (1H, brd, *J* = 9.1 Hz), 3.45 (1H, dt, *J* = 5.6, 11.3 Hz), 3.53-3.64 (3H, m), 3.75 (1H, t, *J* = 11.3 Hz), 3.84 (1H, brt, *J* = 7.3 Hz), 3.94-4.09 (3H, m), 4.36 (1H, d, *J* = 11.5 Hz), 4.55 (1H, d, *J* = 12.5 Hz), 4.68 (1H, d, *J* = 12.5 Hz), 4.72 (1H, d, *J* = 11.5 Hz), 5.61 (brddd, *J* = 1.6, 6.8, 9.9 Hz), 5.71-5.84 (2H, m), 5.88 (1H, dd, *J* = 5.9, 10.5 Hz), 7.20 (1H, dd, *J* = 1.8, 8.7 Hz), 7.40-7.48 (5H, m), 7.51 (1H, s), 7.62-7.68 (2H, m), 7.70 (1H, s), 7.73-7.81 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2 (C), 22.5 (C), 27.1 (CH_3×3), 27.4 (CH_3×3), 32.25 (CH_2), 32.27 (CH_2), 32.6 (CH_2), 67.4 (CH_2), 69.1 (CH_2), 71.6 (CH_2), 73.4 (CH_2), 77.7 (CH), 77.8 (CH), 77.9 (CH), 83.8 (CH), 84.7 (CH), 84.9 (CH), 125.6 (CH), 125.8 (CH), 125.85 (CH), 125.86 (CH), 126.0 (CH), 126.1 (CH), 126.2 (CH), 126.4 (CH), 126.9 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH×2), 128.0 (CH), 128.09 (CH), 128.12 (CH), 128.2 (CH), 132.9 (C), 133.0 (C), 133.2 (C×2), 135.6 (C), 135.8 (C), 137.4 (CH); FD-HRMS (m/z) calcd for $C_{45}H_{56}O_6Si$ $[M]^+$ 720.3846, found: 720.3856.

Compound 3-46.

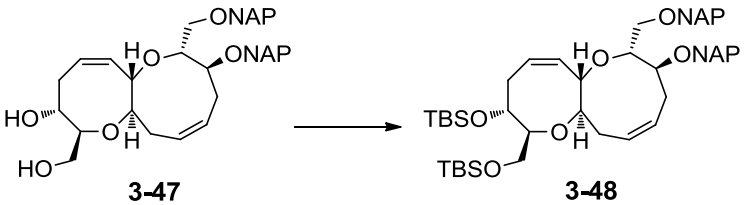


To a solution of **3-46** (459.5 mg, 0.6373 mmol) in THF (6.0 mL) was added TBAF (1.0 mol/L in THF,

1.95 mL, 1.95 mmol) at 23 °C, and the mixture was stirred for 10 h. Then, the reaction mixture was diluted with water, and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1 → EtOAc) to give **3-47** (364.8 mg, 0.6282 mmol, 99%) as a colorless solid.

3-47: mp 115 °C; $[\alpha]_D^{22}$ –41.2 (*c* 0.930, $CHCl_3$); IR (KBr) ν 3296, 3056, 3014, 2975, 2926, 2912, 2891, 2855, 1735, 1601, 1509, 1449, 1365, 1355, 1340, 1306, 1274, 1245, 1127, 1098, 1088, 1060, 1049, 1025, 986, 955, 895, 855, 821, 778, 753, 699, 651, 627, 606, 550, 518, 489, 475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (1H, brs), 2.01 (1H, brs), 2.08-2.21 (2H, m), 2.36 (1H, brd, *J* = 13.9 Hz), 2.57 (1H, ddd, *J* = 2.6, 10.5, 13.5 Hz), 2.71 (1H, brddd, *J* = 4.0, 10.0, 13.9 Hz), 2.97 (1H, brt, *J* = 9.5 Hz), 3.22 (1H, brd, *J* = 8.8 Hz), 3.31 (1H, td, *J* = 5.0, 10.2 Hz), 3.52-3.70 (4H, m), 3.76 (1H, dd, *J* = 5.0, 11.7 Hz), 3.84-3.92 (2H, m), 3.96 (1H, brtd, *J* = 2.9, 8.8 Hz), 4.36 (1H, d, *J* = 11.5 Hz), 4.55 (1H, d, *J* = 12.3 Hz), 4.67 (1H, d, *J* = 12.3 Hz), 4.73 (1H, d, *J* = 11.5 Hz), 5.60 (1H, brddd, *J* = 1.8, 6.7, 10.5 Hz), 5.75-5.87 (2H, m), 5.92 (1H, dd, *J* = 5.9, 10.9 Hz), 7.20 (1H, dd, *J* = 1.7, 8.6 Hz), 7.41-7.48 (5H, m), 7.52 (1H, s), 7.62-7.69 (2H, m), 7.70 (1H, s), 7.74-7.81 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.41 (CH_2), 27.43 (CH_2), 32.5 (CH_2), 64.5 (CH_2), 69.1 (CH_2), 71.7 (CH_2), 73.3 (CH), 73.4 (CH_2), 77.7 (CH), 83.0 (CH), 83.7 (CH), 85.0 (CH), 86.2 (CH), 124.5 (CH), 125.8 (CH), 125.85 (CH), 125.89 (CH), 126.0 (CH), 126.1 (CH), 126.2 (CH), 126.4 (CH), 127.0 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH×2), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 132.9 (C), 133.0 (C), 133.2 (C×2), 135.6 (C), 135.7 (C), 138.1 (CH); FD-HRMS (m/z) calcd for $C_{37}H_{40}O_6$ $[M]^+$: 580.2825, found: 580.2838.

Compound 3-48.

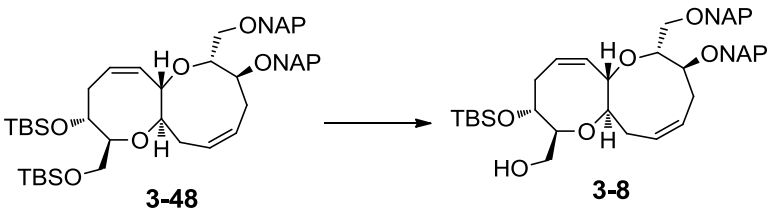


To a solution of **3-47** (209.9 mg, 0.3615 mmol) and 2,6-lutidine (0.350 mL, 3.02 mmol) in CH_2Cl_2 (3.0 mL) was added TBSOTf (0.340 mL, 1.48 mmol) at 0 °C, and the mixture was stirred for 15 min at 27 °C. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with water, 0.2 mol/L aq. HCl, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-48** (278.1 mg, 0.3437 mmol, 95%) as a colorless oil.

3-48: $[\alpha]_D^{22}$ –67.9 (*c* 0.660, $CHCl_3$); IR (neat) ν 3058, 3020, 2954, 2932, 2860, 1599, 1506, 1473, 1357, 1253, 1087, 840, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.04 (6H, s), 0.05 (3H, s), 0.86 (9H, s), 0.88 (9H, s), 1.98-2.05 (1H, m), 2.29 (1H, d, *J* = 11.8 Hz), 2.35 (1H, d, *J* = 13.3 Hz), 2.52 (1H,

ddd, J = 2.4, 9.8, 16.1 Hz), 2.72 (1H, t, J = 11.7 Hz), 2.91 (1H, t, J = 10.2 Hz), 3.19-3.29 (2H, m), 3.48 (1H, dd, J = 7.3, 10.8 Hz), 3.52-3.61 (3H, m), 3.71-3.78 (2H, m), 3.84 (1H, t, J = 7.7 Hz), 3.96 (1H, d, J = 9.8 Hz), 4.36 (1H, d, J = 11.8 Hz), 4.54 (1H, d, J = 12.5 Hz), 4.68 (1H, d, J = 13.1 Hz), 4.73 (1H, d, J = 11.3 Hz), 5.51 (1H, brddd, J = 1.7, 6.5, 10.6 Hz), 5.74-5.88 (3H, m), 7.21 (1H, dd, J = 1.9, 9.1 Hz), 7.39-7.47 (5H, m), 7.52 (1H, s), 7.61-7.68 (2H, m), 7.01 (1H, s), 7.72-7.80 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4 (CH_3), -5.3 (CH_3), -5.0 (CH_3), -4.4 (CH_3), 17.9 (C), 18.3 (C), 25.7 ($CH_3\times3$), 25.9 ($CH_3\times3$), 27.4 (CH_2), 32.0 (CH_2), 32.7 (CH_2), 65.0 (CH_2), 69.2 (CH_2), 71.6 (CH_2), 72.5 (CH), 73.4 (CH_2), 78.0 (CH), 84.1 (CH), 84.8 (CH), 85.3 (CH), 86.0 (CH), 125.3 (CH), 125.76 (CH), 125.81 (CH), 125.9 (CH), 125.97 (CH), 126.04 (CH), 126.2 (CH), 126.4 (CH), 126.9 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH×2), 128.0 (CH), 128.1 (CH), 128.8 (CH), 132.9 (C), 133.0 (C), 133.2 (C×2), 135.7 (C), 135.8 (C), 137.2 (CH); FD-HRMS (m/z) calcd for $C_{49}H_{68}O_6Si_2$ $[M]^+$: 808.4554, found: 808.4550.

Compound 3-8.

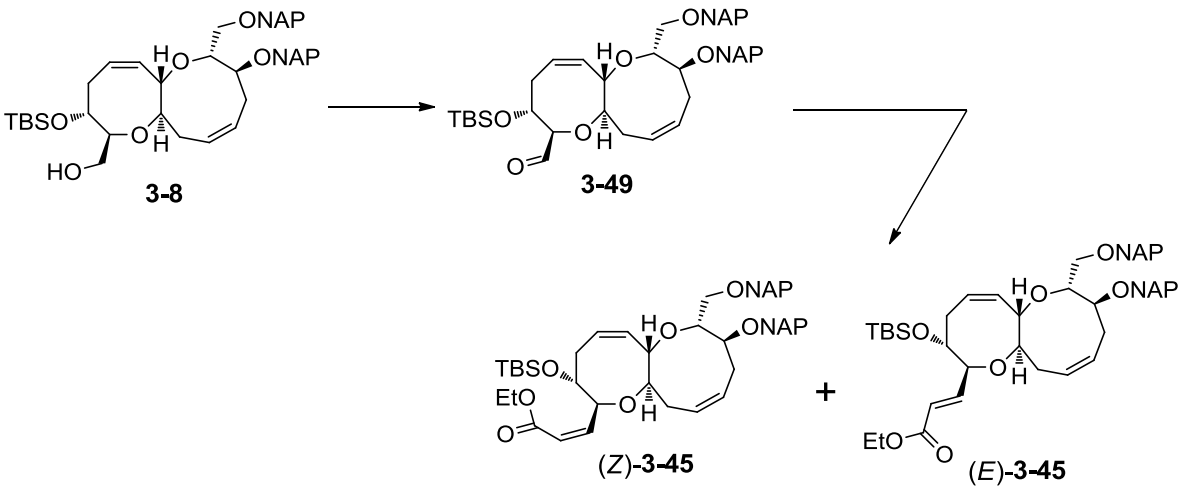


To a solution of **3-48** (278.1 mg, 0.3437 mmol) in EtOH (5.0 ml) was added PPTS (25.4 mg, 0.101 mmol) at 26 °C, and the mixture was stirred for 5 days. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **3-8** (198.7 mg, 0.2859 mmol, 83%) as a colorless oil.

3-8: $[\alpha]_D^{22}$ –63.2 (c 0.660, $CHCl_3$); IR (neat) ν 3483, 3053, 3020, 2932, 2855, 1919, 1600, 1512, 1468, 1363, 1254, 1099, 951, 841, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 1.86 (1H, t, J = 6.5 Hz), 2.07 (1H, ddd, J = 3.7, 6.5, 13.9 Hz), 2.13 (1H, d, J = 13.0 Hz), 2.35 (1H, d, J = 13.9 Hz), 2.49 (1H, ddd, J = 2.8, 10.7, 13.0 Hz), 2.72 (1H, ddd, J = 3.7, 9.2, 13.9 Hz), 2.98 (1H, t, J = 10.2 Hz), 3.22 (1H, d, J = 8.8 Hz), 3.33 (1H, ddd, J = 3.2, 6.0, 8.7 Hz), 3.48 (1H, dd, J = 5.9, 11.5 Hz), 3.52-3.63 (3H, m), 3.70-3.77 (1H, m), 3.81-3.90 (2H, m), 3.96 (1H, d, J = 8.3 Hz), 4.36 (1H, d, J = 11.6 Hz), 4.55 (1H, d, J = 12.5 Hz), 4.67 (1H, d, J = 12.8 Hz), 4.73 (1H, d, J = 11.2 Hz), 5.53 (1H, ddt, J = 1.8, 6.7, 10.3 Hz), 5.76-5.87 (3H, m), 7.20 (1H, dd, J = 1.8, 8.3 Hz), 7.41-7.48 (5H, m), 7.52 (1H,s), 7.62-7.69 (2H, m), 7.71 (1H, s), 7.74-7.81 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0 (CH_3), -4.5 (CH_3), 17.9 (C), 25.7 ($CH_3\times3$), 27.5 (CH_2), 32.5 (CH_2), 32.7 (CH_2), 63.8 (CH_2), 69.9 (CH_2), 71.7 (CH_2), 72.6 (CH), 73.4 (CH_2), 78.1 (CH), 83.7 (CH), 84.0 (CH), 85.0 (CH), 85.8 (CH), 125.3 (CH), 125.7 (CH), 125.75 (CH), 125.80 (CH), 125.9 (CH), 126.0 (CH), 126.3 (CH), 126.8 (CH), 127.59 (CH), 127.64 (CH), 127.8 (CH×2), 127.9 (CH), 127.97 (CH), 128.00 (CH), 128.3 (CH), 133.0 (C), 133.1 (C), 133.3 (C×2),

135.8 (C), 135.9 (C), 137.1 (CH); FD-HRMS (m/z) calcd for $C_{43}H_{54}O_6Si$ $[M]^+$: 694.3690, found: 694.3699.

Compound (*Z*)-3-45 and (*E*)-3-45.



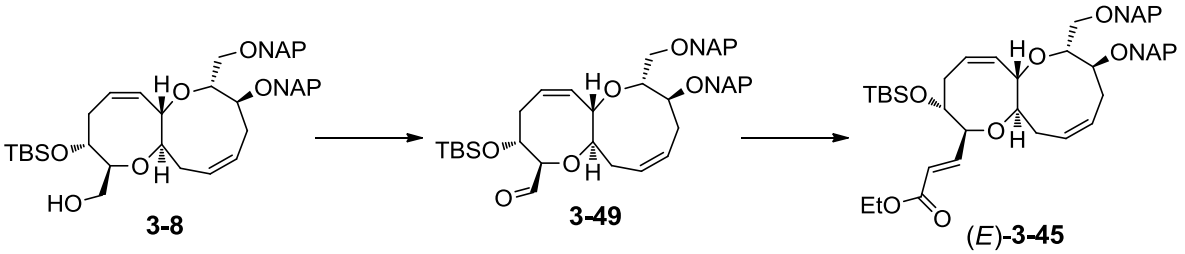
To a solution of $(COCl)_2$ (16.0 μL, 0.187 mmol) in CH_2Cl_2 (0.5 mL) was added DMSO (23.0 μL, 0.324 mmol) at –78 °C, and the mixture was stirred for 10 min. Then, to the mixture was added a solution of **3-8** (11.0 mg, 0.0158 mmol) in CH_2Cl_2 (0.5 mL) at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added Et_3N (90.0 μL, 0.646 mmol) at –78 °C, and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **3-49**, which was used immediately in the next reaction.

To a solution of phosphonic ester **3-50** (23.7 mg, 0.0680 mmol) in THF (0.5 mL) was added NaH (60% in mineral oil, 7.8 mg, 0.20 mmol) at 0 °C, and the mixture was stirred for 30 min. Then, to the mixture was added a solution of the above crude **3-49** in THF (0.5 mL) at –78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 3) to give a mixture of (*Z*)-**3-45** and (*E*)-**3-45** (8.1 mg, 0.011 mmol, 67% from **3-8**, (*Z*)-**3-45**:(*E*)-**3-45** = 4:1) as a colorless oil.

(*Z*)-**3-45** and (*E*)-**3-45**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (24/5H, d, *J* = 5.3 Hz), 0.12 (6/5H, d, *J* = 7.0 Hz), 0.88 (36/5H, s), 0.96 (9/5H, s), 1.32-1.38 (3H, m), 2.10-2.21 (2H, m), 2.29-2.47 (2H, m), 2.60-2.71 (1H, m), 2.78 (1H, brt, *J* = 10.3 Hz), 2.98 (1H, m), 3.30 (1H, brd, *J* = 9.0 Hz), 3.53-3.59 (1/5H, m), 3.66 (2H, dq, *J* = 2.7, 10.2 Hz), 3.76 (1H, td, *J* = 2.7, 9.2 Hz), 3.81-3.87 (4/5H, m), 3.93 (1H, brt, *J* = 7.0 Hz), 4.03 (1H, brd, *J* = 9.1 Hz), 4.16-4.31 (2H, m), 4.44 (1/5H, d, *J* = 10.8 Hz), 4.45 (4/5H, d, *J* = 11.9 Hz), 4.63 (1H, d, *J* = 12.4 Hz), 4.75 (1/5H, d, *J* = 13.0 Hz), 4.76 (4/5H, d, *J* = 12.4 Hz), 4.81 (1H, d, *J* = 11.3

Hz), 5.10 (4/5H, t, J = 9.2 Hz), 5.56-5.72 (1H, m), 5.82-6.03 (16/5H, m), 6.07 (4/5H, dd, J = 9.1, 11.3 Hz), 6.17 (1/5H, dd, J = 2.1, 15.7 Hz), 7.18 (1/5H, dd, J = 3.8, 15.8 Hz), 7.29 4/5H, dd, J = 1.8, 8.4 Hz), 7.49-7.55 (5H, m), 7.61 (1H, s,), 7.70-7.88 (7H, m)

Compound (*E*)-3-45.

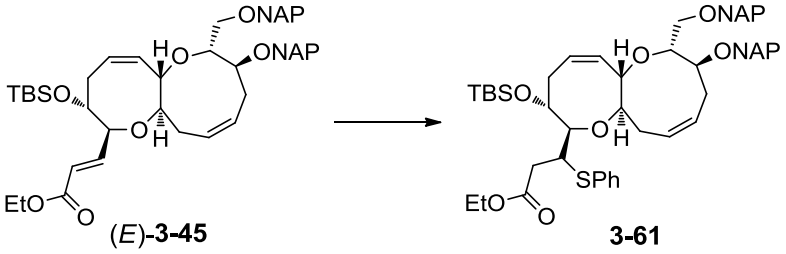


To a solution of $(COCl)_2$ (50.0 μL, 0.583 mmol) in CH_2Cl_2 (2.0 mL) was added DMSO (67.0 μL, 0.943 mmol) at –78 °C, and the mixture was stirred for 10 min. Then, to the mixture was added a solution of **3-8** (128.3 mg, 0.1846 mmol) at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added Et_3N (0.260 mL, 1.87 mmol) at –78 °C, and the mixture was stirred for 40 min at 0 °C. Then, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with 0.5 mol/L aq. HCl, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **3-49**, which was used immediately in the next reaction.

To a solution of triethyl phosphonoacetate (120.7 mg, 0.5384 mmol) in THF (2 mL) was added NaH (60% in mineral oil, 25.2 mg, 0.630 mmol) at 0 °C, and the mixture was stirred for 30 min. Then, to the mixture was added a solution of the above **3-49** in THF (3 mL) at –78 °C, and the mixture was stirred for 1.5 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10) to give (*E*)-**3-45** (70.7 mg, 0.0944 mmol, 51% from **3-8**) as a colorless oil.

(*E*)-**3-45**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, d, J = 7.3 Hz), 0.89 (9H, s), 1.28 (3H, t, J = 7.3 Hz), 2.09 (1H, ddd, J = 2.5, 6.2, 13.3 Hz), 2.26 (1H, brd, J = 13.3 Hz), 2.36 (1H, brd, J = 13.3 Hz), 2.57 (1H, ddd, J = 2.9, 10.4, 13.3 Hz), 2.71 (1H, tt, J = 3.7, 10.0 Hz), 2.95 (1H, brt, J = 8.3 Hz), 3.23 (1H, brd, J = 8.7 Hz), 3.48 (1H, brd, J = 6.8 Hz), 3.57 (2H, dq, J = 2.3, 10.0 Hz), 3.68 (1H, td, J = 2.9, 9.0 Hz), 3.85-3.93 (2H, m), 4.14-4.23 (2H, m), 4.36 (1H, d, J = 11.3 Hz), 4.55 (1H, d, J = 12.7 Hz), 4.67 (1H, d, J = 12.7 Hz), 4.73 (1H, d, J = 11.3 Hz), 5.53 (1H, brddd, J = 1.5, 6.6, 10.6 Hz), 5.78-5.92 (3H, m), 6.10 (1H, dd, J = 2.1, 15.8 Hz), 7.10 (1H, dd, J = 3.4, 15.8 Hz), 7.20 (1H, dd, J = 1.3, 8.2 Hz), 7.40-7.48 (5H, m), 7.52 (1H, s), 7.63-7.69 (2H, m), 7.71 (1H, s), 7.74-7.81 (4H, m)

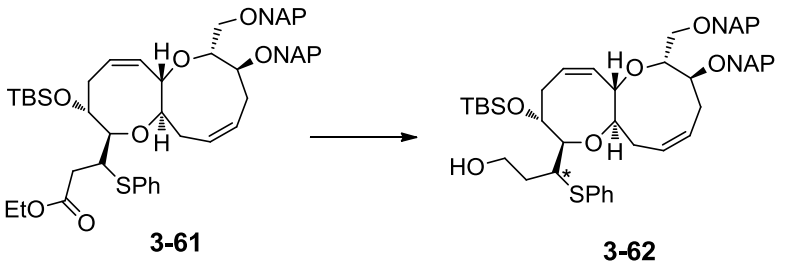
Compound 3-61.



To a solution of PhSH (80.0 μL, 0.784 mmol) in THF (0.5 mL) was added BuLi (1.55 mol/L in hexane, 0.200 mL, 0.310 mmol) at 0 °C, and the mixture was stirred for 5 min. Then, to the mixture was added a solution of (*E*)-**3-45** (9.8 mg, 0.013 mmol) in THF (0.5 mL) at 0 °C, and the mixture was stirred for 14 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 20 → 10) to give **3-61** (8.6 mg, 0.0098 mmol, 75%) as a colorless oil.

3-61: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, d, *J* = 2.5 Hz), 0.84 (9H, s), 1.22 (3H, t, *J* = 7.0 Hz), 2.06 (1H, ddd, *J* = 3.1, 6.5, 13.1 Hz), 2.33-2.51 (2H, m), 2.56 (1H, dd, *J* = 10.9, 16.2 Hz), 2.65 (1H, dd, *J* = 3.5, 16.2 Hz), 2.69-2.78 (1H, m), 2.94 (1H, brs), 3.22 (1H, brd, *J* = 8.7 Hz), 3.50-3.58 (3H, m), 3.64-3.70 (1H, m), 3.76 (1H, td, *J* = 2.8, 8.9 Hz), 3.78-3.84 (2H, m), 3.94 (1H, brd, *J* = 8.4 Hz), 4.05-4.18 (2H, m), 4.37 (1H, d, *J* = 11.4 Hz), 4.53 (1H, d, *J* = 12.5 Hz), 4.66 (1H, d, *J* = 12.5 Hz), 4.73 (1H, d, *J* = 11.4 Hz), 5.43 (1H, brddd, *J* = 1.5, 6.8, 10.8 Hz), 5.75-5.85 (3H, m), 7.15-7.25 (4H, m), 7.35-7.47 (7H, m), 7.53 (1H, s), 7.62-7.70 (3H, m), 7.73-7.80 (4H, m)

Compound 3-62.

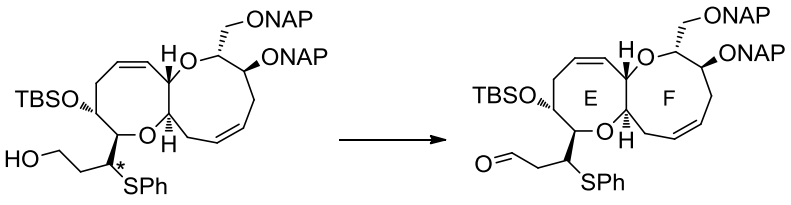


To a suspension of $LiAlH_4$ (4.7 mg, 0.12 mmol) in THF (0.5 mL) was added a solution of **3-61** (36.0 mg, 0.0412 mmol) in THF (0.5 mL) at –20 °C, and the mixture was stirred for 45 min. Then, to the mixture was added extra $LiAlH_4$ (5.2 mg, 0.14 mmol) at –20 °C, and the mixture was stirred for 80 min at 0 °C. The reaction was quenched with saturated aq. potassium sodium tartrate, and the mixture was diluted with EtOAc. After being stirred for 2 h at 21 °C, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column

chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **3-62** (31.0 mg, 0.0373 mmol, 91%) as a colorless oil.

3-62: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (6H, d, *J* = 11.9 Hz), 0.86 (9H, s), 1.88-2.12 (3H, m), 2.36 (1H, brd, *J* = 12.6 Hz), 2.43-2.54 (2H, m), 2.72 (1H, brt, *J* = 9.4 Hz), 2.92-3.03 (2H, m), 3.21 (1H, brd, *J* = 8.9 Hz), 3.50-3.76 (9H, m), 3.83 (1H, brt, *J* = 7.4 Hz), 3.91-4.02 (3H, m), 4.36 (1H, d, *J* = 11.6 Hz), 4.52 (1H, d, *J* = 12.4 Hz), 4.65 (1H, d, *J* = 12.4 Hz), 4.73 (1H, d, *J* = 11.6Hz), 5.43 (1H, brddd, *J* = 1.4, 6.4, 10.6 Hz), 5.74-5.87 (4H, m), 7.15-7.28 (4H, m), 7.30-7.34 (2H, m), 7.39-7.48 (5H, m), 7.52 (1H, s), 7.62-7.70 (3H, m), 7.73-7.80 (3H, m)

Compound 3-57.

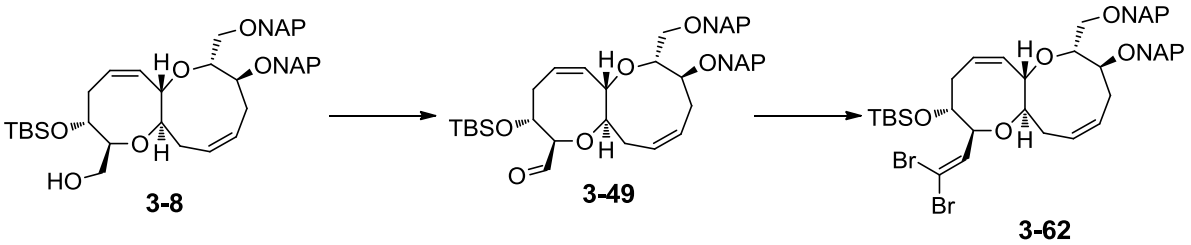


3-62 **3-57**

To a solution of **3-62** (31.0 mg, 0.0373 mmol) and $NaHCO_3$ (57.5 mg, 0.684 mmol) in CH_2Cl_2 (1.0 mL) was added DMPI (71.1 mg, 0.168 mmol) at 0 °C, and the mixture was stirred for 1 h. Then to the mixture were added extra $NaHCO_3$ (55.2 mg, 0.657 mmol) and DMPI (71.7 mg, 0.169 mmol) at 0 °C, and the mixture was stirred for 30 min. Then, the reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **3-57** (27.4 mg, 0.0330 mmol, 89%) as a colorless oil.

3-57: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, d, *J* = 16.3 Hz), 0.85 (9H, s), 2.06 (1H, ddd, *J* = 3.1, 6.5, 13.8 Hz), 2.33-2.51 (3H, m), 2.62 (1H, dd, *J* = 3.5, 16.9 Hz), 2.67-2.77 (2H, m), 2.96 (1H, brt, *J* = 9.9 Hz), 3.21 (1H, brd, *J* = 8.7 Hz), 3.48-3.60 (3H, m), 3.67 (1H, brtd, *J* = 3.1, 8.5 Hz), 3.78-3.87 (2H, m), 3.93 (1H, brd, *J* = 8.5 Hz), 4.36 (1H, d, *J* = 11.4 Hz), 4.52 (1H, d, *J* = 12.4 Hz), 4.66 (1H, d, *J* = 12.4 Hz), 4.73 (1H, d, *J* = 11.4 Hz), 5.43 (1H, brddd, *J* = 1.7, 6.6, 10.8 Hz), 5.74-5.85 (3H, m), 7.19-7.30 (4H, m), 7.34-7.47 (7H, m), 7.53 (1H, s), 7.62-7.70 (3H, m), 7.73-7.80 (4H, m)

Compound 3-62.

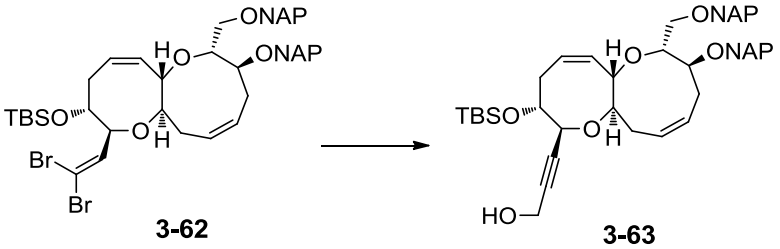


To a solution of $(COCl)_2$ (28.0 μL, 0.233 mmol) in CH_2Cl_2 (1.0 mL) was added DMSO (28.0 μL, 0.394 mmol) at –78 °C, and the mixture was stirred for 10 min. Then, to the mixture was added a solution of **3-8** (13.1 mg, 0.0188 mmol) at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added Et_3N (0.110 mL, 0.789 mmol) at –78 °C, and the mixture was stirred for 30 min at 0 °C. Then, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with 0.5 mol/L aq. HCl, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **3-49**, which was used immediately in the next reaction.

To a solution of the above crude **3-49** and CBr_4 (32.7 mg, 0.0986 mmol) in CH_2Cl_2 (0.5 mL) was added PPh_3 (51.2 mg, 0.195 mmol) at 0 °C, and the mixture was stirred for 3 h at 25 °C. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-62** (8.8 mg, 0.010 mmol, 53% from **3-8**) as a colorless oil.

3-62: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, d, J = 11.5 Hz), 0.87 (9H, s), 2.09 (1H, ddd, J = 3.3, 7.0, 14.1 Hz), 2.15 (1H, brd, J = 13.3 Hz), 2.35 (1H, brd, J = 13.3 Hz), 2.54 (1H, ddd, J = 2.9, 10.4, 13.3 Hz), 2.70 (1H, ddd, J = 2.9, 10.8, 13.7 Hz), 2.93 (1H, brt, J = 8.7 Hz), 3.22 (1H, brd, J = 8.3 Hz), 3.54 (1H, dd, J = 2.7, 10.0 Hz), 3.59 (1H, dd, J = 2.7, 10.4 Hz), 3.68-3.74 (1H, m), 3.76 (1H, td, J = 2.6, 8.9 Hz), 3.84 (1H, brt, J = 8.2 Hz), 3.95 (1H, brd, J = 8.7 Hz), 3.99 (1H, t, J = 8.9 Hz), 4.36 (1H, d, J = 11.2 Hz), 4.55 (1H, d, J = 12.5 Hz), 4.68 (1H, d, J = 12.5 Hz), 4.73 (1H, d, J = 11.2 Hz), 5.59 (1H, brddd, J = 1.3, 6.7, 10.8 Hz), 5.71-5.85 (2H, m), 5.92 (1H, dd, J = 5.9, 11.0 Hz), 6.36 (1H, d, J = 8.7 Hz), 7.21 (1H, dd, J = 1.6, 8.3 Hz), 7.41-7.49 (5H, m), 7.52 (1H, s), 7.63-7.72 (3H, m), 7.74-7.82 (4H, m)

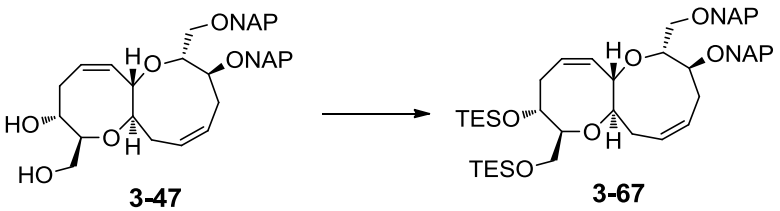
Compound 3-63.



To a solution of **3-62** (13.4 mg, 0.0158 mmol) in THF (0.5 mL) was added MeLi (1.08 mol/L in Et_2O, 0.150 mL, 0.162 mmol) at –20 °C, and the mixture was stirred for 15 min. Then, to the mixture was added $(CH_2O)_n$ (21.6 mg) at –20 °C, and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 3) to give **3-63** (6.9 mg, 9.6 μmol, 61%) as a colorless oil.

3-63: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 2.08 (1H, ddd, *J* = 2.4, 6.7, 13.8 Hz), 2.24 (1H, brd, *J* = 13.0 Hz), 2.35 (1H, brd, *J* = 13.0 H), 2.53 (1H, brddd, *J* = 2.4, 10.3, 13.0 Hz), 2.70 (1H, brt, *J* = 9.8 Hz), 2.95 (1H, brs), 3.20 (1H, brd, *J* = 9.1 Hz), 3.53 (1H, dd, *J* = 2.6, 10.2 Hz), 3.58 (1H, dd, *J* = 2.6, 10.2 Hz), 3.61-3.67 (1H, m), 3.83 (1H, brt, *J* = 7.3 Hz), 3.90-3.99 (3H, m), 4.28 (2H, brd, *J* = 5.8 Hz), 4.35 (1H, d, *J* = 11.2 Hz), 4.54 (1H, d, *J* = 12.4 Hz), 4.67 (1H, d, *J* = 12.4 Hz), 4.73 (1H, d, *J* = 11.2 Hz), 4.93 (1H, brddd, *J* = 1.8, 6.5, 10.6 Hz), 5.77-5.88 (3H, m), 7.20 (1H, dd, *J* = 1.7, 8.6 Hz), 7.40-7.49 (5H, m), 7.52 (1H, s), 7.62-7.72 (3H, m), 7.74-7.81 (3H, m)

Compound 3-67.

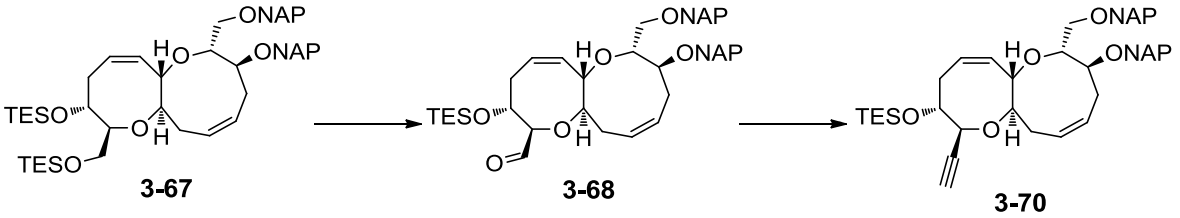


To a solution of **3-47** (19.6 mg, 0.0338 mmol) and 2,6-lutidine (50.0 μL, 0.432 mmol) in CH_2Cl_2 (0.5 mL) was added TESOTf (33.0 μL, 0.146 mmol) at 0 °C, and the mixture was stirred for 35 min. Then, the reaction was quenched with water, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-67** (27.9 mg, 0.0344 mmol, ~100%) as a colorless oil.

3-67: $[\alpha]_D^{22}$ –62.7 (*c* 0.740, $CHCl_3$); IR (neat) ν 3056, 3021, 2953, 2919, 2872, 2802, 2731, 1735, 1636, 1605, 1509, 1457, 1415, 1379, 1355, 1340, 1308, 1291, 1270, 1242, 1210, 1196, 1098, 1060, 1014, 983, 951, 933, 884, 855, 817, 774, 746, 687, 644, 627 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, measured at 50 °C) δ

0.58 (6H, q, J = 8.0 Hz), 0.60 (6H, q, J = 8.0 Hz), 0.94 (9H, t, J = 8.0 Hz), 0.96 (9H, t, J = 8.0 Hz), 2.04 (1H, ddd, J = 3.3, 6.6, 13.3 Hz), 2.27-2.39 (2H, m), 2.55 (1H, ddd, J = 2.9, 10.4, 13.3 Hz), 2.72 (1H, ddd. J = 3.4, 10.9, 14.2 Hz), 2.89 (1H, brddd, J = 4.2, 10.9, 14.2 Hz), 3.26-3.31 (2H, m), 3.51 (1H, dd, J = 7.2, 10.3 Hz), 3.56-3.64 (3H, m), 3.77-3.81 (2H, m), 3.87 (1H, brt, J = 7.6 Hz), 3.92 (1H, brtd, J = 3.4, 8.7 Hz), 4.43 (1H, d, J = 11.7 Hz), 4.56 (1H, d, J = 12.3 Hz), 4.67 (1H, d, J = 12.3 Hz), 4.74 (1H, d, J = 11.7 Hz), 5.54 (1H, ddd, J = 1.6, 6.6, 10.4 Hz), 5.75-5.89 (3H, m), 7.26 (1H, dd, J = 1.4, 8.3 Hz), 7.39-7.45 (5H, m), 7.58 (1H, s), 7.64-7.69 (2H, m), 7.71 (1H, s), 7.73-7.79 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, measured at 50 °C) δ 4.7 (CH_2×3), 5.1 (CH_2×3), 6.8 (CH_3×6), 27.7 (CH_2), 32.1 (CH_2), 33.1 (CH_2), 65.0 (CH_2), 70.1 (CH_2), 71.8 (CH_2), 72.8 (CH), 73.5 (CH_2), 78.3 (CH), 84.3 (CH), 85.1 (CH), 85.6 (CH), 86.3 (CH), 125.3 (CH), 125.8 (CH×2), 126.0 (CH), 126.06 (CH), 126.09 (CH), 126.2 (CH), 126.5 (CH), 126.9 (CH), 127.7 (CH), 127.78 (CH), 127.82 (CH), 128.0 (CH×2), 128.08 (CH), 128.12 (CH), 129.0 (CH), 133.1 (C), 133.2 (C), 133.5 (C×2), 136.0 (C), 136.1 (C), 137.6 (CH); FD-HRMS (m/z) calcd for $C_{49}H_{68}O_6Si_2$ $[M]^+$: 808.4554, found: 808.4544.

Compound 3-70.



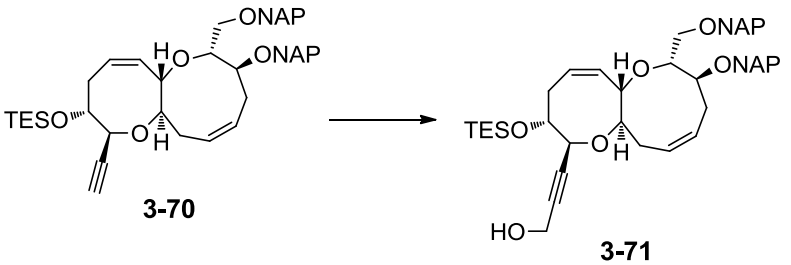
To a solution of $(COCl)_2$ (26.0 μL, 0.303 mmol) in CH_2Cl_2 (1.0 mL) was added DMSO (35.0 μL, 0.493 mmol) at –78 °C, and the mixture was stirred for 10 min. Then, to the mixture was added a solution of **3-67** (39.2 mg, 0.0484 mmol) in CH_2Cl_2 (1.0 mL) at –78 °C, and the mixture was stirred for 5 min. The mixture was warmed to –40 °C, and stirred for 30 min. Then, to the solution was added Et_3N (0.140 mL, 1.00 mmol) at –78 °C, and the mixture was warmed to 0 °C. After being stirred for 30 min, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with 0.5 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **3-68**, which was used immediately in the next reaction.

To a solution of the above crude **3-68** in THF-MeOH (0.5 mL: 0.5 mL) were added Ohira-Bestmann reagent (**3-69**) (19.0 μL, 0.126 mmol) and K_2CO_3 (16.7 mg, 0.121 mmol) at 16 °C, and the mixture was stirred for 4 h. Then, the reaction was quenched with saturated NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10) to give **3-70** (21.2 mg, 0.0308 mmol, 64% from **3-67**) as a colorless oil.

3-70: $[\alpha]_D^{22}$ –59.5 (c 0.990, $CHCl_3$); IR (neat) ν 3307, 3058, 3019, 2955, 2917, 2878, 1729, 1634, 1603,

1507, 1454, 1447, 1413, 1362, 1310, 1290, 1273, 1241, 1217, 1199, 1174, 1104, 1083, 1058, 1015, 977, 945, 900, 857, 815, 776, 751, 628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, measured at 50 °C) δ 0.62 (6H, q, *J* = 8.0 Hz), 0.96 (9H, t, *J* = 8.0 Hz), 2.08 (1H, ddd, *J* = 2.7, 6.2, 13.3 Hz), 2.25 (1H, brd, *J* = 13.7 Hz), 2.34 (1H, brtd, *J* = 3.9, 13.8 Hz), 2.38 (1H, d, *J* = 2.2 Hz), 2.55 (1H, ddd, *J* = 3.1, 10.6, 13.3 Hz), 2.69 (1H, ddd, *J* = 3.2, 10.2, 13.8 Hz), 2.93 (1H, brddd, *J* = 4.4, 10.2, 13.7 Hz), 3.26 (1H, brtd, *J* = 2.7, 9.2 Hz), 3.54-3.64 (3H, m), 3.84-3.93 (3H, m), 3.97 (1H, td, *J* = 3.1, 9.2 Hz), 4.42 (1H, d, *J* = 11.3 Hz), 4.56 (1H, d, *J* = 12.2 Hz), 4.65 (1H, d, *J* = 12.2 Hz), 4.73 (1H, d, *J* = 11.3 Hz), 5.52 (1H, ddd, *J* = 1.4, 6.2, 10.6 Hz), 5.77-5.89 (3H, m), 7.25 (1H, d, *J* = 8.0 Hz), 7.39-7.45 (5H, m), 7.57 (1H, s), 7.64-7.71 (3H, m), 7.72-7.79 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, measured at 50 °C) δ 5.1 (CH_2×3), 6.84 (CH_3×3), 27.6 (CH_2), 32.4 (CH_2), 33.0 (CH_2), 70.0 (CH_2), 71.8 (CH_2), 73.3 (C), 73.5 (CH_2), 74.6 (CH), 75.8 (CH), 78.3 (CH), 83.6 (CH), 84.3 (CH), 85.2 (CH), 85.8 (CH), 124.8 (CH), 125.87 (CH), 125.90 (CH), 125.94 (CH), 126.09 (CH), 126.14 (CH), 126.2 (CH), 126.5 (CH), 126.9 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH × 2), 128.1 (CH), 128.2 (CH), 128.27 (CH), 128.31 (CH), 133.1 (C), 133.2 (C), 133.4 (C×2), 135.9 (C), 136.1 (C), 137.7 (CH); FD-HRMS (m/z) calcd for $C_{44}H_{52}O_5Si$ $[M]^+$: 688.3584, found: 688.3602.

Compound 3-71.

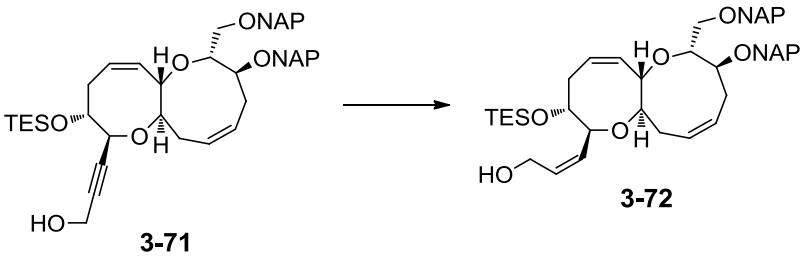


To a solution of **3-70** (21.2 mg, 0.0308 mmol) in THF (1.0 mL) was added MeLi (1.17 mol/L in Et_2O, 0.260 mL, 0.304 mmol) at –78 °C, and the mixture was stirred for 15 min. Then, to the solution was added a suspension of $(CH_2O)_n$ (22.2 mg) in THF (0.5 mL) at –78 °C, and the mixture was rapidly warmed to 19 °C. After being stirred for 40 min, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 3) to give **3-71** (20.9 mg, 0.0291 mmol, 94%) as a colorless oil.

3-71: $[\alpha]_D^{23}$ –76.7 (*c* 0.660, $CHCl_3$); IR (neat) ν 3443, 3056, 3020, 2953, 2915, 2875, 2805, 2732, 1949, 1914, 1731, 1635, 1604, 1509, 1456, 1414, 1379, 1354, 1308, 1287, 1273, 1241, 1217, 1199, 1171, 1107, 1051, 1015, 977, 949, 903, 857, 815, 776, 748, 685, 667, 621 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, measured at 50 °C) δ 0.62 (6H, q, *J* = 7.9 Hz), 0.96 (9H, t, *J* = 7.9 Hz), 1.40 (1H, t, *J* = 6.3 Hz), 2.08 (1H, dd, *J* = 6.4, 12.7 Hz), 2.25 (1H, brd, *J* = 13.1 Hz), 2.34 (1H, brtd, *J* = 4.2, 14.0 Hz), 2.55 (1H, brt, *J* = 12.7 Hz), 2.70 (1H, ddd, *J* = 3.4, 10.2, 14.0 Hz), 2.93 (1H, brddd, *J* = 4.7, 9.7, 13.1 Hz), 3.26 (1H, brtd, *J* = 2.9, 9.0 Hz), 3.54-3.63 (3H, m), 3.86 (1H, brt, *J* = 7.5 Hz), 3.91 (1H, brtd, *J* = 3.3, 9.0 Hz), 3.95 (2H,

brs), 4.27 (2H, d, J = 6.3 Hz), 4.42 (1H, d, J = 11.7 Hz), 4.56 (1H, d, J = 12.3 Hz), 4.65 (1H, d, J = 12.3 Hz), 4.73 (1H, d, J = 11.7 Hz), 5.52 (1H, dddd, J = 1.9, 6.4, 8.7, 10.5 Hz), 5.77-5.84 (2H, m), 5.86 (1H, dd, J = 6.0, 11.7 Hz), 7.25 (1H, dd, J = 1.7, 8.1 Hz), 7.39-7.45 (5H, m), 7.57 (1H, s), 7.65-7.70 (3H, m), 7.73-7.79 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, measured at 50 °C) δ 5.1 (CH_3×3), 6.8 (CH_2×3), 27.6 (CH_2), 32.4 (CH_2), 33.1 (CH_2), 51.5 (CH_2), 70.0 (CH_2), 71.8 (CH_2), 73.5 (CH_2), 74.6 (CH), 75.8 (CH), 78.3 (CH), 83.4 (C), 83.6 (CH), 85.2 (CH), 85.6 (CH), 86.3 (C), 124.8 (CH), 125.88 (CH), 125.91 (CH), 125.94 (CH), 126.09 (CH), 126.14 (CH), 126.2 (CH), 126.5 (CH), 126.9 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH×2), 128.1 (CH), 128.16 (CH), 128.22 (CH), 128.4 (CH), 133.1 (C), 133.2 (C), 133.4 (C×2), 135.9 (C), 136.1 (C), 137.7 (CH); FD-HRMS (m/z) calcd for $C_{45}H_{54}O_6Si$ $[M]^+$: 718.3690, found: 718.3695.

Compound 3-72.



To a solution of **3-71** (137.8 mg, 0.1917 mmol) in EtOH (10 mL) were added gold nano particles (1% on TiO_2, 214.1 mg) and $Me_2NH \cdot BH_3$ (1.148 g, 19.48 mmol) at 19 °C, and the mixture was stirred for 3 days. The reaction mixture was filtered through a Celite pad, and the mixture was diluted with water. Then, the mixture was evaporated to remove organic solvent, and the residue was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 3) to give **3-72** (128.1 mg, 0.1777 mmol, 93%) as a colorless oil.

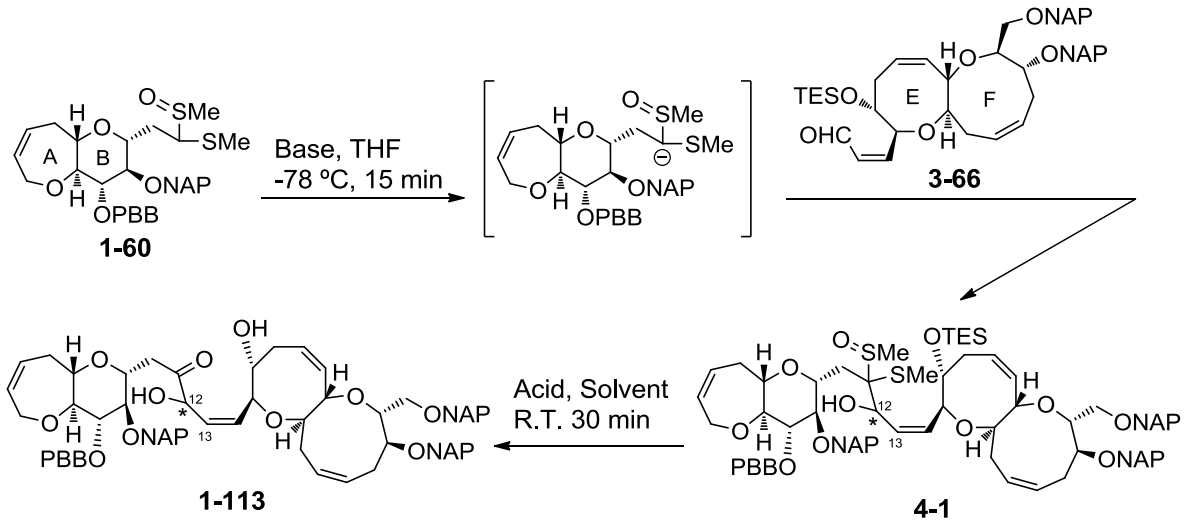
3-72: $[\alpha]_D^{23}$ –74.2 (c 0.690, $CHCl_3$); IR (neat) v 3454, 3056, 3020, 2953, 2918, 2875, 2802, 1727, 1635, 1604, 1511, 1458, 1416, 1373, 1353, 1307, 1292, 1271, 1243, 1219, 1173, 1127, 1102, 1060, 1017, 947, 898, 859, 817, 778, 750, 687, 669, 627 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, measured at 50 °C) δ 0.58 (6H, q, J = 8.0 Hz), 0.93 (9H, t, J = 8.0 Hz), 2.08-2.15 (2H, m), 2.34 (1H, brtd, J = 3.4, 13.9 Hz), 2.61 (1H, ddd, J = 2.9, 10.5, 13.4 Hz), 2.70 (1H, brddd, J = 3.8, 10.0, 13.9 Hz), 2.90 (1H, ddd, J = 4.3, 10.1, 13.9 Hz), 3.28 (1H, brtd, J = 2.8, 8.9 Hz), 3.52-3.63 (3H, m), 3.72 (1H, td, J = 2.9, 9.2 Hz), 3.88-3.94 (2H, m), 4.07-4.17 (3H, m), 4.44 (1H, d, J = 11.3 Hz), 4.57 (1H, d, J = 12.2 Hz), 4.66 (1H, d, J = 12.2 Hz), 4.74 (1H, d, J = 11.3 Hz), 5.49-5.58 (2H, m), 5.73-5.84 (3H, m), 5.90 (1H, dd, J = 5.9, 11.2 Hz), 7.27 (1H, dd, J = 1.6, 8.5 Hz), 7.40-7.45 (5H, m), 7.58 (1H, s), 7.65-7.71 (3H, m), 7.73-7.80 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, measured at 50 °C) δ 5.0 (CH_2×3), 6.7 (CH_3×3), 27.6 (CH_2), 32.5 (CH_2), 33.0 (CH_2), 59.5 (CH_2), 70.2 (CH_2), 71.8 (CH_2), 73.6 (CH_2), 75.6 (CH), 78.4 (CH), 79.6 (CH), 83.9 (CH), 84.7 (CH), 65.1

(CH), 124.9 (CH), 125.9 (CH×2), 126.0 (CH), 126.09 (CH), 126.12 (CH), 126.2 (CH), 126.5 (CH), 126.9 (CH), 127.74 (CH), 127.78 (CH), 128.0 (CH×2), 128.1 (CH), 128.2 (CH), 128.3 (CH×2), 130.8 (CH), 132.9 (CH), 133.1 (C), 133.2 (C), 133.4 (C×2), 136.0 (C), 136.1 (C), 137.9 (CH); FD-HRMS (m/z) calcd for $C_{45}H_{56}O_6Si$ $[M]^+$: 720.3846, found: 720.3838.

4. Synthesis of the ABCDEF-ring

4-1. Examination of anion coupling of AB-ring with EF-ring and hydrolysis

With the AB- and EF-ring in hand, the author undertook the synthesis of ABCDEF-ring **1-58** according to the plan shown in Scheme 1-13. Initially, the coupling reaction between **1-60** and **3-66** followed by the hydrolysis of the dimethyldithio acetal mono-*S*-oxide moiety and the triethylsilyl ether was examined (Table 4-1). Treatment of **1-60** with LHMDS in THF at –78 °C for 15 min and then with aldehyde **3-66**, prepared from alcohol **3-72**, for 15 min followed by acidic treatment (TFA-THF-H_2O) only resulted in decomposition of aldehyde **3-66** with almost complete recovery of **1-60** (Entry 1). After extensive optimization using model compound, the author found that the deprotonation of **1-60** with NHMDS gave the corresponding anion species and that the hydrolysis of the dimethyldithio acetal mono-*S*-oxide group of the adduct proceeded smoothly with PTS·H_2O in CH_2Cl_2-MeOH. Thus, the anion generated from **1-60** using NHMDS reacted with aldehyde **3-66** to give **4-1** cleanly. However, the hydrolysis of **4-1** with PTS·H_2O in CH_2Cl_2-MeOH gave α,ε-dihydroxy ketone **1-113** only in 19% yield from alcohol **3-72** along with unknown byproducts (Entry 2). After further optimization of the solvent in the hydrolysis, the author found that the treatment of **4-1** with PTS·H_2O in CF_3CH_2OH-H_2O produced α,ε-dihydroxy ketone **1-113**, which was obtained as a single diastereomer at C12 with unknown stereochemistry, in an acceptable yield (40% from **3-72**, Entry 3). Thus, a sufficient amount of α,ε-dihydroxy ketone **1-113** was synthesized.

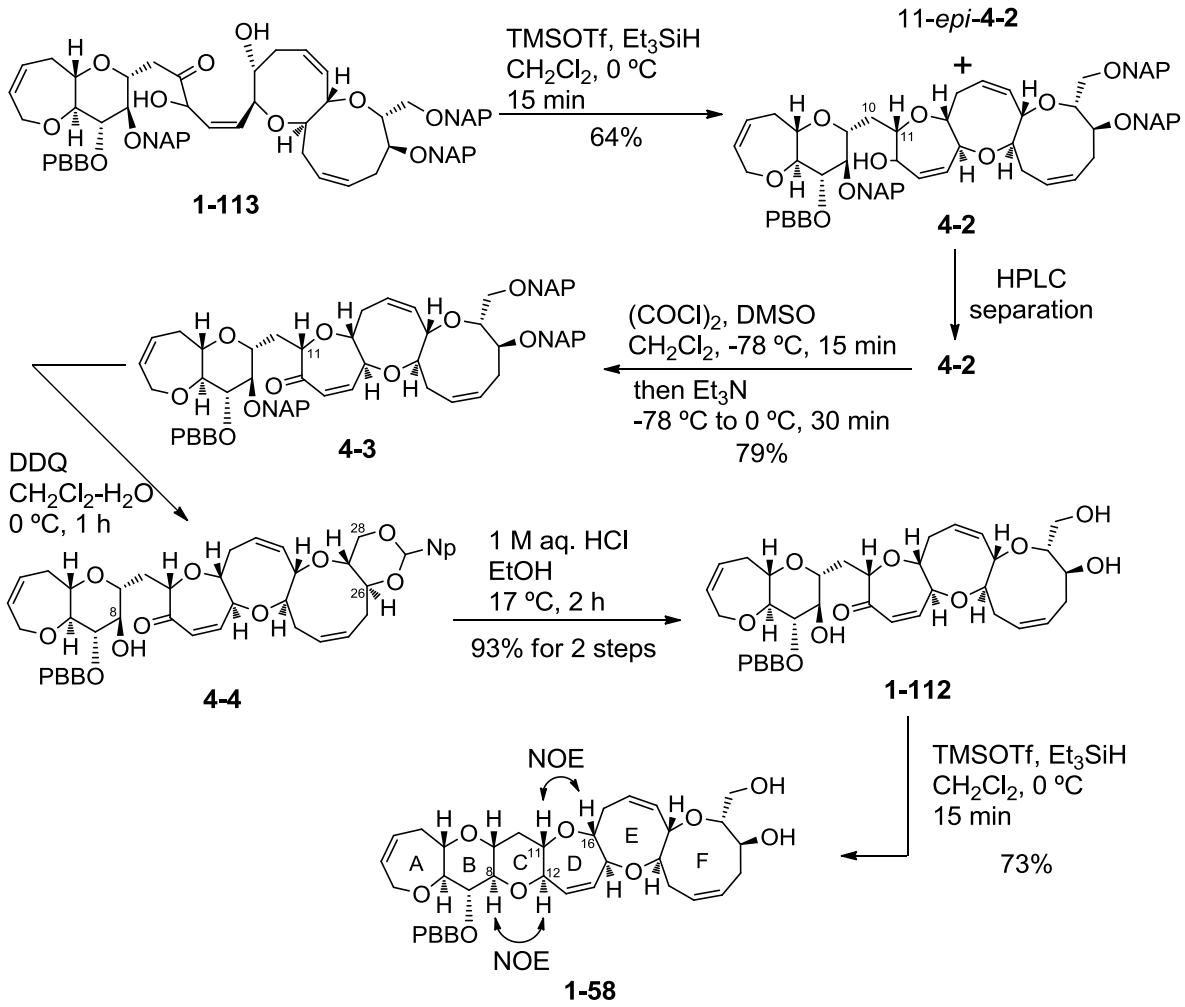


Entry	Base	Acid	Solvent	Yield from **3-66**
1	LHMDS	TFA	THF-H_2O	decomp
2	NHMDS	PTS·H_2O	CH_2Cl_2-MeOH	19%
3	NHMDS	PTS·H_2O	CF_3CH_2OH-H_2O	40%

Table 4-1. Optimization of anion coupling of AB-ring with EF-ring and hydrolysis

4-2. Completion of the synthesis of the ABCDEF-ring

Finally, ABCDEF-ring **1-58** was synthesized from α,ε-dihydroxy ketone **1-113** (Scheme 4-1). The D-ring moiety was constructed by reductive etherification using Et_3SiH and TMSOTf, and a 1:1 mixture of **4-2** and 11-*epi*-**4-2** was obtained in 64% combined yield. The diastereomers were separated from each other by HPLC. However, the stereochemistry at C11 could not be determined at this stage and was intended to be confirmed after formation of the C-ring. Then, alcohol **4-3** was oxidized under Swern conditions to furnish ketone **4-3** (79%). Alcohol 11-*epi*-**4-2** was also oxidized to corresponding ketone 11-*epi*-**4-3**, which was isomerized with DBU in CH_2Cl_2 to afford a 3:1 mixture of **4-3** and 11-*epi*-**4-3** in a small scale experiment.[1] To remove the tri-NAP group, ketone **4-3** was reacted with DDQ.[2] However, undesired formation of 2-naphthylmethyliden acetal between O26 and O28 occurred along with the detachment of the NAP group at O8 to give **4-4**.[3] Therefore, the acetal **4-4** was hydrolyzed under acidic conditions to give triol **1-112** (93% for 2 steps). Triol **1-112** was cyclized with Et_3SiH and TMSOTf to complete the construction of ABCDEF-ring **1-58** (73%). The stereochemistry of C11 and C12 was determined by the presence of NOEs between H11 and H16, and between H8 and H12. Furthermore, after extensive attempts at recrystallization, a single crystal of **1-58** was obtained. The X-ray crystallographic analysis of the single crystal demonstrated the stereostructure of **1-58** (Figure 4-1). Thus, the author achieved the convergent synthesis of ABCDEF-ring **1-58** of CTX3C in 6.9% over 7 steps from EF-ring **3-66**.



Scheme 4-1. Synthesis of ABCDEF-ring of CTX3C

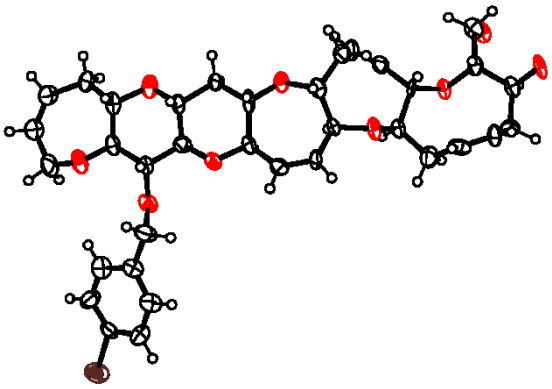


Figure 4-1. ORTEP diagram of **1-58**

References

[1] Maruyama, M.; Inoue, M.; Oishi, T.; Oguri, H.; Ogasawara, Y.; Shindo, Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 1835.

[2] (a) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172. (b) Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033. (c) Xia, J.; Alderfer, J. L.; Piskorz, C. F.; Matta, K. L. *Chem. Eur. J.* **2001**, *7*, 356.

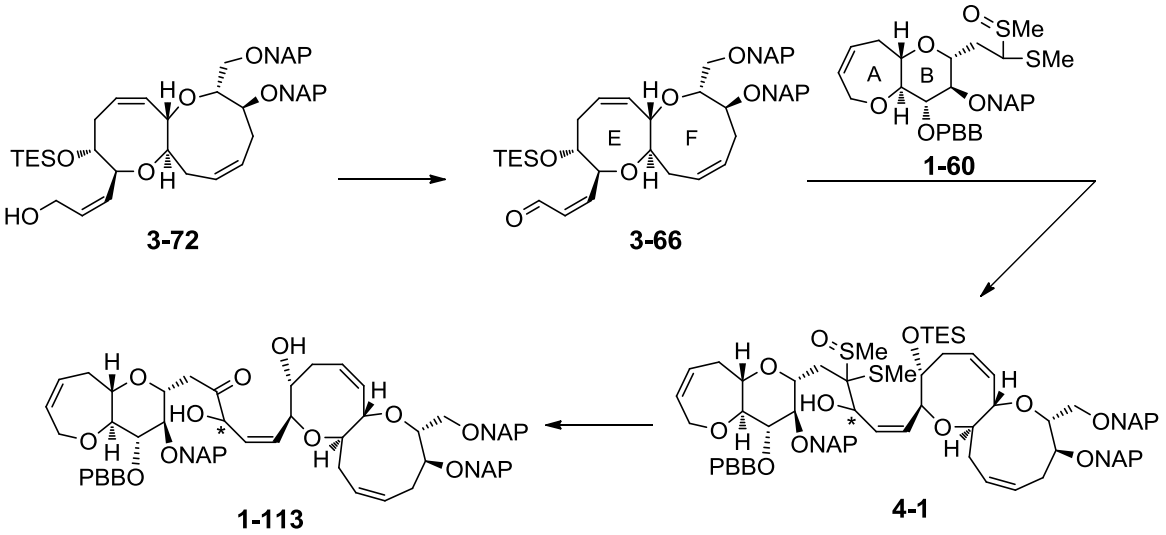
[3] Similar result was reported, see: Inoue, M.; Miyazaki, K.; Ishihara, Y.; Tatami, A.; Ohnuma, Y.; Kawada, Y.; Komano, K.; Yamashita, S.; Lee, N.; Hirama, M. *J. Am. Chem. Soc.* **2006**, *128*, 9352.

Experimental sections

General methods

All air sensitive reactions were carried out under nitrogen in oven-dried glassware using standard syringe, cannula and septa techniques. All dry solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F_{254}). Plates were visualized by ultraviolet light and by treatment with phosphomolybdic acid stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63-40 μm for flash chromatography) as a stationary phase. High-performance liquid chromatography (HPLC) was performed on a JASCO 880-PU HPLC pump equipped with a pre-packed column (YMC-Pack SIL-06, 5 μm, 150 mm × 4.6 mm ID [for normal-phase chromatography]) and a JASCO UV-975 UV detector (UV 254 nm detection). Melting points were measured on a YAMATO apparatus model MP-21 without calibration. Optical rotations were recorded on a JASCO P-1020 digital polarimeter at 589 nm. Infrared spectra (IR) were measured on a JEOL JIR-WINSPEC100 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) or a Bruker AMX500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of the residual solvent (^{1}H NMR: 7.15 ppm in C_6D_6, ^{13}C NMR: 128.0 ppm in C_6D_6) as the internal standard. The following abbreviations are used to describe spin multiplicity: s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad, dd= double doublets, dt= double triplets, td= triple doublets and ddd= double double doublets; other combination is derived from those listed. Coupling constants (*J*) are reported in Hz. High resolution mass spectra (HRMS) were measured on a JEOL JMS-T100GCV (under field desorption [FD] conditions) double focusing magnetic sector mass spectrometer.

Compound 1-113.



To a solution of $(COCl)_2$ (46.5 μL, 0.542 mmol) in CH_2Cl_2 (2 mL) was added DMSO (64.1 μL, 0.903 mmol) at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added a solution of **3-72** (130.2 mg, 0.1806 mmol) in CH_2Cl_2 (2 mL) at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added Et_3N (0.252 mL, 1.81 mmol) at –78 °C, and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with 0.5 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **3-66**, which was used immediately in the next reaction.

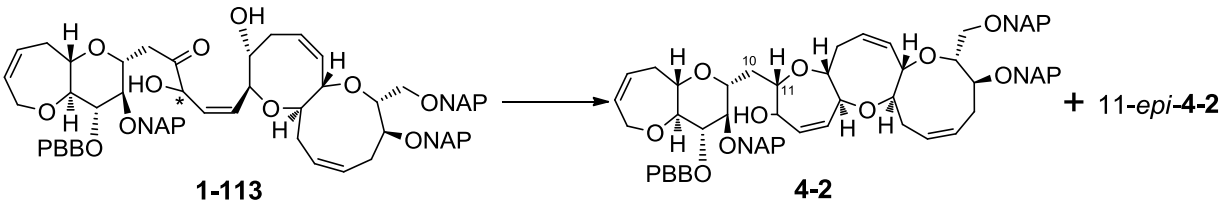
3-66: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51 (6H, q, *J* = 8.0 Hz), 0.89 (9H, t, *J* = 8.0 Hz), 2.07-2.20 (1H, m), 2.32-2.40 (1H, m), 2.62 (1H, ddd, *J* = 3.1, 10.5, 13.1 Hz), 2.70 (1H, ddd, *J* = 3.5, 9.6, 13.5 Hz), 2.93 (1H, brt, *J* = 11.0 Hz), 3.24 (1H, brd, *J* = 8.3 Hz), 3.52-3.62 (3H, m), 3.65 (1H, brd, *J* = 4.2 Hz), 3.77 (1H, td, *J* = 3.1, 8.7 Hz), 3.89 (1H, brt, *J* = 8.3 Hz), 3.95 (1H, brd, *J* = 8.8 Hz), 4.37 (1H, d, *J* = 11.3 Hz), 4.42 (1H, t, *J* = 8.8 Hz), 4.56 (1H, d, *J* = 12.3 Hz), 4.67 (1H, d, *J* = 12.3 Hz), 4.74 (1H, d, *J* = 11.3 Hz), 5.56 (1H, ddd, *J* = 1.5, 6.7, 10.5 Hz), 5.74-5.87 (2H, m), 5.91 (1H, dd, *J* = 5.7, 11.0 Hz), 5.96 (1H, dddd, *J* = 1.0, 8.3, 11.4, 19.6 Hz), 6.52 (1H, dd, *J* = 8.3, 11.4 Hz), 7.22 (1H, dd, *J* = 1.8, 8.4 Hz), 7.41-7.49 (5H, m), 7.53 (1H, s), 7.63-7.69 (2H, m), 7.71 (1H, s), 7.74-7.82 (4H, m), 9.96 (1H, d, *J* = 8.1 Hz)

To a solution of **1-60** (356.2 mg, 0.5418 mmol) in THF (2 mL) was added NHMDS (1.10 mol/L in THF, 0.490 mL, 0.539 mmol) at –78 °C, and the mixture was stirred for 20 min. Then, to the solution was added a solution of the above crude **3-66** in THF (2 mL) at –78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2 → 1) to give **4-1** (brown oil, diastereomer mixture), which was used immediately in the next reaction.

To a solution of the above crude **4-1** in CF_3CH_2OH-water (3.0 mL: 0.3 mL) was added PTS·H_2O (20.5

mg, 0.107 mmol) at 19 °C, and the suspension was stirred for 1 h. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2 → 1 → 0.5) to give **1-113** (81.0 mg, 0.0709 mmol, 40% from **3-72**) as a colorless oil. **1-113**: $[\alpha]_D^{23}$ +7.5 (*c* 1.11, $CHCl_3$); IR (neat) ν 3438, 3052, 3021, 2920, 2889, 2862, 2727, 1953, 1915, 1719, 1655, 1634, 1605, 1511, 1488, 1447, 1396, 1362, 1271, 1244, 1092, 893, 859, 818, 774, 750, 737, 703 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, measured at 50 °C) δ 2.13 (1H, ddd, *J* = 2.5, 6.5, 13.3 Hz), 2.20-2.34 (3H, m), 2.35-2.43 (1H, m), 2.61-2.78 (3H, m), 2.88 (1H, dd, *J* = 3.2, 14.8 Hz), 3.05-3.13 (2H, m), 3.30 (1H, t, *J* = 9.1 Hz), 3.35 (1H, t, *J* = 9.1 Hz), 3.46-3.54 (2H, m), 3.58 (1H, t, *J* = 9.1 Hz), 3.63-3.71 (3H, m), 3.77 (1H, brtd, *J* = 2.9, 8.6 Hz), 3.85-3.98 (3H, m), 4.14 (1H, brddd, *J* = 1.6, 5.6, 8.6 Hz), 4.30 (1H, t, *J* = 8.7 Hz), 4.39 (1H, d, *J* = 11.9 Hz), 4.45 (1H, d, *J* = 12.3 Hz), 4.52 (1H, d, *J* = 12.3 Hz), 4.59 (1H, d, *J* = 11.9 Hz), 4.62 (1H, d, *J* = 11.9 Hz), 4.70 (1H, d, *J* = 11.9 Hz), 4.81 (1H, d, *J* = 11.9 Hz), 4.89 (1H, dd, *J* = 1.0, 8.6 Hz), 4.97 (1H, d, *J* = 11.9 Hz), 5.39 (1H, ddd, *J* = 0.8, 8.6, 11.1 Hz), 5.43-5.56 (2H, m), 5.63 (1H, brddd, *J* = 1.0, 8.7, 11.1 Hz), 5.89-6.07 (2H, m), 6.10 (1H, dd, *J* = 5.6, 11.2 Hz), 7.02 (2H, d, *J* = 8.1 Hz), 7.22-7.40 (10H, m), 7.57-7.70 (13H, m); ^{13}C NMR (100 MHz, C_6D_6, measured at 50 °C) δ 27.3 (CH_2), 32.0 (CH_2), 32.7 (CH_2), 34.3 (CH_2), 40.9 (CH_2), 67.4 (CH_2), 71.1 (CH_2), 71.3 (CH_2), 73.1 (CH_2), 74.2 (CH_2), 74.59 (CH), 74.61 (CH_2), 75.0 (CH), 75.4 (CH), 75.8 (CH), 78.7 (CH), 79.8 (CH), 81.0 (CH), 83.3 (CH), 84.9 (CH), 85.1 (CH), 85.6 (CH), 88.0 (CH), 121.1 (C), 125.0 (CH), 125.58 (CH×2), 125.64 (CH), 125.72 (CH), 125.74 (CH), 125.8 (CH), 125.9 (CH×2), 126.1 (CH), 126.2 (CH), 126.3 (CH), 126.4 (CH), 126.6 (CH), 127.4 (CH), 127.65 (CH×2), 127.67 (CH), 127.76 (CH), 127.79 (CH×2), 127.9 (CH), 128.08 (CH), 128.14 (CH×2), 128.5 (CH), 129.2 (CH×2), 131.2 (CH×2), 131.3 (CH), 133.2 (C×2), 133.5 (C×2), 133.6 (C), 135.9 (C), 136.2 (C), 136.4 (C), 136.6 (CH), 138.0 (CH), 138.5 (C), 207.4 (C); FD-HRMS (m/z) calcd for $C_{68}H_{69}{}^{79}BrO_{11}$ $[M]^+$: 1140.4023, found: 1140.4029.

Compound 4-2 and 11-*epi*-4-2.



To a solution of **1-113** (11.4 mg, 9.98 μmmol) in CH_2Cl_2-Et_3SiH (0.4 mL: 0.2 mL) was added TMSOTf (4.0 μL, 0.022 mmol) at 0 °C, and the mixture was stirred for 15 min. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3 → 2) to give a 1:1 diastereomer mixture of **4-2** and 11-*epi*-**4-2** (7.2 mg, 64%).

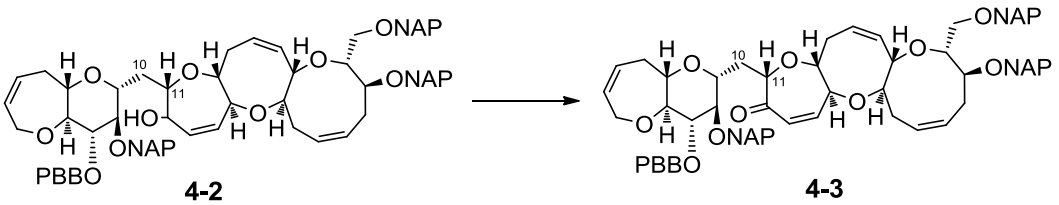
The mixture of **4-2** and 11-*epi*-**4-2** was separated by HPLC (hexane/EtOAc = 2) to give **4-2** (colorless oil) as a less-polar component and 11-*epi*-**4-2** (colorless solid) as a polar component.

4-2: $[\alpha]_D^{23}$ –29.6 (*c* 0.410, $CHCl_3$); IR (neat) ν 3464, 3056, 3024, 2956, 2922, 2854, 1727, 1632, 1601, 1512, 1484, 1467, 1449, 1361, 1308, 1290, 1266, 1209, 1171, 1093, 1012, 987, 962, 896, 853, 815, 779, 755, 741, 702, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, measured at 50 °C) δ 1.80 (1H, td, *J* = 6.4, 14.1 Hz), 2.07-2.19 (2H, m), 2.22 (1H, ddd, *J* = 2.1, 6.4, 13.1 Hz), 2.27-2.39 (3H, m), 2.55-2.65 (2H, m), 2.66-2.74 (1H, m), 2.89-2.99 (1H, m), 3.21 (1H, dt, *J* = 4.1, 9.7 Hz), 3.26 (1H, brtd, *J* = 2.6, 9.0 Hz), 3.36 (1H, t, *J* = 8.8 Hz), 3.38 (1H, t, *J* = 8.8 Hz), 3.40-3.46 (1H, m), 3.52-3.66 (5H, m), 3.71-3.78 (2H, m), 3.88 (1H, brt, *J* = 6.6 Hz), 3.93 (1H, brtd, *J* = 3.2, 8.8 Hz), 3.98 (1H, brdd, *J* = 2.3, 15.4 Hz), 4.15 (1H, brd, *J* = 8.1 Hz), 4.25 (1H, dd, *J* = 5.9, 15.4 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.56 (1H, d, *J* = 12.4 Hz), 4.66 (1H, d, *J* = 12.4 Hz), 4.726 (1H, d, *J* = 11.5 Hz), 4.732 (1H, d, *J* = 11.7 Hz), 4.83 (1H, d, *J* = 11.3 Hz), 4.88 (1H, d, *J* = 11.3 Hz), 4.97 (1H, d, *J* = 11.5 Hz), 5.61 (1H, brq, *J* = 9.4 Hz), 5.72-5.91 (7H, m), 7.19 (2H, d, *J* = 8.3 Hz), 7.25 (1H, dd, *J* = 1.6, 8.3 Hz), 7.36-7.47 (10H, m), 7.57 (1H, s), 7.64-7.82 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$, measured at 50 °C) δ 27.5 (CH_2), 32.58 (CH_2), 32.64 (CH_2), 34.6 (CH_2), 35.4 (CH_2), 67.9 (CH_2), 69.4 (CH), 69.8 (CH_2), 71.6 (CH_2), 73.4 (CH_2), 74.6 (CH_2), 75.1 (CH_2), 75.6 (CH), 75.9 (CH), 78.1 (CH), 80.2 (CH), 81.5 (CH), 81.8 (CH), 83.7 (CH), 85.0 (CH), 85.1 (CH), 85.3 (CH), 85.7 (CH), 88.2 (CH), 121.3 (C), 125.1 (CH), 125.71 (CH), 125.74 (CH), 125.78 (CH), 125.83 (CH×2), 125.9 (CH), 126.00 (CH), 126.02 (CH), 126.04 (CH), 126.3 (CH), 126.5 (CH), 126.7 (CH), 127.0 (CH), 127.58 (CH), 127.63 (CH×2), 127.79 (CH), 127.80 (CH), 127.89 (CH), 127.94 (CH), 128.0 (CH), 128.06 (CH), 128.14 (CH), 128.2 (CH), 129.4 (CH×2), 131.3 (CH×2), 131.4 (CH), 132.97 (C), 133.04 (C), 133.28 (C), 133.34 (C), 135.8 (C), 135.85 (C), 135.94 (C), 137.6 (CH), 138.3 (C), 139.5 (CH); FD-HRMS (m/z) calcd for $C_{68}H_{69}{}^{79}BrO_{10}$ $[M]^+$: 1124.4074, found: 1124.4068.

11-*epi*-**4-2**: mp 143-144 °C; $[\alpha]_D^{23}$ –36.1 (*c* 0.390, $CHCl_3$); IR (neat) ν 3393, 3056, 3027, 2922, 2900, 2875, 1727, 1601, 1510, 1489, 1450, 1394, 1359, 1348, 1309, 1274, 1260, 1218, 1172, 1126, 1109, 1091, 1031, 1013, 996, 950, 932, 907, 890, 858, 816, 770, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, measured at 50 °C) δ 1.53 (1H, m), 2.08-2.22 (3H, m), 2.27-2.38 (2H, m), 2.52 (1H, ddd, *J* = 3.6, 10.7, 13.8 Hz), 2.60 (1H, ddd, *J* = 4.1, 8.2, 16.4 Hz), 2.70 (1H, brtt, *J* = 3.6, 9.7 Hz), 2.94 (1H, brddd, *J* = 4.0, 9.7, 13.6 Hz), 3.20-3.29 (2H, m), 3.26 (1H, t, *J* = 9.5 Hz), 3.37 (1H, t, *J* = 8.8 Hz), 3.47 (1H, dt, *J* = 1.5, 9.9 Hz), 3.54-3.61 (3H, m), 3.63 (1H, t, *J* = 8.8 Hz), 3.76-3.87 (2H, m), 3.90-4.02 (3H, m), 4.20-4.29 (2H, m), 4.43 (1H, d, *J* = 11.7 Hz), 4.55 (1H, d, *J* = 12.4 Hz), 4.66 (1H, d, *J* = 12.4 Hz), 4.74 (1H, d, *J* = 11.7 Hz), 4.75 (1H, d, *J* = 11.8 Hz), 4.78 (1H, d, *J* = 11.3 Hz), 4.90 (1H, d, *J* = 11.8 Hz), 5.00 (1H, d, *J* = 11.3 Hz), 5.52-5.60 (2H, m), 5.72-5.91 (6H, m), 7.22 (2H, d, *J* = 8.3 Hz), 7.26 (1H, dd, *J* = 1.7, 8.3 Hz), 7.35-7.47 (10H, m), 7.57 (1H, s), 7.64-7.81 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$, measured at 50 °C) δ 27.5 (CH_2), 32.4 (CH_2), 32.6 (CH_2), 34.5 (CH_2), 35.1 (CH_2), 67.8 (CH_2), 69.8 (CH_2), 71.7 (CH_2), 71.9 (CH), 73.4 (CH_2), 74.7 (CH_2), 75.2 (CH_2), 75.3 (CH), 75.6 (CH), 75.8 (CH), 76.2 (CH), 78.1 (CH), 79.5 (CH), 81.8 (CH), 83.6 (CH), 85.0 (CH), 85.2 (CH), 85.8 (CH), 88.1 (CH), 131.3 (C), 124.9 (CH), 125.7(CH), 125.76 (CH), 125.77 (CH), 125.92 (CH×2), 125.94 (CH), 125.99 (CH), 126.02 (CH), 126.1 (CH), 126.3 (CH), 126.6 (CH), 126.7 (CH), 127.0 (CH), 127.58 (CH), 127.63 (CH), 127.7 (CH), 127.8 (CH×2), 127.9

(CH), 128.0 (CH), 128.05 (CH), 128.12 (CH), 128.14 (CH), 128.2 (CH), 129.3 (CH), 129.4 (CH×2), 131.37 (CH×2), 131.44 (CH), 132.98 (C), 133.04 (C), 133.1 (C), 133.28 (C×2), 133.33 (C), 135.5 (CH), 135.75 (C), 135.76 (C), 135.9 (C), 137.8 (CH), 138.2 (C); FD-HRMS (m/z) calcd for $C_{68}H_{69}{}^{79}BrO_{10}$ $[M]^+$: 1124.4074, found: 1124.4096.

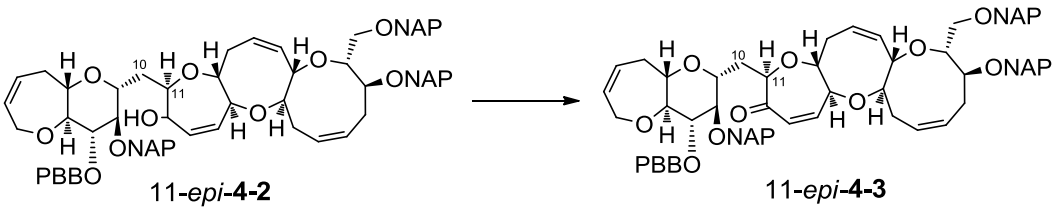
Compound 4-3.



To a solution of $(COCl)_2$ (14.0 μL, 0.150 mmol) in CH_2Cl_2 (0.5 mL) was added DMSO (18.0 μL, 0.253 mmol) at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added a solution of **4-2** (10.3 mg, 9.15 μmol) in CH_2Cl_2 (1.0 mL) at –78 °C, and the mixture was stirred for 10 min. Then, to the solution was added Et_3N (70.0 μL, 0.502 mmol) at –78 °C, and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with 0.5 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 3) to give **4-3** (8.1 mg, 7.2 μmol, 79%) as a colorless oil.

4-3: $[\alpha]_D^{26}$ –16.0 (*c* 0.410, $CHCl_3$); IR (neat) ν 3056, 3024, 2960, 2918, 2847, 2724, 1953, 1914, 1727, 1667, 1632, 1604, 1512, 1488, 1460, 1403, 1389, 1358, 1333, 1277, 1160, 1096, 1012, 959, 896, 857, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, measured at 50 °C) δ 1.89 (1H, ddd, *J* = 4.6, 8.7, 13.7 Hz), 2.14-2.39 (5H, m), 2.54 (1H, ddd, *J* = 4.2, 7.5, 16.2 Hz), 2.62 (1H, brddd, *J* = 3.7, 10.4, 14.1 Hz), 2.70 (1H, brddd, *J* = 3.3, 10.4, 13.3 Hz), 2.98 (1H, brddd, *J* = 4.2, 10.4, 14.1 Hz), 3.15 (1H, dt, *J* = 4.2, 9.9 Hz), 3.23-3.33 (3H, m), 3.51 (1H, dt, *J* = 3.1, 9.1 Hz), 3.54-3.68 (6H, m), 3.88-3.99 (3H, m), 4.06 (1H, brtd, *J* = 2.3, 9.2 Hz), 4.19-4.31 (2H, m), 4.43 (1H, d, *J* = 11.6 Hz), 4.57 (1H, d, *J* = 12.5 Hz), 4.67 (1H, d, *J* = 12.5 Hz), 4.73 (1H, d, *J* = 11.6 Hz), 4.74 (1H, d, *J* = 11.6 Hz), 4.77 (1H, d, *J* = 11.3 Hz), 4.87 (1H, d, *J* = 11.6 Hz), 4.95 (1H, d, *J* = 11.3 Hz), 5.65 (1H, brq, *J* = 9.5 Hz), 5.69-5.87 (5H, m), 5.94 (1H, dd, *J* = 5.8, 10.8 Hz), 6.42 (1H, dd, *J* = 2.3, 12.8 Hz), 7.19 (2H, d, *J* = 8.3 Hz), 7.25 (1H, dd, *J* = 1.6, 8.3 Hz), 7.35-7.47 (10H, m), 7.57 (1H, s), 7.64-7.82 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$, measured at 50 °C) δ 27.6 (CH_2), 31.6 (CH_2), 32.5 (CH_2), 34.4 (CH_2), 36.1 (CH_2), 68.1 (CH_2), 70.0 (CH_2), 71.8 (CH_2), 73.6 (CH_2), 74.3 (CH), 74.6 (CH_2), 75.1 (CH_2), 76.1 (CH), 78.2 (CH), 80.8 (CH), 81.8 (CH), 83.1 (CH), 83.5 (CH), 83.7 (CH), 85.2 (CH), 85.3 (CH), 85.9 (CH), 88.3 (CH), 121.3 (C), 125.2 (CH), 125.85 (CH), 125.86 (CH), 125.89 (CH), 125.92 (CH), 126.0 (CH), 126.06 (CH), 126.10 (CH), 126.14 (CH), 126.2 (CH), 126.4 (CH), 126.6 (CH), 126.8 (CH), 127.0 (CH×2), 127.7 (CH), 127.8 (CH×2), 127.86 (CH), 127.90 (CH×2), 128.0 (CH), 128.1 (CH), 128.15 (CH), 128.18 (CH), 128.5 (CH), 129.5 (CH×2), 131.2 (CH), 131.4 (CH×2), 133.1 (C), 133.2 (C), 133.4 (C×2), 133.5 (C), 135.8 (C), 135.9 (C), 136.0 (C), 138.3 (CH), 138.4 (C), 146.1 (CH), 203.7 (C); FD-HRMS (m/z) calcd for $C_{68}H_{67}{}^{79}BrO_{10}$ $[M]^+$: 1122.3918, found: 1122.3933.

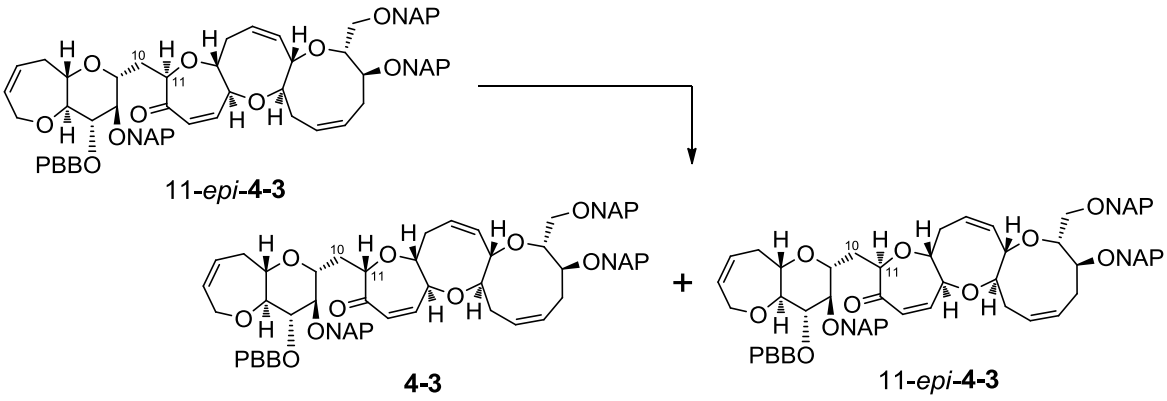
Compound 11-*epi*-4-3.



To a solution of $(COCl)_2$ (14.0 μL, 0.150 mmol) in CH_2Cl_2 (0.5 mL) was added DMSO (19.0 μL, 0.267 mmol) at –78 °C, and the mixture was stirred for 10 min. Then, to the mixture was added a solution of 11-*epi*-**4-2** (10.0 mg, 8.88 μmol) in CH_2Cl_2 (0.5 mL) at –78 °C, and the mixture was stirred for 10 min. Then, to the solution was added Et_3N (70.0 μL, 0.502 mmol) at –78 °C, and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with 0.5 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 3) to give 11-*epi*-**4-3** (7.4 mg, 6.6 μmol, 74%) as a colorless oil.

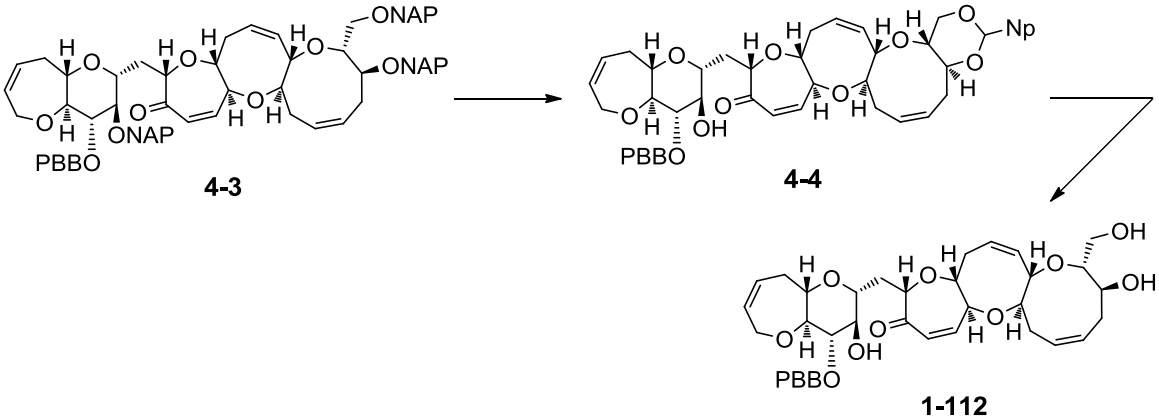
11-*epi*-**4-3**: $[\alpha]_D^{23}$ –34.3 (*c* 0.37, $CHCl_3$); IR (neat) ν 3059, 3026, 2916, 2899, 2849, 1727, 1666, 1600, 1512, 1490, 1445, 1358, 1281, 1099, 901, 857, 819, 758, 736, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, measured at 50 °C) δ 2.00 (1H, ddd, *J* = 2.6, 10.5, 15.0 Hz), 2.09-2.40 (5H, m), 2.47 (1H, ddd, *J* = 4.1, 10.5, 14.2 Hz), 2.59 (1H, ddd, *J* = 3.8, 7.5, 16.1 Hz), 2.69 (1H, ddd, *J* = 3.4, 10.5, 13.8 Hz), 2.97 (1H, ddd, *J* = 4.1, 11.6, 14.2 Hz), 3.19-3.26 (2H, m), 3.29 (1H, t, *J* = 9.2 Hz), 3.39 (1H, t, *J* = 9.0 Hz), 3.49-3.57 (3H, m), 3.61-3.67 (2H, m), 3.64 (1H, t, *J* = 8.6 Hz), 3.79 (1H, ddd, *J* = 1.6, 6.1, 8.6 Hz), 3.93 (1H, td, *J* = 3.0, 8.6 Hz), 4.01 (1H, ddd, *J* = 2.6, 5.1, 15.0 Hz), 4.16 (1H, td, *J* = 2.6, 9.0 Hz), 4.25 (1H, dd, *J* = 6.1, 15.7 Hz), 4.37 (1H, dd, *J* = 2.5, 11.4 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.54 (1H, d, *J* = 12.4 Hz), 4.64 (1H, d, *J* = 12.4 Hz), 4.735 (1H, d, *J* = 11.4 Hz), 4.740 (1H, d, *J* = 11.7 Hz), 4.75 (1H, d, *J* = 11.7 Hz), 4.91 (1H, d, *J* = 11.4 Hz), 5.01 (1H, d, *J* = 11.4 Hz), 5.53-5.61 (1H, m), 5.72-5.93 (6H, m), 6.53 (1H, dd, *J* = 2.6, 12.4 Hz), 7.21 (2H, d, *J* = 8.6 Hz), 7.29 (1H, ddd, *J* = 1.3, 8.0, 16.0 Hz), 7.37-7.80 (9H, m), 7.59 (1H, s), 7.63-7.80 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$, measured at 50 °C) δ 27.6 (CH_2), 31.7 (CH_2), 32.5 (CH_2), 33.2 (CH_2), 34.6 (CH_2), 68.0 (CH_2), 69.9 (CH_2), 71.8 (CH_2), 73.5 (CH_2), 74.6 (CH), 74.7 (CH_2), 75.4 (CH_2), 75.8 (CH), 78.2 (CH), 79.3 (CH), 80.4 (CH), 80.5 (CH), 82.2 (CH), 83.5 (CH), 85.2 (CH), 85.4 (CH), 86.1 (CH), 88.3 (CH), 121.4 (C), 124.9 (CH), 125.8 (CH), 125.86 (CH × 2), 125.91 (CH), 126.0 (CH), 126.08 (CH), 126.10 (CH), 126.2 (CH), 126.39 (CH), 126.43 (CH), 126.9 (CH), 127.0 (CH), 127.3 (CH), 127.7 (CH), 127.75 (CH), 127.77 (CH), 127.8 (CH), 127.85 (CH), 127.91 (CH × 2), 128.1 (CH), 128.15 (CH), 128.18 (CH), 128.6 (CH), 129.4 (CH × 2), 131.45 (CH), 131.46 (CH × 2), 133.1 (C × 2), 133.2 (C), 133.38 (C), 133.40 (C × 2), 135.8 (C), 135.9 (C), 136.0 (C), 138.35 (CH), 138.37 (C), 148.0 (CH), 202.9 (C); FD-HRMS (m/z) calcd for $C_{68}H_{67}{}^{79}BrO_{10}$ $[M]^+$: 1122.3918, found: 1122.3904.

Epimerization of 11-*epi*-4-3.



To a solution of 11-*epi*-**4-3** (3.0 mg, 2.7 μmol) in CH_2Cl_2 (0.5 mL) was added DBU (2 drops) at 24 °C, and the mixture was stirred for 7 h. Then, the reaction was quenched with 0.5 mol/L aq. HCl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 3) to give a 3:1 mixture of **4-3** and 11-*epi*-**4-3** (1.6 mg, 1.4 μmol, 53%) as a colorless oil.

Compound 1-112.



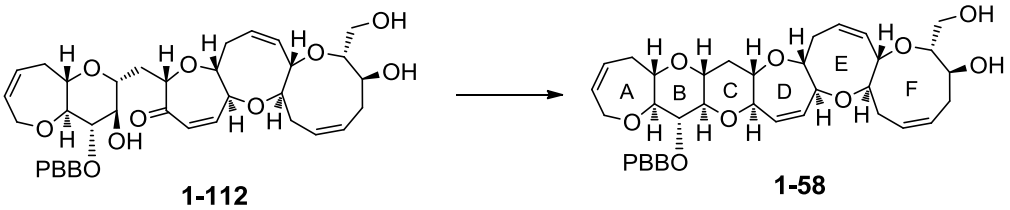
To a solution of **4-3** (2.3 mg, 2.1 μmmol) in CH_2Cl_2-water (1.0 mL: 0.5 mL) was added DDQ (6.2 mg, 0.027 mmol) at 17 °C, and the mixture was stirred for 1 h. Then, the reaction was quenched with saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3 → 2) to give **4-4**, which was used immediately in the next reaction.

To a solution of the above crude **4-4** in EtOH (0.2 mL) was added 1.0 mol/L aq. HCl (0.1 mL) at 17 °C, and the mixture was stirred for 2 h. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed

with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1 → 0.5 → 0.2) to give **1-112** (1.4 mg, 1.9 μmol, 93% from **4-3**) as a colorless oil.

1-112: $[\alpha]_D^{25}$ –23 (*c* 0.12, $CHCl_3$); IR (neat) ν 3429, 3024, 2956, 2918, 2854, 1741, 1724, 1664, 1597, 1486, 1468, 1446, 1405, 1380, 1359, 1331, 1284, 1126, 1088, 1013, 943, 911, 873, 845, 802, 781, 739, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, measured at 50 °C) δ 1.80-1.86 (1H, m), 1.86-1.94 (1H, m), 2.15 (1H, brd, *J* = 14.2 Hz), 2.21-2.31 (3H, m), 2.40 (1H, brddd, *J* = 2.0, 6.1, 13.8 Hz), 2.53 (1H, ddd, *J* = 4.0, 8.1, 16.2 Hz), 2.69 (1H, ddd, *J* = 4.1, 9.4, 13.8 Hz), 2.81 (1H, brddd, *J* = 3.6, 10.1, 13.8 Hz), 2.91 (1H, brddd, *J* = 4.0, 9.7, 13.8 Hz), 3.11-3.19 (2H, m), 3.26 (1H, t, *J* = 8.5 Hz), 3.31 (1H, t, *J* = 8.5 Hz), 3.33 (1H, t, *J* = 8.5 Hz), 3.41 (1H, dt, *J* = 2.0, 8.5 Hz), 3.61-3.80 (4H, m), 3.89-4.06 (3H, m), 4.11 (1H, td, *J* = 2.9, 8.9 Hz), 4.22 (1H, dd, *J* = 5.7, 15.8 Hz), 4.26-4.32 (1H, m), 4.69 (1H, d, *J* = 12.0 Hz), 4.89 (1H, d, *J* = 12.0 Hz), 5.70-5.89 (7H, m), 6.46 (1H, dd, *J* = 2.9, 13.3 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, measured at 50 °C) δ 31.5 (CH_2), 32.5 (CH_2), 34.4 (CH_2), 36.2 (CH_2), 63.8 (CH_2), 65.5 (CH_2), 67.9 (CH_2), 71.7 (CH), 73.7 (CH), 74.2 (CH_2), 74.5 (CH), 76.1 (CH), 80.7 (CH), 83.0 (CH), 83.7 (CH), 85.2 (CH), 85.3 (CH), 87.2 (CH), 87.6 (CH), 121.5 (C), 126.3 (CH), 126.97 (CH), 127.03 (CH), 127.9 (CH), 128.2 (CH), 128.8 (CH), 129.3 (CH×2), 130.9 (CH), 131.2 (CH), 131.6 (CH×2), 137.6 (CH), 138.2 (C), 146.1 (CH), 203.5 (C); FD-HRMS (m/z) calcd for $C_{35}H_{43}{}^{79}BrO_{10}$ $[M]^+$: 702.2040, found: 702.2042.

Compound 1-58.



To a solution of **1-112** (1.4 mg, 2.0 μmol) in CH_2Cl_2-Et_3SiH (0.2 mL: 0.1 mL) was added TMSOTf (3.0 μL, 0.017 mmol) at 0 °C, and the mixture was stirred for 15 min. Then, the reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1 → 0.8 → 0.5) to give **1-58** (1.0 mg, 1.5 μmol, 73%) as a colorless solid.

1-58: mp 168-169 °C; $[\alpha]_D^{24}$ –22 (*c* 0.050, $CHCl_3$); IR (KBr) ν 3418, 3024, 2953, 2925, 2879, 2858, 2823, 1724, 1660, 1632, 1445, 1386, 1294, 1262, 1135, 1086, 1072, 1051, 1015, 804, 769, 687, 670 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.67 (1H, q, *J* = 11.6 Hz), 1.95 (1H, brd, *J* = 13.5 Hz), 2.15 (1H, ddd, *J* = 2.5, 6.3, 13.1 Hz), 2.17-2.27 (2H, m), 2.32 (1H, td, *J* = 4.7, 11.6 Hz), 2.52 (1H, ddd, *J* = 1.0, 2.4, 6.6 Hz), 2.56 (1H, dd, *J* = 3.7, 7.5 Hz), 2.64 (1H, ddd, *J* = 4.3, 10.9, 13.8 Hz), 2.72 (1H, brddd, *J* = 3.2, 9.4, 13.5 Hz), 2.83-2.94 (2H, m), 3.00-3.08 (2H, m), 3.11 (1H, t, *J* = 9.2 Hz), 3.22-3.26 (1H, m), 3.27 (1H, t, *J* =

9.2 Hz), 3.37 (1H, brtd, J = 2.8, 8.4 Hz), 3.48-3.57 (3H, m), 3.61-3.69 (1H, m), 3.70-3.75 (2H, m), 3.80 (1H, brd, J = 6.9 Hz), 3.91 (1H, brt, J = 8.4 Hz), 4.00-4.07 (2H, m), 4.81 (1H, d, J = 12.7 Hz), 4.88 (1H, d, J = 12.7 Hz), 5.44-5.56 (2H, m), 5.63 (1H, dd, J = 5.6, 10.8 Hz), 5.71-5.77 (2H, m), 5.87-6.03 (3H, m), 7.17 (2H, m), 7.36 (2H, d, J = 8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, measured at 50 ºC) δ 31.9 (CH_2), 32.5 (CH_2), 32.9 (CH_2), 34.7 (CH_2), 37.0 (CH_2), 63.9 (CH_2), 68.4 (CH_2), 71.8 (CH), 73.3 (CH), 74.2 (CH), 76.9 (CH), 78.1 (CH), 80.7 (CH), 81.0 (CH), 82.3 (CH), 82.4 (CH), 84.0 (CH), 85.0 (CH), 86.1 (CH), 87.4 (CH), 121.2 (C), 126.6 (CH), 126.7 (CH), 127.6 (CH), 128.6 (CH), 129.3 (CH×2), 130.5 (CH), 130.9 (CH), 131.2 (CH), 131.3 (CH×2), 136.2 (CH), 136.5 (CH), 138.5 (C); FD-HRMS (m/z) calcd for $C_{35}H_{43}{}^{79}BrO_9$ $[M]^+$: 686.2090, found: 686.2117.

Crystal Data for 1-58.

Crystals were obtained by recrystallizing from EtOAc/benzene. $C_{43}H_{53}O_{10}Br$, M = 809.79, colorless needle, 0.50 × 0.02 × 0.01 mm^3, monoclinic $P2_1$ (No. 4), a = 16.716(12) Å, b = 5.985(4) Å, c = 19.98(2) Å, β = 100.006(13)°, V = 1968(3) Å^3, ρ_{calcd}(Z = 2) = 1.366 g cm^{-3}. A total 744 unique data ($2\theta_{max}$ = 55°) were measured at T = 150 K by Rigaku Mercury 70 apparatus (Mo Kα radiation, λ = 0.71070 Å). Numerical absorption correction was applied (μ = 11.056 cm^{-1}). The structure was solved by the direct method (SIR2004) and refined by the full-matrix least-squares method of F^2. Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were included but not refined. The final wR value is 0.2301 (all data) for 5928 reflections and 480 parameters. CCDC 1517386.

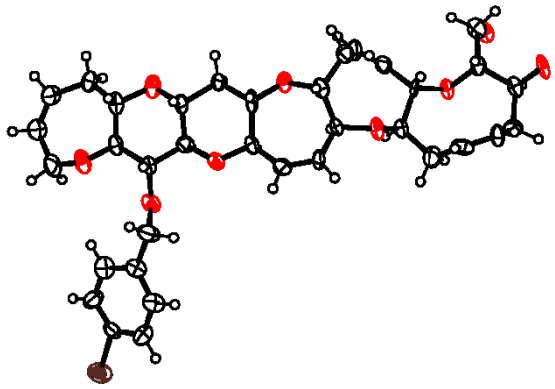
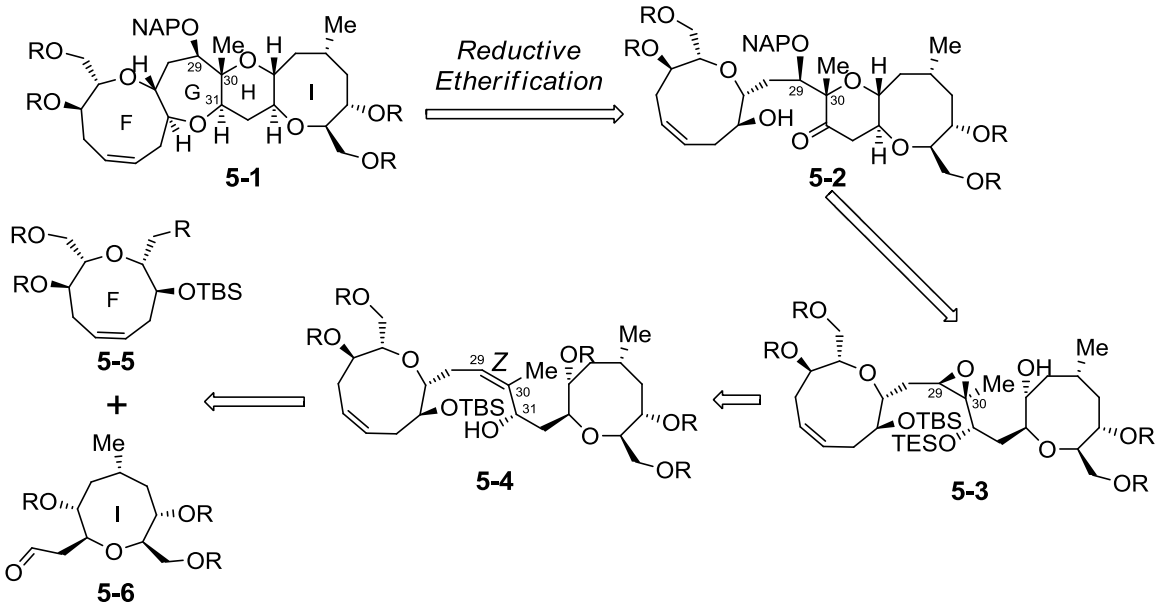


Figure 4-A. The ORTEP diagram of compound **1-58**

5. Synthetic studies on the FGHI-ring

5-1. New synthetic plan for FGHI-ring

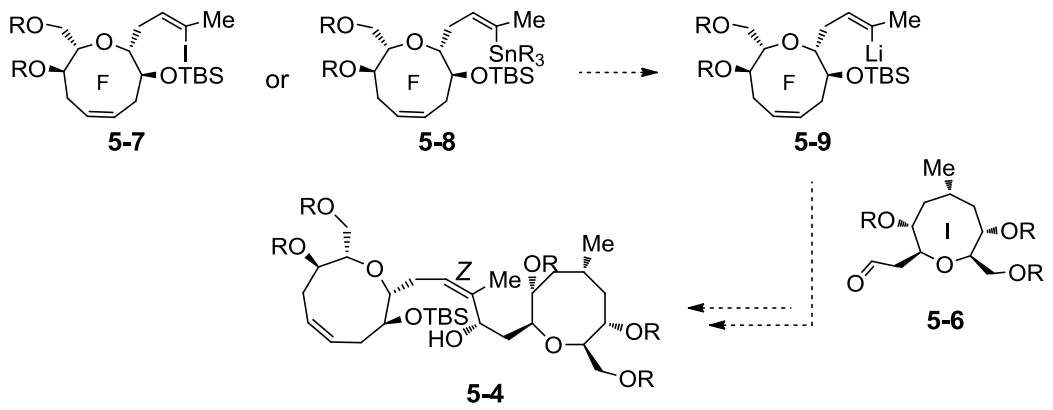
As shown in section 1-3-6, the previous synthesis of the FGHI-ring was successfully performed by Takizawa and Doi, but the route, including stereo-inversion at C29 and very slow reaction step, was somewhat inefficient.[1] Therefore, the author planned a new synthetic route for the FGHI-ring from the F- and I-rings without inefficient steps (Scheme 5-1). FGHI-ring **5-1** was intended to be constructed from ε-hydroxy ketone **5-2** via the formation of the G-ring by reductive etherification. FHI-ring **5-2** would be synthesized by cyclization of hydroxy epoxide **5-3**, which would be derived from (*Z*)-allylic alcohol **5-4** by diastereoselective epoxidation. The stereoselective formation of trisubstituted (*Z*)-alkene **5-4** from F-ring **5-5** and I-ring aldehyde **5-6** is a problem to be solved. Because the stereochemistries at C29 and C30 of **5-1** result from the stereochemistry at C31 and the (*Z*)-geometry of the alkene at C29 of **5-4**, (*Z*)-Alkene **5-4** is a key intermediate in the synthesis.



Scheme 5-1. New synthetic plan for FGHI-ring **5-1**

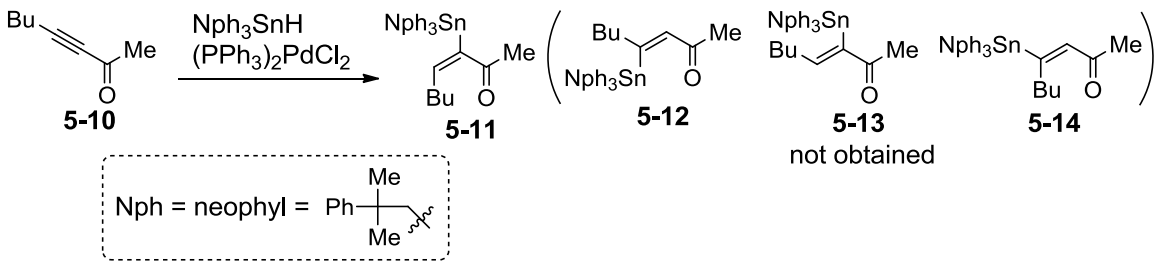
The previous synthesis employed Nozaki-Hiyama-Kishi (NHK) reaction[2] for the connection of (*E*)-iodoalkene **1-104** with aldehyde **1-105** to give an (*E*)-alkene at C29-C30, of which the (*E*)-geometry caused the problematic inversion of stereochemistry at C29, as shown in Scheme 1-12. Therefore, (*Z*)-iodoalkene **5-7** may be expected as a substrate which would directly afford (*Z*)-alkene **5-4**. However, Kishi reported a trisubstituted (*Z*)-alkene gave an (*E*)-allyl alcohol in low yield instead of a (*Z*)-allyl alcohol under NHK coupling conditions.[2b] Thus, the author searched other methods for the construction of (*Z*)-alkene **5-4**. Although alkenyl lithium **5-9**, which would be generated from iodoalkene **5-7** or alkenyl tin **5-8**, was predicted to reacted with aldehyde **5-6** to produce (*Z*)-alkene **5-4** straightforwardly (Scheme 5-2), the use of the alkenyl lithium was renounced due to the suspected high basicity, which includes a risk of inducing predominant deprotonation from the

α-position of aldehyde **5-6**. Furthermore, the protonated form of **5-9** is difficult to be reused for the coupling reaction with **5-6**. Therefore, the author further searched other effective methods for the preparation of **5-4**.

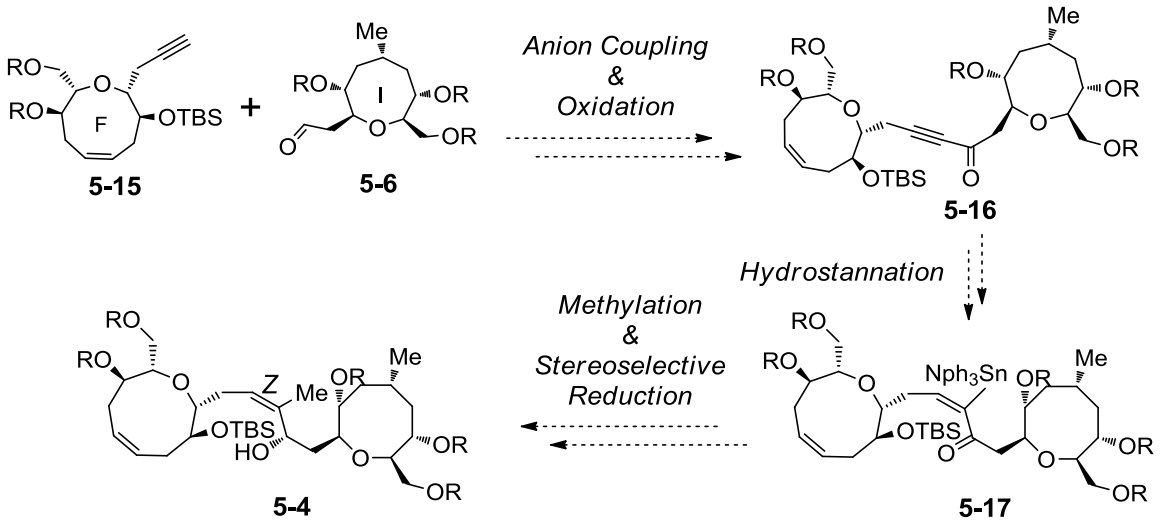


Scheme 5-2. Synthetic plan of (*Z*)-alkene **5-4** via alkyl lithium

The Podestá group reported that trineophyltin hydride was reacted to alkynyl ketone **5-10** in the presence of $(PPh_3)_2PdCl_2$ as a catalyst to furnish (*E*)-β-stannyl enone **5-11** regio- and stereo-selectively as shown in Scheme 5-3.[3] The report prompted the author to plan a new route to (*Z*)-alkene **5-4**, which included the catalytic hydrostannation reaction (Scheme 5-4). The connection between the F- and I- rings would be employed by the coupling reaction of I-ring aldehyde **5-6** with an acetylide generated from F-ring alkyne **5-15**. The resulting adduct would be oxidized to give alkynone **5-16**, which would be reacted with trineophyltin hydride to produce (*E*)-β-stannyl enone **5-17** according to Podestá's procedure. Trisubstituted (*Z*)-olefin **5-4** would be formed from **5-17** via methylation and stereoselective reduction of the ketone. In this route, if an excess amount of alkyne **5-15** is used in the coupling reaction, unreacted **5-15** can be recovered intactly and be reused. Thus, the author examined the availability of the acetylide coupling / enone formation / hydrostannnation / methylation sequence for the preparation of (*Z*)-alkene **5-4**.



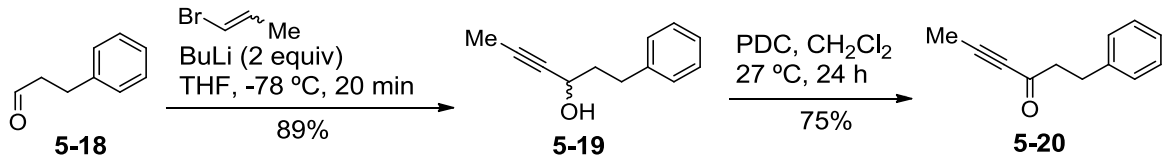
Scheme 5-3. Selective hydrostannation reaction of an alkynyl ketone reported by Podestá[3]



Scheme 5-4. Synthetic plan for (*Z*)-alkene **5-4** via hydrostannation

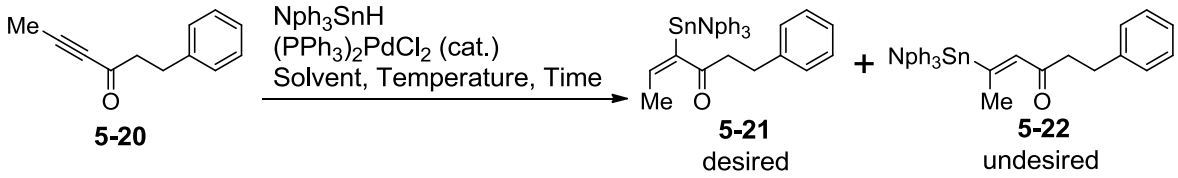
5-2. Model studies for construction of (*Z*)-trisubstituted alkene 5-4

To confirm the availability of the above synthetic plan illustrated in Scheme 5-4, the author performed model studies to construct a (*Z*)-trisubstituted alkene via the hydrostannation reaction. The preparation of model alkynyl ketone **5-20** is outlined in Scheme 5-5. A mixture of *cis*- and *trans*-1-bromopropene was exposed to 2 equivalent of BuLi, and the resulting lithium acetylide was reacted with 3-phenylpropanal (**5-18**) in situ to afford alcohol **5-19** (89%). Oxidation of alcohol **5-19** by PDC gave alkynyl ketone **5-20** (75%).



Scheme 5-5. Synthesis of model alkynyl ketone **5-20**

Next, the conditions for the regio- and stereo-selective hydrostannation reaction of alkynyl ketone **5-20** was optimized (Table 5-1). According to Podestá's procedure, alkynone **5-20** was treated with Nph_3SnH and $(PPh_3)_2PdCl_2$ in THF at 26 °C to give a mixture of **5-21** and **5-22** (3:1) with exclusive *syn*-selectivity in 77% (Entry 1). To investigate the effect of temperature, the reaction was then conducted at 0 °C. However, the ratio of **5-21** and **5-22** remained unchanged (Entry 2). On the other hand, when Et_2O was used as a solvent, **5-21** was obtained with exclusive *syn*-selectivity and relatively high regio-selectivity (**5-21**:**5-22** = 7:1, Entry 3). Since the result suggested that solvent affected the regio-selectivity, the author next tried various solvents. The use of $PhCH_3$ resulted in decomposition of a part of the substrate and a decreased yield (68%, Entry 4). When the hydrostannation was performed in DMF, the ratio of the byproduct **5-22** was increased (**5-21**:**5-22** = 4:1, Entry 5). The employment of CH_2Cl_2 as a solvent furnished desired α-stannyl enone **5-21** in good yield (90%) and relatively high regio-selectivity (**5-21**:**5-22** = 7:1). Thus, the author found optimized conditions for the regio- and stereo-selective hydrostannation step.

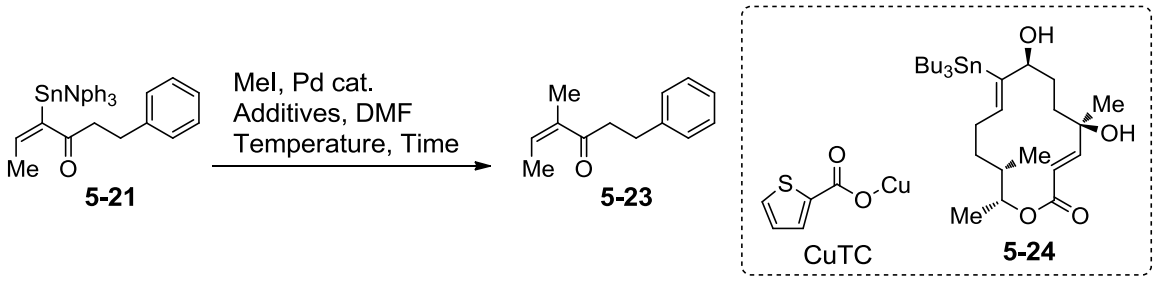


Entry	Solvent	Temperature	Time	Yield	**5-21**:**5-22** [a]
1	THF	26 ºC	2 h	77%	3:1
2	THF	0 ºC	19 h	76%	3:1
3	Et_2O	26 ºC	1 h	78%	7:1
4	$PhCH_3$	25 ºC	1 h	68%	6:1
5	DMF	25 ºC	30 min	72%	4:1
6	CH_2Cl_2	25 ºC	2 h	90%	7:1

[a] The ratio was determined by ^{1}H NMR spectra

Table 5-1. Hydrostannation of alkynyl ketone **5-20**

Then, the methylation of α-stannyl enone **5-21** was attempted (Table 5-2). Since Suzuki reported a rapid Stille cross-coupling reaction of various tributylstannanes with $^{11}CH_3I$ using $Pd_2(dba)_3$, $P(o\text{-}CH_3C_6H_4)_3$, CuCl, and K_2CO_3,[4] the author applied Suzuki's modified-Stille coupling procedure to the methylation of trineophylstannane **5-21**. However, the reaction resulted only in decomposition of the substrate (Entry 1). Application of Fürstner's procedure, which successfully promoted the reaction of tributylstannane **5-24** with MeI in the presence of $Pd(PPh_3)_4$, [Ph2PO2][NBu_4], and CuTC to give a trisubstituted alkene,[5] to the coupling reaction of **5-21** with MeI, however, resulted in no reaction (Entry 2). The neophyl group, which is more bulky than butyl group, might be prevented from reacting with a palladium complex due to steric hindrance.

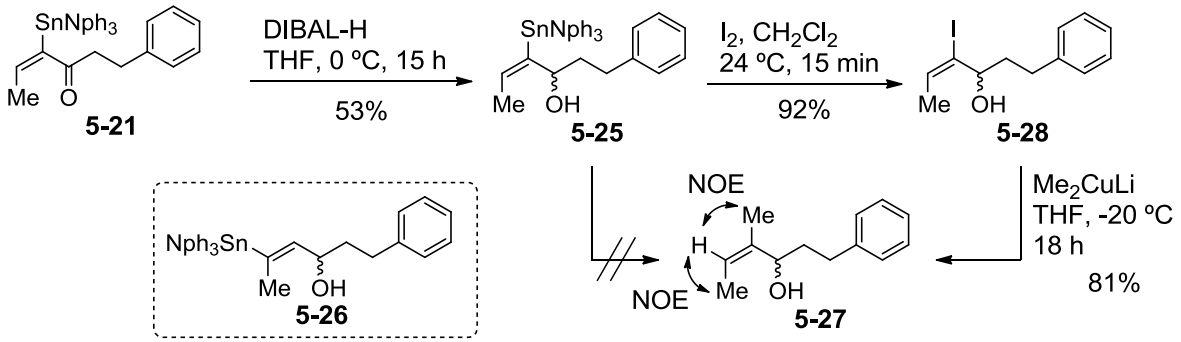


Entry	Pd cat.	Additives	Temperature	Time	Yield
1	$Pd_2(dba)_3$	$P(o\text{-}CH_3C_6H_4)_3$ CuCl K_2CO_3	60 °C	2 h	decomposition
2	$Pd(PPh_3)_4$	$[Ph_2PO_2][NBu_4]$ CuTC	24 °C	2 days	no reaction

Table 5-2. Methylation of (*Z*)-α-stannyl enone **5-21**

The author, then, decided to employ the methylation of **5-21** via iodoalkene **5-28** (Scheme 5-6). Ketone **5-21**, which was used as a mixture with a small amount of **5-22**, was reduced with DIBAL-H to give alcohol **5-25**, which was easily separated from **5-26** generated from **5-22** by silicagel column chromatography. Since ketone **5-21** was less-reactive to DIBAL-H, unreacted **5-21** was recovered, and the yield of **5-25** was moderate (53%). At this stage, the Stille coupling conditions shown in Scheme 5-2 were also examined for the reaction of **5-25** with MeI, but the reactions did not furnish trisubstituted alkene **5-27**. Treatment of stannane **5-25** with I_2 cleanly produced iodoalkene **5-28** (92%). Finally, iodoalkene **5-28** was successfully methylated with Me_2CuLi to afford (*Z*)-trialkyl olefin **5-27** in 81% yield. The geometry of alkene was determined by the presence of NOEs between the alkene proton and each of two methyl groups.

Thus, the author developed a prototype method for the construction of (*Z*)-trisubstituted alkene **5-4** using a 6-step process including acetylide coupling / enone formation / hydrostannnation / reduction / iodination / methylation.



Scheme 5-6. Preparation of (*Z*)-trialkyl olefin **5-27**

References

[1] (a) Takizawa, A.; Fujiwara, K.; Doi, E.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2006**, *47*, 747. (b) Takizawa, A.; Fujiwara, K.; Doi, E.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron* **2006**, *62*, 7408.

[2] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

[3] Dodero, V. I.; Koll, L. C.; Faraoni, M. B.; Mitchell, T. N.; Podestá, J. C. *J. Org. Chem.* **2003**, *68*, 10087.

[4] Suzuki, M.; Doi, H.; Koyama, H.; Zhang, Z.; Hosoya, T.; Onoe, H.; Watanabe, Y. *Chem. Rec.* **2014**, *14*, 516.

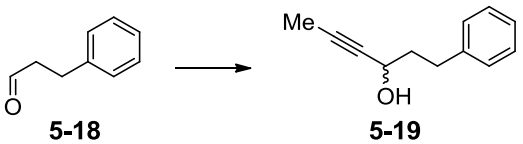
[5] Rummelt, S. M.; Preindl, J.; Sommer, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 6241.

Experimental sections

General methods

All air sensitive reactions were carried out under argon or nitrogen in oven-dried glassware using standard syringe, cannula and septa techniques. Anhydrous tetrahydrofuran (THF) was prepared by Glass Contour Solvent Dispensing System (Nikko Hansen & Co., Ltd.) or purchased from commercial sources. Other dry solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F_{254}). Plates were visualized by ultraviolet light and by treatment with acidic anisaldehyde or phosphomolybdic acid stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63-40 μm for flash chromatography, 230-63 μm for gravity chromatography) as a stationary phase. High-performance liquid chromatography (HPLC) was performed on a JASCO 880-PU HPLC pump equipped with a pre-packed column (YMC-Pack SIL-06, 5 μm, 150 mm × 4.6 mm ID [for normal-phase chromatography]) and a JASCO UV-975 UV detector (UV 254 nm detection). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) or a JEOL JNM-ECA500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of the residual solvent (^{1}H NMR: 7.15 ppm in C_6D_6, ^{13}C NMR: 128.0 ppm in C_6D_6) as the internal standard. The following abbreviations are used to describe spin multiplicity: s= singlet, d= doublet, t= triplet, q= quartet, qn= quintet, m= multiplet, br= broad, dd= double doublets, dt= double triplets, td= triple doublets, ddd= double double doublets, and dtd= double triple dublets; other combination is derived from those listed. Coupling constants (J) are reported in Hz.

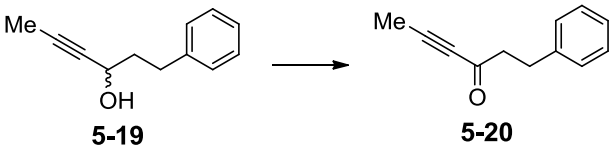
Compound 5-19.



To a solution of 1-bromo-1-propene (0.260 mL, 3.03 mmol) in THF (20 mL) was added BuLi (1.63 mol/L, 3.60 mL, 5.87 mmol) at –78 °C, and the mixture was stirred for 20 min. Then, to the mixture was added **5-18** (0.260 mL, 1.98 mmol) at –78 °C, and the mixture was stirred for 20 min. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **5-19** (311.4 mg, 1.787 mmol, 89%) as a colorless oil.

5-19: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (1H, d, J = 5.8 Hz), 1.87 (3H, d, J = 2.1 Hz), 1.95-2.03 (2H, m), 2.79 (2H, t, J = 7.8 Hz), 4.34 (1H, brdq, J = 2.1, 6.5 Hz), 7.16-7.31 (5H, m)

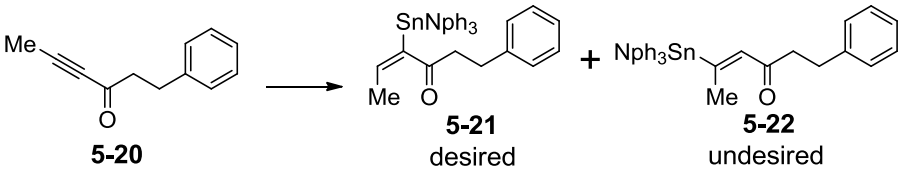
Compound 5-20.



To a solution of **5-19** (26.8 mg, 0.154 mmol) and Celite (269.9 mg) was added PDC (98.2 mg, 0.261 mmol) at 27 °C, and the mixture was stirred for 24 h. Then, the mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **5-20** (20.0 mg, 0.116 mmol, 75%) as a colorless oil.

5-20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (3H, s), 2.86 (2H, t, J = 8.0 Hz), 2.98 (2H, t, J = 8.0 Hz), 7.17-7.22 (3H, m), 7.25-7.31 (2H, m)

Compound 5-21 and 5-22.

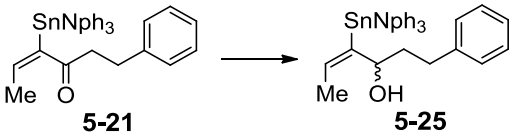


To a solution of **5-20** (82.1 mg, 0.482 mmol) in CH_2Cl_2 (5.0 mL) were added Nph_3SnH (251.7 mg, 0.4846 mmol) and $(PPh_3)_2PdCl_2$ (10.7 mg, 0.0152 mmol) at 18 °C, and the mixture was stirred for 2 h. Then, the mixture was diluted with hexane (10 mL) and cooled in the refrigerator for 2.5 h. Then, the

residual Pd was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50) to give a mixture of **5-21** and **5-22** (300.8 mg, 0.435 mmol, 90%, **5-21**:**5-22** = 7:1) as a colorless oil.

5-21 and **5-22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (6H, s), 1.13-1.16 (18H, m), 1.51-1.55 (3H, m), 2.59-2.68 (2H, m), 2.87-2.94 (2H, m), 5.23 (6/7H, q, J = 7.0 Hz), 5.98 (1/7H, q, J = 1.7 Hz), 7.07-7.33 (20H, m)

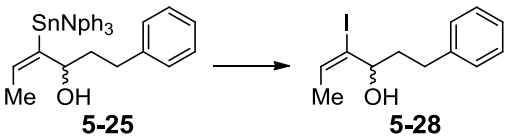
Compound 5-25.



To a solution of **5-21** (53.1 mg, 0.0768 mmol) containing a small amount of **5-22** in CH_2Cl_2 (1.0 mL) was added DIBAL-H (1.02 mol/L, 0.150 mL, 0.153 mmol) at 0 °C, and the mixture was stirred for 1.5 h. Then, the reaction was quenched with saturated aq. potassium sodium tartrate, and the mixture was stirred for 15 h at 26 °C. The mixture was extracted with EtOAc several times, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10) to give a mixture of **5-25** (28.2 mg, 0.0407 mmol, 53%) as a colorless oil.

5-25: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, J = 13.4 Hz), 1.21 (18H, d, J = 6.5 Hz), 1.39 (3H, d, J = 6.5 Hz), 1.40-1.48 (1H, m), 1.66 (1H, dtd, J = 4.8, 9.8, 18.6 Hz), 2.50 (1H, ddd, J = 7.0, 9.8, 14.2 Hz), 2.66 (1H, ddd, J = 4.8, 10.2, 14.2 Hz), 3.96 (1H, brt, J = 4.8 Hz), 5.26 (1H, dq, J = 1.5, 6.6 Hz), 7.13-7.31 (20H, m)

Compound 5-28.

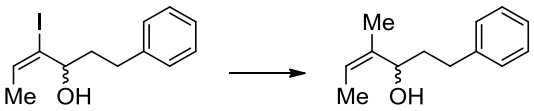


To a solution of **5-25** (28.2 mg, 0.0406 mmol) in CH_2Cl_2 (0.5 mL) was added I_2 (15.4 mg, 0.0607 mmol) at 24 °C, and the mixture was stirred for 15 min. Then, the reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 5) to give a mixture of **5-28** (11.3 mg, 0.0374 mmol, 92%) as a colorless oil.

5-28: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (3H, d, J = 7.2 Hz), 1.74-1.85 (1H, m), 1.91-2.01 (1H, m), 2.64

(2H, t, J = 7.8 Hz), 3.78 (1H, brq, J = 7.0 Hz), 6.39 (1H, dq, J = 0.9, 7.2 Hz), 7.17-7.23 (3H, m), 7.27-7.32 (2H, m)

Compound 5-27.



5-28 **5-27**

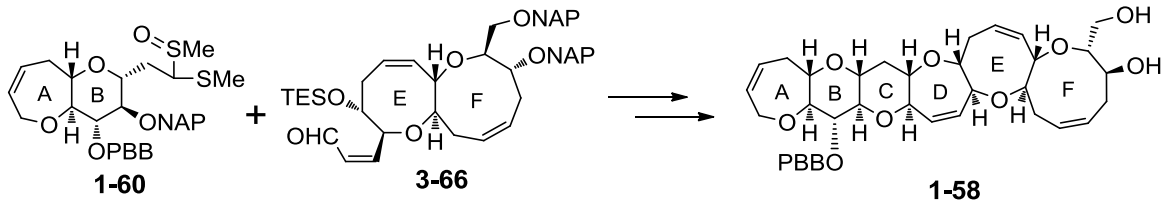
To a suspension of CuCN (29.4 mg, 0.328 mmol) in THF (0.5 mL) was added MeLi (1.08 mol/L in Et_2O, 0.600 mL, 0.648 mmol) at –78 °C, and the mixture was stirred for 15 min. Then, to the mixture was added a solution of **5-28** (19.8 mg, 0.0655 mmol) in THF (0.5 mL) at –78 °C, and the mixture was stirred for 17 h at –20 °C. The reaction was quenched with a mixture of saturated aq. NH_4Cl and 25% aq. NH_3 (v/v = 9/1), and the mixture was stirred vigorously in air for 3 h at 26 ° C. Then, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10) to give **5-27** (9.9 mg, 0.053 mmol, 81%) as a colorless oil.

5-27: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (3H, qd, J = 1.5, 6.9 Hz), 1.71 (3H, qn, J = 1.5 Hz), 1.74-1.82 (1H, m), 1.93-2.03 (1H, m), 2.56-2.74 (2H, m), 4.62 (1H, t, J = 6.9 Hz), 5.36 (1H, brq, J = 6.9 Hz), 7.16-7.23 (3H, m), 7.26-7.31 (2H, m)

6. Conclusion

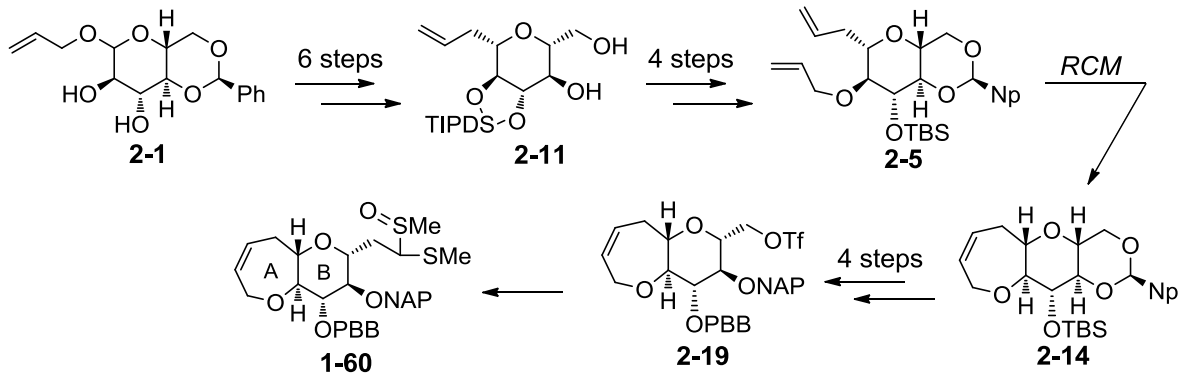
6-1. Conclusion

The author studied the synthesis of the ABCDEF-ring of CTX3C, isolated as a causative toxin of ciguatera fish poisoning from the dinoflagellate *Gambierdiscus toxicus*. In this dissertation, the followings are described: (i) optimization of the preparation of AB-ring **1-60**, (ii) construction of EF-ring **3-66**, (iii) synthesis of ABCDEF-ring **1-58** from the AB- and EF-rings (**1-60**, and **3-66**, respectively) (Scheme 6-1), and (iv) investigation of a new methodology for the convergent construction of the FGHI-ring.



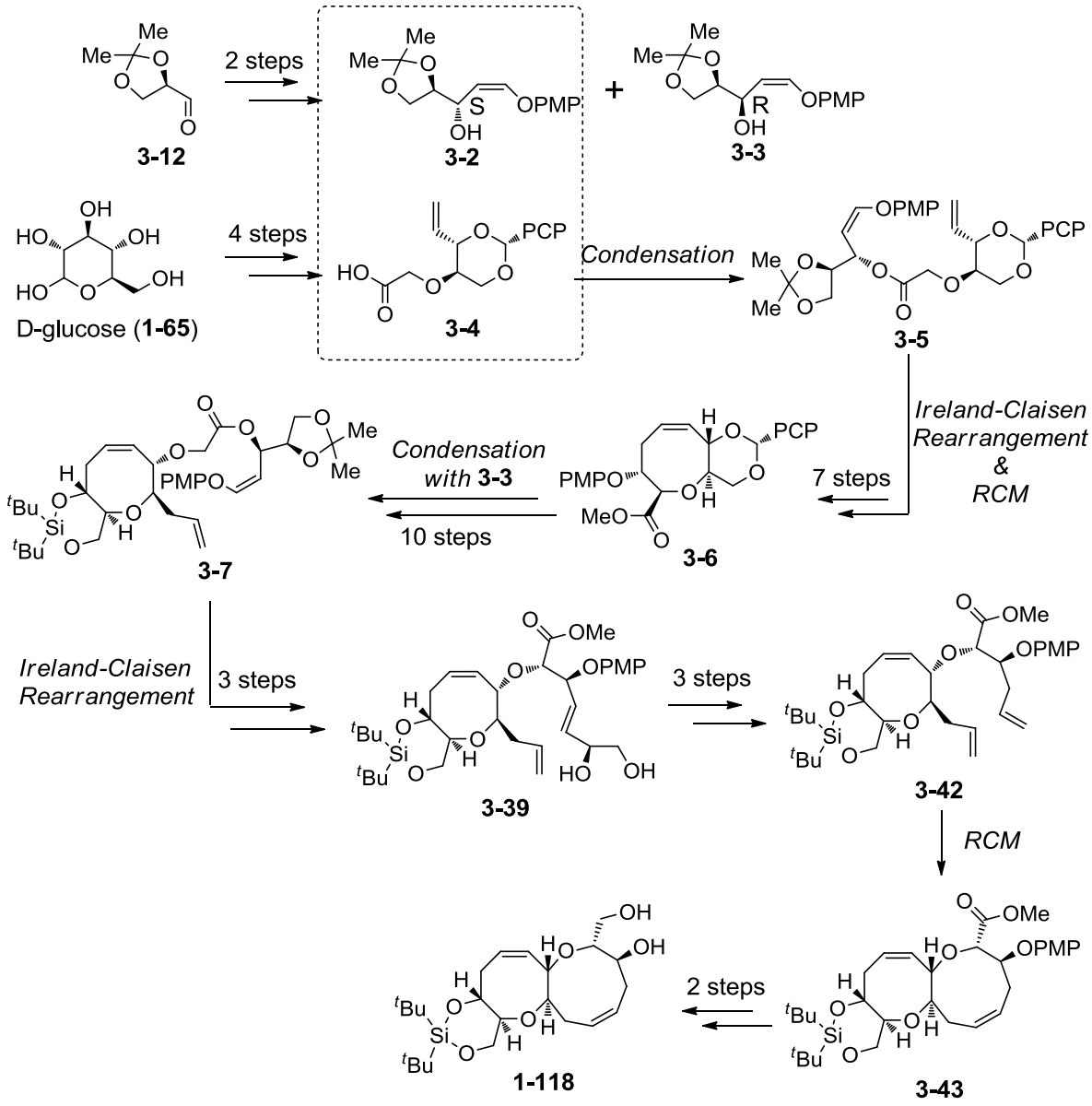
Scheme 6-1. Synthesis of the ABCDEF-ring from the AB- and EF-rings

Although AB-ring **1-60** was previously synthesized by Goto, improvement was required for large-scale synthesis. Therefore the author optimized the process and performed the large-scale synthesis of **1-60** (Scheme 6-2). First, D-glucose derivative **2-1** was converted to **2-11** using reductive etherification, and tetrahydropyrane **2-11** was transformed to diene **2-5** by a 4-steps process. In the previous method for RCM of **2-5**, the suppression of the amounts of solvent (CH_2Cl_2, 5 mM) and first generation Grubbs catalyst (10 mol%) was a problem. Therefore, the author optimized the reaction conditions to solve the problem. Thus, the author found that the use of 1 mol% of second generation Grubbs catalyst reduced the amount of solvent (20 mM) without decrease in yield. In the next conversion of the resulting bicyclic ether **2-14** to triflate **2-19**, the previous method, in which the triflate was purified, was found to provide significant decrease in yield in large scale synthesis due to instability of **2-19** to silica gel. Therefore, triflate **2-19** was used immediately without purification in the next installation of a dimethyldithioacetal mono-*S*-oxide moiety, and the yield of the AB-ring **1-60** was improved (96% for 2 steps). Thus, AB-ring **1-60** was synthesized from **2-1** in 16 steps in 19% yield, and all above reactions were demonstrated to be available for decagram scale synthesis.



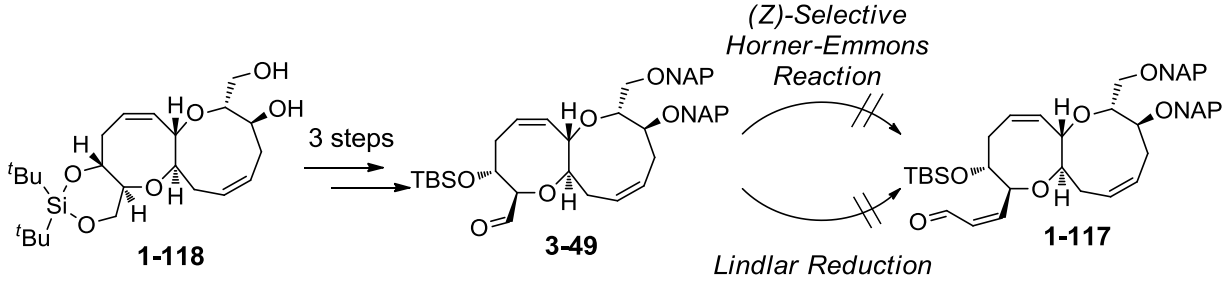
Scheme 6-2. Synthesis of AB-ring **1-60**

EF-Ring **3-66** was constructed via bicyclic ether **1-118**, synthesized previously by Nogoshi (Scheme 6-3). During the preparation of **1-118** by Nogoshi's procedure, low reproducibility in the Ireland-Claisen rearrangement of **3-7** using TMSCl as a silylation agent was found to be a problem. The author discovered the undesired generation of α-silylated ester during the reaction, which caused the problem. Therefore, the author optimized the silylation agent for the enolate formation step in the rearrangement and found that Me_2SiCl_2 showed good yield and reproducibility. As a consequence, bicyclic ether **1-118** was prepared from D-glucose (**1-65**) in 32 steps.



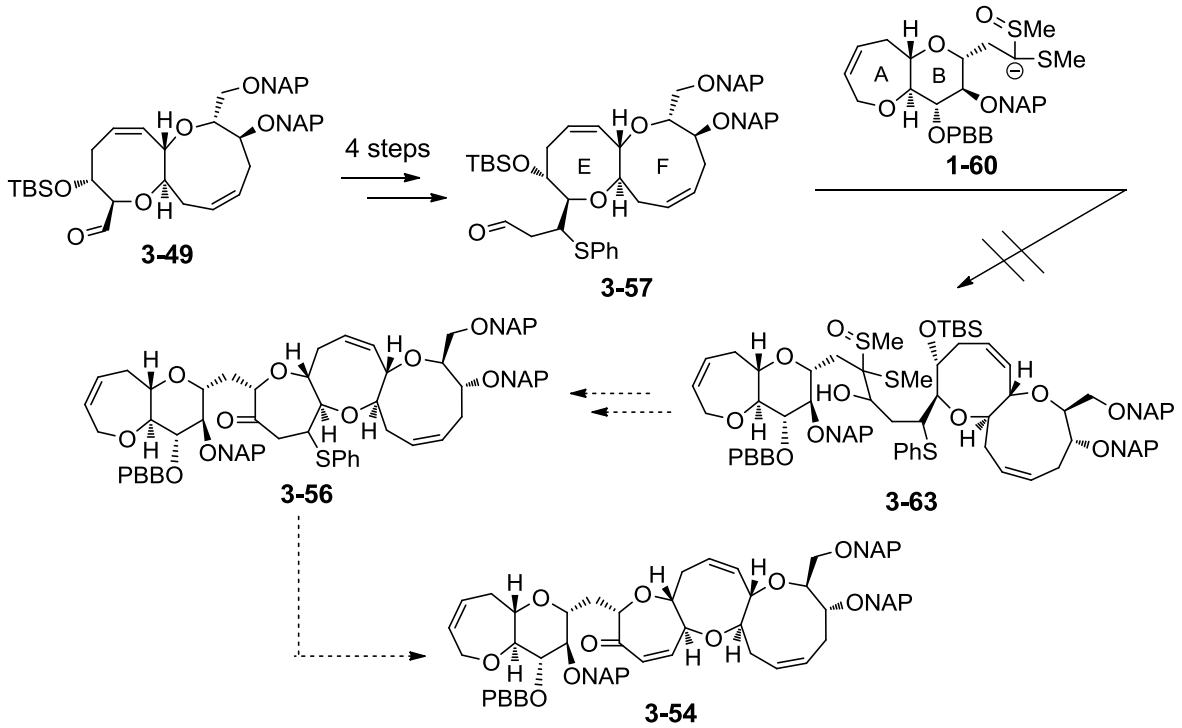
Scheme 6-3. Formation of EF-ring framework

On the contrary to the previous synthesis of E-ring aldehyde **1-61** by Goto (Scheme 1-6), the attachment of (*Z*)-α,β-unsaturated aldehyde moiety to the E-ring of **1-118** was problematic. As shown in Scheme 6-4, the attempts to construct the (*Z*)-α,β-unsaturated aldehyde using (*Z*)-selective Horner-Emmons reaction or Lindlar hydrogenation were failed. Horner-Emmons reaction of aldehyde **3-49** resulted in low (*E*)/(*Z*)-selectivity, and Lindlar hydrogenation of an alkyne derived from **3-49** was very sluggish and afforded trace amount of the corresponding alkene.



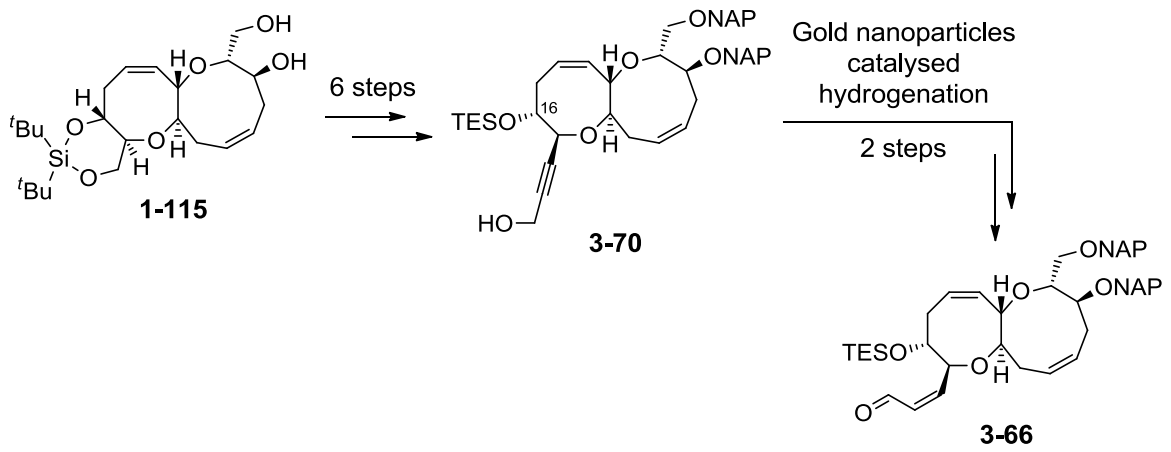
Scheme 6-4. Attempts at attachment of (*Z*)-olefin

Then, the author planned to install the (*Z*)-olefin at C13-C14 after formation of the D-ring via elimination of a sulfide at C14 (Scheme 6-5). However, EF-ring **3-57** having a sulfide at C14, prepared from **3-49**, was unstable and was decomposed under the conditions of anion coupling with AB-ring **1-60**.



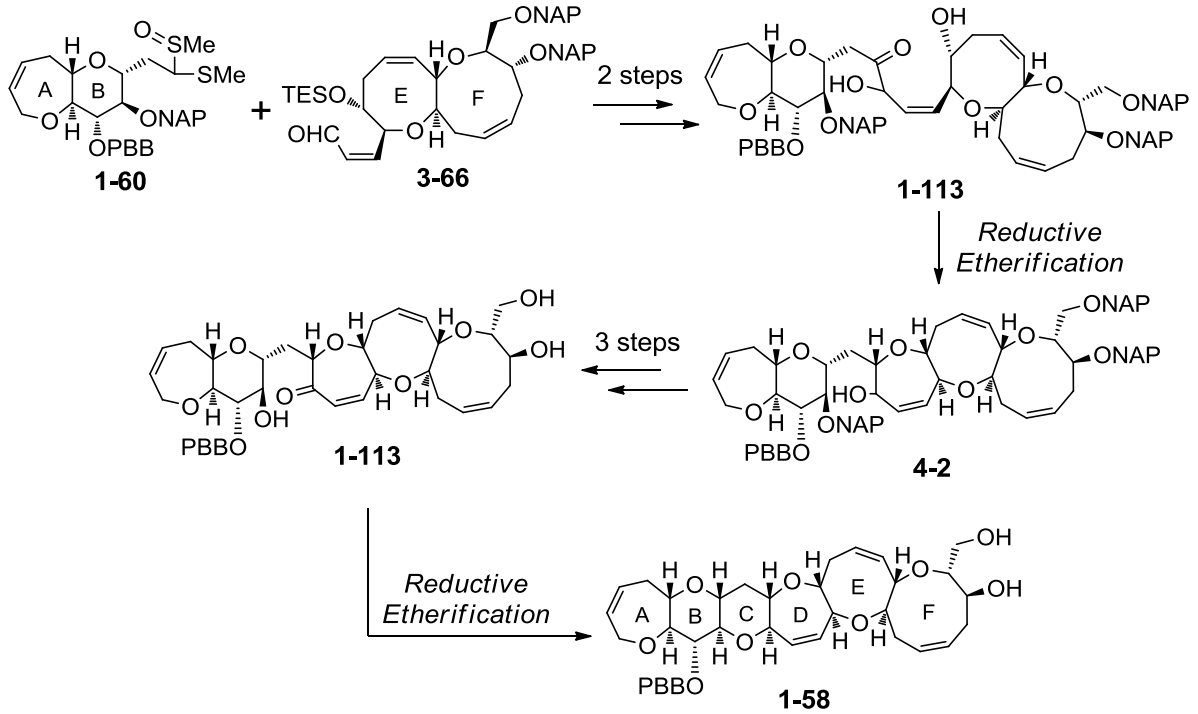
Scheme 6-5. Attempt to construct the (*Z*)-olefin at C13-C14 after the coupling reaction

Alternatively, the author found that alkyne **3-70** having a small TES group at O16 was facilely hydrogenated with gold nanoparticles catalyst and $Me_2NH \cdot BH_3$ to give the corresponding (*Z*)-alkene smoothly, thereby establishing the route to EF-ring **3-66**. (Scheme 6-6).



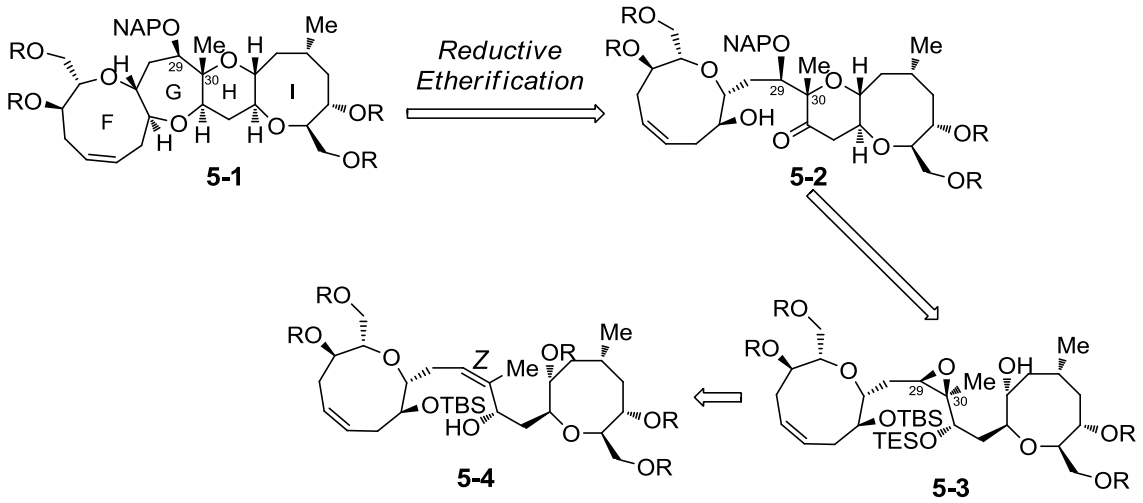
Scheme 6-6. Successful synthesis of EF-ring **3-66**

Finally, ABCDEF-ring **1-58** was synthesized from AB-ring **1-60** and EF-ring **3-66** (Scheme 6-7). The deprotonation of AB-ring **1-60** with NHMDS followed by the reaction with **3-66** produced an adduct, which was subsequently hydrolyzed with PTS·H_2O in CF_3CH_2OH-H_2O to give α,ε-dihydoxy ketone **1-113** in an acceptable yield. Afterward, a process including stepwise reductive etherification constructed the C- and D-rings to furnish ABCDEF-ring **1-58**. The stereostructure of **1-58** was confirmed by X-ray crystallographic analysis. Thus, the author achieved the synthesis of ABCDEF-ring **1-58** of CTX3C from AB-ring **1-60** and EF-ring **3-66** in 7 steps in 6.9% yield (from **3-66**).



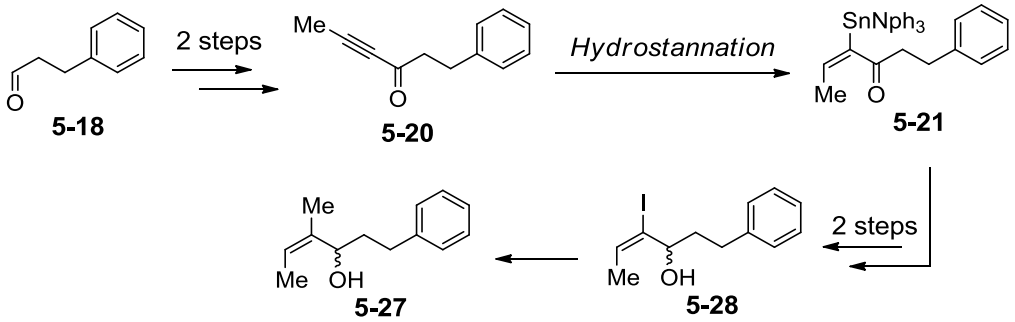
Scheme 6-7. Synthesis of ABCDEF-ring **1-58**

The previous synthesis of the FGHI-ring by Takizawa and Doi, including stereo-inversion at C29 and very slow reaction step, was somewhat inefficient. Therefore, the author planned a new synthetic route for the FGHI-ring from (*Z*)-alkene **5-4** without inefficient steps (Scheme 6-8). FGHI-ring **5-1** was intended to be constructed from ε-hydroxy ketone **5-2** via the formation of the G-ring by reductive etherification. FHI-ring **5-2** would be synthesized by cyclization of hydroxy epoxide **5-3**, which would be derived from (*Z*)-allylic alcohol **5-4** by diastereoselective epoxidation. Because the stereochemistries at C29 and C30 of **5-1** result from the stereochemistry at C31 and the (*Z*)-geometry of the alkene at C29 of **5-4**, (*Z*)-Alkene **5-4** is a key intermediate in the synthesis.



Scheme 6-8. New synthetic plan of FGHI-ring

The construction plan for (*Z*)-alkene **5-4**, including acetylide coupling of the F- and I-rings and (*Z*)-alkene formation, was investigated using model compounds (Scheme 6-9). 3-phenylpropanal (**5-18**) was transformed to alkynone **5-20**, which was hydrostannated with Nph_3SnH to give α-stannyl enone **5-21** selectively. While the direct methylation of **5-21** was failed, a stepwise process including reduction of the ketone, iodination, and methylation of the resulting **5-28** with Me_2CuLi produced alkene **5-27** successfully. The author believes that this method would be available for (*Z*)-alkene **5-4**.



Scheme 6-9. Construction of (*Z*)-trisubstituted alkene **5-27** in a model system

The author hopes that these studies will make a contribution to the completion of the total synthesis of CTX3C and that the synthetic CTX3C will be readily available for biological research.

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