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Synthetic Studies on the BCD-Ring of Armatol F

**Keita Tanaka
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Abbreviations

Ac	acetyl
Ar	aryl
BBN	borabicyclononanyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
coll	2,4,6-collidine
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
d	day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DHP	3,4-dihydro-2 <i>H</i> -pyran
DIBAH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMPI	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq	equivalent
Et	ethyl
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro- <i>iso</i> -propanol
HWE	Horner-Wadsworth-Emmons
IBX	2-iodoxybenzoic acid
IR	infrared absorption spectroscopy
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide

Mc	monochloromethanesulfonyl
Me	methyl
Mes	2,4,6-trimethylphenyl
min	minute(s)
MOM	methoxymethyl
Ms	methanesulfonyl
MS	mass spectrometry
MS 4A	molecular sieves 4 angstrom
NBS	<i>N</i> -bromosuccinimide
NBSH	<i>N</i> -2-nitrobenzensulfonyl hydrazine
NHMDS	sodium hexamethyldisilazide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
Oct	octyl
Ph	phenyl
Piv	pivaloyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
PPTS	pyridinium 4-toluenesulfonate
<i>i</i> -Pr	isopropyl
RCM	ring-closing olefin metathesis
RRCM	relay ring-closing olefin metathesis
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butylhydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography

TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	4-toluenesulfonyl

Chapter 1.

Introduction

1-1. Background

In nature, a diverse set of secondary metabolites are produced by living organisms. Some of them possess strong and useful bioactivities, which have been expected as an important tool for the research in the field of biological science or a new lead-compound for pharmaceutical and agricultural industries.¹ However, imperfect stereochemical information of the secondary metabolites² and difficulty in obtaining sufficient supply of the compounds, due to the limited amount available from nature, often interfere the progress of the researches using the compounds. At present, synthetic organic chemistry is expected to play a significant role to solve such problems of unknown stereochemistry and scarcity of promising natural products. In fact, through total synthesis, stereochemical assignment and material supply of a great number of natural products have been accomplished successfully.³ However, although synthetic organic chemistry is still presenting a brilliant progress, represented partly by the development of various catalytic asymmetric reactions in recent years, increasing structural complexity and decreasing isolation amount of newly isolated natural products owing to the progress of natural products chemistry has increased the severeness of the above problems, thereby increasing difficulty in solving the problems by synthetic organic chemistry.

By the way, since the land of the earth is surrounded by the sea, many people who live near the sea are familiar with seafood, and many kinds of fish and shellfish as well as seaweed from the sea near the shore have been eaten by such people. Hence, they have shared a lot of knowledge about assessment and management of seafood safety: especially, they have concerned about fatal seafood poisoning, such as puffer-fish poisoning, which has been feared Japanese people since ancient times. In this context, many researchers have long engaged in the investigations of toxins from marine organisms, and various marine natural products have been isolated and structurally assigned since early 20th century (Figure 1-1).⁴ Among the marine natural products, tetrodotoxin (**1-1**), isolated as a toxin of puffer-fish poisoning by Tahara and coworkers in 1907,⁵ is one of the most famous compounds. The structure was proposed independently by Hirata,⁶ Tsuda,⁷ and R. B. Woodward in 1964,⁸ and the absolute stereochemistry of **1-1** was confirmed through X-ray crystal structure analysis by Furusaki, Tomiie, and Nitta in 1970.⁹ These marine natural products are

secondary metabolites produced mainly by bacteria or dinoflagellates,¹⁰ and some of these are known to be accumulated in living bodies of fish and shellfish through food chain process.¹¹ Thus, marine natural products have long attracted attention of researchers due to their strong bioactivity or toxicity, and the intensive structural and biological analyses on them have elucidated their unique structures and biological properties.

As shown in Figure 1-1, some marine natural products have unique structures including a number of oxygen functional groups and cyclic-ether systems, and such complex polycyclic ether structures inspired synthetic organic chemists including the author to perform the total synthesis of them.^{9,12} In fact, the synthetic studies on polycyclic ether natural products have been carried out by many synthetic chemists around the world, and as a result, several total syntheses of some polycyclic ether compounds have been reported since late 20th century.³ However, because of the complexity of their multicyclic structure and large molecular size with many asymmetric centers, the synthesis of polycyclic ethers generally took a long process for cyclization and asymmetric induction. Therefore, at present, more efficient methodologies are required for constructing the rings and the stereocenters in the total synthesis of polycyclic ethers.

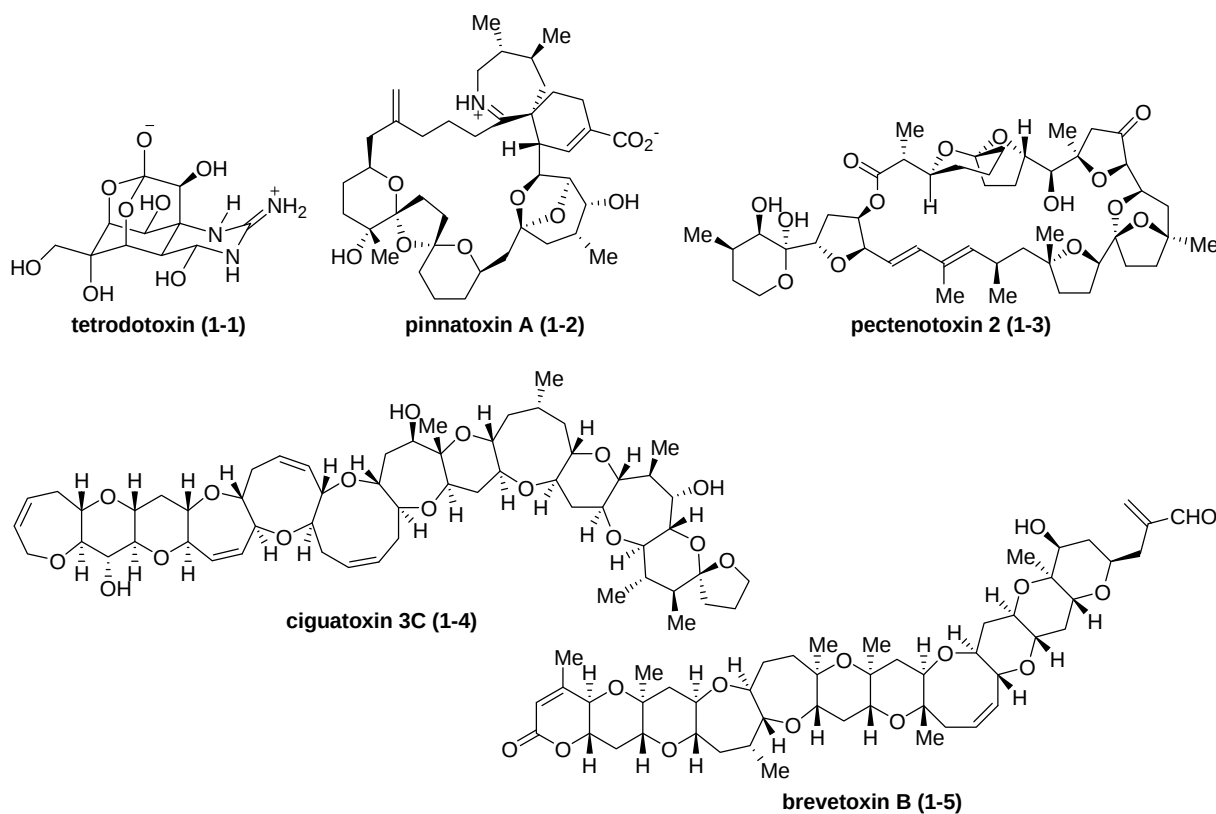


Figure 1-1. Representative marine toxins.

1-2. Armatol F and armatol family

The author have interested in the unique and complex structure of marine polycyclic ethers, described in the preceding section, from the stand point of a synthetic organic chemist. Thus, the author selected armatol F (**1-6**) (Figure 1-2) as a target compound for the synthetic study of this dissertation work, because armatol F has a distinctive triterpene polyether framework with a *cis*-ring fusion, which has not been synthesized.

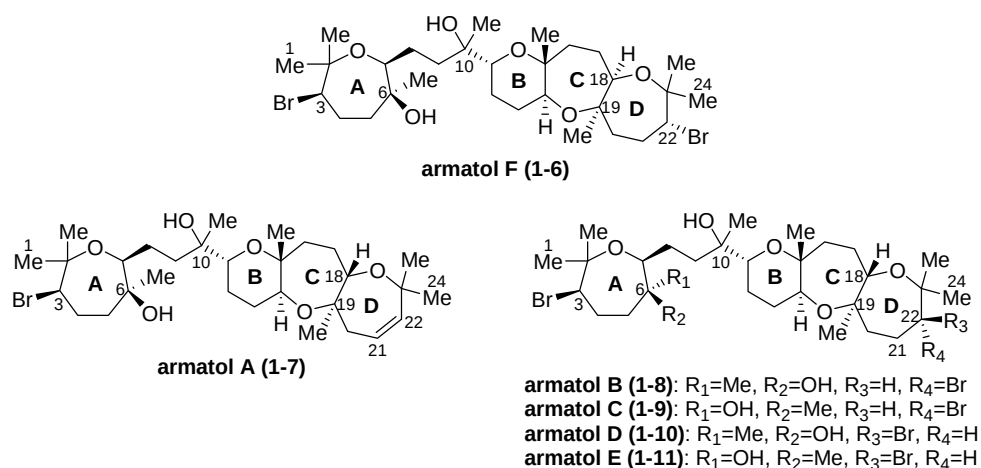


Figure 1-2. Structures of armatols A-F reported by Ciavtta.

Armatol F (**1-6**) was isolated as a new type of fused triterpe polyether from the red alga *Chondria armata* along with five analogs (**1-7**, **1-8**, **1-9**, **1-10**, and **1-11**) by Ciavatta and coworkers in 2000 (Figure 1-2).¹³ The structure of **1-6** is featured by a solitary oxepane with a tertiary hydroxyl group at C6 (A-ring), a 6,7,7'-fused tricyclic ether system (BCD-ring), and a propylene chain with a tertiary hydroxyl group at C10, which connects the A-ring with the BCD-ring. It is notable that **1-6** has a *cis* ring fusion at C18-19 between the C- and D-rings. A *cis*-ring fusion in a fused polycyclic ether system is rare,¹⁴ because fused polycyclic-ether natural products generally have a *trans* ring fusion in every ring-junction as seen in ciguatoxin 3C (**1-4**)¹⁵ and brevetoxin B (**1-5**)¹⁶ in Figure 1-1. Four oxygen-bound tetrasubstituted stereocenters (C6, C10, C15, and C19) and two bromine groups at opposite ends (C3 and C22) of the skeleton also reveal the uniqueness of **1-6**. As for the stereochemical information, although the respective partial relative configurations of the A- and BCD-rings have been determined by NMR experiments, the full assignment of the

absolute configuration of **1-6** including the stereochemistry at C10 remains unaccomplished. At present, there is no report of the synthesis and bioactivity of **1-6**. Thus the author has been attracted to the uniqueness of **1-6** and has undertaken the studies toward total synthesis of **1-6** aiming at full assignment of absolute stereochemistry and material supply for biological research.

The five analogues of **1-6**, mentioned above, possess a similar skeleton: A-ring, BCD-ring, and a propylene connection part. However, all armatol analogues except **1-6** have a *trans* ring fusion at C18-19. Furthermore, the configurations at C6 and C22 of them are different from each other. Armatols B-E are diastereomers at C6 and C22, and armatol A has a structure that would result from the elimination of hydrogen bromide at C21-22 of armatol B or D. Similarly to **1-6**, the stereochemical information of armatols B-E is limited to the respective partial relative configurations of the A- and BCD-rings, and full assignment of their absolute stereochemistries is uncompleted. There are also no reports of their synthesis and bioactivity.

On the other hand, partial absolute stereochemistry of armatol A (**1-7**) has been reported. After chemical degradation of **1-7** by reductive cleavage of the bromo ether parts, the resulting alcohol was subjected to modified Mosher's method, and the absolute configurations of C3, C6 and C7 of **1-7** were determined to be (3*R*,6*S*,7*S*). The structural similarity of armatols suggested that all armatol analogues would have the same (3*R*,7*S*)-configuration. The suggestion limited the number of possible stereostructures for the correct absolute stereochemistry of each armatol analogue to four stereostructures.

Just recently, the total synthesis of armatol A was reported by Jamison's group.¹⁷ They also proposed the correct structure of natural armatol A as **1-12** (Figure 1-3) through the comparison of the NMR data between synthetic products and natural armatol A. Although the stereochemistry at C10 of synthetic compound was only deduced to be (*R*)-configuration based on the reaction mechanism in the C10 methylation reaction, the accordance of NMR spectra of synthetic compound with those of the natural product clearly demonstrated the completion of the total synthesis of armatol A.

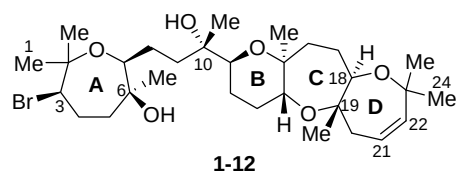


Figure 1-3. Absolute configuration of armatol A proposed by Jamison.

1-3. Polyether triterpenes

One of the earliest reports of structural determination of fused polycyclic ether natural products is that of brevetoxin B (**1-5**) by Nakanishi in early 1980's.¹⁸ Since then, many fused polycyclic ethers have been isolated.¹¹ These are classified into two groups: one group includes polyketides from dinoflagellates, represented by brevetoxin B (**1-5**) and ciguatoxin 3C (**1-4**), and the other consists of triterpenes from red algae. The two different but similar modes of biogenesis of fused polycyclic ethers were proposed for brevetoxin B independently by Nakanishi¹⁵ and Shimizu¹⁹, respectively (Figure 1-4): the fused polycyclic ether skeleton of brevetoxin B would be biosynthesized from a polyepoxide precursor (**1-13** or **1-14**) through a cascade of *endo*-mode epoxide ring opening reactions. The biogenesis is now widely accepted for both polyketide and triterpene polyethers.

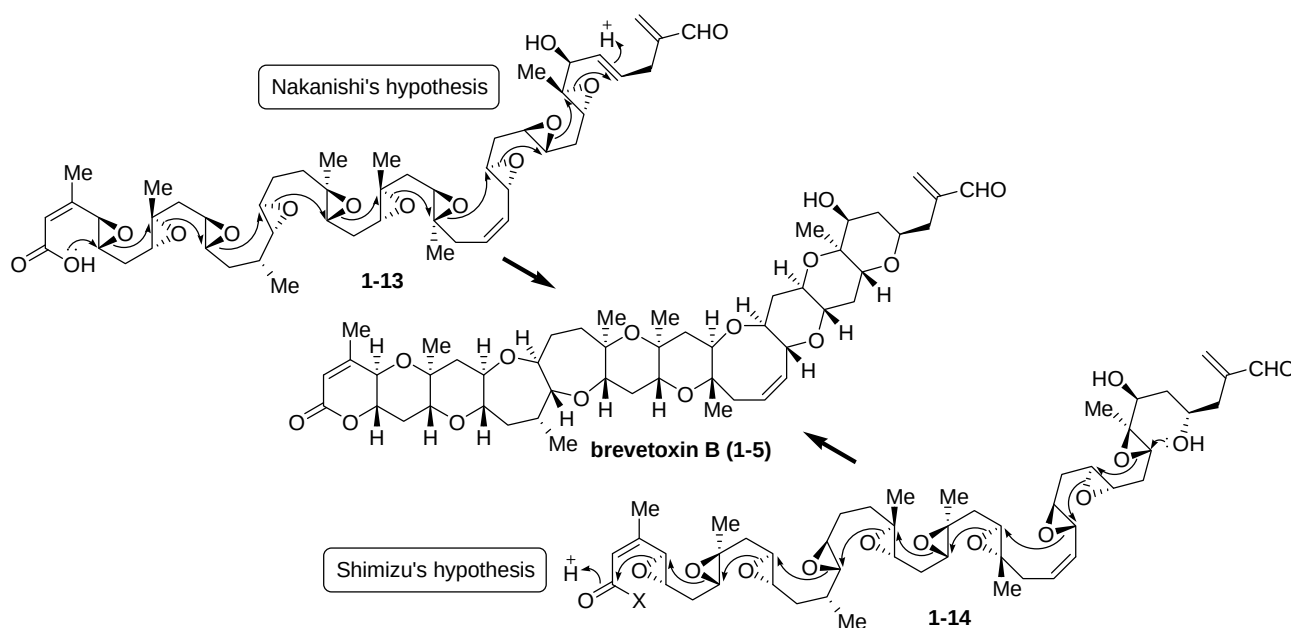


Figure 1-4. Two modes of biogenesis of brevetoxin B (1-5**) proposed by Nakanishi and Shimizu.**

Triterpene fused polycyclic ethers were isolated mainly from *Chondria* and *Laurencia* genera of red algae.^{20,21} The triterpene polyethers are structurally featured by a highly oxygenated squalene skeleton and separated cyclic ether systems as exemplified in Figure 1-5. In addition, these often have one or more halogen atoms, mostly bromine atoms, at the terminal of the skeleton.

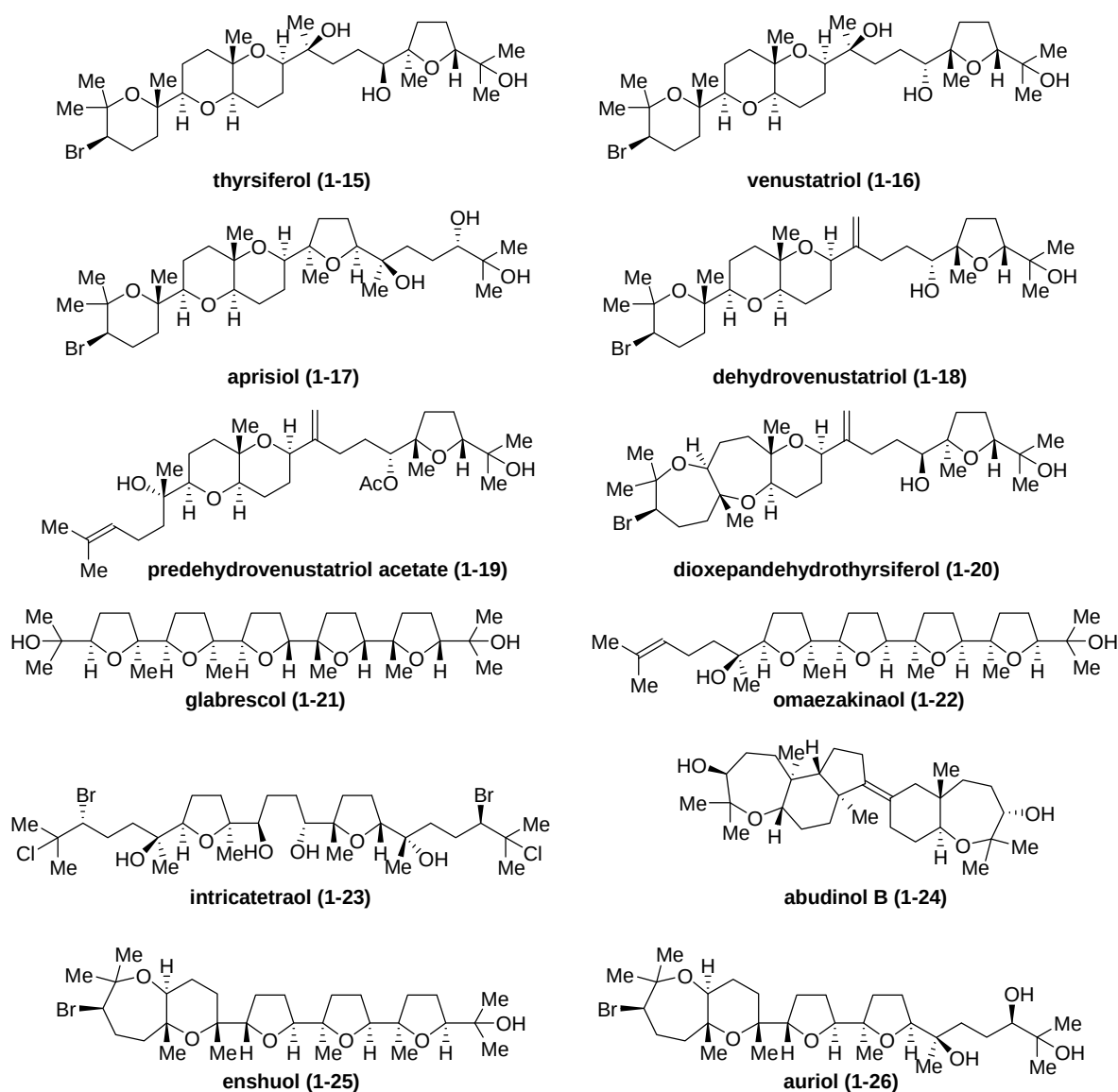


Figure 1-5. Reprensative triterpen polyether natural products.

Some bromopolyethers are thought to be biosynthesized via a process including independent haloetherification and polyepoxide ring opening reactions.²¹ For example, dioxepandehydrothysiferol (**1-20**), isolated from *Laurencia viridis* by Fernández and coworkers in 2001, was assumed to be constructed *in vivo* through the following process (Figure 1-6).²² First, (10*R*,11*R*)-squalene-10,11-epoxide (**1-27**), which has been proved to be generated by red alga *Laurencia okamurai*,²³ would be converted to tetraepoxide **1-28**. An acid catalyzed cascade of 6-*endo* and 7-*endo* epoxide-opening reactions of **1-28** would produce BC-ring **1-29**. After epoxidation of olefin at C2 of **1-29**, the resulting **1-30** would be cyclized by acid-mediated 5-*exo* epoxide-opening reaction to form **1-31**. Finally, elimination of tertiary alcohol at C10 and

bromoetherification in a 7-*endo* fashion constructing the D-ring would produce **1-20**.

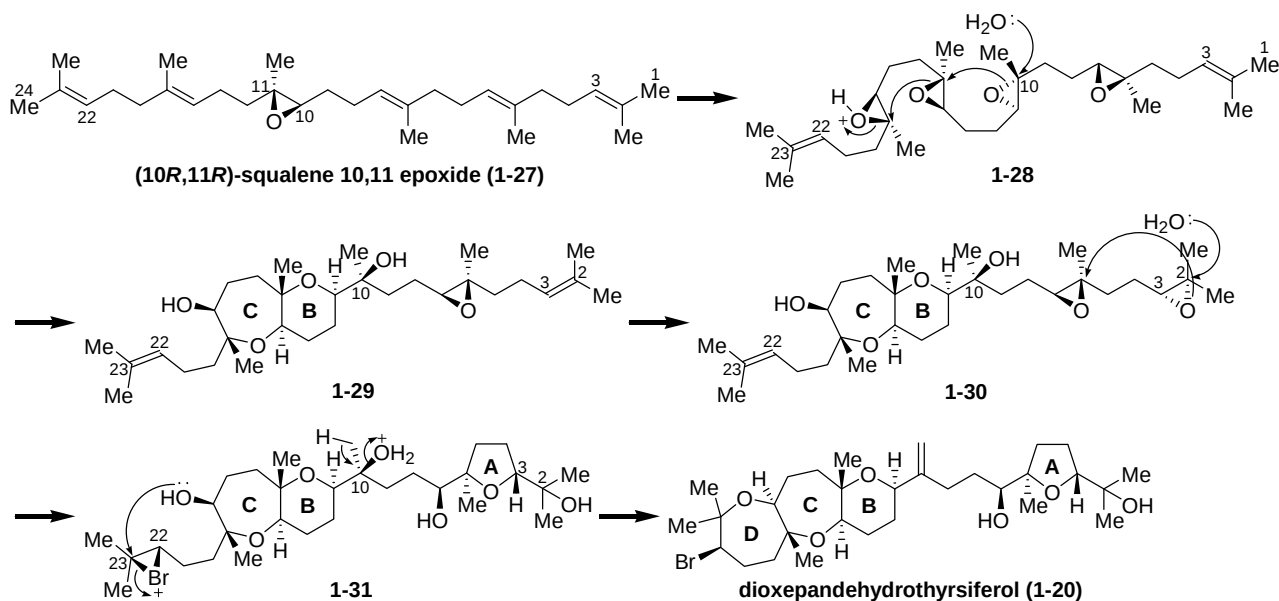
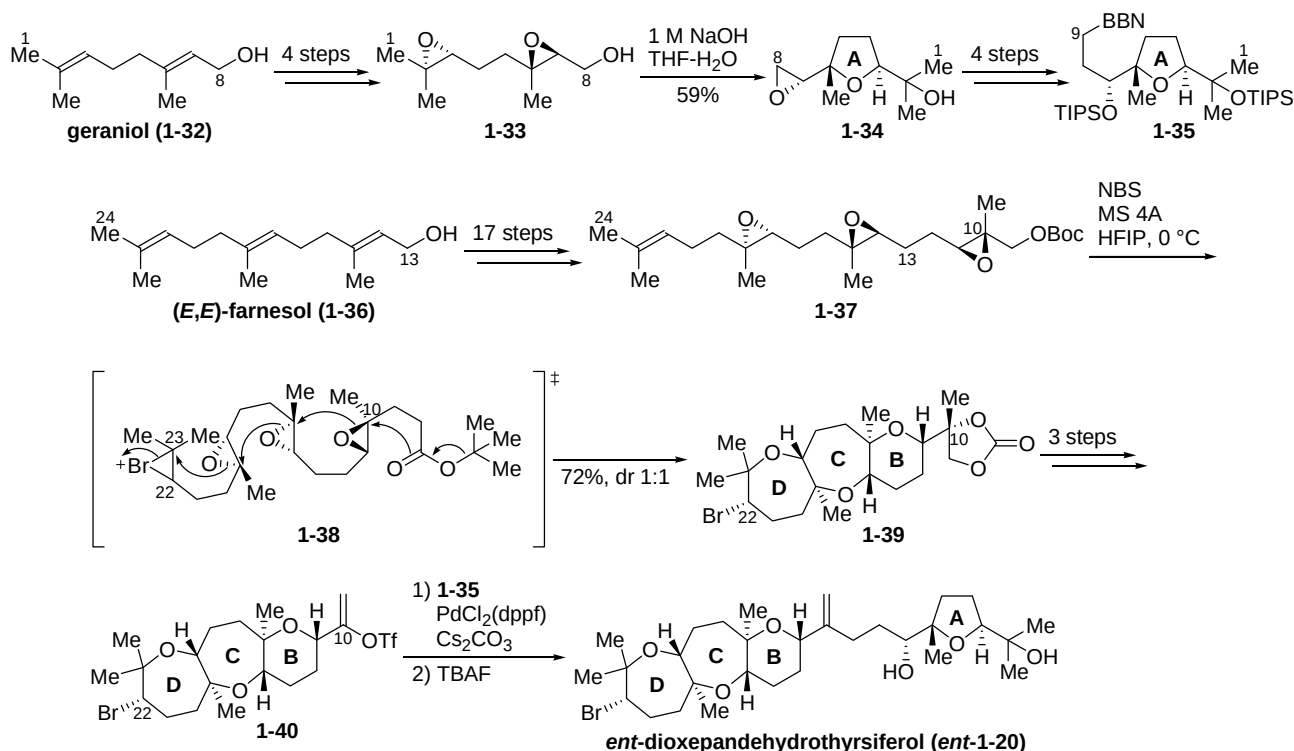


Figure 1-6. Fernández's biogenetic hypothesis of dioxepanedehydrothysiferol (1-20**).**

On the other hand, a biogenesis, in which an epoxide-opening cascade is initiated by formation of a bromonium ion, has been proposed for thysiferol (**1-15**),²⁴ venustatriol (**1-16**),²⁵ enshuol (**1-25**),²⁶ and auriol (**1-26**).²⁷

Based on this hypothesis, Jamison's group studied the bromonium-initiated epoxide-opening reaction and has achieved the first total synthesis of *ent*-dioxepanedehydrothysiferol (*ent*-**1-20**) by application of the biomimetic reaction.²⁸ Initially, geraniol (**1-32**) was transformed to diepopoxide **1-33**, which was reacted with NaOH in THF/H₂O to construct A-ring **1-34** via Payne rearrangement. Additional four steps gave intermediate **1-35**. Then, the BCD-ring was synthesized via the biomimetic bromonium-initiated epoxide-opening reaction. After triepoxy ester **1-37** was synthesized from (*E,E*)-farnesol (**1-36**) through a process including Katsuki-Sharpless asymmetric epoxidation,²⁹ Shi epoxidation,³⁰ and Wittig reaction,³¹ **1-37** was treated with NBS in HFIP at 0 °C to generate bromonium ion specie **1-38**. As a result, an epoxide-opening reaction cascade proceeded in an all-*endo* fashion to construct a *trans*-fused 6,7,7-tricyclic ether system successfully in one operation, though the orientation of the bromine group at C22 was unselective (dr 1:1). Finally, compound **1-39** was converted to triflate **1-40**, which

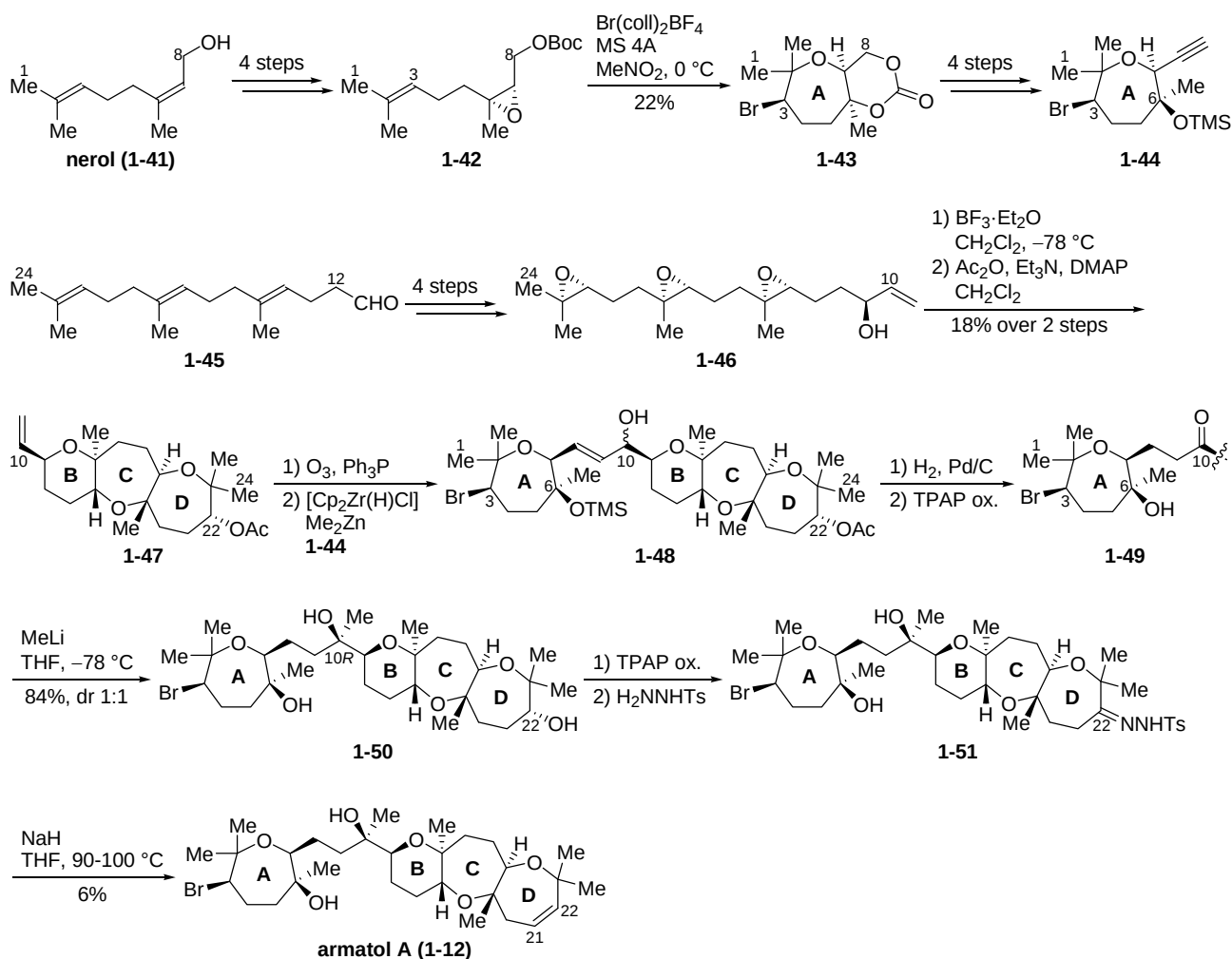
was then connected with C1-C9 fragment **1-35** by Suzuki-Miyaura coupling³² to complete the total synthesis of *ent*-**1-20**.



Scheme 1-1. Total synthesis of *ent*-dioxepanedehydrothysiferol (*ent*-**1-20**) by Jamison's group.

In the wake of the successful synthesis of *ent*-**1-20**, Jamison applied their methodology to the total synthesis of armatol A (**1-12**) (Scheme 1-2).¹⁷ First, nerol (**1-41**) was transformed to epoxy ester **1-42** via Katsuki-Sharpless asymmetric epoxidation²⁹ and enzymatic resolution.³³ Then, the bromonium-initiated 7-*endo* cyclization of **1-42** using Br(coll)₂BF₄ in the presence of molecular sieves 4 Å in nitromethane at 0 °C produced the desired bromo-oxepane (**1-43**, 22%), which was converted to alkyne **1-44** as an A-ring segment. The synthesis of the BCD-ring fragment was commenced from aldehyde **1-45**,³⁴ which was transformed to triepoxide **1-46** via vinyl metal addition, enzymatic resolution, and Shi asymmetric epoxidation. Treatment of **1-46** with BF₃·Et₂O induced a Lewis acid-initiated epoxide-opening cascade in an all-*endo* fashion to construct BCD-ring **1-47** in 18% yield from **1-46** after acetylation. Ozonolysis of **1-47** followed by the Schwartz's reagent mediated reaction with alkyne **1-44** to provide allyl alcohol **1-48**,³⁵ which was converted to ketone **1-49**. The reaction of **1-49** with methyllithium in THF at −78 °C gave **1-50** as a 1:1 mixture

of C10 epimers. Compound (10*R*)-**1-50**, which could also be obtained by the reaction of **1-49** with MeMgBr, was transformed to **1-12** via Bamford-Stevens reaction.³⁶ The ¹H/¹³C NMR and optical rotation data of **1-12** were almost identical to those of natural armatol A. Thus, the first total synthesis and determination of absolute stereochemistry of armatol A have been achieved.



Scheme 1-2. Total synthesis of armatol A by Jamison's group.

1-4. Model synthesis of the BC-ring of armatol F

For the total synthesis of armatol F (**1-6**), which has a unique fused tricyclic system including a *cis* ring fusion, the author planned a non-biomimetic synthesis. Although the BCD-ring of **1-6** has a similar framework with that of dioxepanedehydrothysiferol (**1-20**),^{22,28} they have different ring-fusion pattern and C22-configuration. Therefore, the application of the bromonium-mediated biomimetic cascade cyclization, which successfully provided the BCD-ring of **1-20**, to the construction of the BCD-ring of **1-6** was hesitated. Alternatively, the author intended to apply a non-biomimetic synthesis for the BCD-ring of **1-6**.

At the beginning of the synthetic study on **1-6**, the author planned the connection of the A- and BCD-ring segments at the final stage of the synthesis. According to this plan, aldehyde **1-52** (Figure 1-7) was decided to be a BCD-ring segment. In the synthesis of **1-52**, there were three problems: (i) stereoselective construction of the *syn*- β -alkoxy ether structure corresponding to the CD-ring junction at C18-19 including an oxygen-bound tetrasubstituted stereocenter (C19), (ii) formation of two fused 7-membered cyclic ethers (the C- and D-rings), and (iii) installation of bromine group to sterically hindered C22 position.

First, in order to solve the above problems (i) and (ii), the author examined the syntheses of the C- and BC-ring models (**1-53** and **1-54**, respectively) in advance of the assembly of BCD-ring **1-52**.³⁷

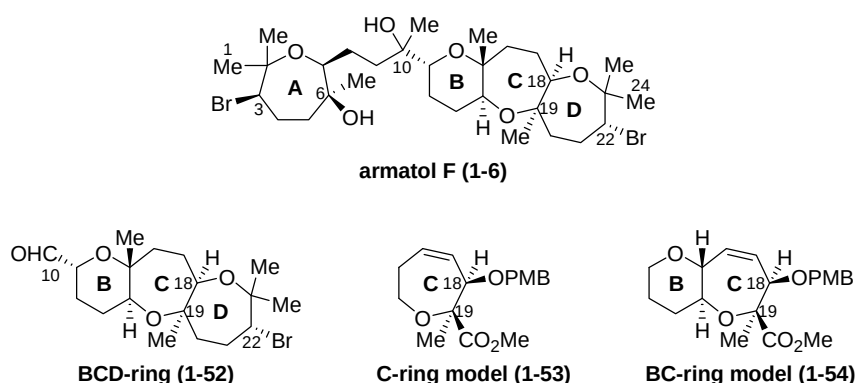
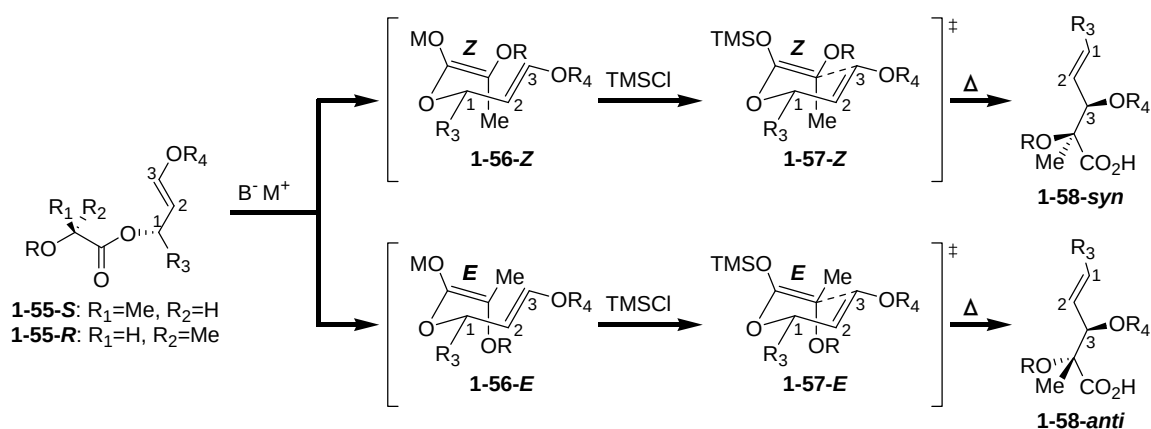


Figure 1-7. Structures of the BCD-ring (**1-52**), the C-ring model (**1-53**), and the BC-ring model (**1-54**).

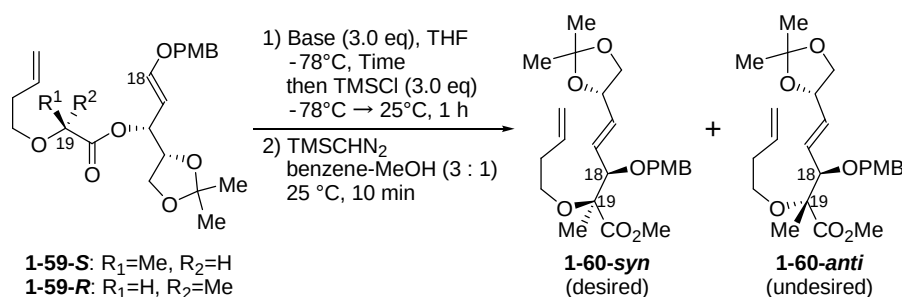
For the stereoselective construction of the *syn*- β -alkoxy ether corresponding to C18-19 position, an approach based on a chirality transferring Ireland-Claisen rearrangement,^{38, 39} developed by the author's research group,⁴⁰ was adopted (Scheme 1-3). In this approach, *E*-3-alkoxyallyl lactate ester **1-55** was employed as a substrate for the rearrangement. If *Z*-ketene silyl acetal **1-57-Z** is generated from **1-55** via *Z*-enolate **1-56-Z**, Ireland-Claisen rearrangement would proceed with rising temperature to produce a *syn*- β -alkoxy ether with an oxygen-bound tetrasubstituted stereocenter (**1-58-*syn***) via a stable chair-formed transition state with equatorial R³ group at C1. During the rearrangement, the stereochemistry at C1 would be transferred to C3. On the other hand, if *Z*-ketene silyl acetal **1-57-E** arises from **1-55** via *E*-enolate **1-56-E**, undesired rearrangement product **1-58-*anti*** would be formed by the rearrangement. The selective formation of *Z*-enolate **1-56-Z** is critical for the desired stereoselectivity. Hence, the author first explored the optimal conditions for the rearrangement using model substrates **1-59-S/R**.



Scheme 1-3. Plausible mechanism for the chirality transferring Ireland-Claisen rearrangement of 1-55.

First, simple esters **1-59-S** and **1-59-R** were prepared separately in order to investigate the influence of the diastereotopic relationship between stereocenters of the lactate ester and C1 on the *E/Z*-selectivity of enolate formation. The results of the Ireland-Claisen rearrangement of **1-59-S** and **1-59-R** are shown in Table 1-1. Each ester was treated with LDA or KHMDS in THF at $-78\text{ }^{\circ}\text{C}$ for 10 or 30 min and then with TMSCl at $-78\text{ }^{\circ}\text{C}$, and the resulting ketene silyl acetal was rearranged by warming to ambient temperature to produce carboxylic acids, which were converted to **1-60-*syn***

and **1-60-anti** by methylation with TMS-diazomethane. Both LDA and KHMDS produced desired **1-60-syn** as a major product along with **1-60-anti** (entries 1–8). Increasing time of LDA exposure did not affect the selectivity of **1-60-syn** but slightly decreased the yield (entries 1, 2, 5, and 6). Although the treatment of **1-59-S** with KHMDS showed a good ratio of **1-60-syn** (>20–9:1), longer treatment of **1-59-S** or **1-59-R** with KHMDS decomposed the substrate and decreased the yield (entries 3, 4, 7 and 8). Thus, the Ireland-Claisen rearrangement of simple *E*-3-alkoxyallyl lactate esters **1-59-S** and **1-59-R** was found to produce the desired *syn*- β -alkoxy ether with an oxygen-bound tetrasubstituted stereocenter in moderate-to-high selectivity.

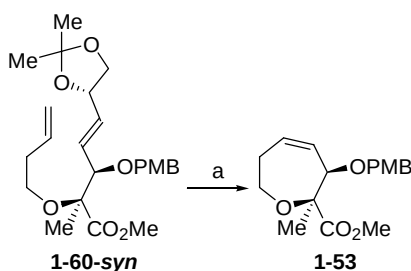


Entry	Substrate	Base	Time	Yield (3 steps ^a) (<i>syn</i> + <i>anti</i>)	<i>syn</i> : <i>anti</i>
1	1-59-S	LDA	10 min	74%	3.0 : 1.0
2		LDA	30 min	67%	3.0 : 1.0
3		KHMDS	10 min	53%	9.0 : 1.0
4		KHMDS	30 min	16%	>20 : 1.0
5	1-59-R	LDA	10 min	74%	4.0 : 1.0
6		LDA	30 min	57%	4.0 : 1.0
7		KHMDS	10 min	58%	3.0 : 1.0
8		KHMDS	30 min	Decomposition	—

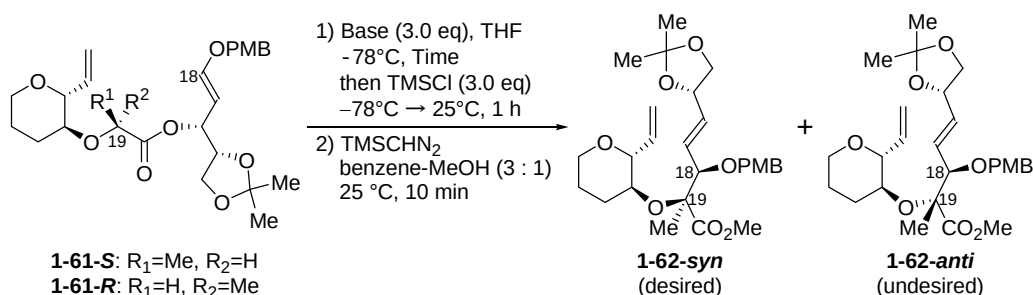
Table 1-1. Examination of the Ireland-Claisen rearrangement using simple esters **1-59-S and **1-59-R**.**

(a) The steps include the esterification step to afford **1-59-S** or **1-59-R**.

Next, cyclization of **1-60-syn** by ring-closing olefin metathesis (RCM)⁴¹ was examined as a solution for the problem (ii). When diene **1-60-syn** was treated with the 2nd generation Grubbs' catalyst,⁴² the diene was directly cyclized to give 7-membered ring ether **1-53**, corresponding to the C-ring, in 67% yield (Scheme 1-4).



Scheme 1-4. Cyclization to 1-53 by RCM. Reagents and conditions: (a) the 2nd generation Grubbs' catalyst (0.1 eq), (CH₂Cl)₂, reflux, 16 h, 67%.



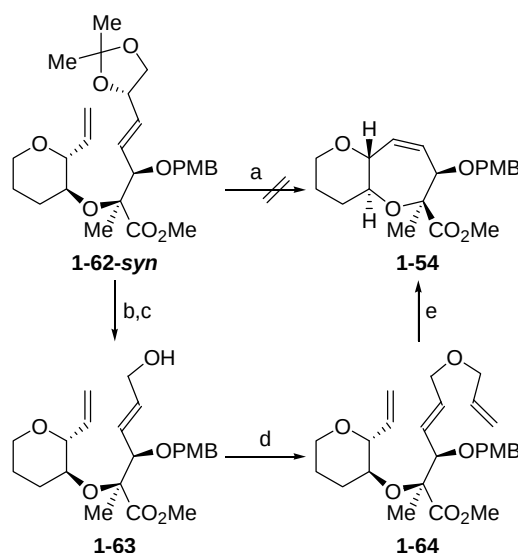
Entry	Substrate	Base	Time	Yield (2 steps) (<i>syn</i> + <i>anti</i>)	<i>syn</i> : <i>anti</i>
1	1-61-S	LDA	10 min	59%	1.0 : 4.0
2		LDA	30 min	35%	1.0 : 4.0
3		KHMDS	10 min	No reaction ^a	—
4		KHMDS	30 min	No reaction ^a	—
5	1-61-R	LDA	10 min	66%	1.0 : 4.0
6		LDA	30 min	62%	1.0 : 4.0
7		KHMDS	10 min	53%	9.0 : 1.0
8		KHMDS	30 min	26%	16 : 1.0

Table 1-2. Examinaiton of the Ireland-Claisen rearrangement using THP-ring attached esters 1-61-S and 1-61-R. (a) Unreacted substrate was recovered.

In order to examine the influence of the presence of B-ring on the selectivity of the Ireland-Claisen rearrangement, esters with a THP-ring corresponding to the B-ring (**1-61-S** and **1-61-R**) were prepared selectively as substrates for the rearrangement. The rearrangement of **1-61-S** and **1-61-R** was performed under the same conditions as the above rearrangement of **1-59-S** and **1-59-R** (Table 1-2). It is notable that the LDA-promoted rearrangement of **1-61-S** and **1-61-R** afforded undesired **1-62-anti** as a major product (entries 1, 2, 5, and 6), contrary to the results from **1-59-S** and **1-59-R**. Interestingly, KHMDS was effective for **1-61-R** to produce desired **1-62-syn** with good selectivity (16:9:1) but was unproductive for **1-61-S** (entries 3, 4, 7, and 8). It was also

observed that the yield from **1-61-R** was decreased with increasing time of KHMDS exposure (entry 8). Although significant dependence of reactivity/stereoselectivity on the substrate structure was observed, the Ireland-Claisen rearrangement producing the required stereochemistry at C18 and C19 for armatol F (or its enantiomer) was thus optimized by applying the 10-min treatment with KHMDS to the (19*R*)-lactate substrate.

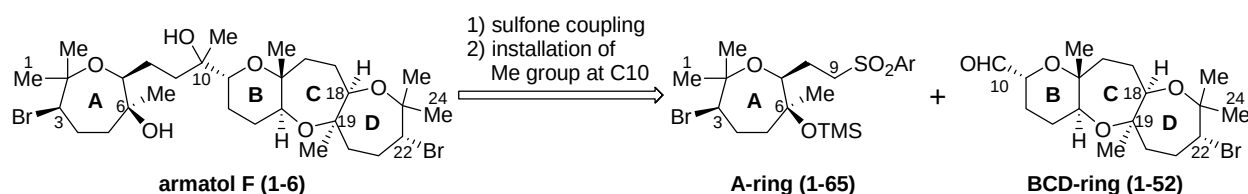
Subsequently, the construction of the C-ring by RCM was examined (Scheme 1-5). The direct cyclization of **1-62-syn** with the 2nd generation Grubbs' catalyst⁴² did not give BC-ring model **1-54**. This suggested that the steric hindrance around the terminal olefin of **1-62-syn** became higher than that of **1-60-syn** due to the presence of the THP-ring, which would disturb the access of the ruthenium catalyst to the terminal olefin. Therefore, a relay-type RCM (RRCM),⁴³ reported to be effective for preparing sterically hindered cyclic alkenes, was applied to the formation of the C-ring. After transformation of **1-62-syn** to triene **1-64**, the treatment with the 2nd generation Grubbs' catalyst successfully produced BC-ring model **1-54** in good yield. This fact indicated that RRCM was effective for the construction of a fused 7-membered cyclic ether skeleton in a steric hindered situation.



Scheme 1-5. Cyclization to 1-54 by RRCM. Reagents and conditions: (a) the 2nd generation Grubbs' catalyst (0.2 eq), (CH₂Cl)₂, reflux, 24 h, **1-54**: not detected; (b) 2 M HCl aq.-THF (1:1), 25 °C, 2 h, then NaIO₄ (2.0 eq), pH 7 buffer, 25 °C, 1.5 h; (c) NaBH₄ (2.5 eq), CeCl₃·7H₂O (1.6 eq), MeOH, -78 °C, 10 min, 98% from **1-62-syn**; (d) 3-bromo-propene (3.0 eq), NaH (3.0 eq), TBAI (0.1 eq), DMF-THF (2:1), 0 → 25 °C, 20 h, 91%; (e) the 2nd generation Grubbs' catalyst (0.1 eq), (CH₂Cl)₂, reflux, 4 h, 73%.

1-5. Plan for the synthesis of armatol F

The author intended to synthesize stereostructure **1-6**, depicted as armatol F in Ciavatta's report,¹³ as the first target of this synthetic study. Considering the synthesis of diastereomers of armatol F for the determination of the absolute stereochemistry of natural armatol F, the author planned to synthesize **1-6** via a route including the sulfone coupling of A-ring segment **1-65** with BCD-ring segment **1-52** and the installation of a methyl group at C10 at the final stage (Scheme 1-6). After the establishment of the synthesis of **1-52**, the enantiomer of **1-52** would be preparable by similar procedure and usable for the synthesis of diastereomers of **1-6**.



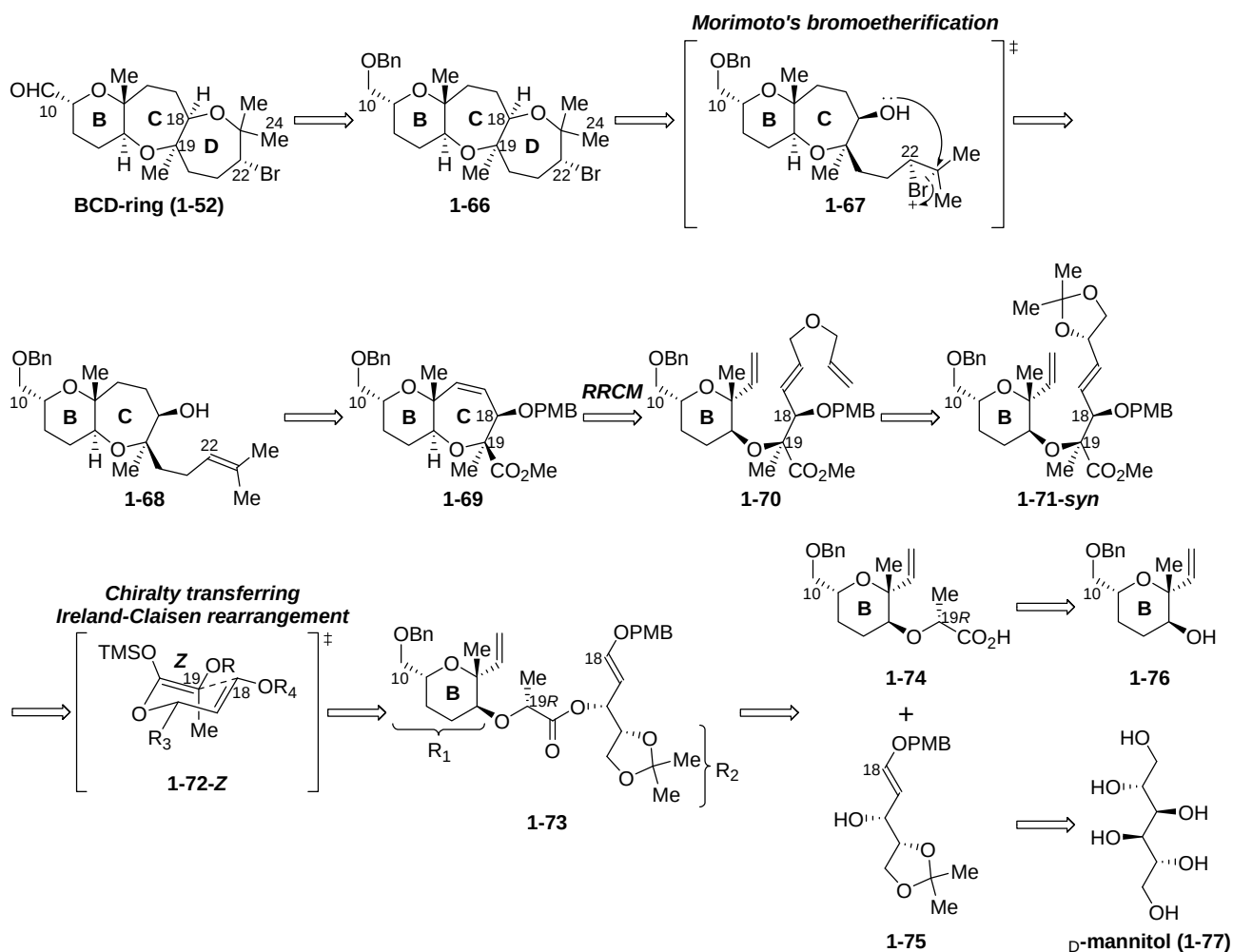
Scheme 1-6. Final stage strategy for the synthesis of armatol F.

Based on the knowledge from the model synthesis mentioned above, the assembly of BCD-ring **1-52** was designed as shown in Scheme 1-7.

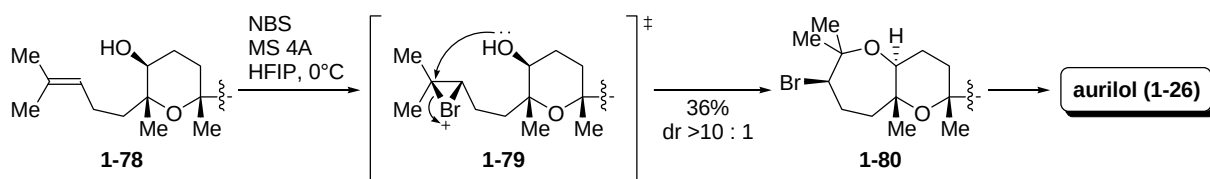
The D-ring of BCD-ring **1-52**, which would be easily convertible from its synthetic equivalent (**1-66**), was initially envisioned to be formed by applying a bromoetherification method reported by Morimoto and coworkers.⁴⁴ In total synthesis of auriol (**1-26**), treatment of isopropylidene alcohol **1-78** with NBS in HFIP successfully promoted a *7-endo* cyclization to produce *trans*-6,7-fused bromo-oxepane **1-80** (Scheme 1-8). The author noticed the possibility of this method to solve the above mentioned problems (ii) and (iii) simultaneously, though the application to *cis*-fused system was unreported. Thus, isopropylidene alcohol **1-68** was designed as a substrate for Morimoto's method. Intermediate **1-68** would be derived from **1-69** via a sequence of functional group interconversion reactions. However, the initial plan for the D-ring formation was forced to be abandoned, and alternative methods have been tried as described in Chapter 3.

The C-ring of **1-69** was expected to be constructed by RRCM⁴³ of triene **1-70**. The triene would be prepared from **1-71-syn**, which would be synthesized by the Ireland-Claisen

rearrangement of **1-73** including (19*R*)-ester attached with the B-ring. The desired stereochemistry of **1-71-syn** was expected to be constructed via a chair-formed transition state from *Z*-keten silyl acetal **1-72-Z**. Ester **1-73** would be derived from **1-74** and *E*-3-alkoxyallyl alcohol **1-75** available from *D*-mannitol (**1-77**).^{37,45} Lactic acid derivative **1-74** would be synthesized from B-ring **1-76**, an enantiomer of known alcohol,⁴⁶ and (*S*)-(-)-2-bromopropionic acid.



Scheme 1-7. Synthetic plan of the BCD-ring of armatol F.



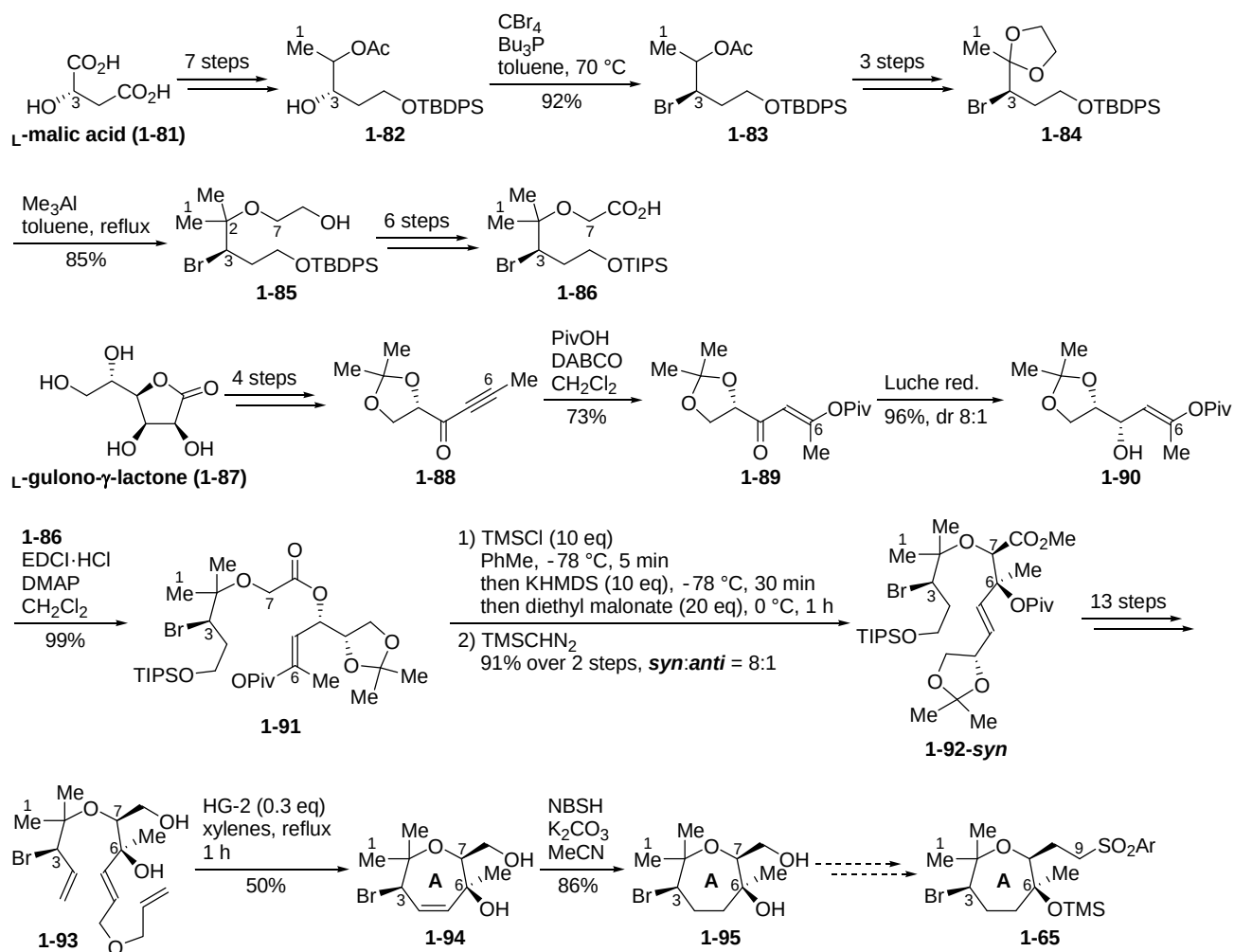
Scheme 1-8. Bromoetherification performed in total synthesis of auriol (1-26) by Morimoto's group.

It should be mentioned that Hirose, a collaborator in the author's laboratory, developed recently a method for the stereoselective synthesis of the A-ring of armatol F (**1-6**) based on a non-biomimetic route.⁴⁷ A-ring **1-95**, which would be convertible to key intermediate **1-65**, was successfully synthesized from L-malic acid and L-gulono- γ -lactone via a process including a chirality transferring Ireland-Claisen rearrangement^{38,40} and RRCM⁴³ (Scheme 1-9).

After L-malic acid (**1-81**) was converted to secondary alcohol **1-82**, which was brominated by an S_N2 reaction using carbon tetrabromide and tributylphosphine to afford **1-83**.⁴⁸ Conventional three-step conversion of **1-83** gave acetal **1-84**, which was methylated with trimethylaluminum in toluene under reflux condition to produce **1-85**. The following 6 steps-sequence transformed **1-85** into enantio-pure glycolic acid **1-86**.

Separately, *E*-3-alkoxyallyl alcohol **1-90** was prepared from alkynone **1-88**, derived from L-gulono- γ -lacton (**1-87**) over 4 steps, via a process involving the conjugate addition^{49,50} of pivalic acid and the Luche reduction⁵¹ of the resulting *E*-enone **1-89**. Condensation of **1-90** with **1-86** provided ester **1-91**. Then the Ireland-Claisen rearrangement of **1-91** was performed by treatment with KHMDS in the presence of TMSCl in toluene at -78 °C followed by warming to 0 °C to produce **1-92-syn** selectively in 92% in a ratio of *syn:anti* = 8:1 after methylation. After multi-step conversion of **1-92-syn**, the resulting triene **1-93** was cyclized by RRCM in the presence of the 2nd generation Hoveyda-Grubbs' catalyst (HG-2)⁵² in xylenes to afford bromo-oxepene **1-94**. Finally, the NBSH⁵³ mediated diimide reduction of **1-94** successfully furnished bromo-oxepane **1-95**.

Hirose's successful synthesis of the A-ring of armatol F has encouraged the author to perform the synthesis of the BCD-ring. Especially, his non-biomimetic installation of the bromine group has inspired the author to develop a new bromine-installation method during the D-ring construction, as described in Chapter 3.



Scheme 1-9. Synthesis of the A-ring of armatol F by Hirose.

1-6. Plan for the determination of the full absolute stereochemistry of armatol F

After the completion of the synthesis of **1-6** and its C10 epimer, the remaining two diastereomers were scheduled to be prepared via a similar procedure. The full assignment of the absolute configuration of natural armatol F is planned by comparison of $^1\text{H}/^{13}\text{C}$ NMR and optical rotation data between each synthetic product and natural armatol F. The direct assignment of the absolute stereochemistry at C10 may be difficult. However, determination of the configuration via chemical degradation of the synthetic compound identical with natural armatol F would be effective.

1-7. Outline of this dissertation

In this dissertation, the synthetic studies on the BCD-ring (**1-52**) of armatol F (**1-6**) are described.

The synthesis of the BC-ring was investigated. As a result, it was found that a chirality transferring Ireland-Claisen rearrangement was also effective for the stereoselective construction of the *cis*-junction at C18-19 in the real system. For the formation of the congested C-ring, RRCM was successfully applied. Details are explained in Chapter 2.

After establishment of the synthetic route to the BC-ring, the formation of the D-ring was examined. However, the difficulty of the D-ring formation was beyond initial anticipation. The author attempted to form the D-ring by the following three methods: (i) NBS promoted bromoetherification according to Morimoto's protocol, (ii) 7-*exo* cyclization of hydroxy epoxide, and (iii) the combination of alkylation-based ether formation and bromination by regioselective epoxide ring opening with bromide ion. After intensive experiments, it was found that cyclization of the D-ring by nucleophilic C-O bond formation and installation of a bromine group at congested C22 by an $\text{S}_{\text{N}}2$ reaction were inappropriate in the D-ring synthesis. Thus, the author newly designed an alternative method for D-ring formation relied on RCM and a bromine-installation reaction by an electrophilic addition reaction to olefin. The details of this method are explained in Chapter 3.

Chapter 4 describes the conclusion and scope for future work.

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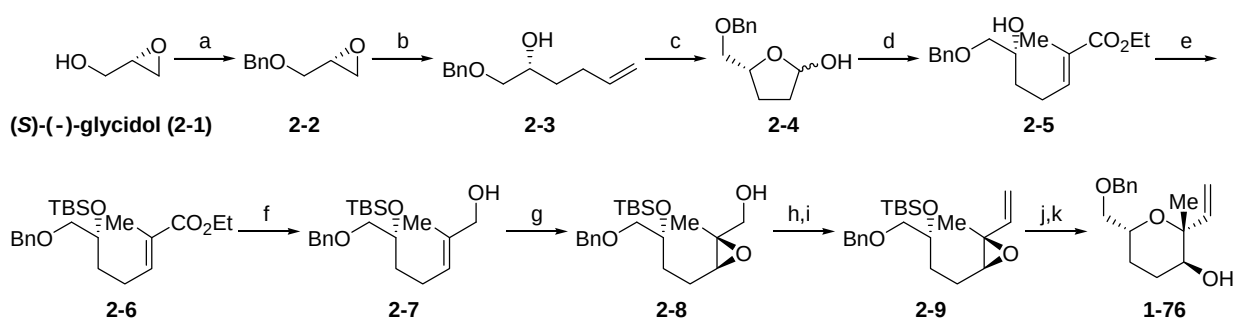
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Chapter 2.

Synthesis of the BC-ring of Armatol F

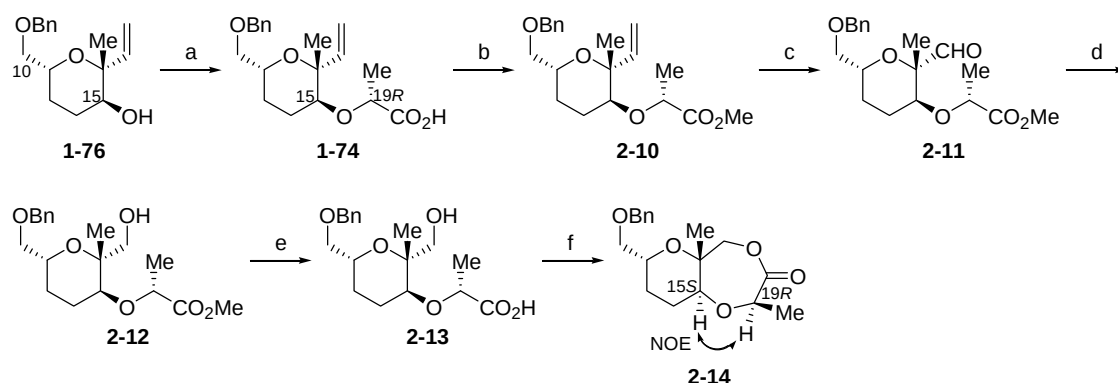
2-1. Synthesis of intermediate ester 1-73

First, oxane **1-76**, of which the enantiomer was known,¹ was synthesized as the B-ring of armatol F on the basis of the reported procedure (Scheme 2-1). Protection of (*S*)-(-)-glycidol (**2-1**) as a benzyl ether (**2-2**) followed by a sequence of allylation and one-pot, stepwise oxidative cleavage of the resulting alkene **2-3** produced hemiacetal **2-4**, which was selectively converted to *E*- α,β -unsaturated ester **2-5** by a Wittig reaction² in 71% overall yield from **2-1**. After alcohol **2-5** was silylated as a TBS ether under standard conditions, the resulting **2-6** was reduced with DIBAH to furnish allyl alcohol **2-7** in 89% overall yield from **2-5**. Katsuki-Sharpless asymmetric epoxidation³ of **2-7** using *L*-(+)-DET under standard conditions at $-25\text{ }^{\circ}\text{C}$ afforded hydroxy epoxide **2-8** in 97% yield as a single diastereomer. Treatment of **2-8** with $\text{SO}_3\cdot\text{pyridine}$ and DMSO gave aldehyde, which was transformed to vinyl epoxide **2-9** through the Wittig reaction² using methyltriphenylphosphonium bromide and NHMDS in THF at $-78\text{ }^{\circ}\text{C}$. Finally, desilylation of **2-9** followed by the 6-*endo*-type cyclization of the resulting hydroxy epoxide with a catalytic amount of CSA produced B-ring **1-76** regio- and stereoselectively in 88% yield over 4 steps.



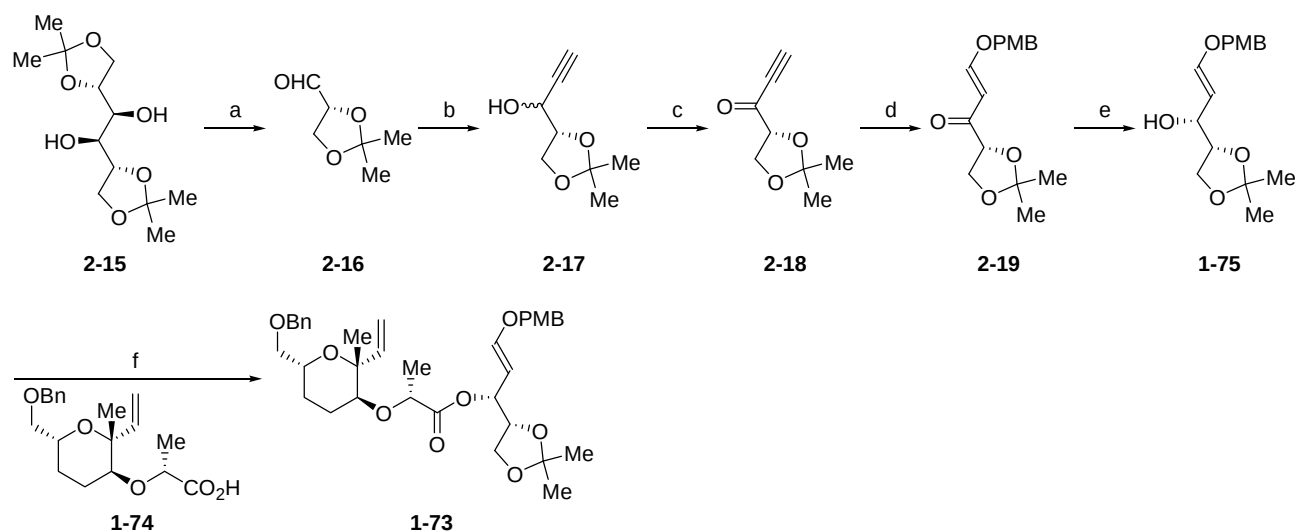
Scheme 2-1. Synthesis of B-ring 1-76. Reagents and conditions: (a) NaH (1.9 eq), BnBr (2.1 eq), DMF, $0 \rightarrow 25\text{ }^{\circ}\text{C}$, 40 min, 99%; (b) allylMgCl (1.4 eq), Et_2O , $-20\text{ }^{\circ}\text{C}$, 30 min; (c) OsO_4 (0.02 eq), NMO (2.6 eq), 1,4-dioxane-pH 7 buffer (1:1), $25\text{ }^{\circ}\text{C}$, 15.5 h, then KIO_4 (2.5 eq), $25\text{ }^{\circ}\text{C}$, 24 h, 74% from **2-2**; (d) $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$ (1.3 eq), benzene, $25\text{ }^{\circ}\text{C}$, 1 d, 97%; (e) TBSCl (1.7 eq), imidazole (3.9 eq), DMF, $25\text{ }^{\circ}\text{C}$, 20 h, 95%; (f) DIBAH (2.6 eq), Et_2O , $-78\text{ }^{\circ}\text{C}$, 35 min, 94%; (g) *L*-(+)-DET (0.2 eq), $\text{Ti}(\text{O}i\text{-Pr})_4$ (0.15 eq), TBHP (2.0 eq), MS 4A, CH_2Cl_2 , $-40 \rightarrow -25\text{ }^{\circ}\text{C}$, 43 h, 97%; (h) $\text{SO}_3\cdot\text{pyridine}$ (3.1 eq), Et_3N (6.0 eq), CH_2Cl_2 -DMSO (6:1), $0\text{ }^{\circ}\text{C}$, 4.5 h; (i) $\text{Ph}_3\text{PCH}_3\text{Br}$ (2.0 eq), NHMDS (1.9 eq), THF, $-78 \rightarrow 25\text{ }^{\circ}\text{C}$, 14.5 h; (j) TBAF (2.5 eq), THF, $25\text{ }^{\circ}\text{C}$, 16 h; (k) CSA (0.2 eq), CH_2Cl_2 , $25\text{ }^{\circ}\text{C}$, 22 h, 88% from **2-8**.

Next, lactic acid derivative **1-74** was synthesized by the reaction of **1-76** with (*S*)-(-)-2-bromopropionic acid in the presence of sodium hydride in 1,4-dioxane at a concentration of more than 0.2 M (Scheme 2-2).⁴ This reaction proceeded in an S_N2 fashion to afford **1-74** with an (*R*)-configuration at the α position as a single stereoisomer in excellent yield (93%). To confirm the stereochemistry at the α position, carboxylic acid **1-74** was transformed to lactone **2-14**. After the conversion of **1-74** to methyl ester **2-10**,⁵ a sequence of oxidative cleavage of olefin moiety of **2-10**,^{6,7} reduction of the resulting aldehyde **2-11**,⁸ hydrolysis of ester moiety of **2-12**, and the intramolecular condensation of **2-13** produced lactone **2-14** in 7% yield over 4 steps along with 63% recovery of **2-13**. The (*R*)-configuration at the α position (C19) was confirmed on the basis of the *cis*-relationship of H15 and H19 of **2-14**, which was determined by the presence of an NOE correlation between the protons, and the (*S*)-configuration of C15.



Scheme 2-2. Syntheses of lactic acid derivative 1-74 and lactone 2-14. Reagents and conditions: (a) (*S*)-(-)-2-bromopropionic acid (1.2 eq), NaH (5.3 eq), 1,4-dioxane, 65 °C, 19.5 h, 93%; (b) TMSCHN₂ (2.1 eq), benzene-MeOH (3:1), 25 °C, 10 min, 85%; (c) OsO₄ (0.03 eq), NMO (2.7 eq), 1,4-dioxane-pH 7 buffer (1:1), 25 °C, 25 h, then NaIO₄ (3.0 eq), 25 °C, 3 h; (d) NaBH₄ (1.7 eq), CeCl₃·7H₂O (1.6 eq), MeOH, -20 °C, 10 min; (e) 2 M NaOH aq.-MeOH (1:1), 25 °C, 4 h; (f) EDCI·HCl (3.6 eq), DMAP (0.7 eq), CH₂Cl₂, 25 °C, 19.5 h, 7% from **2-10**, 63% recovery of **2-13**.

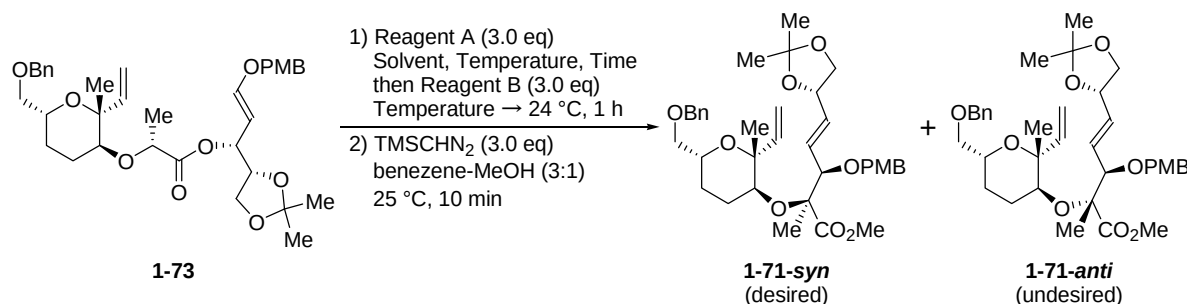
Preparation of intermediate ester **1-73** was commenced from 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol (**2-15**, Scheme 2-3).⁹ Oxidative cleavage of **2-15** with KIO₄ followed by the reaction with ethynyl magnesium bromide produced **2-17**, which was oxidized with IBX¹⁰ in refluxing ethyl acetate to give alkynone **2-18**.¹¹ Conjugate addition of 4-methoxybenzyl alcohol to **2-18** in the presence of tributyl phosphine selectively afforded *E*-enone **2-19** in 31% over 4 steps.¹² The enone was diastereoselectively reduced under Luche conditions⁸ with the assistance of the neighboring chiral 2,2-dimethyl-1,3-dioxolan-4-yl group¹³ to provide alcohol **1-75** in 78% yield in a ratio of >7:1. Condensation of **1-75** with **1-74** mediated by EDCI·HCl and DMAP produced ester **1-73** in 92% yield.



Scheme 2-3. Synthesis of ester 1-73. Reagents and conditions: (a) KIO₄ (2.6 eq), CH₂Cl₂-pH 7 buffer (4:1), 25 °C, 15 h; (b) ethynyl magnesium bromide (1.9 eq), THF, 0 °C, 1 h; (c) IBX (2.7 eq), AcOEt, reflux, 1 d; (d) PMBOH (1.1 eq), Bu₃P (0.2 eq), CH₂Cl₂, 0 °C, 15 min, 31% from **2-15**; (e) NaBH₄ (2.5 eq), CeCl₃·7H₂O (2.4 eq), MeOH, -78 °C, 20 min, 78% (dr >7:1); (f) **1-74** (1.5 eq), EDCI·HCl (5.0 eq), DMAP (1.1 eq), CH₂Cl₂, 25 °C, 2.5 h, 92%.

2-2. Stereoselective construction of the *syn*- β -alkoxy ether moiety by Ireland-Claisen rearrangement

Table 2-1 shows a summary of the conditions attempted to stereoselectively construct ether **1-71-*syn***, which has a *syn*- β -alkoxy ether structure corresponding to the CD-ring junction of armatol F, by the chirality-transferring version of Ireland-Claisen rearrangement.



Entry	Reagent A	Solvent	Reagent B	Time	Temperature	Yield (2 steps) (<i>syn</i> + <i>anti</i>)	<i>syn</i> : <i>anti</i>	Recovery of 1-73
1	KHMDS	THF	TMSCl	10 min	-78 °C	7%	10 : 1.0	47%
2	KHMDS	PhMe	TMSCl	10 min	-78 °C	33%	6.8 : 1.0	trace ^a
3	LDA (in THF)	PhMe	TMSCl	3 min	-78 °C	19%	1.0 : 3.5	51%
4	LDA (in PhMe)	PhMe	TMSCl	10 min	-78 °C	34%	4.4 : 1.0	23%
5	KHMDS	PhMe	TMSCl	10 min	-20 °C	17%	9.8 : 1.0	0% ^a
6	KHMDS	PhMe	TMSCl	3 min	-20 °C	12%	7.6 : 1.0	0% ^a
7	TMSCl	PhMe	KHMDS	1 min	-20 °C	77%	9.1 : 1.0	0%
8	TMSCl	PhMe	LDA (in PhMe)	2 min	-20 °C	46%	5.7 : 1.0	0% ^a
9	TMSCl	THF	KHMDS	1 min	-20 °C	17%	4.6 : 1.0	59%
10	TMSCl	PhMe	KHMDS	1 min	-78 °C	54%	5.9 : 1.0	33%

Table 2-1. Examination of the Ireland-Claisen rearrangement to form the *syn*- β -alkoxy ether structure (1-71-*syn***).** (a) Decomposition of substrate **1-73** was observed.

Initially, the optimal conditions in the synthesis of the BC-ring model (**1-54**) were applied to substrate **1-73** (entry 1). Ester **1-73** was treated with KHMDS (3 eq) as a base in THF at -78 °C for 10 minutes and then with TMSCl (3 eq) at the same temperature for 30 minutes, and the resulting ketene silyl acetals were rearranged through warming to ambient temperature to produce carboxylic acids, which were converted to methyl esters **1-71-*syn*** and **1-71-*anti*** by methylation with TMS-diazomethane. After isolation of a mixture of **1-71-*syn*** and **1-71-*anti***, the diastereoselectivity was determined by ¹H-NMR analysis. As a result, the desired product (**1-71-*syn***) was obtained in a ratio of 10:1. However, the yield of the products was low, and a

significant amount of the substrate was recovered. It was notable that the recovered substrate was obtained as an almost single stereoisomer with the retained (*R*)-configuration at the α position, which was confirmed by $^1\text{H-NMR}$. The fact suggested that the deprotonation of **1-73** was incomplete under the conditions shown in entry 1: if the recovery resulted from incomplete rearrangement of completely generated ketene silyl acetals, the recovered substrate ester would be obtained as a mixture of diastereomers at the α position because complete generation of enolates/ketene silyl acetals lost the stereochemistry at the α position. Thus, for the improvement of the yield of **1-71-syn**, the author focused on the optimization of the deprotonation conditions.

Next, toluene was used as a solvent instead of THF under the same conditions as entry 1 (entry 2). Although the yield increased up to 30% range, the diastereoselectivity diminished in some degree. In addition, the decomposition of the substrate became more significant, and the amount of the starting material recovered decreased compared to that shown in entry 1. From the fact that carboxylic acid **2-23** and TMS-ether **2-24** were detected as main decomposition products, it is plausible that **2-23** and **2-24** would be derived from ketene **2-21** and alkoxide **2-22**, respectively, which would be produced via α elimination of enolate **2-20** (Figure 2-1). Moreover, an increase in proportion of (*S*)-epimer at α -position in the recovered substrate was observed. These observations suggested that ester **1-73** was more effectively deprotonated in toluene than in THF, which encouraged the author to use toluene as the solvent for the rearrangement. Then, the author optimized the rearrangement conditions other than the solvent.

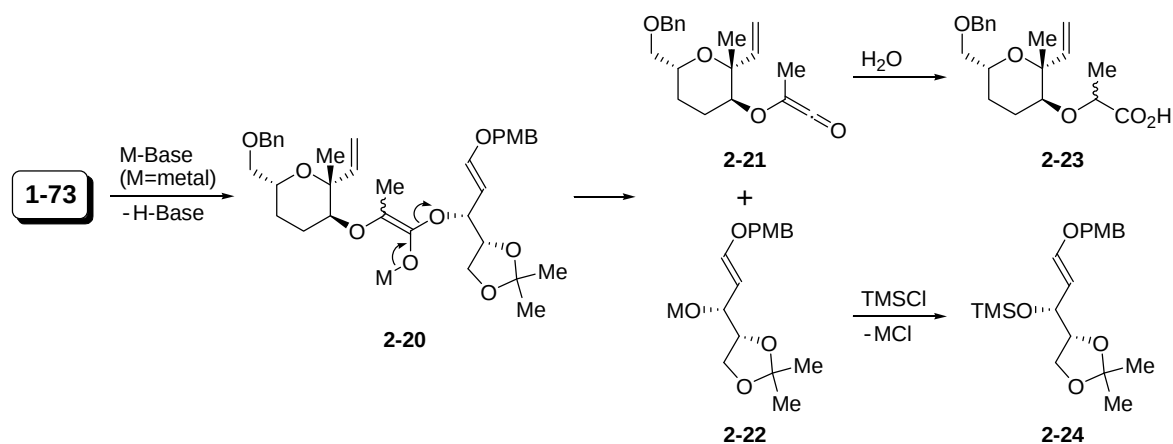


Figure 2-1. Plausible mechanism of the decomposition of the substrate **1-73**.

Treatment of the substrate in toluene with a 1.0 M solution of LDA in THF at $-78\text{ }^{\circ}\text{C}$ for 3 min and then with TMSCl provided undesired **1-71-*anti*** in preference to desired **1-71-*syn*** in a ratio of 1:3.5 in a decreased yield (19%) (entry 3). However, when a 1.0 M solution of LDA in toluene was used, desired **1-71-*syn*** was furnished preferentially in a ratio of 4.4:1 in more than 30% yield (entry 4). Since the results from entries 1–4 showed that KHMDS exhibited higher diastereoselectivity in the rearrangement than LDA, the author intended to employ KHMDS as base for the rearrangement. When the temperature during the deprotonation was changed to $-20\text{ }^{\circ}\text{C}$, the substrate was decomposed drastically and the yield of the products decreased to 17% (entry 5). Although the time of deprotonation was shortened in order to suppress the decomposition, no improvement was observed (entry 6). The rapid decomposition of the substrate with KHMDS in toluene suggested an initial rapid deprotonation of the substrate under the conditions. Therefore, the author next examined the conditions that substrate **1-73** was deprotonated with KHMDS in the presence of TMSCl. Under the conditions, the enolate generated in situ from **1-73** would be immediately trapped with TMSCl to form ketene silyl acetal without decomposition. As a result, the production yield (77%) as well as the diastereoselectivity (**1-71-*syn*:1-71-*anti*** = 9.1:1) was improved dramatically (entry 7). These conditions also showed good reproducibility.

Next, some comparative experiments were conducted under the same conditions as entry 7 except each one of base, solvent, and temperature (entries 8–10). The use of LDA (in toluene) decreased the yield compared to the use of KHMDS in entry 7 though the yield was better than that of entry 4 (entry 8). Employment of THF as a solvent (entry 9) or deprotonation at lower temperature (entry 10) resulted in incomplete deprotonation of the substrate to recover a significant amount of the substrate without epimerization. These results are also consistent with the above considerations that toluene induces rapid deprotonation from **1-73** than THF and that higher temperature during deprotonation also promote rapid deprotonation. Langlois and coworkers reported a similar solvent effect in their examination of Ireland-Claisen rearrangement.¹⁴ The elevating temperature is presumed to facilitate overcoming the activation barrier of the deprotonation.

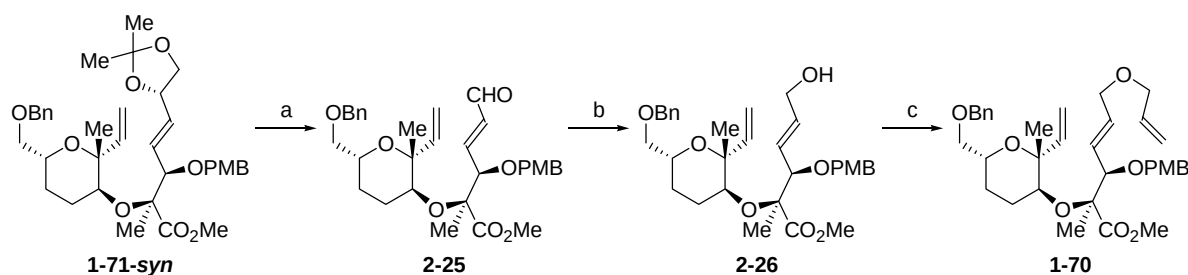
Thus, the author found optimized conditions for the stereoselective construction of desired

1-71-syn, which has a *syn*- β -alkoxy ether structure corresponding to the CD-ring junction of armatol F, by the chirality-transferring version of Ireland-Claisen rearrangement.

2-3. Construction of the C-ring by relay ring-closing olefin metathesis

After the optimal conditions were established for the synthesis of *syn*- β -alkoxy ether **1-71-syn**, the construction of the C-ring by RRCM was examined.

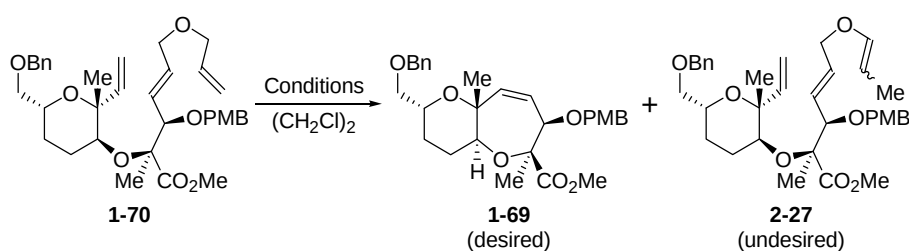
First, compound **1-71-syn** was converted to triene **1-70**, a substrate for RRCM, by the following 3 steps: one-pot acidic hydrolysis/oxidative diol cleavage,⁷ Luche reduction,⁸ and allyl ether formation with allyl bromide in the presence of sodium hydride and TBAI (Scheme 2-4).



Scheme 2-4. Synthesis of triene 1-70. Reagents and conditions: (a) 2 M HCl aq.-THF (1:1), 25 °C, 4 h, then NaIO₄ (3.0 eq), pH 7 buffer, 25 °C, 1.5 h; (b) NaBH₄ (5.7 eq), CeCl₃·7H₂O (5.0 eq), MeOH, -78 °C, 15 min, 94% from **1-71-syn**; (c) allyl bromide (4.1 eq), NaH (4.2 eq), TBAI (0.5 eq), DMF, 0 → 25 °C, 1.5 h, 86%.

Selected results of the formation of the C-ring by RRCM¹⁵ are shown in Table 2-2. Initially, triene **1-70** was treated with the 2nd generation Grubbs' catalyst (G-2)¹⁶ in refluxing 1,2-dichloroethane according to the best conditions for the C-ring formation in the BC-ring model synthesis. However, BC-ring **1-69** was given in only 17% yield along with the recovery of the starting material, and the undesired product **2-27** was produced due to olefin isomerization of **1-70** (entry 1). Then, the 2nd generation Hoveyda-Grubbs' catalyst (HG-2),¹⁷ known as a superior catalyst to G-2 in thermal stability and reactivity, was employed at a dilute concentration (0.5 mM) for the cyclization. As a result, the yield of **1-69** was improved up to 59%, but the consumption of the substrate was incomplete (entry 2). Because it was suspected that the inactivation of the catalyst during the RRCM reaction would retard the reaction, a periodic, portionwise addition of the catalyst

was examined to compensate for the increasing inactivated catalyst as shown in entries 3 and 4. The addition of about 0.1 equivalent of fresh HG-2 in every 30 min or one day resulted in complete consumption of triene **1-70** (entries 3 and 4). In entry 3, the reaction, which finished within 2 h, showed a similar yield of **1-69** to entry 2 but an increased the yield of **2-27**. In addition, several examinations performed under the same conditions as entry 3 gave inconsistent yields of **1-69** and **2-27** (data not shown). The low reproducibility was thought to result from the variable competition between the RRCM by intact HG-2 and the olefin isomerization by the inactivated catalyst, and the variability would be caused by an irregular inactivation of the catalyst due to thermal decomposition. Therefore, the RRCM at lower temperature (55 °C) was attempted in order to suppress the thermal decomposition of the catalyst (entry 4). As a result, the reproducibility was improved, but there were still problems of the slow reaction and the low turnover of the catalyst (0.35 eq of HG-2).



Entry	Catalyst ^a	Equivalent	Additive	Concentration	Temperature	Time	Yield		Recovery of 1-70
							1-69	2-27	
1	G-2	0.17 eq	—	3.6 mM	83 °C	2.5 h	17%	27%	17%
2	HG-2	0.11 eq	—	0.5 mM	83 °C	26 h	59%	18%	17%
3	HG-2	0.10 → 0.29 eq ^b	—	0.8 mM	83 °C	2 h	56%	32%	0%
4	HG-2	0.10 → 0.35 eq ^c	—	0.8 mM	55 °C	4 d	65%	22%	0%
5	HG-2	0.16 eq	1,4-benzoquinone (0.6 eq)	1.6 mM	55 °C	19 h	67%	25%	0%
6	HG-2	0.15 eq	1,4-benzoquinone (2.2 eq)	1.6 mM	83 °C	18 h	72%	15%	0%

Table 2-2. Examination of the RRCM to construct the BC-ring (1-69). (a) G-2: The 2nd generation Grubbs' catalyst; HG-2: The 2nd generation Hoveyda-Grubbs' catalyst. (b) Less than 0.1 equivalent of the catalyst was added every 30 minutes after the first addition of one. (c) Less than 0.1 equivalent of the catalyst was added every one day after the first addition of one.

As for the decomposition of the ruthenium metathesis catalysts and olefin isomerization as a side reaction in olefin metathesis, Grubbs and coworkers reported that the ruthenium hydride specie (**2-28**, Figure 2-2) was formed from the decomposition of the 2nd generation type of the ruthenium metathesis catalysts, and **2-28** catalyzed the olefin migration under metathesis conditions.¹⁸ Also they have found that 1,4-benzoquinone was effective in preventing olefin isomerization of a number of allylic ethers and long-chain aliphatic alkenes during olefin metathesis reactions without reducing the catalyst activity.¹⁹

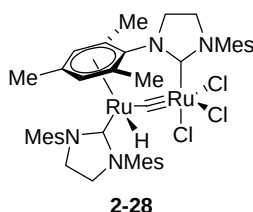


Figure 2-2. Structure of the ruthenium hydride specie (2-28) reported by Grubbs' group.

On the basis of this report, 1,4-benzoquinone (0.6 eq) was added to the reaction of triene **1-70** with 0.16 eq of HG-2 in 1,2-dichloroethane at 55 °C for 19 h to produce **1-69** in 67% yield along with **2-27** (25%, entry 5). As a result, the amount of the catalyst and the reaction time were reduced. Furthermore, the RRCM with 1,4-benzoquinone (2.2 eq) at 83 °C also promoted the construction of the C-ring in 72% yield with decreased byproduction of **2-27** (15%) (entry 6). The presence of 1,4-benzoquinone might prevent thermal decomposition of HG-2 even at higher temperature, which might also assist the rapid and predominant RRCM at the temperature. Thus, the optimized RRCM conditions were established.

The stereochemistry of **1-69** was confirmed by NOE experiments (Figure 2-3). The presence of NOE between H18 and the protons of the methyl group at C19 confirmed the *cis*-relationship between H18 and the methyl group at C19. The NOE correlation between H14 and the protons of C19-methyl group indicated the *cis*-relationship between H14 and the C19-methyl group. The NOE enhancement between H18 and H14 also exhibited the *cis*-orientation between these protons. Based on this relative stereochemistry and the (14*R*)-configuration, (18*R*,19*S*)-configuration of **1-69** was deduced. Accordingly, the author has unambiguously synthesized **1-69** corresponding to the BC-ring skeleton of armatol F.

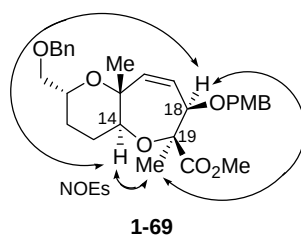


Figure 2-3. Confirmation of the *cis*-configuration at the C18-19 in the BC-ring (**1-69**) by the NOEs observed.

References

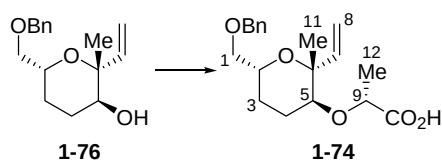
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Experimental sections

General methods

All reactions involving air- or moisture-sensitive reagents were carried out in an anhydrous solvent system under an argon atmosphere in oven-dried glassware capped with septa, and sensitive liquids and solutions were transferred by using syringe- or cannula-techniques, unless otherwise noted. All commercially available reagents including anhydrous solvents, such as benzene, CH_2Cl_2 , DMF, 1,4-dioxane, and MeOH were used without further purification with the following exceptions: THF was distilled from sodium-benzophenone ketyl under argon or prepared by Glass Contour Solvent Dispensing System (Nikko Hansen & Co., Ltd.). 1,2-Dichloroethane and toluene was distilled from CaH_2 prior to use. Normal reagent-grade solvents were used for flash chromatography and extraction. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel (SiO_2) plates (Merck, silica gel 60 F₂₅₄). 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 Gel60 (63-43 μm for flash chromatography, 230-63 μm for gravity chromatography) as a stationary phase. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. Infrared spectra (IR) were measured on a JOEL JIR-WINSPEC100 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^1H -NMR and ^{13}C -NMR spectra were recorded on JEOL JNM-AL300 (^1H at 300MHz, ^{13}C at 75 MHz) and JNM- α -400 (^1H at 400 MHz, ^{13}C at 100 MHz) magnetic resonance spectrometer. ^1H -NMR spectra are reported as chemical shifts (δ) in parts-per-million (ppm) based on tetramethylsilane (0.00 ppm) as an 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 doublet; other combination is derived from those listed. Coupling constants (J) are reported in Hertz (Hz). ^{13}C -NMR spectra are reported as chemical shifts (δ) in ppm based on ^{13}C CDCl₃ (77.0 ppm) or $^{13}\text{C}^{12}\text{C}_5\text{D}_6$ (128 ppm). Low and high resolution mass spectra were measured on a JEOL JMS-600H mass spectrometer under electron ionization (EI) condition and JEOL JMS-SX102A mass spectrometer under field desorption (FD) condition.

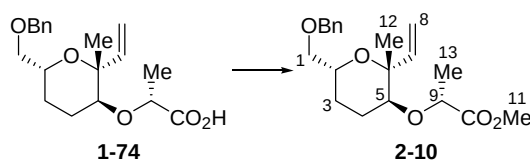
Compound 1-74.



To a suspension of NaH (834.5 mg, assay 60%, 20.86 mmol) in 1,4-dioxane (8.0 mL) was added a solution of **1-76** (1.0231 g, 3.9000 mmol) in 1,4-dioxane (11.0 mL), and the mixture was heated to 65 °C. To this was then added (*S*)-(-)-2-bromopropionic acid (430.0 μ L, 4.78 mmol), and the resulting suspension was stirred at 65 °C for 19.5 h. After the reaction mixture was cooled to ambient temperature, the reaction was quenched slowly with H₂O (30 mL) at 0 °C. The mixture was washed with ether, and then the resulting aqueous layer was acidified with 2M HCl aq.. The acidic solution was extracted with CH₂Cl₂ ($\times$ 3), and the combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to give **1-74** (1.2134 g, 3.6285 mmol, 93%).

1-74: a yellow oil; $[\alpha]_D^{25} = +12.8$ ($c = 0.220$, CHCl₃); IR (neat), $\nu_{\max}$ (cm⁻¹) 2985, 2939, 1725, 1497, 1454, 1409, 1370, 1206, 1115, 1028, 994, 925, 892, 738, 699; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 1.31-1.48 (1H, m, H_{3ax}), 1.35 (3H, s, H₁₁ (Me)), 1.42 (3H, d, $J = 7.0$ Hz, H₁₂ (Me)), 1.58-1.75 (1H, m, H_{4ax}), 1.81-1.90 (1H, m, H_{3eq}), 1.95-2.05 (1H, m, H_{4eq}), 3.26 (1H, dd, $J = 4.8, 11.4$ Hz, H₅), 3.38 (1H, dd, $J = 5.1, 9.9$ Hz, H_{1a}), 3.51 (1H, dd, $J = 5.1, 9.9$ Hz, H_{1b}), 3.78-3.90 (1H, m, H₂), 4.07 (1H, q, $J = 7.0$ Hz, H₉), 4.56 (2H, $J = 1.7$ Hz, Bn), 5.29 (1H, dd, $J = 1.1, 10.8$ Hz, H_{8a}), 5.39 (1H, dd, $J = 1.1, 17.6$ Hz, H_{8b}), 6.01 (1H, dd, $J = 10.8, 17.6$ Hz, H₇), 7.23-7.40 (5H, m, Bn); ¹³C-NMR (75 MHz, CDCl₃) δ (ppm) 14.6 (CH₃), 19.2 (CH₃), 24.7 (CH₂), 27.8 (CH₂), 69.0 (CH), 73.1 (CH), 73.3 (CH₂), 73.4 (CH₂), 76.1 (C), 80.2 (CH), 114.2 (CH₂), 127.56 (CH), 127.65 (CH $\times$ 2), 128.3 (CH $\times$ 2), 138.3 (C), 143.6 (CH), 175.5 (C); LR-EIMS m/z 334 (2.6%, [M]⁺), 91 (bp, [Bn]⁺); HR-EIMS calcd. for C₁₉H₂₆O₅ [M]⁺: 334.1780, found 334.1780.

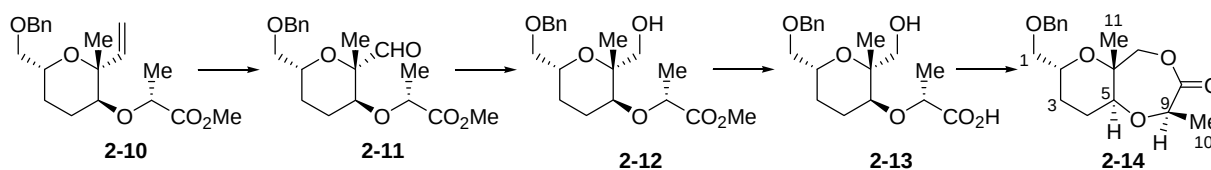
Compound 2-10.



To a solution of **1-74** (245.5 mg, 0.7610 mmol) in benzene (6.0 mL) and MeOH (2.0 mL) was added TMSCHN₂ (0.80 mL, 2.0 M in ether, 1.6 mmol) at 0 °C, and the reaction mixture was stirred for 10 min. After the mixture was condensed under reduced pressure, the resulting residue was purified by silica gel column chromatography (12.5 g, hexane/AcOEt = 10) to give **2-10** (224.9 mg, 0.6455 mmol, 85%).

2-10: a colorless oil; $[\alpha]_D^{23} = +45.8$ ($c = 1.79$, CHCl₃); IR (neat), $\nu_{\max}$ (cm⁻¹) 3089, 3064, 3030, 2986, 2939, 2870, 1754, 1737, 1642, 1497, 1453, 1408, 1370, 1277, 1204, 1097, 1075, 1029, 994, 923, 891, 866, 845, 737, 698, 665; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 1.23-1.43 (1H, m, H3_{ax.}), 1.28 (3H, s, H13 (Me)), 1.35 (3H, d, $J = 6.8$ Hz, H13 (Me)), 1.51-1.67 (1H, m, H4_{ax.}), 1.74-1.85 (1H, m, H3_{eq.}), 1.92-2.02 (1H, m, H4_{eq.}), 3.21 (1H, dd, $J = 4.6, 11.4$ Hz, H5), 3.39 (1H, dd, $J = 5.1, 10.1$ Hz, H1a), 3.53 (1H, dd, $J = 5.3, 10.1$ Hz, H1b), 3.70 (3H, s, H11 (Me)), 3.77-3.87 (1H, m, H2), 4.08 (1H, q, $J = 6.8$ Hz, H9), 4.55 (1H, d, $J = 12.3$ Hz, Bn), 4.60 (1H, d, $J = 12.3$ Hz, Bn), 5.06 (1H, dd, $J = 1.8, 11.0$ Hz, H8a), 5.30 (1H, dd, $J = 1.8, 17.4$ Hz, H8b), 6.17 (1H, dd, $J = 11.0, 17.4$ Hz, H7), 7.25-7.37 (5H, m, Bn); ¹³C-NMR (75 MHz, CDCl₃) δ (ppm) 15.6 (CH₃), 19.1 (CH₃), 24.5 (CH₂), 28.0 (CH₂), 51.7 (CH₃), 69.1 (CH), 72.9 (CH), 73.4 (CH₂), 73.5 (CH₂), 76.0 (C), 79.6 (CH), 112.1 (CH₂), 127.5 (CH), 127.6 (CH $\times$ 2), 128.3 (CH $\times$ 2), 138.5 (C), 143.6 (CH), 173.3 (C); LR-FDMS m/z 350 (12.3%, [M+2]⁺), 349 (85.7%, [M+1]⁺), 348 (bp, [M]⁺), 91 (54.5%, [Bn]⁺); HR-FDMS calcd. for C₂₀H₂₈O₅ [M]⁺: 348.1937, found 348.1941.

Compound 2-14..



To a solution of **2-10** (141.2 mg, 0.4052 mmol) in 1,4-dioxane (1.5 mL) and pH 7 buffer

(1.5 mL) were added NMO (112.3 mg, 1.100 mmol) and OsO₄ (0.70 mL, 0.0197 M in MeOH, 0.014 mmol), and the reaction mixture was stirred for 25 h. Then, NaIO₄ (261.2 mg, 1.221 mmol) was added, and the mixture was stirred for 3 h. After saturated aqueous Na₂S₂O₃ (10 mL) was added, the mixture was extracted with CH₂Cl₂ (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude aldehyde (**2-11**) was used immediately in the next reaction without further purification.

To a solution of crude **2-11** in MeOH (4.0 mL) were added CeCl₃·7H₂O (237.1 mg, 0.6364 mmol) and NaBH₄ (25.3 mg, 0.669 mmol) at -20 °C, and the reaction mixture was stirred at -20 °C for 10 min. After saturated aqueous NH₄Cl (5.0 mL) was added, the mixture was extracted with CH₂Cl₂ (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to give crude **2-12**.

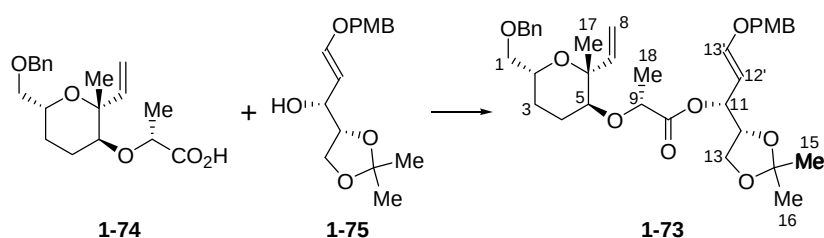
To a solution of crude **2-12** in MeOH (3.0 mL) was added 2 M NaOH aq. (3.0 mL), the reaction mixture was stirred for 4 h. After 2 M HCl aq. (7.0 mL) was added, the mixture was extracted with CH₂Cl₂ (×2). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to give crude **2-13**. The next reaction was carried out without further purification of **2-13**.

To a solution of crude **2-13** in CH₂Cl₂ (35 mL) were added a solution of EDCI·HCl (262.4 mg, 1.369 mmol) and DMAP (32.4 mg, 0.265 mmol) in CH₂Cl₂ (15 mL), and the reaction mixture was stirred for 19.5 h. After saturated aqueous NaHCO₃ (30 mL) was added, the mixture was extracted with CH₂Cl₂ (×3) and washed with 0.2 M HCl aq. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (3.5 g, hexane/AcOEt/Et₃N = 30/1/1.5) to give **2-14** (9.0 mg, 28 μmol, 7% over 4 steps) and recover **2-13** (86.8 mg, 0.257 mmol, 63%).

2-14: a yellow oil; $[\alpha]_D^{22} = +50.8$ (c = 0.445, CHCl₃); IR (neat), $\nu_{\max}$ (cm⁻¹) 2990, 2941, 2859, 1746, 1497, 1468, 1453, 1388, 1372, 1351, 1308, 1247, 1207, 1178, 1119, 1086, 1046, 1028, 983, 741, 698, 665; ¹H-NMR (300 MHz, C₆D₆) δ (ppm) 1.05 (3H, s, H11 (Me)), 1.11-1.23 (1H, m, H3_{ax.}), 1.25-1.42 (2H, m, H3_{eq.}, H4_{ax.}), 1.38 (3H, d, *J* = 6.2 Hz, H10 (Me)), 1.47-1.57 (1H, m, H4_{eq.}), 2.80 (1H, dd, *J* = 4.4 Hz, 11.4 Hz, H5), 3.16 (1H, dd, *J* = 5.1, 9.9 Hz, H1a), 3.29 (1H, dd, *J* = 5.1, 9.9 Hz,

H1b), 3.41 (1H, q, J = 6.2 Hz, H9), 3.47-3.57 (1H, m, H2), 3.68 (1H, d, J = 12.1 Hz, H7a), 3.75 (1H, d, J = 12.1 Hz, H7b), 4.32 (2H, s, Bn), 7.06-7.32 (5H, m, Bn); ^{13}C -NMR (75 MHz, C_6D_6) δ (ppm) 12.2 (CH_3), 18.4 (CH_3), 25.4 (CH_2), 28.5 (CH_2), 69.1 (CH), 73.3 (CH_2), 73.4 (CH_2), 73.8 (C), 74.9 (CH_2), 75.3 (CH), 86.5 (CH), 127.8 ($\text{CH}\times 2$), 127.9 (CH), 128.6 ($\text{CH}\times 2$), 139.0 (C), 171.2 (C); LR-FDMS m/z 321 (26.1%, $[\text{M}+1]^+$), 320 (bp, $[\text{M}]^+$), 91 (3.5%, $[\text{Bn}]^+$); HR-FDMS calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_5$ $[\text{M}]^+$: 320.1624, found 320.1637.

Compound 1-73.

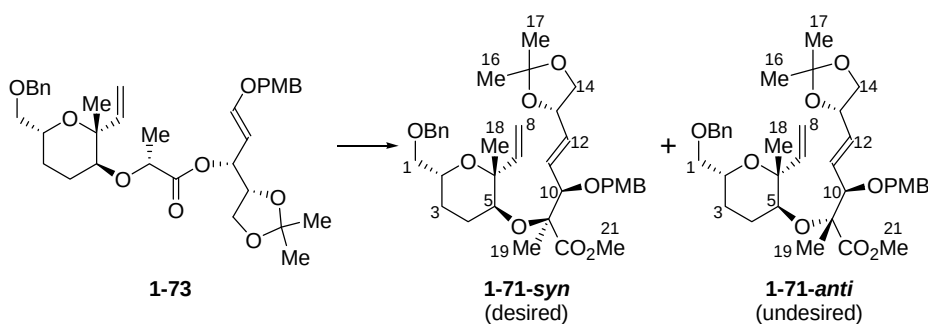


To a solution of **1-75** (1.7650 g, 5.9965 mmol), EDCI·HCl (5.7615 g, 30.055 mmol) and DMAP (778.6 mg, 6.373 mmol) in CH_2Cl_2 (80 mL) was added a solution of **1-74** (2.9164 g, 8.7210 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred for 3 h. After saturated aqueous NaHCO_3 (50 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were washed with brine ($\times 2$), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (150 g, hexane/AcOEt/ Et_3N = 60/1/3 $\rightarrow$ 40/1/2) to give **1-73** (3.3734 g, 5.5236 mmol, 92%).

1-73: a pale yellow oil; $[\alpha]_{\text{D}}^{23} = +21.2$ (c = 0.545, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 3065, 3031, 2985, 2936, 2872, 1746, 1693, 1670, 1650, 1613, 1587, 1515, 1497, 1371, 1304, 1251, 1112, 1070, 1036, 994, 927, 849, 823, 738, 699, 681, 665; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.24-1.44 (1H, m, $\text{H}_{3\text{ax}}$), 1.28 (3H, s, H17 (Me)), 1.32 (3H, s, H15 (Me)), 1.34 (3H, d, J = 6.8 Hz, H18 (Me)), 1.39 (3H, s, H16 (Me)), 1.50-1.69 (1H, m, $\text{H}_{4\text{ax}}$), 1.73-1.84 (1H, m, $\text{H}_{3\text{eq}}$), 1.90-2.03 (1H, m, $\text{H}_{4\text{eq}}$), 3.28 (1H, dd, J = 4.6, 11.4 Hz, H5), 3.39 (1H, dd, J = 5.1, 9.9 Hz, H1a), 3.52 (1H, dd, J = 5.1, 9.9 Hz, H1b), 3.68 (1H, dd, J = 6.8, 8.6 Hz, H13a), 3.76-3.87 (1H, m, H2), 3.79 (3H, s, PMB), 3.95 (1H, dd, J = 6.8, 8.6 Hz, H13b), 4.06 (1H, q, J = 6.8 Hz, H9), 4.18 (1H, ddd, J = 6.8, 6.8, 12.5 Hz, H12), 4.57 (2H, d, J = 2.8 Hz, Bn), 4.68 (2H, s, PMB), 4.79 (1H, dd, J = 9.5, 12.5 Hz, H11), 5.05 (1H, dd,

$J = 1.8, 10.8$ Hz, H8a), 5.26 (1H, dd, $J = 7.3, 9.5$ Hz, H12'), 5.31 (1H, dd, $J = 1.8, 17.4$ Hz, H8b), 6.20 (1H, dd, $J = 10.8, 17.4$ Hz, H7), 6.74 (1H, d, $J = 12.6$ Hz, H13'), 6.88 (2H, d, $J = 8.6$ Hz, PMB), 7.24 (2H, d, $J = 8.6$ Hz, PMB), 7.27-7.35 (5H, m, Bn); ^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) 15.6 (CH_3), 19.2 (CH_3), 24.6 (CH_2), 25.4 (CH_3), 26.5 (CH_3), 28.0 (CH_2), 55.2 (CH_3), 66.0 (CH_2), 69.0 (CH), 71.4 (CH_2), 73.0 (CH), 73.4 (CH_2), 73.5 (CH_2), 74.0 (CH), 76.1 (CH), 76.9 (C), 79.4 (CH), 98.8 (CH), 110.0 (C), 112.3 (CH_2), 113.9 ($\text{CH}\times 2$), 127.5 (CH), 127.6 ($\text{CH}\times 2$), 128.1 (C), 128.3 ($\text{CH}\times 2$), 129.3 ($\text{CH}\times 2$), 138.4 (C), 143.6 (CH), 152.8 (CH), 159.6 (C), 172.1 (C); LR-FDMS m/z 612 (12.0%, $[\text{M}+2]^+$), 611 (42.7%, $[\text{M}+1]^+$), 610 (bp, $[\text{M}]^+$), 121 (23.8%, $[\text{PMB}]^+$), 91 (10.3%, $[\text{Bn}]^+$); HR-FDMS calcd. for $\text{C}_{35}\text{H}_{46}\text{O}_9$ $[\text{M}]^+$: 610.3142, found 610.3115.

Compound **1-71-syn** and **1-71-anti**.



To a solution of **1-73** (238.3 mg, 0.3902 mmol) in toluene (4.0 mL) was added TMSCl (152.0 μL , 1.20 mmol) at -20 $^{\circ}\text{C}$, and the mixture was stirred for 1 min. Then KHMDS (2.40 mL, 0.5 M in toluene, 1.20 mmol) was added, and the reaction mixture was stirred at -20 $^{\circ}\text{C}$ for 30 min. The mixture was warmed to ambient temperature and stirred for 30 min. After 1 M HCl aq. (2.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (3.5 g, hexane/AcOEt/ Et_3N = 25/1/1.25 $\rightarrow$ MeOH) to give crude rearrangement products (251.6 mg) including a small amount of byproducts.

To a solution of the above crude product in benzene (3.0 mL) and MeOH (1.0 mL) was added TMSCHN₂ (530.0 μL , 2.0 M in ether, 1.060 mmol), and the reaction mixture was stirred for 10 min. After the mixture was condensed under reduced pressure, the resulting residue was purified

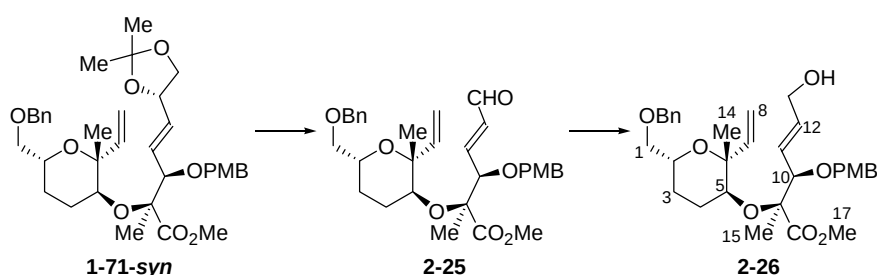
by silica gel column chromatography (6.0 g, hexane/AcOEt = 10 → 5) to give a mixture of **1-71-syn** and **1-71-anti** (187.2 mg, 0.29965 mmol, 77% over 2 steps, *syn:anti* = 9.1:1.0).

1-71-syn: a colorless oil; $[\alpha]_D^{26} = +1.07$ ($c = 0.260$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 2987, 2948, 2871, 1738, 1641, 1613, 1586, 1514, 1497, 1461, 1454, 1435, 1370, 1302, 1249, 1173, 1062, 996, 924, 863, 834, 737, 698, 665, 642; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 1.22-1.35 (1H, m, $\text{H}_{3\text{ax}}$), 1.31 (3H, s, H_{16} (Me)), 1.34 (3H, s, H_{17} (Me)), 1.38 (3H, s, H_{18} (Me)), 1.41 (3H, s, H_{19} (Me)), 1.58-1.79 (3H, m, $\text{H}_{3\text{eq}}$, H_4), 3.37 (1H, dd, $J = 5.1, 9.9$ Hz, H_{1a}), 3.45-3.59 (3H, m, H_{1b} , H_5 , H_{14a}), 3.65 (3H, s, H_{21} (Me)), 3.75-3.85 (1H, m, H_2), 3.80 (3H, s, PMB), 3.94-3.99 (1H, m, H_{10}), 4.08 (1H, dd, $J = 6.2, 8.1$ Hz, H_{14b}), 4.38 (1H, d, $J = 11.6$ Hz, PMB), 4.47-4.62 (4H, m, H_{13} , Bn, PMB), 5.02 (1H, dd, $J = 1.8, 11.0$ Hz, H_{8a}), 5.29 (1H, dd, $J = 1.8, 17.4$ Hz, H_{8b}), 5.62-5.67 (2H, m, H_{11} , H_{12}), 6.05 (1H, dd, $J = 11.0, 17.4$ Hz, H_7), 6.85 (2H, d, $J = 8.6$ Hz, PMB), 7.20 (2H, d, $J = 8.6$ Hz, PMB), 7.24-7.37 (5H, m, Bn); $^{13}\text{C-NMR}$ (75 MHz, C_6D_6) δ (ppm) 16.4 (CH_3), 16.5 (CH_3), 25.7 (CH_2), 26.1 (CH_3), 26.9 (CH_3), 28.3 (CH_2), 51.3 (CH_3), 54.7 (CH_3), 69.4 (CH), 69.7 (CH_2), 71.5 (CH_2), 73.4 (CH_2), 73.9 (CH_2), 75.3 (CH), 76.38 (CH), 76.45 (C), 81.9 (C), 84.6 (CH), 109.5 (C), 112.0 (CH_2), 114.0 ($\text{CH}\times 2$), 127.6 (CH), 127.7 ($\text{CH}\times 2$), 128.5 ($\text{CH}\times 2$), 129.1 (CH), 129.5 ($\text{CH}\times 2$), 130.8 (C), 134.2 (CH), 139.4 (C), 144.5 (CH), 159.7 (C), 173.3 (C); LR-FDMS m/z 625 (24.0%, $[\text{M}+1]^+$), 624 (33.7%, $[\text{M}]^+$), 121 (bp, $[\text{PMB}]^+$), 91 (57.3%, $[\text{Bn}]^+$); HR-FDMS calcd. for $\text{C}_{36}\text{H}_{48}\text{O}_9$ $[\text{M}]^+$: 624.3298, found 624.3322.

1-71-anti: a colorless oil; $[\alpha]_D^{25} = +42.5$ ($c = 0.150$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 2986, 2949, 1738, 1641, 1613, 1586, 1514, 1497, 1454, 1370, 1303, 1249, 1097, 924, 850, 823, 737, 698, 665, 642; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 1.23 (3H, s, H_{16} (Me)), 1.26-1.35 (1H, m, $\text{H}_{3\text{ax}}$), 1.31 (3H, s, H_{17} (Me)), 1.41 (3H, s, H_{18} (Me)), 1.43 (3H, s, H_{19} (Me)), 1.52-1.76 (2H, m, $\text{H}_{3\text{eq}}$, $\text{H}_{4\text{ax}}$), 1.78-1.90 (1H, m, $\text{H}_{4\text{eq}}$), 3.28 (1H, dd, $J = 4.6, 11.0$ Hz, H_5), 3.37 (1H, dd, $J = 5.1, 9.9$ Hz, H_{1a}), 3.50 (1H, dd, $J = 5.1, 9.9$ Hz, H_{1b}), 3.56-3.65 (4H, m, H_{14a} , H_{21} (Me)), 3.73-3.83 (1H, m, H_2), 3.79 (3H, s, PMB), 4.11 (1H, dd, $J = 6.2, 8.1$ Hz, H_{14b}), 4.24-4.31 (2H, m, H_{10} , PMB), 4.50 (1H, d, $J = 11.2$ Hz, PMB), 4.54-4.64 (3H, m, H_{13} , Bn), 4.99 (1H, dd, $J = 2.0, 10.8$ Hz, H_{8a}), 5.25 (1H, dd, $J = 2.0, 17.4$ Hz, H_{8b}), 5.73-5.79 (2H, m, H_{11} , H_{12}), 5.99 (1H, dd, $J = 10.8, 17.4$ Hz, H_7), 6.84 (2H, d, $J = 8.6$ Hz, PMB), 7.15 (2H, d, $J = 8.6$ Hz, PMB), 7.23-7.39 (5H, m, Bn); $^{13}\text{C-NMR}$ (75

MHz, C₆D₆) δ (ppm) 16.2 (CH₃), 16.8 (CH₃), 26.2 (CH₃), 27.0 (CH₃), 28.1 (CH₂), 28.2 (CH₂), 51.3 (CH₃), 54.7 (CH₃), 69.3 (CH), 69.8 (CH₂), 71.7 (CH₂), 73.4 (CH₂), 73.9 (CH₂), 76.3 (C), 76.5 (CH), 76.6 (CH), 82.3 (CH), 82.7 (C), 109.5 (C), 111.5 (CH₂), 114.0 (CH $\times$ 2), 127.6 (CH), 127.8 (CH $\times$ 2), 128.5 (CH $\times$ 2), 128.9 (CH), 129.5 (CH $\times$ 2), 130.7 (C), 133.1 (CH), 139.3 (C), 144.2 (CH), 159.7 (C), 171.9 (C); LR-FDMS m/z 625 (17.6%, [M+1]⁺), 624 (28.3%, [M]⁺), 121 (bp, [PMB]⁺), 91 (39.8%, [Bn]⁺); HR-FDMS calcd. for C₃₆H₄₈O₉ [M]⁺: 624.3298, found 624.3272.

Compound 2-26.



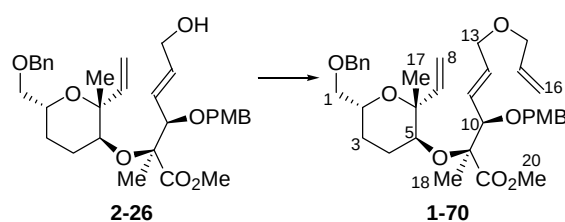
To a solution of **1-71-syn** (179.8 mg, 0.2878 mmol) in THF (7.0 mL) was added 2 M HCl aq. (7.0 mL), the reaction mixture was stirred for 4 h. Then, pH 7 buffer (7.0 mL) and NaIO₄ (187.4 mg, 0.8759 mmol) were added, and the mixture was stirred for 1.5 h. After saturated aqueous NaHCO₃ (10 mL) was added, the mixture was extracted with CH₂Cl₂ ($\times$ 2) and ether. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude aldehyde (**2-25**) was used immediately in the next reaction without further purification.

To a solution of crude **2-25** in MeOH (10 mL) were added CeCl₃·7H₂O (535.3 mg, 1.437 mmol) and NaBH₄ (62.1 mg, 1.64 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 15 min. After saturated aqueous NH₄Cl (7.0 mL) was added, the mixture was extracted with CH₂Cl₂ ($\times$ 3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (6.5 g, hexane/AcOEt = 3) to give **2-26** (150.2 mg, 0.2708 mmol, 94% over 2 steps).

2-26: a colorless oil; $[\alpha]_D^{27} = +11.1$ ($c = 0.0800$, CHCl₃); IR (neat), $\nu_{\max}$ (cm⁻¹) 3458, 2991, 2950, 2870, 1738, 1641, 1613, 1586, 1514, 1497, 1454, 1376, 1303, 1249, 1173, 1095, 996, 924, 821, 737,

699, 665; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 1.24-1.37 (1H, m, $\text{H}_{3\text{ax.}}$), 1.30 (3H, s, H_{14} (Me)), 1.35 (3H, s, H_{15} (Me)), 1.56-1.78 (3H, m, $\text{H}_{3\text{eq.}}$, H_4), 3.37 (1H, dd, $J = 5.1, 9.9$ Hz, $\text{H}_{1\text{a}}$), 3.44-3.54 (2H, m, $\text{H}_{1\text{b}}$, H_5), 3.65 (3H, s, H_{17} (Me)), 3.75-3.86 (1H, m, H_2), 3.80 (3H, s, PMB), 3.96 (1H, d, $J = 7.8$ Hz, H_{10}), 4.10-4.19 (2H, m, H_{13}), 4.40 (1H, d, $J = 11.5$ Hz, PMB), 4.53 (1H, d, $J = 11.5$ Hz, PMB), 4.54 (1H, d, $J = 12.3$ Hz, Bn), 4.59 (1H, d, $J = 12.3$ Hz, Bn), 5.01 (1H, dd, $J = 1.8, 11.0$ Hz, $\text{H}_{8\text{a}}$), 5.29 (1H, dd, $J = 1.8, 17.4$ Hz, $\text{H}_{8\text{b}}$), 5.59 (1H, br-dd, $J = 7.8, 15.6$ Hz, H_{11}), 5.81 (1H, td, $J = 5.5, 15.6$ Hz, H_{12}), 6.05 (1H, dd, $J = 11.0, 17.4$ Hz, H_7), 6.85 (2H, d, $J = 8.6$ Hz, PMB), 7.22 (2H, d, $J = 8.6$ Hz, PMB), 7.24-7.38 (5H, m, Bn); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) 15.9 (CH_3), 16.1 (CH_3), 25.2 (CH_2), 28.0 (CH_2), 51.8 (CH_3), 55.3 (CH_3), 62.9 (CH_2), 69.0 (CH), 71.0 (CH_2), 73.4 (CH_2), 73.5 (CH_2), 74.8 (CH), 76.1 (C), 81.7 (C), 84.0 (CH), 112.4 (CH_2), 113.6 ($\text{CH}\times 2$), 127.2 (CH), 127.5 (CH), 127.6 ($\text{CH}\times 2$), 128.3 ($\text{CH}\times 2$), 129.3 ($\text{CH}\times 2$), 130.4 (C), 134.7 (CH), 138.5 (C), 143.9 (CH), 159.1 (C), 173.9 (C); LR-FDMS m/z 555 (39.9%, $[\text{M}+1]^+$), 554 (23.4%, $[\text{M}]^+$), 433 (bp, $[\text{M}-\text{PMB}]^+$), 121 (47.9%, $[\text{PMB}]^+$), 91 (30.0%, $[\text{Bn}]^+$); HR-FDMS calcd. for $\text{C}_{32}\text{H}_{43}\text{O}_8$ $[\text{M}+\text{H}]^+$: 555.2958, found 555.2986.

Compound 1-70.

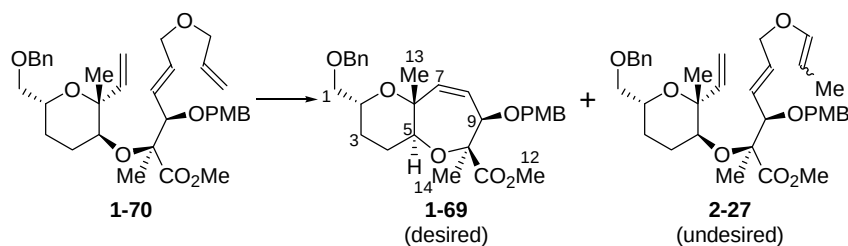


To a solution of **2-26** (200.5 mg, 0.3615 mmol) in DMF (10 mL) were added NaH (61.0 mg, assay 60%, 1.53 mmol), TBAI (70.7 mg, 0.191 mmol) and 3-bromo-propene (125.0 μL , 1.48 mmol) at 0 $^\circ\text{C}$, and the reaction mixture was stirred at 25 $^\circ\text{C}$ for 1.5 h. After saturated aqueous NH_4Cl (5.0 mL) was added at 0 $^\circ\text{C}$, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 g, hexane/AcOEt = 9 $\rightarrow$ 8) to give **1-70** (184.9 mg, 0.3109 mmol, 86%).

1-70: a pale yellow oil; $[\alpha]_{\text{D}}^{26} = -14.8$ ($c = 0.315$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 3088, 3064, 2990,

2948, 2858, 1738, 1644, 1613, 1586, 1514, 1497, 1454, 1376, 1303, 1248, 1173, 1097, 992, 924, 821, 738, 698, 665; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 1.24-1.38 (1H, m, $\text{H}_{3\text{ax.}}$), 1.30 (3H, s, H_{17} (Me)), 1.35 (3H, s, H_{18} (Me)), 1.53-1.79 (3H, m, $\text{H}_{3\text{eq.}}$, H_4), 3.38 (1H, dd, $J = 5.1, 9.9$ Hz, H_{1a}), 3.44-3.54 (2H, m, H_{1b} , H_5), 3.64 (3H, s, H_{20} (Me)), 3.74-3.85 (1H, m, H_2), 3.80 (3H, s, PMB), 3.92-4.02 (5H, m, H_{10} , H_{13} , H_{14}), 4.37 (1H, d, $J = 11.5$ Hz, PMB), 4.50-4.63 (3H, m, Bn, PMB), 5.01 (1H, dd, $J = 1.8, 10.8$ Hz, H_{8a}), 5.19 (1H, dd, $J = 0.9, 10.5$ Hz, H_{16a}), 5.23-5.34 (2H, m, H_{8b} , H_{16b}), 5.60 (1H, dd, $J = 7.8, 15.6$ Hz, H_{11}), 5.75 (1H, td, $J = 5.5, 15.6$ Hz, H_{12}), 5.91 (1H, dddd, $J = 5.5, 10.5, 16.1, 22.7$ Hz, H_{15}), 6.05 (1H, dd, $J = 10.8, 17.4$ Hz, H_7), 6.85 (2H, d, $J = 8.6$ Hz, PMB), 7.21 (2H, d, $J = 8.6$ Hz, PMB), 7.24-7.37 (5H, m, Bn); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) 16.3 (CH_3), 16.6 (CH_3), 25.7 (CH_2), 28.5 (CH_2), 52.2 (CH_3), 55.6 (CH_3), 69.4 (CH), 70.3 (CH_2), 71.2 (CH_2), 71.3 (CH_2), 73.8 (CH_2), 74.0 (CH_2), 75.2 (CH), 76.6 (C), 82.1 (C), 84.4 (CH), 112.7 (CH_2), 114.0 ($\text{CH}\times 2$), 117.4 (CH_2), 127.9 (CH), 128.0 ($\text{CH}\times 2$), 128.7 ($\text{CH}\times 2$), 128.9 (CH), 129.7 ($\text{CH}\times 2$), 130.7 (C), 132.8 (CH), 135.0 (CH), 138.9 (C), 144.3 (CH), 159.5 (C), 174.2 (C); LR-FDMS m/z 595 (12.9%, $[\text{M}+1]^+$), 594 (13.1%, $[\text{M}]^+$), 121 (bp, $[\text{PMB}]^+$), 91 (24.8%, $[\text{Bn}]^+$); HR-FDMS calcd. for $\text{C}_{35}\text{H}_{46}\text{O}_8$ $[\text{M}]^+$: 594.3193, found 594.3240.

Compound 1-69.



To a refluxing solution of **1-70** (52.3 mg, 87.9 μmol) in 1,2-dichloroethane (50.0 mL) was added a solution of the 2nd generation Hoveyda-Grubbs' catalyst (8.3 mg, 13 μmol) in 1,2-dichloroethane (5.0 mL) and 1,4-benzoquinone (21.0 mg, 194 μmol), and the reaction mixture was refluxed for 18 h. After cooling to ambient temperature, the reaction mixture was stirred under O_2 atmosphere for 1 h to inactivate the catalyst and then condensed under reduced pressure. The resulting residue was purified by column chromatography (Florisil[®] 3.0 g and silica gel 2.5 g, hexane/AcOEt = 10 $\rightarrow$ 5) to give **1-69** (desired, 31.6 mg, 63.6 μmol , 72%) and olefin isomer **2-27**

(undesired, 7.6 mg, 13 μ mol, 15%).

1-69: a pale yellow oil; $[\alpha]_D^{26} = -155$ ($c = 0.265$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 3062, 3027, 2948, 1764, 1732, 1693, 1658, 1612, 1586, 1514, 1497, 1454, 1375, 1301, 1249, 1173, 1099, 1036, 990, 912, 861, 821, 793, 737, 699, 665, 645, 614; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.32-1.40 (1H, m, $\text{H}_{3\text{ax}}$), 1.47 (3H, s, H_{13} (Me)), 1.52 (3H, s, H_{14} (Me)), 1.69-1.91 (3H, m, $\text{H}_{3\text{eq}}$, H_4), 3.38 (1H, dd, $J = 4.8, 9.9$ Hz, H_{1a}), 3.47 (1H, dd, $J = 5.7, 9.9$ Hz, H_{1b}), 3.69 (3H, s, H_{12} (Me)), 3.73-3.83 (2H, m, H_2 , H_5), 3.80 (3H, s, PMB), 4.04 (1H, d, $J = 6.4$ Hz, H_9), 4.32 (1H, d, $J = 10.8$ Hz, PMB), 4.54 (1H, d, $J = 12.1$ Hz, Bn), 4.56 (1H, d, $J = 10.8$ Hz, PMB), 4.60 (1H, d, $J = 12.1$ Hz, Bn), 5.57 (1H, dd, $J = 6.4, 12.3$ Hz, H_8), 5.97 (1H, d, $J = 12.3$ Hz, H_7), 6.84 (2H, d, $J = 8.6$ Hz, PMB), 7.18 (2H, d, $J = 8.6$ Hz, PMB), 7.24-7.37 (5H, m, Bn); ^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) 16.2 (CH_3), 20.0 (CH_3), 26.6 (CH_2), 28.4 (CH_2), 52.3 (CH_3), 55.2 (CH_3), 68.5 (CH), 70.5 (CH_2), 72.1 (CH), 73.3 (CH_2), 73.4 (CH_2), 77.9 (CH), 78.9 (C), 82.1 (C), 113.6 ($\text{CH}\times 2$), 122.1 (CH), 127.5 (CH), 127.7 ($\text{CH}\times 2$), 128.3 ($\text{CH}\times 2$), 129.4 ($\text{CH}\times 2$), 130.1 (C), 138.4 (C), 145.1 (CH), 159.1 (C), 173.1 (C); LR-FDMS m/z 497 (37.6%, $[(\text{M}+\text{H})^+]$), 496 (bp, $[\text{M}^+]$), 121 (39.0%, $[\text{PMB}^+]$), 91 (12.7%, $[\text{Bn}^+]$); HR-FDMS calcd. for $\text{C}_{29}\text{H}_{36}\text{O}_7$ $[\text{M}^+]$: 496.2461, found 496.2463.

Chapter 3.

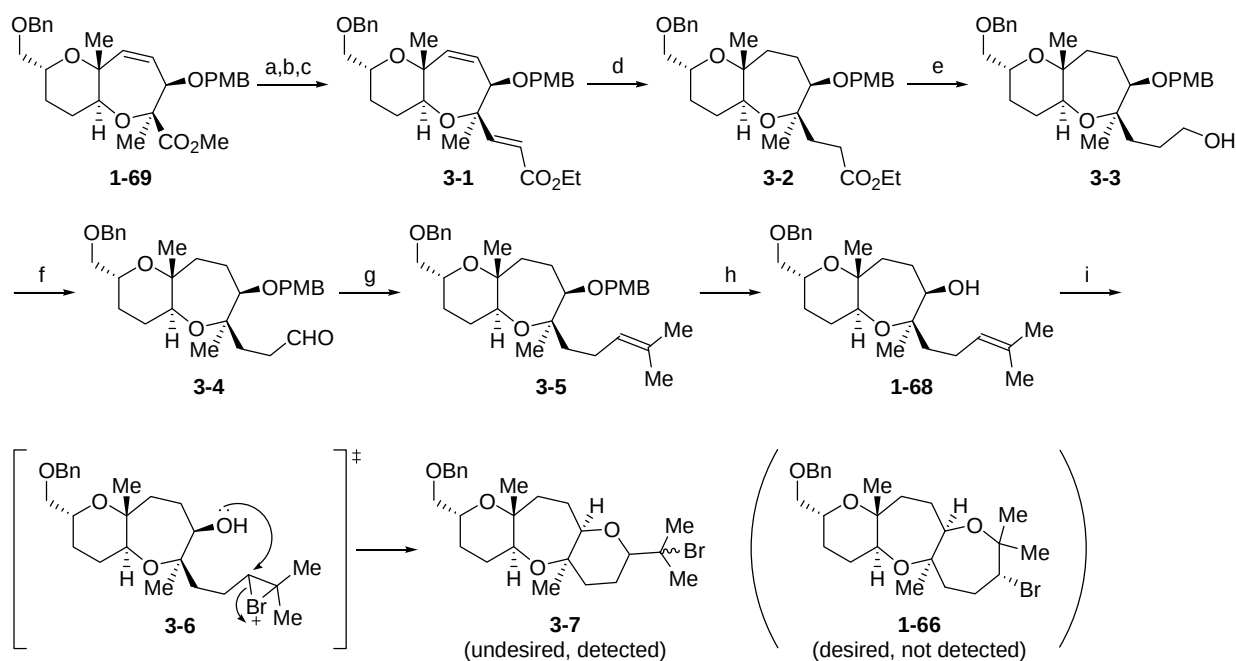
Synthetic Studies of the D-ring of Aramatol F

3-1. The first approach based on Morimoto's intramolecular bromoetherification

As described in the previous chapter, the synthetic process of BC-ring **1-66** based on chirality-transferring Ireland-Claisen rearrangement and RRCM was established. Next, the author attempted to construct the D-ring of armatol F by the application of Morimoto's intramolecular bromoetherification¹ to isopropylidene alcohol **1-68**, which was synthesized from **1-69**. Because the bromoetherification was effectively applied to the formation of *trans*-fused 7-membered ring bromoethers, the author expected a facile formation of a *cis*-fused analogue by the reaction (Scheme 3-1).

First, reduction of **1-69** with lithium aluminum hydride gave an alcohol, which was then subjected to Dess-Martin oxidation² followed by a HWE reaction³ to afford unsaturated ester **3-1** (90% over three steps). The double bonds of **3-1** were hydrogenated by use of NBSH⁴ (90%), and the resulting saturated ester **3-2** was converted to primary alcohol **3-3** with DIBAH (77%). After oxidation of **3-3** with DMPI,² the resulting aldehyde **3-4** was subjected to a Wittig reaction⁵ to introduce an isopropylidene group. However, the reactivity of **3-4** to the ylide prepared from isopropyltriphenylphosphonium iodide was poor, and alkene **3-5** was furnished in only 15% yield over two steps. Finally, treatment of **3-5** with DDQ removed the PMB group to produce **1-68** (49%).⁶

Subsequently, isopropylidene alcohol **1-68** was treated with NBS in the presence of molecular sieves 4 Å in HFIP at 0 °C according to Morimoto's report. However, the reaction only produced undesired tricyclic ether **3-7** in relatively high yield (74%), and *trans/cis*-6,7,7-tricyclic ethers **1-66** was not detected. This result indicated that bromonium ion **3-6**, formed from **1-68** with NBS, did not promote the desired 7-*endo* cyclization, but induced 6-*exo* cyclization. This result suggests that formation of a 7,7-*cis*-fused system is outside the scope of application of Morimoto's biomimetic conditions.



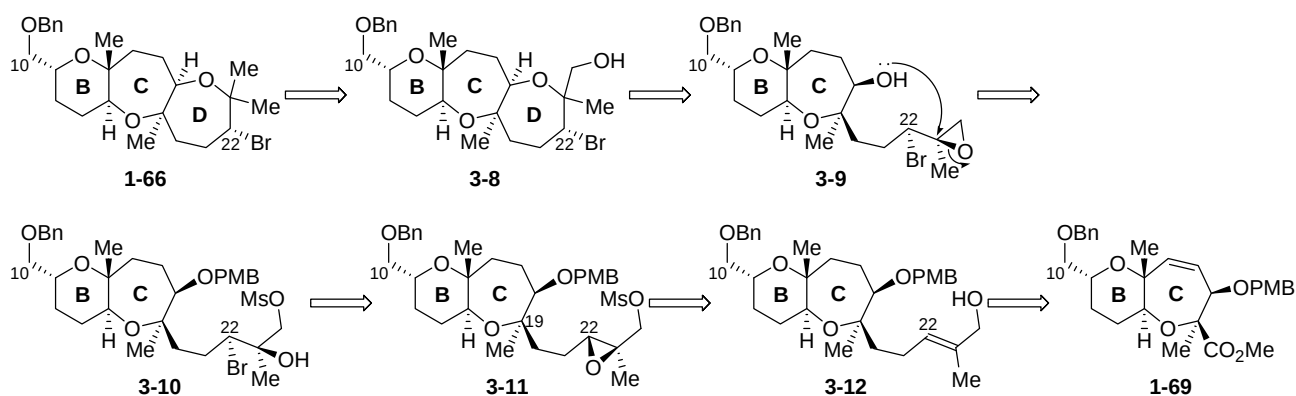
Scheme 3-1. An attempt to cyclize isopropylidene alcohol 1-68 by Morimoto's intramolecular bromoetherification. Reagents and conditions: (a) LiAlH_4 (4.4 eq), THF, 0 °C, 15 min; (b) DMPI (11 eq), CH_2Cl_2 , 25 °C, 2.5 h; (c) diethyl ethoxycarbonylmethylphosphonate (18 eq), NaH (16 eq), THF, 0 → 25 °C, 14 h, 90% from **1-69**; (d) NBSH (50 eq), Et_3N (125 eq), CH_2Cl_2 , 25 °C, 16 h, 90%; (e) DIBAH (4.1 eq), CH_2Cl_2 , 0 °C, 15 min, 77%; (f) DMPI (12 eq), CH_2Cl_2 , 25 °C, 2 h; (g) isopropyltriphenylphosphonium iodide (3.5 eq), BuLi (3.0 eq), THF, 0 → 25 °C, 1 h, 15% from **3-4**, 42% recovery of **3-4**; (h) DDQ (2.4 eq), CH_2Cl_2 - H_2O (10:1), 0 °C, 50 min, 49%; (i) NBS (3.1 eq), MS 4A, HFIP, 0 °C, 30 min, **3-7**: 74%, **1-66**: not detected.

3-2. The second approach based on regioselective formation of a bromoepoxide and its 7-*exo* cyclization

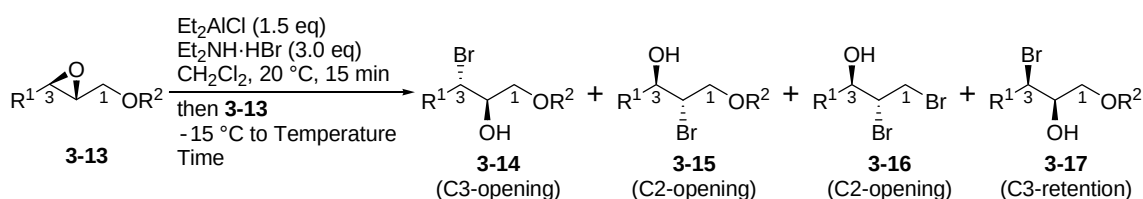
After consideration of the results of the preceding section, the author designed a new plan for the synthesis of the D-ring by 7-*exo* cyclization of a hydroxy epoxide as shown in Scheme 3-2. The construction of the D-ring of BCD-ring **1-52** was envisioned by the 7-*exo* cyclization of hydroxy epoxide **3-9** to form **3-8** followed by the removal of the hydroxyl group of **3-8**. The 7-*exo-tet* cyclization is permitted in Baldwin's rule,⁷ and several successful examples of this mode of cyclization have been reported.

In the preparation of hydroxy epoxide **3-9**, regio- and stereoselective formation of the bromoepoxide was a problem. The author intended to solve the problem by applying a process including regioselective epoxide ring opening with bromide ion and chemoselective epoxide cyclization to a bromoepoxide, reported by Murai.⁸ Thus, epoxymesylate **3-11**, which would be prepared via Sharpless asymmetric epoxidation of allylic alcohol **3-12**, was planned to be subjected to regioselective bromohydrin formation to give **3-10** followed by chemoselective epoxide formation. Murai and coworkers reported that, in the presence of diethylaluminum chloride, 2,3-epoxy-1-sulfonates reacted with diethylamine hydrobromide highly regioselectively at C3 position of the epoxide in an S_N2 fashion to produce 3-bromo-2-hydroxy-1-sulfonates **3-14** in good yield, as shown in (Table 3-1). Murai also reported selective formation of 3-bromo-1,2-epoxides from 3-bromo-2-hydroxy-1-sulfonates **3-14**.

E-allyl alcohol **3-12** was scheduled to be derived from BC-ring **1-69** via a process including HWE and Wittig reactions.^{3,5}



Scheme 3-2. The second approach to the D-ring formation.



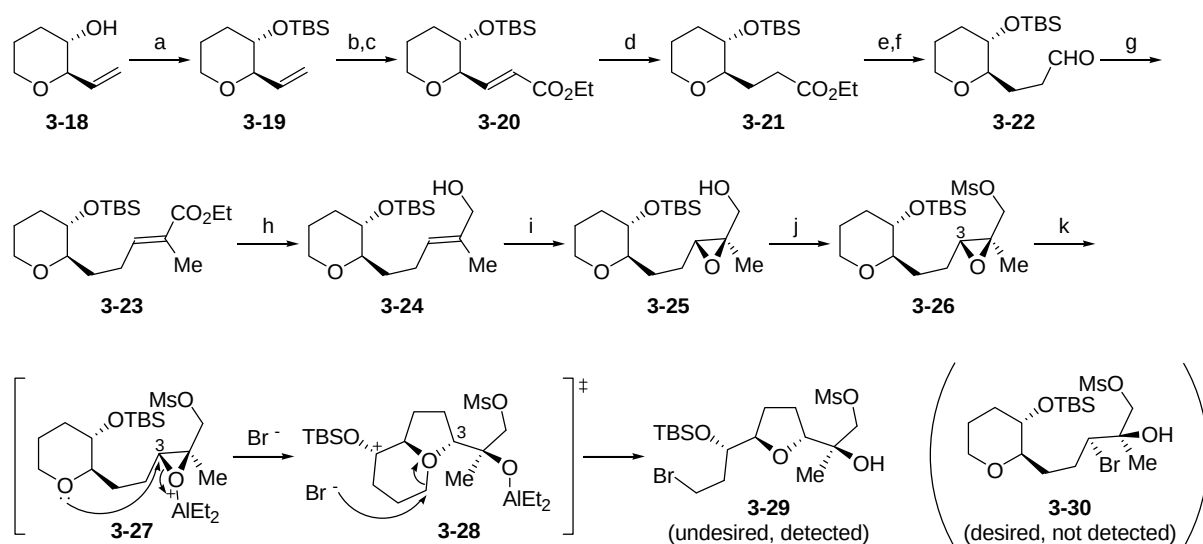
Entry	3-13		Temperature	Time	Ratio				Yield
	R ¹	R ²			3-14	3-15	3-16	3-17	
1	Pr	H	-5 °C	2 h	96	4	0	0	98%
2	Pr	Ms	-5 °C	2 h	120	1	0	0	100%
3	Pr	Ts	-5 °C	2 h	160	1	0	0	100%
4	Cy	Ms	-5 °C	4 h	97	3	0	0	100%
5	Ph	Ms	-5 °C	2 h	98	0	0	2	100%

Table 3-1. Regioselective bromohydrin formation from epoxy sulfonates reported by Murai.⁸

First, in order to estimate the availability of Murai's regioselective bromohydrin formation and 7-*exo* cyclization for the construction of the D-ring, a model synthesis of bromohydrin **3-30** was attempted from the known alcohol **3-18**,⁹ which was preparable from tri-*O*-acetyl-D-glucal over eight steps, as shown in Scheme 3-3.

After alcohol **3-18** was protected with TBSCl (52%), the resulting TBS-ether **3-19** was subjected to one-pot dihydroxylation/oxidative diol cleavage^{10,11} followed by a HWE reaction³ to produce unsaturated ester **3-20** (76% over two steps). Hydrogenation of **3-20** (100%) and the subsequent two-step reduction/oxidation sequence afforded aldehyde **3-22**, which was then reacted with a stable ylide to provide *E*-enoate **3-23** in 26% isolated yield (over three steps) with low selectivity (*E*:*Z* = 2:1). Next, ester **3-23** was reduced to *E*-allylic alcohol **3-24** (69%), which was subjected to Katsuki-Sharpless asymmetric epoxidation¹² to afford hydroxy epoxide **3-25** (66%).

After mesylation of **3-25**, the resulting epoxy mesylate (**3-26**) was treated with diethylaluminum chloride and diethylamine hydrobromide according to Murai's report. However, desired bromohydrin **3-30** was not detected, and, surprisingly, five-membered-cyclic ether **3-29** was produced (31% over two steps) along with the recovery of epoxy mesylate **3-26** (64%). The formation of **3-29** from **3-26** would be explained as follows: the oxygen of the oxane of **3-26** instead of bromide ion first attacked at C3 of the epoxide (**3-27**) and produced a bicyclic oxonium ion (**3-28**), which was then reacted with bromide ion at the terminal carbon to produce oxolane **3-29**.



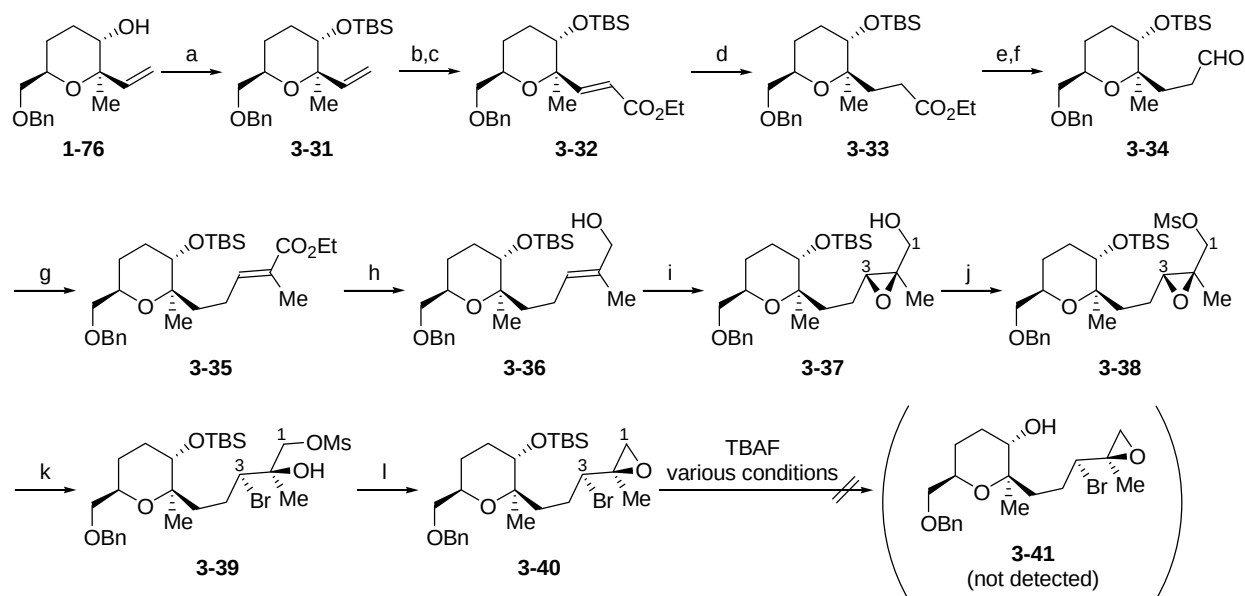
Scheme 3-3. Attempting bromohydrin formation using a simple model without a junction methyl group.

Reagents and conditions: (a) TBSCl (1.2 eq), 2,6-lutidine (2.3 eq), DMF, 25 °C, 20 h, 52%; (b) OsO₄ (0.05 eq), NMO (3.3 eq), 1,4-dioxane-pH 7 buffer (1:1), 25 °C, 22 h, then NaIO₄ (2.6 eq), 25 °C, 7 h; (c) diethyl ethoxycarbonylmethylphosphonate (12 eq), NaH (9.9 eq), THF, 0 → 25 °C, 14 h, 76% from **3-19**; (d) H₂, 5% Pd/C, AcOEt, 21.5 h, 100%; (e) LiAlH₄ (1.6 eq), THF, 0 °C, 2.5 h; (f) DMPI (2.9 eq), CH₂Cl₂, 25 °C, 2 h; (g) (1-ethoxycarbonyl ethylidene)triphenylphosphorane (2.0 eq), toluene, 25 °C, 12h, 26% from **3-21**, *E:Z* = 2:1; (h) LiAlH₄ (3.0 eq), THF, 0 °C, 2.5 h, 69%; (i) D-(−)-DET (0.25 eq), Ti(O*i*-Pr)₄ (0.20 eq), TBHP (2.0 eq), MS 4A, CH₂Cl₂, −40 → −25 °C, 14.5 h, 66%; (j) Ms₂O (2.2 eq), Et₃N (4.8 eq), CH₂Cl₂, 35 °C, 7 h; (k) Et₂AlCl (1.5 eq), Et₂NH·HBr (3.3 eq), CH₂Cl₂, −20 → 25 °C, 7 h, **3-29**: 31% from **3-25**, **3-30**: not detected, 64% recovery of **3-26**.

Although the above model study gave a problem of an intramolecular nucleophilic attack, the problem was attributable to the inappropriate design of the model compound and was expected to be avoidable by use of an appropriate system. Because epoxy mesylate **3-11**, a designed intermediate in the second plan shown in Scheme 3-2, has a methyl group at C19 as a steric hindrance to the nucleophilic oxygen of the oxepane, the unfavorable intramolecular attack of the oxygen would be inhibited in the bromohydrin formation from **3-11**. For this reason, oxane **1-76**¹³ possessing a methyl group at the carbon adjacent to the oxygen of the oxane was adopted as a starting material for a revised model synthesis (Scheme 3-4).

Oxane **1-76** was first transformed to epoxy mesylate **3-38** through a manner similar to Scheme 3-3. Then, mesylate **3-38** was treated with diethylaluminum chloride and diethylamine hydrobromide at $-20\text{ }^{\circ}\text{C}$, and the reaction mixture was allowed to warm to ambient temperature. As a result, bromohydrin **3-39** was produced in 67% yield over two steps without any byproduct such as **3-29**. Thus, the problem of an intramolecular nucleophilic attack of the ether oxygen of the substrate during bromohydrin formation was avoided.

Next, formation of bromoepoxide **3-40** was attempted. When **3-39** was treated with potassium carbonate, the tertiary hydroxyl group attacked selectively at the carbon at C3 to give **3-38** as a main product, and the desired epoxide **3-40** was obtained in only 12%. Although the yield of **3-40** was low, the author intended to examine the 7-*exo* cyclization after the removal of the TBS group of **3-40**. However, the removal of the TBS group was failed even under various conditions. Therefore, it was found that an alternative protecting group was required instead of the TBS group.



Scheme 3-4. Attempting D-ring formation by the second approach using a model compound with a junction methyl group. Reagents and conditions: (a) TBSCl (1.5 eq), imidazole (3.5 eq), DMF, 25 °C, 17.5 h, 79%, 19% recovery of **1-76**; (b) OsO₄ (0.05 eq), NMO (3.3 eq), 1,4-dioxane-pH 7 buffer (1:1), 25 °C, 14.5 h, then NaIO₄ (2.7 eq), 25 °C, 4 h; (c) diethyl ethoxycarbonylmethylphosphonate (12 eq), NaH (10 eq), THF, 0 → 25 °C, 14 h, 84% from **3-31**; (d) NBSH (5.1 eq), Et₃N (11 eq), CH₂Cl₂, 25 °C, 13 h; (e) DIBAH (2.2 eq), CH₂Cl₂, 0 °C, 50 min; (f) DMPI (3.1 eq), NaHCO₃ (6.1 eq), CH₂Cl₂, 25 °C, 1.5 h; (g) (1-ethoxycarbonyl ethylidene)triphenylphosphorane (2.1 eq), toluene, 25 °C, 15 h; (h) DIBAH (1.7 eq), CH₂Cl₂, 0 °C, 20 min, 58% from **3-32**; (i) D-(-)-DET (0.25 eq), Ti(O*i*-Pr)₄ (0.20 eq), TBHP (2.0 eq), MS 4A, CH₂Cl₂, -40 → -25 °C, 17 h, 95%; (j) Ms₂O (2.9 eq), Et₃N (6.4 eq), CH₂Cl₂, 35 °C, 70 min; (k) Et₂AlCl (1.5 eq), Et₂NH·HBr (7.0 eq), CH₂Cl₂, -20 → 25 °C, 2 h, 67% from **3-37**, 16% recovery of **3-38**; (l) K₂CO₃ (1.1 eq), MeOH, -20 °C, 70 min, **3-40**: 12%, **3-38**: 86%.

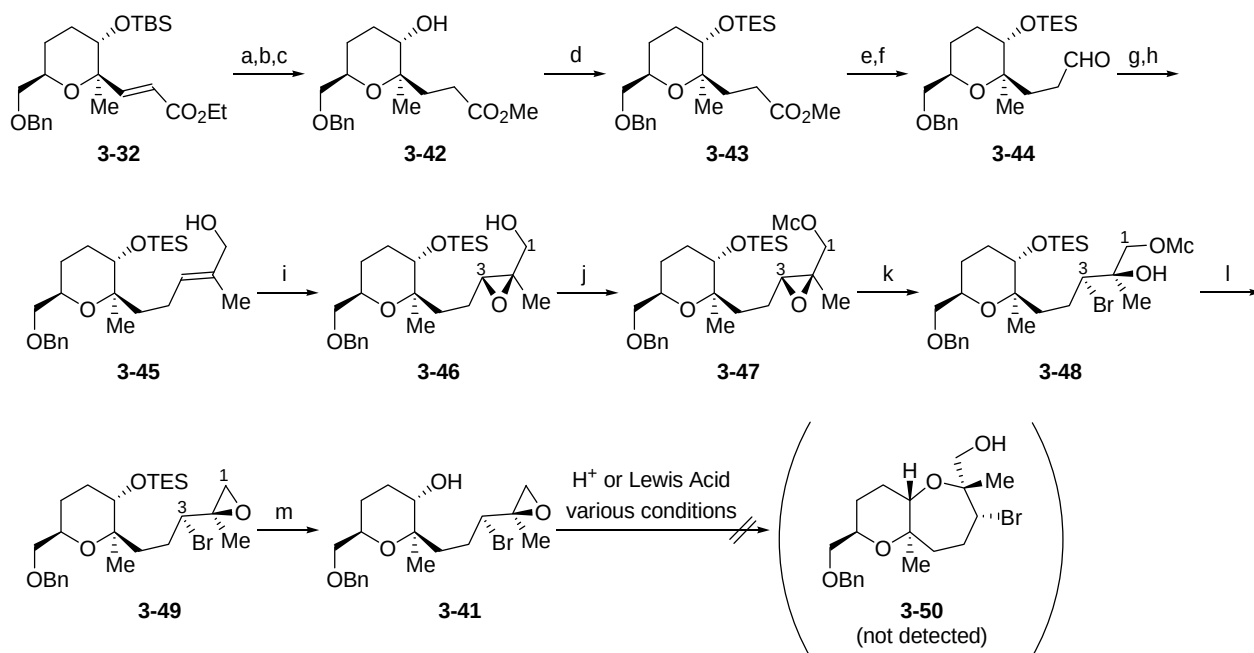
To improve the regioselectivity of epoxide formation from the 3-bromo-2-hydroxy-1-sulfonyloxy substrate, the author newly employed monochloromethanesulfonyl group having higher leaving ability than methanesulfonyl group for the terminal sulfonyl group of the substrate. Although the installation of a monochloromethanesulfonyl group should be performed to a hydroxy epoxide before the bromohydrin formation, the regioselectivity in the bromohydrin formation from the resulting monochloromethanesulfonyloxy epoxide was expected to be similar to that of **3-38**. In addition, to facilitate the deprotection preparing **3-41**, the TBS group of **3-40** was replaced by a TES group.

The revised model synthesis is illustrated in Scheme 3-5. Intermediate TBS ether **3-32** was first converted to TES ether **3-43** by a four-step process (59% over four steps). The transformation

of **3-43** to **3-46** was according to the above model synthesis. Hydroxy epoxide **3-46** was then converted to epoxy monochloromethanesulfonate **3-47**, which was subjected to Murai's protocol to produce desired product **3-48** in 46% yield over two steps along with recovery of **3-47** (26%). In the sulfonylation step, chlorination at C1 was observed and resulted in the low yield of **3-48**.

With monochloromethanesulfonate **3-48** in hand, the author next examined the bromoepoxide formation. When bromohydrin **3-48** was treated with potassium carbonate, desired epoxide **3-49** was formed preferentially in 72% yield along with epoxy sulfonate **3-47** in 28% yield. Further, deprotection of the TES group proceeded smoothly to produce hydroxy epoxide **3-41**. Thus, the above described two issues, selective bromoepoxide formation and the final deprotection, were solved.

Hydroxy epoxide **3-41**, however, was not cyclized even under various conditions using several Brønsted- and Lewis-acids. Due to the difficulty of 7-*exo* cyclization of **3-41**, the second plan was brought to a halt.



Scheme 3-5. Attempting D-ring formation by the second approach using a modified model compound with a junction methyl group. Reagents and conditions: (a) NBSH (4.1 eq), Et₃N (8.7 eq), CH₂Cl₂, 25 °C, 19 h; (b) TBAF (4.2 eq), THF, 45 °C, 2.5 h; (c) TMSCHN₂ (2.7 eq), benzene-MeOH (3:1), 25 °C, 10 min, 89% from **3-32**; (d) TESOTf (2.0 eq), 2,6-lutidine (4.1 eq), CH₂Cl₂, 25 °C, 20 h, 66%; (e) DIBAH (2.1 eq), CH₂Cl₂, 0 °C, 10 min; (f) DMPI (3.0 eq), NaHCO₃ (6.9 eq), CH₂Cl₂, 25 °C, 1.5 h; (g) (1-ethoxycarbonylethylidene)triphenylphosphorane (2.1 eq), toluene, 25 °C, 12.5 h; (h) DIBAH (2.6 eq), CH₂Cl₂, 0 °C, 20 min, 71% from **3-43**; (i) D-(-)-DET (0.30 eq), Ti(O*i*-Pr)₄ (0.24 eq), TBHP (2.2 eq), MS 4A, CH₂Cl₂, -40 → -25 °C, 17.5 h, 73%; (j) MeCl (3.0 eq), Et₃N (6.3 eq), CH₂Cl₂, 25 °C, 2 h; (k) Et₂AlCl (1.5 eq), Et₂NH·HBr (16 eq), CH₂Cl₂, -20 → 25 °C, 18 h, 46% from **3-46**, 26% recovery of **3-47**; (l) K₂CO₃ (1.0 eq), MeOH, -20 °C, 1 h, **3-49**: 72%, **3-47**: 28%; (m) TBAF (1.0 eq), 1,4-dioxane, 25 °C, 4.5 h, 96%.

3-3. The third approach based on regioselective epoxide opening with bromide ion and RCM

The failure of oxepane formation by intramolecular bromoetherification and 7-*exo* cyclization of a hydroxy epoxide in the above described model synthesis suggested that the D-ring was difficult to construct by a C-O bond forming intramolecular nucleophilic reaction. Therefore, the author next intended to construct the D-ring by C-C bond formation using ring-closing olefin metathesis (RCM).

However, the use of RCM posed a problem of the timing of bromine installation at C22 during the D-ring construction. Hirose, a collaborator in the author's laboratory, encountered the same problem in his synthesis of the A-ring of armatol F.¹⁴ Although, in his initial approach, the A-ring skeleton having a hydroxy group at C3 was successfully synthesized,^{14,15} the installation of bromine group at C3 by S_N2 reaction was difficult to achieve due to the steric hindrance of the dimethyl group at C2 and undesired neighboring participation of the oxepane oxygen (Table 3-1). Because the situation of the D-ring is similar to that of the A-ring, the author decided to install the bromine at C22 before the D-ring closure by RCM.

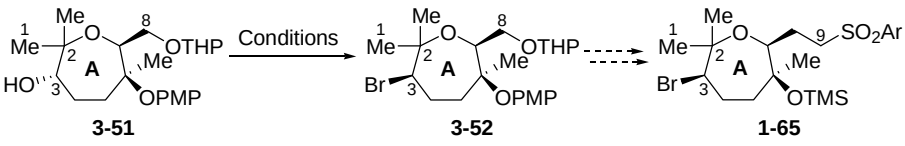
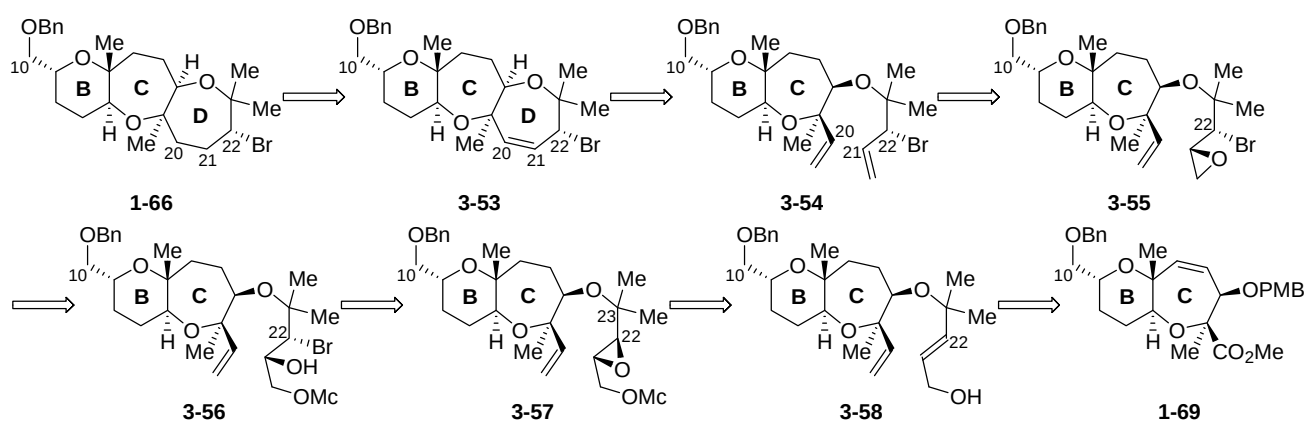
		
Entry	Conditions	Results
1	Oct ₃ P (10 eq), CBr ₄ (5.0 eq), toluene, 70 °C, 3.5 h	Decomposition
2	1) Tf ₂ O (10 eq), 2,6-lutidine (20 eq), CH ₂ Cl ₂ , 24 °C, 8 h 2) LiBr (excess), THF, 27 °C, 3 h	Decomposition
3	MgCl (5.0 eq), DMAP (0.1 eq), TBAB (excess), 2,6-lutidine (15 eq) THF, 25 °C, 10 h	Decomposition

Table 3-1. Attempting bromination of 3-51 aiming at the synthesis of A-ring of armatol F by Hirose.¹⁴

On the other hand, aforementioned model synthesis demonstrated an effective, stereoselective installation of a bromine group at C22 by Murai's regioselective epoxy sulfonate ring opening by bromide ion. Therefore, the author intended to apply this reaction to the construction of the C22-bromine group in the third approach.

The third approach to the BCD-ring of armatol F is shown in Scheme 3-6. In this approach,

RCM was adopted for the cyclization of the D-ring with C20-21 double bond formation at the final stage of the synthesis. Thus, BCD-ring **1-66** would be derived from diene **3-54** by RCM followed by hydrogenation of the C20-21 double bond of **3-53**. The installation of the bromine group at C22 was planned to be performed stereoselectively by the regioselective epoxy sulfonate ring opening reaction before the RCM step. Consequently, epoxy sulfonate **3-57** would be converted regioselectively to bromohydrin **3-56**, which would lead to bromoepoxide **3-55** selectively under basic conditions, and the epoxide (**3-55**) would be deoxygenated¹⁶ to form diene **3-54**. For the preparation of epoxy sulfonate **3-57**, Katsuki-Sharpless asymmetric epoxidation¹² of **3-58** followed by monochloromethanesulfonylation would be employed. Allyl alcohol **3-58** would be obtainable from BC-ring **1-69**.

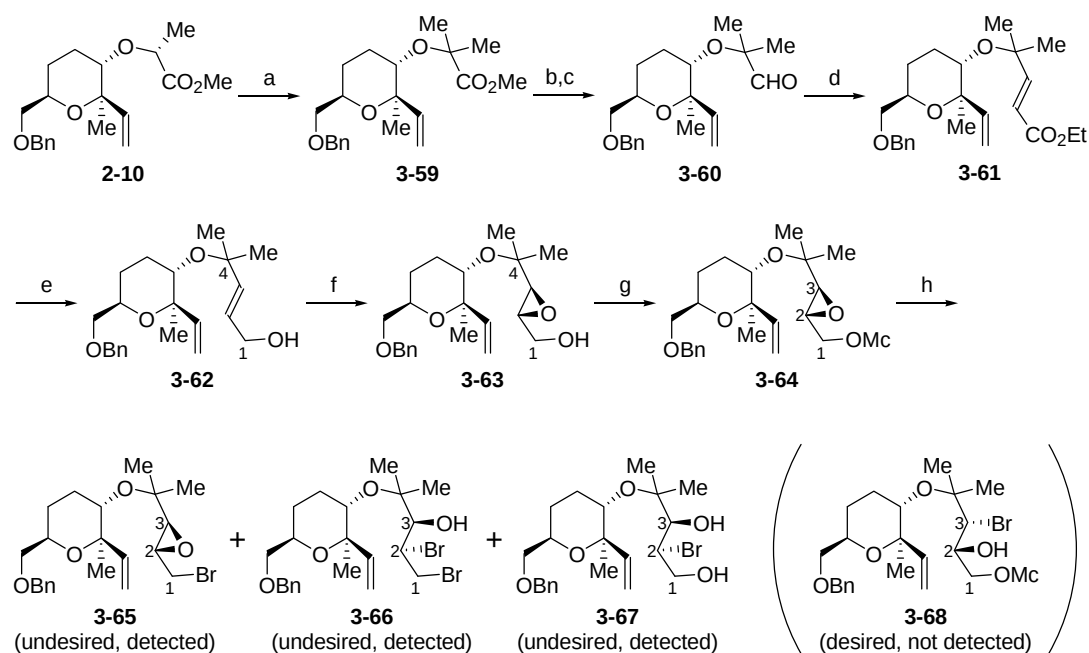


Scheme 3-6. The third approach to the D-ring formation.

Although the availability of Murai's bromohydrin formation was shown in the above model synthesis, the bulky dimethyl group at C23 of epoxy sulfonate **3-57** raised a suspicion that the bulkiness would hinder the attack of bromide ion at C22 of the epoxide. Thus, in order to estimate the applicability of Murai's method to **3-57**, a preliminary model study was performed using sterically hindered epoxy sulfonate **3-64** (Scheme 3-7).

Epoxy sulfonate **3-64** was synthesized from methyl ester **2-10**. First, ester **2-10** was treated with KHMDS to form an enolate, which was reacted with methyl iodide to afford α -methylated product **3-59**. Transformation of **3-59** by a three-step process including reduction, oxidization, and

HWE reaction³ produced α,β -unsaturated ester **3-61** in 57% yield over four steps. The DIBAH reduction of **3-61** followed by the Katsuki-Sharpless epoxidation¹² provided hydroxy epoxide **3-63** (97% over two steps). Then, the hydroxy epoxide was converted to epoxy monochloromesylate **3-64**, which was immediately used in the next reaction due to instability. When Murai's method was applied to **3-64** under the same conditions as the case of **3-47**, the desired product (**3-68**) was not detected. Among obtained several byproducts, epoxide **3-65**, which would arise from substitution of bromide for the monochloromethanesulfonyloxy group, was obtained as a major component (82%), and C2-opening products **3-66** and **3-67** were also detected in similar yield (<10%), respectively. Accordingly, it is obvious that the bulky dimethyl group at C4 hindered the S_N2 attack of bromide ion at C3 as the author suspected. By this disappointing result, the author decided to apply an alternative method, other than an S_N2-type reaction, to the installation of the bromine group at C22.



Scheme 3-7. A model study for the third approach to the D-ring formation. Reagents and conditions: (a) KHMDS (3.0 eq), MeI (5.1 eq), toluene, $-20 \rightarrow 25$ °C, 1 h; (b) DIBAH (2.6 eq), CH_2Cl_2 , 0 °C, 20 min; (c) DMPI (2.1 eq), NaHO_3 (3.5 eq), CH_2Cl_2 , 25 °C, 2 h; (d) diethyl ethoxycarbonylmethylphosphonate (12 eq), NaH (10 eq), THF, $0 \rightarrow 25$ °C, 1.5 h, 57% from **2-10**; (e) DIBAH (2.5 eq), CH_2Cl_2 , 0 °C, 20 min; (f) D-(-)-DET (0.20 eq), $\text{Ti}(\text{O}i\text{-Pr})_4$ (0.15 eq), TBHP (2.0 eq), MS 4A, CH_2Cl_2 , $-40 \rightarrow -25$ °C, 15 h, 97% from **3-61**; (g) MgCl (3.0 eq), Et_3N (6.5 eq), CH_2Cl_2 , 0 °C, 2 h; (k) Et_2AlCl (1.4 eq), $\text{Et}_2\text{NH}\cdot\text{HBr}$ (12 eq), CH_2Cl_2 , $-20 \rightarrow 35$ °C, 19 h, **3-65**: 82%, **3-66**: <10%, **3-67**: <10% from **3-63**, **3-68**: not detected.

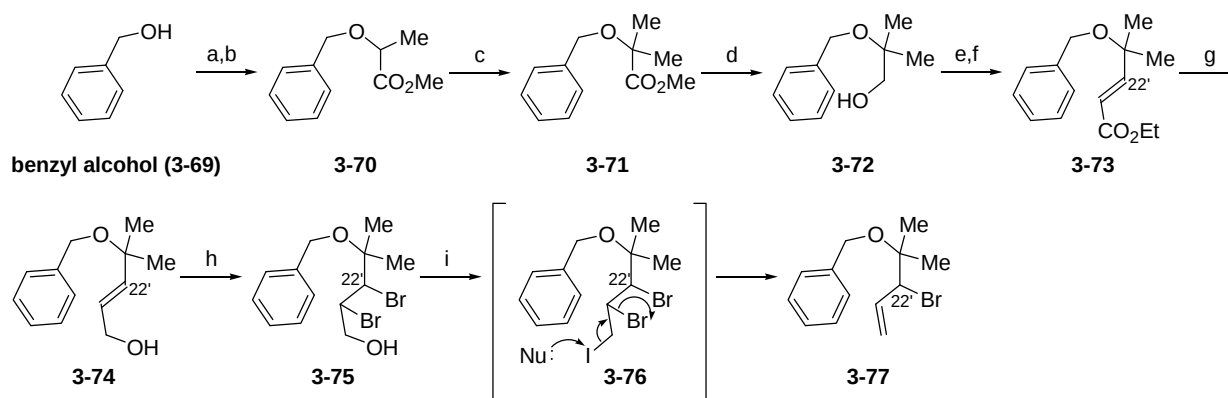
3-4. The fourth approach based on dibromination, vinylation of bromohydrin, and RCM

The problems in the D-ring synthesis are summarized as follows: 1) for the D-ring formation, cyclization by a C-O bond forming intramolecular S_N2 reaction is ineffective; 2) in the presence of the dimethyl group at C23, installation of a bromine group at C22 position through S_N2 reaction is almost impossible. To solve the former problem, RCM was employed as described in Section 3-3. For the latter problem, an alternative methodology was required.

When the author carefully re-examined the results of the above model synthesis, a hint for the installation of the bromine at C22 was implied from the successful epoxidation of congested allylic alcohol **3-62** shown in Scheme 3-7. Because the dimethyl group at C4 of **3-62** did not interfere with the electrophilic epoxidation, the author expected that the electrophilic dibromination would resist the steric hindrance and could be an effective introduction method for the C22-bromine group. Therefore, the author planned a new route including electrophilic dibromination as a key reaction for introducing the C22-bromine group.

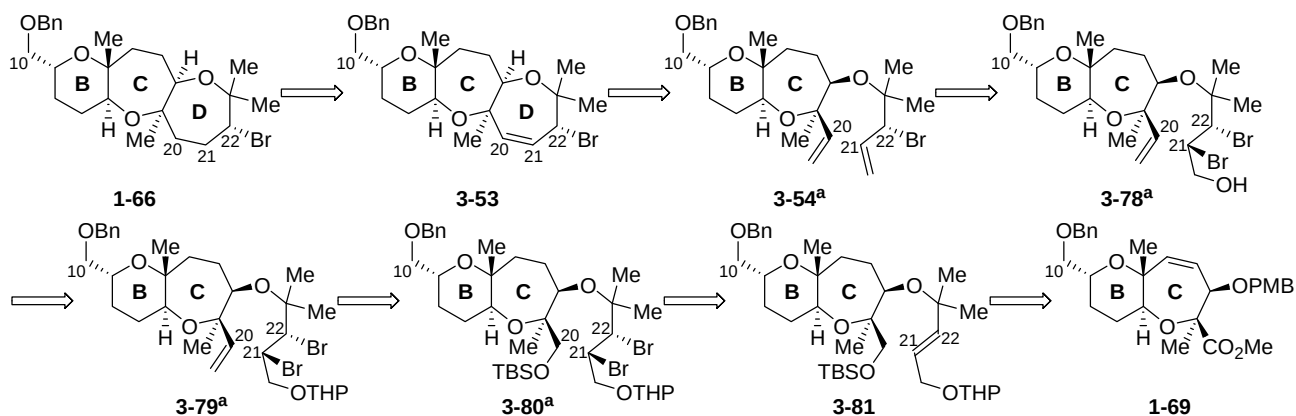
However, there was a question: how would the produced dibromide be converted to an allyl bromide, corresponding to a precursor for the D-ring formation by RCM?

To answer the question and to examine the validity of the above idea for the C22-bromine installation, several model studies were carried out. As a result, a promising method, illustrated in Scheme 3-8, was elaborated. The substrate, allyl alcohol **3-74**, for the model synthesis was prepared from benzyl alcohol (**3-69**) through a seven-step process according to the procedure for the transformation from **2-10** to **3-62** shown in Scheme 3-7. Treatment of **3-74** with bromine in the presence of DTBMP in dichloromethane smoothly produced dibromo alcohol **3-75**, thereby establishing an introduction method for the bromine group at C22. In this reaction, DTBMP, employed as a bulky, non-nucleophilic base, suppressed the fragmentation of ether moiety of **3-74** and/or **3-75** that would be attributable to a small amount of hydrogen bromide formed from bromine. The next dehydroxybromination of **3-75** was performed by treatment with triphenylphosphine and iodine in the presence of DTBMP in toluene at 100 °C to produce the desired allyl bromide (**3-77**). It is presumed that alcohol **3-75** was first iodinated to give **3-76**, which was then attacked at the iodine by any nucleophile species to produce **3-77** via an E2-type elimination process.



Scheme 3-8. Model synthesis of allyl bromide 3-77 via electrophilic dibromination. Reagents and conditions: (a) 2-bromopropionic acid (1.5 eq), NaH (4.9 eq), 1,4-dioxane, 65 °C, 18 h; (b) TMSCHN₂ (2.0 eq), benzene-MeOH (3:1), 25 °C, 15 min, 98% from **3-69**; (c) KHMDs (3.0 eq), MeI (3.0 eq), THF, -78 → 25 °C, 1 h; (d) DIBAH (2.5 eq), CH₂Cl₂, -78 °C, 1 h; (e) SO₃·pyridine (3.0 eq), Et₃N (6.2 eq), CH₂Cl₂-DMSO (6:1), 0 → 25 °C, 13 h; (f) diethyl ethoxycarbonylmethylphosphonate (12 eq), NaH (10 eq), THF, 0 → 25 °C, 3 h; (g) DIBAH (4.5 eq), CH₂Cl₂, -78 °C, 25 min, 63% from **3-70**; (h) Br₂ (1.5 eq), DTBMP (15 eq), CH₂Cl₂, 0 °C, 20 min, 57%; (i) Ph₃P (2.3 eq), I₂ (2.1 eq), DTBMP (20 eq), toluene, 100 °C, 2.5 h, 75%.

According to the above successful model study, the author formulated a new synthetic plan for the D-ring formation as shown in Scheme 3-9. The cyclic structure of the D-ring of **1-66** would be constructed by RCM of diene **3-54** followed by hydrogenation. Diene **3-54** would be prepared from alkene **3-81** on the basis of the model synthesis. However, there was a problem in the timing of the double bond formation at C20 of **3-54**: the double bond should be constructed after the dibromination of **3-81** and before the formation of the labile 1-bromo-2-propene-1-yl moiety at C23. Thus, dibromination of alkene **3-81** was first undertaken to obtain dibromide **3-80**, which would be converted to **3-79** having a vinyl group. Removal of the THP group of **3-79** followed by the iodination/elimination process would produce **3-54**. Because the dibromination of **3-81** would be non-stereoselective and gave a mixture of diastereomers, the undesired stereoisomer at C22 should be separated from the desired isomer at later stage of the synthesis. Alkene **3-81** would be prepared from BC-ring **1-69** through a process similar to that for **3-74**.



Scheme 3-9. The fourth approach to the D-ring formation. (a) including diastereomer at C22 (and C21).

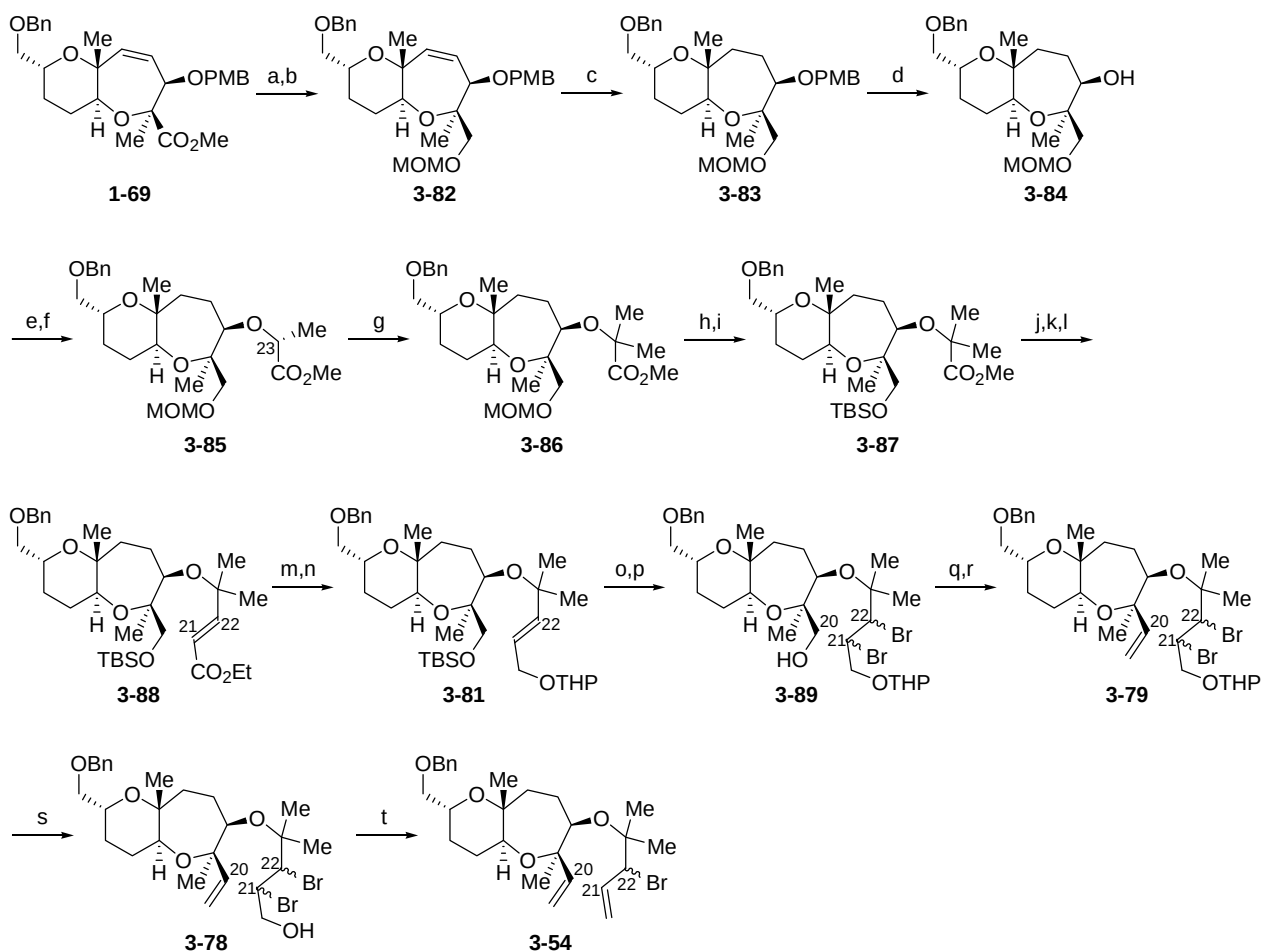
The synthesis of diene **3-54** from **1-69** is shown in Scheme 3-10. First, BC-ring **1-66** was converted to **3-83** through a three-step process including reduction of the ester, MOM-protection of the resulting alcohol, and diimide hydrogenation (100% over three steps). Treatment of **3-83** with DDQ provided secondary alcohol **3-84** in 94% yield.⁶

Next, alcohol **3-84** was selectively converted to (*R*)-lactate derivative **3-85**, because the corresponding (*S*)-lactate ester was predicted not to be deprotonated in the next methylation step from the results of the previous model synthesis of the BC-ring: deprotonation of (*S*)-lactate ester **1-61-S** with KHMDS in the Ireland-Claisen rearrangement was difficult in spite of the easy deprotonation from (*R*)-lactate ester **1-61-R** (Table 1-2).¹⁷ Thus, **3-84** was reacted with (*S*)-(-)-2-bromopropionic acid in the presence of sodium hydride to produce a carboxylic acid with (23*R*)-configuration, which was reacted with trimethylsilyldiazomethane to give methyl ester **3-85** selectively (97% over two steps).¹⁸ Then, ester **3-85** was treated with KHMDS in toluene at -20 °C, and the resulting enolate was reacted with MeOTf to produce **3-86**. The MOM group was removed with TFA to give an alcohol, which was protected with TBSOTf to afford **3-87** in 86% yield over three steps.

Ester **3-87** was transformed to α,β -unsaturated ester **3-88** (78% over three steps) through a process involving reduction, Dess-Martin oxidation,² and HWE reaction.³ Reduction of **3-88** with DIBAH followed by protection with DHP furnished THP ether **3-81** quantitatively over two steps.

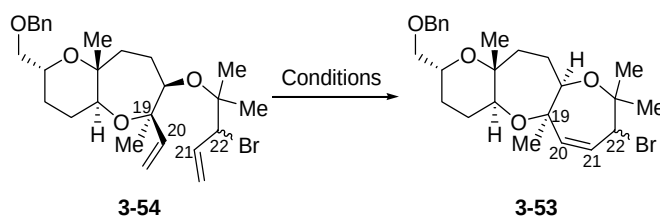
With key intermediate **3-81** in hand, the author next examined the formation of diene **3-54**. Although the treatment of **3-81** with bromine in the presence of DTBMP produced dibromide **3-80**,

removal of the TBS group of **3-80** induced elimination reactions and gave **3-89** only in low yield in spite of attempts to optimize the reaction conditions. Therefore, the TBS group of **3-81** was first removed with TBAF, and the resulting alcohol was reacted with bromine in the presence of DTBMP to produce dibromide **3-89** as a diastereomeric mixture in 65% yield over two steps without any problems. Then, Dess-martin oxidation² of alcohol **3-89** gave an aldehyde, which was subjected to a Wittig reaction⁵ to provide **3-79**. Finally, after the THP group of **3-79** was deprotected under the acidic conditions, the resulting bromohydrin **3-78** was reacted with triphenylphosphine and iodine in toluene at 100 °C according to the above mentioned method and produced diene **3-54** in 91% over two steps.



Scheme 3-10. Synthesis of diene 3-58. Reagents and conditions: (a) LiAlH_4 (2.3 eq), THF, 0 °C, 15 min; (b) MOMBr (3.9 eq), $i\text{Pr}_2\text{NEt}$ (7.8 eq), CH_2Cl_2 , 40 °C, 24 h; (c) NBSH (82 eq), Et_3N (excess), CH_2Cl_2 , 25 °C, 5 d, 100% from **1-69**; (d) DDQ (1.4 eq), CH_2Cl_2 -pH 7 buffer (10:1), 25 °C, 7 h, 94%; (e) (*S*)-(-)- 2-bromopropionic acid (1.9 eq), NaH (22 eq), 1,4-dioxane, 85 °C, 22 h; (f) TMSCHN_2 (5.2 eq), benzene-MeOH (3:1), 25 °C, 10 min, 97% from **3-84**; (g) KHMDS (1.4 eq), MeOTf (3.0 eq), toluene, -20 °C, 30 min; (h) TFA (ca. 1.0 eq), CH_2Cl_2 , 40 °C, 24 h; (i) TBSOTf (5.0 eq), 2,6-lutidine (11 eq), CH_2Cl_2 , 25 °C, 9 h, 86% from **3-85**; (j) LiAlH_4 (2.6 eq), THF, 0 °C, 20 min; (k) DMPI (5.9 eq), NaHCO_3 (20 eq), CH_2Cl_2 , 25 °C, 3 h; (l) diethyl ethoxycarbonylmethylphosphonate (12 eq), NaH (11 eq), THF, 0 → 25 °C, 10 h, 78% from **3-87**; (m) DIBAH (2.4 eq), CH_2Cl_2 , -20 °C, 25 min; (n) 3,4-dihydro-2*H*-pyran (2.4 eq), PPTS (0.2 eq), CH_2Cl_2 , 25 °C, 1 d, 100% from **3-88**; (o) TBAF (20 eq), THF, 40 °C, 19.5 h; (p) Br_2 (1.9 eq), DTBMP (23 eq), CH_2Cl_2 , 0 °C, 1 min, 65% from **3-81**; (q) DMPI (6.3 eq), NaHCO_3 (14 eq), CH_2Cl_2 , 25 °C, 3.5 h; (r) $\text{Ph}_3\text{PCH}_3\text{Br}$ (6.5 eq), NHMDS (6.3 eq), THF, -78 → 25 °C, 14.5 h, 30% from **3-89**; (s) AcOH- H_2O -THF (4:1:2), 40 °C, 23 h; (t) Ph_3P (37 eq), I_2 (35 eq), DTBMP (58 eq), toluene, 100 °C, 26 h, 91% from **3-79**.

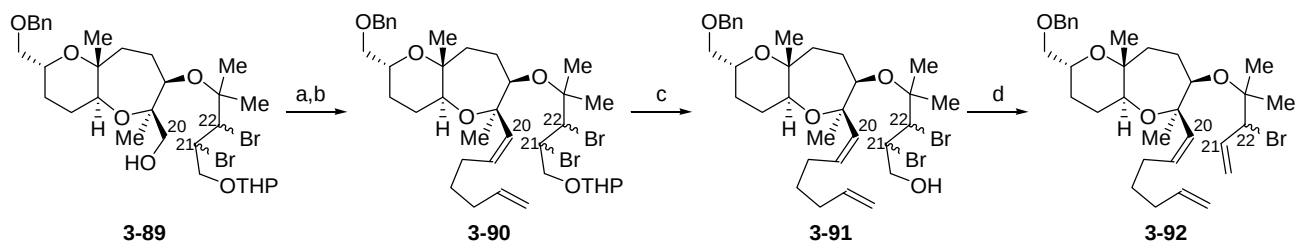
Attempts to cyclize diene **3-54** into **3-53** by RCM are summarized in Table 3-2. From the previous favorable results in RRCM of **1-70**, 1,4-benzoquinone was employed in this RCM reaction as an inhibitor of undesired olefin migration.¹⁹ However, the RCM reaction of **3-54**, catalyzed by the 2nd generation Hoveyda-Grubbs' catalyst (HG-2),²⁰ never proceeded even for prolonged time or at higher temperature. The author thought that this fact would result from the difficulty in the approach of the catalyst to the vinyl groups of **3-54** due to steric hinderance by bulky groups at C19 and C22. Therefore, the author decided to examine altanatively an RRCM²¹ approach to construct the D-ring.



Entry	Conditions	Result
1	HG-2 (0.5 eq), 1,4-benzoquinone (11 eq), (CH ₂ Cl) ₂ ^a , reflux, 15.5 h	No reaction
2	HG-2 (1.2 eq), 1,4-benzoquinone (17 eq), toluene ^a , reflux, 17 h	No reaction
3	HG-2 (1.1 eq), 1,4-benzoquinone (17 eq), xylenes ^a , reflux, 21 h	Decomposition

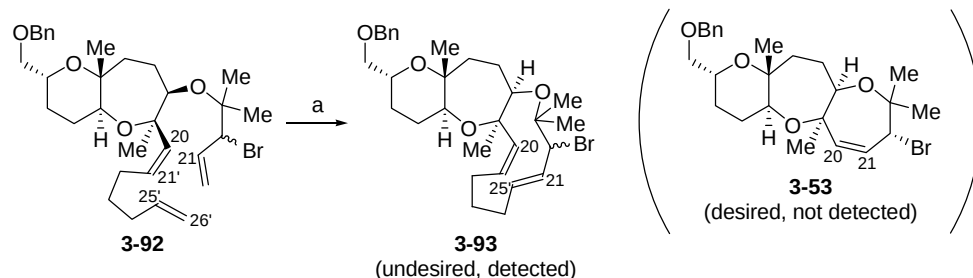
Table 3-2. Attempt to cyclize the D-ring from diene 3-54 by RCM. (a) degassed by bubbling with argon prior to use.

The author next designed triene **3-92** as a substrate for RRCM (Scheme 3-11). The triene was thought to be obtained by a simple change of the Wittig reagent in the reaction of an aldehyde obtained from **3-89**. Thus, an unstabilized ylide generated from 1-hexenyltriphenylphosphonium bromide, prepared from 1-hexeny bromide and triphenylphosphine,²² with BuLi was reacted with the aldehyde generated from **3-89** to produce **3-90** in 38% yield over two steps. Then, removal of THP group followed by dehydroxybromination of the resulting bromohydrin **3-91** furnished triene **3-92** in 62% yield along with about 30% recovery of **3-91**.



Scheme 3-11. Synthesis of triene 3-92. Reagents and conditions: (a) DMPI (16 eq), NaHCO_3 (62 eq), CH_2Cl_2 , 25 °C, 16.5 h; (b) 1-hexenyltriphenylphosphonium bromide (12 eq), BuLi (11 eq), THF, 0 $\rightarrow$ 25 °C, 15.5 h, 38% from **3-89**; (c) AcOH- H_2O -THF (4:1:2), 40 °C, 16 h; (d) Ph_3P (19 eq), I_2 (17 eq), DTBMP (excess), toluene, 100 °C, 17.5 h, 62% from **3-90**, <30% recovery of **3-91**.

Subsequently, the author examined the RRCM of **3-92** (Scheme 3-12). Triene **3-92** was treated with HG-2 in the presence of 1,4-benzoquinone in refluxing toluene. This reaction proceeded cleanly and finished within 1 h judged by TLC analysis. However, the resulting product was not the desired **3-53**, but macrocycle **3-93**, whose structure was confirmed by ^1H -NMR (COSY) and mass spectrometry analyses.



Scheme 3-12. Attempt to cyclize the D-ring from diene 3-92 by RRCM. Reagents and conditions: (a) HG-2 (1.5 eq), 1,4-benzoquinone (16 eq), toluene, reflux, 2 h, **3-93**: 63%, **3-53**: not detected.

In the design of substrate **3-92**, the author expected the initial metathesis between the catalyst and the olefin at C25' of **3-92**, which was proved by the production of **3-93**. However, the relay process producing cyclopentene, which was supposed to relocate the catalyst to C20, could not work. Therefore, the ruthenium carbene complex at C26' reacted with the olefin at C21 to produce **3-93**. From the consideration, it is suggested that the approach of C26'-ruthenium complex to the olefin at C21 was hindered due to some steric repulsions. Although the RRCM of **3-92** provided a disappointing result, this declared that the C21-olefin, which was inactive in **3-54**,

became reactive in **3-92**. Thus, the next issue in the RRCM strategy for the D-ring formation is the activation of the relay process: the transfer of catalyst from C26' to C21'. The author expects that structural revision of the alkyl-chain at C21'-26' of triene **3-92** leads to an answer for the issue, which is a final challenge to complete the synthesis of the BCD-ring of armatol F.

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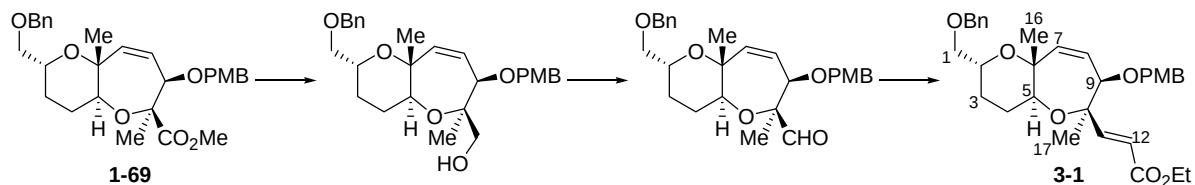
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Experimental section

General methods

All reactions involving air- or moisture-sensitive reagents were carried out in an anhydrous solvent system under an argon atmosphere in oven-dried glassware capped with septa, and sensitive liquids and solutions were transferred by using syringe- or cannula-techniques, unless otherwise noted. All commercially available reagents including anhydrous solvents, such as benzene, CH_2Cl_2 , DMF, 1,4-dioxane, and MeOH were used without further purification with the following exceptions: THF was distilled from sodium-benzophenone ketyl under argon or prepared by Glass Contour Solvent Dispensing System (Nikko Hansen & Co., Ltd.). 1,2-Dichloroethane and toluene was distilled from CaH_2 prior to use. Normal reagent-grade solvents were used for flash chromatography and extraction. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel (SiO_2) plates (Merck, silica gel 60 F₂₅₄). 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 Gel60 (63-43 μm for flash chromatography, 230-63 μm for gravity chromatography) as a stationary phase. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. Infrared spectra (IR) were measured on a JOEL JIR-WINSPEC100 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^1H -NMR and ^{13}C -NMR spectra were recorded on JEOL JNM-AL300 (^1H at 300MHz, ^{13}C at 75 MHz) and JNM- α -400 (^1H at 400 MHz, ^{13}C at 100 MHz) magnetic resonance spectrometer. ^1H -NMR spectra are reported as chemical shifts (δ) in parts-per-million (ppm) based on tetramethylsilane (0.00 ppm) as an 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 doublet; other combination is derived from those listed. Coupling constants (J) are reported in Hertz (Hz). ^{13}C -NMR spectra are reported as chemical shifts (δ) in ppm based on ^{13}C - CDCl_3 (77.0 ppm) or ^{13}C - $^{12}\text{C}_5\text{D}_6$ (128 ppm). Low and high resolution mass spectra were measured on a JEOL JMS-600H mass spectrometer under electron ionization (EI) condition and JEOL JMS-SX102A mass spectrometer under field desorption (FD) condition.

Compound 3-1.



To a solution of **1-69** (63.1 mg, 0.127 mmol) in THF (5.0 mL) was added LiAlH_4 (21.2 mg, 0.559 mmol) at 0 °C, and the reaction mixture was 15 min. Then, H_2O (10 drops), 1 M NaOH aq. (3.0 mL) and H_2O (2.0 mL) were added in order, and the mixture was stirred for several minutes. The mixture was extracted with ether and CH_2Cl_2 ($\times 2$), and the combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

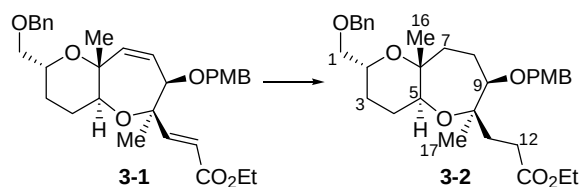
To a solution of the above alcohol in CH_2Cl_2 (10 mL) was added DMPI (596.1 mg, 1.405 mmol), and the reaction mixture was stirred for 2.5 h. After the reaction was quenched with saturated aqueous NaHCO_3 (25 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (15 mL), the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of NaH (83.4 mg, assay 60%, 2.09 mmol) in THF (17 mL) was added diethyl ethoxycarbonylmethylphosphonate (470.0 μL , 2.348 mmol) at 0 °C, the mixture was stirred at 25 °C for 2 h. To this was then added a solution of the above crude aldehyde in THF (5.0 mL) at -78 °C, and the reaction mixture was stirred at 25 °C for 14 h. After saturated aqueous NH_4Cl (20 mL) was added, the mixture was extracted with ether ($\times 3$). The combined organic layers were washed with 0.5 M NaOH aq., dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (3.5 g, hexane/AcOEt = 20 $\rightarrow$ 8) to give **3-1** (61.3 mg, 0.114 mmol, 90% over 3 steps).

3-1: a pale yellow oil; $[\alpha]_{\text{D}}^{23} = -120$ ($c = 0.0850$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 3063, 2938, 2868, 1713, 1658, 1586, 1514, 1497, 1454, 1367, 1251, 1180, 1152, 1097, 1036, 987, 909, 821, 736, 699, 665, 648; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.24-1.34 (1H, m, $\text{H}_{3\text{ax}}$), 1.28 (3H, t, $J = 7.0$ Hz, H_{15} (Et)), 1.31 (3H, s, H_{16} (Me)), 1.43 (3H, s, H_{17} (Me)), 1.69-1.87 (3H, m, $\text{H}_{3\text{eq}}$, H_4), 3.37 (1H,

dd, $J = 4.8, 9.9$ Hz, H1a), 3.47 (1H, dd, $J = 4.8, 9.9$ Hz, H1b), 3.73-3.91 (2H, m, H2, H5), 3.81 (3H, s, PMB), 4.04 (1H, d, $J = 4.4$ Hz, H9), 4.18 (2H, q, $J = 7.0$ Hz, H14 (Et)), 4.34 (1H, d, $J = 11.9$ Hz, PMB), 4.53 (1H, d, $J = 12.3$ Hz, Bn), 4.60 (1H, d, $J = 12.3$ Hz, Bn), 4.64 (1H, d, $J = 11.9$ Hz, PMB), 5.55 (1H, dd, $J = 4.4, 12.3$ Hz, H8), 5.78 (1H, d, $J = 12.3$ Hz, H7), 6.06 (1H, d, $J = 15.6$ Hz, H12), 6.87 (2H, d, $J = 8.6$ Hz, PMB), 6.94 (1H, d, $J = 15.6$ Hz, H11), 7.23 (2H, d, $J = 8.6$ Hz, PMB), 7.25-7.38 (5H, m, Bn); ^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) 14.3 (CH_3), 16.7 (CH_3), 23.8 (CH_3), 26.5 (CH_2), 28.5 (CH_2), 55.2 (CH_3), 60.2 (CH_2), 68.6 (CH), 71.0 (CH_2), 71.5 (CH), 73.3 (CH_2), 73.4 (CH_2), 78.5 (C), 78.9 (CH), 79.9 (C), 113.7 ($\text{CH}\times 2$), 119.9 (CH), 125.1 (CH), 127.6 (CH), 127.7 ($\text{CH}\times 2$), 128.3 ($\text{CH}\times 2$), 129.5 ($\text{CH}\times 2$), 129.7 (C), 138.3 (C), 140.7 (CH), 151.5 (CH), 159.2 (C), 166.9 (C); LR-EIMS m/z 536 (5.1%, $[\text{M}]^+$), 518 (4.1%, $[\text{M}-\text{Me}-3\text{H}]^+$), 121 (bp, $[\text{PMB}]^+$), 91 (90.3%, $[\text{Bn}]^+$); HR-EIMS calcd. for $\text{C}_{32}\text{H}_{40}\text{O}_7$ $[\text{M}]^+$: 536.2774, found 536.2789.

Compound 3-2.

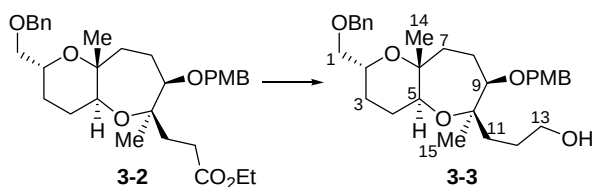


To a solution of **3-1** (24.7 mg, 46.0 μmol) in CH_2Cl_2 (4.0 mL) were added Et_3N (800.0 μL , 5.75 mmol) and NBSH (625.5 mg, 2.308 mmol), and the reaction mixture was stirred for 16 h. After H_2O (10 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were washed with 1 M NaOH aq. ($\times 2$), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0.6 g, hexane/AcOEt = 20 $\rightarrow$ 10) to give **3-2** (24.2 mg, 44.8 μmol , 97%).

3-2: a yellow oil; IR (neat), ν_{max} (cm^{-1}) 3030, 2936, 2861, 1732, 1612, 1586, 1514, 1453, 1376, 1303, 1249, 1180, 1092, 1036, 985, 821, 735, 698, 665, 642; ^1H -NMR (300 MHz, C_6D_6) δ (ppm) 0.97 (3H, t, $J = 7.2$ Hz, H15 (Et)), 1.05 (3H, s, H17 (Me)), 1.19 (3H, s, H16 (Me)), 1.20-1.30 (1H, m, $\text{H}_{3\text{ax}}$), 1.40-1.62 (5H, m, $\text{H}_{3\text{eq}}$, H4, H7), 1.75-1.93 (2H, m, H8), 2.08 (1H, ddd, $J = 5.7, 9.7, 15.0$ Hz, H11a), 2.28 (1H, ddd, $J = 6.4, 9.5, 15.0$ Hz, H11b), 2.43 (1H, ddd, $J = 5.7, 9.5, 15.4$ Hz, H12a), 2.64 (1H, ddd, $J = 6.4, 9.7, 15.4$ Hz, H12b), 3.10 (1H, dd, $J = 8.1, 8.1$ Hz, H5), 3.23 (1H,

br-d, $J = 10.1$ Hz, H9), 3.30 (3H, s, PMB), 3.32 (1H, dd, $J = 5.1, 9.7$ Hz, H1a), 3.48 (1H, dd, $J = 5.1, 9.7$ Hz, H1b), 3.63-3.74 (1H, m, H2), 3.98 (2H, q, $J = 7.2$ Hz, H14 (Et)), 4.02 (1H, d, $J = 11.5$ Hz, PMB), 4.35 (1H, d, $J = 11.5$ Hz, PMB), 4.37 (1H, d, $J = 12.3$ Hz, Bn), 4.42 (1H, d, $J = 12.3$ Hz, Bn), 6.78 (2H, d, $J = 8.4$ Hz, PMB), 7.06-7.23 (5H, m, Bn), 7.31 (2H, d, $J = 8.4$ Hz, PMB); ^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) 14.2 (CH_3), 15.8 (CH_3), 21.6 (CH_3), 24.0 (CH_2), 27.1 (CH_2), 28.4 (CH_2), 29.0 (CH_2), 30.2 (CH_2), 41.9 (CH_2), 55.2 (CH_3), 60.0 (CH_2), 68.3 (CH), 71.5 (CH_2), 71.6 (CH), 73.3 (CH_2), 73.5 (CH_2), 76.5 (C), 77.1 (C), 87.1 (CH), 113.7 ($\text{CH}\times 2$), 127.5 (CH), 127.7 ($\text{CH}\times 2$), 128.3 ($\text{CH}\times 2$), 129.3 ($\text{CH}\times 2$), 130.5 (C), 138.4 (C), 159.1 (C), 174.5 (C); LR-EIMS m/z 540 (46.7%, $[\text{M}]^+$), 419 (29.2%, $[\text{M}-\text{PMB}]^+$), 121 (bp, $[\text{PMB}]^+$), 91 (82.1%, $[\text{Bn}]^+$).

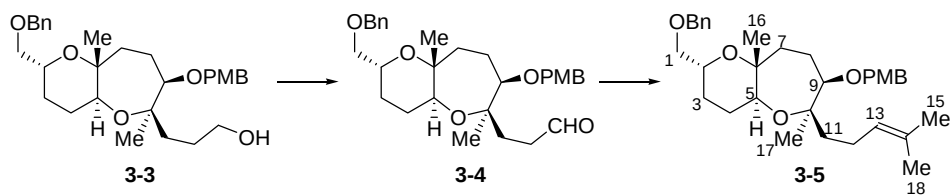
Compound 3-3.



To a solution of **3-2** (33.5 mg, 62.0 μmol) in CH_2Cl_2 (4.0 mL) was added DIBAH (250.0 μL , 1.02 M in hexane, 255 μmol) at 0 $^\circ\text{C}$, and the reaction mixture was stirred at 0 $^\circ\text{C}$ for 15 min. Then, the reaction was quenched carefully with MeOH (1.5 mL), and to this mixture was added saturated aqueous Rochelle salt (4.0 mL). After the mixture was stirred for about 1 h, this was extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (1.5 g, hexane/AcOEt = 5) to give **3-3** (23.7 mg, 47.5 μmol , 77%).

3-3: a pale yellow oil; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.15 (3H, s, H15 (Me)), 1.19 (3H, s, H14 (Me)), 1.22-1.92 (12H, m, H3, H4, H7, H8, H11, H12), 2.69 (1H, br-s, OH), 3.26 (1H, dd, $J = 5.5, 11.0$ Hz, H5), 3.33 (1H, dd, $J = 4.8, 9.9$ Hz, H1a), 3.38-3.47 (2H, m, H1b, H9), 3.49-3.75 (3H, m, H2, H13), 3.80 (3H, s, PMB), 4.28 (1H, d, $J = 11.5$ Hz, PMB), 4.53 (1H, d, $J = 12.3$ Hz, Bn), 4.56 (1H, d, $J = 11.5$ Hz, PMB), 4.58 (1H, d, $J = 12.3$ Hz, Bn), 6.87 (2H, d, $J = 8.6$ Hz, PMB), 7.22 (2H, d, $J = 8.6$ Hz, PMB), 7.25-7.38 (5H, m, Bn).

Compound 3-5.

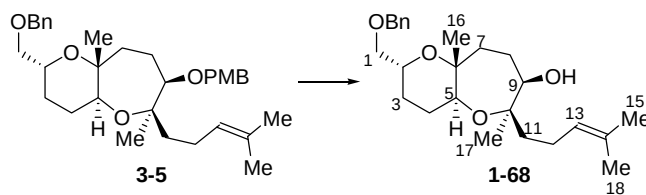


To a solution of **3-3** (23.7 mg, 47.5 μmol) in CH_2Cl_2 (5.0 mL) was added DMPI (238.0 mg, 0.5611 mmol), and the reaction mixture was stirred for 2 h. After the reaction was quenched with saturated aqueous NaHCO_3 (15 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude aldehyde (**3-4**) was used immediately in the next reaction without further purification.

To an isopropyltriphenylphosphonium iodide (72.5 mg, 0.168 mmol) in THF (3.0 mL) was added BuLi (85.0 μL , 1.67 M in hexane, 0.142 mmol) at 0 $^\circ\text{C}$, and the mixture was stirred at 0 $^\circ\text{C}$ for a few minutes. To this was then added a solution of crude **3-4** in THF (2.0 mL), and the reaction mixture was stirred at 25 $^\circ\text{C}$ for 1 h. After H_2O (5.0 mL) was added, the mixture was extracted with ether ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (1.3 g, hexane/AcOEt = 20 $\rightarrow$ 5) to give **3-5** (3.6 mg, 6.9 μmol , 15% over 2 steps) and recover **3-4** (9.8 mg, 20 μmol , 42%).

3-5: a yellow oil; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.11 (3H, s, H17 (Me)), 1.18 (3H, s, H16 (Me)), 1.21-1.89 (10H, m, H3, H4, H7, H8, H11), 1.58 (3H, s, H15 (Me)), 1.65 (3H, s, H18 (Me)), 3.17 (1H, dd, J = 5.5, 10.5 Hz, H5), 3.29-3.40 (2H, m, H1a, H9), 3.44 (1H, dd, J = 5.3, 9.9 Hz, H1b), 3.65-3.77 (1H, m, H2), 3.81 (3H, s, PMB), 4.28 (1H, d, J = 11.5 Hz, PMB), 4.53 (1H, d, J = 12.3 Hz, Bn), 4.55 (1H, d, J = 11.5 Hz, PMB), 4.58 (1H, d, J = 12.3 Hz, Bn), 5.12 (1H, t, J = 7.0 Hz, H13), 6.86 (2H, d, J = 8.4 Hz, PMB), 7.22 (2H, d, J = 8.4 Hz, PMB), 7.25-7.38 (5H, m, Bn).

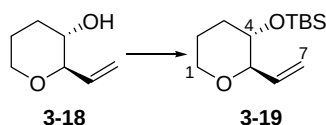
Compound 1-68.



To a solution of **3-5** (7.1 mg, 14 μ mol) in CH_2Cl_2 (2.0 mL) and H_2O (0.2 mL) was added DDQ (7.5 mg, 33 μ mol), and the reaction mixture was stirred at 0 $^\circ\text{C}$ for 50 min. After saturated aqueous NaHCO_3 (3.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0.5 g, hexane/AcOEt = 10 $\rightarrow$ 5) to give **1-68** (2.7 mg, 6.7 μ mol, 49%).

1-68: a pale yellow oil; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.18 (3H, s, H17 (Me)), 1.22 (3H, s, H16 (Me)), 1.24-1.80 (10H, m, H3, H4, H7, H8, H11), 1.61 (3H, s, H15 (Me)), 1.68 (3H, s, H18 (Me)), 1.93-2.24 (2H, m, H12), 3.22 (1H, dd, J = 5.5, 11.0 Hz, H5), 3.33 (1H, dd, J = 4.8, 9.9 Hz, H1a), 3.44 (1H, dd, J = 5.5, 9.9 Hz, H1b), 3.65-3.79 (2H, m, H2, H9), 3.82 (1H, d, J = 3.7 Hz, OH), 4.53 (1H, d, J = 12.3 Hz, Bn), 4.58 (1H, d, J = 12.3 Hz, Bn), 5.14 (1H, t, J = 7.0 Hz, H13), 7.21-7.38 (5H, m, Bn).

Compound 3-19.

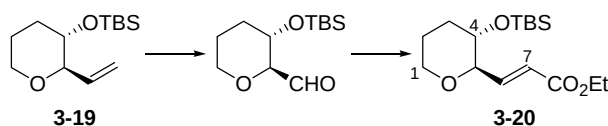


To a solution of **3-18** (723.7 mg, 5.646 mmol) in DMF (40 mL) were added 2,6-lutidine (1.50 mL, 12.9 mmol) and TBSCl (1.0497 g, 6.9646 mmol) at 0 $^\circ\text{C}$, and the reaction mixture was stirred at 25 $^\circ\text{C}$ for 20 h. After MeOH (20 mL) was added, the mixture was extracted with ether ($\times 3$). The combined organic layers were washed with H_2O , saturated aqueous NH_4Cl and brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (50 g, hexane/AcOEt = 100 $\rightarrow$ 60) to give **3-19** (708.6 mg, 2.923 mmol, 52%).

3-19: a colorless oil; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 0.027 (3H, s, TBS), 0.045 (3H, s, TBS),

0.87 (9H, s, TBS), 1.40-1.57 (1H, m, H_{2ax.}), 1.61-1.74 (2H, m, H_{2eq.}, H_{3ax.}), 1.98-2.08 (1H, m, H_{3eq.}), 3.26-3.43 (2H, m, H1), 3.47-3.54 (1H, m, H5), 3.90-3.98 (1H, m, H4), 5.18 (1H, td, $J = 1.7$, 10.6 Hz, H7a), 5.31 (1H, td, $J = 1.7$, 17.4 Hz, H7b), 5.92 (1H, ddd, $J = 5.9$, 10.6, 17.4 Hz).

Compound 3-20.

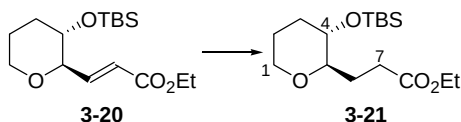


To a solution of **3-19** (644.1 mg, 2.657 mmol) in 1,4-dioxane (5.0 mL) and pH 7 buffer (5.0 mL) were added NMO (890.5 mg, 8.721 mmol) and OsO₄ (6.8 mL, 0.0197 M in ^tBuOH, 0.13 mmol), and the reaction mixture was stirred for 22 h. Then, NaIO₄ (1.4949 g, 6.9868 mmol) was added, and the mixture was stirred for 7 h. After saturated aqueous Na₂S₂O₃ (8.0 mL) was added, the mixture was extracted with CH₂Cl₂ (×2). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of NaH (1.0495 g, assay 60%, 26.24 mmol) in THF (40 mL) was added diethyl ethoxycarbonylmethanephosphonate (6.50 mL, 32.5 mmol) at 0 °C, the mixture was stirred at 25 °C for 1.5 h. To this was then added a solution of the above crude aldehyde in THF (10 mL) at 0 °C, and the reaction mixture was stirred at 25 °C for 14 h. After saturated aqueous NH₄Cl (70 mL) was added, the mixture was extracted with ether (×2). The combined organic layers were washed with 0.5 M NaOH aq., dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (90 g, hexane/AcOEt = 30) to give **3-20** (635.7 mg, 2.021 mmol, 76% over 2 steps).

3-20: a colorless oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.044 (6H, s, TBS), 0.89 (9H, s, TBS), 1.27 (3H, t, $J = 7.2$ Hz, H10 (Et)), 1.43-1.58 (1H, m, H_{2ax.}), 1.63-1.74 (2H, m, H_{2eq.}, H_{3ax.}), 1.99-2.09 (1H, m, H_{3eq.}), 3.26-3.44 (2H, m, H1), 3.68 (1H, ddd, $J = 1.7$, 4.4, 5.9 Hz, H5), 3.91-3.99 (1H, m, H4), 4.13-4.26 (2H, m, H9 (Et)), 6.04 (1H, dd, $J = 1.7$, 16.0 Hz, H6), 7.10 (1H, dd, $J = 4.4$, 16.0 Hz, H7).

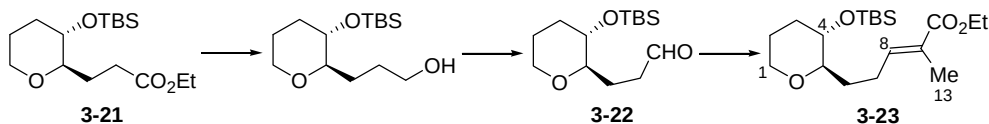
Compound 3-21.



To a solution of **3-20** (635.7 mg, 2.021 mmol) in AcOEt (60 mL) was added 5% palladium-carbon (65.3 mg), and the mixture was stirred for 21.5 h under H₂ atmosphere. The reaction mixture was filtered through a pad of Celite, and condensed under reduced pressure to give **3-21** (639.8 mg, 2.021 mmol, 100%).

3-21: a colorless oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.062 (3H, s, TBS), 0.071 (3H, s, TBS), 0.88 (9H, s, TBS), 1.24 (3H, t, *J* = 7.2 Hz, H10 (Et)), 1.36-1.49 (1H, m, H2_{ax.}), 1.52-1.70 (3H, m, H2_{eq.}, H3_{ax.}, H6a), 1.94-2.04 (1H, m, H3_{eq.}), 2.13-2.26 (1H, m, H6b), 2.29-2.53 (2H, m, H7), 2.99 (1H, dt, *J* = 2.6, 9.2 Hz, H5), 3.22-3.34 (2H, m, H1), 3.81-3.89 (1H, m, H4), 4.12 (2H, q, *J* = 7.2 Hz, H9 (Et)).

Compound 3-23.



To a solution of **3-21** (639.8 mg, 2.021 mmol) in THF (40 mL) was added LiAlH₄ (120.3 mg, 3.170 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2.5 h. After H₂O (10 drops), 1 M NaOH aq. (30 mL) and H₂O (10 mL) were added in order, and the mixture was stirred for about 1 h. The mixture was extracted with ether and CH₂Cl₂ (×3), and then the combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

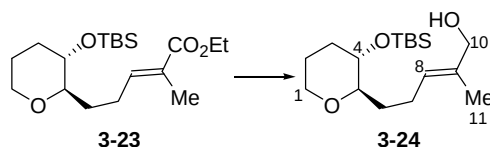
To a solution of the above alcohol in CH₂Cl₂ (40 mL) was added DMPI (2.5151 g, 5.9300 mmol), and the reaction mixture was stirred for 2 h. After the reaction was quenched with saturated aqueous NaHCO₃ (20 mL) and Na₂S₂O₃ (20 mL), the mixture was extracted with CH₂Cl₂ (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude aldehyde (**3-22**) was used immediately in the next reaction

without further purification.

To a solution of crude **3-22** in toluene (30 mL) was added (1-ethoxycarbonylethylidenetriphenylphosphorane (1.5342 g, 4.2334 mmol), and the reaction mixture was stirred for 12 h. After H₂O was added, the mixture was extracted with ether (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (30 g, hexane/AcOEt = 50) to give **3-23** (187.2 mg, 0.5250 mmol, 26% over 2 steps, *E:Z* = 2:1).

3-23: colorless needles; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.056 (6H, s, TBS), 0.88 (9H, s, TBS), 1.29 (3H, t, *J* = 7.2 Hz, H12 (Et)), 1.36-1.51 (2H, m, H2_{ax.}, H6a), 1.58-1.71 (2H, m, H2_{eq.}, H3_{ax.}), 1.84 (3H, s, H13 (Me)), 1.87-2.08 (2H, m, H3_{eq.}, H6b), 2.19-2.40 (2H, m, H7), 2.96 (1H, dt, *J* = 2.4, 9.2 Hz, H5), 3.22-3.34 (2H, m, H1), 3.82-3.92 (1H, m, H4), 4.19 (2H, q, *J* = 7.2 Hz, H11 (Et)), 6.76 (1H, t, *J* = 7.0 Hz, H8).

Compound 3-24.

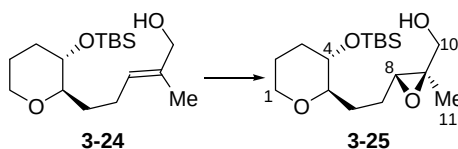


To a solution of **3-23** (65.8 mg, 0.185 mmol) in THF (3.0 mL) was added LiAlH₄ (21.2 mg, 0.559 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. After H₂O (5 drops), 1 M NaOH aq. (2.0 mL) and H₂O (1.0 mL) were added in order, and the mixture was stirred for several minutes. The mixture was extracted with ether (×2), and then the combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (2.0 g, hexane/AcOEt = 10) to give **3-24** (40.1 mg, 0.127 mmol, 69%).

3-24: a colorless oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.057 (6H, s, TBS), 0.88 (9H, s, TBS), 1.20-1.49 (3H, m, H2_{ax.}, H6), 1.58-1.71 (2H, m, H2_{eq.}, H3_{ax.}), 1.68 (3H, s, H11 (Me)), 1.79-1.93 (1H, m, H7a), 1.93-2.06 (1H, m, H3_{eq.}), 2.07-2.26 (1H, m, H7b), 2.97 (1H, dt, *J* = 2.4, 9.2 Hz, H5), 3.21-3.34 (2H, m, H1), 3.83-3.92 (1H, m, H4), 4.01 (2H, d, *J* = 5.9 Hz, H10), 5.41 (1H, t, *J* = 7.0

Hz, H8).

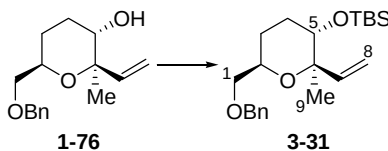
Compound 3-25.



To a mixture of *D*-(-)-DET (5.5 μ L, 32 μ mol) and pre-dried MS 4A (42.3 mg, 100 wt%) in CH_2Cl_2 (1.0 mL) was added $\text{Ti}(\text{O}^i\text{Pr})_4$ (7.5 μ L, 25 μ mol) at -40°C , and the mixture was stirred at -40°C for 30 min. To this was then added TBHP (85.0 μ L, 3.05 M in toluene, 259 μ mol), and the mixture was stirred at -40°C for 15 min. After a solution of **3-24** (40.1 mg, 127 μ mol) in CH_2Cl_2 (1.5 mL) was added, the reaction mixture was stirred at -25°C for 14.5 h. Me_2S (18.0 μ L, 246 μ mol) was added to consume unreacted TBHP before to the mixture were added 10% *DL*-tartaric acid (5 drops) and NaF (ca. 10 mg) at 25°C . Then, the mixture was stirred at 25°C for about 1 h, filtered through a pad of Celite, and condensed under reduced pressure. The resulting residue was purified by silica gel column chromatography (3.0 g, hexane/AcOEt = 10 $\rightarrow$ 5 $\rightarrow$ 3) to give **3-25** (27.9 mg, 84.4 μ mol, 66%) as almost a single diastereomer.

3-25: a colorless oil; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 0.067 (6H, s, TBS), 0.88 (9H, s, TBS), 1.29 (3H, s, H11 (Me)), 1.36-1.71 (5H, m, H2, H3_{ax.}, H6), 1.74-2.07 (4H, m, H3_{eq.}, H7, OH), 2.97-3.07 (2H, m, H5, H8), 3.22-3.36 (2H, m, H1), 3.53-3.71 (2H, m, H10), 3.82-3.92 (1H, m, H4).

Compound 3-31.

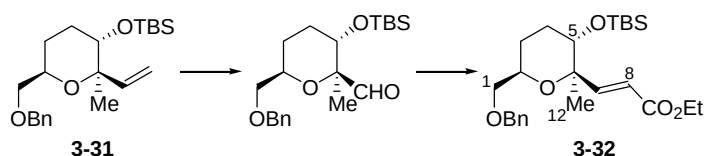


To a solution of **1-76** (712.4 mg, 2.716 mmol) in DMF (10 mL) were added imidazole (644.1 mg, 9.461 mmol) and TBSCl (609.1 mg, 4.041 mmol) at 0°C , and the reaction mixture was stirred at 25°C for 17.5 h. After saturated aqueous NH_4Cl (10 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 ,

filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (50 g, hexane/AcOEt = 100 → 5) to give **3-31** (808.4 mg, 2.147 mmol, 79%) and recover **1-76** (135.2 mg, 0.3590 mmol, 19%).

3-31: a colorless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) -0.020 (3H, s, TBS), -0.013 (3H, s, TBS), 0.84 (9H, s, TBS), 1.22 (3H, s, H9 (Me)), 1.25-1.43 (1H, m, H3_{ax.}), 1.57-1.78 (3H, m, H3_{eq.}, H4), 3.37 (1H, dd, J = 5.0, 10.1 Hz, H1a), 3.41 (1H, dd, J = 4.8, 11.0 Hz, H5), 3.50 (1H, dd, J = 5.3, 10.1 Hz, H1b), 3.74-3.83 (1H, m, H2), 4.54 (1H, d, J = 12.3 Hz, Bn), 4.58 (1H, d, J = 12.3 Hz, Bn), 5.03 (1H, dd, J = 1.8, 10.8 Hz, H8a), 5.25 (1H, dd, J = 1.8, 17.4 Hz, H8b), 5.96 (1H, dd, J = 10.8, 17.4 Hz, H7), 7.21-7.36 (5H, m, Bn).

Compound 3-32.



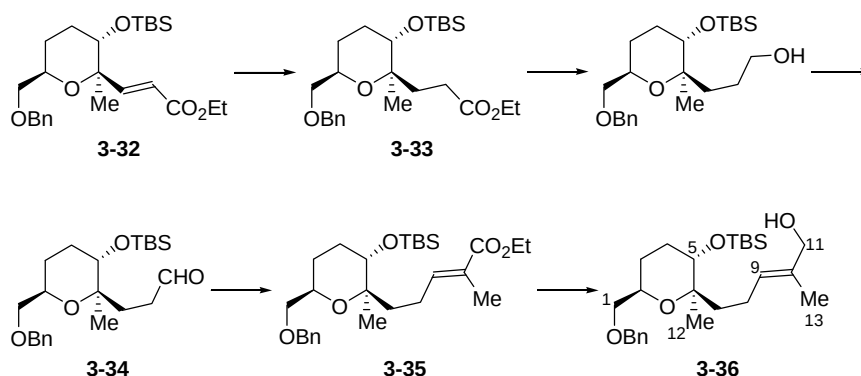
To a solution of **3-31** (791.9 mg, 2.103 mmol) in 1,4-dioxane (5.0 mL) and pH 7 buffer (5.0 mL) were added NMO (698.0 mg, 6.836 mmol) and OsO_4 (5.4 mL, 0.0197 M in $t\text{BuOH}$, 0.11 mmol), and the reaction mixture was stirred for 14.5 h. Then, NaIO_4 (1.2013 g, 5.6146 mmol) was added, and the mixture was stirred for 4 h. After saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) was added, the mixture was extracted with ether ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of NaH (857.4 mg, assay 60%, 21.44 mmol) in THF (40 mL) was added diethyl ethoxycarbonylmethanephosphonate (5.10 mL, 25.5 mmol) at 0 °C, the mixture was stirred at 25 °C for 2 h. To this was then added a solution of the above crude aldehyde in THF (10 mL) at 0 °C, and the reaction mixture was stirred at 25 °C for 14 h. After saturated aqueous NH_4Cl (30 mL) was added, the mixture was extracted with ether ($\times 3$). The combined organic layers were washed with 0.5 M NaOH aq. ($\times 2$), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (50 g,

hexane/AcOEt = 30) to give **3-32** (797.0 mg, 1.776 mmol, 84% over 2 steps).

3-32: a colorless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 0.024 (3H, s, TBS), 0.031 (3H, s, TBS), 0.89 (9H, s, TBS), 1.23-1.44 (1H, m, $\text{H}_{3\text{ax}}$), 1.281 (3H, s, H_{12} (Me)), 1.284 (3H, t, $J = 7.2$ Hz, Et), 1.59-1.81 (3H, m, $\text{H}_{3\text{eq}}$, H_4), 3.39 (1H, dd, $J = 5.0, 9.9$ Hz, $\text{H}_{1\text{a}}$), 3.43 (1H, dd, $J = 4.8, 11.0$ Hz, H_5), 3.51 (1H, dd, $J = 5.5, 9.9$ Hz, $\text{H}_{1\text{b}}$), 3.76-3.86 (1H, m, H_2), 4.13-4.26 (2H, m, Et), 4.56 (1H, d, $J = 12.3$ Hz, Bn), 4.60 (1H, d, $J = 12.3$ Hz, Bn), 6.04 (1H, d, $J = 15.7$ Hz, H_8), 7.10 (1H, d, $J = 15.7$ Hz, H_7), 7.24-7.40 (5H, m, Bn).

Compound 3-36.



To a solution of **3-32** (270.1 mg, 0.6020 mmol) in CH_2Cl_2 (5.0 mL) were added Et_3N (900.0 μL , 6.47 mmol) and NBSH (838.0 mg, 3.092 mmol), and the reaction mixture was stirred for 13 h. After H_2O (20 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were washed with 0.5 M NaOH aq. ($\times 2$), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resultant saturated ester (**3-33**) was almost pure and was used in the next reaction without further purification.

To a solution of **3-33** in CH_2Cl_2 (12 mL) was added DIBAH (1.30 mL, 1.02 M in hexane, 1.33 mmol) at 0°C , and the reaction mixture was stirred at 0°C for 50 min. Then, the reaction was quenched carefully with MeOH (3.0 mL), and to this mixture was added saturated aqueous Rochelle salt (10 mL). After the mixture was stirred for about 1 h, this was extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resultant alcohol was almost pure and was used in the next reaction without further purification.

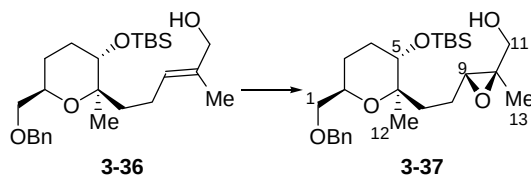
To a solution of the above alcohol in CH₂Cl₂ (6.0 mL) were added NaHCO₃ (306.8 mg, 3.652 mmol) and DMPI (780.3 mg, 1.840 mmol), and the reaction mixture was stirred for 100 min. After the reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and Na₂S₂O₃ (10 mL), the mixture was extracted with CH₂Cl₂ (×2) and ether. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude aldehyde (**3-34**) was used immediately in the next reaction without further purification.

To a solution of crude **3-34** in toluene (6.0 mL) was added (1-ethoxycarbonylethylidenetriphenylphosphorane (463.5 mg, 1.279 mmol), and the reaction mixture was stirred for 15 h. After H₂O was added, the mixture was extracted with ether (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 g, hexane/AcOEt = 30) to give the crude *E*-enoate (**3-35**) including a small amount of PPh₃.

To a solution of crude **3-35** in CH₂Cl₂ (8.0 mL) was added DIBAH (1.30 mL, 1.02 M in hexane, 1.33 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 20 min. Then, the reaction was quenched carefully with MeOH (2.0 mL), and to this mixture was added saturated aqueous Rochelle salt (10 mL). After the mixture was stirred for about 1 h, this was extracted with CH₂Cl₂ (×2) and ether. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 g, benzene → hexane/AcOEt = 7) to give **3-36** (157.0 mg, 0.3499 mmol, 58% over 5 steps).

3-36: a colorless oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.040 (6H, s, TBS), 0.86 (9H, s, TBS), 1.13 (3H, s, H12 (Me)), 1.21-1.40 (2H, m, H3_{ax}, H7a), 1.42-1.58 (1H, m, H7b), 1.59-1.77 (3H, m, H3_{eq}, H4), 1.67 (3H, s, H13 (Me)), 2.05 (1H, s, OH), 2.08-2.21 (2H, m, H8), 3.36 (1H, dd, *J* = 4.8, 10.1 Hz, H1a), 3.41-3.50 (2H, m, H1b, H5), 3.66-3.76 (1H, m, H2), 3.99 (2H, br-d, *J* = 5.1 Hz, H11), 4.55 (1H, *J* = 12.3 Hz, Bn), 4.61 (1H, d, *J* = 12.3 Hz, Bn), 5.41 (1H, t, *J* = 7.0 Hz, H9), 7.23-7.38 (5H, m, Bn).

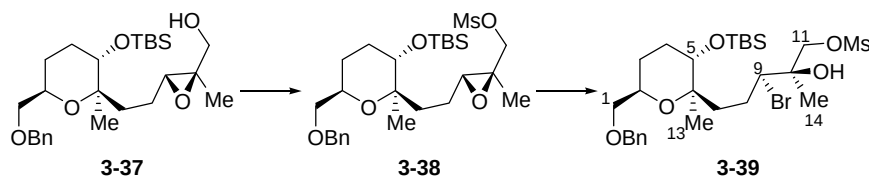
Compound 3-37.



To a mixture of $D(-)$ -DET (15.0 μ L, 87.6 μ mol) and pre-dried MS 4A (ca. 200 mg, 100 wt%) in CH_2Cl_2 (3.0 mL) was added $\text{Ti}(\text{O}^i\text{Pr})_4$ (21.0 μ L, 71.2 μ mol) at -40°C , and the mixture was stirred at -40°C for 2 h. To this was then added TBHP (230.0 μ L, 3.05 M in toluene, 702 μ mol), and the mixture was stirred at -40°C for 15 min. After a solution of **3-35** (157.0 mg, 349.9 μ mol) in CH_2Cl_2 (1.0 mL) was added, the reaction mixture was stirred at -25°C for 17 h. Me_2S (45.0 μ L, 615 μ mol) was added to consume unreacted TBHP before to the mixture were added 10% D_L -tartaric acid (10 drops) and NaF (ca. 20 mg) at 25°C . Then, the mixture was stirred at 25°C for about 1 h, filtered through a pad of Celite, and condensed under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 g, hexane/AcOEt = 7 $\rightarrow$ 3) to give **3-37** (155.1 mg, 333.8 μ mol, 95%) as almost a single diastereomer.

3-37: a colorless oil; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 0.045 (6H, s, TBS), 0.86 (9H, s, TBS), 1.14 (3H, s, H12 (Me)), 1.18-1.38 (3H, m, $\text{H3}_{\text{ax.}}$, H7), 1.51-1.84 (5H, m, $\text{H3}_{\text{eq.}}$, H4, H8), 1.57 (3H, s, H13 (Me)), 2.04 (1H, br-s, OH), 3.03-3.16 (1H, m, H9), 3.34 (1H, dd, $J = 4.8, 10.1$ Hz, H1a), 3.38-3.50 (2H, m, H1b, H5), 3.55-3.62 (2H, m, H11), 3.62-3.75 (1H, m, H2), 4.52 (1H, d, $J = 12.3$ Hz, Bn), 4.57 (1H, d, $J = 12.3$ Hz, Bn), 7.23-7.39 (5H, m, Bn).

Compound 3-39.



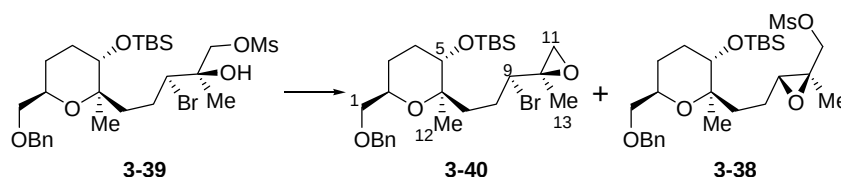
To a solution of **3-37** (155.1 mg, 0.3338 mmol) in CH_2Cl_2 (3.5 mL) were added Et_3N (300.0 μ L, 2.16 mmol) and Ms_2O (170.7 mg, 0.9799 mmol), and the reaction mixture was stirred at 35°C for 70 min. After saturated aqueous NaHCO_3 (3.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 ,

filtered, and concentrated under reduced pressure. The resulting crude epoxide mesylate (**3-38**) was used immediately in the next reaction without further purification.

To a suspension of pre-sublimed $\text{Et}_2\text{NH}\cdot\text{HBr}$ (359.2 mg, 2.332 mmol) in CH_2Cl_2 (2.0 mL) was Et_2AlCl (550.0 μL , 0.92 M in hexane, 0.51 mmol), and the mixture was stirred for 20 min. To this was then added a solution of crude **3-37** in CH_2Cl_2 (2.0 mL) at $-20\text{ }^\circ\text{C}$, and the reaction mixture was stirred at $25\text{ }^\circ\text{C}$ for 2 h. After 0.5 M HCl aq. (4.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 g, hexane/ AcOEt = 6 $\rightarrow$ 3) to give **3-39** (139.0 mg, 0.2229 mmol, 67% over 2 steps) as a colorless oil and recover **3-38** (29.8 mg, 0.0549 mmol, 16%).

3-39: a colorless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 0.046 (3H, s, TBS), 0.068 (3H, s, TBS), 0.87 (9H, s, TBS), 1.14 (3H, s, H13 (Me)), 1.22-1.34 (2H, m, H3_{ax}, H4_{ax}), 1.30 (3H, s, H14 (Me)), 1.40-1.65 (2H, m, H3_{eq}, H7a), 1.65-1.86 (2H, m, H4_{eq}, H8a), 1.97-2.08 (1H, m, H7b), 2.37-2.51 (1H, m, H8b), 3.05 (3H, s, Ms), 3.31 (1H, dd, J = 3.7, 10.1 Hz, H1a), 3.36-3.48 (3H, m, H1b, H5, OH), 3.61-3.73 (1H, m, H2), 4.16 (1H, d, J = 9.7 Hz, H11a), 4.32 (1H, dd, J = 1.8, 10.2 Hz, H9), 4.46 (1H, d, J = 9.7 Hz, H11b), 4.50 (1H, d, J = 12.3 Hz, Bn), 4.64 (1H, d, J = 12.3 Hz, Bn), 7.23-7.37 (5H, m, Bn).

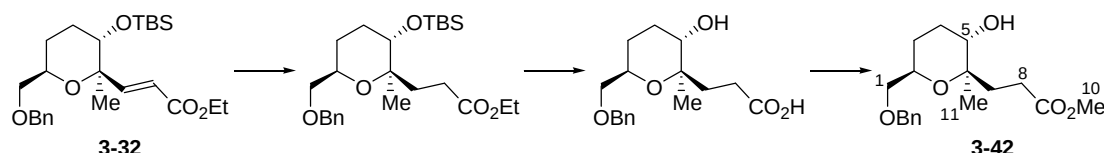
Compound 3-40.



To a solution of **3-39** (95.3 mg, 153 μmol) in MeOH (5.0 mL) was added K_2CO_3 (24.1 mg, 174 μmol), and the reaction mixture was stirred at $-20\text{ }^\circ\text{C}$ for 70 min. After saturated aqueous NH_4Cl (5.0 mL) was added, the mixture was extracted with ether ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (5.0 g, hexane/ AcOEt = 20 $\rightarrow$ 3) to give **3-40** (9.4 mg, 18 μmol , 12%) as a colorless oil and **3-38** (70.9 mg, 131 μmol , 86%).

3-40: a colorless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 0.026-0.088 (6H, m, TBS), 0.87 (9H, s, TBS), 1.12 (3H, s, H12 (Me)), 1.17-1.49 (2H, m, H3_{ax.}, H4_{ax.}), 1.26 (3H, s, H13 (Me)), 1.58-2.24 (6H, m, H3_{eq.}, H4_{eq.}, H7, H8), 2.67 (1H, $J = 4.8$ Hz, H11a), 2.71 (1H, d, $J = 4.8$ Hz, H11b), 3.30-3.53 (4H, m, H1, H5, H9), 3.63-3.73 (1H, m, H2), 4.56 (2H, s, Bn), 7.23-7.38 (5H, m, Bn).

Compound 3-42.



To a solution of **3-32** (333.1 mg, 0.7424 mmol) in CH_2Cl_2 (5.0 mL) were added Et_3N (900.0 μL , 6.47 mmol) and NBSH (815.0 mg, 3.007 mmol), and the reaction mixture was stirred for 19 h. After H_2O (20 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were washed with 1 M NaOH aq. ($\times 2$), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting saturated ester was almost pure and was used in the next reaction without further purification.

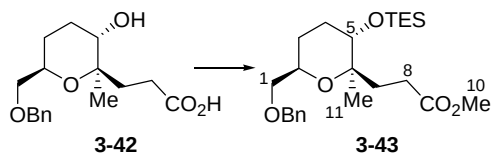
To a solution of the above saturated ester in THF (5.0 mL) was added TBAF (3.10 mL, 1 M in THF, 3.10 mmol), and the reaction mixture was stirred at 45 $^\circ\text{C}$ for 2.5 h. The mixture was condensed under reduced pressure to give the crude hydroxy carboxylic acid.

To a solution of the above crude hydroxy carboxylic acid in benzene (6.0 mL) and MeOH (2.0 mL) was added TMSCHN_2 (1.00 mL, 2.0 M in ether, 2.0 mmol), and the reaction mixture was stirred for 10 min. After saturated aqueous NH_4Cl (8.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. 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 silica gel column chromatography (10 g, hexane/AcOEt = 3) to give **3-42** (214.1 mg, 0.6641 mmol, 89% over 3 steps).

3-42: a yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 1.19 (3H, s, H11 (Me)), 1.21-1.39 (1H, m, H3_{ax.}), 1.51-1.69 (1H, m, H4_{ax.}), 1.69-1.79 (1H, m, H3_{eq.}), 1.79-1.92 (2H, m, H4_{eq.}, H7a), 1.93-2.06 (1H, m, H7b), 2.29-2.46 (2H, m, H8a, OH), 2.59 (1H, td, $J = 7.2, 17.4$ Hz, H8b), 3.28-3.40 (2H, m,

H1a, H5), 3.44 (1H, dd, $J = 5.7, 10.1$ Hz, H1b), 3.66-3.78 (1H, m, H2), 3.68 (3H, s, H10 (Me)), 4.52 (1H, d, $J = 12.3$ Hz, Bn), 4.58 (1H, d, $J = 12.3$ Hz, Bn), 7.23-7.38 (5H, m, Bn).

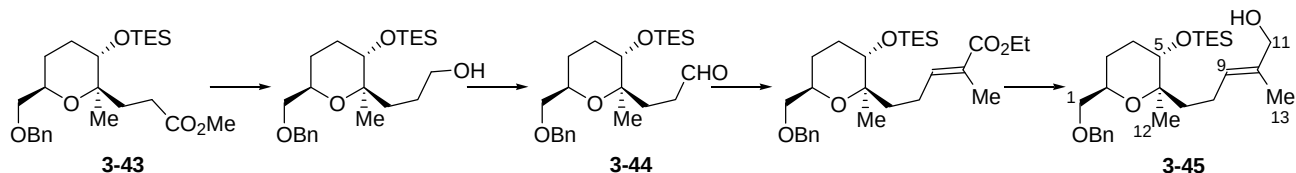
Compound 3-43.



To a solution of **3-42** (214.1 mg, 0.6641 mmol) in CH_2Cl_2 (6.5 mL) were added 2,6-lutidine (320.0 μL , 2.75 mmol) and TESOTf (305.0 μL , 1.35 mmol) at 0 °C, and the reaction mixture was stirred at 25 °C for 20 h. After H_2O (6.0 mL) was added at 0 °C, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were washed with 0.2 M HCl aq. and saturated aqueous NaHCO_3 , dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (12 g, hexane/AcOEt = 30) to give **3-43** (191.2 mg, 0.4379 mmol, 66%).

3-42: a colorless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 0.58 (6H, q, $J = 7.9$ Hz, TES), 0.94 (9H, t, $J = 7.9$ Hz, TES), 1.12 (3H, s, H11 (Me)), 1.19-1.37 (1H, m, $\text{H3}_{\text{ax.}}$), 1.59-1.85 (4H, m, $\text{H3}_{\text{eq.}}$, H4, H7a), 1.99 (1H, ddd, $J = 6.8, 9.5, 13.8$ Hz, H7b), 2.42 (2H, ddd, $J = 2.8, 6.8, 9.5$ Hz, H8), 3.31 (1H, dd, $J = 5.1, 9.9$ Hz, H1a), 3.38-3.48 (2H, m, H1b, H5), 3.63-3.72 (1H, m, H2), 3.65 (3H, s, H10 (Me)), 4.52 (1H, d, $J = 12.3$ Hz, Bn), 4.57 (1H, d, $J = 12.3$ Hz, Bn), 7.23-7.38 (5H, m, Bn).

Compound 3-45.



To a solution of **3-43** (191.2 mg, 0.4379 mmol) in CH_2Cl_2 (8.0 mL) was added DIBAH (900.0 μL , 1.02 M in hexane, 0.918 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. Then, the reaction was quenched carefully with MeOH (10 drops), and to this mixture was added saturated aqueous Rochelle salt (8.0 mL). After the mixture was stirred for about 1 h, this was

extracted with CH₂Cl₂ (×2) and ether. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

To a solution of the above alcohol in CH₂Cl₂ (5.0 mL) were added NaHCO₃ (255.0 mg, 3.035 mmol) and DMPI (563.0 mg, 1.327 mmol), and the reaction mixture was stirred for 1.5 h. After the reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and Na₂S₂O₃ (10 mL), the mixture was extracted with CH₂Cl₂ and ether (×2). The combined organic layers were washed with brine and saturated aqueous Na₂S₂O₃, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude aldehyde (**3-44**) was used immediately in the next reaction without further purification.

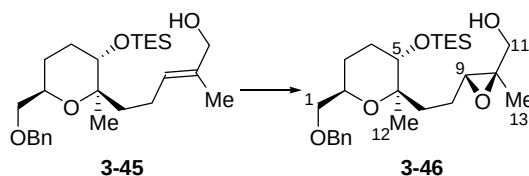
To a solution of crude **3-44** in toluene (5.0 mL) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (328.0 mg, 0.9051 mmol), and the reaction mixture was stirred for 12.5 h. After H₂O was added, the mixture was extracted with ether (×3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 g, hexane/AcOEt = 30) to give the crude *E*-enoate (179.5 mg) including a small amount of PPh₃.

To a solution of the above crude *E*-enoate in CH₂Cl₂ (7.0 mL) was added DIBAH (1.10 μL, 1.02 M in hexane, 1.12 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 20 min. Then, the reaction was quenched carefully with MeOH (1.0 mL), and to this mixture was added saturated aqueous Rochelle salt (7.0 mL). After the mixture was stirred for about 1 h, this was extracted with CH₂Cl₂ (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (10 g, benzene → hexane/AcOEt = 7) to give **3-45** (157.0 mg, 0.3089 mmol, 71% over 4 steps).

3-45: a colorless oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.57 (6H, q, *J* = 7.9 Hz, TES), 0.94 (9H, t, *J* = 7.9 Hz, TES), 1.14 (3H, s, H12 (Me)), 1.24-1.35 (2H, m, H3_{ax}, H7a), 1.41-1.60 (1H, m, H7b), 1.60-1.81 (3H, m, H3_{eq}, H4), 1.67 (3H, s, H13 (Me)), 2.06-2.21 (2H, m, H8), 3.36 (1H, dd, *J* = 4.8, 10.1 Hz, H1a), 3.41-3.51 (2H, m, H1b, H5), 3.66-3.76 (1H, m, H2), 3.96-4.02 (2H, m, H11), 4.55

(1H, d, $J = 12.3$ Hz, Bn), 4.60 (1H, d, $J = 12.3$ Hz, Bn), 5.42 (1H, t, $J = 7.2$ Hz, H9), 7.23-7.38 (5H, m, Bn).

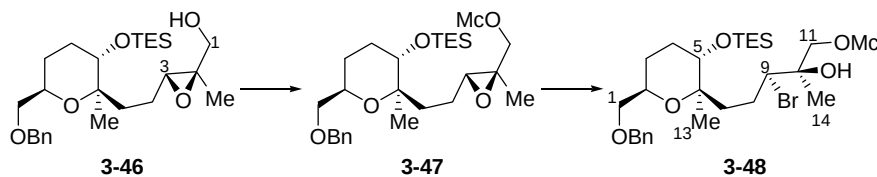
Compound 3-46.



To a mixture of $D(-)$ -DET (16.0 μ L, 93.4 μ mol) and pre-dried MS 4 A (ca. 200 mg, 100 wt%) in CH_2Cl_2 (5.0 mL) was added $\text{Ti}(\text{O}^i\text{Pr})_4$ (21.5 μ L, 72.8 μ mol) at -40 $^\circ\text{C}$, and the mixture was stirred at -40 $^\circ\text{C}$ for 2 h. To this was then added TBHP (220.0 μ L, 3.05 M in toluene, 671 μ mol), and the mixture was stirred at -40 $^\circ\text{C}$ for 10 min. After a solution of **3-45** (138.6 mg, 308.9 μ mol) in CH_2Cl_2 (1.0 mL) was added, the reaction mixture was stirred at -25 $^\circ\text{C}$ for 17.5 h. Me_2S (50.0 μ L, 683 μ mol) was added to consume unreacted TBHP before to the mixture were added 10% D_L -tartaric acid (15 drops) and NaF (ca. 20 mg) at 25 $^\circ\text{C}$. Then, the mixture was stirred at 25 $^\circ\text{C}$ for about 1 h, filtered through a pad of Celite, and condensed under reduced pressure. The resulting residue was purified by silica gel column chromatography (8.0 g, hexane/AcOEt = 7 $\rightarrow$ 3) to give **3-46** (104.7 mg, 225.3 μ mol, 73%) as almost a single diastereomer.

3-46: a colorless oil; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 0.57 (6H, q, $J = 7.7$ Hz, TES), 0.94 (9H, t, $J = 7.7$ Hz, TES), 1.15 (3H, s, H12 (Me)), 1.23-1.37 (1H, m, $\text{H}_{3\text{ax}}$), 1.51-1.87 (7H, m, $\text{H}_{3\text{eq}}$, H4, H7, H8), 1.57 (3H, s, H13 (Me)), 3.08 (1H, br-t, $J = 5.5$ Hz, H9), 3.34 (1H, dd, $J = 4.8, 10.1$ Hz, H1a), 3.38-3.50 (2H, m, H1b, H5), 3.56-3.75 (3H, m, H2, H11), 4.52 (1H, d, $J = 12.3$ Hz, Bn), 4.57 (1H, d, $J = 12.3$ Hz, Bn), 7.23-7.38 (5H, m, Bn).

Compound 3-48.

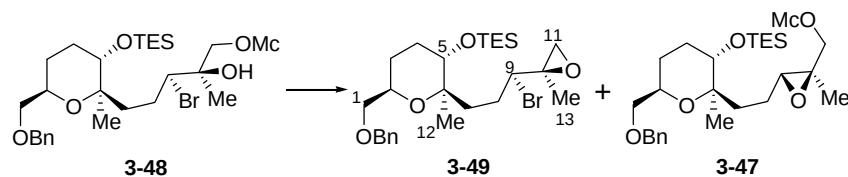


To a solution of **3-46** (40.5 mg, 0.0872 mmol) in CH₂Cl₂ (2.0 mL) were added Et₃N (76.0 μ L, 0.546 mmol) and MeCl (23.0 μ L, 0.258 mmol), and the reaction mixture was stirred for 2 h. After saturated aqueous NaHCO₃ (2.0 mL) was added, the mixture was extracted with CH₂Cl₂ ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude epoxide monochlate (**3-47**) was used immediately in the next reaction without further purification.

To a suspension of pre-sublimed Et₂NH·HBr (210.0 mg, 1.363 mmol) in CH₂Cl₂ (2.0 mL) was Et₂AlCl (145.0 μ L, 0.92 M in hexane, 0.13 mmol), and the mixture was stirred for 20 min. To this was then added a solution of crude **3-47** in CH₂Cl₂ (1.0 mL) at $-20\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred at $25\text{ }^{\circ}\text{C}$ for 18 h. After 0.2 M HCl aq. (3.0 mL) was added, the mixture was extracted with CH₂Cl₂ ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (3.0 g, hexane/AcOEt = 15 $\rightarrow$ 10) to give **3-48** (26.6 mg, 0.0404 mmol, 46% over 2 steps) and recover **3-47** (13.3 mg, 0.0230 mmol, 26%).

3-48 : a white oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.58 (6H, q, J = 7.9 Hz, TES), 0.95 (9H, t, J = 7.9 Hz, TES), 1.15 (3H, s, H13 (Me)), 1.20-1.34 (2H, m, H3_{ax}, H4_{ax}), 1.31 (3H, s, H14 (Me)), 1.40-1.66 (2H, m, H3_{eq}, H7a), 1.66-1.88 (2H, m, H4_{eq}, H8a), 2.00-2.11 (1H, m, H7b), 2.37-2.49 (1H, m, H8b), 3.31 (1H, dd, J = 3.7, 10.3 Hz, H1a), 3.38-3.46 (2H, m, H1b, H5), 3.50 (1H, s, OH), 3.62-3.73 (1H, m, H2), 4.28-4.38 (2H, m, H9, H11a), 4.49 (1H, d, J = 12.6 Hz, H11b), 4.59-4.73 (3H, m, Bn, Mc), 7.21-7.39 (5H, m, Bn).

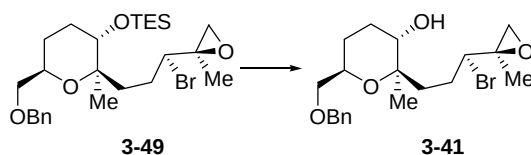
Compound 3-49.



To a solution of **3-48** (35.6 mg, 54.1 μmol) in MeOH (2.0 mL) was added K_2CO_3 (7.5 mg, 54 μmol), and the reaction mixture was stirred at $-20\text{ }^\circ\text{C}$ for 1 h. After saturated aqueous NH_4Cl (3.0 mL) was added, the mixture was extracted with ether ($\times 2$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (1.5 g, hexane/AcOEt = 30 $\rightarrow$ 3) to give **3-49** (20.4 mg, 38.7 μmol , 72%) and **3-47** (8.6 mg, 15 μmol , 28%).

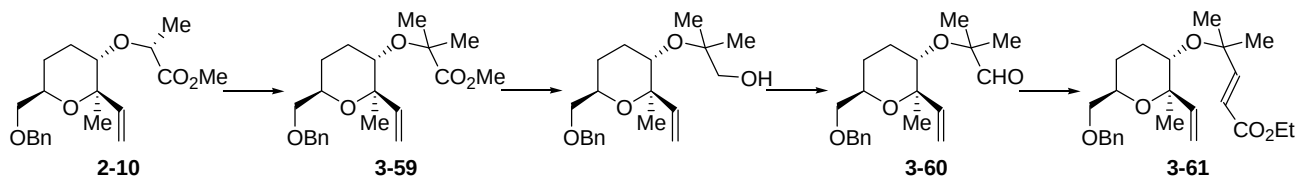
3-49: a yellow oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 0.58 (6H, q, $J = 7.9\text{ Hz}$, TES), 0.95 (9H, t, $J = 7.9\text{ Hz}$, TES), 1.13 (3H, s, H12 (Me)), 1.20-1.40 (2H, m, H3_{ax}, H4_{ax}), 1.47 (3H, s, H13 (Me)), 1.58-1.80 (3H, m, H3_{eq}, H4_{eq}, H7a), 1.84-2.06 (2H, m, H7b, H8a), 2.13-2.29 (1H, m, H8b), 2.67 (1H, d, $J = 4.8\text{ Hz}$, H11a), 2.71 (1H, d, $J = 4.8\text{ Hz}$, H11b), 3.34 (1H, dd, $J = 5.0, 10.1\text{ Hz}$, H1a), 3.38-3.47 (2H, m, H1b, H9), 3.50 (1H, dd, $J = 4.2, 9.9\text{ Hz}$, H5), 3.62-3.73 (1H, m, H2), 4.56 (2H, br-s, Bn), 7.23-7.39 (5H, m, Bn).

Compound 3-41.



To a solution of **3-49** (20.4 mg, 38.7 μmol) in 1,4-dioxane (1.0 mL) was added TBAF (40.0 μL , 1 M in THF, 40.0 μmol), and the reaction mixture was stirred for 4.5 h. After the mixture was condensed under reduced pressure, the resulting residue was purified by silica gel column chromatography (1.0 g, hexane/AcOEt = 10 $\rightarrow$ 3) to give **3-41** (15.4 mg, 37.3 μmol , 96%).

Compound 3-61.



To a solution of **2-10** (607.7 mg, 1.744 mmol) in toluene (8.00 mL) was added KHMDS (10.50 mL, 0.5 M in toluene, 5.250 mmol) at $-20\text{ }^{\circ}\text{C}$. Then MeI (550.0 μL , 8.83 mmol) was added, and the reaction mixture was stirred at $-20\text{ }^{\circ}\text{C}$ for 10 min. The mixture was warmed to ambient temperature and stirred for 50 min. After saturated aqueous NH_4Cl (18 mL) was added, the mixture was extracted with ether ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting product (**3-59**) was almost pure and was used in the next reaction without further purification.

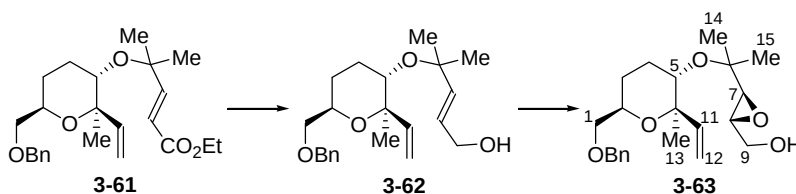
To a solution of **3-59** in CH_2Cl_2 (10 mL) was added DIBAH (4.50 mL, 1.02 M in hexane, 4.59 mmol) at $0\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 20 min. Then, the reaction was quenched carefully with MeOH (3.0 mL), and to this mixture was added saturated aqueous Rochelle salt (20 mL). After the mixture was stirred for about 1 h, this was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

To a solution of the above alcohol in CH_2Cl_2 (20 mL) were added NaHCO_3 (516.8 mg, 6.152 mmol) and DMPI (1.5496 g, 3.6536 mmol), and the reaction mixture was stirred for 2 h. After the reaction was quenched with saturated aqueous NaHCO_3 (15 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL), the mixture was extracted with CH_2Cl_2 and ether ($\times 2$). The combined organic layers were washed with and saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of NaH (704.0 mg, assay 60%, 17.60 mmol) in THF (20 mL) was added diethyl ethoxycarbonylmethanephosphonate (4.30 mL, 21.5 mmol) at $0\text{ }^{\circ}\text{C}$, the mixture was stirred at $25\text{ }^{\circ}\text{C}$ for 2.5 h. To this was then added a solution of the above crude aldehyde in THF (10 mL) at

0 °C, and the reaction mixture was stirred at 25 °C for 1.5 h. After saturated aqueous NH₄Cl (20 mL) was added, the mixture was extracted with ether (×3). The combined organic layers were washed with 0.5 M NaOH aq., dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (30 g, hexane/AcOEt = 15) to give **3-61** (399.6 mg, 0.9927 mmol, 57% over 4 steps).

Compound 3-63.



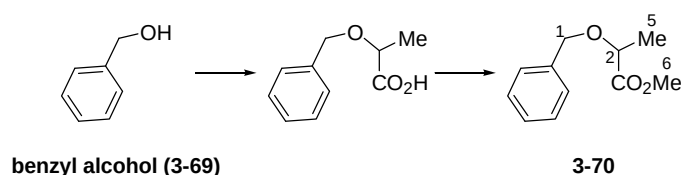
To a solution of **3-61** (386.0 mg, 0.9590 mmol) in CH₂Cl₂ (8.0 mL) was added DIBAH (2.30 mL, 1.02 M in hexane, 2.35 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 20 min. Then, the reaction was quenched carefully with MeOH (2.0 mL), and to this mixture was added saturated aqueous Rochelle salt (9.0 mL). After the mixture was stirred for about 1 h, this was extracted with CH₂Cl₂ (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting alcohol (**3-62**) was almost pure and was used in the next reaction without further purification.

To a mixture of D-(–)-DET (33.0 μL, 193 μmol) and pre-dried MS 4 A (ca. 600 mg, 100 wt%) in CH₂Cl₂ (6.5 mL) was added Ti(O^{*i*}Pr)₄ (43.0 μL, 146 μmol) at –40 °C, and the mixture was stirred at –40 °C for 2 h. To this was then added TBHP (640.0 μL, 3.05 M in toluene, 1.95 mmol), and the mixture was stirred at –40 °C for 50 min. After a solution of the above **3-62** in CH₂Cl₂ (2.0 mL) was added, the reaction mixture was stirred at –25 °C for 15 h. Me₂S (140.0 μL, 1.91 mmol) was added to consume unreacted TBHP before to the mixture were added 10% DL-tartaric acid (10 drops) and NaF (ca. 60 mg) at 25 °C. Then, the mixture was stirred at 25 °C for about 1 h, filtered through a pad of Celite, and condensed under reduced pressure. The resulting residue was purified by silica gel column chromatography (18 g, hexane/AcOEt = 3) to give **3-63** (351.6 mg, 0.9339 mmol, 97% over 2 steps) as almost a single diastereomer.

3-63: a colorless oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 1.11 (3H, s, H14 (Me)), 1.13 (3H, s, H15

(Me)), 1.26 (3H, s, H13 (Me)), 1.32-1.47 (1H, m, H3_{ax.}), 1.53-1.81 (2H, m, H3_{eq.}, H4_{ax.}), 1.89-1.99 (1H, m, H4_{eq.}), 2.94 (1H, d, $J = 2.5$ Hz, H7), 3.02 (1H, td, $J = 2.5, 4.3$ Hz, H8), 3.38 (1H, dd, $J = 4.6, 11.2$ Hz, H5), 3.39 (1H, dd, $J = 5.1, 9.9$ Hz, H1a), 3.52 (1H, dd, $J = 5.2, 9.9$ Hz, H1b), 3.57-3.67 (1H, m, H9a), 3.77 (1H, m, H2), 3.91 (1H, br-d, $J = 12.5$ Hz, H9b), 4.55 (1H, d, $J = 12.2$ Hz, Bn), 4.60 (1H, d, $J = 12.2$ Hz, Bn), 5.05 (1H, dd, $J = 1.9, 10.9$ Hz, H12a), 5.28 (1H, dd, $J = 1.9, 17.4$ Hz, H12b), 6.02 (1H, dd, $J = 10.9, 17.4$ Hz, H11), 7.22-7.38 (5H, m, Bn).

Compound 3-70.

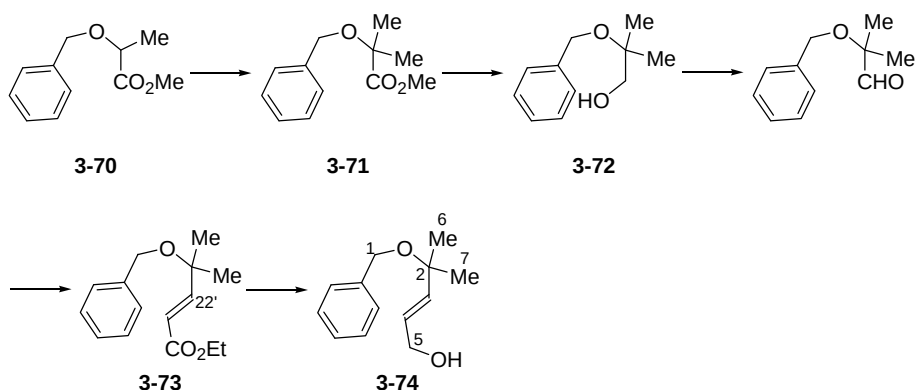


To a suspension of NaH (1.7002 g, assay 60%, 42.51 mmol) in 1,4-dioxane (30 mL) was added **3-69** (900.0 μ L, 8.66 mmol) at 0 °C, and the mixture was heated to 65 °C. To this was then added 2-bromopropionic acid (1.20 mL, 13.3 mmol), and the resulting suspension was stirred at 65 °C for 18 h. After the reaction mixture was cooled to ambient temperature, the reaction was quenched slowly with H₂O (30 mL) at 0 °C. The mixture was washed with ether, and then the resulting aqueous layer was acidified with 2M HCl aq.. The acidic solution was extracted with CH₂Cl₂ ($\times 3$), and the combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting carboxylic acid was almost pure and was used in the next reaction without further purification.

To a solution of the above carboxylic acid in benzene (6.0 mL) and MeOH (2.0 mL) was added TMSCHN₂ (8.80 mL, 2.0 M in ether, 17.6 mmol), and the reaction mixture was stirred for 15 min. After the mixture was condensed under reduced pressure, the resulting residue was purified by silica gel column chromatography (60 g, hexane/AcOEt = 15 $\rightarrow$ 5) to give a **3-70** (1.6544 g, 8.52 mmol, 98% over 2 steps).

3-70: a colorless oil; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 1.44 (3H, d, $J = 6.9$ Hz, H5 (Me)), 3.76 (3H, s, H4 (Me)), 4.07 (1H, q, $J = 6.9$ Hz, H2), 4.45 (1H, d, $J = 11.7$ Hz, H1a), 4.70 (1H, d, $J = 11.7$ Hz, H1b), 7.24-7.42 (5H, m, Ph).

Compound 3-74.



To a solution of **3-70** (301.8 mg, 1.554 mmol) in THF (15.0 mL) was added MeI (290.0 μ L, 4.66 mmol) at -78 $^{\circ}$ C. Then KHMDS (9.30 mL, 0.5 M in toluene, 4.65 mmol) was added, and the reaction mixture was stirred at -78 $^{\circ}$ C for 10 min. The mixture was warmed to ambient temperature and stirred for 50 min. After saturated aqueous NH_4Cl (15 mL) was added, the mixture was extracted with ether ($\times 2$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting product (**3-71**) was almost pure and was used in the next reaction without further purification.

To a solution of **3-71** in CH_2Cl_2 (7.0 mL) was added DIBAH (3.80 mL, 1.03 M in hexane, 3.91 mmol) at -78 $^{\circ}$ C, and the reaction mixture was stirred at -78 $^{\circ}$ C for 1 h. Then, the reaction was quenched carefully with MeOH (1.5 mL), and to this mixture was added saturated aqueous Rochelle salt (10 mL). After the mixture was stirred for about 1 h, this was extracted with CH_2Cl_2 ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol (**3-72**) was almost pure and was used in the next reaction without further purification.

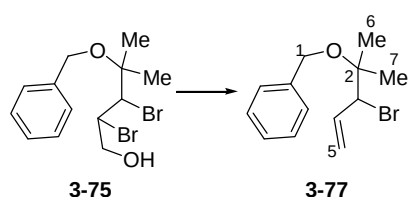
To a solution of **3-72** in CH_2Cl_2 (5.40 mL) were added Et_3N (1.35 mL, 9.70 mmol), DMSO (0.90 mL, 13 mmol), $\text{SO}_3 \cdot \text{pyridine}$ (742.3 mg, 4.664 mmol) at 0 $^{\circ}$ C, and the reaction mixture was stirred at 25 $^{\circ}$ C for 13 h. After H_2O (10 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were washed with brine and 0.5 M HCl aq., dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of NaH (623.4 mg, assay 60%, 15.59 mmol) in THF (10.0 mL) was added

under reduced pressure. The resulting residue was purified by silica gel column chromatography (2.0 g, hexane/AcOEt = 20 → 15 → 10) to give **3-75** (14.1 mg, 0.0385 mmol, 57%).

3-75: a colorless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 1.56 (3H, s, H6 (Me)), 1.58 (3H, s, H7 (Me)), 3.52 (1H, dd, $J = 5.2, 8.9$, Hz, OH), 3.80 (1H, ddd, $J = 5.4, 8.9, 12.3$ Hz, H5a), 4.10 (1H, ddd, $J = 5.2, 7.2, 12.3$ Hz, H5b), 4.47 (1H, d, $J = 1.8$ Hz, H3), 4.49 (1H, d, $J = 10.8$ Hz, H1a), 4.58 (1H, d, $J = 10.8$ Hz, H1b), 4.62 (1H, ddd, $J = 1.8, 5.4, 7.2$ Hz, H4), 7.22-7.42 (5H, m, Ph).

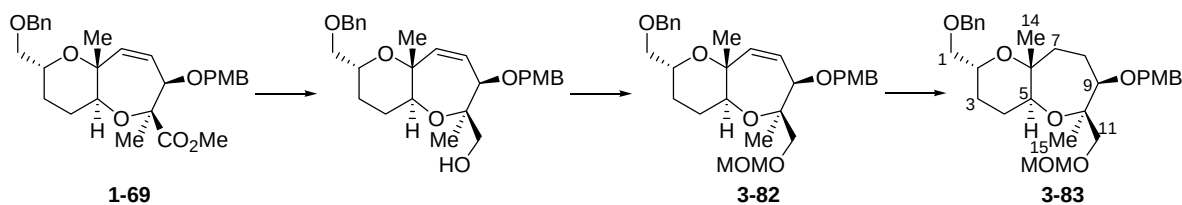
Compound 3-77.



A suspension of triphenylphosphine (28.1 mg, 107 μmol) and iodine (24.5 mg, 96.5 μmol) in toluene (1.00 mL) was stirred at 50 $^{\circ}\text{C}$ and sometimes sonicated to dissolve iodine completely. To this was added a solution of DTBMP (191.9 mg, 934.5 μmol) in toluene (0.50 mL), which followed by the addition of a solution of **3-75** (17.0 mg, 46.4 μmol) in toluene (0.50 mL). After stirring at 100 $^{\circ}\text{C}$ for 2.5 h, the reaction mixture was cooled to 0 $^{\circ}\text{C}$. 2-Methyl-2-butene (10 drops) and saturated aqueous NaHCO_3 (4.0 mL) were added to the reaction mixture at 0 $^{\circ}\text{C}$, which was extracted with ether ($\times 2$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0.6 g, hexane/AcOEt = 50) to give **3-77** (9.4 mg, 35 μmol , 75%).

3-77: a colorless oil; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 1.39 (3H, s, H6 (Me)), 1.40 (3H, s, H7 (Me)), 4.49 (1H, d, $J = 11.0$ Hz, H1a), 4.55 (1H, d, $J = 11.0$ Hz, H1b), 4.63 (1H, d, $J = 9.9$ Hz, H3), 5.15 (1H, dd, $J = 1.1, 10.3$ Hz, H5a), 5.29 (1H, br-d, $J = 16.9$ Hz, H5b), 6.14 (1H, td, $J = 9.9, 16.9$ Hz, H4), 7.20-7.42 (5H, m, Ph).

Compound 3-83.



To a solution of **1-69** (309.3 mg, 0.6228 mmol) in THF (30 mL) was added LiAlH_4 (55.2 mg, 1.45 mmol) at 0 °C, and the reaction mixture was 15 min. Then, H_2O (10 drops), 1 M NaOH aq. (7.0 mL) and H_2O (10 mL) were added in order, and the mixture was stirred for several minutes. The mixture was extracted with ether ($\times 2$) and AcOEt, and the combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

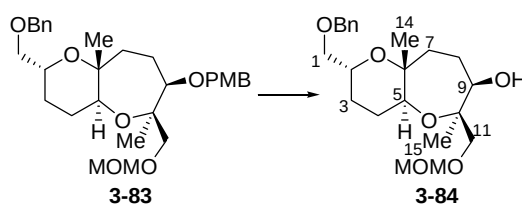
To a solution of the above alcohol in CH_2Cl_2 (25 mL) were added $i\text{Pr}_2\text{NEt}$ (840.0 μL , 4.874 mmol) and MOMBr (200.0 μL , 2.450 mmol) at 0 °C, and the reaction mixture was stirred at 40 °C for 24 h. The mixture was condensed under reduced pressure to give the crude MOM-ether (**3-82**).

To a solution of crude **3-82** in CH_2Cl_2 (40 mL) were added Et_3N (15 mL) and NBSH (13.8180 g, 50.985 mmol), and the reaction mixture was stirred for 5 d. After H_2O (30 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were washed with 1 M NaOH aq. ($\times 2$), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (24 g, hexane/AcOEt = 20 $\rightarrow$ 10) to give **3-83** (320.5 mg, 0.6228 mmol, 100% over 3 steps).

3-83: a yellow oil; $[\alpha]_{\text{D}}^{21} = -43.5$ ($c = 0.0700$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 3063, 3030, 2936, 1612, 1586, 1547, 1514, 1497, 1454, 1364, 1303, 1250, 1215, 1148, 1095, 985, 916, 879, 823, 780, 738, 699, 681, 665; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.10 (3H, s, H15 (Me)), 1.19-1.47 (2H, m, H3_{ax}, H7a), 1.23 (3H, s, H14 (Me)), 1.50-1.87 (4H, m, H3_{eq}, H4, H8a), 1.82 (1H, ddd, $J = 1.5, 5.7, 13.2$ Hz, H7b), 2.04-2.22 (1H, m, H8b), 3.21 (1H, dd, $J = 6.0, 10.4$ Hz, H5), 3.30-3.37 (1H, m, H1a), 3.33 (3H, s, MOM), 3.38-3.46 (2H, m, H1b, H9), 3.49 (1H, d, $J = 10.7$ Hz, H11a), 3.67-3.77 (1H, m, H2), 3.72 (1H, d, $J = 10.7$ Hz, H11b), 3.81 (3H, s, PMB), 4.29 (1H, d, $J = 11.5$ Hz, PMB), 4.53 (1H, d, $J = 12.4$ Hz, Bn), 4.58 (1H, d, $J = 12.4$ Hz, Bn), 4.59 (1H, d, $J = 11.5$ Hz, PMB), 4.64 (2H, s, MOM), 6.87 (2H, d, $J = 8.7$ Hz, PMB), 7.22 (2H, d, $J = 8.7$ Hz, PMB), 7.25-7.38 (5H, m, Bn);

^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) 15.8 (CH_3), 20.3 (CH_3), 24.6 (CH_2), 27.4 (CH_2), 28.5 (CH_2), 42.0 (CH_2), 55.0 (CH_3), 55.2 (CH_3), 68.4 (CH), 71.1 (CH_2), 71.6 (CH_2), 72.0 (CH), 73.3 (CH_2), 73.5 (CH_2), 76.7 (C), 78.3 (C), 85.9 (CH), 96.7 (CH_2), 113.7 ($\text{CH}\times 2$), 127.5 (CH), 127.6 ($\text{CH}\times 2$), 128.3 ($\text{CH}\times 2$), 129.3 ($\text{CH}\times 2$), 130.4 (C), 138.4 (C), 159.1 (C); LR-FDMS m/z 516 (9.1%, $[\text{M}+2]^+$), 515 (34.3%, $[\text{M}+1]^+$), 514 (bp, $[\text{M}]^+$); HR-FDMS calcd. for $\text{C}_{30}\text{H}_{42}\text{O}_7$ $[\text{M}]^+$: 514.2931, found 514.2954.

Compound 3-84.

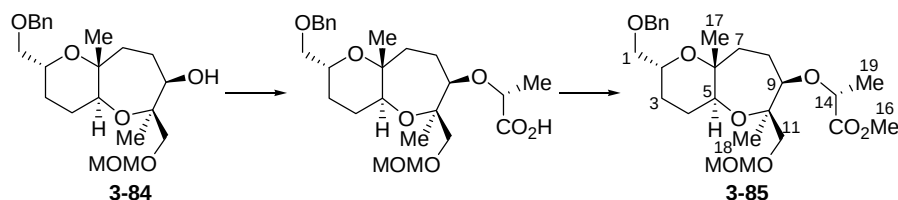


To a solution of **3-83** (202.5 mg, 393.5 μmol) in CH_2Cl_2 (10 mL) and H_2O (1.0 mL) was added DDQ (128.8 mg, 567.4 μmol), and the reaction mixture was stirred for 7 h. After saturated aqueous NaHCO_3 (10 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (9.0 g, hexane/ AcOEt = 3 $\rightarrow$ 2) to give **3-84** (146.4 mg, 371.1 μmol , 94%).

3-84: a pale yellow oil; $[\alpha]_{\text{D}}^{24} = -13.5$ ($c = 0.0400$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 3477, 3088, 3063, 3030, 2933, 1753, 1737, 1732, 1605, 1497, 1453, 1403, 1376, 1314, 1270, 1216, 1094, 1047, 985, 954, 917, 881, 842, 739, 698, 665; ^1H -NMR (300 MHz, CDCl_3) δ (ppm) 1.19 (3H, s, H15 (Me)), 1.24-1.41 (1H, m, $\text{H}_{3\text{ax}}$), 1.29 (3H, s, H14 (Me)), 1.43-1.83 (6H, m, $\text{H}_{3\text{eq}}$, H4, H7, H8a), 2.06-2.22 (1H, m, H8b), 3.00 (1H, d, $J = 7.9$ Hz, OH), 3.26 (1H, dd, $J = 5.1, 11.2$ Hz, H5), 3.33 (1H, dd, $J = 5.1, 9.9$ Hz, H1a), 3.37 (3H, s, MOM), 3.44 (1H, dd, $J = 5.3, 9.9$ Hz, H1b), 3.52 (1H, d, $J = 10.2$ Hz, H11a), 3.65 (1H, d, $J = 10.2$ Hz, H11b), 3.65-3.81 (2H, m, H2, H9), 4.53 (1H, d, $J = 12.6$ Hz, Bn), 4.58 (1H, d, $J = 12.6$ Hz, Bn), 4.61 (1H, d, $J = 6.4$ Hz, MOM), 4.65 (1H, d, $J = 6.4$ Hz, MOM), 7.22-7.42 (5H, m, Bn); ^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) 15.7 (CH_3), 21.3 (CH_3), 27.4 (CH_2), 28.5 (CH_2), 30.4 (CH_2), 41.6 (CH_2), 55.5 (CH_3), 68.4 (CH), 72.3 (CH), 72.4 (CH_2), 73.3 (CH_2), 73.5 (CH_2), 76.5 (C), 77.37 (C), 80.1 (CH), 96.8 (CH_2), 127.5 (CH), 127.6 ($\text{CH}\times 2$), 128.3 ($\text{CH}\times 2$),

138.4 (C); LR-FDMS m/z 396 (11.8%, $[M+2]^+$), 395 (53.9%, $[M+1]^+$), 394 (bp, $[M]^+$), 393 (25.4%, $[M-1]^+$); HR-FDMS calcd. for $C_{22}H_{34}O_6$ $[M]^+$: 394.2355, found 394.2382.

Compound 3-85.



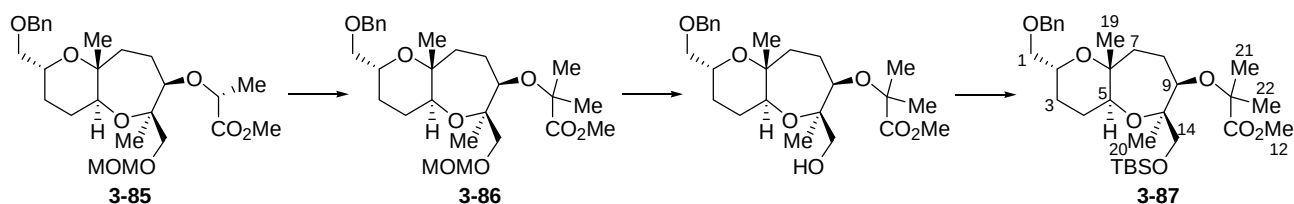
To a solution of **3-84** (45.5 mg, 0.115 mmol) in 1,4-dioxane (540.0 μ L) was added NaH (100.8 mg, assay 60%, 2.520 mmol), and the mixture was heated to 85 $^{\circ}$ C. To this was then added (*S*)-(-)-2-bromopropionic acid (20.0 μ L, 0.222 mmol), and the resulting suspension was stirred at 85 $^{\circ}$ C for 22 h. After the reaction mixture was cooled to ambient temperature, the reaction was quenched slowly with 2 M HCl aq. (3.0 mL) at 0 $^{\circ}$ C. The mixture was extracted with CH_2Cl_2 ($\times 2$) and AcOEt, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting carboxylic acid was used in the next reaction without further purification.

To a solution of the above crude carboxylic acid in benzene (1.5 mL) and MeOH (0.5 mL) was added $TMSCHN_2$ (300.0 μ L, 2.0 M in ether, 0.6000 mmol), and the reaction mixture was stirred for 10 min. After the mixture was condensed under reduced pressure, the resulting residue was purified by silica gel column chromatography (2.2 g, hexane/AcOEt = 30 $\rightarrow$ 5 $\rightarrow$ 2) to give a **3-85** (53.8 mg, 0.112 mmol, 97% over 2 steps).

3-85: a colorless oil; $[\alpha]_D^{23} = +9.15$ ($c = 0.115$, $CHCl_3$); IR (neat), ν_{max} (cm^{-1}) 3088, 3063, 3029, 2933, 1956, 1755, 1497, 1453, 1376, 1279, 1204, 1108, 985, 917, 845, 738, 698, 665; ^1H -NMR (300 MHz, $CDCl_3$) δ (ppm) 1.15-1.45 (2H, m, H_{3ax} , H7a), 1.21 (3H, s, H18 (Me)), 1.22 (3H, s, H17 (Me)), 1.36 (3H, d, $J = 6.6$ Hz, H19 (Me)), H1.53-1.84 (5H, m, H_{3eq} , H4, H7b, H8a), 2.10-2.27 (1H, m, H8b), 3.24 (1H, dd, $J = 5.5, 10.6$ Hz, H5), 3.29-3.39 (1H, m, H1a), 3.36 (3H, s, MOM), 3.39-3.47 (2H, m, H1b, H9), 3.49 (1H, d, $J = 10.6$ Hz, H11a), 3.62-3.78 (2H, m, H2, H11a), 3.72 (3H, s, H16 (Me)), 3.97 (1H, q, $J = 6.6$ Hz, H14), 4.53 (1H, d, $J = 12.4$ Hz, Bn), 4.58 (1H, d, $J = 12.4$ Hz, Bn), 4.64 (1H, d, $J = 6.6$ Hz, MOM), 4.67 (1H, d, $J = 6.6$ Hz, MOM), 7.20-7.39 (5H, m,

Bn); ^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) 15.8 (CH_3), 18.3 (CH_3), 20.5 (CH_3), 26.3 (CH_2), 27.3 (CH_2), 28.4 (CH_2), 42.0 (CH_2), 51.8 (CH_3), 55.0 (CH_3), 68.3 (CH), 71.0 (CH_2), 72.1 (CH_2), 73.2 (CH_2), 73.4 (CH_2), 75.7 (CH), 76.5 (C), 78.2 (C), 87.8 (CH), 96.7 (CH_2), 127.5 (CH), 127.6 ($\text{CH}\times 2$), 128.2 ($\text{CH}\times 2$), 138.3 (C), 173.3 (C); LR-FDMS m/z 482 (7.5%, $[\text{M}+2]^+$), 481 (34.2%, $[\text{M}+1]^+$), 480 (bp, $[\text{M}]^+$), 479 (5.9%, $[\text{M}-1]^+$); HR-FDMS calcd. for $\text{C}_{26}\text{H}_{40}\text{O}_8$ $[\text{M}]^+$: 480.2723, found 480.2752.

Compound 3-87.



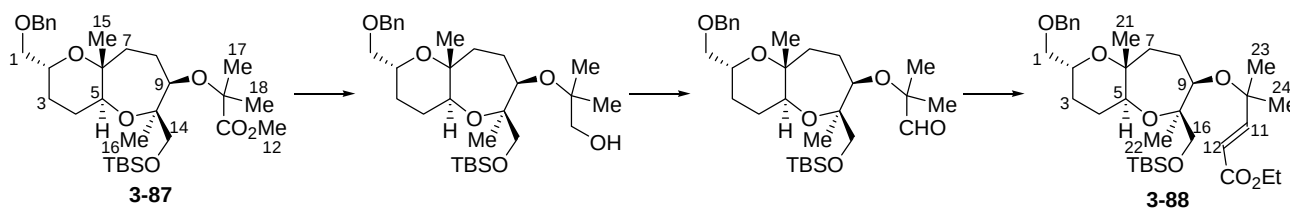
To a solution of **3-85** (38.3 mg, 79.7 μmol) in toluene (1.50 mL) was added KHMDS (210.0 μL , 0.5 M in toluene, 105.0 μmol) at $-20\text{ }^\circ\text{C}$, and the mixture was stirred for 1 min. Then MeOTf (26.0 μL , 238 μmol) was added, and the reaction mixture was stirred at $-20\text{ }^\circ\text{C}$ for 30 min. After saturated aqueous NaHCO_3 (6.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude product (**3-86**) was used in the next reaction without further purification.

To a solution of crude **3-86** in CH_2Cl_2 (2.5 mL) was added TFA (ca. 6.0 μL , ca.81 μmol), and the reaction mixture was stirred at $40\text{ }^\circ\text{C}$ for 24 h. After the mixture was condensed under reduced pressure, the resulting crude alcohol was used in the next reaction without further purification.

To a solution of the above crude alcohol in CH_2Cl_2 (2.5 mL) were added 2,6-lutidine (95.0 μL , 816 μmol) and TBSOTf (92.0 μL , 401 μmol) at $0\text{ }^\circ\text{C}$, and the reaction mixture was stirred at $25\text{ }^\circ\text{C}$ for 9 h. After saturated aqueous NaHCO_3 (5.0 mL) was added at $0\text{ }^\circ\text{C}$, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (2.0 g, hexane/AcOEt = 20 $\rightarrow$ 10) to give **3-87** (38.7 mg, 68.5 μmol , 86% over 3 steps).

3-87: a colorless oil; $[\alpha]_D^{25} = -12.4$ ($c = 0.460$, CHCl_3); IR (neat), ν_{max} (cm^{-1}) 3088, 3064, 3030, 2928, 2856, 1737, 1497, 1463, 1454, 1372, 1282, 1252, 1097, 1029, 1006, 985, 938, 837, 816, 776, 735, 697, 666; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) 0.03 (3H, s, TBS), 0.05 (3H, s, TBS), 0.89 (9H, s, TBS), 1.09 (3H, s, H20 (Me)), 1.21 (3H, s, H19 (Me)), 1.22-1.47 (2H, m, H3_{ax.}, H7a), 1.39 (3H, s, H21 (Me)), 1.40 (3H, s, H22(Me)), 1.50-1.78 (5H, m, H3_{eq.}, H4, H7b, H8a), 2.17-2.35 (1H, m, H8b), 3.24 (1H, dd, $J = 6.2, 10.1$ Hz, H5), 3.34 (1H, dd, $J = 4.9, 9.9$ Hz, H1a), 3.44 (1H, dd, $J = 5.3, 9.9$ Hz, H1b), 3.56 (1H, d, $J = 10.5$ Hz, H14a), 3.62-3.78 (2H, m, H2, H9), 3.69 (3H, s, H12 (Me)), 3.72 (1H, d, $J = 10.5$ Hz, H14b), 4.54 (1H, $J = 12.5$ Hz, Bn), 4.58 (1H, $J = 12.5$ Hz, Bn), 7.22-7.39 (5H, m, Bn); $^{13}\text{C-NMR}$ (75 MHz, C_6D_6) δ (ppm) -5.1 (CH_3), -4.9 (CH_3), 16.3 (CH_3), 18.7 (C), 19.8 (CH_3), 25.0 (CH_3), 25.5 (CH_3), 26.3 ($\text{CH}_3 \times 3$), 27.8 (CH_2), 28.2 (CH_2), 29.0 (CH_2), 42.3 (CH_2), 51.3 (CH_3), 67.7 (CH_2), 68.8 (CH), 72.5 (CH), 73.4 (CH_2), 74.2 (CH_2), 76.6 (C), 77.4 (C), 78.9 (C), 81.6 (CH), 127.6 (CH), 127.8 ($\text{CH} \times 2$), 128.5 ($\text{CH} \times 2$), 139.4 (C), 173.6 (C); LR-FDMS m/z 566 (11.0%, $[\text{M}+2]^+$), 565 (27.4%, $[\text{M}+1]^+$), 564 (27.7%, $[\text{M}]^+$), 509 (11.9%, $[\text{M}+2-t\text{-Bu}]^+$), 508 (36.6%, $[\text{M}+1-t\text{-Bu}]^+$), 507 (bp, $[\text{M}-t\text{-Bu}]^+$); HR-FDMS calcd. for $\text{C}_{31}\text{H}_{52}\text{O}_7\text{Si}$ $[\text{M}]^+$: 564.3482, found 564.3494.

Compound 3-88.



To a solution of **3-87** (38.7 mg, 68.5 μmol) in THF (2.0 mL) was added LiAlH_4 (6.8 mg, 0.18 mmol) at 0 $^\circ\text{C}$, and the reaction mixture was 20 min. Then, H_2O (5 drops), 1 M NaOH aq. (3.0 mL) and H_2O (3.0 mL) were added in order, and the mixture was stirred for several minutes. The mixture was extracted with CH_2Cl_2 ($\times 2$) and ether, and the combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

To a solution of the above alcohol in CH_2Cl_2 (2.0 mL) were added NaHCO_3 (112.6 mg, 1.340 mmol) and DMPI (171.9 mg, 405.3 μmol), and the reaction mixture was stirred for 3 h. After

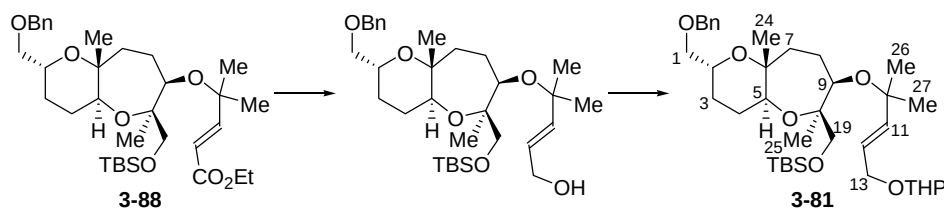
the reaction was quenched with saturated aqueous NaHCO₃ (5.0 mL) and Na₂S₂O₃ (7.0 mL), the mixture was extracted with ether (×3). The combined organic layers were washed with brine and saturated aqueous Na₂S₂O₃, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of NaH (31.1 mg, assay 60%, 778 μmol) in THF (2.0 mL) was added diethyl ethoxycarbonylmethanephosphonate (170.0 μL, 849 μmol) at 0 °C, the mixture was stirred at 25 °C for 1 h. To this was then added a solution of the above crude aldehyde in THF (2.0 mL) at 0 °C, and the reaction mixture was stirred at 25 °C for 10 h. After H₂O (3.0 mL) and 1 M NaOH aq. (1.0 mL) were added at 0 °C, the mixture was extracted with ether (×3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (1.8 g, hexane/AcOEt = 15 → 10 → 5) to give **3-88** (32.1 mg, 53.1 μmol, 78% over 3 steps).

3-88: a yellow oil; $[\alpha]_D^{24} = -18.8$ (c = 0.0750, CHCl₃); IR (neat), $\nu_{\max}$ (cm⁻¹) 3088, 3064, 3030, 2935, 2856, 2710, 1721, 1656, 1497, 1463, 1366, 1292, 1251, 1198, 1096, 986, 938, 910, 837, 816, 776, 734, 698, 666, 647; ¹H-NMR (300 MHz, CDCl₃) δ (ppm) 0.04 (3H, s, TBS), 0.05 (3H, s, TBS), 0.90 (9H, s, TBS), 1.10 (3H, s, H22(Me)), 1.20 (3H, s, H21 (Me)), 1.22-1.46 (3H, m, H3_{ax.}, H7), 1.29 (6H, br-s, H23 (Me), H24 (Me)), 1.30 (3H, t, *J* = 7.1 Hz, Et), 1.53-1.75 (4H, m, H3_{eq.}, H4, H8a), 2.19-2.37 (1H, m, H8b), 3.22 (1H, dd, *J* = 6.2, 9.9 Hz, H5), 3.34 (1H, dd, *J* = 5.0, 9.9 Hz, H1a), 3.436 (1H, dd, *J* = 5.3, 9.9 Hz, H1b), 3.445 (1H, br-d, *J* = 10.3 Hz, H9), 3.57 (1H, d, *J* = 10.6 Hz, H16a), 3.66-3.77 (1H, m, H2), 3.71 (1H, d, *J* = 10.6 Hz, H16b), 4.21 (2H, q, *J* = 7.1 Hz, Et), 4.53 (1H, d, *J* = 12.1 Hz, Bn), 4.58 (1H, d, *J* = 12.1 Hz, Bn), 5.88 (1H, d, *J* = 16.0 Hz, H12), 6.90 (1H, d, *J* = 12.1 Hz, H11), 7.22-7.39 (5H, m, Bn); ¹³C-NMR (75 MHz, C₆D₆) δ (ppm) -5.1 (CH₃), -4.9 (CH₃), 14.2 (CH₃), 16.3 (CH₃), 18.7 (C), 20.3 (CH₃), 26.1 (CH₃), 26.2 (CH₃), 26.3 (CH₃×3), 27.8 (CH₂), 29.0 (CH₂), 29.3 (CH₂), 42.1 (CH₂), 60.3 (CH₂), 67.9 (CH₂), 68.8 (CH), 72.5 (CH), 73.4 (CH₂), 74.1 (CH₂), 75.1 (C), 76.6 (C), 78.9 (C), 80.6 (CH), 120.1 (CH), 127.6 (CH), 127.8 (CH×2), 128.5 (CH×2), 139.3 (C), 153.5 (CH), 166.1 (C); LR-FDMS *m/z* 606 (15.0%, [M+2]⁺), 605 (36.3%, [M+1]⁺), 604 (24.0%, [M]⁺), 549 (13.2%, [M+2-*t*-Bu]⁺), 548 (39.7%, [M+1-*t*-Bu]⁺),

547 (bp, $[M-t-Bu]^+$); HR-FDMS calcd. for $C_{34}H_{56}O_7Si$ $[M]^+$: 604.3795, found 604.3807.

Compound 3-81.

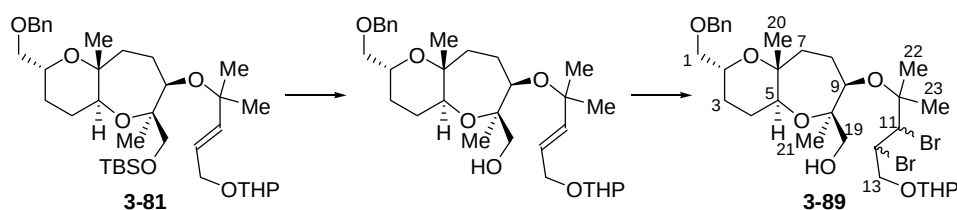


To a solution of **3-88** (28.1 mg, 46.5 μ mol) in CH_2Cl_2 (1.0 mL) was added DIBAH (110.0 μ L, 1.02 M in hexane, 112 μ mol) at $-20^\circ C$, and the reaction mixture was stirred at $-20^\circ C$ for 25 min. Then, the reaction was quenched carefully with MeOH (10 drops), and to this mixture was added saturated aqueous Rochelle salt (8.0 mL). After the mixture was stirred for about 1 h, this was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

To a solution of the above alcohol and 3,4-dihydro-2*H*-pyran (10.0 μ L, 110 μ mol) in CH_2Cl_2 (1.0 mL) was added PPTS (2.2 mg, 8.7 μ mol), and the reaction mixture was stirred for 1 d. After a saturated aqueous $NaHCO_3$ (4.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (2.5 g, hexane/AcOEt = 20) to give **3-81** (30.1 mg, 46.5 μ mol, 100% over 2 steps). **3-81**: a colorless oil; $[\alpha]_D^{25} = -8.7$ ($c = 0.080$, $CHCl_3$); IR (neat), ν_{max} (cm^{-1}) 3030, 2935, 2855, 1497, 1495, 1467, 1463, 1442, 1435, 1377, 1360, 1322, 1285, 1251, 1201, 1183, 1084, 1055, 1028, 984, 906, 836, 776, 735, 697, 665; ^1H -NMR (300 MHz, $CDCl_3$) δ (ppm) 0.03 (3H, s, TBS), 0.05 (3H, s, TBS), 0.89 (9H, s, TBS), 1.09 (1/2 $\times$ 3H, s, 1/2 $\times$ H25(Me)), 1.10 (1/2 $\times$ 3H, s, 1/2 $\times$ H25(Me)), 1.12-1.91 (13H, m, H3, H4, H7, H8a, THP (6H)), 1.20 (3H, s, H24 (Me)), 1.24 (3H, s, H26 (Me)), 1.26 (3H, s, H27 (Me)), 2.10-2.28 (1H, m, H8b), 3.23 (1H, dd, $J = 6.4, 9.7$ Hz, H5), 3.33 (1H, dd, $J = 4.8, 9.8$ Hz, H1a), 3.38-3.47 (2H, m, H1b, H9), 3.47-3.58 (1H, m, THP), 3.58 (1H, d, $J = 10.6$ Hz, H19a), 3.63-3.77 (1H, m, THP), 3.70 (1H, d, $J = 10.6$ Hz, H19b), 3.81-3.92 (1H, m, H2), 3.98 (1H, dd, $J = 4.7, 12.6$ Hz, H13a), 4.25 (1H, dd, $J = 4.0, 12.6$ Hz, H13b), 4.53 (1H, d, $J = 12.3$ Hz, Bn),

4.58 (1H, d, $J = 12.3$ Hz, Bn), 4.61-4.68 (1H, m, THP), 5.60-5.78 (2H, m, H11, H12), 7.20-7.39 (5H, m, Bn); ^{13}C -NMR (75 MHz, CDCl_3) δ (ppm) -5.14 (CH_3), -5.06 (CH_3), 16.1 (CH_3), 18.4 (C), 19.4 (CH_2), 19.9 (CH_3), 25.4 (CH_2), 26.0 ($\text{CH}_3 \times 3$), 26.5 ($\text{CH}_3 \times 1/2$), 26.7 ($\text{CH}_3 \times 1/2$), 27.1 ($\text{CH}_3 \times 1/2$), 27.3 ($\text{CH}_2 + \text{CH}_3 \times 1/2$), 28.6 (CH_2), 28.8 (CH_2), 30.6 (CH_2), 41.7 (CH_2), 62.05 ($\text{CH}_2 \times 1/2$), 62.09 ($\text{CH}_2 \times 1/2$), 67.1 (CH_2), 67.3 ($\text{CH}_2 \times 1/2$), 67.4 ($\text{CH}_2 \times 1/2$), 68.4 (CH), 71.8 (CH), 73.3 (CH_2), 73.6 (CH_2), 75.31 (C), 75.34 (C), 78.8 (C), 79.3 ($\text{CH} \times 1/2$), 79.4 ($\text{CH} \times 1/2$), 98.0 ($\text{CH} \times 1/2$), 98.1 ($\text{CH} \times 1/2$), 125.7 (CH), 127.5 (CH), 127.7 ($\text{CH} \times 2$), 128.3 ($\text{CH} \times 2$), 138.4 (C), 138.7 ($\text{CH} \times 1/2$), 138.8 ($\text{CH} \times 1/2$); LR-FDMS m/z 648 (5.5%, $[\text{M}+2]^+$), 647 (17.2%, $[\text{M}+1]^+$), 646 (32.8%, $[\text{M}]^+$), 85 (bp, $[\text{C}_6\text{H}_9\text{O}]^+$); HR-FDMS calcd. for $\text{C}_{37}\text{H}_{62}\text{O}_7\text{Si}$ $[\text{M}]^+$: 646.4265, found 646.4247.

Compound 3-89.



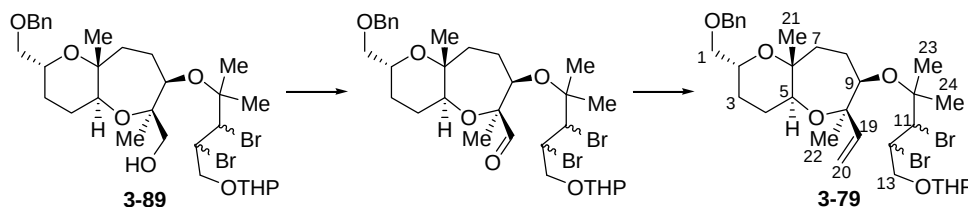
To a solution of **3-81** (6.6 mg, 10 μmol) in THF (1.0 mL) was added TBAF (200.0 μL , 1 M in THF, 200.0 μmol), and the reaction mixture was stirred at 40 $^\circ\text{C}$ for 19.5 h. After saturated aqueous NH_4Cl (4.0 mL) was added, the mixture was extracted with ether ($\times 2$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol was almost pure and was used in the next reaction without further purification.

To a solution of the above alcohol and DTBMP (47.1 mg, 229 μmol) in CH_2Cl_2 (300.0 μL) was added bromine (1.0 μL , 19 μmol) at 0 $^\circ\text{C}$, and the reaction mixture was stirred at 0 $^\circ\text{C}$ for 1 min. Then, the reaction was quenched with 2-methyl-2-butene (5 drops). After saturated aqueous NaHCO_3 (4.0 mL) was added, the mixture was extracted with CH_2Cl_2 ($\times 2$) and AcOEt. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0.6 g, hexane/AcOEt = 10 $\rightarrow$ 5 $\rightarrow$ 3 $\rightarrow$ AcOEt) to give **3-89** (4.0 mg, 6.6 μmol , 65% over 2 steps).

3-89: a colorless oil; LR-FDMS m/z 694 (11.9%, $[\text{M}+2]^+$), 693 (10.5%, $[\text{M}+1]^+$), 692 (19.7%, $[\text{M}]^+$),

691 (9.6%, $[M-1]^+$), 690 (9.4%, $[M-2]^+$), 85 (bp, $[C_6H_9O]^+$); HR-FDMS calcd. for $C_{31}H_{48}Br_2O_7$ $[M]^+$: 690.1767, found 690.1795.

Compound 3-79.

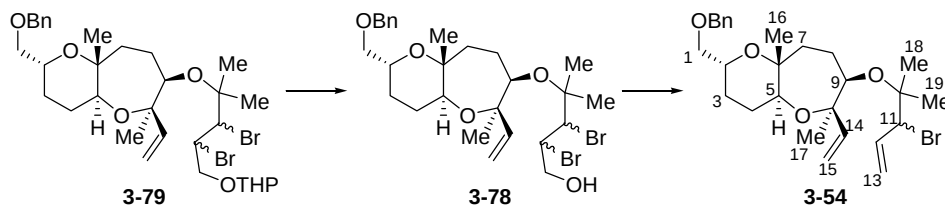


To a solution of **3-89** (10.0 mg, 14.4 μ mol) in CH_2Cl_2 (1.0 mL) were added $NaHCO_3$ (17.3 mg, 206 μ mol) and DMPI (38.5 mg, 90.8 μ mol), and the reaction mixture was stirred for 3.5 h. After the reaction was quenched with saturated aqueous $NaHCO_3$ (3.0 mL) and $Na_2S_2O_3$ (5.0 mL), the mixture was extracted with ether ($\times 2$). The combined organic layers were washed with brine and saturated aqueous $Na_2S_2O_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of methyltriphenylphosphonium bromide (33.7 mg, 94.3 μ mol) in THF (1.0 mL) was added NHMDS (83.0 μ L, 1.10 M in THF, 91.3 μ mol), the mixture was stirred at 25 $^{\circ}C$. After 1.5 h, the resulting yellow suspension was cooled to $-78^{\circ}C$. To this was then added a solution of the above crude aldehyde in THF (1.0 mL) at $-78^{\circ}C$, and the reaction mixture was stirred at 25 $^{\circ}C$ for 14.5 h. After saturated aqueous NH_4Cl (4.0 mL) was added, the mixture was extracted with ether ($\times 2$). 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 silica gel column chromatography (0.6 g, hexane/ $AcOEt$ = 20 $\rightarrow$ 15 $\rightarrow$ 10 $\rightarrow$ 3) to give **3-79** (3.0 mg, 4.4 μ mol, 30% over 2 steps).

3-79: a colorless oil; LR-FDMS m/z 690 (9.2%, $[M+2]^+$), 689 (8.6%, $[M+1]^+$), 688 (16.4%, $[M]^+$), 687 (9.1%, $[M-1]^+$), 686 (8.0%, $[M-2]^+$), 85 (bp, $[C_6H_9O]^+$); HR-FDMS calcd. for $C_{32}H_{48}Br_2O_6$ $[M]^+$: 686.1818, found 686.1801.

Compound 3-54.

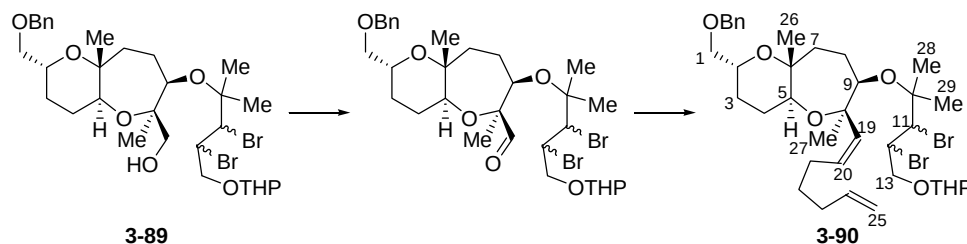


To a solution of **3-79** (3.0 mg, 4.4 μmol) in THF (0.40 mL) and H_2O (0.20 mL) was added AcOH (0.80 mL), and the reaction mixture was stirred at 40 $^\circ\text{C}$ for 23 h. After the reaction was quenched carefully with saturated aqueous NaHCO_3 (10 mL) at 0 $^\circ\text{C}$, the mixture was extracted with CH_2Cl_2 and ether. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting alcohol (**3-78**) was almost pure and was used in the next reaction without further purification.

A suspension of triphenylphosphine (42.7 mg, 163 μmol) and iodine (39.0 mg, 154 μmol) in toluene (400.0 μL) was stirred at 50 $^\circ\text{C}$ and sometimes sonicated to dissolve iodine completely. To this was added a solution of DTBMP (51.9 mg, 253 μmol) in toluene (400.0 μL), which followed by the addition of a solution of **3-78** in toluene (400.0 μL). After stirring at 100 $^\circ\text{C}$ for 26 h, the reaction mixture was cooled to 0 $^\circ\text{C}$. 2-Methyl-2-butene (5 drops) and saturated aqueous NaHCO_3 (3.0 mL) were added to the reaction mixture at 0 $^\circ\text{C}$, which was extracted with ether ($\times 2$). 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 silica gel column chromatography (0.6 g, hexane/AcOEt = 50 $\rightarrow$ 20 $\rightarrow$ 5 $\rightarrow$ 2) to give **3-54** (2.0 mg, 4.3 μmol , 91% over 2 steps).

3-54: a colorless oil; LR-FDMS m/z 508 (38.9%, $[\text{M}+1]^+$), 506 (33.6%, $[\text{M}-1]^+$), 256 (bp); HR-FDMS calcd. for $\text{C}_{27}\text{H}_{39}\text{BrO}_4$ $[\text{M}]^+$: 506.2032, found 506.2011.

Compound 3-90.

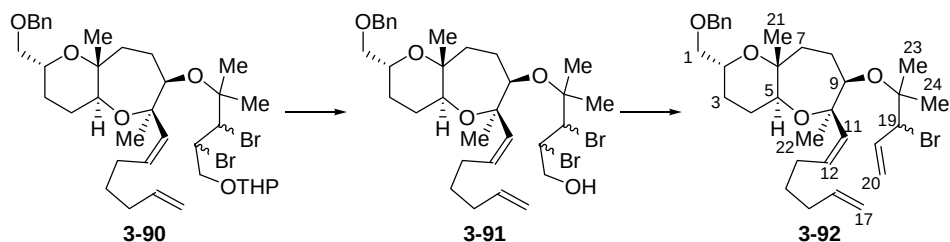


To a solution of **3-89** (11.6 mg, 16.8 μmol) in CH_2Cl_2 (1.5 mL) were added NaHCO_3 (87.4 mg, 1.04 mmol) and DMPI (114.4 mg, 269.7 μmol), and the reaction mixture was stirred for 16.5 h. After NaHCO_3 (3.0 mL) was added at 0 $^\circ\text{C}$, the mixture was extracted with ether ($\times 3$). The combined organic layers were washed with brine ($\times 2$), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude aldehyde was used immediately in the next reaction without further purification.

To a suspension of 1-hexenyltriphenylphosphonium bromide (83.0 mg, 195 μmol) in THF (500.0 μL) was added BuLi (120.0 μL , 1.58 M in hexane, 190 μmol), the mixture was stirred at 25 $^\circ\text{C}$. After 10 min, the resulting dark red suspension was cooled to 0 $^\circ\text{C}$. To this was then added a solution of the above crude aldehyde in THF (500.0 μL) at 0 $^\circ\text{C}$, and the reaction mixture was stirred at 0 $^\circ\text{C}$ for 30 min. Then the reaction mixture was warmed to 25 $^\circ\text{C}$ and stirred for 15 h. After saturated aqueous NH_4Cl (4.0 mL) was added at 0 $^\circ\text{C}$, the mixture was extracted with ether ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0.6 g, hexane/ AcOEt = 40 $\rightarrow$ 15 $\rightarrow$ 3) to give **3-90** (4.8 mg, 6.3 μmol , 38% over 2 steps).

3-90: a colorless oil; LR-FDMS m/z 758 (2.7%, $[\text{M}+2]^+$), 757 (3.2%, $[\text{M}+1]^+$), 756 (5.1%, $[\text{M}]^+$), 755 (3.0%, $[\text{M}-1]^+$), 754 (3.2%, $[\text{M}-2]^+$), 85 (bp, $[\text{C}_6\text{H}_9\text{O}]^+$); HR-FDMS calcd. for $\text{C}_{37}\text{H}_{56}\text{Br}_2\text{O}_6$ $[\text{M}]^+$: 754.2444, found 754.2427.

Compound 3-92.



To a solution of **3-90** (4.8 mg, 6.3 μmol) in THF (0.40 mL) and H₂O (0.20 mL) was added AcOH (0.80 mL), and the reaction mixture was stirred at 40 °C for 16 h. After the reaction was quenched carefully with saturated aqueous NaHCO₃ (10 mL) at 0 °C, the mixture was extracted with CH₂Cl₂ ($\times 2$) and ether. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting alcohol (**3-91**) was almost pure and was used in the next reaction without further purification.

A suspension of triphenylphosphine (31.8 mg, 121 μmol) and iodine (26.5 mg, 104 μmol) in toluene (400.0 μL) was stirred at 50 °C and sometimes sonicated to dissolve iodine completely. To this was added a solution of DTBMP (154.2 mg, 750.9 μmol) in toluene (400.0 μL), which followed by the addition of a solution of **3-91** in toluene (400.0 μL). After stirring at 100 °C for 17.5 h, the reaction mixture was cooled to 0 °C. 2-Methyl-2-butene (10 drops), saturated aqueous NaHCO₃ (3.0 mL), and saturated aqueous Na₂S₂O₃ (3.0 mL) were added to the reaction mixture at 0 °C, which was extracted with ether ($\times 2$). The combined organic layers were washed with 0.5 M HCl aq., dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (0.6 g, hexane/AcOEt = 60 $\rightarrow$ 40 $\rightarrow$ 20) to give **3-92** (2.3 mg, 4.0 μmol , 62% over 2 steps) and recover **3-91** (ca. 1.3 mg, <1.9 μmol , <30%)

3-92: a yellow oil; LR-FDMS m/z 577 (9.9%, [M+2]⁺), 576 (22.9%, [M+1]⁺), 575 (12.9%, [M]⁺), 574 (19.6%, [M-1]⁺), 91 (39.5%, [Bn]⁺), 73 (bp); HR-FDMS calcd. for C₃₂H₄₇BrO₄ [M]⁺: 574.2658, found 574.2668.

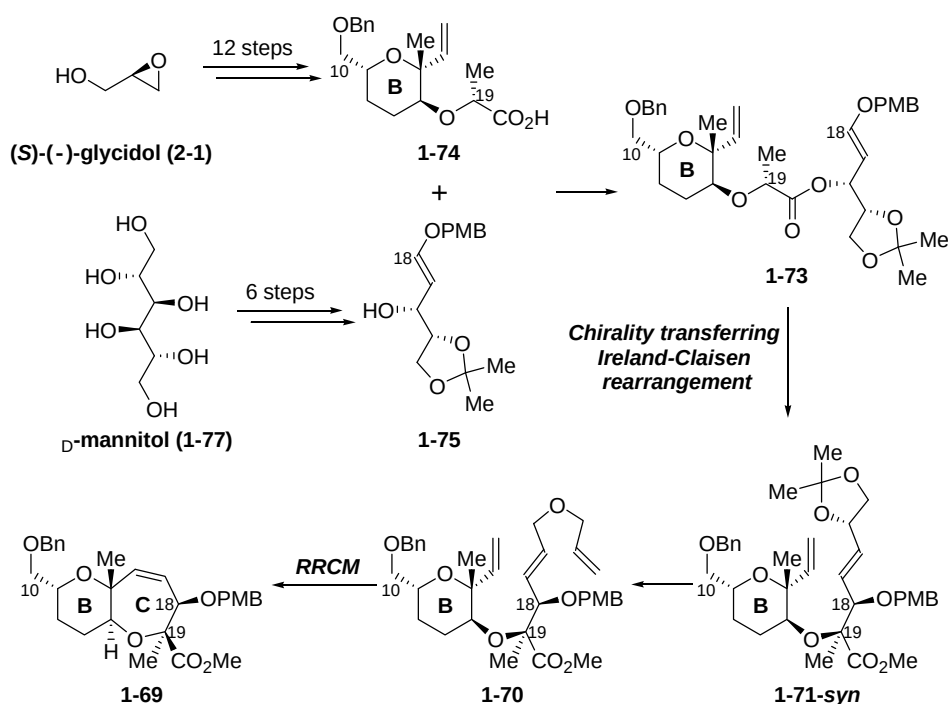
Chapter 4.

Conclusion and Scope for Future Work

4-1. Conclusion

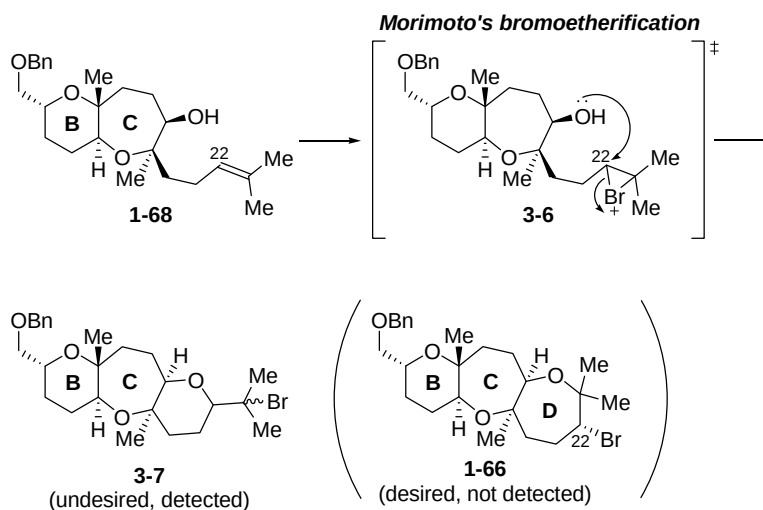
In this dissertation work, the author studied the synthesis of the BCD-ring of armatol F, a new type of fused triterpene polyether isolated from the red alga *Chondria armata*.

First, according to the plan illustrated in Scheme 1-7, the BC-ring (**1-69**) was synthesized based on chirality transferring Ireland-Claisen rearrangement and RRCM (Scheme 4-1). Lactic acid derivative **1-74** corresponding to the B-ring was synthesized from (*S*)-(-)-glycidol (**2-1**) over 12 steps. Acid **1-74** was condensed with *E*-3-alkoxyallyl alcohol **1-75**, derived from *D*-mannitol (**1-77**) over 6 steps, to give ester **1-73**. The Ireland-Claisen rearrangement of **1-73** was successfully performed with KHMDS in the presence of TMSCl in toluene at $-20\text{ }^{\circ}\text{C}$, and the desired *syn*- β -alkoxy ether (**1-71-syn**) was produced in a good yield (77%) and ratio (*syn:anti* = 9.1:1.0). The RRCM of triene **1-70** by the 2nd generation Hoveyda-Grubbs' catalyst in the presence of 1,4-benzoquinone effectively constructed the congested C-ring, and BC-ring **1-69** was obtained in 72% yield successfully.



Scheme 4-1. Synthesis of the BC-ring (**1-69**) based on chirality transferring Ireland-Claisen rearrangement and RRCM.

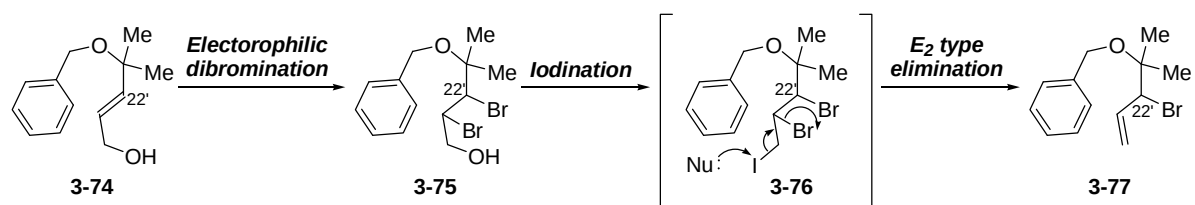
Next, the author examined the construction of the D-ring. Initially, the *7-endo* cyclization of isopropylidene alcohol **1-68** by intramolecular bomoetherification under the Morimoto's conditions was attempted as a concise synthesis of D-ring **1-66**. However, the bromoetherification reaction only produced 6-*exo* product **3-7**.



Scheme 4-2. An attempt to cyclize isopropylidene alcohol 1-68 by Morimoto's bromoetherification.

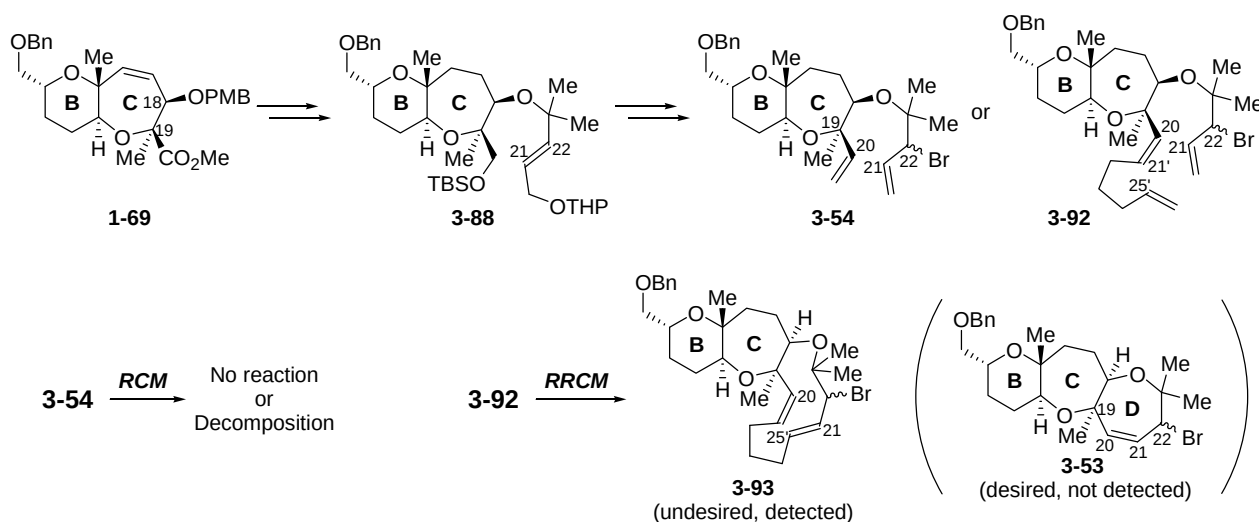
Then, the author further attempted to establish the D-ring by the following two methods: (i) *7-exo* cyclization of hydroxy epoxide, and (ii) the combination of alkylation-based ether formation and bromination by regioselective epoxide ring opening with bromide ion. Disappointingly, these attempts were all unsuccessful. However, the results taught that the D-ring-closure by nucleophilic C-O bond formation as well as an S_N2 -type installation of a bromine group at congested C22 was ineffective for the D-ring synthesis.

Therefore, the author reached the following idea: the D-ring-closure by RCM and electrophilic installation of the bromine group at C22 would be effective for the D-ring synthesis. The latter idea was successfully demonstrated by a model synthesis of allyl bromide **3-77** from allyl alcohol **3-74** via electrophilic dibromination followed by dehydroxybromination (Scheme 4-3).



Scheme 4-3. Model synthesis of allyl bromide 3-77 via electrophilic dibromination.

Hence, the author formulated a new synthetic plan for the D-ring based on the bromination method and RCM, and examined the plan with **1-69**. As a result, the bromine group at C22 was successfully introduced to obtain diene **3-54** and triene **3-92** (Scheme 4-4). The RCM of **3-54** gave no significant product, and the RRCM of **3-92** did not afford the desired **3-53**, but produced macrocyclic ether **3-93**.



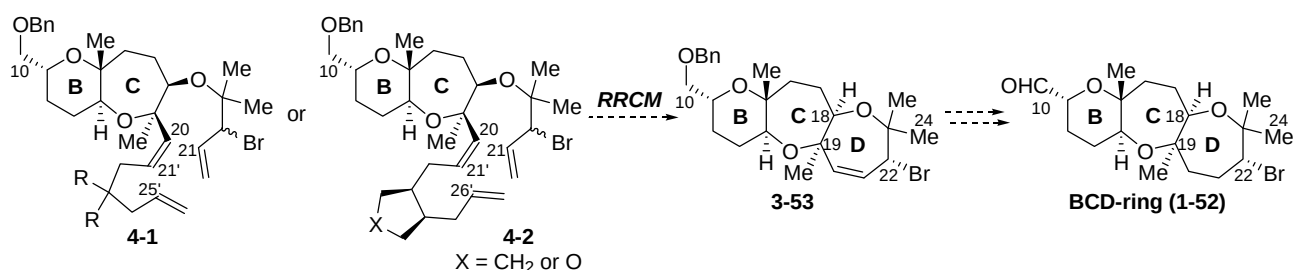
Scheme 4-4. Synthesis of diene 3-54 and triene 3-92, and attempts to cyclize the D-ring by RCM and RRCM.

Although desired **3-53** was not obtained, the production of macrocyclized product **3-93** suggested the participation of C21-olefin in the metathesis reaction. The suggestion inspired the author to revise the structure of substrate for the RRCM in a way that induces an efficient relay of catalyst from C25' to C20.

4-2. Scope for future work

First of all, the RRCM of triene **4-1** or **4-2** should be investigated to construct *trans/cis*-6,7,7-fused tricyclic ether **3-53** (Scheme 4-5). The author believes that the Thorpe-Ingold effect of the substituents at C23' of **4-1** and/or the cyclic structure of **4-2** would put the alkene at C25' or C26' in close proximity to the alkene at C20, which would provide the smooth metathesis between the alkenes at the initial stage of RRCM.

After the establishment of D-ring formation, diimide reduction of **3-53** followed by conversion of C10 to an aldehyde is scheduled to complete the synthesis of the BCD-ring (**1-52**) of armatol F.



Scheme 4-5. A plan for the synthesis of the BCD-ring (1-52) via the RRCM of triene **4-1 or **4-2** to **3-53**.**

Finally, the full assignment of the absolute configuration of natural armatol F is planned, as described in Section 1-6, Chapter 1. The examinations of the bioactivity of armatol F and synthetic analogues produced by this thesis work are also intended in the future. The author hopes the successful determination of the absolute configuration of armatol F and the presence of some valuable bioactivity in armatol F and the analogues.

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Keita Tanaka