Synthetic Studies on Nigricanoside-A Dimethyl Ester

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Contents

Abbreviation

Ac	acetyl
Aux	auxiliary group
Bn	benzyl
Bu	butyl
^{t}Bu	*tert*-butyl
calcd	calculated
CSA	(±)-10-camphorsulfonic acid
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	azodicarboxylic acid diethyl ester
DIAD	azodicarboxylic acid diisopropyl ester
DIBALH	diisobuthylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMB	3,4-dimethoxybenzyl
DMP	3,4-dimethoxyphenyl
DMF	*N*,*N*-dimethylformamide
DMPI	Dess-Martin periodinane
DMSO	dimethylsulfoxide
EE	ethoxyethyl
Et	ethyl
EI	electron impact ionization
FD	field desorption ionization
HMPA	hexamethylphosphoramide
HR	high resolution
IC	inhibitory concentration
IR	infrared absorption spectroscopy

LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LG	leaving group
LR	low resolution
Me	methyl
Mes	mesityl
Ms	mesyl
MS	mass spectrometry
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTS	*p*-toluenesulfonic acid
Py	pyridine
RCM	ring-closing olefin metathesis
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-*N*-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl

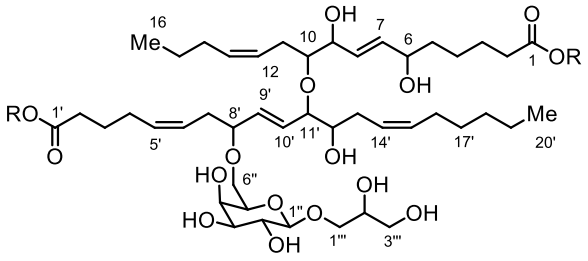
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl / tetramethylsilane
Ts	*p*-toluenesulfonyl

Chapter 1.

Introduction

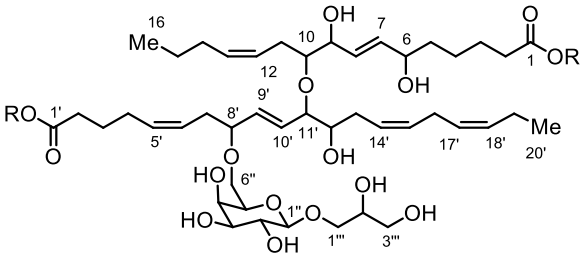
1-1. Introduction

Nigricanoside-A (**1-1**) (Figure 1-1), isolated as a strong antimitotic agent [IC_{50} of nigricanoside-A dimethyl ester (**1-2**): 3 nM against human breast cancer MCF-7 cells] along with nigricanoside-B (**1-3**) from the green alga *Avrainvillea nigricans* by Andersen,[1] is a unique oxylipin derivative including two oxygenated fatty acids and a galactosyl glycerol moiety that are connected to each other by ether bonds. Although the planar structure and the partial relative stereochemistry of **1-1** have been elucidated by intensive NMR analysis of the dimethyl ester (**1-2**) of **1-1**, full assignment of the relative and absolute stereochemistries of **1-1** has yet to be completed. The unique structure and the strong bioactivity of **1-1** have prompted the author to attempt its total synthesis and full stereochemical assignment. At the beginning of the project, the author intended to develop effective methods for the stereoselective construction of the C8'-O-C6'' ether bond connecting the galactose moiety to the C20 lipid chain as well as the stereoselective formation of the C9-C10-O-C11'-C12' region of **1-1**.



Nigricanoside A: R = H (**1-1**)

Nigricanoside A Dimethyl Ester: R = Me (**1-2**)



Nigricanoside B: R = H (**1-3**)

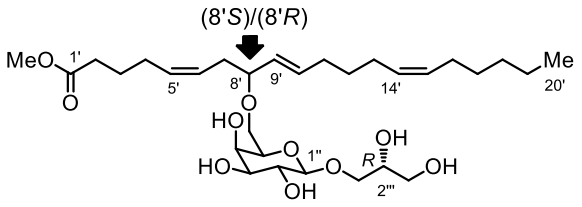
Nigricanoside B Dimethyl Ester: R = Me (**1-4**)

Figure 1-1. Nigricanoside congeners.

In this dissertation work, the author has established a method for the stereoselective construction of the C8'-O-C6'' ether linkage based on chirality transferring Ireland-Claisen rearrangement[2] (Figure 1-2). The details of the development and application of the method to the synthesis of simple models **(8'*S*,2'''*R*)-1-5** and **(8'*R*,2'''*R*)-1-5** for the C20 lipid chain/galactosyl glycerol segment of **1-2** are described in Chapter 2. The author also explored a stereoselective method for the construction of the C9-C10-O-C11'-C12' region and examined the availability of Williamson ether synthesis,[3] Ireland-Claisen rearrangement,[2] and Evans asymmetric aldol reaction to the

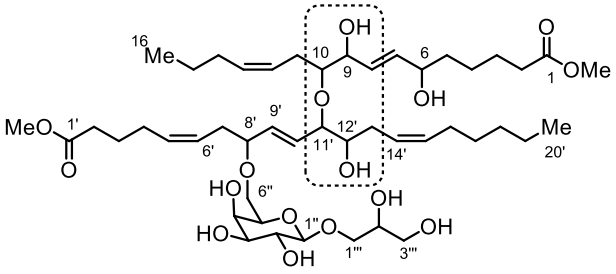
construction.[4] The application of a lithium enolate mediated stereoselective aldol reaction for the formation of the C9-C10-O-C11'-C12' region are described in detail in Chapter 3.

Chapter 2:
Development of a Stereoselective Method for the Construction of the C8'-O-C6'' Ether of Nigricanoside-A Dimethyl Ester



(8'*S*/*R*,2'''*R*)-1-5

Chapter 3:
Exploration of a Stereoselective Method for the Construction of the C9-C10-O-C11'-C12 Region of Nigricanoside-A Dimethyl Ester



1-2

Figure 1-2. The objectives of this dissertation work.

1-2. Nigricanoseide-A and Related Compounds

Nigricanosides-A (**1-1**) and -B (**1-3**) were isolated by Andersen from the green alga *Avrainvillea nigricans*, harvested from reef flats near Portsmouth, Dominica.[1] The sufficient quantities of nigricanosides were isolated from the algal biomass (28 kg wet wt) collected repeatedly during the intervening eight years. Nigricanosides was obtained as dimethyl esters with an 800 μg amount of **1-2** (3×10^{-6} % wet wt.) and a 400 μg amount of **1-4** (1.5×10^{-6} % wet wt.).

Nigricanoside A dimethyl ester (**1-2**) arrests the mitosis of human breast cancer MCF-7 cells with an IC_{50} of 3 nM, and the arrested cells show highly disorganized microtubule spindles. The ester also stimulates the polymerization of pure tubulin in vitro at 10 μM. Furthermore, ester 1-2 inhibits the proliferation of MCF-7 and human colon cancer HCT-116 cells with an IC_{50} of ca. 3 nM. The anti-proliferative activity was significantly reduced ($IC_{50} \approx 300$ nM) when **1-2** was hydrogenated.

Nigricanosides A (**1-1**) and B (**1-2**) are novel glyceroglycolipids including a galactglycerol and two fatty acid chains that are the same components as monogalactosyldiacylglycerols (MGDGs, Figure 1-3), known as chloroplast membrane lipids. The significant structural features of nigricanosides are ether linkages between the C16 and C20 lipid chains and between galactose residue and C20 lipid chain, which are without precedent. Although the planar structure and the partial relative stereochemistry of **1-1** have been elucidated by intensive NMR analysis of the dimethyl ester (**1-2**) of **1-1**, full assignment of the relative and absolute stereochemistries of **1-1** has yet to be completed.

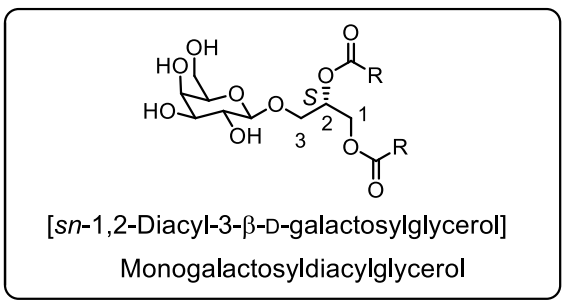
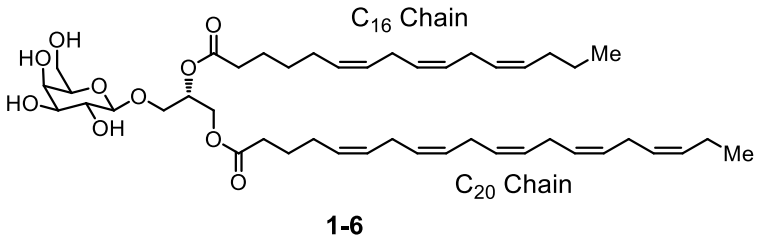


Figure 1-3. Monogalactosyldiacylglycerol

A monogalactosyldiacylglycerol (**1-6**) related to nigricanoside-B (**1-3**) has been reported by

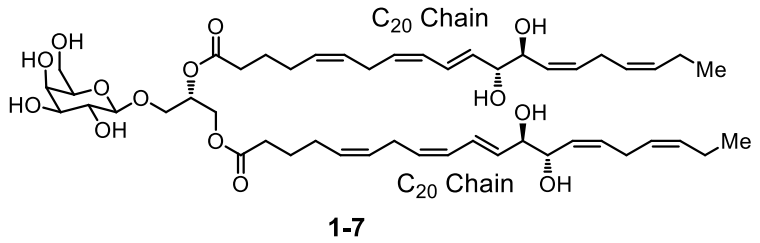
Falkowski (Figure 1-4).[5] Compound **1-6** possessing a galactosylglycerol with a hexadeca-6,9,12-trienoate at *sn*-2 position and eicosa-5,8,11,14,17-pentaenoate at *sn*-1 position was isolated from the diatom *Phaeodactylum tricornutum* as an apoptosis-inducing agent. MGDG **1-6** is thought to be a possible precursor of **1-3** although the presence of **1-6** in *Avrainvillea nigricans* is unknown.



1-6

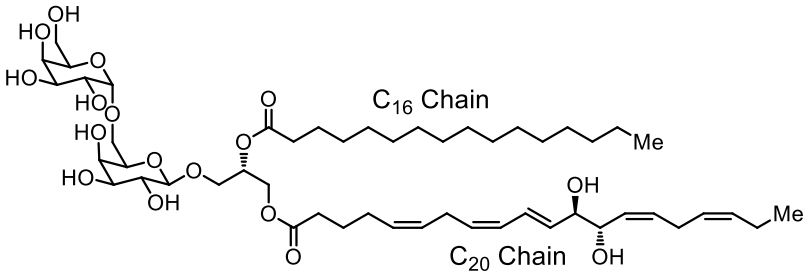
Figure **1-4**. MGDG **1-6** from the diatom *Phaeodactylum tricornutum*

Oxidatively modified MGDGs and DGDG (digalactosyldiacylglycerol) were also reported. MGDG **1-7** having oxidized fatty acid subunit was isolated from the red alga *Gracilariopsis lemaneiformis* by Gerwick (Figure 1-5).[6] DGDGs **1-8**[6] and **1-9**[7] also isolated from the same species (Figure 1-6). Gerwick proposed that the oxidized DGDGs would be generated via the formation of a 12-hydroperoxide with 12S-lipoxygenase followed by diol formation with hydroperoxide isomerase or a sequential C-C bond cleavage with hydroperoxide lyase and 5-hydroperoxide formation with 5-lipoxygenase.



1-7

Figure 1-5. Oxidized MGDG **1-7** from the red alga *Gracilariopsis lemaneiformis*



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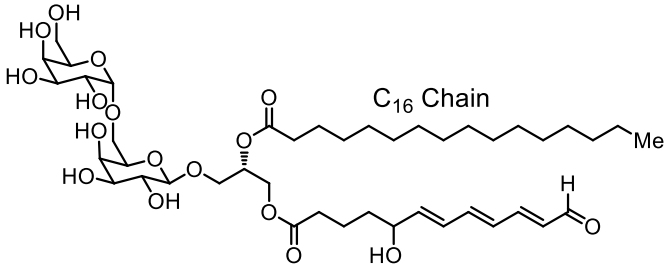
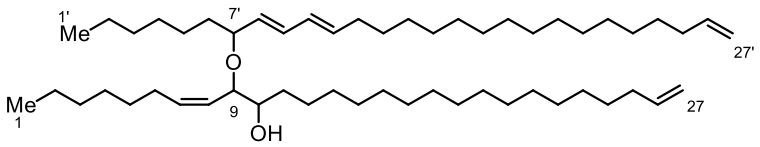


1-9

Figure 1-6. Oxidized DGDGs **1-8** and **1-9** from the red alga *Gracilariopsis lemaneiformis*

For a lipid ether natural product, di-*sec*-alkyl ether **1-10** (Figure 1-7) was isolated from the green alga *Botryococcus Braunii*, which is known to produce hydrocarbons in high yield, by Metzger.[8] The di-*sec*-alkyl ethers are rare among the lipid ether family compounds, in which primary alkyl ethers, such as platelet activating factor,[9] are well known.



1-10

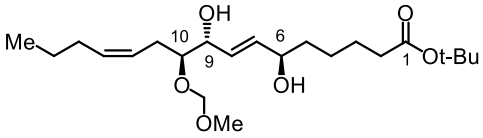
Figure 1-7. Dialkyl ether **1-10** from the green alga *Botryococcus braunii*

Thus, the nigricanosides are reported to be the first examples of a new class of ether-linked glycoglycerolipids by Andersen.[1]

1-3. Synthetic Studies of Nigricanosides by Other Research Groups.

For the synthesis of nigricanosides, only a few reports were published.

MacMillan's group reported a synthetic model compound (**1-11**, Figure 1-8) for C16 lipid chain of nigricanosides in their demonstration of a new NMR technique, MDEC (Multi Frequency Homonuclear Decoupling).[10] The combination of MDEC and 1D-TOCSY-MDEC was successfully applied and elucidated the C9/C10 *anti* stereochemistry of **1-11**. However, the details of the synthesis of **1-11** have not been reported.

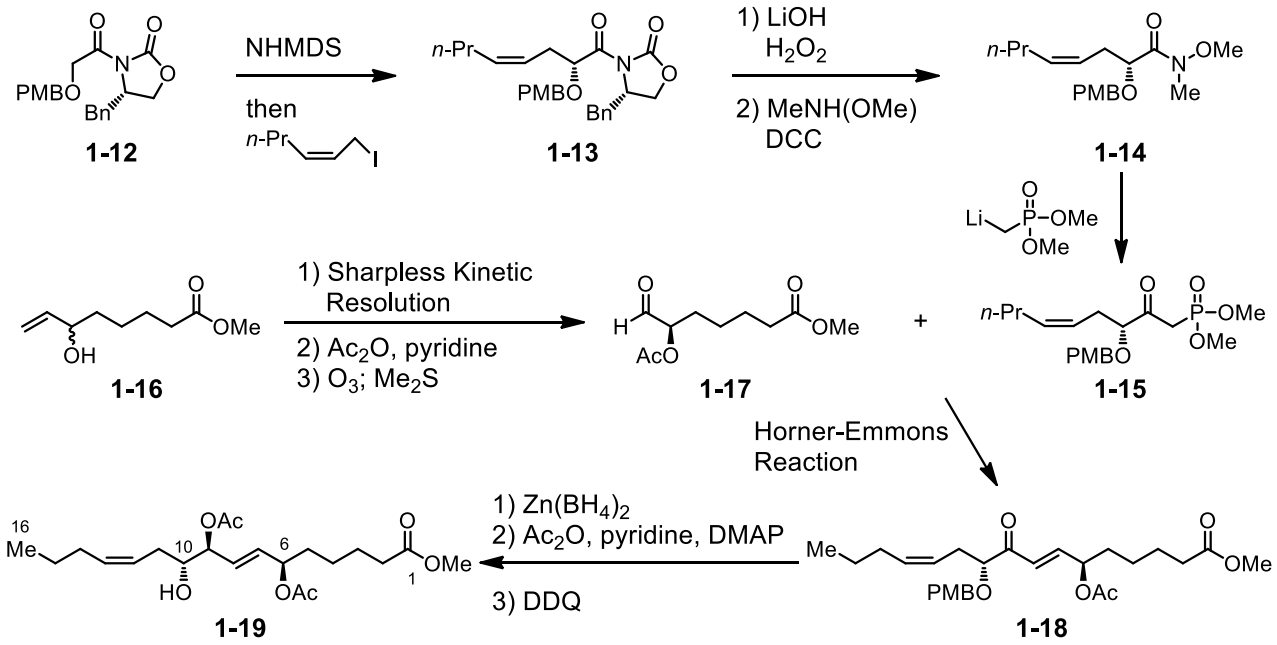


1-11

Figure 1-8. A synthetic model compound for C16 lipid chain of nigricanosides by MacMillan

Recently, Kuwahara's group reported the synthesis of compound **1-19** corresponding to the C16 lipid chain of nigricanosides (Scheme 1-1). The assembly of the lipid was started from amide **1-12** and ester **1-16**. Amide **1-12** was reacted with *Z*-1-iodohex-2-ene under Evans' asymmetric alkylation conditions[11] to produce 1-13, which was converted to Weinreb amide **1-14**.[12] After the reaction of **1-14** with ((dimethoxyphosphoryl)methyl)lithium, the resulting phosphonate **1-15** was reacted with aldehyde **1-17**, prepared from **1-16** by a three-step process, to afford E-enone **1-18**. An additional three-steps [(i) diastereoselective ketone reduction,[13] (ii) acetylation, and (3) removal of the PMB group)[14] produced ester **1-19**. Thus, stereoselective synthesis of a possible diastereomer of the C16 lipid chain of nigricanosides has been achieved.

Although the oxylipins corresponding to C16 lipid chain of nigricanosides has been reported, there is no report about the synthesis of other parts of nigricanosides.

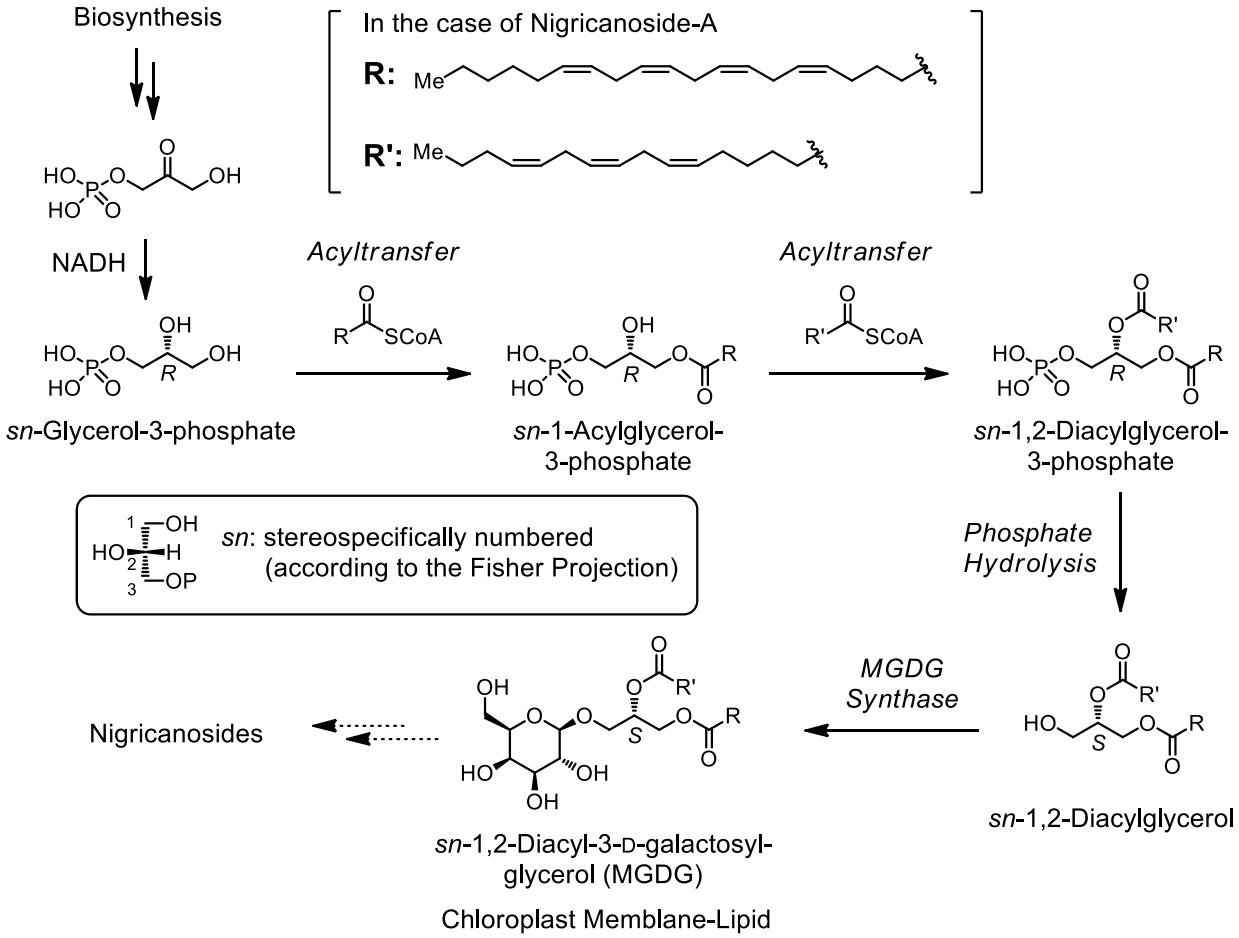


Scheme 1-1. Synthesis of a diastereomer of C16 lipid chain of nigricanosides by Kuwahara[15]

1-4. Outline of the Synthetic Strategy of Nigricanoside-A Aiming at Full Assignment of the Absolute Stereochemistry.

While potent inhibition of proliferation of cancer cells by nigricanoside-A dimethyl ester (**1-2**) is notable as a promising property for a new candidate anti-cancer drug, lack of stereochemical information of **1-2** would be an obstacle for further biological studies on it. Therefore, the author has undertaken the studies toward total synthesis of **1-2** aiming at full assignment of its stereochemistry.

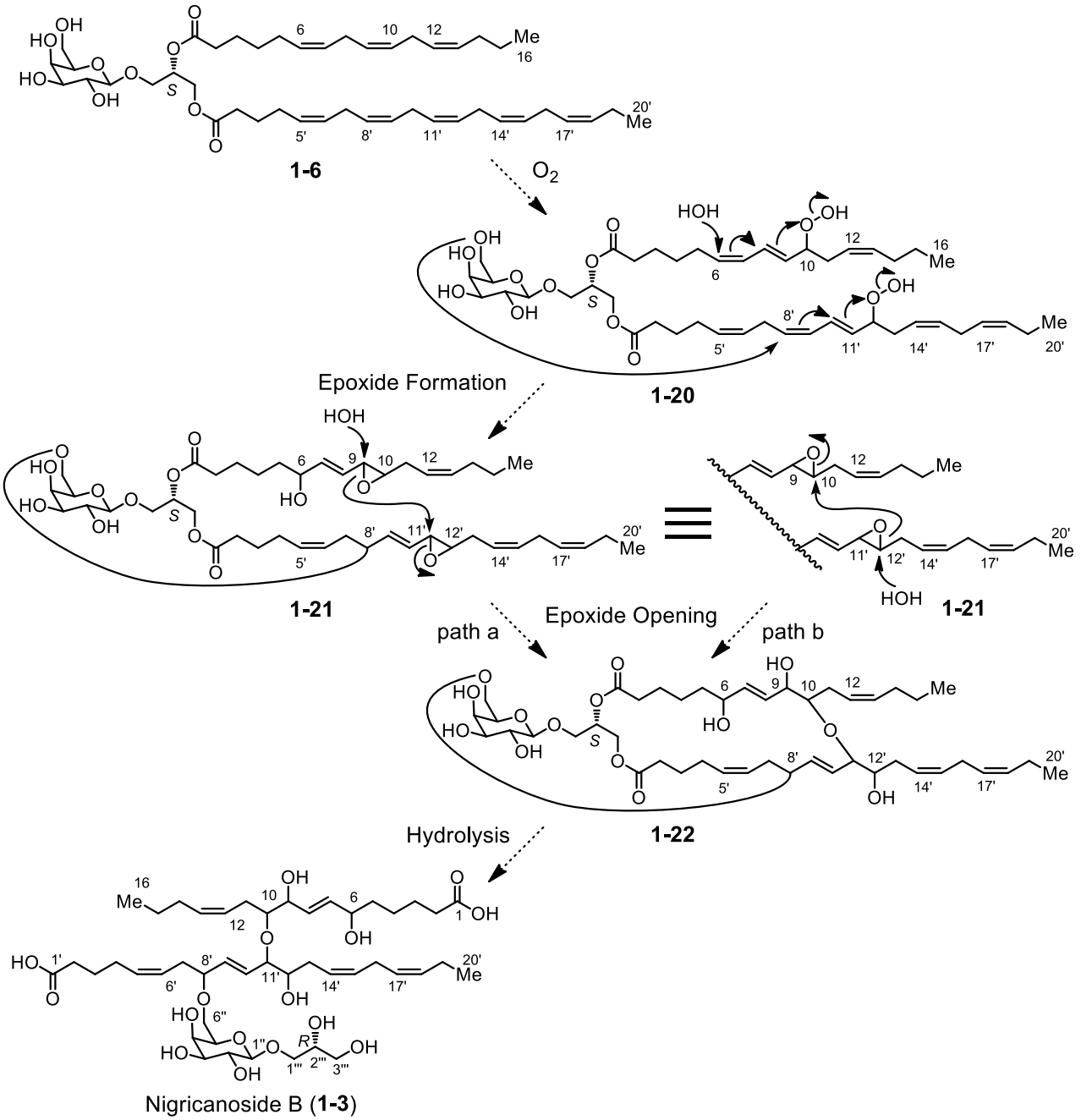
Before the design of the synthesis of **1-2**, the author deduced the stereochemistry at C2‴ of nigricanosides. It would be natural that nigricanosides originate from MGDGs. MGDGs are known to have a common *sn*-3-galactosylglycerol moiety, which is biosynthesized via a route depicted in Scheme 1-2.[16] Therefore, nigricanosides are deduced to have the same *sn*-3-D-galactosylglycerol.



Scheme 1-2. Biosynthetic pathway for MGDG.

The plausible biosynthetic pathway of nigricanoside-B is deduced as shown in Scheme 1-3

based on leukotriene biosynthesis.[17] MGDG **1-6** would be oxidized to dihydroperoxide **1-20,** which would be reacted with H_2O at C6 and with C6''-OH intramolecularly at C8' to produce diepoxide **1-20**. Intramolecular ether formation of C10-O-C11' can occur by either of two modes: (i) the attack of water to C9 followed by the attack of C10-O to C11', or (ii) the attack of water to C12' followed by the attack of C11'-O to C10. The resulting macrocyclic **1-22** would be then hydrolyzed to nigricanoside B (**1-3**). During the biosynthesis, the stereochemistry at C2''' would be retained.

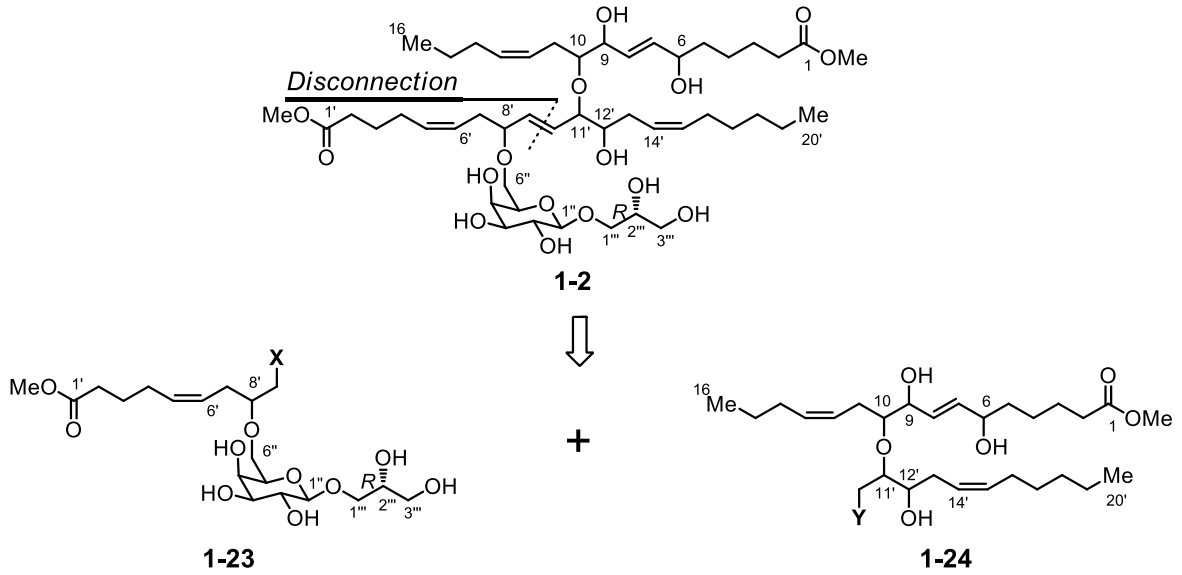


Scheme 1-3. Plausible biosynthetic pathway for nigricanoside B from **1-6**.

Thus, the author intended to synthesize analogues of nigricanoside-A with *sn*-3-D-

galactosylglycerol moiety in this dissertation work.

Next, the author performed retro-synthetic analysis of the final stage of the synthesis. The target nigricanoside-A dimethyl ester (**1-2**) was divided into two imaginary pieces, **1-23** and **1-24**, at C9'-C10' bond (Scheme 1-4), because this division was expected to provide almost equal complexity in both segments.



Scheme 1-4. Disconnection at C9'-C10' double bond in retrosynthetic analysis of **1-2**.

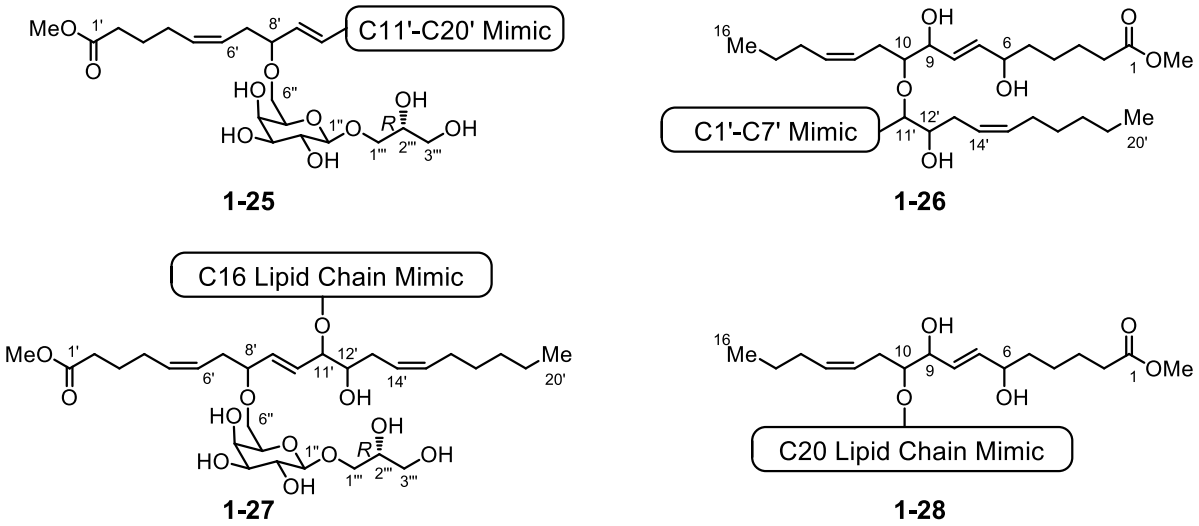
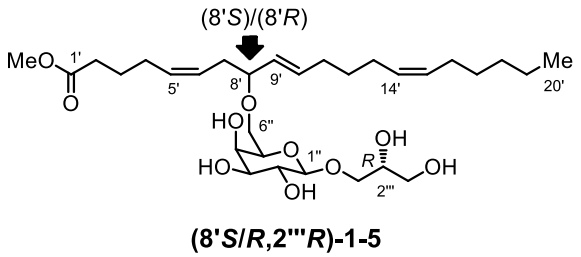


Figure 1-9. Model compounds for the determination of stereochemistry of **1-2**.

Imaginary segment **1-23** stimulated an idea for determination of configuration at C8' of **1-2**:

model compounds **1-25** (Figure 1-9) excluding the C16 lipid chain and oxygen functional groups at C11' and C12' would be easily preparable from **1-23,** and comparison of NMR data of each C8'-epimer of **1-25** with those of natural **1-2** would provide a basis for the determination of the stereochemistry at C8'. More complex model, such as **1-27**, would be usable for the confirmation of the configurations at C11' and C12' in the next stage analysis.

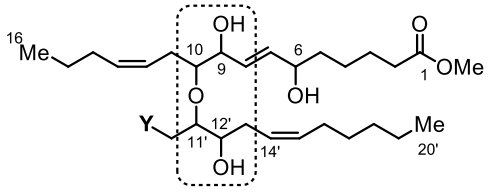
Therefore, the author first planned to synthesize model compounds **(8'*S*/*R*, 2'''*R*)-1-5** (Figure 1-10) aiming at the establishment of the method for the stereoselective construction of C8'-O-C6'' bond and at the determination C8'-configuraion by NMR comparison with **1-2**. The details of the accomplishment of the synthesis are described in Chapter 2.



(8'*S*/*R*,2'''*R*)-1-5

Figure 1-10. C20 Lipid Chain/Galactosyl Glycerol Segment Model

Imaginary segment **1-24** (Figure 1-11) also stimulate the idea of NMR comparison of model compound **1-26** or **1-28** (Figure 1-9) with **1-2** to obtain information of stereochemistry around the C9-C10-O-C11'-C12' region of **1-2**. However, the ether region including two hydroxy groups is difficult to synthesize stereoselectively, and, therefore, an effective synthetic method must be developed for the region. In the latter half of this dissertation work, the author explored the availability of Williamson ether synthesis,[3] Ireland-Claisen rearrangement,[2] and Evans asymmetric aldol reaction[4] to the stereoselective construction of the region. Details are described in Chapter 3.



1-24

Figure 1-11. Problem of stereoselective construction of C9-C10-O-C11'-C12' ether moiety

References

1. Williams, D. E.; Sturgeon, C. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 5822.
2. (a) Ireland, R. E.; Muller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. A review: (b) McFarland, C. M.; McIntosh, M. C. In *The Claisen Rearrangement*, Hiersemann, M.; Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, 2007, p 117.
3. A review: Feuer, H.; Hooz, J. In *The Chemistry of Functional Groups*, Patai, S. Ed. Wiley: New York, 1967, p 445-498.
4. Reviews: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Arya, P.; Qin. H. *Tetrahedron* **2000**, *56*, 917.
5. Andrianasolo, E. H.; Haramaty, L.; Vardi, A.; White, E.; Lutz, R.; Falkowski, P. *J. Nat. Prod.* **2008**, *71*, 1197.
6. Jiang, Z. D.; Gerwick, W. H. *Phytochemistry* **1990**, *29*, 1433.
7. Jiang, Z. D.; Gerwick, W. H. *Lipids* **1991**, *26*, 960.
8. Metzger, P.; Casadevall, E. *Phytochemistry* **1991**, *30*, 1439.
9. For a Review: De Rosa, M.; Gambacorta, A.; Gliozzi, A. Microbiol. *Mol. Biol. Rev.* **1986**, *50*, 70.
10. Espindola, A. P. D. M.; Crouch, R.; DeBergh, J. R.; Ready, J. M.; MacMillan, J. B. *J. Am. Chem. Soc.* **2009**, *131*, 15994.
11. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
12. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
13. Nakata, T.; Oishi T. *Tetrahedron Lett.* **1980**, *21*, 1641.
14. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.c
15. Kurashina, Y.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 605.
16. Maréchal, É.; Block, M. A.; Dorne, A.-J.; Douce, R.; Joyard, J. *Physiol. Plant.* **1997**, *100*, 65.
17. Pace-Asciak, C. R. *J. Biol. Chem.* **1984**, *259*, 8332.

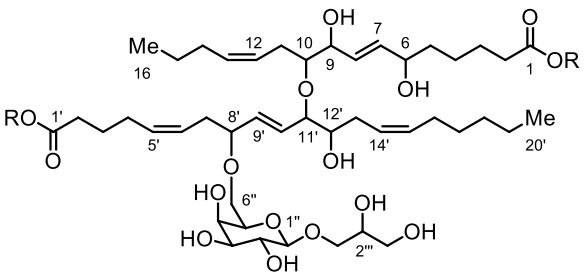
Chapter 2.

Development of a Stereoselective Method for the Construction of the C8'-O-C6'' Ether of Nigricanoside-A Dimethyl Ester

2-1. Introduction

As described in the Chapter 1, the author has been attracted the unique structure and the strong bioactivity of nigricanoside A (**1-1**) and attempted its total synthesis and full stereochemical assignment. At the beginning of the project, the author intended to develop an effective method for the stereoselective construction of the C8'-O-C6" ether bond of **1-1** connecting the galactose moiety to the C20 fatty acid chain. The feasibility of the method was examined through the synthesis of simple model compounds **(8'*S*, 2'''*R*)-1-5** and **(8'*R*, 2'''*R*)-1-5** corresponding to the C20 lipid chain/galactosyl glycerol segment of **1-1** (Figure 2-1).

Model compounds **(8'*S*,2'''*R*)-1-5** and **(8'*R*,2'''*R*)-1-5**, excluding the C16 fatty acid chain and the oxygen functionalities at C11' and C12', were designed for the following purpose: (i) a simple demonstration of the stereoselective construction of the C8'-O-C6" ether of **1-1**, (ii) comparison of the NMR spectra with **1-2** to predict the configuration at C8' of **1-1**, and (iii) investigation of the structure-activity relationship in antimitotic/cytotoxic assays of **1-1**. The 2'''*R* configuration of the models was designed according to the proposed *R* configuration at C2''' of the glycerol of **1-1**, which was based on the assumption that nigricanosides were oxidative metabolites of monogalactosyl diacyl glycerols (MGDGs), known as chloroplast membrane lipids, having a common 3-galactosyl-*sn*-glycerol structure.[1] In this chapter, the author discloses the synthesis and NMR analysis of the models.



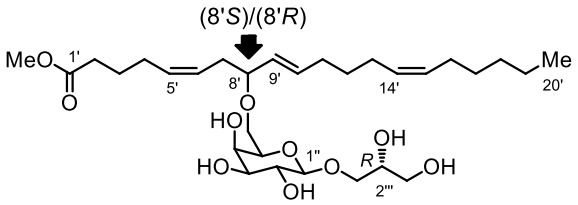


Figure 2-1.

The author undertook three approaches to construct the ether linkage between the galactose moiety and C20 lipid chain as follows: (i) Williamson ether synthesis for the formation of the C6"-O bond [(A) in Figure 2-2], (ii) an asymmetric alkylation for the C7'-C8' bond formation followed by a Julia-Kochienski olefination for the C9'-C10' double bond formation [(B) in Figure 2-2], and (iii) an Ireland-Claisen rearrangment for the C7'-C8' bond formation followed by the C9'-C10' bond forming Julia-Kochienski olefination [(B) in Figure 2-2]. In the latter two approaches, the C6"-O-C8' bond should be prepared as a 6-*O*-(carboxymethyl)galactopyranose derivative prior to the alkylation or the rearrangement. The attempts of the Williamson synthesis and the asymmetric alkylation are described in Section 2-3. The successful synthesis of model compounds **(8'*S*,2'''*R*)-1-5** and **(8'*R*,2'''*R*)-1-5** by Ireland-Claisen rearrangement is explained in Sections 2-4 to 2-6.

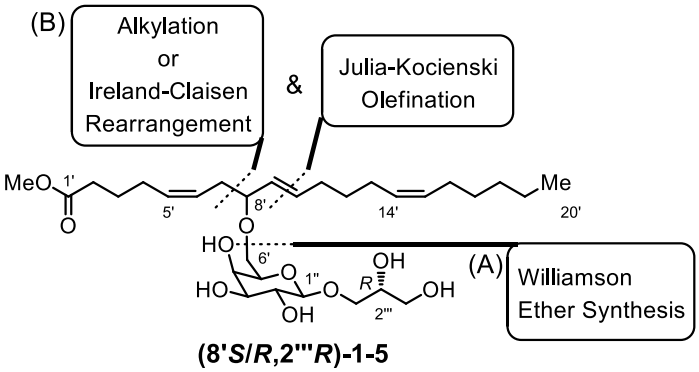
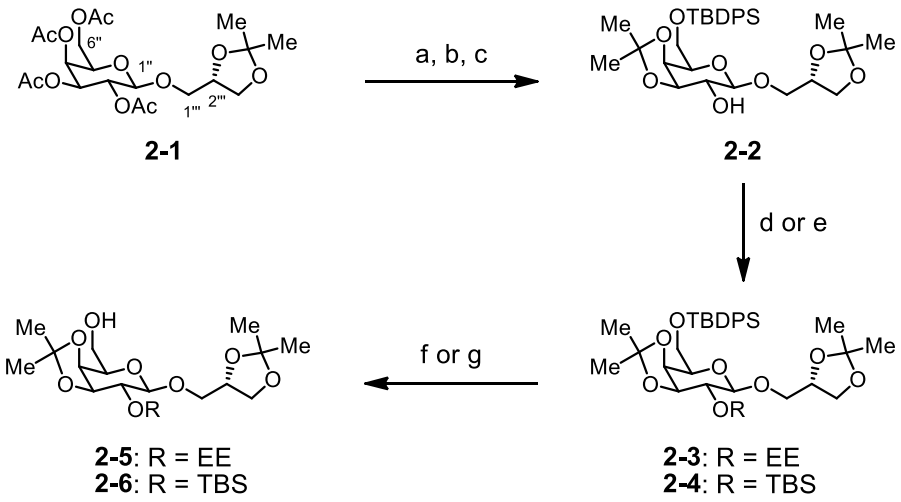


Figure 2-2. Plans for the construction of the ether linkage between the galactosyl glycerol and the C20 lipid chain segments.

2-2. Synthesis of the Galactosyl Glycerol Segment

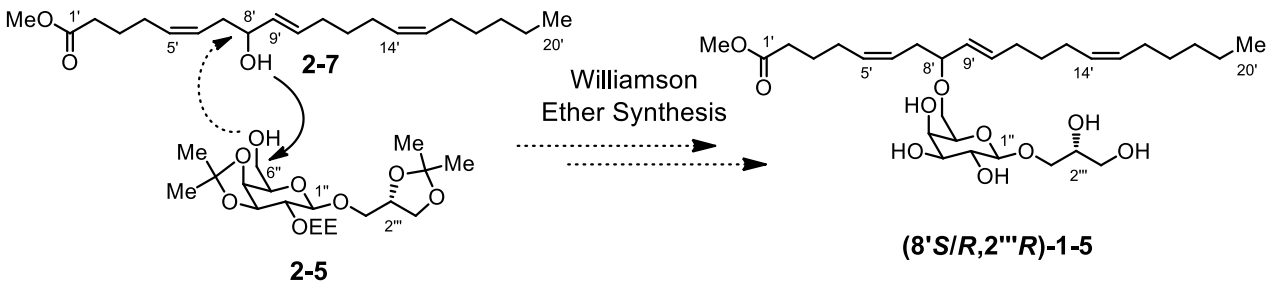
First, the galactosyl glycerol segment was synthesized. As described above, nigricanoside A is deduced to be biosynthesized from a MGDG, a chloroplast lipid, and, therefore, the galactosyl glycerol segment would have a 3-D-galactosyl-*sn*-glycerol stereochemistry. Based on the deduction, the author decided to prepare intermediate alcohols **2-5** and **2-6** steleoselectively. The synthesis of alcohols **2-5** and **2-6** from the known 3-galactosyl-*sn*-glycerol derivative **2-1**[2] is shown in Scheme 2-1. The acetate groups of **2-1** were removed by methanolysis, and the resulting tetraol was subjected to stepwise protection with TBDPSCl and 2,2-dimethoxypropane to give alcohol **2-2** (79% over 3 steps). The protection of **2-2** as an EE ether (95%) and a TBS ether (91%) followed by the selective removal of the TBDPS group[3] produced alcohols **2-5** (79%) and **2-6** (80%), respectively.



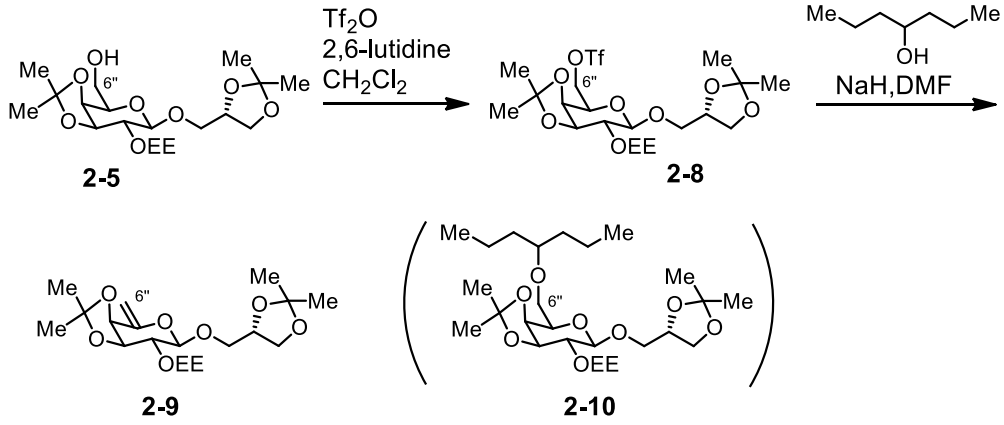
Scheme 2-1. Synthesis of galactosyl glycerols **2-5** and **2-6**. Reagents and conditions: (a) MeONa, MeOH, 23 °C, 1 h; (b) Et_3N, TBDPSCl, DMAP, CH_2Cl_2, 23 °C, 12 h; (c) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 23 °C, 11 h, 79% from **2-1**; (d) EVE, PPTS, CH_2Cl_2, 23 °C, 3 h, **2-3**: 95%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 3 h, **2-4**: 91%; (f) TBAF, THF, 23 °C, 1 h, **2-5**: 79% ; (g) TBAF, AcOH, DMF, 23°C, **2-6**: 80%.

2-3. Attempts to Construct the C8'-O-C6'' Ether Bond by Williamson Ether Synthesis or Enolate Alkylation

For the ether bond formation between the C20 lipid chain (**2-7**) and the galactosyl glycerol moiety (**2-5**) by Williamson ether synthesis, two modes are considered: the ether formations by the attack of the hydroxy group at C6" to C8' carboncenter and by the attack of the hydroxyl group at C8' to C6" center (Scheme 2-2). However, the former attack would be disadvantageous due to the steric hindrance around the electrophilic C8' carboncenter, which would induce undesired E2 to form a conjugate triene. Therefore, the author selected the latter type Williamson ether synthesis. In order to examine the availability of the Williamson ether synthesis, a model synthesis was attempted.



Scheme 2-2. Approach to the model compounds by Williamson ether synthesis.

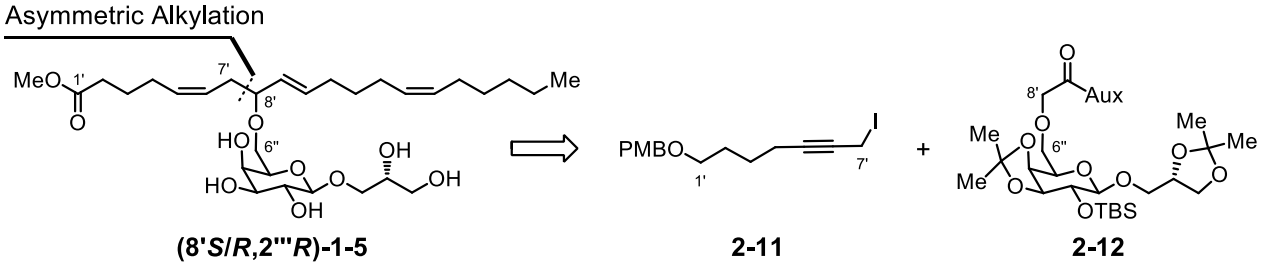


Scheme 2-3. Attempting installation of haptan-4-ol at C6" by Williamson ether synthesis.

In the model synthesis, heptan-4-ol was employed as a mimic for **2-7** (Scheme 2-3). After alcohol **2-5** was reacted with Tf_2O, the resulting **2-8** was treated with an alkoxide derived from

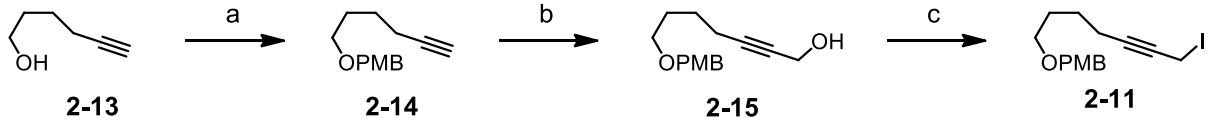
heptan-4-ol with sodium hydride to give only an E2 elimination product **2-9**. Because of this disappointing result, which suggested the low reactivity of the C6"-triflate in the S_N2 reaction, the plan for the C8'-O-C6" bond formation by Williamson ether synthesis was abandoned.

Next, an approach employing asymmetric alkylation was examined for the stereoselective construction of the ether-bond C8' stereocenter (Scheme 2-4). In this approach, successful asymmetric induction during the reaction of a glycolic acid derivative having the galactosyl glycerol moiety (**2-12**) with C1'-C7' carbon chain **2-11** was expected. Here, Evans' asymmetric alkylation was attempted.



Scheme 2-4. Approach to the model compounds by asymmetric alkylation.

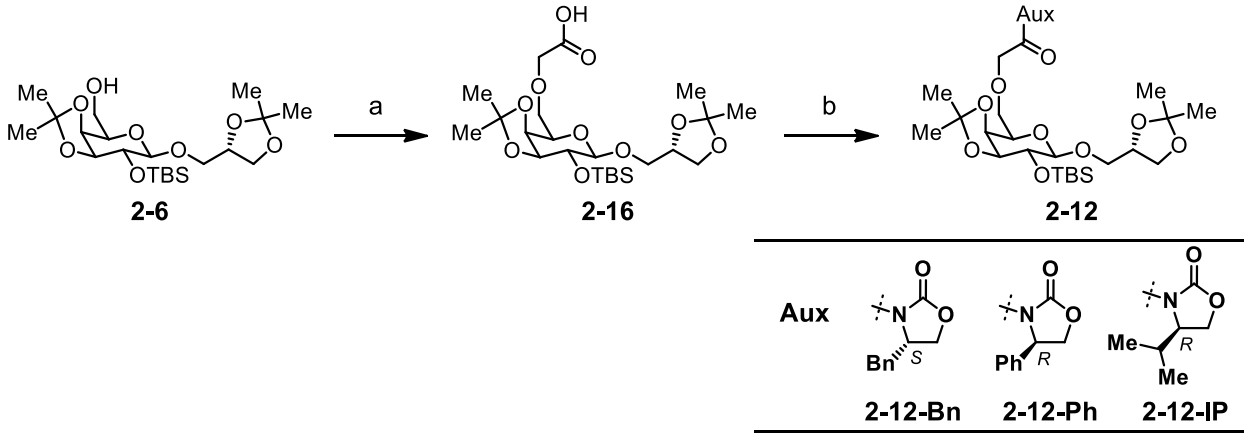
The synthesis of C1'-C7' carbon chain **2-11** was started from hex-5-yn-1-ol (**2-13**) (Scheme 2-5). Protection of **2-13** with PMBCl followed by hydroxymethylation produced propargyl alcohol **2-15** (81% over two steps), which was iodinated to afford **2-11** (57%).



Scheme 2-5. Synthesis of the C1'-C7' segment. Reagents and conditions: (a) NaH, PMBCl, THF, 23 °C, 3 d; (b) BuLi, THF, –78 °C, then $(CH_2O)_n$, 7 h, 73% over 2 steps; (c) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 1 h, 57%

Glycolic acid derivatives having oxazolidinone chiral auxiliaries (**2-12-Bn**, **2-12-Ph**, and **2-12-IP**) were synthesized from alcohol **2-6** (Scheme 2-6). Alcohol **2-6** was converted to glycolic acid **2-**

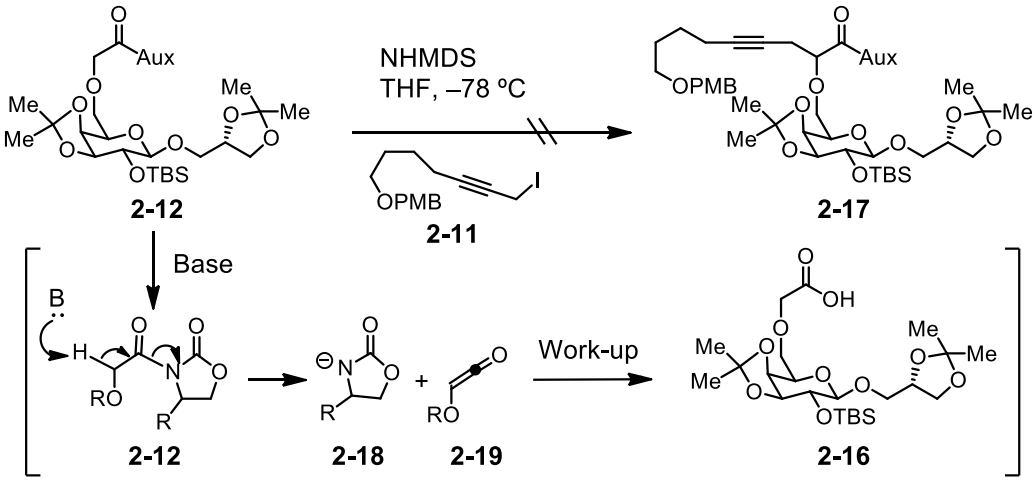
16 through etherification with *tert*-butyl bromoacetate under phase-transfer conditions followed by basic hydrolysis (91%). The acid was condensed with three oxazolidinone chiral auxiliaries under standard conditions via mix-anhydride intermediates to produce **2-12-Bn**, **2-12-Ph**, and **2-12-IP** in good yield (61–87%).



Scheme 2-6. Synthesis of glycolic acid derivatives **2-12**. Reagents and conditions: (a) (i) *tert*-butyl bromoacetate, $Bu_4N{\cdot}HSO_4$, benzene, 4 M aq. NaOH, 23 °C, 29 h; (ii) 4 M aq. NaOH, MeOH, 23 °C, 7 h, 67% over 2 steps; (b) Et_3N, $(CH_3)_3CCOCl$, THF, –20 °C, 0.6-1 h, then 4-substituted-oxazolidin-2-one-3-yl lithium, –20 °C, 0.5-2 h, **2-12-Bn**: 80%, **2-12-Ph**: 61%, **2-12-IP**: 87%.

The alkylation of amides **2-12**, however, did not produce the desired alkylated product **2-17** (Scheme 2-7). After each amide **2-12** was deprotonated with NHMDS, the resulting sodium enolate was reacted with iodide **2-11** to afford only carboxylic acid **2-16**, which would be attributable to the low reactivity of the enolate to **2-11** and the easy elimination of oxazolidinyl anion **2-18** from the enolate.

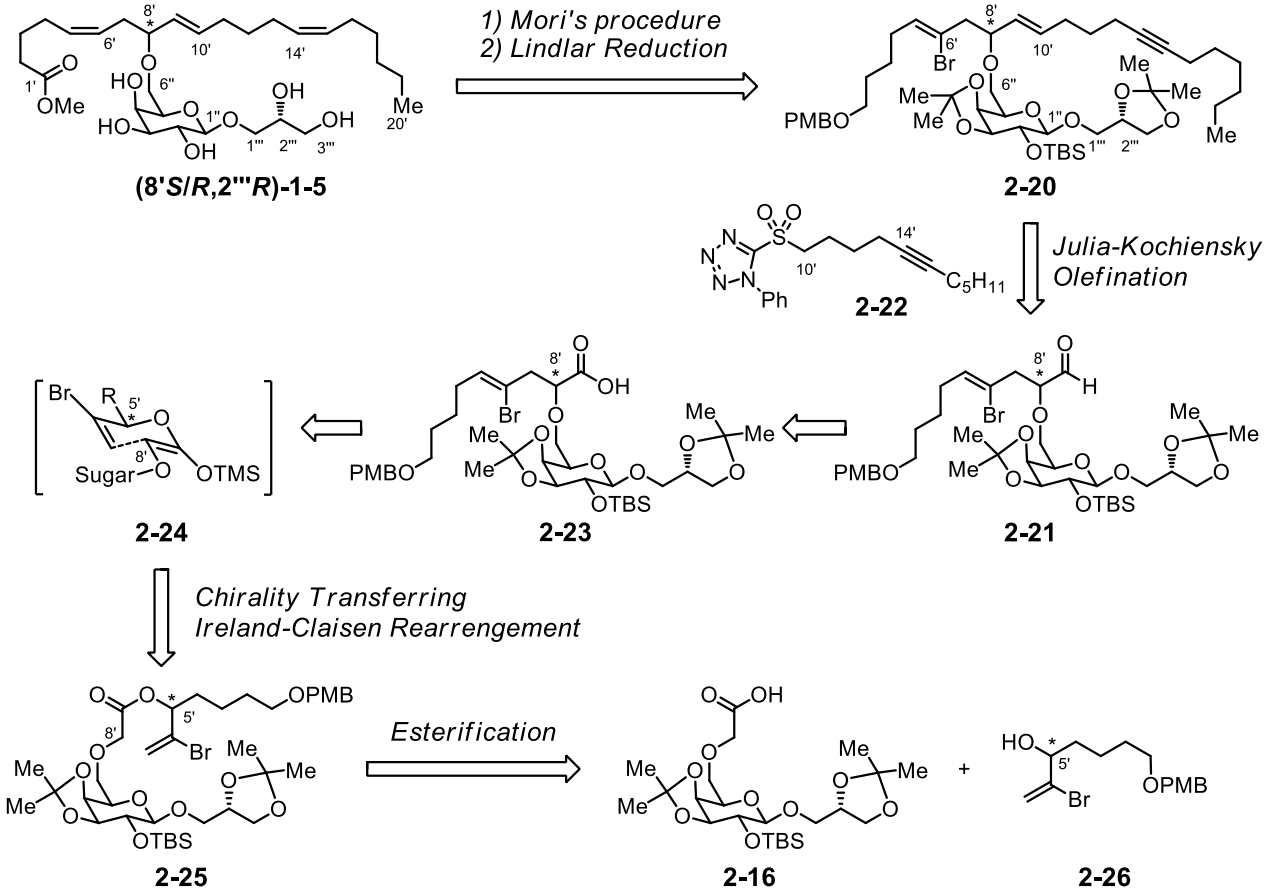
Although several asymmetric alkylation reactions with other chiral auxiliaries were also examined, the desired alkylated compounds could not be obtained. Accordingly, the author decided to revise the approach for the construction of the ether-bound C8' stereocenter.



Scheme 2-7. Attempting asymmetric alkylation of **2-12**.

2-4. Application of Chirality Transferring Ireland-Claisen Rearrangement for the C8'-O-C6'' Ether Formation

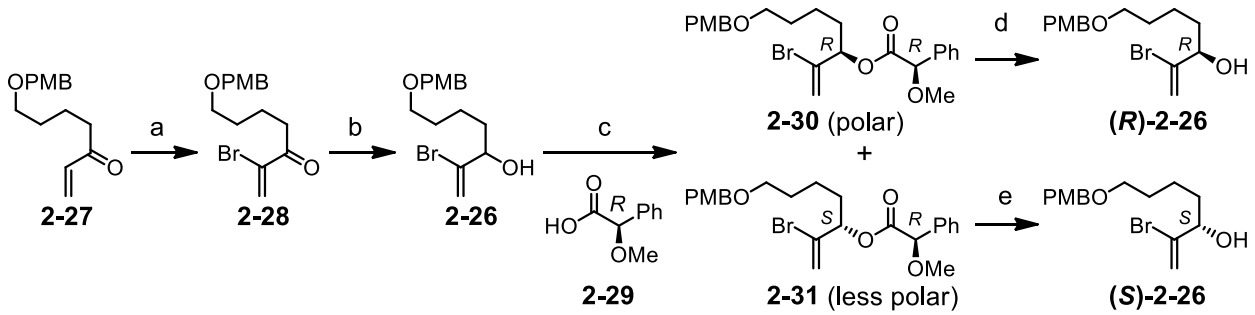
As an alternative approach to the formation of the ether-bound C8' stereocenter for the synthesis of model compounds **(8'*S*/*R*,2'''*R*)-1-5**, the author employed a process based on a chirality transferring Ireland-Claisen rearrangement.



Scheme 2-8. Synthetic plan for models **(8'*S*/*R*,2'''*R*)-1-5.**

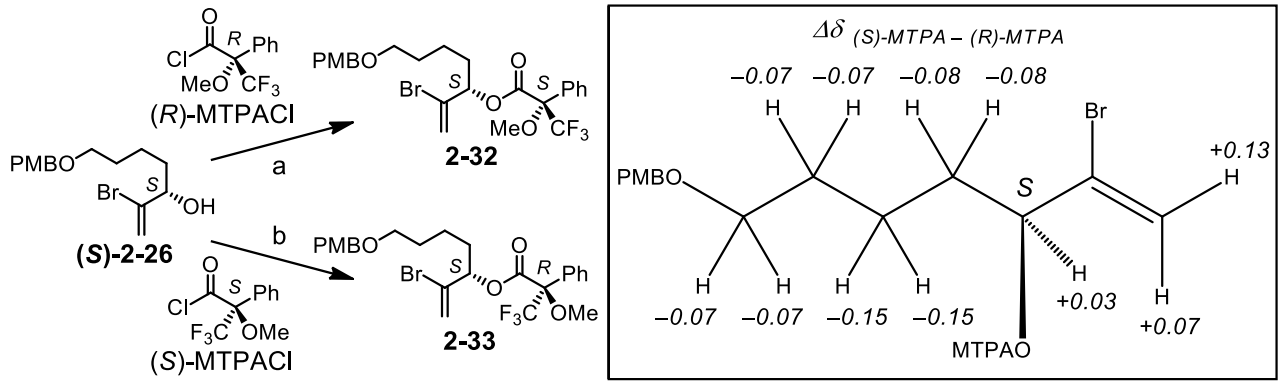
The synthetic plan for the model compounds **(8'*S*/*R*,2'''*R*)-1-5** is outlined in Scheme 2-8. The *Z*-olefin groups at C5' and C14' of **(8'*S*/*R*,2'''*R*)-1-5** were scheduled to be formed by Lindlar hydrogenation of the corresponding alkyne groups at the final stage of the synthesis after aldehyde **2-21** and sulfone **2-22** were connected by Julia-Kocienski olefination[4] to form the *E*-olefin at C9'. The *Z*-bromoalkene at C5' of **2-20** would be converted to an alkyne group under mild basic conditions after the olefination step. For the construction of the C8' stereocenter and the *Z*-bromoalkene of **2-23**,

the Ireland-Claisen rearrangement of ester **2-25** was employed. The rearrangement was expected to exhibit perfect chirality transfer from C5' of **2-25** to C8' of **2-23**. Therefore, bromoalkenol **2-26**, which would be condensed with glycolic acid derivative **2-6** to form **2-25**, must be obtained in enantiomerically pure form. Thus, both enantiomers **(*R*)-2-26** and **(*S*)-2-26** would be prepared by chiral resolution.



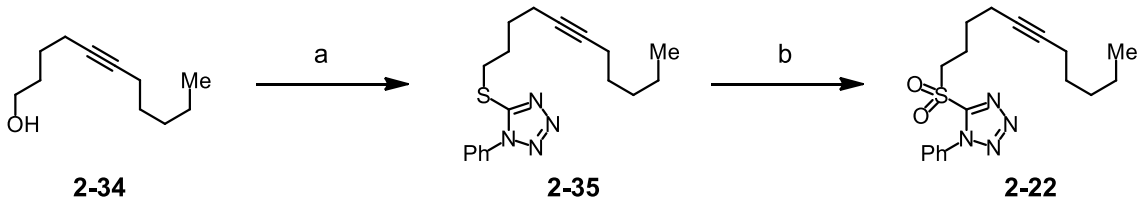
Scheme 2-9. Synthesis of chiral alcohols **(*R*)-2-26** and **(*S*)-2-26**. Reagent and conditions: (a) Br_2, CH_2Cl_2, 0 °C, then Et_3N, 10 min, 86%; (b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, –78 °C, 30 min, 98%; (c) EDCI, **2-29**, DMAP, CH_2Cl_2, 23 °C, 4 h; then separation by HPLC, **2-30**: 34%, **2-31**: 35%; (d) 5 M NaOH, MeOH, 23 °C, 1 h, **(*R*)-2-26**: 100%; (e) 5 M NaOH, MeOH, 23 °C, 1 h, **(*S*)-2-26**: 98%.

The preparation of chiral allylic alcohols **(*R*)-2-26** and **(*S*)-2-26** started from the known enone **2-27**[5] (Scheme 3). Bromination of **2-27** followed by elimination of HBr with Et_3N produced α-bromo enone **2-28** (86%), which was reduced under Luche conditions to give racemic alcohol **2-26** (98%).[6] After the condensation of **2-26** with (*R*)-(–)-α-methoxyphenylacetic acid (**2-29**), the resulting diastereomeric esters **2-30** and **2-31** were separated by preparative HPLC (**2-30**: 34%; **2-31**: 35%).[7] The hydrolysis of esters **2-30** and **2-31** afforded homochiral alcohols **(*R*)-2-26** (100%) and **(*S*)-2-26** (98%), respectively. The absolute configurations of the alcohols were determined by application of the modified Mosher's method on alcohol **(*S*)-2-26** (Scheme 2-10).[8]



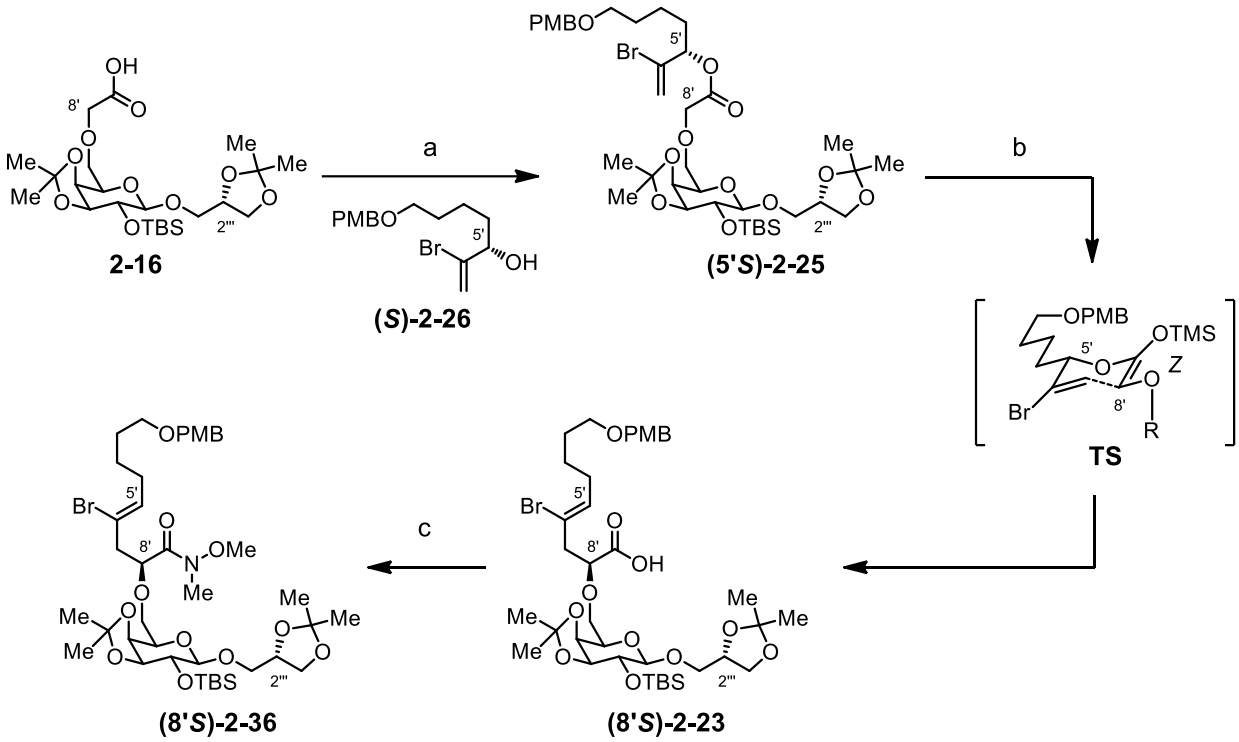
Scheme 2-10. Confirmation of stereochemistry of **(*S*)-2-26** by modified Mosher's method. Reagents and conditions: (a) (–)-(*R*)-MTPACl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 64%; (b) (+)-(*S*)-MTPACl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 68%.

Sulfone **2-22** was prepared from undec-5-yn-1-ol (**2-34**)[9] via a process including Mitsunobu reaction[10] with 1-phenyl-1*H*-tetrazole-5-thiol (62%) and oxidation with H_2O_2 in the presence of ammonium molybdate hydrate[11] (50%) (Scheme 2-11).



Scheme 2-11. Preparation of sulfone **2-22**. Reagents and conditions: (a) 1-Phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF, 0 °C → 23 °C, 1 h, 68%; (b) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0 °C → 23 °C, 19 h, 50%.

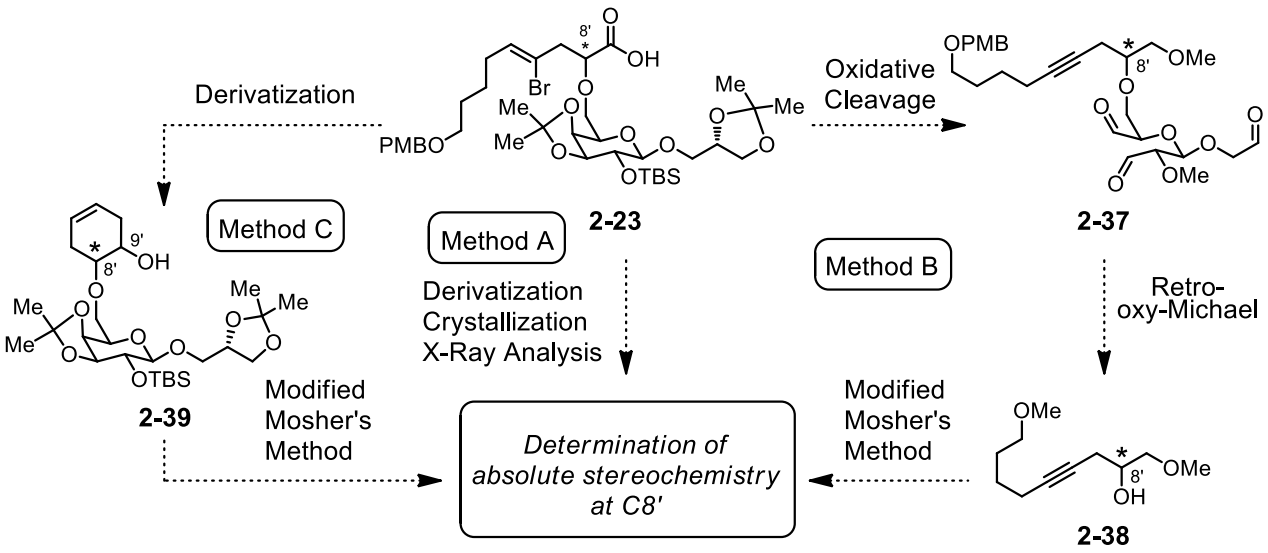
The stereoselective construction of the C8' stereocenter by Ireland-Claisen rearrangement is shown in Scheme 2-12. First, glycolic acid **2-16** was esterified with alcohol **(*S*)-2-26** to afford ester **(5'*S*)-2-25** (97%). The treatment of **(5'*S*)-2-25** with NHMDS in the presence of TMSCl in THF at –78 °C produced a ketene silyl acetal intermediate, which was then warmed to 0 °C to give rearranged product **(8'*S*)-2-23** as a single diastereomer. Carboxylic acid **(8'*S*)-2-23** was condensed with *N*,*O*-dimethylhydroxylamine to furnish *N*-methoxy-*N*-methylamide **(8'*S*)-2-36** in good yield (80% over 2 steps).



Scheme 2-12. The Ireland-Claisen rearrangement of ester **(5'*S*)-2-25**. Reagents and conditions: (a) **(*S*)-2-26**, EDCI·HCl, DMAP, CH_2Cl_2, 23 °C, 19 h, 70%; (b) TMSCl, NHMDS, –78 °C, 10 min, then 0 °C, 10 min; (c) MeNH(OMe)·HCl, EDCI·HCl, DMAP, CH_2Cl_2, 23 °C, 5 h, 80% from **(5'*S*)-2-25**.

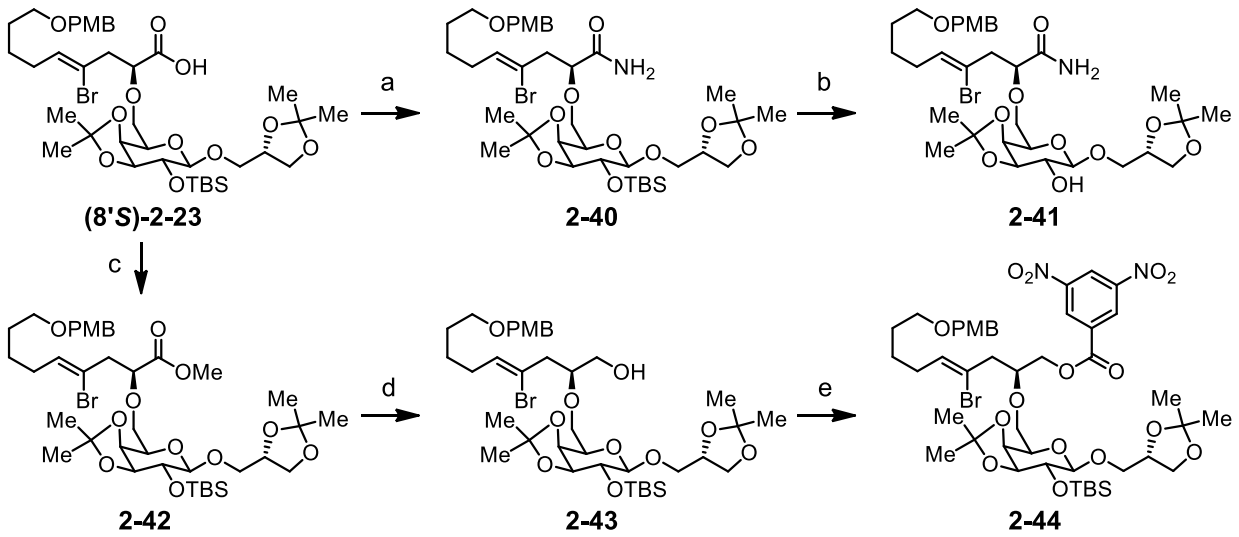
2-5. Determination of Stereochemistry at C8' Stereocenter Derived from the Ether Formation by Ireland-Claisen Rearrangement

In order to confirm absolute stereochemistry at C8' of **2-23**, which was constructed by chirality transferring Ireland-Claisen rearrangement, the following three methods were examined: (i) X-ray analysis of a crystalline compound derived from **2-23** (Method A); (ii) the modified Mosher's analysis of alcohol **2-38** derived from **2-23** by a sequence including oxidative cleavage of the galactose moiety followed by a retro-oxy-Michael reaction to remove the residual propanal moiety from **2-37** (Method B); and (iii) the modified Mosher's analysis of cyclohexenyl alcohol **2-39** derived from **2-32** via a process involving allylation and RCM (Method C) (Scheme 2-13).



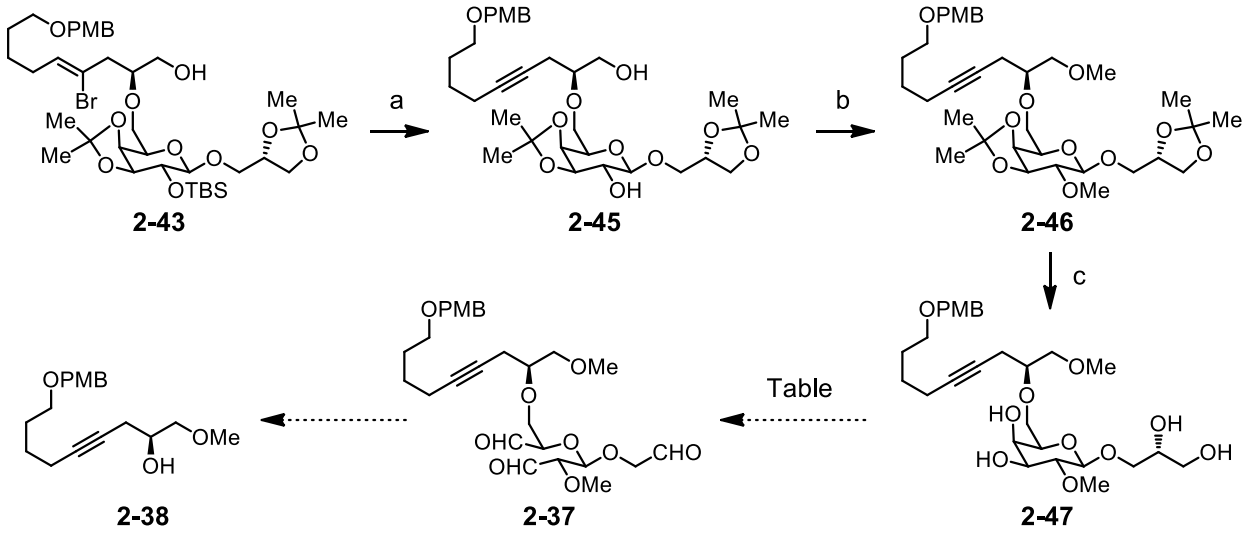
Scheme 2-13. Plans for the determination of stereochemistry at C8' of **(8'*S*)-2-23**.

First, according to Method A, carboxylic acid **(8'*S*)-2-23** was converted to a series of derivatives (Scheme 2-14). Carboxylic acid **(8'*S*)-2-23** was amidated to give **2-40**, of which the TBS group was then removed to afford alcohol **2-41**. Carboxylic acid **(8'*S*)-2-23** was also transformed to methyl ester **2-41**, which was subjected to reduction giving alcohol **2-43** and the subsequent 3,5-dinitrobenzoylation to produce **2-44**. Unfortunately, these derivatives were not crystallized. Additional derivatizations were also in vain. Therefore, the confirmation of C8' stereochemistry by Method A was abandoned.



Scheme 2-14. Derivatization of **(8'*S*)-2-23** for crystallization. Reagents and Conditions: (a) Et_3N, pivaloyl chloride, 0 °C, 20 min, then NH_3(aq.), 35 min, 53% from **(5'*S*)-2-25**; (b) TBAF, THF, 23 °C , 2 h, 97%; (c) $TMSCHN_2$, MeOH, CH_2Cl_2, 23 °C, 20 min, 77% from **(5'*S*)-2-25**; (d) DIBALH, CH_2Cl_2, –10 °C, 1 h, 68%; alternatively: $LiAlH_4$, THF, –78 °C, 35 min; (e) 3,5-dinitorobenzoy chloride, Et_3N, CH_2Cl_2, 0 °C, 15 min, 45% from **2-42**.

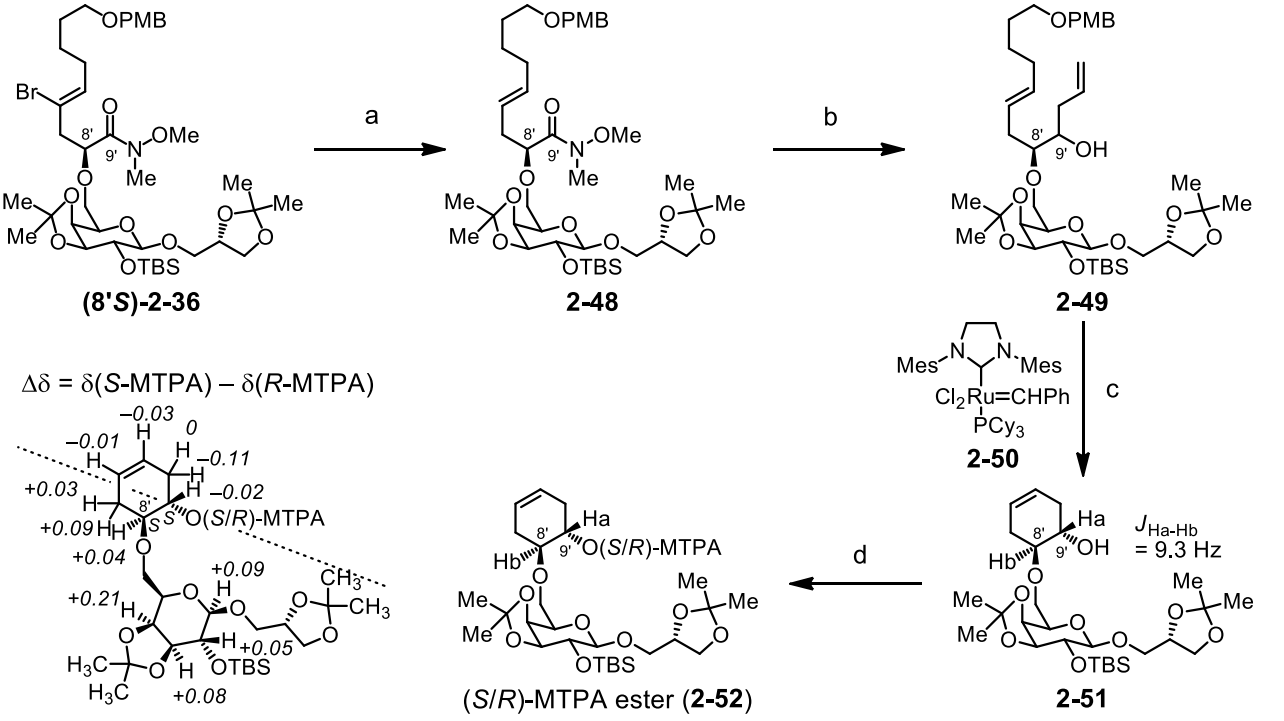
Next, Method B was attempted. After intensive experiments, it was clarified that the protection of the hydroxy groups at C9' and C2'' as methyl ethers and conversion of the bromoalkene group to an alkene were required for clean removal of acetonide group as well as clean oxidative cleavage. Thus, alcohol **2-43**, derived from **(8'*S*)-2-23**, was reacted with TBAF in refluxing THF to induce desilylation and alkynylation, and the resulting alkene diol **2-45** was methlyated to give **2-46** (Scheme 2-15). The removal of the acetonide groups of **2-46** afforded tetraol **2-47**. The oxidative cleavage of **2-47** was performed with $NaIO_4$ or $Pb(OAc)_4$, and the resulting aldehyde was treated with base as shown in inset table in Scheme 2-15. However, the desired alcohol **2-38** was not detected. Accordingly, Method B was discontinued.



	Conditions	Result
Run 1	$NaIO_4$ (8.0 eq), THF, H_2O, 0 ºC 2 h, 23 ºC, 5.5 h; Et_3N, CH_2Cl_2, 23 ºC	complex mixture
Run 2	$Pb(OAc)_4$ (2.5 eq), K_2CO_3 (10.0 eq) CH_2Cl_2, –10 ºC,15 h	complex mixture

Scheme 2-15. Preparation of **2-47** and its attempting oxidative cleavage. (a) TBAF·$3H_2O$, THF, reflux, 2 h, 81%; (b) MeI, NaH, THF, 0 °C, 4 h, ~75%; (c) TFA, MeOH, CH_2Cl_2, 23 °C, 36 h, 75%.

Finally, Method C was examined and resulted in successful determination of stereochemisty at C8' of **(8'*S*)-2-23**. The bromoalkene of **(8'*S*)-2-36**, derived from **(8'*S*)-2-23**, was reduced with Bu_3SnH to alkene **2-48** (37%) (Scheme 2-16). After the reduction of **2-48** with $LiAlH_4$,[12] the resulting aldehyde was reacted with allyl magnesium chloride to give **2-49** as a 1:1 mixture of diastereomers at C9' (61%). Diene **2-49** was then cyclized by ring-closing olefin metathesis with Grubbs' first generation catalyst (**2-50**),[13] and *trans*-disubstituted cyclohexene **2-51**, of which the *trans*-relationship between Ha and Hb was confirmed by the large *J* value (9.3 Hz) between these protons, was obtained in 21% yield after separation from the corresponding *cis*-isomer. Alcohol **2-51** was converted to (*S*)- and (*R*)-MTPA esters (**2-52**). Application of modified Mosher's analysis[11] to these MTPA esters established the (*S*)-configuration at C9', which thus determined the (8'*S*)-configuration in conjunction with the *trans*-relationship between Ha and Hb.

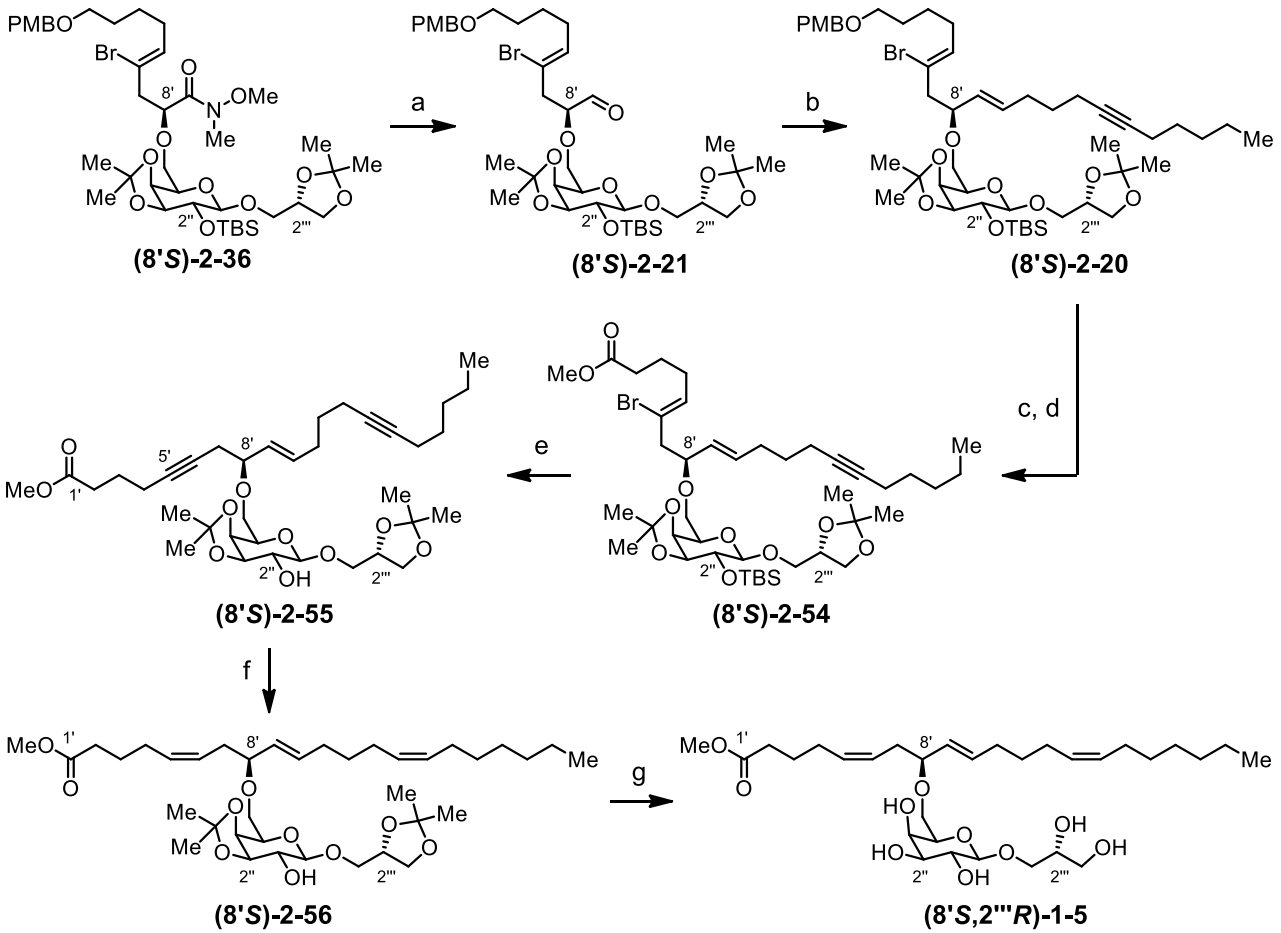


Scheme 2-16. Determination of the stereochemistry at C8' of **(8'*S*)-2-36**. Reagents and conditions: (a) Bu_3SnH, AIBN, toluene, reflux, 1 h, then concentration, 23 °C, 6 days, 76%; (b) $LiAlH_4$, THF, –20 °C, 45 min, then 0 °C, 30 min; allyl magnesium chloride, THF, 2 h, –20 °C, 62% over 2 steps, ds = 1:1; (c) **2-50**, CH_2Cl_2, reflux, 1 h, then separation, 21%; (d) (*S*/*R*)-MTPA, DMF, $(COCl)_2$, hexane, 23 °C, 1 h, then **2-51**, DMAP, Et_3N, $CDCl_3$ or CH_2Cl_2, 0 °C, 10-18 h, **(*S*)-MTPA ester 2-52**: 51%, **(*R*)-MTPA ester 2-52**: 63%.

The established (8'*S*)-configuration of **2-51** also explained the stereoselectivity of the Ireland-Claisen rearrangement of **(5'*S*)-2-25** producing **(8'*S*)-2-23**. The initial formation of the ketene silyl acetal would be highly *Z*-selective, and the Z-ketene silyl acetal would be rearranged via a stable chair form transition state (**TS** in Scheme 2-12), which would effectively promote the chirality transfer from C5' to C8' and produce **(8'*S*)-2-23** exclusively.

2-6. Synthesis of Model Compounds for the C20 Lipid Chain/Galactosyl Glycerol Segment

The completion of the synthesis of model compound **(8'*S*,2'''*R*)-1-5** is illustrated in Scheme 2-17.

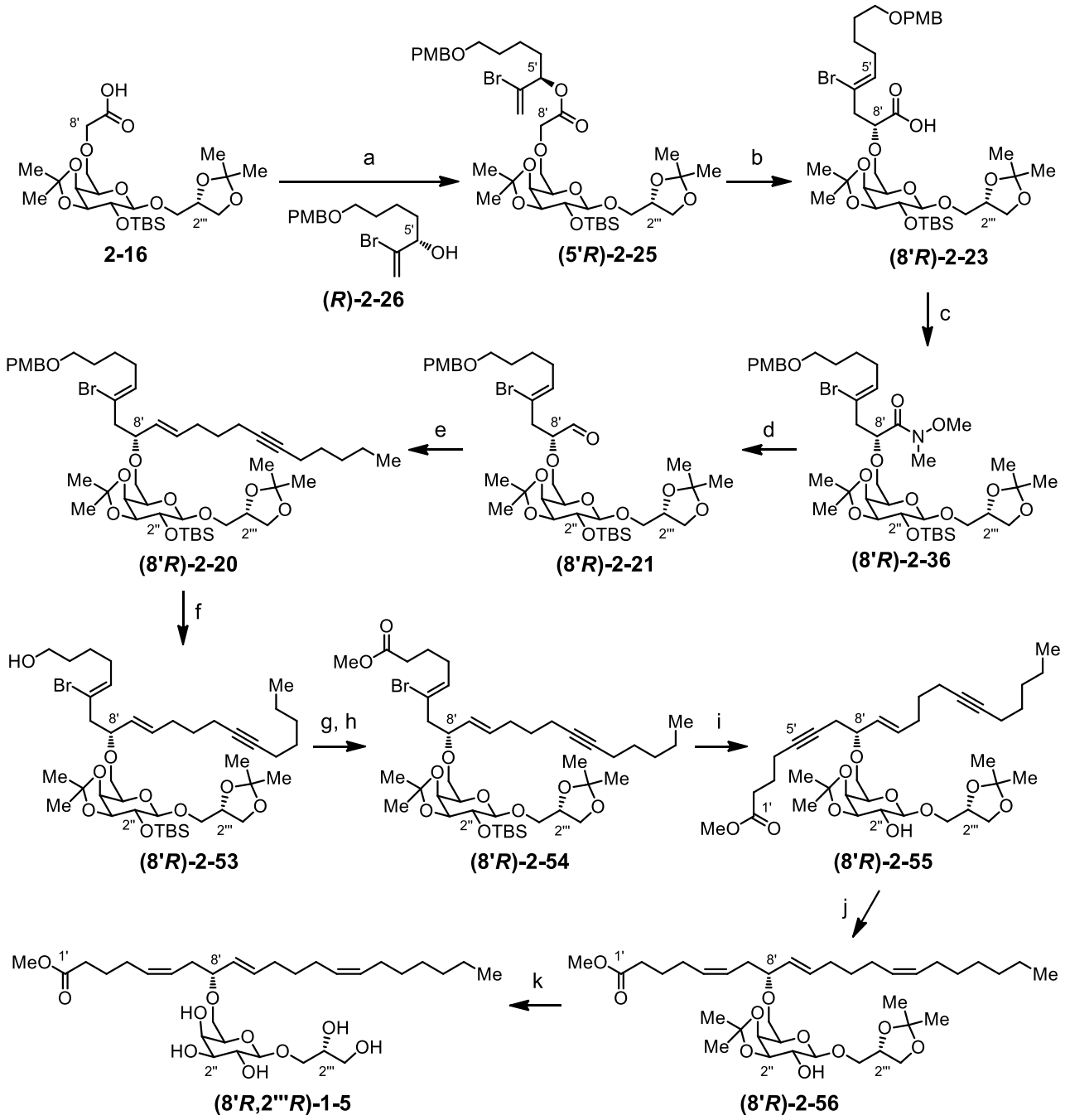


Scheme 2-17. Completion of the synthesis of **(8'*S*, 2'''*R*)-1-5**. Reagents and conditions: (a) $LiAlH_4$, THF, –20 °C, 45 min; (b) **2-22**, KHMDS, THF, –78 °C, 45 min, then **(8'*S*)-2-21**, –78 °C, 1 h, then 23 °C, 1 h, 47% from **(8'*S*)-2-36**; (c) TEMPO, $PhI(OAc)_2$, pH 7.0 buffer, CH_3CN, 45 °C, 21 h; (d) $TMSCHN_2$, MeOH, CH_2Cl_2, 23 °C, 1.5 h, 73% from **(8'*S*)-2-20**; (e) $TBAF{\cdot}3H_2O$, DMF, 75 °C, 3 h, 48%; (f) H_2, Lindlar cat., MeOH, 23 °C, 24.5 h, 100%; (g) TFA, MeOH, CH_2Cl_2, 23 °C, 7 h, 50% from **(8'*S*)-2-55**.

Weinreb amide **(8'*S*)-2-36** was reduced with $LiAlH_4$ to give aldehyde **(8'*S*)-2-21**, which was subjected to Julia-Kocienski olefination with sulfone **2-22** using KHMDS to produce *E*-alkene **(8'*S*)-**

2-20 (47% over 2 steps). The PMB group of **(8'*S*)-2-20** was oxidatively removed by TEMPO oxidation in the presence of water[14], and the resulting carboxylic acid was converted to methyl ester **(8'*S*)-2-54** by treatment with trimethylsilyldiazomethane (73% over 2 steps).[15] The bromoalkene group of **(8'*S*)-2-54** was transformed to an acetylene group [**(8'*S*)-2-55**, 48%] by treatment with TBAF•3H_2O in DMF at 75 °C, which also removed the TBS ether at C2", according to Mori's procedure.[16] Lindlar hydrogenation of **(8'*S*)-2-55** followed by acidic methanolysis of the acetonides produced **(8'*S*,2'''*R*)-1-5** (50% over 2 steps). Thus, model compound **(8'*S*,2'''*R*)-1-5** was stereoselectively synthesized from 3-galactosyl-*sn*-glycerol derivative **2-1** via a route including chirality transferring Ireland-Claisen rearrangement as a key step.

The synthesis of **(8'*R*,2'''*R*)-1-5** from **(*R*)-2-26** and **2-16** was also successfully performed by the almost same route (Scheme 2-18).



Scheme 2-18. The synthesis of **(8'*R*,2'''*R*)-1-5**. Reagents and conditions: (a) **(*R*)-2-26**, EDCI·HCl, DMAP, CH_2Cl_2, 23 °C, 16 h, 66%; (b) TMSCl, KHMDS, –78 °C, 20 min, then 0 °C, 5 min; (c) MeNH(OMe)·HCl, EDCI·HCl, DMAP, CH_2Cl_2, 23 °C, 3.5 h, 67% from **(*R*)-2-26**. (d) $LiAlH_4$, THF, –20 °C → 0 °C, 30 min; (e) **2-22**, KHMDS, THF, –78 °C, 45 min, then **(8'*R*)-2-21**, –78 °C → 23 °C, 3.5 h, 63% from **(8'*R*)-2-36**; (f) DDQ, CH_2Cl_2, pH 7 buffer, 23 °C, 4 h, 64%; (g) TEMPO, $PhI(OAc)_2$, H_2O, CH_2Cl_2, 23 °C, 30 h; (h) $TMSCHN_2$, MeOH, CH_2Cl_2, 23 °C, 10 min, 68% from **(8'*R*)-2-53**; (i) $TBAF{\cdot}3H_2O$, DMF, 75 °C, 3 h, 92%; (j) H_2, Lindlar cat., MeOH, 23 °C, 22 h, 100%; (k) TFA, MeOH, CH_2Cl_2, 23 °C, 17.5 h, 100%.

With both model compounds **(8'*S*,2'''*R*)-1-5** and **(8'*R*,2'''*R*)-1-5** in hand, we compared the ^{1}H NMR data of the model compounds in C_6D_6/DMSO-d_6 (25:2) with the reported data of **1-2**. The deviation of the chemical shifts of the models from those of **1-2** is shown in Fig. 2. While there are large differences in the chemical shifts in the H9'–H16' region between each model and **1-2** due to the absence of the C16 fatty acid chain and the oxygen functionalities at C11' and C12' in the model compounds, the chemical shift deviations in other regions of both models are small (within ±0.1 ppm). The similarity of the ^{1}H NMR spectrum of **(8'*S*,2'''*R*)-1-5** with that of **1-2** is suggested from the fact that the average of the absolute values of the chemical shift deviations of **(8'*S*,2'''*R*)-1-5** from **1-2** (for all protons, except H9'–H16' and hydroxylc protons, of the model) is smaller (0.018 ppm) than that of **(8'*R*,2'''*R*)-1-5** (0.028 ppm). However, the *S*-configuration at C8' of **2** cannot be asserted with confidence at this stage due to the presence of significant chemical shift deviations of H4" and H6"b of **(8'*S*,2'''*R*)-1-5**, as well as the observation that the ^{13}C NMR data of both models significantly deviated from those of **1-2** (Figure 2-4). Further studies with alternative model compounds are required for the determination of the stereochemistry at C8' of **1-2**.

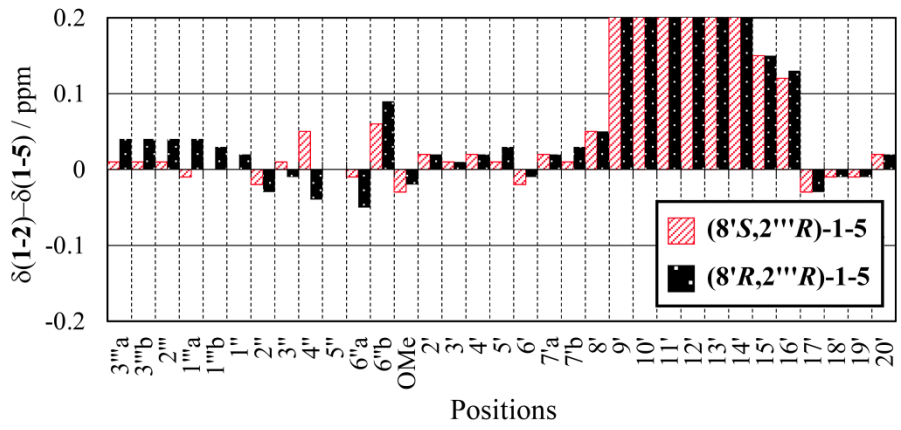


Figure 2-3. Deviation of ^{1}H NMR chemical shifts of **1-5** from the reported values of **1-2**. ^{1}H NMR spectra of **1-5** were measured in 25:2 C_6D_6/DMSO-d_6 according to the literature.

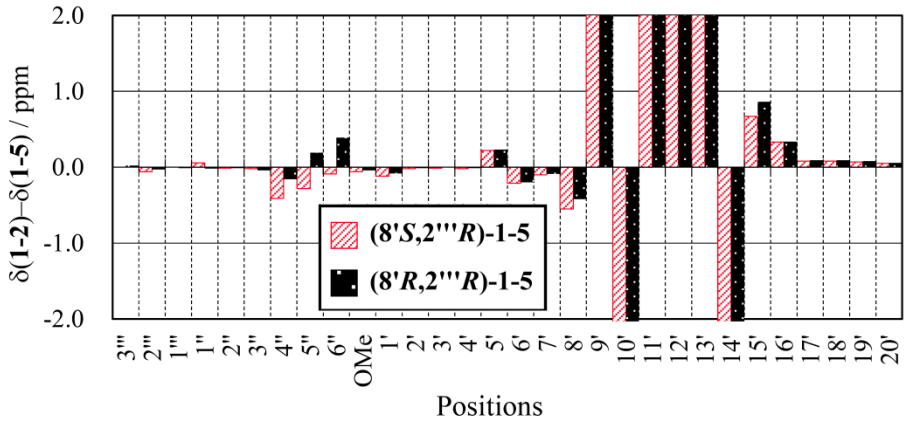


Figure 2-4. Deviation of ^{13}C NMR chemical shifts of **1-5** from the reported values of **1-2**. ^{13}C NMR spectra of **1-5** were measured in 25:2 C_6D_6/DMSO-d_6 according to the literature.

2-7. Conclusion

A method for the stereoselective construction of the C8'-O-C6" ether of nigricanoside-A (**1-1**), an antimitotic natural product from the green alga *Avrainvillea nigricans*, has been developed based on chirality-transferring Ireland-Claisen rearrangement. The method was successfully applied to the synthesis of simple models [**(8'*S*,2'''*R*)-1-5** and **(8'*R*,2'''*R*)-1-5**] for the C20 lipid chain/galactosyl glycerol segment of **1-1**.

References

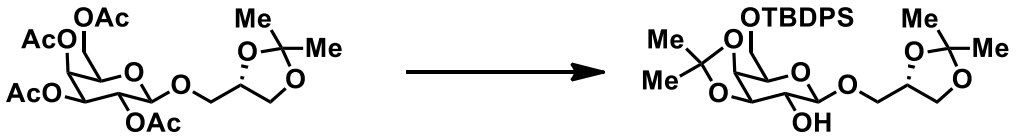
1. For a review: Maréchal, É.; Block, M. A.; Dorne, A.-J.; Douce, R.; Joyard, J. *Physiol. Plant.* **1997**, *100*, 65.
2. Sias, B.; Ferrato, F.; Grandval, P.; Lafont, D.; Boullanger, P.; De Caro, A.; Leboeuf, B.; Veger, R.; Carrière, F. *Biochemistry* **2004**, *43*, 10138.
3. Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, *11*, 1306.
4. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *9*, 26.
5. Jung, S. H.; Kim, S. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 13.
6. Gemal, A. L.; Luche, J.-L. *J Am. Chem. Soc.* **1981**, *103*, 5454.
7. The separation of **2-30** (polar) from **2-31** (less polar) was performed by HPLC using a pre-packed column (YMC-Pack SIL-06-5 μm, 500 mm × 20 mmID) supplied by YMC Co., Ltd. with hexane-ethyl acetate eluent (20 mL/min).
8. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
9. Evans, R. W.; Sprecher, H. *Chem. Phys. Lipids* **1985**, *38*, 327.
10. Mitsunobu, O. *Synthesis* **1981**, *13*, l.
11. Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383.
12. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
13. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
14. Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *J. Org. Chem.* **2009**, *74*, 9524.
15. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1457.
16. Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442.

Experimental Section

General Methods

All reactions sensitive to air or moisture were carried out under an argon atmosphere in freshly distilled dry solvent under anhydrous conditions, unless, otherwise noted. Sensitive liquids and solutions were transferred by syringe-septum and cannula techniques. All commercially available reagents were used without further purification with the following exceptions. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl under argon. Dichloromethane (CH_2Cl_2) and benzene were distilled from CaH_2 prior to use. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel (SiO_2) plates (Merck, silica gel 60 F_{254}). Plates were visualized by ultraviolet light and by treatment with acidic anisaldehyde or phosphomolybdic acid stain followed by heating. Flash chromatography was performed on YMC Silica Gel 60 (230-400 mesh) as a stationary phase. Melting points were measured on a YANAGIMOTO micro-melting apparatus without calibration. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. Infrared spectra (IR) were measured on a JEOL 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 a JEOL JNM-AL300 (^1H at 300 MHz, ^{13}C at 75 MHz) or a 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) or the residual solvent signal (for example, C_6HD_5 as 7.15 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 doublets; 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 the solvent signal (for example, $^{13}CDCl_3$ as 77.0 ppm; $^{13}C^{12}C_5D_6$ as 128 ppm) as an internal standard. Low and high resolution mass spectra were measured on a JEOL JMS-600H mass spectrometer under electron ionization (EI) condition and a JEOL JMS-SX102A mass spectrometer under field desorption (FD) condition.

Compound 2-2:



2-1 **2-2**

To a solution of **2-1** (1.10 g, 2.38 mmol) in MeOH (25 ml) was added MeONa (25.6 mg, 0.474 mmol) at 23 ℃, and the mixture was stirred for 21 h. Then, to the mixture was added Amberlite IR-120-B (270.5 mg, 1.19 mmol) at 23 ℃, and the mixture was stirred for 12 h. The mixture was filtered and concentrated under reduced pressure. The resulting crude tetraol was used without further purification in the next reaction.

To a solution of the crude tetraol in CH_2Cl_2 (60 ml) were added Et_3N (0.663 ml, 4.76 mmol), DMAP (a catalytic amount), and TBDPSCl (0.744 ml, 2.86 mmol) at 23 °C, and the mixture was stirred. After 3 h, an additional TBDPSCl (0.124 ml, 0.477 mmol) was added. After 9 h, an additional TBDPSCl (0.124 ml, 0.477 mmol) was added, and the mixture was stirred for 4 h. Then, MeOH was added, and the mixture was concentrated under reduced pressure. The resulting crude triol was used without further purification in the next reaction.

To a solution of the crude triol in CH_2Cl_2 (5.0 ml) were added $(MeO)_2CMe$ (1.46 ml, 11.9 mmol) and CSA (277 mg, 1.19 mmol) at 23 ℃, and the mixture was stirred for 5.5 h. Then, the reaction was quenched with satd. aq $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10 → 8 → 5 → 3 → 2 → 1 → EtOAc) to give **2-2** (1.08 g, 1.89 mmol, 79% over 3 steps).

2-2: a colorless amorphous; $[\alpha]_D^{21}$ +5.65 (*c* 1.63, $CHCl_3$);

IR (neat) ν 3456, 3071, 3049, 2985, 2955, 2933, 2887, 2858, 1472, 1462, 1428, 1381, 1372, 1244, 1219, 1156, 1114, 1076, 966, 874, 825, 802, 742, 703, 614, 506 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.34 (3H, s), 1.35 (3H, s), 1.41 (3H, s), 1.51 (3H, s), 2.57 (1H, brs), 3.57 (1H, brt, J = 7.9 Hz), 3.58 (1H, dd, J = 5.0, 10.8 Hz), 3.80 (1H, dd, J = 6.1, 8.4 Hz), 3.83-3.94 (3H, m), 3.97 (1H, dd, J = 6.9, 9.3 Hz), 4.03 (1H, dd, J = 6.5, 8.4 Hz), 4.07 (1H, dd, J = 5.5, 7.4 Hz), 4.20 (1H, d, J = 8.2 Hz), 4.25-4.33 (2H, m), 7.34-7.46 (6H, m), 7.66-7.73 (4H, m);

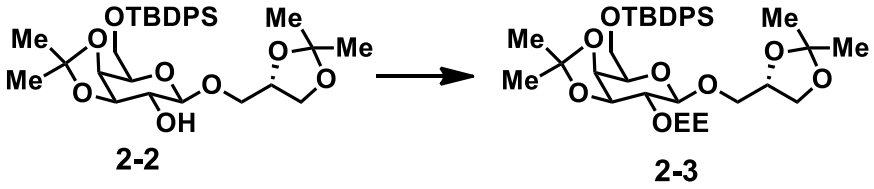
^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C), 25.2 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 26.7 (CH_3×3), 28.2

(CH_3), 62.5 (CH_2), 66.2 (CH_2), 69.7 (CH_2), 73.1 (CH), 73.6 (CH), 73.7 (CH), 74.4 (CH), 78.6 (CH), 102.9 (CH), 109.5 (C), 110.0 (C), 127.6 (CH×2), 127.7 (CH×2), 129.7 (CH×2), 133.2 (C), 133.4 (C), 135.5 (CH×2), 135.6 (CH×2);

FD-LRMS *m/z* 573 (9.9%, [M+H^+]), 515 (bp);

FD-HRMS calcd for $C_{31}H_{45}O_8Si$ [M+H^+]: 573.2884, found 573.2891.

Compound 2-3:

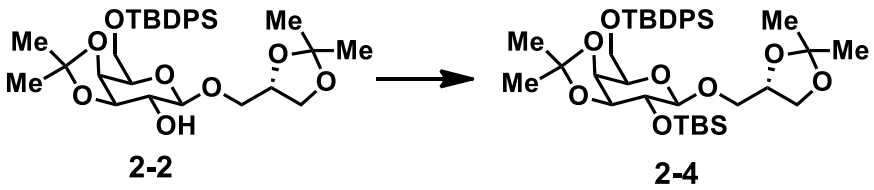


To a solution of alcohol **2-2** (599.8 mg, 1.05 mmol) in CH_2Cl_2 (20 ml) were added ethyl vinyl ether (1.00 ml, 10.5 mmol) and PPTS (26.3 mg, 0.105 mmol) at 23 °C, and the mixture was stirred for 3 h. Then, satd. aq. $NaHCO_3$ was added, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **2-3** (640.5 mg,0.993 mmol, 95%).

2-3: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.16-1.24 (3H, m), 1.30-1.35 (9H, m), 1.39 (3H, s), 1.50 (3H, brs), 3.44-3.58 (5H, m), 3.72-3.86 (2H, m), 3.86-3.96 (2H, m), 3.96-4.06 (1H, m), 4.06-4.13 (1H, m), 4.18-4.31 (3H, m), 4.89-4.98 (1H, m), 7.33-7.47 (6H, m), 7.66-7.73 (4H, m).

Compound 2-4:



To a solution of **2-2** (2.90g, 5.06mmol) in CH_2Cl_2 (100ml) were added 2,6-lutidine (1.70 ml, 14.6 mmol), DMAP (61 mg, 0.50 mmol), and TBSOTf (1.75 ml, 7.62 mmol) at 23°C, and the mixture was

stirred for 4.5 h. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resultant residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 6) to give **2-4** (3.18g, 4.62 mmol, 91%).

2-4: a colorless amorphous; $[\alpha]_D^{23}$ +5.47 (*c* 1.49, $CHCl_3$);

IR (neat) ν 3072, 3050, 2985, 2955, 2932, 2886, 2857, 1472, 1463, 1428, 1381, 1370, 1249, 1219, 1163, 1114, 1079, 1046, 1007, 877, 839, 826, 780, 742, 702, 505 cm^{-1};

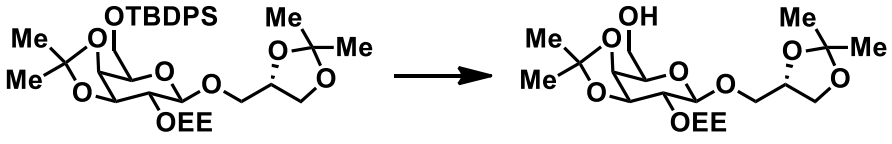
^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 1.05 (9H, s), 1.31 (3H, s), 1.33 (3H, s), 1.39 (3H, s), 1.48 (3H, s), 3.45 (1H, dd, *J* = 7.8, 10.0 Hz), 3.49 (1H, dd, *J* = 6.8, 7.8 Hz), 3.80 (1H, dd, *J* = 5.5, 8.4 Hz), 3.80-3.84 (1H, m), 3.87 (1H, dd, *J* = 4.8, 10.0 Hz), 3.89 (1H, dd, *J* = 6.0, 9.8 Hz), 3.94 (1H, dd, *J* = 7.3, 9.8 Hz), 3.99 (1H, dd, *J* = 5.5, 6.8 Hz), 4.03 (1H, dd, *J* = 6.2, 8.4 Hz), 4.14 (1H, d, *J* = 7.8 Hz), 4.23 (1H, dd, *J* = 2.0, 5.5 Hz), 4.23-4.30 (1H, m), 7.34-7.46 (6H, m), 7.66-7.72 (4H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.5 (CH_3), 18.1 (C), 19.2 (C), 25.3 (CH_3), 25.8 (CH_3×3), 26.4 (CH_3), 26.7 (CH_3×3), 26.9 (CH_3), 28.1 (CH_3), 62.7 (CH_2), 67.5 (CH_2), 70.4 (CH_2), 73.3 (CH), 73.4 (CH), 74.2 (CH), 74.5 (CH), 80.6 (CH), 103.5 (CH), 109.1 (C), 109.6 (C), 127.6 (CH×2), 127.7 (CH×2), 129.67 (CH), 129.69 (CH), 133.3 (C), 133.5 (C), 135.5 (CH×2), 135.6 (CH×2);

FD-LRMS *m/z* 687 (1.8%, $[M+H^+]$), 629 (bp);

FD-HRMS calcd for $C_{37}H_{59}O_8Si_2$ $[M+H^+]$: 687.3748, found 687.3732.

Compound 2-5:



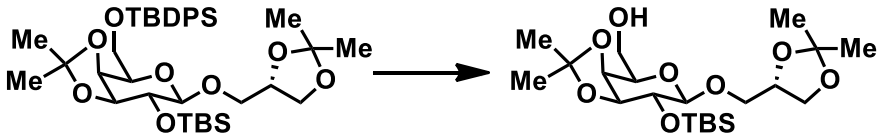
2-3 **2-5**

To a solution of **2-3** (640.5 mg, 0.9932 mmol**)** in THF (10 ml) were added TBAF (1.0 M in THF, 2.9 ml, 2.9 mmol) at 23 °C, and the mixture was stirred for 1 h. Then the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 2 → EtOAc) to give **2-5** (318.7 mg, 0.784 mmol, 79%).

2-5: a colorless amorphous;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.23 (3H, m), 1.30-1.37 (6H, m), 1.35 (3H, s), 1.41 (3H, s), 1.52 (3H, s), 3.44-3.66 (4H, m), 3.68-4.01 (5H, m), 4.03-4.10 (1H, m), 4.10-4.17 (2H, m), 4.24-4.38 (2H, m), 4.91-4.98 (1H, m).

Compound 2-6:



2-4 **2-6**

To a solution of **2-4** (3.18 g, 4.62 mmol) in DMF (50.0 ml) were added AcOH (0.344 ml, 6.01 mmol) and TBAF (1 M in THF, 5.09 ml, 5.09 mmol) at 24 °C, and the mixture was stirred for 2 h. The reaction was quenched with satd. aq $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 4) to give **2-6** (1.67g, 3.72 mmol, 80%).

2-6: a colorless amorphous; $[\alpha]_D^{27}$ +19.2 (*c* 1.00, $CHCl_3$);

IR (neat) ν 3454, 2986, 2952, 2934, 2885, 2858, 1473, 1463, 1455, 1381, 1371, 1249, 1219, 1162, 1142, 1080, 1047, 966, 874, 839, 808, 780, 746, 670, 666 cm^{-1};

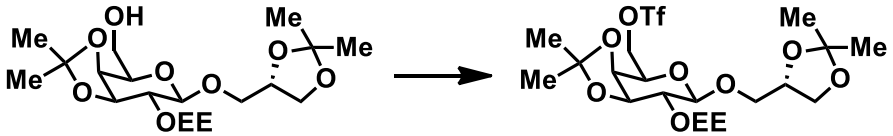
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 1.33 (3H, s), 1.35 (3H, s), 1.41 (3H, s), 1.49 (3H, s), 2.45 (1H, brs), 3.53 (1H, dd, *J* = 6.8, 7.8 Hz), 3.57 (1H, dd, *J* = 6.4, 10.6 Hz), 3.75 (1H, dd, *J* = 6.0, 8.4 Hz), 3.76-3.86 (2H, m), 3.88 (1H, dd, *J* = 5.5, 10.6 Hz), 3.90-4.00 (1H, m), 4.03 (1H, brt, *J* = 6.0 Hz), 4.08 (1H, dd, *J* = 6.4, 8.4 Hz), 4.13 (1H, dd, *J* = 1.8, 5.5 Hz), 4.20 (1H, d, *J* = 7.8 Hz), 4.33 (1H, brqn, *J* = 6.0 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ –5.0 (CH_3), –4.9 (CH_3), 17.7 (C), 24.9 (CH_3), 25.5 (CH_3×3), 26.1 (CH_3), 26.5 (CH_3), 27.6 (CH_3), 61.6 (CH_2), 66.9 (CH_2), 70.6 (CH_2), 73.2 (CH), 73.5 (CH), 74.15 (CH), 74.23 (CH), 80.4 (CH), 103.1 (CH), 108.9 (C), 109.5 (C);

FD-LRMS *m/z* 449 (36.6%, [M+H$^+$]), 391 (bp);

FD-HRMS calcd for $C_{21}H_{41}O_8Si$ [M+H$^+$]: 449.2571, found 449.2598.

Compound 2-8:



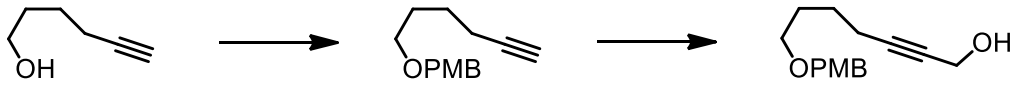
2-5 **2-8**

To a solution of **2-5** (15.6 mg, 0.0384 mmol) in CH_2Cl_2 (0.4 ml) were added 2,6-lutidine (0.011 ml, 0.092 mmol) and Tf_2O (0.0076 ml, 0.046 mmol) at 0 °C, and the mixture was stirred for 30 min. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with 0.5 M aq. HCl and then with satd. aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude **2-8** (15.3 mg, 0.0284 mmol, 74 %), which was used in the next reaction without further purification.

2-8: a colorless amorphous;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.26 (3H, m), 1.30-1.38 (6H, m), 1.35 (3H, s), 1.42 (3H, s), 1.51 (3H, s), 3.41-3.88 (5H, m), 3.88-3.96 (1H, m), 4.02-4.23 (4H, m), 4.24-4.41 (2H, m), 4.62-4.78 (2H, m), 4.88-4.97 (1H, m).

Compound 2-15:



2-13 **2-14** **2-15**

To a solution of **2-13** (2.45 g, 25.0 mmol) in THF (50 ml) were added NaH (60% in oil, 2.0 g, 50 mmol) and PMBCl (5.08 ml, 37.5 mmol) at 0 °C, and the mixture was stirred at 23 °C for 3 days. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resultant residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **2-14** (5.79 g) including small amounts of byproducts from PMBCl [**2-14**: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-1.78 (4H, m), 1.94 (1H, t, *J* = 2.6 Hz), 2.21

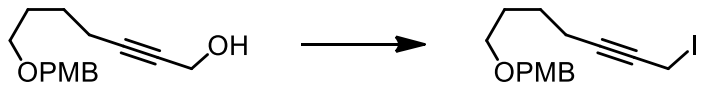
(2H, dt, *J* = 2.6, 6.9 Hz), 3.46 (2H, t, *J* = 6.2 Hz), 3.80 (3H, s), 4.43 (2H, s), 6.87 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, J = 8.8 Hz)].

To a solution of the above **2-14** (5.79 g) in THF (100 ml) were added BuLi (1.65 M in hexane, 32.2 ml, 53.1 mmol) at –78 °C, and the mixture was stirred for 20 min. Then, to the mixture was added paraformaldehyde (1.59 g, 53.1 mmol) at –78°C, and the mixture was allowed to warm to 23 °C and stirred for 7 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through a Celite pad, and concentrated in vacuo. The resultant residue was purified by column chromatography (silica gel, hexane/EtOAc = 4) to give **2-15** (4.52 g, 18.2 mmol, 73% over 2 steps).

2-15: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47-1.76 (4H, m), 2.24 (2H, tt, *J* = 2.2, 6.9 Hz), 3.46 (2H, t, *J* = 6.2 Hz), 3.80 (3H, s), 4.21-4.26 (2H, m), 4.43 (2H, s), 6.87 (2H, d, *J* = 8.6 Hz), 7.25 (2H, d, *J* = 8.6 Hz).

Compound 2-11:



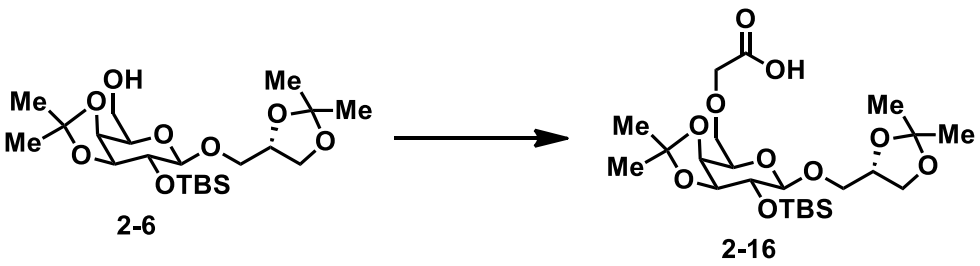
2-15 **2-11**

To a solution of **2-15** (4.52 g, 18.2 mmol) in CH_2Cl_2 (150 ml) were added imidazole (2.48 g, 38.4 mmol) and PPh_3 (7.16 g, 27.3 mmol) at 0 °C, and the mixture was stirred for 15 min. Then, to the mixture was added I_2 (6.93 g, 27.3 mmol) portionwise at 0°C, and the mixture was stirred at 23 °C for 35 min. Then, the reaction was quenched with satd. aq. $Na_2S_2O_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through a Celite pad, and concentrated in vacuo. The resultant residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **2-11** (3.68 g, 10.3 mmol, 57%).

2-11: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.75 (4H, m), 2.22 (2H, tt, *J* = 2.5, 6.9 Hz), 3.46 (2H, t, *J* = 6.2 Hz), 3.69 (2H, t, *J* = 2.5 Hz), 3.80 (3H, s), 4.43 (2H, s), 6.88 (2H, d, *J* = 8.7 Hz), 7.26 (2H, d, *J* = 8.7 Hz).

Compound 2-16:



To a solution of alcohol **2-6** (221.3 mg, 0.4932 mmol) in benzene (2.0 ml) were added 4 M aq. NaOH (4.0 ml), *tert*-butyl bromoacetate (0.250 ml, 1.69 mmol), and $Bu_4N{\cdot}HSO_4$ (628.1 mg, 1.85 mmol) at 23 °C, and the mixture was stirred for 29 h. Then, satd. aq. NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. After the residue was dissolved in MeOH (2.0 ml), 4 M aq. NaOH (4.0 ml) was added to the solution at 23 °C, and the mixture was stirred for 7 h. The mixture was acidified with 1 M aq. HCl and extracted with CH_2Cl_2 and $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give almost pure **2-16** (168.5 mg, 0.3326 mmol, 67% over 2 steps).

2-16: a colorless oil; $[\alpha]_D^{22}$ +2.7 (*c* 2.0, $CHCl_3$);

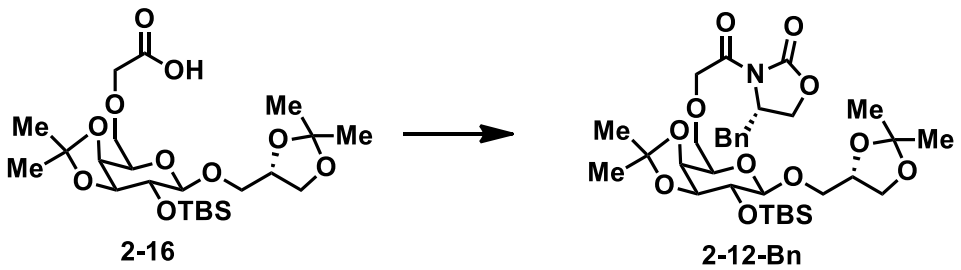
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 1.34 (3H, s), 1.36 (3H, s), 1.41 (3H, s), 1.51 (3H, s), 3.52 (1H, dd, *J* = 7.0, 10.0 Hz), 3.55 (1H, dd, *J* = 6.3, 7.6 Hz), 3.79 (1H, dd, *J* = 5.6, 8.5 Hz), 3.79-3.93 (3H, m), 3.95-4.02 (1H, m), 4.03-4.10 (2H, m), 4.14 (1H, d, *J* = 17.0 Hz), 4.17-4.22 (1H, m), 4.21 (1H, d, *J* = 17.0 Hz), 4.23 (1H, d, *J* = 7.6 Hz), 4.24-4.34 (1H, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7 (CH_3), –4.6 (CH_3), 18.0 (C), 25.1 (CH_3), 25.7 (CH_3×3), 26.2 (CH_3), 26.7 (CH_3), 27.8 (CH_3), 67.2 (CH_2), 68.6 (CH_2), 70.5 (CH_2), 71.1 (CH_2), 71.8 (CH), 73.7 (CH), 73.9 (CH), 74.1 (CH), 80.3 (CH), 103.1 (CH), 109.3 (C), 110.0 (C), 173.5 (C);

FD-LRMS *m/z* 507 (64.3%, [M+H$^+$]), 449 (bp);

FD-HRMS calcd for $C_{23}H_{43}O_{10}Si$ [M+H$^+$]: 507.2626, found 507.2652.

Compound 2-12-Bn:

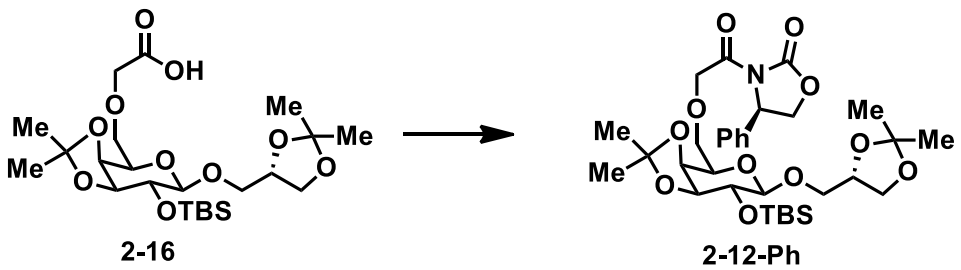


To a solution of **2-16** (31.6 mg, 0.0624 mmol) in THF (0.2 ml) were added Et_3N (0.035 ml, 0.25 mmol) and pivaloyl chloride (0.0153 ml, 0.124 mmol) at –20 °C, and the mixture was stirred for 45 min. To a THF solution of (*S*)-4-benzyloxazolidin-2-one-3-yl lithium, prepared by the reaction of (*S*)-4-benzyloxazolidin-2-one (33.2 mg, 0.187 mmol) with BuLi (1.65 M in hexane, 0.0760 ml, 0.125 mmol) in THF (1.0 ml) at –25 °C for 30 min, was added the above mixed anhydride solution at –20 °C, and the mixture was stirred for 30 min. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc = 2) to give **2-12-Bn** (33.1 mg, 0.0497 mmol, 80%).

2-12-Bn: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.12 (3H, s), 0.90 (9H, s), 1.33 (6H, s), 1.39 (3H, s), 1.48 (3H, s), 2.80 (1H, dd, *J* = 9.6, 13.4 Hz), 3.34 (1H, dd, *J* = 3.3, 13.4 Hz), 3.49 (1H, brt, *J* = 8.0 Hz), 3.52 (1H, dd, *J* = 5.1, 7.7 Hz), 3.79-4.34 (12H, m), 4.68 (1H, tdd, *J* = 3.3, 7.8, 9.6 Hz), 4.79 (2H, s), 7.15-7.38 (5H, m).

Compound 2-12-Ph:



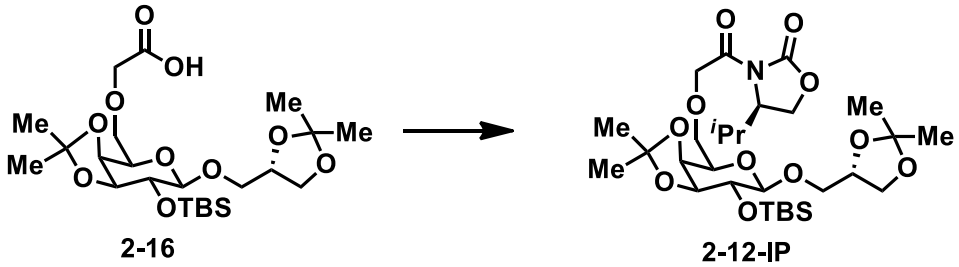
To a solution of **2-16** (76.0 mg, 0.150 mmol) in THF (2 ml) were added Et_3N (0.063 ml, 0.45 mmol)

and pivaloyl chloride (0.037 ml, 0.30 mmol) at –20 °C, and the mixture was stirred for 1 h. To a THF solution of (*R*)-4-phenyloxazolidin-2-one-3-yl lithium, prepared by the reaction of (*R*)-4-phenyloxazolidin-2-one (66.5 mg, 0.408 mmol) with BuLi (1.65 M in hexane, 0.182 ml, 0.300 mmol) in THF (1.0 ml) at –20 °C for 30 min, was added the above mixed anhydride solution at –20 °C, and the mixture was stirred for 30 min. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc = 2) to give **2-12-Ph** (59.6 mg, 0.0914 mmol, 61%).

2-12-Ph: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.30 (3H, s), 1.33 (3H, s), 1.40 (3H, s), 1.47 (3H, s), 3.43-3.51 (2H, m), 3.71-4.14 (8H, m), 4.14 (1H, d, *J* = 7.8 Hz), 4.21.4.33 (1H, m), 4.36 (1H, dd, *J* = 3.7, 9.0 Hz), 4.70-4.87 (3H, m). 5.42 (1H, dd, J = 3.7, 8.7 Hz), 7.28-7.42 (5H, m).

Compound 2-12-IP:



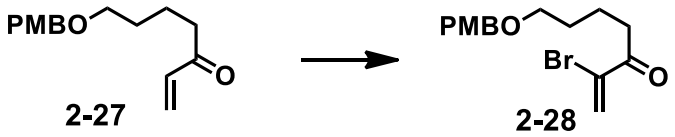
To a solution of **2-16** (70.0 mg, 0.138 mmol) in THF (1 ml) were added Et_3N (0.077 ml, 0.55 mmol) and pivaloyl chloride (0.034 ml, 0.28 mmol) at –20 °C, and the mixture was stirred for 40 min. To a THF solution of (*R*)-4-isopropyloxazolidin-2-one-3-yl lithium, prepared by the reaction of (*R*)-4-isopropyloxazolidin-2-one (44.3 mg, 0.346 mmol) with BuLi (1.65 M in hexane, 0.167 ml, 0.276 mmol) in THF (1.0 ml) at –20 °C for 30 min, was added the above mixed anhydride solution at –20 °C, and the mixture was stirred for 2 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with

brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc = 2) to give **2-12-IP** (74.6 mg, 0.121 mmol, 87%).

2-12-IP: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.11 (3H, s), 0.89 (3H, d, *J* = 7.0 Hz), 0.90 (9H, s), 0.93 (3H, d, *J* = 7.0 Hz), 1.32 (3H, s), 1.34 (3H, s), 1.41 (3H, s), 1.48 (3H, s), 2.36-2.50 (1H, m), 3.46-3.54 (2H, m), 3.73-3.86 (2H, m), 3.87-4.10 (5H, m), 4.14 (1H, dd, *J* = 2.0, 5.5 Hz), 4.18 (1H, d, *J* = 7.9 Hz), 4.22-4.34 (2H, m), 4.34 (1H, brt, *J* = 8.5 Hz), 4.43 (1H, td, *J* = 3.5, 8.2 Hz), 4.76 (1H, d, *J* = 18.1 Hz), 4.81 (1H, d, *J* = 18.1 Hz).

Compound 2-28:



To a solution of **2-27** (2.71 g, 10.9 mmol) in CH_2Cl_2 (200 ml) was added Br_2 (0.609 ml, 11.9 mmol) dropwise over 10 min at –78 °C, and the mixture was stirred for 10 min. Then, to the mixture was added Et_3N (3.80 ml, 27.2 mmol) at 0 °C, and the mixture was stirred for 10 min. Then, the reaction was quenched with satd. aq. $NaHCO_3$ and satd. aq. $Na_2S_2O_3$, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15) to give **2-28** (3.07 g, 9.38 mmol, 86%).

2-28: a colorless oil;

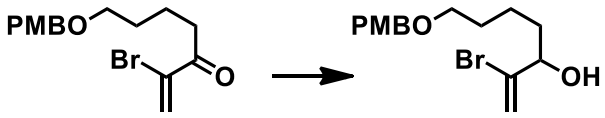
IR (neat) ν 3030, 3001, 2935, 2858, 1698, 1612, 1586, 1513, 1463, 1442, 1393, 1362, 1302, 1247, 1208, 1175, 1149, 1098, 1051, 1036, 820 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-1.80 (4H, m), 2.81 (2H, t, *J* = 7.2 Hz), 3.46 (2H, t, *J* = 6.1 Hz), 3.80 (3H, s), 4.42 (2H, s), 6.35 (1H, d, *J* = 2.4 Hz), 6.76 (1H, d, *J* = 2.4 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 7.25 (2H, d, *J* = 8.6 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (CH_2), 28.6 (CH_2), 37.3 (CH_2), 54.9 (CH_3), 69.2 (CH_2), 72.2

(CH_2), 113.4 (CH×2), 128.4 (CH_2), 128.9 (CH×2), 130.3 (C), 131.4 (C), 158.8 (C), 193.6 (C);

Compound 2-26:



2-28 **2-26**

To a solution of **2-28** (132.3 mg, 0.404 mmol) in MeOH (40 ml) were added $CeCl_3$•$7H_2O$ (301.3 mg, 0.808 mmol) and $NaBH_4$ (7.7 mg, 0.20 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was evaporated to remove MeOH. The concentrated aqueous solution was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **2-26** (129.4 mg, 0.393 mmol, 98%).

2-26: a colorless oil;

IR (neat) ν 3414, 3034, 3000, 2939, 2862, 1612, 1586, 1513, 1463, 1442, 1363, 1303, 1248, 1173, 1092, 1036, 899, 820, 665 cm^{-1};

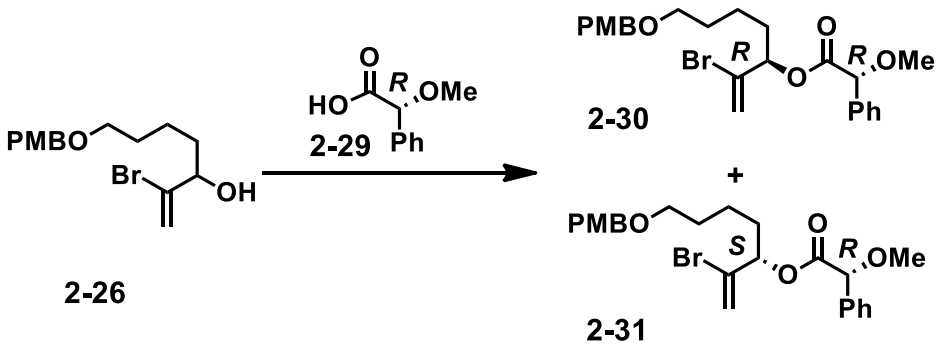
^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.53 (2H, m, -C<u>H</u>$_2$-), 1.53-1.79 (4H, m, -C<u>H</u>$_2$-×2), 1.97 (1H, d, *J* = 6.0 Hz, O<u>H</u>), 3.45 (2H, t, *J* = 6.4 Hz, -OC<u>H</u>$_2$-), 3.80 (3H, s, -OC<u>H</u>$_3$), 4.08 (1H, q, *J* = 6.0 Hz, -C<u>H</u>(OH)-), 4.42 (2H, s, -OC<u>H</u>$_2$-Ar), 5.55 (1H, brd, *J* = 1.8 Hz, =CH-), 5.86 (1H, brs, =CH-), 6.88 (2H, d, *J* = 8.5 Hz, PMB), 7.26 (2H, d, *J* = 8.5 Hz, PMB);

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (CH_2), 29.2 (CH_2), 34.8 (CH_2), 55.2 (CH_3), 69.7 (CH_2), 72.4 (CH_2), 75.7 (CH_2), 113.7 (CH×2), 116.7 (CH_2), 129.2 (CH×2), 130.5 (C), 137.5 (C), 159.0 (C);

EI-LRMS *m/z* 328 (3.5%, [M^+]), 121 (bp);

EI-HRMS calcd for $C_{15}H_{21}BrO_3$ ([M^+]) 328.0674, found 328.0692.

Compounds 2-30 and 2-31:



To a solution of **2-26** (176.7 mg, 0.5367 mmol), DMAP (a catalytic amount), and (*R*)-(–)-α-methoxyphenylacetic acid (133.8 mg, 0.8051 mmol) in CH_2Cl_2 (0.4 ml) was added EDCI (154.3 mg, 0.8051 mmol) at 23 °C, and the mixture was stirred for 2 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 12→10) to give a mixture of **2-30** and **2-31**. Then, the mixture was separated by preparative HPLC using a pre-packed column (YMC-Pack SIL-06-5 μm, 500 mm × 20 mmID) supplied by YMC Co., Ltd. with hexane-ethyl acetate eluent (flow rate: 20 ml/min) to give **2-30** (87.9 mg, 0.184 mmol, 34%) as a polar component and **2-31** (89.5 mg, 0.187 mmol, 35%) as a less polar component.

2-30: a colorless oil; $[\alpha]_D^{25}$ –21 (*c* 0.40, $CHCl_3$);

IR (neat) ν 3063 3032, 2999, 2935, 2863, 2836, 1755, 1627, 1612, 1586, 1513, 1496, 1455, 1443, 1362, 1302, 1247, 1198, 1172, 1101, 1036, 999, 911, 847, 821, 753, 698, 665 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.22-1.44 (2H, m), 1.51-1.65 (2H, m), 1.66-1.86 (2H, m), 3.41 (2H, t, *J* = 6.5 Hz), 3.42 (3H, s), 3.80 (3H, s), 4.41 (2H, s), 4.79 (1H, s), 5.26 (1H, brt, *J* = 6.5 Hz), 5.40 (1H, brd, *J* = 2.1 Hz), 5.50 (1H, brs), 6.87 (2H, d, *J* = 8.7 Hz), 7.25 (2H, d, *J* = 8.7 Hz), 7.28-7.38 (3H, m), 7.40-7.46 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (CH_2), 29.1 (CH_2), 32.3 (CH_2), 55.2 (CH_3), 57.3 (CH_3), 69.5 (CH_2), 72.5 (CH_2), 76.8 (CH), 82.4 (CH), 113.7 (CH×2), 119.0 (CH_2), 127.2 (CH×2), 128.5 (CH×2), 128.7 (CH), 129.1 (CH×2), 130.3 (C), 130.6 (C), 135.8 (C), 159.1 (C), 169.5 (C);

EI-LRMS *m/z* 476 (0.23%, $[M^+]$), 121 (bp);

EI-HRMS calcd for $C_{24}H_{29}O_5{}^{79}Br$ $[M^+]$: 476.1198, found: 476.1187.

2-31: a colorless oil; $[\alpha]_D^{24}$ –36 (*c* 0.40, $CHCl_3$);

IR (neat) ν 3063, 3033, 2997, 2936, 2863, 2836, 2755, 1628, 1612, 1586, 1513, 1496, 1455, 1443, 1362, 1317, 1302, 1248, 1198, 1175, 1101, 1036, 1000, 911, 847, 821, 736, 698, 665 cm^{-1};

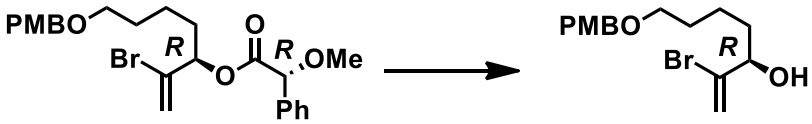
^1H NMR (300 MHz, $CDCl_3$) δ 0.98-1.19 (2H, m), 1.39-1.51 (2H, m), 1.55-1.75 (2H, m), 3.27 (2H, t, *J* = 6.5 Hz), 3.42 (3H, s), 3.80 (3H, s), 4.37 (2H, s), 4.79 (1H, s), 5.22 (1H, brt, *J* = 6.7 Hz), 5.59 (1H, d, *J* = 2.0 Hz), 5.85 (1H, brd, *J* = 2.0 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 7.23 (2H, d, *J* = 8.7 Hz), 7.26-7.37 (3H, m), 7.41-7.47 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_2), 28.8 (CH_2), 32.1 (CH_2), 55.0 (CH_3), 57.1 (CH_3), 69.2 (CH_2), 72.2 (CH_2), 76.7 (CH), 82.2 (CH), 113.5 (CH×2), 119.3 (CH_2), 127.0 (CH×2), 128.3 (CH×2), 128.5 (CH), 128.9 (CH×2), 130.4 (C), 130.8 (C), 135.9 (C), 158.9 (C), 169.4 (C);

EI-LRMS *m/z* 476 (0.57%, [M^+]), 121 (bp);

EI-HRMS calcd for $C_{24}H_{29}O_5{}^{79}Br$ [M^+]: 476.1198, found: 476.1219.

Compound (*R*)-2-26:



2-30 **(*R*)-2-26**

To a solution of **2-30** (87.9 mg, 0.184 mmol) in MeOH (1.0 ml) was added 5 M aq. NaOH (0.5 ml) at 23 °C, and the mixture was stirred for 1.5 h. Then, the mixture was acidified with 1 M aq. HCl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **(*R*)-2-26** (60.8 mg, 0.185 mmol, 100%).

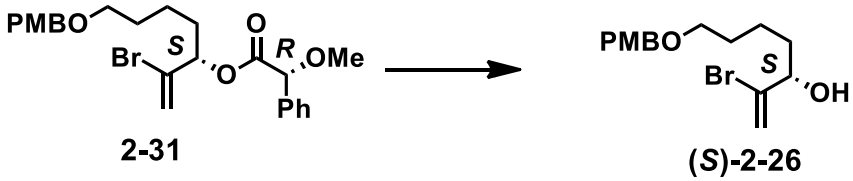
(*R*)-2-26: a colorless oil; $[\alpha]_D^{24}$ –11.2 (*c* 0.14, $CHCl_3$);

IR, ^1H NMR and ^{13}CNMR spectra are identical with those of racemic **2-26**;

EI-LRMS *m/z* 328 (1.4%, [M^+]), 121 (bp);

EI-HRMS *m/z* calcd for $C_{15}H_{21}BrO_3$ ([M^+]) 328.0674, found 328.0696.

Compound (*S*)-2-26:



To a solution of **2-30** (89.5 mg, 0.187 mmol) in MeOH (1.0 ml) was added 5 M aq. NaOH (0.5 ml) at 23 °C, and the mixture was stirred for 1.5 h. Then, the mixture was acidified with 1 M aq. HCl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **(*S*)-2-26** (60.5 mg, 0.184 mmol, 98%).

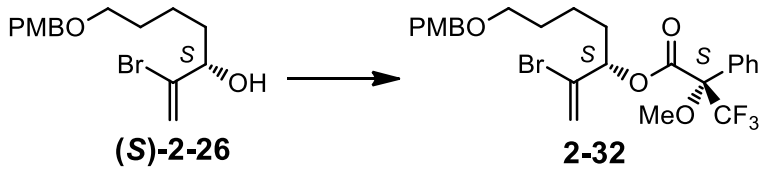
(*S*)-2-26: a colorless oil; $[\alpha]_D^{23}$ +11.1 (*c* 0.14, $CHCl_3$);

IR, ^{1}H NMR and ^{13}CNMR spectra are identical with those of racemic **2-26**;

EI-LRMS *m/z* 328 (1.3%, [M^+]), 121 (bp);

EI-HRMS *m/z* calcd for $C_{15}H_{21}BrO_3$ ([M^+]) 328.0674, found 328.0674.

Compound 2-32:



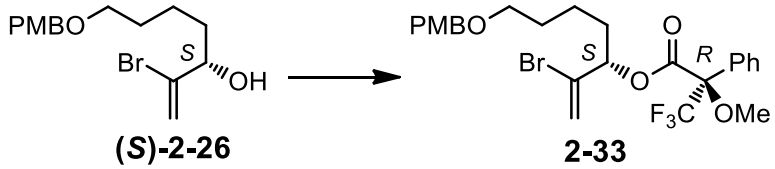
To a solution of **(*S*)-2-26** (3.5 mg, 0.011 mmol) in CH_2Cl_2 (0.3 ml) were added DMAP (a catalytic amount), Et_3N (0.0089 ml, 0.064 mmol), and (–)-(*R*)-MTPACl (0.0030 ml, 0.016 mmol) at 23 °C, and the mixture was stirred for 2 h. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15 → 10) to give **2-32** (3.8 mg, 0.0070 mmol, 64%).

2-32: a colorless oil; $[\alpha]_D^{24}$ –29 (*c* 0.30, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (brqn, *J* = 7.6 Hz, H3'), 1.55 (2H, brqn, *J* = 6.5 Hz, H2'), 1.76 (2H, brq, *J* = 6.6Hz, H4'), 3.36 (2H, t, *J* = 6.4 Hz, H1'), 3.58 (3H, brs, MTPA), 3.80 (3H, s, PMB), 4.40 (2H, s, PMB), 5.44 (1H, t, *J* = 6.8 Hz, H5'), 5.70 (1H, d, *J* = 2.0 Hz, H7'a), 5.99 (1H, d, *J* = 2.0 Hz, H7'b), 6.87 (2H, d, *J* = 8.7 Hz, PMB), 7.24 (2H, d, *J* = 8.7 Hz, PMB), 7.34-7.41 (3H, m, MTPA),

7.50-7.56 (2H, m, MTPA);

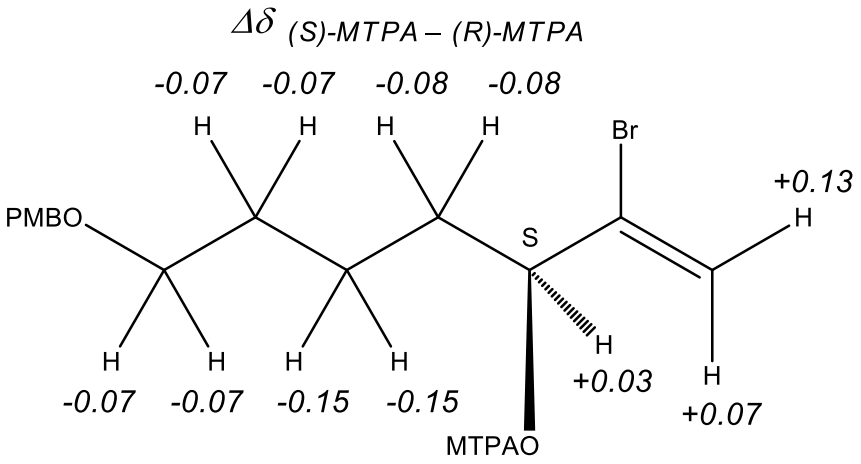
Compound 2-33:



To a solution of **(*S*)-2-26** (3.5 mg, 0.011 mmol) in CH_2Cl_2 (0.3 ml) were added DMAP (a catalytic amount), Et_3N (0.0089 ml, 0.064 mmol), and (+)-(*S*)-MTPACl (0.0030 ml, 0.016 mmol) at 23 °C, and the mixture was stirred for 5 h. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15 → 10) to give **2-33** (4.1 mg, 0.0075 mmol, 68%).

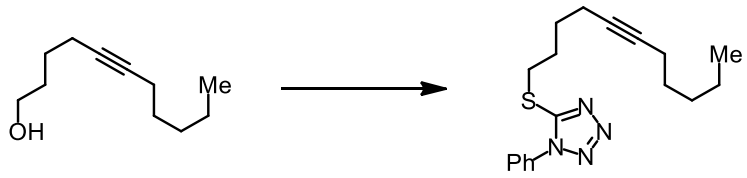
2-33: a colorless oil; $[\alpha]_D^{24}$ +3.0 (*c* 0.50, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36-1.46 [center: 1.41] (2H, m, H3'), 1.62 (2H, brqn, *J* = 6.9 Hz, H2'), 1.84 (2H, td, *J* = 6.7, 8.9 Hz, H4'), 3.43 (2H, t, *J* = 6.3 Hz, H1'), 3.54 (3H, brs, MTPA), 3.80 (3H, s, PMB), 4.41 (2H, s, PMB), 5.41 (1H, t, *J* = 6.6 Hz, H5'), 5.63 (1H, d, *J* = 2.1 Hz, H7'a), 5.86 (1H, d, *J* = 2.1 Hz, H7'b), 6.87 (2H, d, *J* = 8.7 Hz, PMB), 7.24 (2H, d, *J* = 8.7 Hz, PMB), 7.35-7.42 (3H, m, MTPA), 7.48-7.54 (2H, m, MTPA);



The result of modified Mosher's method for **(*S*)-2-26**.

Compound 2-35:



2-34 **2-35**

To a solution of **2-34** (168.5 mg, 1.001 mmol) in THF (10 ml) were added PPh_3 (340.9 mg,1.300 mmol) and PTSH (214.1 mg, 1.201 mmol) at 0 ℃, and the mixture was stirred for 10 min. To the mixture was added DEAD (0.205 ml, 1.30 mmol) at 0 ℃, and the mixture was stirred for 10 min. Then, the mixture was stirred at 23 ℃ for 50 min. Then, the mixture was concentrated directly under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 15) to give **2-35** (223.0 mg, 0.6789 mmol, 68%).

2-35: a coloreless oil;

IR (neat) ν 3062, 2931, 2859, 1598, 1500, 1461, 1454, 1440, 1432, 1426, 1421, 1414, 1403, 1397, 1389, 1386, 1333, 1315, 1295, 1279, 1243, 1089, 1074, 1055, 1014, 761, 694, 686, 665 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz), 1.22-1.40 (4H, m), 1.40-1.53 (2H, m), 1.64 (2H, qn, *J* = 7.3 Hz), 1.95 (2H, qn, *J* = 7.4 Hz), 2.12 (2H, tt, *J* = 2.3, 7.0 Hz), 2.21 (2H, tt, *J* = 2.3, 6.9 Hz), 3.43 (2H, t, *J* = 7.3 Hz), 7.49-7.61 (5H, m);

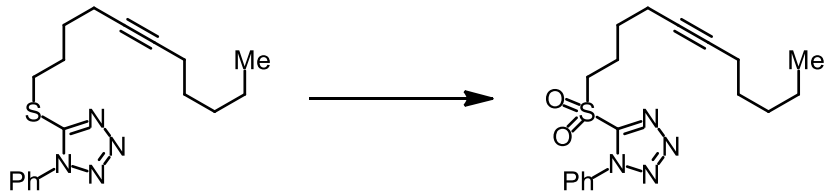
^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.1 (CH_2), 18.5 (CH_2), 22.0 (CH_2), 27.7 (CH_2), 28.0

(CH_2), 28.6 (CH_2), 30.9 (CH_2), 32.7 (CH_2), 78.9 (C), 80.9 (C), 123.6 (CH×2), 129.6 (CH×2), 129.9 (CH), 133.5 (C), 154.2 (C);

EI-LRMS *m/z* 328 (5.8%, [M^+]), 101 (bp);

EI-HRMS calcd for $C_{18}H_{24}N_4S$ [M^+]: 328.1722, found 328.1718.

Compound 2-22:



2-35 **2-22**

To a 30% aq. H_2O_2 solution (ca. 8.8 M, 0.773 ml, 6.82 mmol) was added $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O$(84.3 mg, 0.0682 mmol) at 0 °C, and the mixture was stirred for 10 min. Then, to a solution of **2-35** (224.0 mg, 0.6819 mmol) in EtOH (4.0 ml) was added the above oxidant solution at 0 °C, and the mixture was stirred at 23 °C for 19 h. Then, the reaction was quenched with satd. aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 15 → 10) to give **2-22** (122.6 mg, 0.3401 mmol, 50%).

2-22: a colorless oil;

IR (neat) ν 3069, 2955, 2931, 2871, 2860, 1596, 1497, 1461, 1434, 1407, 1342, 1298, 1268, 1247, 1220, 1201, 1154, 1100, 1076, 1047, 1015, 763, 730, 688, 665, 626 cm^{-1};

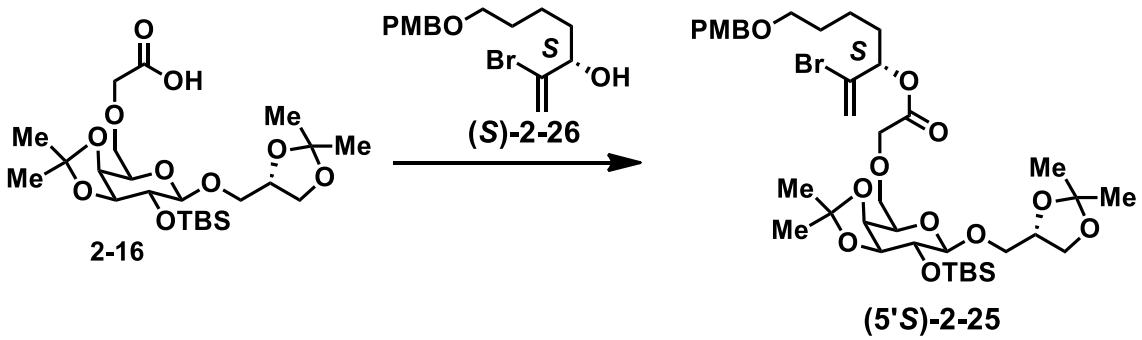
^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, t, *J* = 7.0 Hz), 1.22-1.40 (4H, m), 1.40-1.53 (2H, m), 1.69 (2H, qn, *J* = 7.2 Hz), 2.03-2.16 (4H, m), 2.25 (2H, tt, *J* = 2.3, 6.8 Hz), 3.78 (2H, t, *J* = 7.9 Hz), 7.56-7.73 (5H, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.0 (CH_2), 18.5 (CH_2), 21.0 (CH_2), 22.0 (CH_2), 27.1 (CH_2), 28.5 (CH_2), 30.9 (CH_2), 55.4 (CH_2), 78.1 (C), 81.6 (C), 125.0 (CH×2), 129.5 (CH×2), 131.3 (CH), 132.9 (C), 153.3 (C);

EI-LRMS *m/z* 361 (0.33%, [M+H^+]), 118 (bp);

EI-HRMS calcd for $C_{18}H_{25}N_4O_2S$ [M+H$^+$]: 361.1698, found 361.1727.

Compound (5'*S*)-2-25:



To a solution of **2-16** (10.0 mg, 0.0197 mmol) in CH_2Cl_2 (0.4 ml) were added DMAP (a catalytic amount) and a solution of **(*S*)-2-26** (7.8 mg, 0.024 mmol) in CH_2Cl_2 (0.3 ml) at 23 °C, and the mixture was stirred for 5 min. Then, to the mixture was added EDCI·HCl (7.6 mg, 0.039 mmol) at 23 °C, and the mixture was stirred for 17.5 h. Then, an additional EDCI·HCl (7.6 mg, 0.039 mmol) was added, and the mixture was stirred for 1.5 h. The reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 9 → 5) to give **(5'*S*)-2-25** (11.2 mg, 0.0137 mmol, 70%).

(5'*S*)-2-25: a colorless oil; $[\alpha]_D^{25}$ –3.5 (*c* 0.30, $CHCl_3$);

IR (neat) ν 3103, 3062, 3033, 2985, 2933, 2857, 1760, 1629, 1613, 1586, 1514, 1463, 1381, 1371, 1302, 1248, 1219, 1175, 1128, 1079, 1051, 976, 872, 839, 822, 809, 780, 748, 665 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.30-1.44 (2H, m), 1.31 (3H, s), 1.34 (3H, s), 1.40 (3H, s), 1.47 (3H, s), 1.57-1.69 (2H, m), 1.70-1.84 (2H, m), 3.40-3.54 (2H, m), 3.43 (2H, t, *J* = 6.3 Hz), 3.73-3.83 (2H, m), 3.80 (3H, s), 3.87-4.34 (10H, m), 4.42 (2H, s), 5.29 (1H, t, *J* = 6.7 Hz), 5.64 (1H, brd, *J* = 2.0 Hz), 5.91 (1H, brd, *J* = 2.0 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 7.25 (2H, d, *J* = 8.5 Hz);

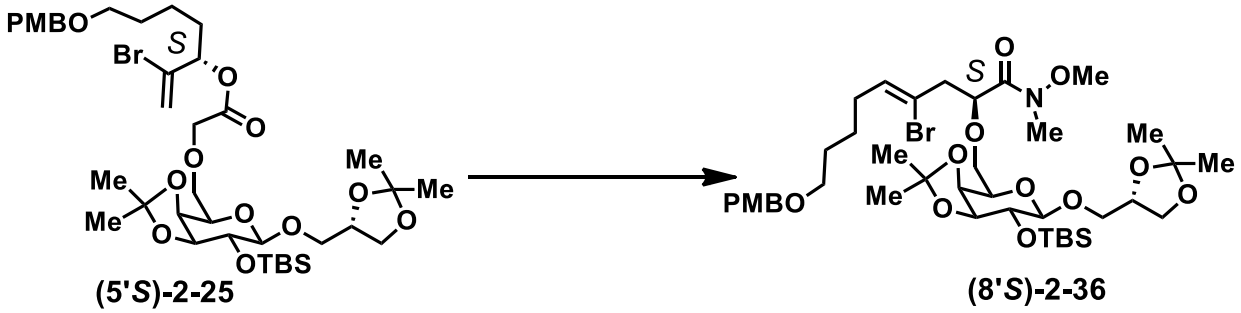
^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7 (CH_3), –4.5 (CH_3), 18.1 (C), 21.6 (CH_2), 25.2 (CH_3), 25.8 (CH_3×3), 26.4 (CH_3), 26.9 (CH_3), 27.9 (CH_3), 29.2 (CH_2), 32.3 (CH_2), 55.2 (CH_3), 67.4 (CH_2), 68.8 (CH_2),

69.5 (CH_2), 70.5 (CH_2), 70.9 (CH_2), 72.3 (CH), 72.5 (CH_2), 73.7 (CH), 74.13 (CH), 74.18 (CH), 76.9 (CH), 80.5 (CH), 103.2 (CH), 109.2 (C), 109.8 (C), 113.7 (CH×2), 120.1 (CH_2), 129.2 (CH×2), 130.5 (C), 131.1 (C), 159.1 (C), 169.4 (C);;

FD-LRMS *m/z* 818 (bp, [M^+: $C_{38}H_{61}O_{12}Si^{81}Br$]), 816 (89%, [$M^+$: $C_{38}H_{61}O_{12}Si^{79}Br$]);

FD-HRMS calcd for $C_{38}H_{61}O_{12}Si^{79}Br$ [M^+]: 816.3116, found 816.3123.

Compound (8'*S*)-2-36:



To a solution of **(5'*S*)-2-25** (28.0 mg, 0.0342 mmol) in THF (1.0 ml) was added TMSCl (0.0130 ml, 0.103 mmol) at –78 °C, and the mixture was stirred for 2 min. To the mixture was added NHMDS (1.09 M in THF, 0.094 ml, 0.102 mmol) at –78 °C, and the mixture was stirred for 10 min. Then, the mixture was warmed to 0 °C and stirred for 10 min. The reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude carboxylic acid {**(8'*S*)-2-23**} was used in the next reaction without further purification.

To a solution of the crude carboxylic acid {**(8'*S*)-2-23**} in CH_2Cl_2 (3 ml) were added DMAP (a catalytic amount) and HNMe(OMe)·HCl (6.7 mg, 0.068 mmol) at 23 °C, and the mixture was stirred for 25 min. To the mixture was added EDCI·HCl (13.1 mg, 0.0684 mmol), and the mixture was stirred for 75 min. Then, additional EDCI·HCl (13.1 mg, 0.0684 mmol) was added, and the mixture was stirred for 195 min. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 3 → 1) to give **(8'*S*)-2-36** (23.6 mg, 0.0274 mmol, 80% for 2 steps).

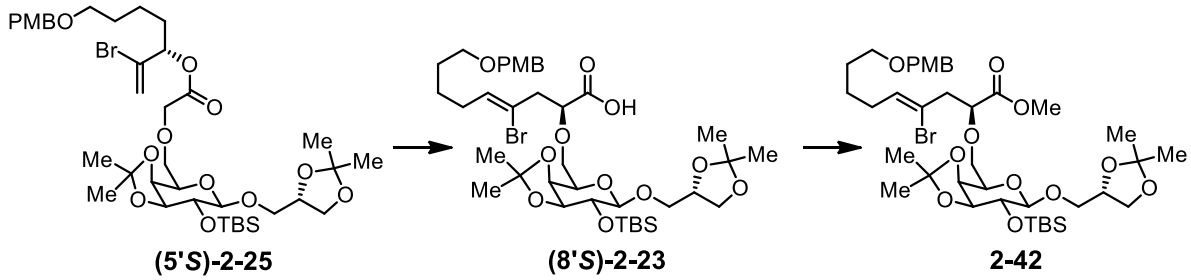
(8'*S*)-2-36: a colorless oil; $[\alpha]_D^{24}$ –2.11 (*c* 1.00, $CHCl_3$);

IR (neat) ν 3062, 2986, 2935, 2857, 1677, 1613, 1514, 1463, 1381, 1371, 1302, 1248, 1219, 1173, 1101, 1042, 989, 874, 839, 809, 780, 756, 666 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s, TBS), 0.10 (3H, s, TBS), 0.89 (9H, s, TBS), 1.29 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.40 (3H, s, acetonide), 1.40-1.53 (2H, m, H3'), 1.48 (3H, s, acetonide), 1.53-1.70 (2H, m, H2'), 2.06-2.27 (2H, m, H4'), 2.76 (1H, dd, *J* = 7.9, 14.3 Hz, H7'a), 2.83 (1H, dd, *J* = 4.8, 14.3 Hz, H7'b), 3.20 (3H, brs, NCH_3), 3.40-3.51 (4H, m, H1', H2", H1'"a), 3.62 (1H, dd, *J* = 7.0, 10.4 Hz, H6"a), 3.74 (3H, s, $NOCH_3$), 3.76-4.00 (5H, m, H3", H5", H6"b, H1'"b, H3'"a), 3.80 (3H, s, OCH_3), 4.03-4.12 (2H, m, H4", H3'"b), 4.15 (1H, d, *J* = 7.9 Hz, H1"), 4.22-4.32 (1H, m, H2'"), 4.42 (2H, s, PMB), 4.66-4.76 (1H, m, H8'), 5.77 (1H, t, *J* = 6.9 Hz, H5'), 6.87 (2H, d, *J* = 8.5 Hz, PMB), 7.25 (2H, d, *J* = 8.5 Hz, PMB);

^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7 (CH_3), –4.6 (CH_3), 18.1 (C), 24.9 (CH_2), 25.2 (CH_3), 25.7 (CH_3×3), 26.3 (CH_3), 26.8 (CH_3), 27.9 (CH_3), 29.1 (CH_2), 31.1 (CH_2), 32.3 (CH_3), 44.3 (CH_2), 55.2 (CH_3), 61.6 (CH_3), 67.4 (CH_2), 69.5 (CH_2), 69.7 (CH_2), 70.3 (CH_2), 72.4 (CH), 72.5 (CH_2), 74.0 (CH), 74.1 (CH), 74.2 (CH), 74.8 (CH), 80.4 (CH), 103.0 (CH), 109.0 (C), 109.7 (C), 113.7 (CH×2), 122.2 (C), 129.1 (CH×2), 130.6 (C), 132.3 (CH), 159.0 (C), 172.0 (C);

Compound 2-42:



To a solution of **(5'*S*)-2-25** (289.7 mg, 0.3542 mmol) in THF (4.0 ml) was added TMSCl (0.134 ml, 1.06 mmol) at –78 °C, and the mixture was stirred for 3 min. To the mixture was added NHMDS (1.09 M in THF, 0.972 ml, 1.06 mmol) at –78 °C, and the mixture was stirred for 7 min. Then, the mixture was warmed to 0 °C and stirred for 10 min. The reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed

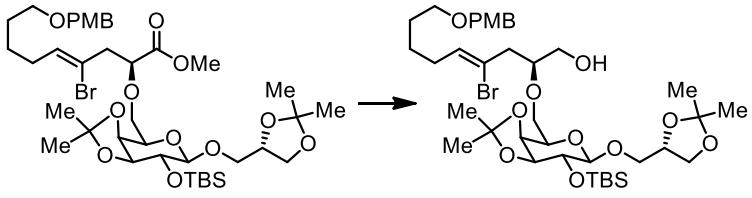
with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude carboxylic acid {**(8'*S*)-2-23**} was used in the next reaction without further purification.

To a solution of the above crude **(8'S)-2-23** in MeOH/CH_2Cl_2 (0.5 ml/0.1 ml) was added $TMSCHN_2$ (2.0 M in Et_2O, 0.354 ml, 0.708 mmol) at 23 °C, and the mixture was stirred for 20 min. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15 → 12 → 5) to give methyl ester **2-42** (228.1 mg, 0.2742 mmol, 77%).

2-42: colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) 0.07 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.30 (3H, s), 1.34 (3H, s), 1.38-1.52 (2H, m), 1.40 (3H, s), 1.47 (3H, s), 1.52-1.68 (2H, m), 2.06-2.27 (2H, m), 2.74-2.89 (2H, m), 3.43 (2H, t, *J* = 6.4 Hz), 3.45-3.52 (2H, m), 3.68 (1H, dd, *J* = 8.4, 12.3 Hz), 3.74 (3H, s), 3.80 (3H, s), 3.81 (1H, dd, *J* = 5.8, 8.2 Hz), 3.86-4.00 (4H, m), 4.02-4.10 (2H, m), 4.16 (1H, d, *J* = 7.7 Hz), 4.22-4.34 (1H, m), 4.34 (1H, dd, *J* = 5.7, 7.5 Hz), 4.42 (2H, s), 5.75 (1H, t, *J* = 6.9 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 7.25 (2H, d, *J* = 8.7 Hz).

Compound 2-43:



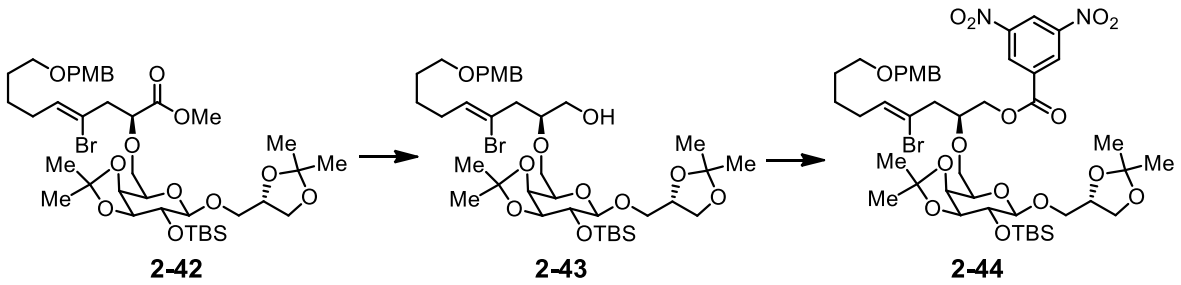
2-42 **2-43**

To a solution of **2-42** (210.6 mg, 0.2532 mmol) in CH_2Cl_2 (4.0 ml) was added DIBALH (0.971 ml, 1.01 mmol) at –10 °C, and the mixture was stirred for 1 h. Then, the reaction was quenched with satd. aq. Rochelle salt, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 8 → 4 → 3 → 1 → EtOAc) to give **2-43** (138.3 mg, 0.1720 mmol, 68%).

2-43: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.34 (3H, s), 1.35 (3H, s), 1.40 (3H, s), 1.43-1.69 (4H, m), 1.50 (3H, s), 2.18 (2H, q, *J* = 7.1 Hz), 2.53 (1H, dd, *J* = 6.3, 14.4 Hz), 2.64 (1H, dd, *J* = 6.9, 14.4 Hz), 3.44 (2H, t, *J* = 6.3 Hz), 3.43-3.55 (2H, m), 3.67-3.94 (7H, m), 3.81 (3H, s), 4.00-4.31 (6H, m), 4.43 (2H, s), 5.73 (1H, t, *J* = 6.8 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 7.26 (2H, d, *J* = 8.7 Hz).

Compound 2-44:



2-42 **2-43** **2-44**

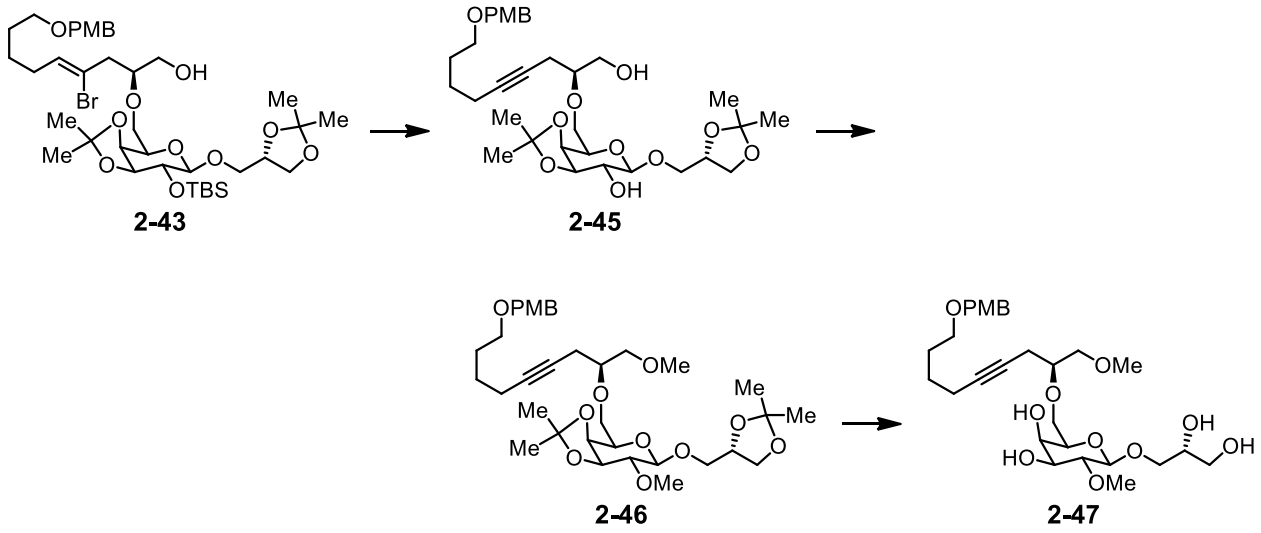
To a solution of **2-42** (74.5 mg, 0.0896 mmol) in THF (2.0 ml) was added $LiAlH_4$ (6.8 mg, 0.18 mmol) at –20 °C, and the mixture was stirred for 35 min. Then, the reaction was quenched with satd. aq. Rochelle salt, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. To a solution of the resulting crude alcohol **2-43** in CH_2Cl_2 (1 ml) were added Et_3N (0.0167 ml, 0.119 mmol) and 3,5-dinitrobenzoyl chloride (20.6 mg, 0.0894 mmol) at 0 °C, and the mixture was stirred for 15 min. Then, after the mixture was diluted with MeOH, the mixture was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 8 → 5) to give **2-44** (40.4 mg, 0.0405 mmol, 45% for 2 steps).

2-44: a pale yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.27 (3H, s), 1.33 (3H, s), 1.39 (3H, s), 1.41-1.68 (4H, m), 1.46 (3H, s), 2.19 (2H, q, *J* = 7.1 Hz), 2.70 (1H, dd, *J* = 7.1, 14.3 Hz), 2.87 (1H, dd, *J* = 6.4, 14.3 Hz), 3.43 (2H, t, *J* = 6.3 Hz), 3.42-3.52 (2H, m), 3.77-3.90 (4H, m), 3.79 (3H, s), 3.98 (1H, dd, *J* = 5.6, 6.5 Hz), 4.05 (1H, dd, *J* = 6.1, 8.4 Hz), 4.07-4.17 (3H, m), 4.16 (1H, d, *J* = 7.7 Hz), 4.21-4.33 (1H, m), 4.38-4.45 (1H, m), 4.01 (2H, s), 4.63 (1H, dd, *J* = 3.6, 11.7 Hz), 5.81

(1H, t, *J* = 6.9 Hz), 6.85 (2H, d, *J* = 8.7 Hz), 7.23 (2H, d, *J* = 8.7 Hz), 9.15 (2H, d, *J* = 2.1 Hz), 9.22 (1H, t, *J* = 2.1 Hz).

Compound 2-47:



To a solution of **2-43** (6.2 mg, 0.0077 mmol) in THF (0.3 ml) was added TBAF·$3H_2O$ (an excess amount) at 23 °C, and the mixture was refluxed for 2 h. Then, the mixture was concentrated in vacuo. The resulting residue was roughly purified by column chromatography (silica gel, hexane/EtOAc = $1 \rightarrow 0.5 \rightarrow 0.3$) to give **2-45** (3.8 mg, 0.0062 mmol, 81%), which was used immediately in the next reaction.

To a solution of the diol **2-45** (3.8 mg, 0.0062 mmol) in THF (0.7 ml) were added NaH (3.0 mg, 0.062 mmol) and MeI (0.0040 ml, 0.062 mmol) at 0 °C, and the mixture was stirred for 4 h. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude **2-46** (ca. 3 mg, ~75%). The crude product was combined with an alternative crude **2-46** (ca. 3 mg) obtained by a similar process, and the combined crude 2-46 (5.8 mg) was used in the next reaction without further purification.

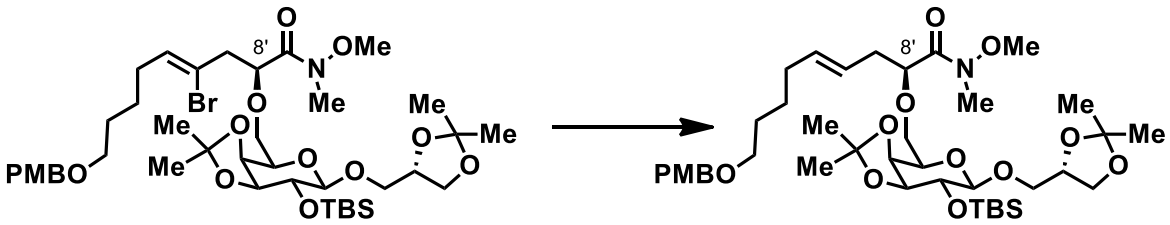
To a solution of crude **2-46** (5.8 mg, 0.0091 mmol) in MeOH (0.2 ml) and CH_2Cl_2 (0.5 ml) was added TFA (0.0067 ml 0.091 mmol) at 23 °C, and the mixture was stirred for 36 h. The mixture was diluted with toluene and concentrated in vacuo. The resulting residue was purified by column

chromatography (silica gel, CH_2Cl_2/MeOH = 20) to give **2-47** (3.8 mg, 0.0068 mmol, 75%).

2-47: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.75 (4H, m), 2.16 (2H, t *J* = 7.0 Hz), 2.32-2.42 (2H, m), 3.38 (3H, s), 3.35-3.98 (11H, m), 3.45 (2H, t, *J* = 6.3 Hz), 3.61 (3H, s), 3.80 (3H, s), 3.98-4.06 (1H, m), 4.24-4.32 (1H, m), 4.43 (2H, s), 6.88 (2H, d, *J* = 8.6 Hz), 7.26 (2H, d, *J* = 8.6 Hz).

Compound (8'*S*)-2-48:



(8'*S*)-2-36 **2-48**

To a solution of **(8'*S*)-2-36** (95.1 mg, 0.110 mmol) in toluene (2.0 ml) were added Bu_3SnH (0.3 ml, 1.13 mmol) and AIBN (20.0 mg, 0.122 mmol) at 23 °C, and the mixture was heated to 110 °C and stirred for 1 h. Then, the mixture was cooled to 23 °C and concentrated in vacuo. The resulting mixture was stirred for 6 days at 23°C. The mixture was directly subjected to column chromatography (silica gel, hexane/EtOAc = 3) to give **2-48** (66.1 mg, 0.0845 mmol, 76%).

2-48: a colorless oil; $[\alpha]_D^{24}$ –1.5 (*c* 0.30, $CHCl_3$);

IR (neat) ν 3061, 2985, 2934, 2857, 1739, 1677, 1613, 1586, 1514, 1463, 1443, 1381, 1371, 1322, 1303, 1248, 1219, 1173, 1101, 1078, 1051, 1006, 990, 973, 875, 839, 822, 809, 780, 746, 665 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s, TBS), 0.10 (3H, s, TBS), 0.89 (9H, s, TBS), 1.29 (3H, s, acetonide), 1.33 (3H, s, acetonide), 1.35-1.51 (2H, m, H3'), 1.40 (3H, s, acetonide), 1.46 (3H, s, acetonide), 1.51-1.70 (2H, m, H2'), 1.94-2.10 (2H, m, H4'), 2.35-2.51 (2H, m, H7'), 3.19 (3H, brs, NCH_3), 3.38-3.52 (4H, m, H1', H2", H1'"a), 3.58 (1H, dd, *J* = 7.7, 10.4 Hz, H6"a), 3.70 (3H, s, $NOCH_3$), 3.76-3.39 (2H, m, H6"b,H3'"a), 3.80 (3H, s, OCH_3), 3.90-4.00 (3H, m, H3", H5", H1'"b), 4.00-4.10 (2H, m, H4", H3'"b), 4.15 (1H, d, *J* = 7.8 Hz, H1"), 4.20-4.43 (2H, m, H8', H2'"), 4.42 (2H, s, PMB), 5.38-5.56 (2H, m, H5', H6'), 6.87 (2H, d, *J* = 8.5 Hz, PMB), 7.25 (2H, d, *J* = 8.5 Hz, PMB);

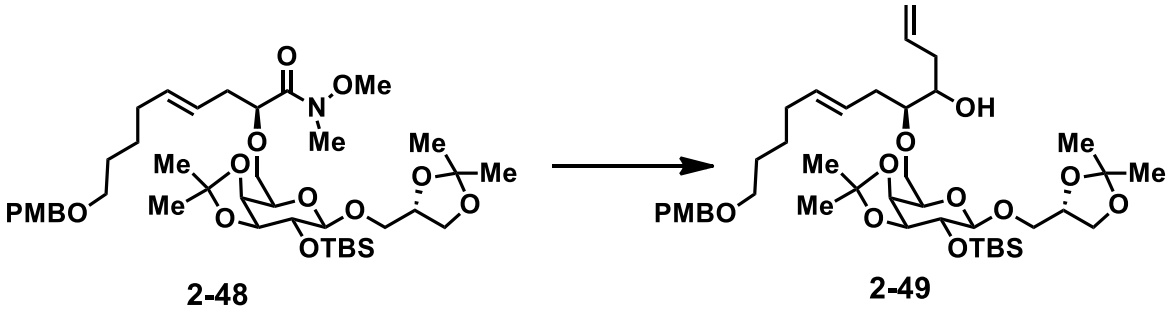
^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7 (CH_3), –4.5 (CH_3), 18.1 (C), 25.3 (CH_3), 25.7 (CH_3×3), 25.9

(CH_2), 26.3 (CH_3), 26.9 (CH_3), 27.1 (CH_2), 27.9 (CH_3), 29.2 (CH_2), 32.3 (CH_3), 35.6 (CH_2), 55.1 (CH_3), 61.4 (CH_3), 67.4 (CH_2), 69.4 (CH_2), 70.4 (CH_2), 72.4 (CH_2), 72.6 (CH), 74.0 (CH), 74.1 (CH), 74.3 (CH), 80.60 (CH), 80.63 (CH), 103.0 (CH), 109.1 (C), 109.3 (C), 113.7 (CH×2), 125.0 (CH), 129.1 (CH×2), 130.7 (C), 133.4 (CH), 159.0 (C), [The signal of the carbonyl carbon was missed.];

FD-LRMS *m/z* 781 (bp, [M^+]);

FD-HRMS calcd for $C_{40}H_{67}NO_{12}Si$ [M^+]: 781.4433, found 781.4418.

Compound (8'*S*)-2-49:



To a solution of **2-48** (38.2 mg, 0.0488 mmol) in THF (2.0 ml) was added $LiAlH_4$ (12.3 mg, 0.342 mmol) at –20 °C, and the mixture was stirred for 45 min. Then, the mixture was stirred at 0 °C for 30 min. After the mixture was diluted with Et_2O and satd. aq. Rochelle salt, the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude aldehyde was immediately used in the next reaction without further purification.

To a solution of the crude aldehyde in THF (1.0 ml) was added allylmagnesium chloride (0.8 M in THF, 0.176 ml, 0.141 mmol) at –20 °C, and the mixture was stirred for 0.5 h. Then, the reaction was quenched with satd. aq. NH_4Cl (2 drops). After the addition of anhydrous $MgSO_4$, the mixture was filtrated through a celite pad and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc=10→5) to give **2-49** (23.0 mg, 0.0301 mmol 62% over 2 steps) as a 1:1 mixture of diastereomers.

2-49: a colorless oil; $[\alpha]_D^{24}$ +1.8 (*c* 0.10, $CHCl_3$) [for a 1:1 mixture of diastereomers];

IR (neat) ν 3492, 3074, 2986, 2933, 2883, 2857, 1613, 1514, 1472, 1463, 1455, 1442, 1381, 1371, 1302, 1248, 1219, 1172, 1103, 1081, 1050, 1042, 870, 839, 780, 665 cm^{-1};

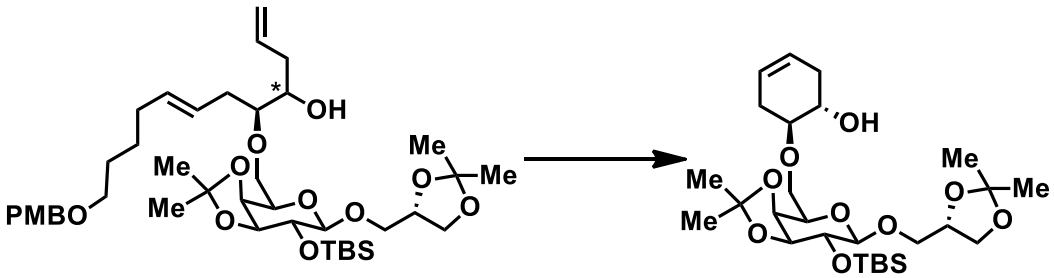
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s, TBS), 0.11 (3H, s, TBS), 0.90 (9H, s, TBS), 1.34 (6H, s, acetonide), 1.36-1.52 (2H, m, H3'), 1.40 (3H, s, acetonide), 1.49 (3H, s, acetonide), 1.52-1.68 (2H, m, H2'), 1.96-2.12 (2H, m, H4'), 2.12-2.44 (4H, m, H7', H10'), 3.32-3.60 (6H, m, H1', H2", H6"a, H8', H1'"a), 3.64-3.93 (5H, m, H9', H3", H6"b, H1'"b, H3'"a), 3.80 (3H, s, OCH_3), 3.97-4.09 (2H, m, H5", H3'"b), 4.13-4.33 (3H, m, H1", H4", H2'"), 4.43 (2H, s, PMB), 5.04-5.15 (2H, m, H12'), 5.35-5.56 (2H, m, H5', H6'), 5.78-5.96 (1H, m, H11'), 6.87 (2H, d, *J* = 8.5 Hz, PMB), 7.26 (2H, d, *J* = 8.5 Hz, PMB);

^{13}C NMR (75 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.5 (CH_3), 18.1 (C), 25.3 (CH_3), 25.8 (CH_3×3), 26.0 (CH_2/2), 26.2 (CH_2/2), 26.38 (CH_3/2), 26.43 (CH_3/2), 26.9 (CH_3), 27.9 (CH_3), 29.2 (CH_2/2), 29.4 (CH_2/2), 32.4 (CH_2), 33.4 (CH_2/2), 33.7 (CH_2/2), 36.2 (CH_2/2), 37.5 (CH_2/2), 55.2 (CH_3), 67.5 (CH_2), 68.77 (CH_2/2), 68.84 (CH_2/2), 69.9 (CH_2), 70.5 (CH_2), 71.2 (CH), 71.5 (CH/2), 72.0 (CH/2), 72.5 (CH_2), 73.5 (CH), 74.2 (CH), 74.24 (CH/2), 74.29 (CH/2), 80.4 (CH), 82.4 (CH/2), 82.9 (CH/2), 103.2 (CH), 109.2 (C), 109.78 (C/2), 109.81 (C/2), 113.7 (CH×2), 117.1 (CH_2/2), 117.2 (CH_2/2), 125.5 (CH/2), 126.1 (CH/2), 129.2 (CH×2), 130.7 (C), 133.0 (CH/2), 133.3 (CH/2), 134.8 (CH/2), 135.3 (CH/2), 159.1 (C);

FD-LRMS *m/z* 764 (bp%, [M^+]);

FD-HRMS calcd for $C_{41}H_{68}O_{11}Si$ [M^+]: 764.4531, found 764.4557.

Compound (8'*S*)-2-51:



2-49 **2-51**

To a solution of **2-49** (23.0 mg, 0.0301 mmol) in CH_2Cl_2 (10 ml) was added a solution of Grubbs' second generation catalyst (**2-50**) (2.2 mg, 0.0026 mmol) in CH_2Cl_2 (5 ml) at refluxing temperature, and the mixture was stirred for 1 h. Then, the mixture was cooled to 23 °C and stirred under air for

30 min. Then, the mixture was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 7 → 5) to give **2-51** (3.5 mg, 0.0064 mmol, 21%) and **9'-*epi*-2-51** (2.3 mg, 0.0042 mmol, 14%).

2-51: a colorless oil:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s, TBS), 0.11 (3H, s, TBS), 0.90 (9H, s, TBS), 1.34 (3H, s, acetonide), 1.36 (3H, s, acetonide), 1.40 (3H, s, acetonide), 1.50 (3H, s, acetonide), 1.94-2.14 (2H, m, H7'a, H10'a), 2.44-2.57 (2H, m, H7'b, H10'b), 3.40 (1H, dt, *J* = 5.7, 9.4 Hz, H8'), 3.44-3.56 (3H, m, H2", H6"a, H1'"a), 3.69-3.98 (5H, m, H9', H5", H6"b, H1'"b, H3'"a), 4.00-4.09 (2H, m, H3", H3'"b), 4.18 (1H, d, *J* = 7.7 Hz, H1"), 4.24-4.33 (1H, m, H2'"), 4.25 (1H, dd, *J* = 1.8, 4.1 Hz, H4"), 5.54 (2H, brs, H6', H11');

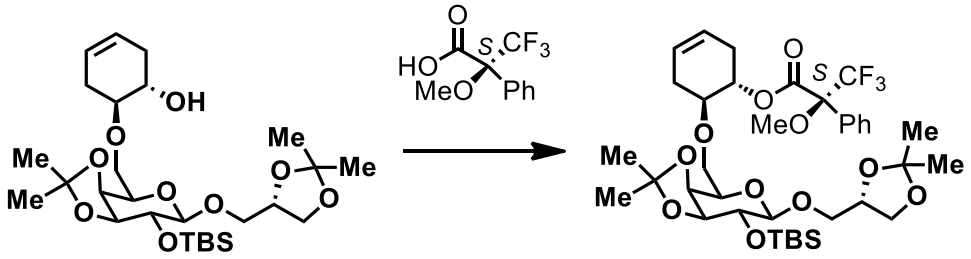
^{13}C NMR (75 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.5 (CH_3), 18.1 (C), 25.3 (CH_3), 25.8 (CH_3×3), 26.3 (CH_3), 26.9 (CH_3), 27.9 (CH_3), 30.8 (CH_2), 32.8 (CH_2), 67.5 (CH_2), 68.4 (CH_2), 70.6 (CH_2), 70.7 (CH), 71.2 (CH), 73.6 (CH), 74.2 (CH×2), 80.5 (CH), 80.7 (CH), 103.3 (CH), 109.2 (C), 109.9 (C), 124.0 (CH), 124.7 (CH);

9'-*epi*-2-51: a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, TBS), 0.11 (3H, s, TBS), 0.90 (9H, s, TBS), 1.34 (3H, s, acetonide), 1.36 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.50 (3H, s, acetonide), 2.20-2.38 (2H, m, H7', H10'), 3.45-3.54 (2H, m, H2", H1'"a), 3.64-3.69 (1H, m, H8'), 3.78-3.97 (5H, m, H5", H6", H1'"b, H3'"a), 4.01-4.09 (3H, m, H7', H3", H3'"b), 4.17 (1H, d, *J* = 7.7 Hz, H1"), 4.24 (1H, dd, *J* = 2.3, 5.7 Hz, H4"), 4.24-4.32 (1H, m, H2'"), 5.57 (2H, brs, H6', H11');

^{13}C NMR (75 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.5 (CH_3), 18.1 (C), 25.3 (CH_3), 25.8 (CH_3×3), 26.4 (CH_3), 26.9 (CH_3), 27.9 (CH_3), 28.5 (CH_2), 31.1 (CH_2), 66.3 (CH), 67.2 (CH_2), 67.5 (CH_2), 70.6 (CH_2), 71.3 (CH), 73.6 (CH), 74.2 (CH×2), 74.3 (CH), 80.5 (CH), 103.3 (CH), 109.2 (C), 109.9 (C), 123.6 (CH), 124.0 (CH);

Compound (*S*)-MTPA-ester 2-52:



2-51 **(*S*)-MTPA-ester 2-52**

To a solution of (*S*)-(–)-2-methoxy-2-trifluoromethylphenylacetic acid [(*S*)-(–)-MTPA] (50.0 mg, 0.214 mmol) in hexane (0.5 ml) was added DMF (1 drop) at 23 °C, and the white suspension was stirred for 10 min. Then, to the mixture was added $(COCl)_2$ (0.050 ml, 0.58 mmol), and the mixture was stirred for 1 h. The resulting mixture was concentrated in vacuo. The residue was dissolved in $CDCl_3$ (0.5 ml), and the resulting MTPACl solution was used immediately in the next reaction. To a solution of **2-51** (3.5 mg, 0.0064 mmol), DMAP (a catalytic amount), and Et_3N (0.050 ml) in $CDCl_3$ (0.5 ml) was added the above MTPACl solution at 0 °C, and the yellow solution was stirred for 18 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 20 → 10→ 4) and HPLC (YMC SIL-06, 150 mm × 4.6 mmID, eluent: hexane/EtOAc = 4) to give **(*S*)-MTPA ester 2-52** (2.3 mg, 0.0033 mmol, 51%).

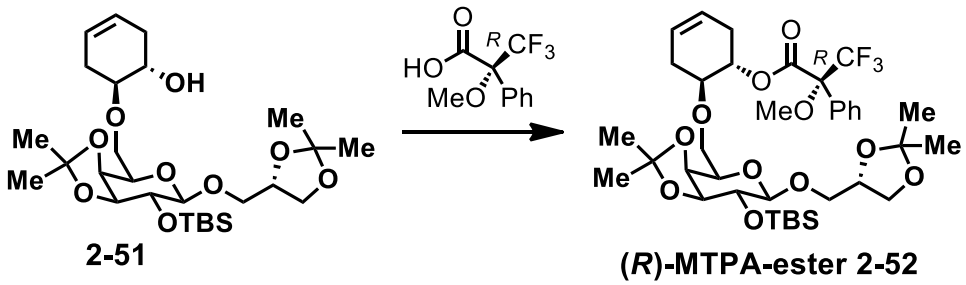
(*S*)-MTPA ester 2-52: a colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07, (3H, s, TBS), 0.11 (3H, s, TBS), 0.90 (9H, s, TBS), 1.24 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.46 (3H, s, acetonide), 2.09 (1H, m, H10'a), 2.16 (1H, m, H7'a), 2.56 (1H, m, H7'b), 2.67 (1H, m, H10'b), 3.48 (1H, dd, *J* = 6.8, 7.7 Hz, H2''), 3.48 (1H, dd, *J* = 7.6, 9.6 Hz, H1'''a), 3.54 (3H, s, OMe), 3.74 (1H, m, H8'), 3.76 (3H, brs, H5'', H6''), 3.81 (1H, dd, *J* = 5.7, 8.4 Hz, H3'''a), 3.90 (1H, dd, *J* = 4.8, 9.6 Hz, H1'''b), 3.92 (1H, dd, *J* = 5.3, 6.8 Hz, H3''), 3.97 (1H, dd, *J* = 1.3, 5.3 Hz, H4''), 4.06 (1H, dd, *J* = 6.1, 8.4 Hz, H3'''b), 4.12 (1H, d, *J* = 7.7 Hz, H1''), 4.28 (1H, m, H2'''), 5.21 (1H, ddd, *J* = 6.0, 8.1, 8.8 Hz, H9'), 5.51 (1H, m, H11'), 5.57 (1H, m, H6'), 7.36-7.43 (3H, m), 7.53-7.58 (2H, m).

FD-LRMS *m/z* 761 (2.0%, $[M+H^+]$), 703 (bp);

FD-HRMS calcd for $C_{37}H_{56}O_{11}F_3Si$ $[M+H^+]$: 761.3544, found 761.3578.

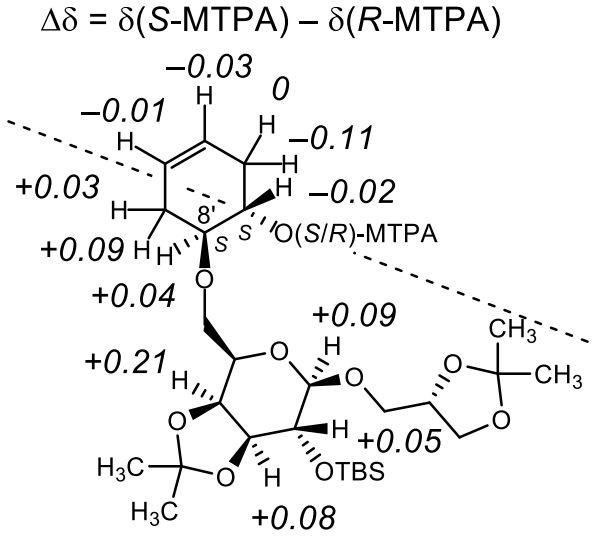
Compound (*R*)-MTPA-ester-2-52:



To a solution of (*R*)-(+)-2-methoxy-2-trifluoromethylphenylacetic acid [(*R*)-(+)-MTPA] (50.0 mg, 0.214 mmol) in hexane (0.5 ml) was added DMF (1 drop) at 23 °C, and the white suspension was stirred for 10 min. Then, to the mixture was added $(COCl)_2$ (0.050 ml, 0.58 mmol), and the mixture was stirred for 1 h. The resulting mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 ml), and the resulting MTPACl solution was used immediately in the next reaction. To a solution of **2-51** (2.2 mg, 0.0040 mmol), DMAP (a catalytic amount), and Et_3N (0.050 ml) in CH_2Cl_2 (0.5 ml) was added the above MTPACl solution at 0 °C, and the yellow solution was stirred for 10 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10→ 1) and HPLC (YMC SIL-06, 150 mm × 4.6 mmID, eluent: hexane/EtOAc = 4) to give **(*R*)-MTPA ester 2-52** (1.8 mg, 0.0025 mmol, 63%).

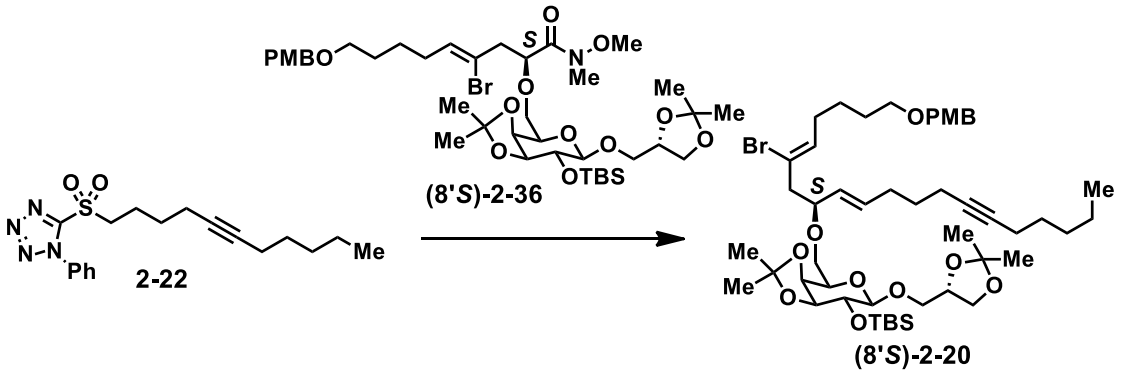
(*R*)-MTPA ester 2-52: a colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06, (3H, s, TBS), 0.10 (3H, s, TBS), 0.90 (9H, s, TBS), 1.25 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.45 (3H, s, acetonide), 2.13 (1H, m, H7'a), 2.20 (1H, m, H10'a),2.47 (1H, m, H7'b), 2.67 (1H, m, H10'b), 3.43 (1H, m, H2''), 3.45 (1H, m, H1'''a), 3.45-3.70 (3H, m, H5'', H6''), 3.59 (3H, s, OMe), 3.70 (1H, m, H8'), 3.76 (1H, m, H4''), 3.81 (1H, m, H3'''a), 3.84 (1H, m, H3''), 3.87 (1H, dd, J = 5.1, 10.1 Hz, H1'''b), 4.03 (1H, d, *J* = 7.9 Hz, H1''), 4.05 (1H, dd, *J* = 6.2, 8.5 Hz, H3'''b), 4.28 (1H, m, H2'''), 5.23 (1H, m, H9'), 5.54 (1H, m, H11'), 5.58 (1H, m, H6'), 7.36-7.43 (3H, m), 7.53-7.58 (2H, m).



The result of modified Mosher's method for **2-51**.

Compound (8'*S*)-2-20:



To a solution of **(8'*S*)-2-36** (23.6 mg, 0.0274 mmol) in THF (0.5 ml) were added $LiAlH_4$ (0.5 mg, 0.014 mmol) at –20 °C, and the mixture was stirred for 45 min. Then, the reaction was quenched with satd. aq. Rochelle salt, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude aldehyde {**(8'*S*)-2-21**} was immediately used in the next reaction without further purification. To a solution of **2-22** (29.6 mg, 0.0821 mmol) in THF (0.5 ml) were added KHMDS (0.5 M in toluene, 0.16 ml, 0.080 mmol) at –78 °C, and the mixture was stirred for 45 min. To the mixture was added a solution of the above crude aldehyde {**(8'*S*)-2-21**} in THF (0.4 ml) at –78 °C, and the mixture was stirred for 1 h. Then, the stirred mixture was allowed to warm to ambient temperature (23 °C) for 1 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 15 → 10 → 5) to give **(8'*S*)-2-20** (12.2 mg, 0.0130 mmol, 47%).

(8'*S*)-2-20: a colorless oil; $[\alpha]_D^{25}$ –10 (*c* 0.15, $CHCl_3$);

IR (neat) ν 3065, 2985, 2931, 2857, 1513, 1462, 1380, 1370, 1302, 1248, 1219, 1172, 1102, 1042, 968, 873, 839, 809, 780, 665 cm^{-1};

^1H NMR (400 MHz, CD_3CN, $C\underline{H}D_2CN$ as 1.93 ppm) δ 0.07 (3H, s, TBS), 0.09 (3H, s, TBS), 0.88 (9H, s, TBS), 0.88 (3H, t, *J* = 7.1 Hz, H20'), 1.26 (3H, s, acetonide), 1.26-1.37 (4H, m, [four protons among H2', H3', H12', H17', H18', and H19']), 1.27 (3H, s, acetonide), 1.33 (3H, s, acetonide), 1.37-1.48 (4H, m, [four protons among H2', H3', H12', H17', H18', and H19']), 1.42 (3H, s, acetonide), 1.48-1.59 (4H, m, [four protons among H2', H3', H12', H17', H18', and H19']), 2.05-2.17 (8H, m, H4', H11', H13', H16'), 2.50 (1H, dd, *J* = 6.7, 14.2 Hz, H7'a), 2.67 (1H, dd, *J* = 6.8, 14.2 Hz, H7'b), 3.37

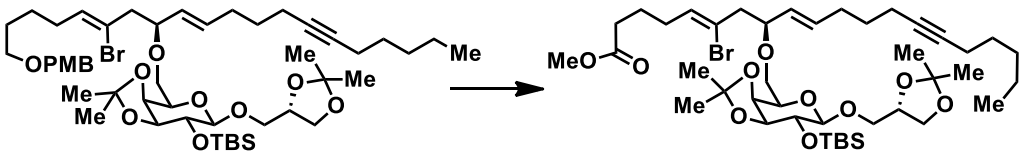
(1H, dd, *J* = 6.7 Hz, 7.9 Hz, H2"), 3.41 (2H, t, *J* = 6.4 Hz, H1'), 3.47 (1H, dd, *J* = 5.9, 10.3 Hz, H1'"a), 3.48 (1H, dd, *J* = 6.8, 10.7 Hz, H6"a), 3.64 (1H, dd, *J* = 5.3, 10.7 Hz, H6"b), 3.65 (1H, dd, *J* = 6.2, 8.3 Hz, H3'"a), 3.76 (3H, s, PMB), 3.80 (1H, dd, *J* = 5.9, 10.3 Hz, H1'"b), 3.84 (1H, ddd, *J* = 2.1, 5.3, 6.8 Hz, H5"), 3.91 (1H, dd, *J* = 5.6, 6.7 Hz, H3"), 4.00 (1H, dd, *J* = 6.4, 8.3 Hz, H3'"b), 4.06 (1H, brq, *J* = 7.1 Hz, H8'), 4.08 (1H, dd, *J* = 2.1, 5.6 Hz, H4"), 4.12 (1H, d, *J* = 7.9 Hz, H1"), 4.23 (1H, brqn, *J* = 6.1 Hz, H2'"), 4.37 (2H, s, PMB), 5.27 (1H, tdd, *J* = 1.3, 8.0, 15.4 Hz, H9'), 5.66 (1H, td, *J* = 7.0, 15.4 Hz, H10'), 5.73 (1H, t, *J* = 7.0 Hz, H5'), 6.88 (2H, d, *J* = 8.7 Hz, PMB), 7.23 (2H, d, *J* = 8.7 Hz, PMB);

^{13}C NMR (75 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.5 (CH_3), 14.0 (CH_3), 18.2 (CH_2 + C), 18.7 (CH_2), 22.2 (CH_2), 25.1 (CH_2), 25.3 (CH_3), 25.8 (CH_3×3), 26.4 (CH_3), 26.9 (CH_3), 28.0 (CH_3), 28.5 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 31.1 (CH_2×2), 31.2 (CH_2), 47.8 (CH_2), 55.3 (CH_3), 67.0 (CH_2), 67.6 (CH_2), 69.8 (CH_2), 70.5 (CH_2), 72.0 (CH), 72.6 (CH_2), 73.9 (CH), 74.2 (CH), 74.4 (CH), 78.8 (CH), 79.6 (C), 80.5 (CH), 80.7 (C), 103.3 (CH), 109.1 (C), 109.6 (C), 113.8 (CH×2), 123.8 (C), 129.2 (CH×2), 129.7 (CH), 130.7 (C), 131.1 (CH), 133.8 (CH), 159.1 (C);

FD-LRMS *m/z* 936 (14.3%, [M^+: $C_{49}H_{79}O_{10}Si^{81}Br$]), 934 (13.2%, [$M^+$: $C_{49}H_{79}O_{10}Si^{79}Br$]), 121 (bp);

FD-HRMS calcd for $C_{49}H_{79}O_{10}Si^{79}Br$ [M^+]: 934.4626, found 934.4599.

Compound (8'*S*)-2-54:



(8'*S*)-2-20 **(8'*S*)-2-54**

To a solution of **(8'*S*)-2-20** (12.2 mg, 0.0130 mmol) in CH_3CN (1.0 ml) were added TEMPO (1.0 mg, 0.0064 mmol) and $PhI(OAc)_2$ (17.0 mg, 0.0528 mmol) at 23 °C, and the mixture was stirred for 5 min. Then, pH 7.0 phosphate buffer (0.1 ml) was added, and the mixture was stirred for 10 min. Then, the mixture was warmed to 45 °C and stirred for 50 min. Then, TEMPO (2.0 mg, 0.0128 mmol) and $PhI(OAc)_2$ (12.6 mg, 0.0391 mmol) was added at the same temperature, and the mixture was stirred for 17.5 h. Then, $PhI(OAc)_2$ (8.4 mg, 0.0260 mmol) was added at the same temperature, and the mixture was stirred for 1.5 h. Then, $PhI(OAc)_2$ (8.4 mg, 0.0260 mmol) was added at the same

temperature, and the mixture was stirred for 45 min. Then, the reaction was quenched with satd. aq. $Na_2S_2O_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. After the resulting residue was dissolved in MeOH/CH_2Cl_2 (0.3 ml/0.1 ml), $TMSCHN_2$ (2 M in Et_2O, 0.039 ml, 0.078 mmol) was added to the solution at 23 °C, and the mixture was stirred for 1.5 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10 → 1) to give **(8'*S*)-2-54** (8.0 mg, 0.0095 mmol, 73%).

(8'*S*)-2-54: a colorless oil; $[\alpha]_D^{25}$ –7.1 (*c* 0.10, $CHCl_3$);

IR (neat) ν 2984, 2929, 2856, 1740, 1461, 1438, 1380, 1370, 1247, 1219, 1165, 1135, 1102, 1082, 1048, 968, 873, 839, 780, 665 cm^{-1};

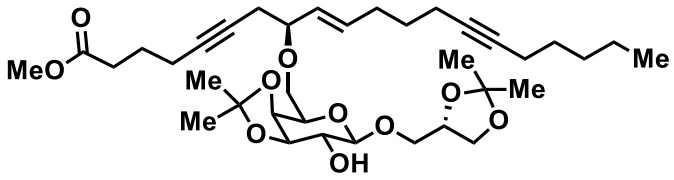
^1H NMR (400 MHz, CD_3CN, $C\underline{H}D_2CN$ as 1.93 ppm) δ 0.07 (3H, s, TBS), 0.09 (3H, s, TBS), 0.88 (9H, s, TBS), 0.88 (3H, t, *J* = 6.7 Hz, H20'), 1.26-1.59 (8H, m, H12', H17', H18', H19'), 1.266 (3H, s, acetonide), 1.274 (3H, s, acetonide), 1.33 (3H, s, acetonide), 1.42 (3H, s, acetonide), 1.65 (2H, qn, *J* = 7.4 Hz, H3'), 2.07-2.18 (8H, m, H4', H11', H13', H16'), 2.29 (2H, t, *J* = 7.5 Hz, H2'), 2.51 (1H, dd, *J* = 6.4, 14.2 Hz, H7'a), 2.68 (1H, dd, *J* = 7.0, 14.2 Hz, H7'b), 3.37 (1H, dd, *J* = 6.7 Hz, 7.9 Hz, H2"), 3.48 (2H, m, H1'"a, H6"a), 3.60 (3H, s, OMe), 3.64 (1H, dd, *J* = 5.4, 10.7 Hz, H6"b), 3.66 (1H, dd, *J* = 6.2, 8.2 Hz, H3'"a), 3.81 (1H, dd, *J* = 5.9, 10.3 Hz, H1'"b), 3.85 (1H, brddd, *J* = 2.0, 5.4, 6.8 Hz, H5"), 3.93 (1H, dd, *J* = 5.6, 6.7 Hz, H3"), 4.00 (1H, dd, *J* = 6.4, 8.2 Hz, H3'"b), 4.07 (1H, brq, *J* = 7.1 Hz, H8'), 4.09 (1H, dd, *J* = 2.0, 5.6 Hz, H4"), 4.13 (1H, d, *J* = 7.9 Hz, H1"), 4.24 (1H, brqn, *J* = 6.1 Hz, H2'"), 5.28 (1H, tdd, *J* = 1.3, 8.0, 15.4 Hz, H9'), 5.67 (1H, td, *J* = 6.9, 15.4 Hz, H10'), 5.73 (1H, t, *J* = 7.0 Hz, H5');

^{13}C NMR (100 MHz, CD_3CN, $CD_3{}^{13}CN$ as 118.2 ppm) δ –4.4 (CH_3), –4.2 (CH_3), 14.2 (CH_3), 18.4 (CH_2), 18.7 (C), 19.0 (CH_2), 22.8 (CH_2), 24.3 (CH_2), 25.5 (CH_3), 26.1 (CH_3×3), 26.6 (CH_3), 27.1 (CH_3), 28.4 (CH_3), 29.2 (CH_2), 29.5 (CH_2), 31.2 (CH_2), 31.69 (CH_2), 31.73 (CH_2), 33.6 (CH_2), 48.3 (CH_2), 51.9 (CH_3), 67.5 (CH_2), 67.8 (CH_2), 71.2 (CH_2), 72.9 (CH), 74.9 (CH), 75.3 (CH), 75.7 (CH), 79.5 (CH), 80.5 (C), 81.3 (CH), 81.4 (C), 103.6 (CH), 109.8 (C), 110.2 (C), 125.3 (C), 130.9 (CH), 131.4 (CH), 134.7 (CH), 174.4 (C);

FD-LRMS *m/z* 844 (22.8%, [M^+: $C_{42}H_{71}O_{10}Si^{81}Br$]), 842 (23.8%, [$M^+$: $C_{42}H_{71}O_{10}Si^{79}Br$]), 57 (bp);

FD-HRMS calcd for $C_{42}H_{71}O_{10}Si^{79}Br$ [M^+]: 842.4000, found 842.4011.

Compound (8'*S*)-2-55:



(8'*S*)-2-55

To a solution of **(8'*S*)-2-54** (6.0 mg, 0.0071 mmol) in DMF (0.3 ml) was added TBAF·$3H_2O$ (9.1 mg, 0.029 mmol) at 75 °C, and the mixture was stirred for 3 h. Then, the mixture was diluted with a 1:1 mixture of hexane and EtOAc and acidified with 0.1 M HCl. The mixture was extracted with a 1:1 mixture of hexane and EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Because partial hydrolysis of the methyl ester was observed, the resulting residue was dissolved in methanol (ca. 1 ml) and was treated with $TMSCHN_2$ (2 M in Et_2O). The reaction mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 1→ EtOAc) to give **(8'*S*)-2-55** (2.2 mg, 0.0034 mmol, 48%).

(8'*S*)-2-55: a colorless oil; $[\alpha]_D^{26}$ –7.0 (*c* 0.050, $CHCl_3$);

IR (neat) ν 3451, 2983, 2931, 2859, 1738, 1455, 1435, 1380, 1371, 1246, 1218, 1164, 1077, 968, 933, 873, 844, 689, 665 cm^{-1};

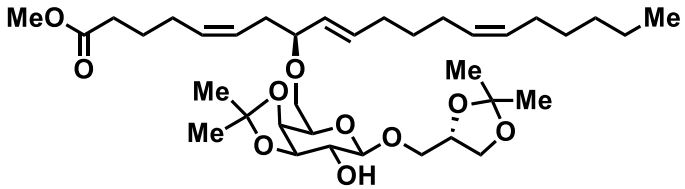
^1H NMR (400 MHz, CD_3CN, $C\underline{H}D_2CN$ as 1.93 ppm) δ 0.88 (3H, t, *J* = 7.1 Hz, H20'), 1.25-1.59 (8H, m, H12', H17', H18', H19'), 1.27 (3H, s, acetonide), 1.29 (3H, s, acetonide), 1.35 (3H, s, acetonide), 1.42 (3H, s, acetonide), 1.70 (2H, qn, *J* = 7.2 Hz, H3'), 2.08-2.34 (10H, m, H4', H7', H11', H13', H16'), 2.38 (2H, t, *J* = 7.4 Hz, H2'), 3.26-3.31 (1H, m, H2''), 3.50 (1H, dd, *J* = 7.3, 10.5 Hz, H6''a), 3.52 (1H, dd, *J* = 5.7, 10.5 Hz, H1'''a), 3.61 (3H, s, OMe), 3.65 (1H, dd, *J* = 5.2, 10.5 Hz, H6''b), 3.71 (1H, dd, *J* = 6.1, 8.3 Hz, H3'''a), 3.80 (1H, dd, *J* = 5.8, 10.5 Hz, H1'''b), 3.81-3.89 (2H, m, H8', H5''), 3.93 (1H, dd, *J* = 5.4, 7.0 Hz, H3''), 4.02 (1H, dd, *J* = 6.4, 8.3 Hz, H3'''b), 4.10 (1H, dd, *J* = 2.1, 5.4 Hz, H4''), 4.16 (1H, d, *J* = 8.0 Hz, H1''), 4.21-4.28 (1H, m, H2'''), 5.36 (1H, brdd, *J* = 7.6, 15.6 Hz, H9'), 5.69 (1H, td, *J* = 6.9, 15.6 Hz, H10');

^{13}C NMR (100 MHz, CD_3CN, $CD_3{}^{13}CN$ as 118.2 ppm) δ 14.2 (CH_3), 18.4 (CH_2), 18.5 (CH_2), 19.0 (CH_2), 22.8 (CH_2), 25.1 (CH_2), 25.5 (CH_3), 26.5 (CH_3), 26.6 (CH_2), 27.0 (CH_3), 28.3 (CH_3), 29.3 (CH_2), 29.5 (CH_2), 31.68 (CH_2), 31.74 (CH_2), 33.3 (CH_2), 51.9 (CH_3), 67.1 (CH_2), 67.9 (CH_2), 70.9 (CH_2), 73.0 (CH), 74.1 (CH), 74.6 (CH), 75.3 (CH), 78.4 (C), 80.0 (CH), 80.3 (CH), 80.6 (C), 81.4 (C), 81.5 (C), 103.7 (CH), 109.9 (C), 110.1 (C), 131.1 (CH), 134.4 (CH), 174.3 (C);

FD-LRMS *m/z* 649 (84.4%, [M+H$^+$]), 43 (bp);

FD-HRMS calcd for $C_{36}H_{57}O_{10}$ [M+H$^+$]: 649.3952, found 649.3993.

Compound (8'*S*)-2-56:



(8'*S*)-2-56

To a solution of **(8'*S*)-2-55** (2.2 mg, 0.0034 mmol) and 1-hexene (0.050 ml, 0.40 mmol) in MeOH (1.0 ml) was added Lindlar catalyst (2.2 mg) at 23 °C, and the mixture was stirred for 24.5 h under H_2 atmosphere. The mixture was filtered through a celite pad and concentrated in vacuo to give almost pure **(8'*S*)-2-56** (2.2 mg, 0.0034 mmol, 100%).

(8'*S*)-2-56: a colorless oil; $[\alpha]_D^{22}$ +4.5 (*c* 0.10, $CHCl_3$);

IR (neat) ν 3447, 2925, 1740, 1457, 1437, 1380, 1370, 1245, 1219, 1164, 1075, 969, 872, 845, 665 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, H20'), 1.22-1.73 (10H, m, H3', H12', H17', H18', H19'), 1.35 (3H, s, acetonide), 1.36 (3H, s, acetonide), 1.43 (3H, s, acetonide), 1.52 (3H, s, acetonide), 1.93-2.11 (9H, m, H4', H7'a, H11', H13', H16'), 2.26-2.35 (3H, m, H2', H7'b), 3.53-3.68 (3H, m, H2", H6"a, H1'"a), 3.66 (3H, s, OMe), 3.74 (1H, dd, *J* = 5.8, 9.8 Hz, H6"b), 3.82 (1H, dd, *J* = 6.0, 8.3 Hz, H3'"a), 3.82-3.91 (2H, m, H8', H5"), 3.93 (1H, dd, *J* = 5.2, 10.7 Hz, H1'"b), 4.02-4.08 (2H, m, H3", H3'"b), 4.18-4.21 (1H, m, H4"), 4.20 (1H, d, *J* = 8.2 Hz, H1"), 4.27-4.34 (1H, m, H2'"), 5.24-5.46 (5H, m, H5', H6', H9', H14', H15'), 5.58-5.67 (1H, m, H10');

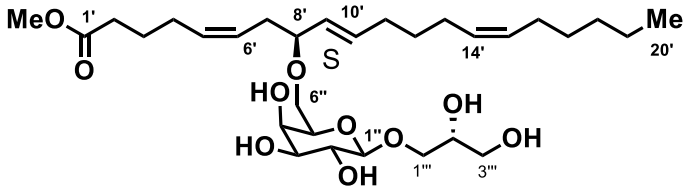
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 24.7 (CH_2), 25.2 (CH_3), 26.3 (CH_3), 26.6

(CH_3), 26.7 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 28.2 (CH_3), 31.5 (CH_2), 31.8 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 33.6 (CH_2), 51.5 (CH_3), 66.3 (CH_2), 66.8 (CH_2), 69.8 (CH_2), 72.3 (CH), 73.5 (CH), 73.6 (CH), 74.4 (CH), 78.5 (CH), 81.4 (CH), 102.9 (CH), 109.5 (C), 110.0 (C), 126.6 (CH), 129.2 (CH), 130.1 (CH), 130.2 (CH), 130.4 (CH), 134.0 (CH), 174.0 (C);

FD-LRMS *m/z* 652 (3.2%, [M^+]), 242 (bp);

FD-HRMS calcd for $C_{36}H_{60}O_{10}$ [M^+]: 652.4187, found 652.4198.

Compound (8'*S*,2'''*R*)-1-5:



(8'*S*, 2'''*R*)-1-5

To a solution of **(8'*S*)-2-56** (2.2 mg, 0.0034 mmol) in MeOH (0.4 ml) and CH_2Cl_2 (0.2 ml) was added TFA (0.0192 ml, 0.169 mmol) at 23 °C, and the mixture was stirred for 7 h. The mixture was diluted with toluene and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 10 → 5) to give **(8'*S*,2'''*R*)-1-5** (1.0 mg, 0.0017 mmol, 50%).

(8'*S*, 2'''*R*)-1-5: a pale yellow oil; $[\alpha]_D^{23}$ –2.2 (*c* 0.10, $CHCl_3$);

IR (neat) ν 3406, 2925, 2855, 1731 cm^{-1};

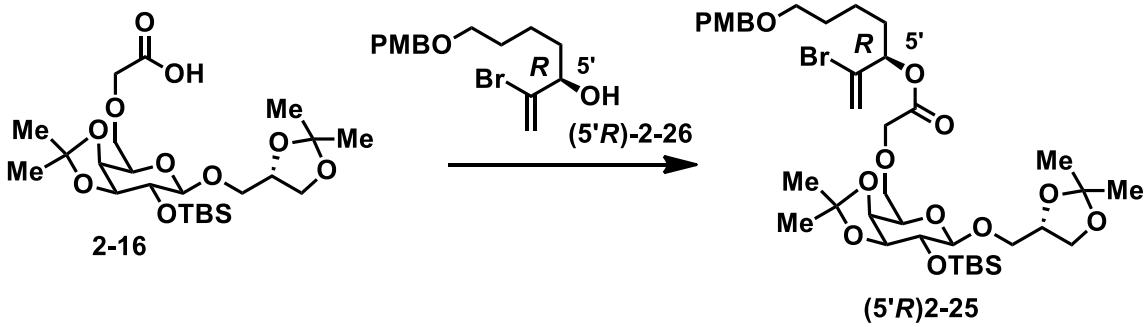
^{1}H NMR (400 MHz, C_6D_6/DMSO-d_6 [25:2], C_6HD_5 as 7.15 ppm) δ 0.86 (3H, t, *J* = 7.0 Hz, H20'), 1.30 (2H, m, H18'), 1.30 (2H, m, H19'), 1.32 (2H, m, H17'), 1.39 (2H, m, H12'), 1.61 (2H, m, H3'), 1.97 (2H, m, H11'), 1.99 (2H, m, H4'), 2.03 (2H, m, H13'), 2.03 (2H, m, H16'), 2.14 (2H, t, *J* = 7.6 Hz, H2'), 2.30 (1H, m, H7'a), 2.47 (1H, m, H7'b), 3.40 (3H, s, OMe), 3.65 (1H, m, H5''), 3.68 (1H, m, H3''), 3.73 (1H, m, H6''a), 3.75 (1H, m, H8'), 3.87 (2H, m, H3'''), 3.95 (1H, m, H6''b), 3.95 (1H, m, H1'''a), 3.97 (1H, m, H2''), 3.98 (1H, m, H4''), 4.08 (1H, m, H2'''), 4.14 (1H, m, H1'''b), 4.41 (1H, d, *J* = 7.6 Hz, H1''), 5.40 (1H, m, H5'), 5.40 (1H, m, H9'), 5.40 (1H, m, H14'), 5.40 (1H, m, H15'), 5.57 (1H, m, H10'), 5.61 (1H, m, H6') [Chemical shifts are shown as exact values derived from 1D, COSY, HSQC, and HMBC measurements.];

^{13}C NMR (100 MHz, C_6D_6/DMSO-d_6 [25:2], C_6D_6 as 128.0 ppm) δ 14.25 (CH_3, C20'), 22.87 (CH_2, C19'), 25.05 (CH_2, C3'), 26.99 (CH_2, C4'), 27.08 (CH_2, C13'), 27.51 (CH_2, C16'), 29.62 (CH_2, C12'), 29.69 (CH_2, C17'), 31.75 (CH_2, C18'), 32.09 (CH_2, C11'), 33.39 (CH_2, C2'), 34.26 (CH_2, C7'), 51.05 (CH_3, OMe), 64.06 (CH_2, C3'''), 68.14 (CH_2, C6''), 69.62 (CH, C4''), 71.64 (CH, C2'''), 71.98 (CH, C2''), 72.39 (CH_2, C1'''), 74.51 (CH, C3''), 74.78 (CH, C5''), 81.38 (CH, C8'), 105.05 (CH, C1''), 127.19 (CH, C6'), 129.77 (CH, C14'), 130.30 (CH, C5'), 130.40 (CH, C15'), 131.33 (CH, C9'), 133.57 (CH, C10'), 173.46 (C, C1');

FD-LRMS *m/z* 595 (bp, [M+Na^+]);

FD-HRMS calcd for $C_{30}H_{52}O_{10}Na$ [M+Na^+]: 595.3458, found: 595.3463.

Compound (5'*R*)-2-25:



To a solution of **2-16** (38.8 mg, 0.0766 mmol) in CH_2Cl_2 (1.0 ml) were added DMAP (a catalytic amount) and a solution of **(*R*)-2-26** (21.0 mg, 0.0638 mmol) in CH_2Cl_2 (0.3 ml) at 23 ℃, and the mixture was stirred for 5 min. Then, to the mixture was added EDCI·HCl (24.5 mg, 0.128 mmol) at 23 ℃, and the mixture was stirred for 16 h. The reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 7 → 5) to give **(5'*R*)-2-25** (34.5 mg, 0.0422 mmol, 66%).

(5'R)-2-25: a colorless oil;

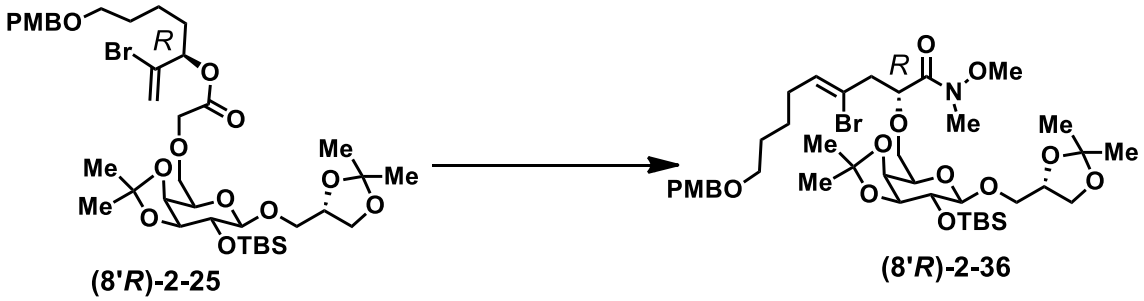
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.32 (3H, s), 1.33-1.43 (2H, m), 1.34 (3H, s), 1.40 (3H, s), 1.48 (3H, s), 1.57-1.69 (2H, m), 1.70-1.84 (2H, m), 3.43 (2H, t, *J* = 6.4 Hz), 3.43-3.53 (2H, m), 3.73-3.83 (2H, m), 3.80 (3H, s), 3.87-4.34 (10H, m), 4.42 (2H, s), 5.29 (1H,

t, *J* = 6.7 Hz), 5.64 (1H, brd, *J* = 2.1 Hz), 5.91 (1H, brd, *J* = 2.1 Hz), 6.88 (2H, d, *J* = 8.6 Hz), 7.25 (2H, d, *J* = 8.6 Hz);

FD-LRMS *m/z* 818 (bp, [M^+: $C_{38}H_{61}O_{12}Si^{81}Br$]), 816 (82.0%, [$M^+$: $C_{38}H_{61}O_{12}Si^{79}Br$]);

FD-HRMS calcd for $C_{38}H_{61}O_{12}Si^{79}Br$ [M^+]: 816.3116, found 816.3120.

Compound (8'*R*)-2-36:



To a solution of **(5'*R*)-2-25** (78.8 mg, 0.0963 mmol) in THF (1.4 ml) was added TMSCl (0.0370 ml, 0.293 mmol) at –78 °C, and the mixture was stirred for 2 min. To the mixture was added KHMDS (0.5 M in toluene, 0.578 ml, 0.289 mmol) at –78 °C, and the mixture was stirred for 20 min. Then, the mixture was warmed to 0 °C and stirred for 5 min. The reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude carboxylic acid {**(8'*R*)-2-23**} was used in the next reaction without further purification.

To a solution of the crude carboxylic acid {**(8'*R*)-2-23**} in CH_2Cl_2 (1.0 ml) were added DMAP (a catalytic amount), HNMe(OMe)·HCl (28.1 mg, 0.289 mmol), and $NaHCO_3$ (solid, a small amount) at 23 °C, and the mixture was stirred for 5 min. To the mixture was added EDCI·HCl (55.3 mg, 0.288 mmol), and the mixture was stirred for 3.5 h. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 8 → 3) to give **(8'*R*)-2-36** (55.9 mg, 0.0649 mmol, 67% for 2 steps).

(8'*R*)-2-36: a colorless oil; $[\alpha]_D^{22}$ +3.18 (*c* 3.00, $CHCl_3$);

IR (neat) ν IR (neat) ν 3062, 3033, 2986, 2934, 2857, 1677, 1613, 1514, 1463, 1421, 1381, 1371,

1248, 1219, 1173, 1100, 1041, 989, 872, 839, 809, 780, 665 cm^{-1};

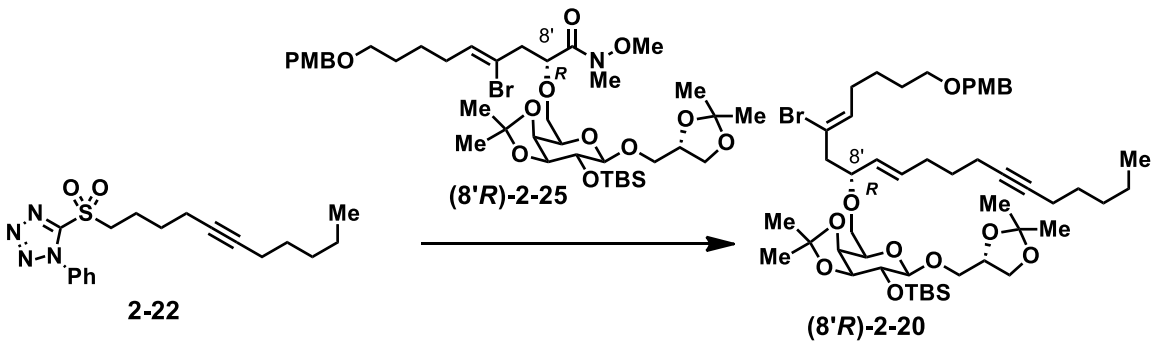
^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s, TBS), 0.10 (3H, s, TBS), 0.89 (9H, s, TBS), 1.33 (6H, s, acetonide), 1.40-1.50 (2H, m, H3'), 1.40 (3H, s, acetonide), 1.48 (3H, s, acetonide), 1.54-1.65 (2H, m, H2'), 2.07-2.23 (2H, m, H4'), 2.74 (1H, dd, *J* = 8.0, 14.4 Hz, H7'a), 2.82 (1H, dd, *J* = 4.6, 14.4 Hz, H7'b), 3.21 (3H, brs, NCH_3), 3.42 (2H, t, *J* = 6.4 Hz, H1'), 3.44 (1H, dd, *J* = 7.6, 10.1 Hz, H1'"a), 3.48 (1H, dd, *J* = 6.8, 7.7 Hz, H2"), 3.67 (1H, dd, *J* = 7.7, 9.2 Hz, H6"a), 3.75 (3H, s, $NOCH_3$), 3.78 (1H, dd, *J* = 5.7, 8.4 Hz, H3'"a), 3.79 (1H, dd, *J* = 5.4, 9.2 Hz, H6"b), 3.80 (3H, s, OCH_3), 3.87 (1H, dd, *J* = 4.6, 10.1 Hz, H1'"b), 3.87 (1H, ddd, *J* = 2.4, 5.4, 7.7 Hz, H5"), 3.97 (1H, dd, *J* = 5.4, 6.8 Hz, H3"), 4.04 (1H, dd, *J* = 6.1, 8.4 Hz, H3'"b), 4.12 (1H, d, *J* = 7.7 Hz, H1"), 4.15 (1H, dd, *J* = 2.4, 5.4 Hz, H4"), 4.23-4.30 (1H, m, H2'"), 4.42 (2H, s, PMB), 4.58-4.67 (1H, m, H8'), 5.75 (1H, t, *J* = 6.8 Hz, H5'), 6.87 (2H, d, *J* = 8.7 Hz, PMB), 7.25 (2H, d, *J* = 8.7 Hz, PMB);

^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7 (CH_3), –4.5 (CH_3), 18.1 (C), 24.9 (CH_2), 25.3 (CH_3), 25.8 (CH_3×3), 26.6 (CH_3), 26.9 (CH_3), 28.0 (CH_3), 29.2 (CH_2), 31.2 (CH_2), 32.3 (CH_3), 44.3 (CH_2), 55.2 (CH_3), 61.6 (CH_3), 67.5 (CH_2), 68.6 (CH_2), 69.7 (CH_2), 70.4 (CH_2), 71.4 (CH), 72.5 (CH_2), 73.3 (CH), 74.1 (CH), 74.3 (CH), 75.1 (CH), 80.3 (CH), 103.3 (CH), 109.1 (C), 109.5 (C), 113.7 (CH×2), 122.3 (C), 129.2 (CH×2), 130.6 (C), 132.2 (CH), 159.1 (C), 171.8 (C);

FD-LRMS *m/z* 861 (bp, [M^+: $C_{40}H_{66}NO_{12}Si^{81}Br$]), 859 (79.1%, [$M^+$: $C_{40}H_{66}NO_{12}Si^{79}Br$]);

FD-HRMS calcd for $C_{40}H_{66}NO_{12}Si^{79}Br$ [M^+]: 859.3538, found 859.3515.

Compound (8'*R*)-2-20:



To a solution of **(8'*R*)-2-36** (21.2 mg, 0.0246 mmol) in THF (0.5 ml) were added $LiAlH_4$ (1.0 mg, 0.026 mmol) at –20 °C, and the mixture was stirred for 5 min. Then, the reaction mixture was warmed

to 0 °C and stirred for 25 min. Then, the reaction was quenched with satd. aq. Rochelle salt, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude aldehyde {**(8'*R*)-2-21**} was immediately used in the next reaction without further purification.

To a solution of **2-22** (19.1 mg, 0.0527 mmol) in THF (0.3 ml) were added KHMDS (0.5 M in toluene, 0.105 ml, 0.0525 mmol) at –78 °C, and the mixture was stirred for 45 min. To the mixture was added a solution of the above crude aldehyde {**(8'*R*)-2-21**} in THF (0.3 ml) at –78 °C, and the mixture was stirred for 10 min. Then, the stirred mixture was allowed to warm to ambient temperature (23 °C) for 3.5 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 1) to give **(8'*R*)-2-20** (14.5 mg, 0.0155 mmol, 63% over 2 steps).

(8'*R*)-2-20: a colorless oil; $[\alpha]_D^{23}$ +5.1 (*c* 0.30, $CHCl_3$);

IR (neat) ν 3065, 2985, 2931, 2857, 1513, 1462, 1380, 1370, 1302, 1248, 1219, 1172, 1102, 1042, 968, 873, 839, 809, 780, 665 cm^{-1};

^1H NMR (400 MHz, CD_3CN, $C\underline{H}D_2CN$ as 1.93 ppm) δ 0.06 (3H, s, TBS), 0.09 (3H, s, TBS), 0.88 (9H, s, TBS), 0.88 (3H, t, *J* = 7.1 Hz, H20'), 1.270 (3H, s, acetonide), 1.273 (3H, s, acetonide), 1.25-1.59 (12H, m, H2', H3', H12', H17', H18', H19'), 1.33 (3H, s, acetonide), 1.42 (3H, s, acetonide), 2.06-2.15 (8H, m, H4', H11', H13', H16'), 2.50 (1H, dd, *J* = 6.5, 14.2 Hz, H7'a), 2.67 (1H, dd, *J* = 6.8, 14.2 Hz, H7'b), 3.36 (1H, dd, *J* = 6.8 Hz, 7.9 Hz, H2''), 3.41 (2H, t, *J* = 6.4 Hz, H1'), 3.47 (1H, dd, *J* = 6.2, 10.4 Hz, H1'''a), 3.50 (1H, dd, *J* = 5.4, 10.3 Hz, H6''a), 3.59 (1H, dd, *J* = 6.9, 10.3 Hz, H6''b), 3.66 (1H, dd, *J* = 6.1, 8.3 Hz, H3'''a), 3.76 (1H, dd, *J* = 5.9, 10.3 Hz, H1'''b), 3.76 (3H, s, PMB), 3.83 (1H, ddd, *J* = 2.1, 5.4, 6.9 Hz, H5''), 3.92 (1H, dd, *J* = 5.6, 6.8 Hz, H3''), 4.00 (1H, dd, *J* = 6.4, 8.3 Hz, H3'''b), 4.00 (1H, brq, *J* = 7.2 Hz, H8'), 4.08 (1H, dd, *J* = 2.1, 5.6 Hz, H4''), 4.11 (1H, d, *J* = 7.9 Hz, H1''), 4.23 (1H, brqn, *J* = 6.1 Hz, H2'''), 4.37 (2H, s, PMB), 5.28 (1H, tdd, *J* = 1.3, 8.0, 15.4 Hz, H9'), 5.67 (1H, td, *J* = 7.0, 15.4 Hz, H10'), 5.72 (1H, t, *J* = 7.0 Hz, H5'), 6.88 (2H, d, *J* = 8.7 Hz, PMB), 7.23 (2H, d, *J* = 8.7 Hz, PMB);

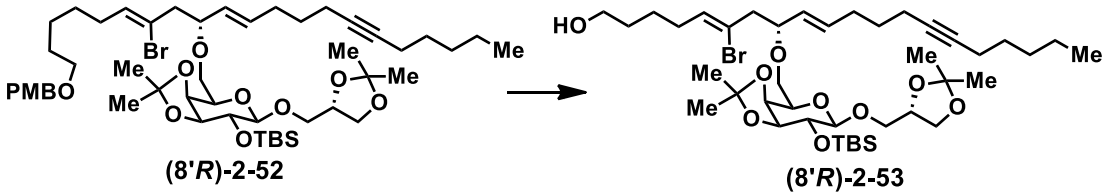
^{13}C NMR (100 MHz, CD_3CN, $CD_3{}^{13}CN$ as 118.2 ppm) δ –4.4 (CH_3), –4.2 (CH_3), 14.3 (CH_3), 18.4

(CH_2), 18.7 (C), 19.1 (CH_2), 22.8 (CH_2), 25.6 (CH_3), 25.7 (CH_2), 26.1 (CH_3×3), 26.7 (CH_3), 27.1 (CH_3), 28.4 (CH_3), 29.2 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 31.69 (CH_2×2), 31.73 (CH_2), 48.2 (CH_2), 55.8 (CH_3), 67.5 (CH_2), 68.0 (CH_2), 70.4 (CH_2), 71.2 (CH_2), 72.4 (CH), 72.9 (CH_2), 74.9 (CH), 75.2 (CH), 75.7 (CH), 79.5 (CH), 80.5 (C), 81.4 (CH + C), 103.7 (CH), 109.8 (C), 110.2 (C), 114.5 (CH×2), 124.5 (C), 130.1 (CH×2), 130.9 (CH), 132.0 (C), 132.2 (CH), 134.7 (CH), 160.0 (C);

FD-LRMS *m/z* 936 (34.4%, [M^+: $C_{49}H_{79}O_{10}Si^{81}Br$]), 934 (26.2%, [$M^+$: $C_{49}H_{79}O_{10}Si^{79}Br$]), 121 (bp);

FD-HRMS calcd for $C_{49}H_{79}O_{10}Si^{79}Br$ [M^+]: 934.4626, found 934.4630.

Compound (8'*R*)-2-53:



To a solution of **(8'*R*)-2-53** (5.3 mg, 0.0056 mmol) in CH_2Cl_2 (0.5 ml) and pH7 buffer (0.05 ml) was added DDQ (2.0 mg, 0.0088 mmol) at 23 °C, and the mixture was stirred for 2 h. Then, DDQ (1.3 mg, 0.0057 mmol) was added, and the mixture was stirred for 2 h. Then, the reaction was quenched with $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **(8'*R*)-2-53** (2.9 mg, 0.0036 mmol, 64%).

(8'*R*)-2-53: colorless oil; a colorless oil; $[\alpha]_D^{24}$ +4.8 (*c* 0.20, $CHCl_3$);

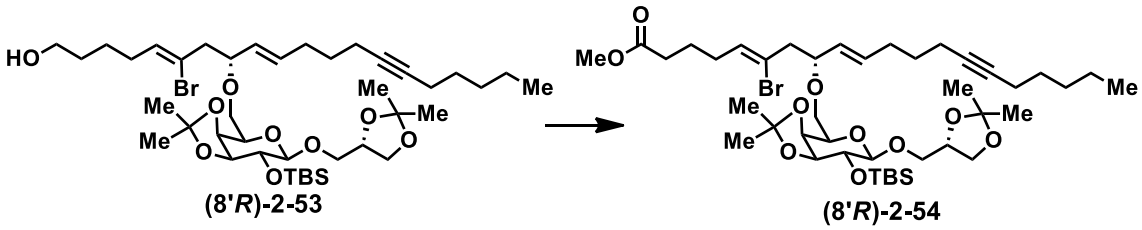
IR (neat) ν 3441, 2984, 2928, 2856, 1472, 1457, 1381, 1370, 1248, 1219, 1163, 1137, 1103, 1078, 1048, 970, 872, 839, 780, 665 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s, TBS), 0.11 (3H, s, TBS), 0.89 (9H, s, TBS), 0.90 (3H, t, *J* = 7.0 Hz, H20'), 1.17-1.66 (12H, m, H2', H3', H12', H17', H18', H19'), 1.25 (3H, s, acetonide), 1.34 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.49 (3H, s, acetonide), 2.10-2.22 (8H, m, H4', H11', H13', H16'), 2.50 (1H, dd, *J* = 6.0, 14.3 Hz, H7'a), 2.71 (1H, dd, *J* = 7.1, 14.3 Hz, H7'b), 3.43-3.52 (2H, m, H2'', H1'''a), 3.58 (1H, dd, *J* = 6.5, 10.0 Hz, H6''a), 3.64 (2H, t, *J* = 6.3 Hz, H1'), 3.71 (1H, dd, *J* = 6.1, 10.0 Hz, H6''b), 3.76-3.83 (1H, m, H5''), 3.82 (1H, dd, *J* = 5.7, 8.3 Hz, H3'''a), 3.92 (1H, dd, *J* = 4.8,

10.1 Hz, H1'"b), 3.95-3.99 (1H, m, H3"), 4.03 (1H, brq, *J* = 7.2 Hz, H8'), 4.07 (1H, dd, *J* = 6.2, 8.3 Hz, H3'"b), 4.10-4.13 (1H, m, H4"), 4.14 (1H, d, *J* = 7.8 Hz, H1"), 4.24-4.34 (1H, m, H2'"), 5.29 (1H, brdd, *J* = 8.0, 15.4 Hz, H9'), 5.62-5.72 (2H, m, H5', H10');

^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.5 (CH_3), 14.0 (CH_3), 18.1 (C), 18.2 (CH_2), 18.7 (CH_2), 22.2 (CH_2), 24.6 (CH_2), 25.3 (CH_3), 25.8 (CH_3×3), 26.6 (CH_3), 26.9 (CH_3), 28.0 (CH_3), 28.5 (CH_2), 28.8 (CH_2), 31.0 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 32.1 (CH_2), 47.8 (CH_2), 62.6 (CH_2), 67.3 (CH_2), 67.6 (CH_2), 70.5 (CH_2), 71.9 (CH), 73.8 (CH), 74.1 (CH), 74.4 (CH), 78.9 (CH), 79.6 (C), 80.5 (CH), 80.7 (C), 103.4 (CH), 109.1 (C), 109.7 (C), 124.0 (C), 129.8 (CH), 130.9 (CH), 133.9 (CH);

Compound (8'*R*)-2-54:



To a solution of **(8'*R*)-2-53** (4.6 mg, 0.0056 mmol) in CH_2Cl_2 (1.0 ml) and H_2O (0.1 ml) were added TEMPO (ca. 1 mg, ca. 0.0064 mmol) and $PhI(OAc)_2$ (5.4 mg, 0.017 mmol) at 23 °C, and the mixture was stirred for 30 h. The reaction was quenched with satd. aq. $Na_2S_2O_3$ and satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude carboxylic acid was dissolved in MeOH/CH_2Cl_2 (0.5 ml/0.1 ml). To the solution was added $TMSCHN_2$ (2.0 M in Et_2O, 0.0169 ml, 0.0338 mmol) at 23 °C, and the mixture was stirred for 30 min. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15 → 10) to give **(8'*R*)-2-54** (3.2 mg, 0.0038 mmol, 68% over 2 steps).

(8'*R*)-2-54: a colorless oil; $[\alpha]_D^{20}$ +1.1 (*c* 0.40, $CHCl_3$);

IR (neat) ν 2985, 2931, 2857, 1741, 1461, 1454, 1439, 1435, 1380, 1370, 1248, 1219, 1194, 1164, 1138, 1102, 1079, 1047, 968, 868, 839, 780, 665 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s, TBS), 0.11 (3H, s, TBS), 0.89 (9H, s, TBS), 0.90 (3H, t,

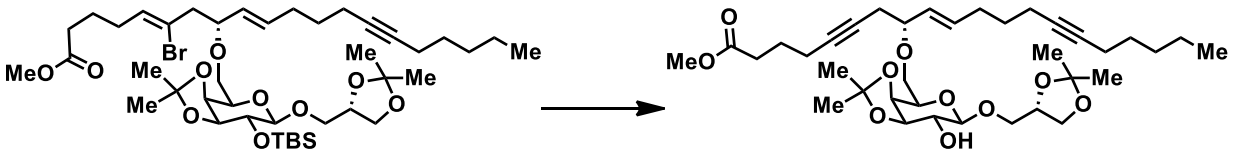
J = 7.0 Hz, H20'), 1.14-1.66 (8H, m, H12', H17', H18', H19'), 1.34 (6H, s, acetonide), 1.41 (3H, s, acetonide), 1.49 (3H, s, acetonide), 1.72 (2H, qn, *J* = 6.8 Hz, H3'), 2.10-2.22 (8H, m, H4', H11', H13', H16'), 2.32 (2H, t, *J* = 7.6 Hz, H2'), 2.50 (1H, dd, *J* = 6.0, 14.2 Hz, H7'a), 2.71 (1H, dd, *J* = 7.1, 14.2 Hz, H7'b), 3.43-3.52 (2H, m, H2", H1'"a), 3.58 (1H, dd, *J* = 6.5, 9.8 Hz, H6"a), 3.67 (3H, s, OMe), 3.70 (1H, dd, *J* = 5.9, 9.8 Hz, H6"b), 3.77-3.83 (1H, m, H5"), 3.82 (1H, dd, *J* = 5.6, 8.3 Hz, H3'"a), 3.92 (1H, dd, *J* = 4.8, 10.0 Hz, H1'"b), 3.94-4.00 (1H, m, H3"), 4.02 (1H, brq, *J* = 7.1 Hz, H8'), 4.06 (1H, dd, *J* = 6.2, 8.3 Hz, H3'"b), 4.11-4.13 (1H, m, H4"), 4.13 (1H, d, *J* = 7.7 Hz, H1"), 4.23-4.33 (1H, m, H2'"), 5.29 (1H, brdd, *J* = 8.0, 15.4 Hz, H9'), 5.65 (1H, t, *J* = 6.9 Hz, H5'), 5.67 (1H, td, *J* = 6.8, 15.4 Hz, H10');

^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.5 (CH_3), 14.0 (CH_3), 18.13 (C), 18.16 (CH_2), 18.7 (CH_2), 22.2 (CH_2), 23.6 (CH_2), 25.3 (CH_3), 25.8 (CH_3×3), 26.6 (CH_3), 26.9 (CH_3), 28.0 (CH_3), 28.5 (CH_2), 28.8 (CH_2), 30.6 (CH_2), 31.1 (CH_2), 31.2 (CH_2), 33.2 (CH_2), 47.8 (CH_2), 51.5 (CH_3), 67.3 (CH_2), 67.6 (CH_2), 70.5 (CH_2), 71.9 (CH), 73.8 (CH), 74.1 (CH), 74.4 (CH), 78.9 (CH), 79.6 (C), 80.5 (CH), 80.7 (C), 103.3 (CH), 109.1 (C), 109.6 (C), 124.8 (C), 129.7 (CH), 129.9 (CH), 134.0 (CH), 173.8 (C);

FD-LRMS *m/z* 844 (16.2%, [M^+: $C_{42}H_{71}O_{10}Si^{81}Br$]), 842 (13.9%, [$M^+$: $C_{42}H_{71}O_{10}Si^{79}Br$]), 57 (bp);

FD-HRMS calcd for $C_{42}H_{71}O_{10}Si^{79}Br$ [M^+]: 842.4000, found 842.4004.

Compound (8'*R*)-2-55:



(8'*R*)-2-54 **(8'*R*)-2-55**

To a solution of **(8'*R*)-2-54** (3.2 mg, 0.0038 mmol) in DMF (0.4 ml) was added TBAF·$3H_2O$ (4.8 mg, 0.015 mmol) at 75 °C, and the mixture was stirred for 3 h. Then, the mixture was diluted with a 1:1 mixture of hexane and EtOAc and acidified with 0.1 M HCl. The mixture was extracted with a 1:1 mixture of hexane and EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Because partial hydrolysis of the

methyl ester was observed, the resulting residue was dissolved in methanol (ca. 1 ml) and was treated with $TMSCHN_2$ (2 M in Et_2O). The reaction mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 1) to give **(8'*R*)-2-55** (2.3 mg, 0.0035 mmol, 92%).

(8'*R*)-2-55: a colorless oil; $[\alpha]_D^{20}$ +1.7 (*c* 0.20, $CHCl_3$);

IR (neat) ν 3451, 2983, 2931, 2859, 1738, 1455, 1435, 1380, 1371, 1246, 1218, 1164, 1077, 968, 933, 873, 844, 689, 665 cm^{-1};

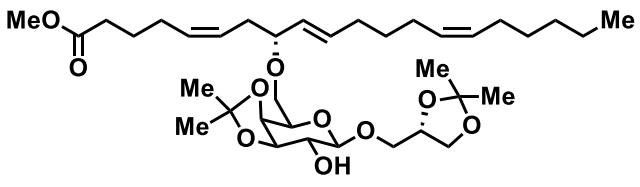
^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, H20'), 1.20-1.66 (8H, m, H12', H17', H18', H19'), 1.36 (6H, s, acetonide), 1.43 (3H, s, acetonide), 1.52 (3H, s, acetonide), 1.79 (2H, qn, *J* = 7.2 Hz, H3'), 2.10-2.24 (9H, m, H4', H7'a, H11', H13', H16'), 2.28-2.38 (1H, m, H7'b), 2.43 (2H, t, *J* = 7.5 Hz, H2'), 3.56 (1H, brt, *J* = 7.8 Hz, H2"), 3.59-3.68 (2H, m, H6"a, H1'"a), 3.68 (3H, s, OMe), 3.74 (1H, dd, *J* = 6.0, 10.0 Hz, H6"b), 3.82 (1H, dd, *J* = 6.1, 8.4 Hz, H3'"a), 3.83 (1H, brq, *J* = 7.0 Hz, H8'), 3.89 (1H, brdt, *J* = 2.2, 6.5 Hz, H5"), 3.93 (1H, dd, *J* = 5.1, 10.8 Hz, H1'"b), 4.03-4.08 (2H, m, H3", H3'"b), 4.20 (1H, dd, *J* = 2.2, 5.4 Hz, H4"), 4.21 (1H, d, *J* = 8.2 Hz, H1"), 4.27-4.35 (1H, m, H2'"), 5.39 (1H, brdd, *J* = 7.8, 15.5 Hz, H9'), 5.69 (1H, td, *J* = 7.0, 15.5 Hz, H10');

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 18.2 (CH_2), 18.3 (CH_2), 18.7 (CH_2), 22.2 (CH_2), 24.1 (CH_2), 25.2 (CH_3), 25.9 (CH_2), 26.3 (CH_3), 26.6 (CH_3), 28.2 (CH_3), 28.5 (CH_2), 28.8 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 32.8 (CH_2), 51.5 (CH_3), 66.3 (CH_2), 67.2 (CH_2), 69.8 (CH_2), 72.4 (CH), 73.5 (CH), 73.6 (CH), 74.4 (CH), 77.4 (C), 78.5 (CH), 79.6 (C), 80.0 (CH), 80.5 (C), 80.7 (C), 102.8 (CH), 109.5 (C), 110.0 (C), 129.9 (CH), 133.9 (CH), 173.7 (C);

FD-LRMS *m/z* 648 (bp, $[M^+]$);

FD-HRMS calcd for $C_{36}H_{56}O_{10}$ $[M^+]$: 648.3874, found 648.3904.

Compound (8'*R*)-2-56:



(8'*R*)-2-56

To a solution of **(8'*R*)-2-55** (2.3 mg, 0.0035 mmol) and 1-hexene (0.10 ml, 0.80 mmol) in MeOH (0.1 ml) was added Lindlar catalyst (2.3 mg) at 23 °C, and the mixture was stirred for 22 h under H_2 atmosphere. The mixture was filtered through a celite pad and concentrated in vacuo to give almost pure **(8'*R*)-2-56** (2.3 mg, 0.0035 mmol, 100%).

(8'*R*)-2-56: a colorless oil; $[\alpha]_D^{22}$ +4.5 (*c* 0.10, $CHCl_3$);

IR (neat) ν 3447, 2925, 1740, 1457, 1437, 1380, 1370, 1245, 1219, 1164, 1075, 969, 872, 845, 665 cm^{-1};

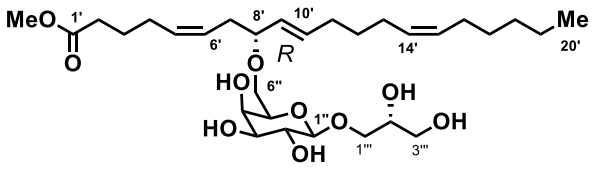
^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz, H20'), 1.22-1.73 (10H, m, H3', H12', H17', H18', H19'), 1.35 (3H, s, acetonide), 1.36 (3H, s, acetonide), 1.43 (3H, s, acetonide), 1.52 (3H, s, acetonide), 1.93-2.11 (9H, m, H4', H7'a, H11', H13', H16'), 2.26-2.35 (3H, m, H2', H7'b), 3.53-3.68 (3H, m, H2", H6"a, H1'"a), 3.66 (3H, s, OMe), 3.74 (1H, dd, *J* = 5.8, 9.8 Hz, H6"b), 3.82 (1H, dd, *J* = 6.0, 8.3 Hz, H3'"a), 3.82-3.91 (2H, m, H8', H5"), 3.93 (1H, dd, *J* = 5.2, 10.7 Hz, H1'"b), 4.02-4.08 (2H, m, H3", H3'"b), 4.18-4.21 (1H, m, H4"), 4.20 (1H, d, *J* = 8.2 Hz, H1"), 4.27-4.34 (1H, m, H2'"), 5.24-5.46 (5H, m, H5', H6', H9', H14', H15'), 5.58-5.67 (1H, m, H10');

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 24.7 (CH_2), 25.2 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 26.7 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 28.2 (CH_3), 31.5 (CH_2), 31.8 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 33.6 (CH_2), 51.5 (CH_3), 66.3 (CH_2), 66.8 (CH_2), 69.8 (CH_2), 72.3 (CH), 73.5 (CH), 73.6 (CH), 74.4 (CH), 78.5 (CH), 81.4 (CH), 102.9 (CH), 109.5 (C), 110.0 (C), 126.6 (CH), 129.2 (CH), 130.1 (CH), 130.2 (CH), 130.4 (CH), 134.0 (CH), 174.0 (C);

FD-LRMS *m/z* 652 (3.2%, $[M^+]$), 242 (bp);

FD-HRMS calcd for $C_{36}H_{60}O_{10}$ $[M^+]$: 652.4187, found 652.4198.

Compound (8'*R*,2'''*R*)-1-5:



(8'*R*, 2'''*R*)-1-5

To a solution of **(8'*R*)-2-56** (2.3 mg, 0.0035 mmol) in MeOH (0.5 ml) and CH_2Cl_2 (0.3 ml) was added

TFA (0.0130 ml, 0.176 mmol) at 23 °C, and the mixture was stirred for 17.5 h. The mixture was diluted with toluene and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 10 → 5) to give **(8'*R*,2'''*R*)-1-5** (2.0 mg, 0.0035 mmol, 100%).

(8'*R*, 2'''*R*)-1-5: a pale yellow oil; $[\alpha]_D^{24}$ +2.8 (*c* 0.10, $CHCl_3$);

IR (neat) ν 3387, 2926, 2861, 1737 cm^{-1}; ^1H NMR (400 MHz, C_6D_6/DMSO-d_6 [25:2], C_6HD_5 as 7.15 ppm) δ 0.86 (3H, t, *J* = 7.0 Hz, H20'), 1.30 (2H, m, H18'), 1.30 (2H, m, H19'), 1.32 (2H, m, H17'), 1.38 (2H, m, H12'), 1.61 (2H, m, H3'), 1.96 (2H, m, H11'), 1.99 (2H, m, H4'), 2.02 (2H, m, H13'), 2.02 (2H, m, H16'), 2.14 (2H, *J* = 7.6 Hz, H2'), 2.30 (1H, m, H7'a), 2.45 (1H, m, H7'b), 3.39 (3H, s, OMe), 3.65 (1H, m, H5''), 3.70 (1H, m, H3''), 3.75 (1H, m, H8'), 3.77 (1H, m, H6''a), 3.84 (2H, m, H3'''), 3.90 (1H, m, H1'''a), 3.92 (1H, m, H6''b), 3.98 (1H, m, H2''), 4.05 (1H, m, H2'''), 4.07 (1H, m, H4''), 4.11 (1H, m, H1'''b), 4.39 (1H, d, *J* = 7.7 Hz, H1''), 5.38 (1H, m, H5'), 5.39 (1H, m, H9'), 5.40 (1H, m, H14'), 5.40 (1H, m, H15'), 5.57 (1H, m, H10'), 5.60 (1H, m, H6') [Chemical shifts are shown as exact values derived from 1D, COSY, HSQC, and HMBC measurements.];

^{13}C NMR (100 MHz, C_6D_6/DMSO-d_6 [25:2], C_6D_6 as 128.0 ppm) δ 14.25 (CH_3, C20'), 22.87 (CH_2, C19'), 25.05 (CH_2, C3'), 26.99 (CH_2, C4'), 27.06 (CH_2, C13'), 27.51 (CH_2, C16'), 29.54 (CH_2, C12'), 29.68 (CH_2, C17'), 31.75 (CH_2, C18'), 32.06 (CH_2, C11'), 33.39 (CH_2, C2'), 34.23 (CH_2, C7'), 51.04 (CH_3, OMe), 64.05 (CH_2, C3'''), 67.67 (CH_2, C6''), 69.38 (CH, C4''), 71.61 (CH, C2'''), 71.99 (CH, C2''), 72.41 (CH_2, C1'''), 74.32 (CH, C5''), 74.54 (CH, C3''), 81.26 (CH, C8'), 105.13 (CH, C1''), 127.19 (CH, C6'), 129.74 (CH, C14'), 130.29 (CH, C5'), 130.41 (CH, C15'), 131.30 (CH, C9'), 133.68 (CH, C10'), 173.43 (C, C1');

FD-LRMS *m/z* 595 (36.8%, $[M+Na^+]$), 242 (bp);

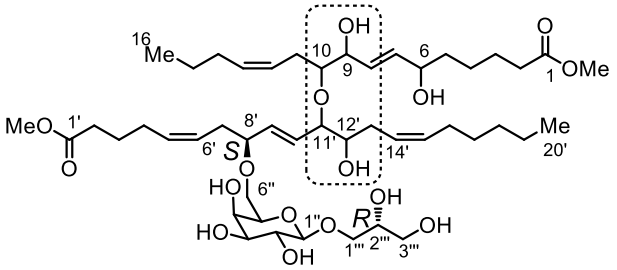
FD-HRMS calcd for $C_{30}H_{52}O_{10}Na$ $[M+Na^+]$: 595.3458, found: 595.3473.

Chapter 3.

Exploration of a Stereoselective Method for the Construction of the C9-C10-O-C11'-C12 Region of Nigricanoside-A Dimethyl Ester

3-1. Introduction

The synthesis of the C9-C10-O-C11'-C12 region of nigricanoside-A dimethyl ester (**1-1**, Figure 3-1) was selected as the second subject of the thesis. The synthesis includes the following problems: (i) formation of di-*sec*-alkyl ether should be achieved in good yield; (ii) the ethereal carbons, C10 and C11', should be constructed stereoselectively; and (iii) the stereocenters, C9 and C12, adjacent to ethereal carbons, C10 and C11', respectively, should also be built stereoselectively and simultaneously with the formation of C10-O-C11' ether bond.



1-1

Figure 3-1. Nigricanoseid-A dimethyl ester (**1-1**) with a predicted (8'*S*,2'''*R*)-configuration.

To date, many effective methods, for example, reductive etherification,[1] Ireland-Claisen rearrangement,[2] and aldol reactions,[3] have been reported for stereoselective ether formation in the research field of total synthesis of naturally occurring cyclic ethers,[4] of which the structures around the ether bonds were closely similar to the C9-C10-O-C11'-C12 region of **1-1**. However, applicability of these methods to the construction of acyclic di-*sec*-alkyl ethers has not been examined. Therefore, the author intended to find out an effective solution for the above problems from the reported methods.

As a preliminary study, the author first planned to synthesize a series of simple model compounds, **3-1a-d** (Figure 3-2), corresponding to the ether linkage between C16 and C20 fatty acid chains for the comparison of NMR spectra between natural **1-1** and each of **3-1a-d** in order to estimate the stereochemistry at C11' and C12' on the basis of the presumed C8' and C2''' configurations described in Chapter 2. Model compounds **3-1a-d** would be assembled from aldehyde **(8'*S*)-2-21** and sulfone **3-2a-d** by a process including Julia-Kocienski olefination,[5] alkyne formation at C5', Lindlar hydrogenation, and deprotection. Thus, stereoselective synthesis of **3-1a-d** was first examined by a

process including reductive etherification. The preliminary results are described in Section 3-2.

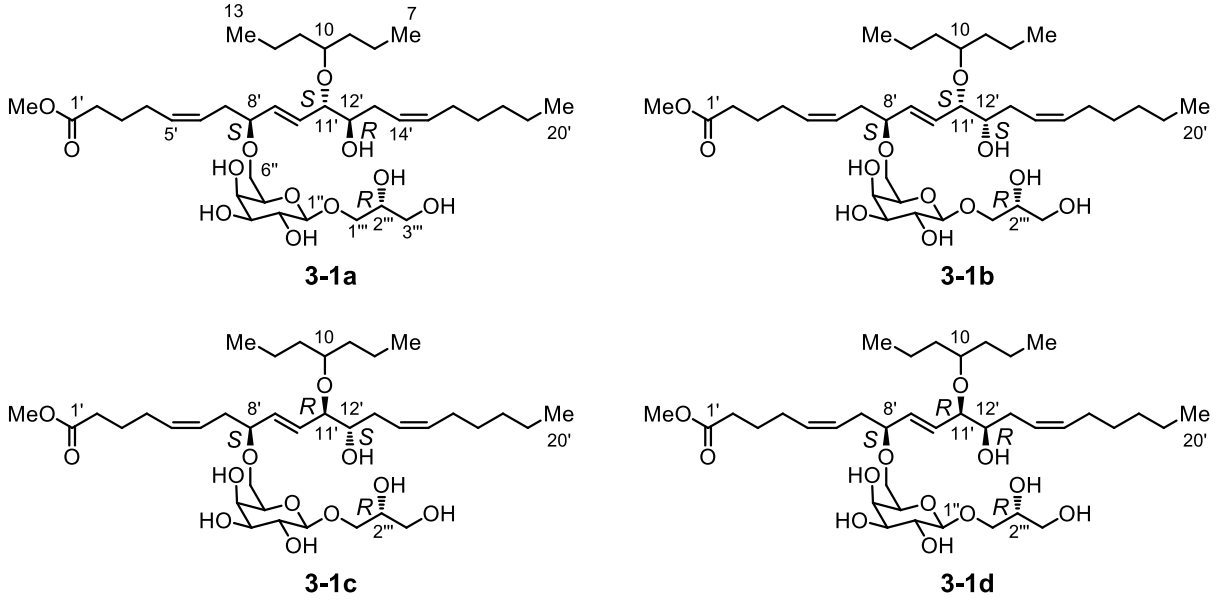
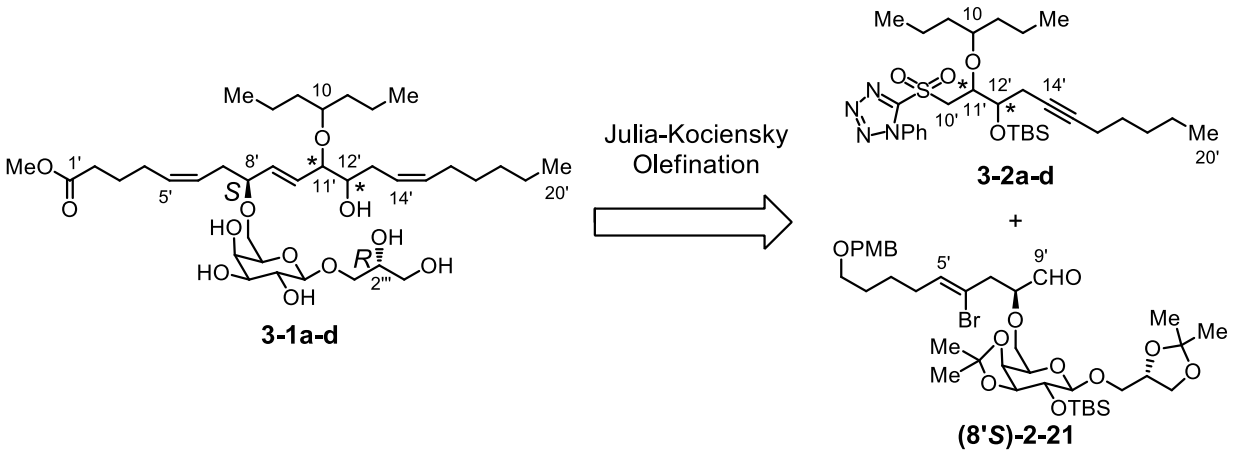


Figure 3-2. Model compounds **3-1a-d** with a galactosyl glycerol, C20 lipid chain, and a mimic C10-O-C11' ether bond.



Scheme 3-1. Outline of the synthetic plan for **3-1a-d**.

The author also examined the synthesis of an alternative series of model compounds, **3-3a-d** (Figure 3-3). The model compounds, which have C16 fatty acid chain and a mimic C10-O-C11' ether bond, were designed for the NMR comparison with **1-1** to find out a plausible combination of relative configurations at C6, C9 and C10 of **1-1**. The attempting synthesis of model compounds **3-3a-d** based

on Ireland-Claisen rearrangement is described in Section 3-3.

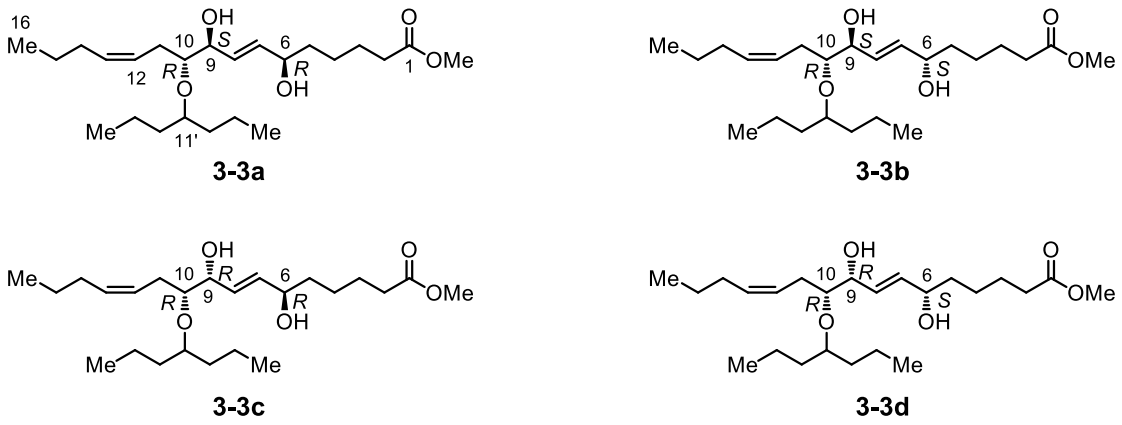
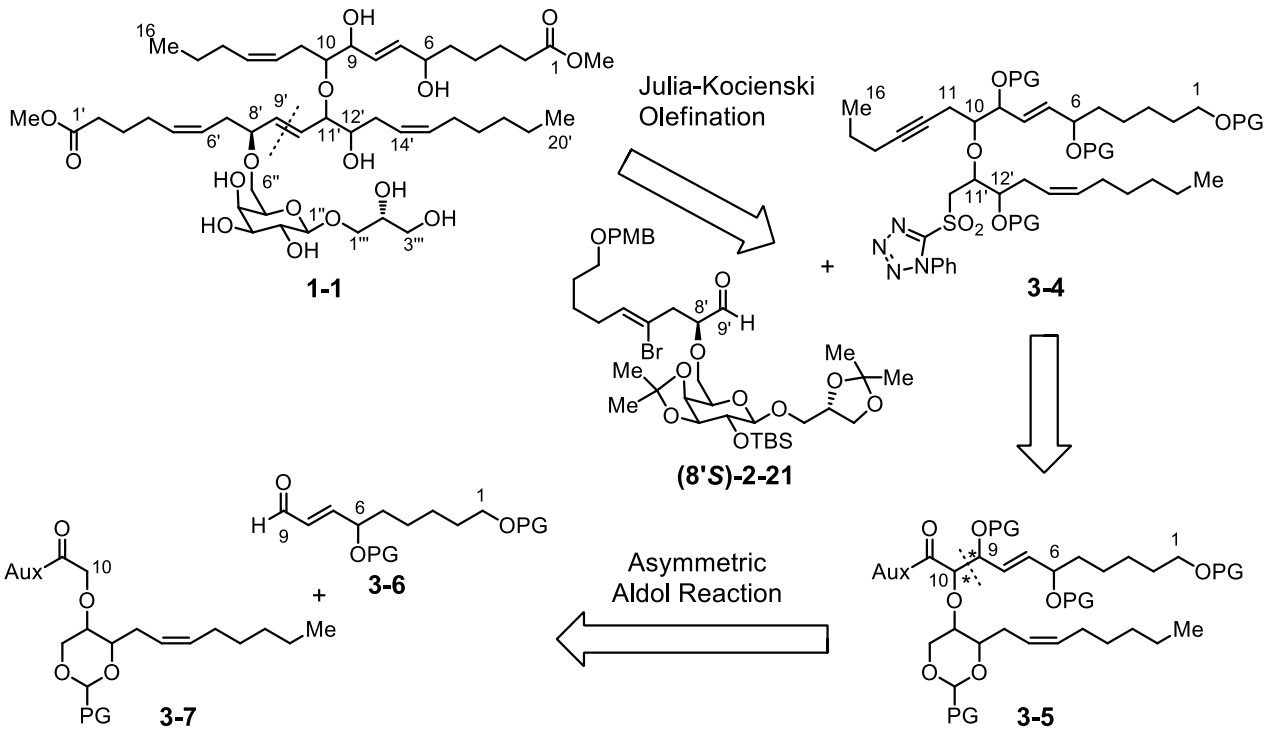


Figure 3-3. Model compounds **3-3a-d** with C16 lipid chain and a mimic C10-O-C11' ether bond.

For the construction of the C9-C10-O-C11'-C12 region of **1-1**, an approach based on an asymmetric aldol reaction[6] was also examined. The successful formation of the region is a key to achieving the total synthesis, and simultaneous generation of multi stereocenters with a stereocontrolled manner is required for efficiency. Therefore, an aldol approach for the construction of stereocenters at C9 and C10 was employed.

The synthetic plan for **1-1** is outlined in Scheme 3-2. At the final stage of the total synthesis of **1-1**, the connection between aldehyde **(8'*S*)-2-21** and sulfone **3-4** by Julia-Kocienski olefination is scheduled. Sulfone **3-4** would be derived from **3-5** via the installation of C12-C16 chain. The C9-C10 bond of **3-5** is intended to be formed by an asymmetric aldol reaction of carboxylate/carboxamide **3-7** with aldehyde **3-6** having C6 stereocenter. In the plan, the preparation of **3-7** should also be performed in a stereoselective way.

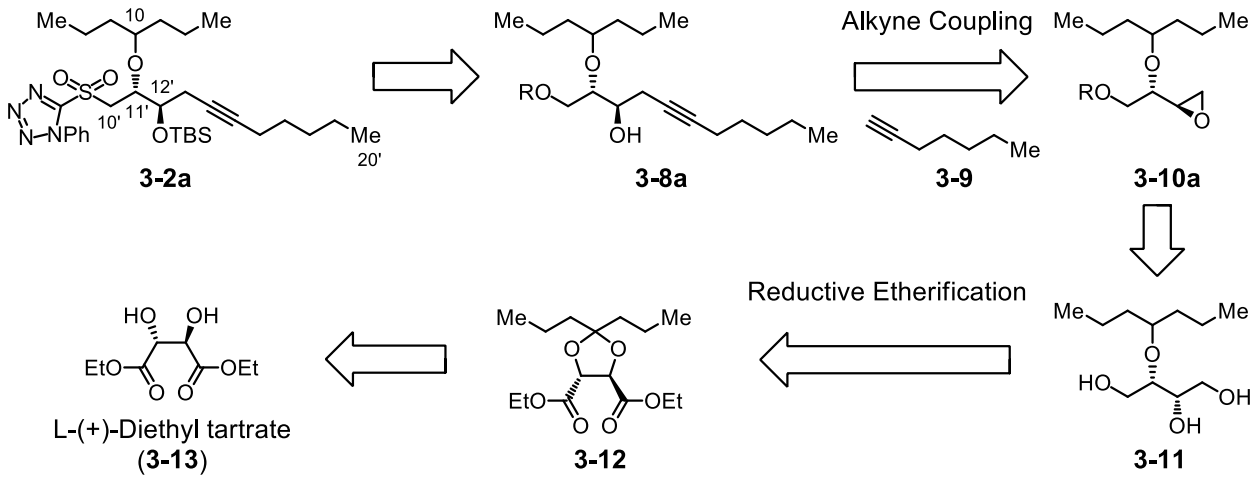
The details of the experiments of the aldol reaction of **3-7** with several aldehydes are described in Section 3-4. Application of the aldol products to further synthesis is also examined. The results are mentioned in Section 3-6.



Scheme 3-2. Outline of the synthetic plan for **1-1** based on an asymmetric aldol reaction.

3-2. An Approach to the Construction of the C10-O-C11' Ether Bond by Reductive Acetal Cleavage

The approach to **3-2a-d** is outlined in Scheme 3-2. The sulfone **3-2a** was planned to be synthesized from alcohol **3-8a**, which would be assembled by an acetylide coupling of epoxide **3-10a** with alkyne **3-9**. Epoxide **3-10a** would be formed from triol **3-11**. The construction of the ether bond of **3-11** corresponding the C10-O-C11' of **1-1** employed reductive etherification of acetal **3-12** , which would be preparable from commercially available L-(+)-diethyl tartrate (**3-13**). This approach would be available for the preparation of all four diastereomers **3-2a-d** by use of both enantiomers of diethyl tartrate and by change of the method of the epoxide formation step.

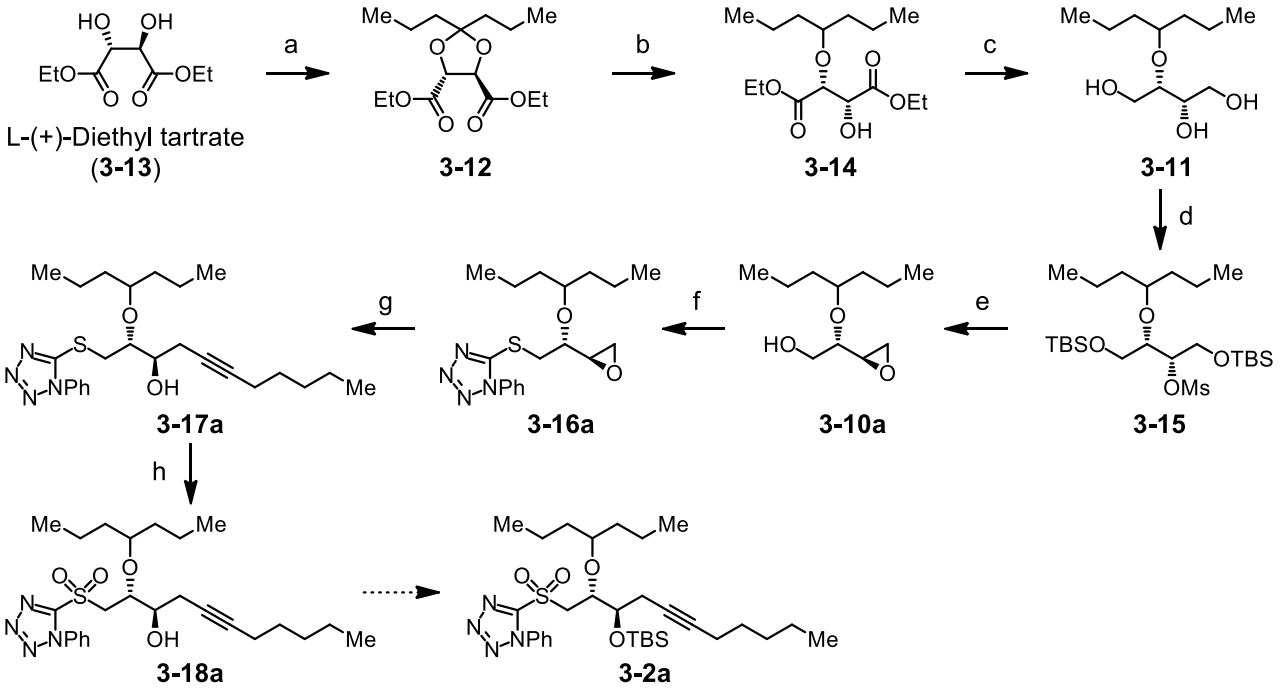


Scheme 3-3. Synthetic plan for sulfone **3-2a**.

An attempt to synthesize **3-2a** is shown in Scheme 3-4. L-(+)-Diethyl tartrate (**3-13**) was reacted with heptane-4-one to give acetal **3-12** (83%),[7] which was reductively cleaved by $TiCl_4$ and Et_3SiH[8] to produce ether **3-14** (97%). After reduction of **3-14** with $LiAlH_4$ (74%), the resulting triol **3-11** was subjected to one-pot sequential reactions with TBSCl and MsCl to afford **3-15**. Treatment of **3-15** with TBAF induced removal of the TBS groups and the simultaneous formation of an epoxide to give **3-10a** (98%). The Mitsunobu reaction[9] of **3-10a** with 1-phenyl-1*H*-tetrazole-5-thiol provided sulfide **3-16a** (45%),[5] which was reacted with hept-1-yne under Yamaguchi's conditions[10] to produce **3-17a** even in modest yield (69%). The obtained small amount of **3-17a** was oxidized with ammonium

molybdate hydrate and hydrogen peroxide[11] to furnish only detectable amount of sulfone **3-18a** (62%). Because of the limited amount of **3-18a**, the final protection reaction could not be conducted.

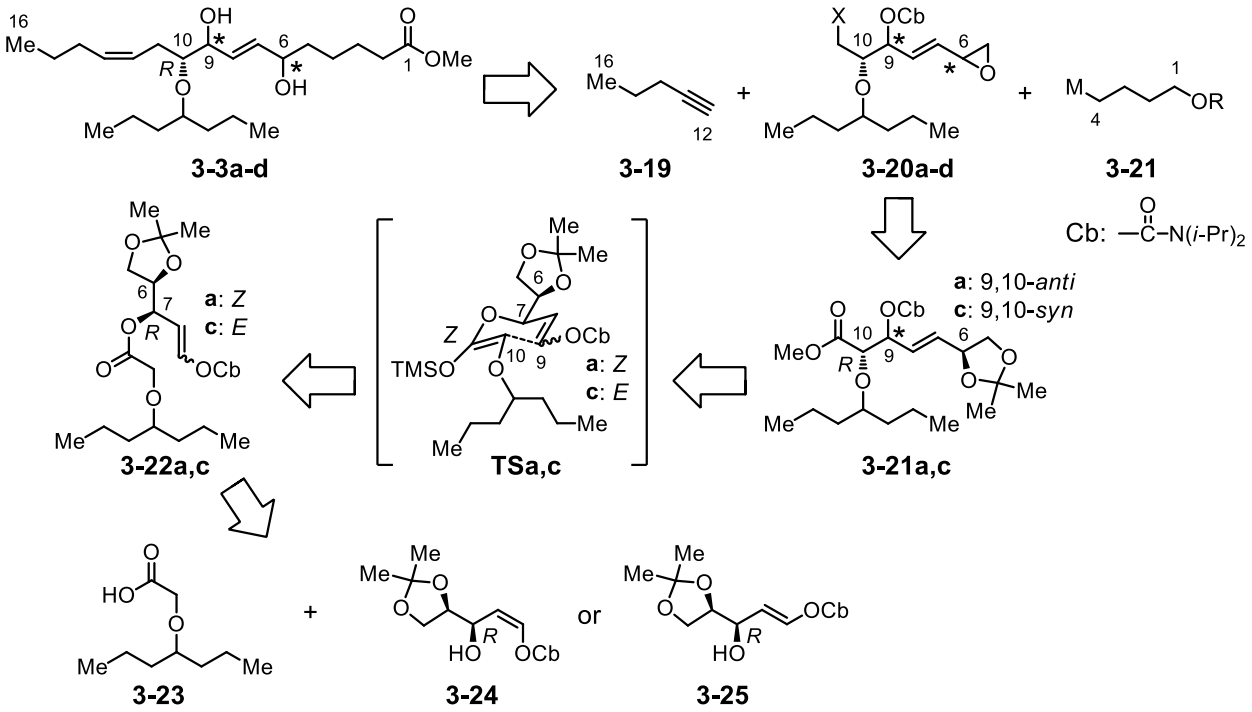
Although there was a low yielding process from **3-10a** to **3-18a** that should be improved, the validity of the ether formation method in this model synthesis was demonstrated. The improved synthesis of **3-2a-d** will be conducted in the near future by other members of the author's laboratory.



Scheme 3-4. Attempting synthesis of sulfone **3-2a**. Reagents and conditions: (a) heptan-4-one, PTS·H_2O (cat.), benzene, reflux, 24 h, 80%; (b) $TiCl_4$, Et_3SiH, CH_2Cl_2, –78 °C, 2 h, then 23 °C, 15 min, 97%; (c) $LiAlH_4$, THF, 23 °C, 16 h, 74%; (d) TBSCl (2.8 eq.), Et_3N (10 eq), DMAP (cat.), CH_2Cl_2, 23 °C, 20 h, then MsCl (2 eq.), 23 °C, 1 h; (e) TBAF·$3H_2O$, THF, 23 °C, 16 h, 98% over 2 steps; (f) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, PPh_3, THF, 0 °C, 14 h, 44%; (g) hept-1-yne (**3-9**), BuLi, BF_3·OEt_2, THF, –78 °C, 68%; (h) ammonium molybdate hydrate (cat.), H_2O_2, EtOH, 0 °C, 13 h, 59%.

3-3. An Alternative Approach to the Construction of the C10-O-C11' Ether Bond by Ireland-Claisen Rearrangement

The synthetic plan for C16 lipid chain model compounds **3-3a-d** is illustrated in Scheme 3-5. This route employs a chirality transferring version of Ireland-Claisen rearrangement[12] for the stereoselective construction of the C10-O-C11' ether bond of the models. The C16 lipid chains of **3-3a-d** are intended to be assembled by C-C bond formation between C12 of **3-19** and C11 of intermediates **3-20a-d** using alkyne coupling and between C5 of **3-20a-d** and C4 of organometallic reagent **3-21** via an epoxide ring opening reaction. Intermediates **3-20a-d** would be derived from esters **3-21a,c**, which would be synthesized stereoselectively from 3-(*N*,*N*-diisopropylcarbamoyloxy)allyl glycolate esters **3-22a,c** by Ireland-Claisen rearrangement .



Scheme 3-5.

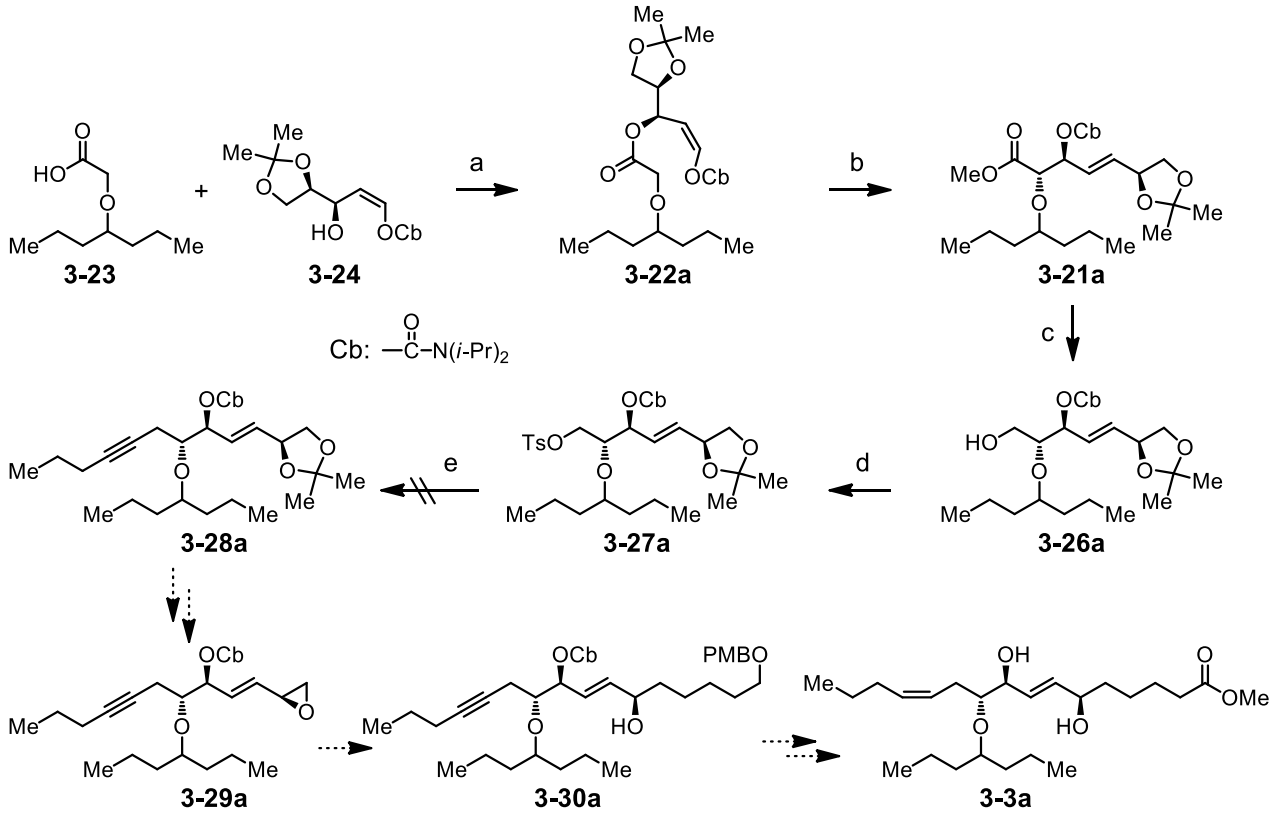
The β-carbamoyloxy/alkoxy ether forming rearrangement was developed by Domon, Kawamura, and Nogoshi, previous members of the author's laboratory.[13,14,15] The rearrangement generally showed good *anti*- or *syn*-stereoselectivity relied on the *Z*- or *E*-geometry of the 3-carbamoyloxyallyl/3-alkoxyallyl group of substrate glycolate esters, respectively. The

stereochemistry of the major rearrangement product is predictable by assuming a stable chair transition state from a *Z*-ketene silyl acetal derived from the substrate.

Thus, during the rearrangement, the stereochemistry at C7 of **3-22** would be transferred to C9 and C10 of **3-21** via **TS**, and the configuration of C9 would also be controlled by the *Z*/*E*-geometry of the 3-carbamoyloxyallyl group of **3-22**.

Esters **3-22a,c** are slated to be prepared from glycolic acid **3-23** and 3-carbamoyloxyallyl alcohol **3-24** or **3-25**.

As a preliminary study, the synthesis of model compound **3-3a** from **3-23** and **3-24** was attempted.

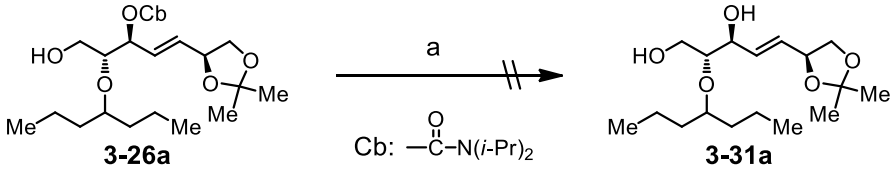


Scheme 3-6. Attempting synthesis of model compound **3-3a**. Reagents and conditions: (a) **3-23** (1.5 eq), **3-24** EDCI·HCl, DMAP (cat.), CH_2Cl_2, 23 °C, 14 h, 96%; (b) KHMDS, THF, –78 °C, 2 min, then TMSCl, –78 °C, 15 min, then 0 °C, 15 min; $TMSCHN_2$, CH_2Cl_2, MeOH, 47% from **3-22a** (ds = 10:1); (c) $LiAlH_4$, THF, –15 °C, 30 min, 100%.; (d) TsCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 24 h, 66% from 2 steps; (e) prop-1-yne (**3-19**), BuLi, THF, –78 °C, 30 min, then **3-27a**, HMPA, 0 °C, 1.5 h, then 23 °C, 20 h.

The attempt for the synthesis of **3-3a** is illustrated in Scheme 3-6. Glycolic acid **3-23**, easily preparable from heptan-1-ol and bromoacetic acid, was esterified with *Z*-3-(*N*,*N*-diisopropylcarbamoyloxy)allyl alcohol **3-24**, prepared according to the procedure developed by Domon[13] and Nogoshi,[14] to produce **3-22a** (96%). According to Nogoshi's procedure,[14] ester **3-22a** was treated with KHMDS in the presence of TMSCl in THF at –78 °C, and the resulting ketene silyl acetal was warmed to 0 °C to induce rearrangement. The resulting carboxylic acid was esterified with $TMSCHN_2$ to give **3-21a** selectively (47% over 2 steps; ds = 10:1). The ester was then reduced to alcohol **3-26a**, which was tosylated to give **3-27a** (97% over 2 steps). The introduction of alkyne did not proceed under several conditions due to low reactivity of the tosylate **3-27a**, thereby interrupting the synthesis of **3-3a**.

The improvement of the reactivity for the alkynylation step would be achieved by applying Kotsuki's method,[16] which employed a triflate as a reactive leaving group. However, there was another problem in removal of the *N*,*N*-diisopropylcarbamoyl (Cb) protecting group. Although the Cb group is an inert protective group, it is known to be removed by treatment with MeLi.[17] However, the Cb group of **3-26a** resisted being removed, and this disturbed the verification of the stereochemistry at newly forming stereocenters (Scheme 3-7). Therefore, revision of the protecting group was required in this synthesis. Since Nogoshi reported a PMP protecting group as an easily removable[14] substitute for the Cb group in his study on the ether-forming Ireland-Claisen rearrangement, this model synthesis should adopt the PMP group.

Thus, the author demonstrated the stereoselective formation of C10-O-C11' ether bond by Ireland-Claisen rearrangement though the synthesis of C16 lipid chain model compounds **3-3a-d** have yet to be completed. The revised synthesis of **3-3a-d** employing a PMP group and Kotsuki's alkyne installation method will be performed in the near future by other members of the author's laboratory.

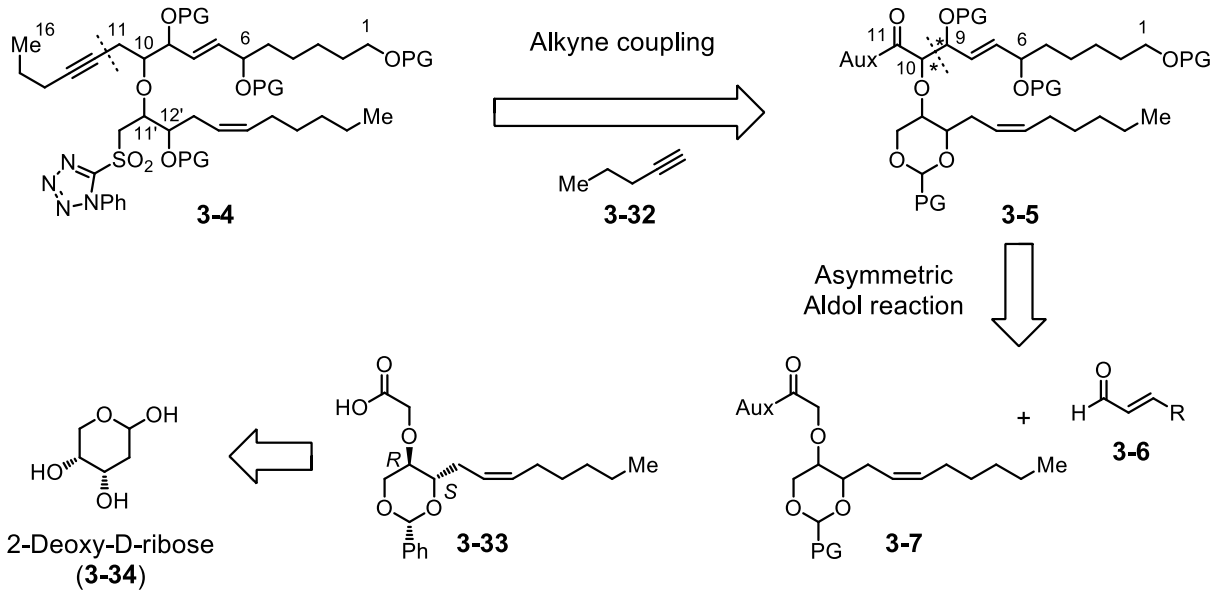


Scheme 3-7. Attempt to remove the Cb group of **3-26a**. Reagents and conditions: (a) MeLi, THF, –10 °C, 1 h.

3-4. Application of an Asymmetric Aldol Reaction for the Construction of the C9-C10-O-C11'-C12 Region

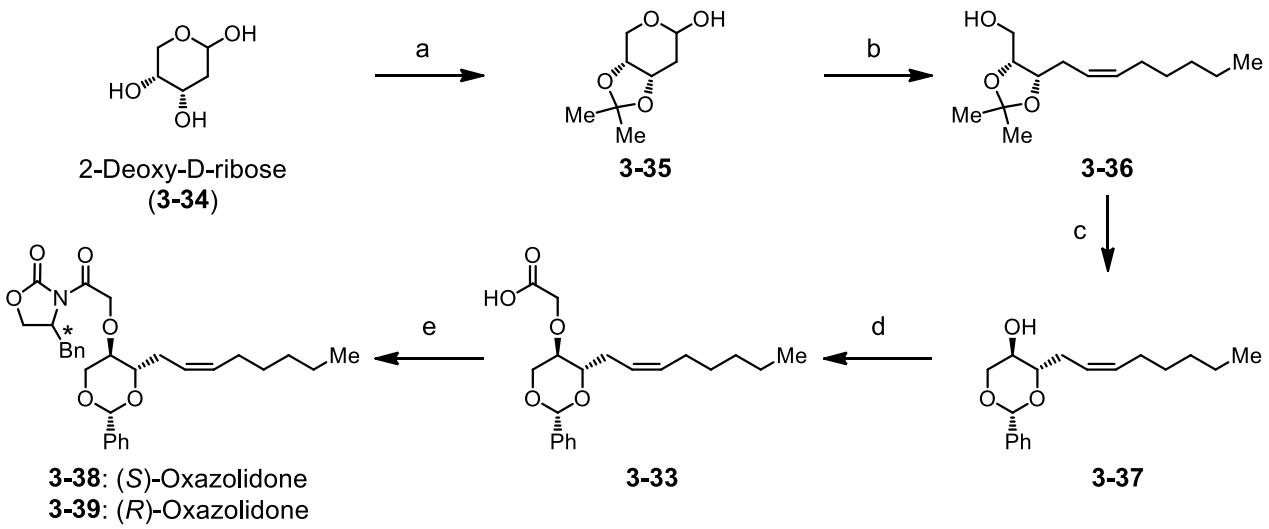
Next, aiming at simultaneous generation of stereocenters C9 and C10 in the synthesis of **3-4**, a key intermediate for the total synthesis of **1-1**, an asymmetric aldol reaction was examined for the C9-C10 bond formation. Since the stereochemistry of **1-1** has not yet been determined, the author proposed to establish a common method for the selective synthesis of all stereoisomers at C9 and C10. At the same time, the author intended to test the validity of the route to **3-4** and undertook the synthesis using a stereoisomer of the aldol reaction as a starting material.

As described in Section 3-1, sulfone **3-4** was planned to be assembled via the installation of C12-C16 alkyne chain (**3-32**) into **3-5** and the aldol reaction to connect **3-7** with C9-C1 chain **3-6** (Scheme 3-8). At the aldol reaction step, an asymmetric type reaction, such as Evans aldol reaction, was employed to achieve effective asymmetric induction at C9 and C10 in addition to segment elongation. Glycolic acid derivative **3-7** having stereocenters at C11' and C12' was intended to be assembled from naturally occurring chiral materials. Here, the synthesis of glycolic acid **3-33** having (11'*R*,12'*S*)-configuration was examined from 2-deoxy-D-ribose (**3-34**).

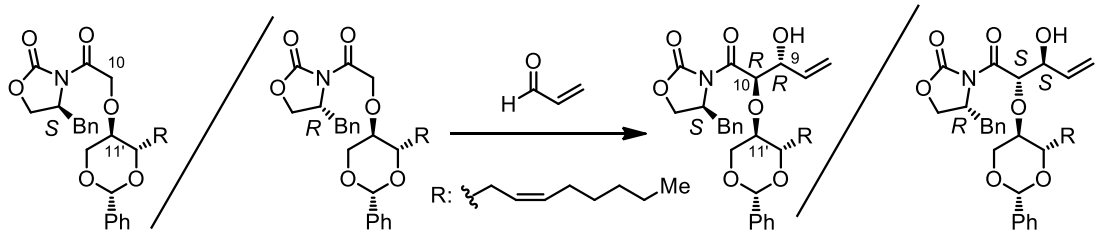


Scheme 3-8. An approach to sulfone **3-4** based on an asymmetric aldol reaction.

The synthesis of glycolic acid **3-33** is shown in Scheme 3-9. 2-Deoxy-D-ribose (**3-34**) was selected as a chiral starting material and was converted to isopropylidene acetal **3-35** according to literature procedure. [18] Wittig reaction [19] of **3-35** with more than two equivalent of hexylidenetriphenylphosphorane gave *cis*-alkene **3-36**, which was then transformed to 6-membered cyclic acetal **3-37** (54% from **3-34**). The preparation of the acetals was achieved efficiently over four steps from **3-34** with only one chromatographic purification. Etherification of alcohol **3-37** with bromoacetic acid gave glycolic acid **3-33** (99%).[20] The acid was then condensed with Evans type chiral auxiliaries, (*S*)- and (*R*)-4-benzyloxazolidin-2-ones, to produce amides **3-38** and **3-39** (100% and 88%, respectively). Thus, substrate amides for the next aldol reactions were synthesized efficiently.

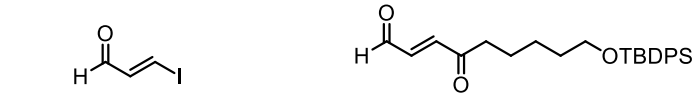


Scheme 3-9. Synthesis of amides **3-38** and **3-39**. Reagents and conditions: (a) 2,2-dimethoxypropane, PTS·H_2O (cat.), Dririte®, acetone, DMF, 0 °C, 30 h; (b) BuLi, $Ph_3PCH_2(CH_2)_4CH_3$·Br, THF, –78 °C, then **3-35**, THF, –78 °C to 23 °C, 3 h; (c) AcOH, 100 °C, 2 h, then evaporation, then PhCHO, PTS·H_2O (cat.), PhH, reflux, 3 h, 54% from **3-34**; (d) NaH, bromoacetic acid, THF, 0 °C to 23 °C, 1 h, then **3-37**, DMF-THF, 23 °C, 17 h, 99%; (e) Et_3N, pivaloyl chloride, THF, –20 °C, 30 min, then lithium (*S*)- or (*R*)-4-benzyl-2-oxooxazolidin-3-ide in THF, –20°C, 1 h, **3-38**: 100% from **3-37**, **3-39**: 88% from **3-37**.



3-38 **3-39** **3-40** (*S*,*R*,*R*) **3-41** (*R*,*S*,*S*)

Entry	Subst.	Aldehyde	Conditions	Yield
1	**3-38** (*S*)	Acrolein	Bu_2BOTf, Et_3N, CH_2Cl_2, –78 °C	Complex Mixt.
2	**3-39** (*R*)	Acrolein	Bu_2BOTf, Et_3N, CH_2Cl_2, –78 °C	Complex Mixt.
3	**3-38** (*S*)	Acrolein	LDA, THF, –78 °C	43% (**3-40**; *S,R,R*)
4	**3-38** (*S*)	Acrolein	LDA, THF-toluene, –78 °C	63% (**3-40**; *S,R,R*)
5	**3-39** (*R*)	Acrolein	LDA, THF-toluene, –78 °C	76% (**3-41**; *R,S,S*)
6	**3-38** (*S*)	(*E*)-β-Iodoacrolein	LDA, THF-toluene, –78 °C	Complex Mixt.
7	**3-38** (*S*)	**3-42**	LDA, THF-toluene, –78 °C	Complex Mixt.



(*E*)-β-Iodoacrolein **3-42**

Table 3-1. Aldol reactions of **3-38** and **3-39** with several aldehydes.

Next, Evans type asymmetric aldol reactions were examined with amides **3-38** and **3-39**. Evans' method was selected because of the reliability of stereoselectivity and the easily removable nature of the oxazolidinone auxiliary.[21] Selected results of the examined aldol reactions are illustrated in Table 3-1. First, the aldol reactions of **3-38** and **3-39** were performed with dibutylboron triflate according to standard boron aldol conditions (Entries 1 and 2).[6] However, each reaction resulted only in decomposition of the substrate due to instability of the cyclic benzylidene acetal under Lewis acidic conditions in spite of the presence of amine base. Although several conditions using other boron reagents[22] were examined, the desired aldol adduct could not be obtained. Therefore, the author next focused on the aldol reactions under basic conditions[23] in hope of preventing decomposition of the substrate. Thus, amide **3-38** was treated with LDA in THF at –78 °C, and the resulting lithium enolate was reacted with acrolein to produce aldol **3-40** as a major product in 43% yield (Entry 3). The moderate yield was due to decomposition of the substrate, which was attributable to ketene formation from the lithium enolate by α-elimination of the oxazolidinone group. When the solvent was changed from THF to a THF-toluene mixed system, decomposition of the substrate was suppressed, and the

yield of **3-40** was improved (63%) (Entry 4). It should be noted that the reaction temperature was required to be maintained strictly at –78 °C during the reaction for good reproducibility of the aldol reaction. The substrate **3-39** having an (*R*)-oxazolidinone also reacted with acrolein in THF-toluene to give aldol adduct **3-41** selectively (76%) (Entry 5).

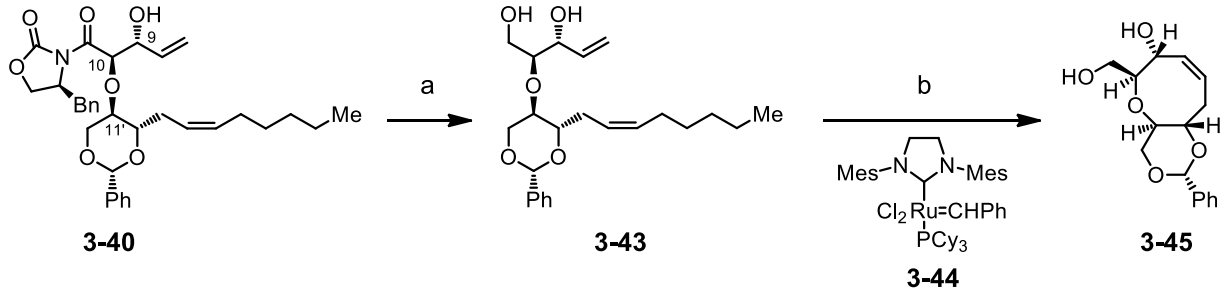
Although the stereochemistry of aldol products **3-40** and **3-41** could not be determined at this stage, the complementary configurations of **3-40** and **3-41** owing to the stereocontrol by Evans' auxiliary were successfully determined after chemical conversion, which is described in the next section. It should be noted that the selective production of an *anti*-aldol derivative (**3-40** or **3-41**) is unusual in lithium-enolate aldol reactions using Evans' auxiliary.[23]

Then, in order to install C6 stereocenter and C1-C9 lipid chain, the aldol reaction of **3-38** was attempted with β-iodo-acrolein[24] and 4-oxo-2-enal[25] **3-42** corresponding to C1-C9 chain (Entries 6 and 7). However, these reactions only produced complex mixtures. Exploration of the aldehydes matched with the carbon chain elongation is now underway.

3-5. Determination of Stereochemistry at C9 and C10 Stereocenters of the Aldol Products

The determination of stereochemistry of newly formed stereocenters at C9 and C10 of aldol products **3-40** and **3-41** was performed by applying the chemical transformation and X-ray crystallographic or NMR analysis.

First, aldol **3-40** was converted to 8-membered ring ether **3-45** as shown in Scheme 3-10. Reductive removal of the oxazolidinone of **3-40** produced diene alcohol **3-43** (58%), which was then cyclized by ring-closing olefin metathesis (RCM) with Grubbs' second generation catalyst[26] (**3-44**) to afford cyclic ether **3-45** as a crystalline compound.



Scheme 3-10: Transformation of **3-40** to cyclic ether **3-45**. Reagents and conditions: (a) $LiBH_4$, THF, MeOH, reflux, 3 h, 58%; (b) **3-44** (cat.), CH_2Cl_2, reflux, 11 h.

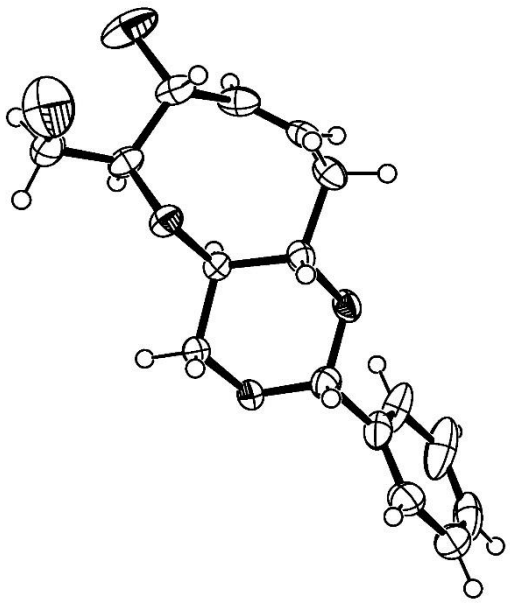
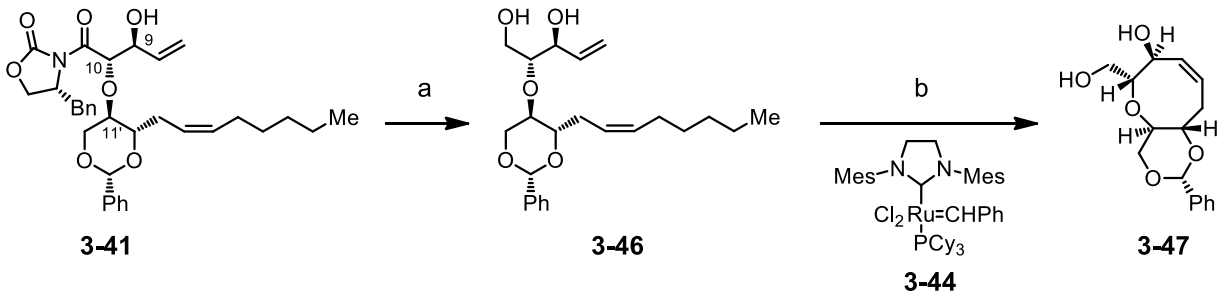


Figure 3-4. ORTEP diagram of cyclic ether **3-45**.

The stereochemistry of **3-45** was determined by X-ray crystallographic analysis on the basis of the (11'*R*,12'*S*)-configuration of **3-45**, derived from 2-deoxy-D-ribose (Figure 3-4). Thus, the stereochemistry of carbon centers C9 and C10 of **3-40**, generated by the aldol reaction, was determined to be (9*R*,10*R*).

The transformation of **3-41** to cyclic ether **3-47** was also performed in the same way (Scheme 3-11). Oxazolidinone **3-41** was reduced to give **3-46** (<30%), which was subjected to RCM in the presence of **3-44** to produce **3-47**.



Scheme 3-11: Transformation of **3-41** to cyclic ether **3-47**. Reagents and conditions: (a) $LiBH_4$, THF, MeOH, reflux, 3 h, <30%; (b) **3-44** (cat.), CH_2Cl_2, reflux, 4 h.

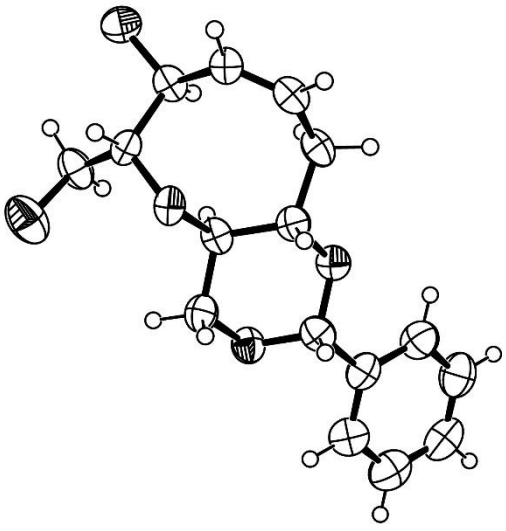


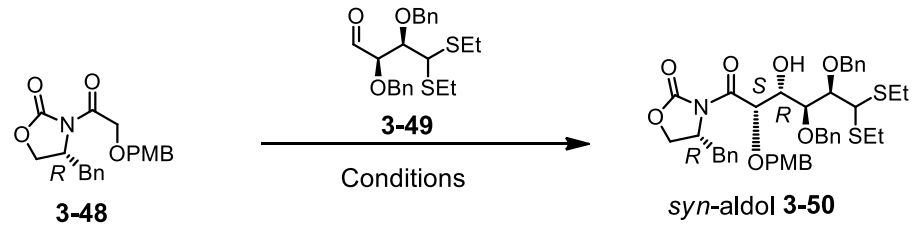
Figure 3-5. ORTEP diagram of cyclic ether **3-47**. One of two crystallographically independent molecules is shown.

The stereochemistry of **3-47** was also determined by X-ray crystallographic analysis on the

basis of the (11'*R*,12'*S*)-configuration of **3-47**, derived from 2-deoxy-D-ribose (Figure 3-5). Thus, the stereochemistry of carbon centers C9 and C10 of **3-41**, generated by the aldol reaction, was determined to be (9*S*,10*S*).

It is notable that, to the best of the author's knowledge, there is no report of systematic explanation for the stereochemistry of the lithium enolate aldol reaction using Evans-type chiral amides. Therefore, from the determined stereochemistry of aldol products **3-40** and **3-41**, the author gave careful consideration to the stereochemical outcome of the lithium enolate aldol reaction of amides **3-38** and **3-39** with acrolein.

Although there are only a few examples of the lithium enolate aldol reactions of Evans-type chiral 2-alkoxyacetamides, Seeberger has reported a typical example: the aldol reaction of 2-(4-methoxybenzyloxy)acetamide **3-48** with **3-49** mediated by LDA produced *syn*-aldol **3-50** as a major product (Table 3-2).[23]

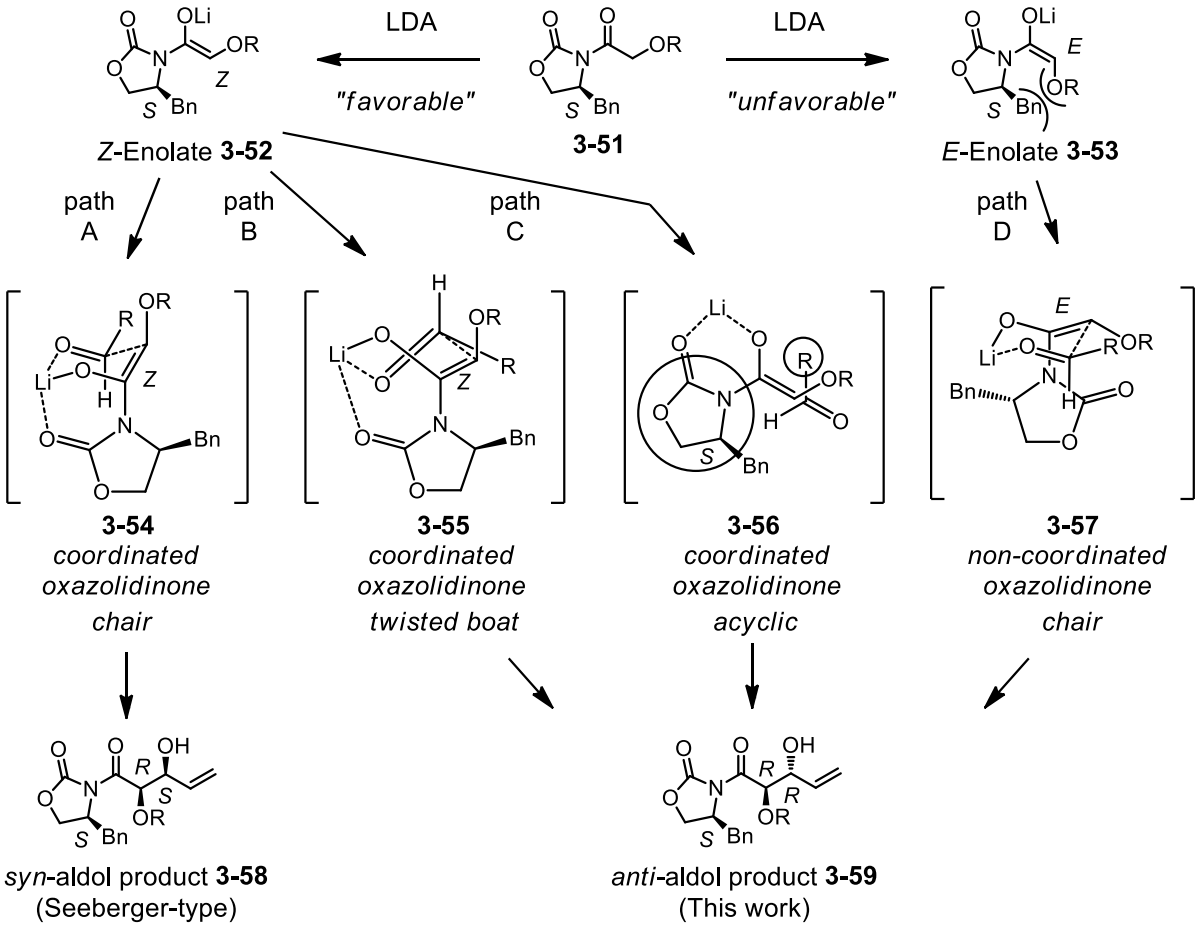


Entry	Conditions	Ratio	Yield
1	LDA, toluene, –78 °C	2.3 : 1	49%
2	LDA, Et_2O, –78 °C	4.6 : 1	50%
3	LDA, THF, –78 °C	4.9 : 1	90%

Table 3-2. Seeberger's *syn* selective aldol reaction using a lithium enolate form **3-48**.

It is well known that the deprotonation of Evans-type amides with alkali metal amide bases, such as LDA, selectively produces *Z*-enolates rather than sterically congested *E*-enolates. This fact also provides a foundation of Evans' asymmetric alkylation method.[27] The production of *syn*-aldol **3-50** in Seeberger's aldol reaction would, therefore, be explained by the formation of a Z-enolate from **3-48** followed by an aldol reaction with aldehyde **3-49** via a stable chair-form cyclic transition state. This process is illustrated as path A from Z-enolate **3-52** to **3-58** in Scheme 3-12 (the stereochemistry

is enantiomeric to that of Seeberger's compounds). The carbamoyl and enolate groups of Z-enolate **3-52** make a plane, from which the benzyl group is projected out, by the coordination of the carbamoyl O=C to the enolate lithium. Z-enolate **3-52** would react with an aldehyde from the less hindered face (from the backside of the benzyl group of the oxazolidinone) to form a stable chair formed transition state (**3-54**), in which the alkyl (R) group of the aldehyde is in an equatorial position. Thus, selective production of *syn*-aldol **3-50** (corresponding to **3-58**) in Seeberger's aldol reaction as a typical example of normal lithium enolate Evans aldol reactions is rationalized.

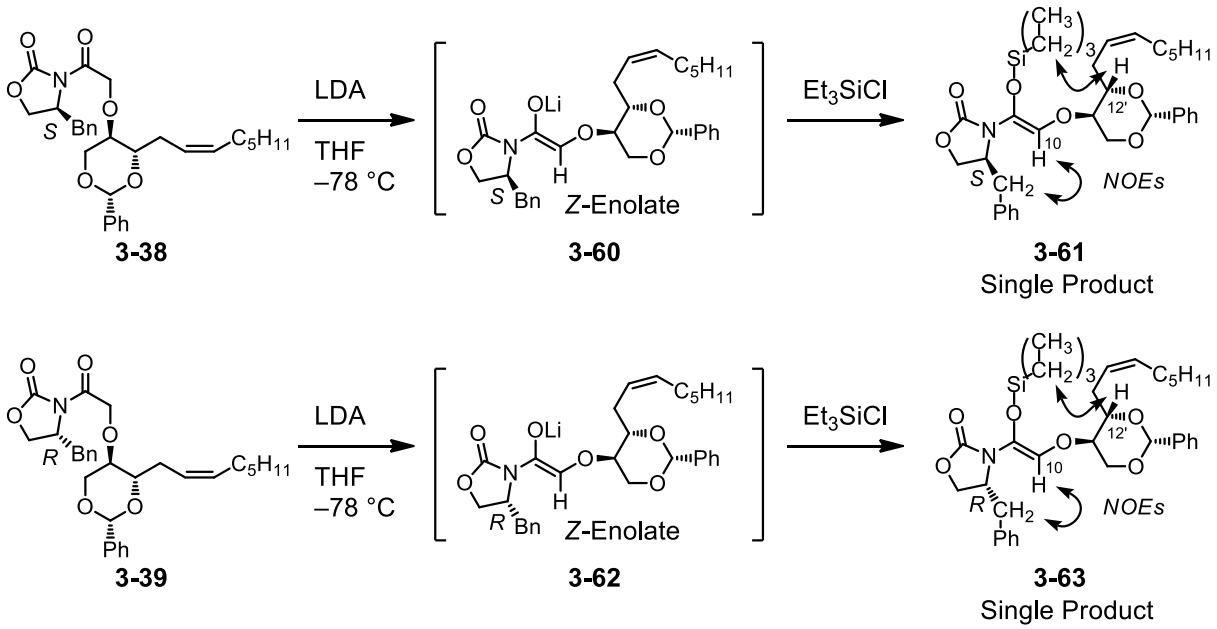


Scheme 3-12. Plausible reaction pathways for the LDA induced aldol reaction.

However, the LDA-mediated aldol reactions of **3-38** and **3-39** exhibited *anti*-selectivity on the contrary to the *syn*-preference of normal Evans aldol reactions using lithium enolates. Because substrates **3-38** and **3-39** have a sterically congested 1,3-dioxane moiety on the oxygen atom at 2-position of the acetamide group, a steric effect of this moiety may result in the production of *E*-enolates (corresponding to **3-53** in Scheme 3-12), which would react with acrolein via a transition

state (corresponding to **3-57**) having a non-coordinating oxazolidinone to produce *anti*-aldols (corresponding to **3-59**) (path D). Alternatively, the following possibilities are also considered: after the normal formation of *Z*-enolates (**3-52**) from the substrates, the *Z*-enolates would reacted with acrolein via a twisted boat form cyclic transition state (corresponding to **3-55**) (path B) or an acyclic transition state (corresponding to **3-56**) (path C), which would avoid the steric repulsion between the congested 1,3-dioxane moiety and the vinyl group of acrolein, to afford *anti*-aldols (corresponding to **3-59**).

The author next examined the trapping of lithium enolates from **3-38** and **3-39** as ketene silyl acetals to elucidate the *E*/*Z*-selectivity of the lithium enolates. The substrates were deprotonated with LDA in THF at –78 °C, and the resulting lithium enolates were reacted with Et_3SiCl to produce *Z*-enolates **3-61** and **3-63** selectively. Each Z-enolate was fairly stable and obtained as a single product. The stereochemistry of enolates **3-61** and **3-63** was determined by NOE experiments: presence of the NOE correlations between H12' and the methylene protons of the TES group and between H10 and the benzyl protons of the oxazolidinone group in both of **3-61** and **3-63** demonstrated their *Z*-geometries. Accordingly, it is suggested that original lithium enolates **3-60** and **3-61** have also *Z*-geometries.



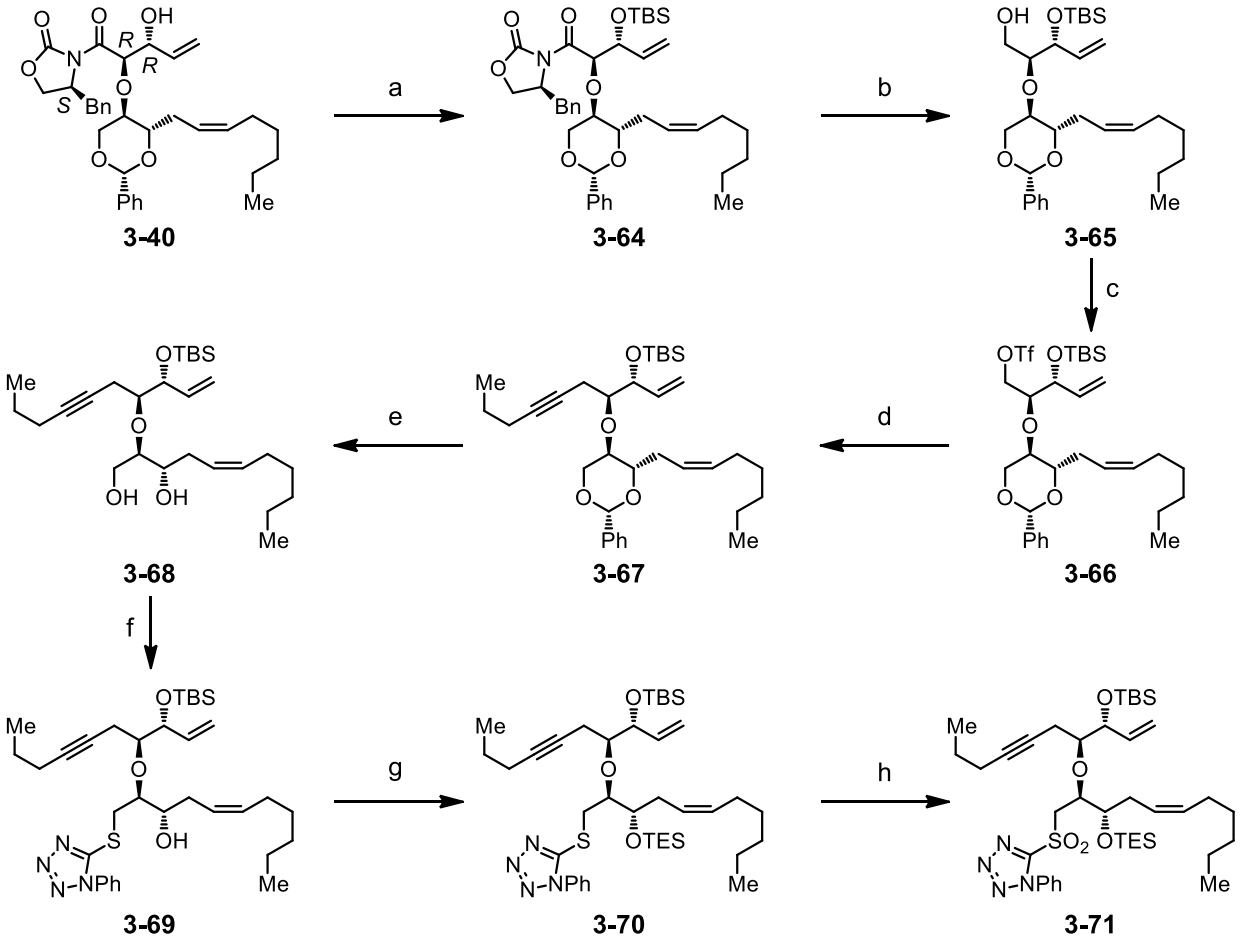
Scheme 3-13. Trapping of *Z*-enolates from **3-38** and **3-39** as ketene silyl acetals.

Therefore, the participation of *E*-enolates from **3-38** and **3-39** in the production of *anti*-aldols

3-40 and **3-41** is excluded. Although the possible reaction pathways to **3-40** and **3-41** are limited to paths B and C in Scheme 3-12, it is difficult to determine the actual pathway for the *anti*-aldol formation at this stage.

3-6. Application of the Aldol Products for Further Synthesis

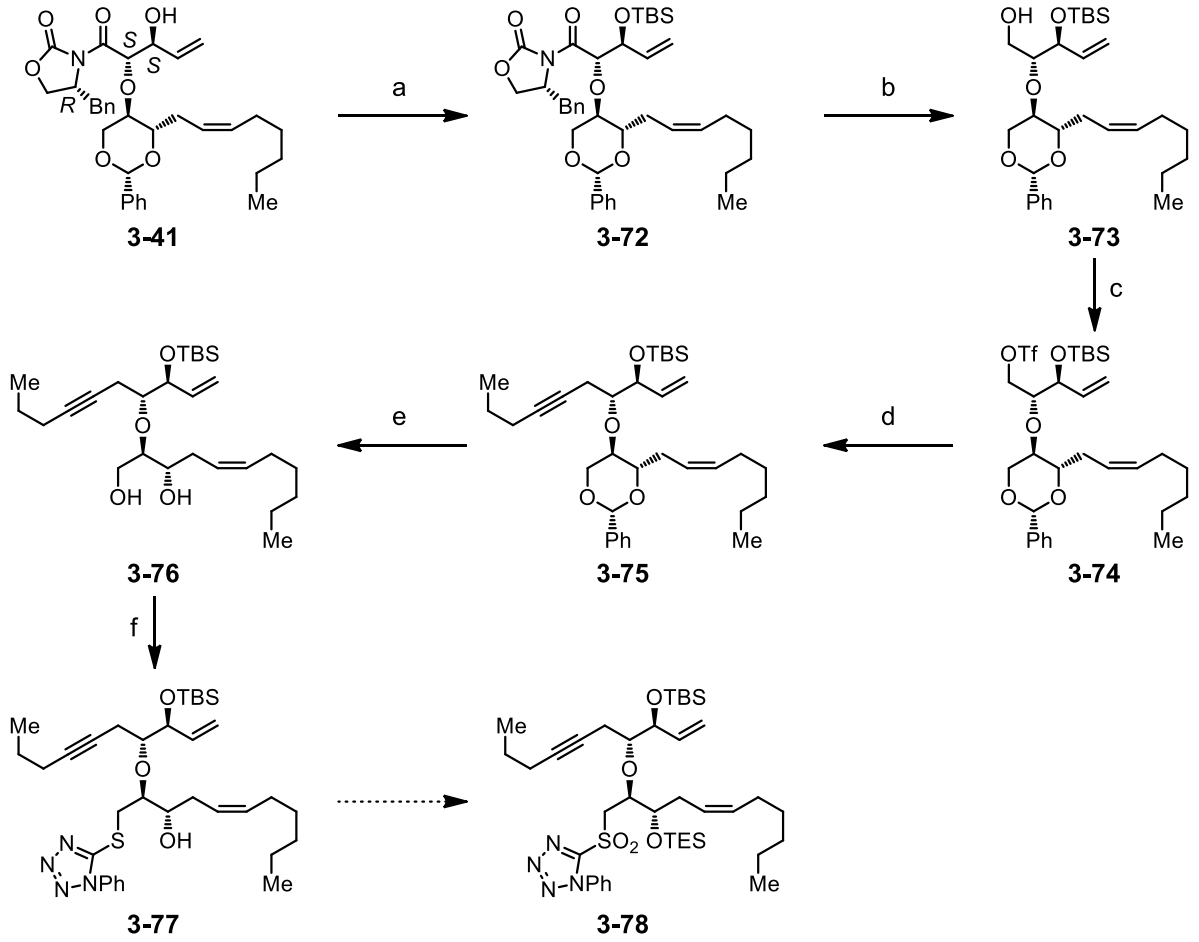
Next, in order to examine the validity of the route to **3-4**, shown in Scheme 3-8, the author undertook the synthesis of model compounds **3-71** and **3-79** using aldol products **3-40** and **3-41**, respectively.



Scheme 3-14. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → 23 °C, 3.5 h; (b) $LiBH_4$, THF, MeOH, 60 °C, 40 min, 71% over 2 steps; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C, 20 min, 63%; (d) hept-1-yne, BuLi, THF, –78 °C, 6 h, 92%; (e) $BF_3{\cdot}OEt_2$, $(CH_2SH)_2$, CH_2Cl_2, –50 °C, 35 min, 73%; (f) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF, 0 °C, 4 h, 76%; g) TESCl, imidazole, CH_2Cl_2, 23 °C, 6 h; (h) ammonium molybdate hydrate (cat.), H_2O_2, EtOH, 0 °C, 46 h; 30% over 2 steps.

The synthesis of sulfone **3-71** is shown in Scheme 3-14. First, the hydroxyl group of **3-40** was protected with TBSOTf to give **3-64**, which was subjected to the removal of the oxazolidinone group under reductive conditions to provide alcohol **3-65** (71% over two steps). Alcohol **3-65** was reacted with Tf_2O to produce triflate **3-66** (63%). The coupling reaction of **3-66** with a lithium acetylide derived from hept-1-yne afforded **3-67** in good yield (92%). As described above, a tosyloxy group at the similar position in **3-27a** could not be substituted by lithium pentynylide. High leaving ability of the triflyloxy group would enhance the reactivity of the alkyne coupling reaction. Although the reductive cleavage of the benzylideneacetal group was then attempted with DIBALH [28], $NaBH_3CN$/TMSCl [29], or borane/Lewis acid [30], the desired benzyl ether could not be obtained. Therefore, the benzylideneacetal of **3-67** was removed by treatment with 1,2-ethanedithiol and $BF_3 \cdot OEt_2$ [31] to give diol **3-68** in 73% yield along with a small amount of a triol. Mitsunobu reaction of **3-68** with 1-phenyl-1*H*-tetrazole-5-thiol selectively produced sulfide **3-69** (76%), which was protected with TESCl to give **3-70**. Finally, oxidation of **3-70** with H_2O_2 in the presence of ammonium molybdate hydrate afforded **3-71** in 30% yield over two steps. Thus, the model compound **3-71** was successfully synthesized from aldol product **3-40** in eight steps. This route is expected to be usable to the preparation of **3-4**, a key intermediate for the total synthesis of **1-1**.

Toward the model compound **3-78**, the C9,C10-epimer of **3-71**, the same eight-step process was applied to aldol **3-41** (Scheme 3-15). Indeed, the process has successfully produced sulfide **3-77**, which would be converted to **3-78** in two steps.



Scheme 3-15. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 6 h, 80%; (b) $LiBH_4$, THF, MeOH, 60 °C, 2 h, 80%; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C, 15 min then 0 °C, 40 min, 89%; (d) hept-1-yne, BuLi, THF, –78 °C, 9 h, 88%; (e) $BF_3{\cdot}OEt_2$, $(CH_2SH)_2$, CH_2Cl_2, –40 °C, 95 min, 85%; (f) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF, 0 °C, 40 min, <92%.

3-7. Conclusion

The synthesis of the C9-C10-O-C11'-C12 region of nigricanoside-A dimethyl ester (**1-1**) was selected as the second subject of the thesis. The synthesis includes the following problems: (i) formation of di-*sec*-alkyl ether should be achieved in good yield; (ii) the ethereal carbons, C10 and C11', should be constructed stereoselectively; and (iii) the stereocenters, C9 and C12, adjacent to ethereal carbons, C10 and C11', respectively, should also be built stereoselectively and simultaneously with the formation of C10-O-C11' ether bond. The author intended to find an effective solution for the above problems and performed the following studies.

The author first planned to synthesize a series of simple model compounds, **3-1a-d** (Figure 3-2), corresponding to the ether linkage between C16 and C20 fatty acid chains for the comparison of NMR spectra between natural **1-1** and each of **3-1a-d** in order to estimate the stereochemistry at C11' and C12' on the basis of the presumed C8' and C2''' configurations described in Chapter 2. The attempting synthesis of **3-2a** was started from L-(+)-diethyl tartrate through a process including reductive cleavage of cyclic acetal to form an ether bond corresponding to C10-O-C11' ether bond. Although the synthesis of **3-2a** has yet to be completed, the validity of the ether formation method in this model synthesis was demonstrated.

The author also examined the synthesis of an alternative series of model compounds, **3-3a-d** (Figure 3-3). The model compounds, which have C16 fatty acid chain and a mimic C10-O-C11' ether bond, were designed for the NMR comparison with **1-1** to find out a plausible combination of relative configurations at C6, C9 and C10 of **1-1**. For the formation of C10-O-C11' ether bond in the model synthesis of **3-3a**, an ether forming Ireland-Claisen rearrangement was applied. As a result, while the synthesis of **3-3a** was suspended due to a protecting group problem, the stereoselective formation of C10-O-C11' ether bond by Ireland-Claisen rearrangement was successfully demonstrated.

For the construction of the C9-C10-O-C11'-C12 region of **1-1**, an approach based on an asymmetric aldol reaction was also examined. The successful formation of the region is a key to achieving the total synthesis, and simultaneous generation of multi stereocenters with a stereocontrolled manner is required for efficiency. Therefore, an aldol approach for the construction of stereocenters at C9 and C10 was examined in the synthesis of **3-4**, a key intermediate for the total

synthesis of **1-1**. As a result, the author found a lithium enolate aldol reaction using Evans-type amide effective for the stereoselective construction of C11'-O-C10-C9 region. Interestingly, a substrate-specific, *anti*-stereoselectivity in the aldol reaction despite the normal *Z*-geometrical selectivity in the enolate formation step was observed. Furthermore, the synthesis of sulfone **3-71**, a model for **3-4**, from aldol products **3-40** was achieved to demonstrate the validity of the synthetic route to **3-4**. The synthesis of model sulfone **3-78** from **3-41** was also examined, and intermediate sulfide **3-77** was successfully obtained in good yield.

References

1. (a) Nicolaou, K. C.; Hwang, C.-K., Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. TMSOTf-Et_3SiH system, (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron, Lett.* **1979**, 4679. (c) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314. (d) Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **1988**, *44*, 3771. $SnCl_4$-Et_3SiH system, (e) Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987. Reduction of 6-membered cyclic acetals and hemiacetals with $BF_3{\cdot}OEt_2$-Et_3SiH system, (f) Rolf, D.; Gray, G. R. *J. Am. Chem. Soc.* **1982**, *104*, 3539. (g) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
2. (a) Whitesell, J. K.; Matthews, R. S.; Helbling, A. M. *J. Org. Chem.* **1978**, *43*, 784. (b) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941. (c) Sato, T; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. (d) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (e) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889. (f) Ireland, R. E.; Wilcox, C. S. *Tetrahedron Lett.* **1977**, *18*, 2839. (g) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (h) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. (i) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (j) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876. (k) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145.
3. (a) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591. (b) Crimmins, M. T.; She, J. *Synlett* **2004**, 1371. (c) Crimmins, M. T.; McDougall, P. J.; Emmitte, K. A. *Org. Lett.* **2005**, ***7***, 4033. (d) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548. (e) Crimmins M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (f) Kobayashi, S.; Takahashi, Y.; Komano, K.; Alizadeh, B. H.; Kawada, Y.; Oishi, T.; Tanaka, S.; Ogasawara, Y.; Sasaki, S.; Hirama, M. *Tetrahedron.* **2004**, *60*, 8375.
4. Reviews: (a) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (b) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (c) Sasaki, M. In *Topics in Heterocyclic Chemistry*; Gupta, R. R.; Kiyota, H., Eds.; Springer:

Berlin, 2006; Vol. 5, pp 149. (d) Fujiwara, K. In *Topics in Heterocyclic Chemistry*; Gupta, R. R.; Kiyota, H., Eds.; Springer: Berlin, 2006; Vol. 5, pp 97.

5. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *9*, 26
6. (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Evans D. A.; Tedrow J. S.; Shaw J. T.; Downey C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.
7. Rueffer, M. E.; Fort, L. K.; MacFarland D. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3297.
8. Sun, H.; Lin, Y.-J.; Wu, Y.-L.; Wu. Y. *Synlett*, **2009**, *15*, 2473.
9. Mitsunobu, O. *Synthesis* **1981**, *13*, l.
10. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
11. Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383.
12. (a) Ireland, R. E.; Muller, R. H.; Willard, A. K. *J. Am. Chem. Soc.***1976**, *98*, 2868. A review: (b) McFarland, C. M.; McIntosh, M. C. In *The Claisen Rearrangement*, Hiersemann, M.; Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, **2007**, p 117.
13. Domon, D. Ph.D. thesis, Hokkaido University, **2008**.
14. Nogoshi, K. Ph.D. thesis, Hokkaido University, **2012**.
15. Nogoshi, K.; Domon, D.; Fujiwara, K.; Kawamura, N.; Katoono, R.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2013**, *54*, 676.
16. Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *31*, 4609.
17. Fujiwara, K.; Kawamura, N.; Kawai, H.; Suzuki T. *Tetrahedron Letters* **2009**, *50*, 1236.
18. Barbat, J.; Gelas, J.; Horton. D. *Carbohydr. Res.* **1983**, *116*, 312.
19. Furstner, A.; Schlede, M. *Adv. Synth. Catal.* **2002**, *344*, 657.
20. Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584.
21. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
22. Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441
23. Stallforth, P.; Adibekian, A.; Seeberger, P. H. *Org. Lett.* ***2008***, *10*, 1573.
24. (a) Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1997**, *74*, 194. (b) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666.

25. (a) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W.-T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556. (b) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998,** *63,* 7505-7515

26. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953

27. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

28. Takano, S.; Akiyama. M.; Sato, S.; Ogasawara, K. *Chem. Lett*. **1983**, *12*, 1593.

29. Box, V.; Hollingsworth, R.; Roberts, E. *Heterocycles* **1980**, *14*, 1713.

30. Hernandez-torres, J. M.; Liew, S.-T.; Anchkar, J.; Wei, A. *Synthesis* **2002**, 487.

31. Konosu, T.; Oida, S. *Chem. Pharm. Bull*. **1991**, *39*, 2212.

Experimental Section

General Methods

All reactions sensitive to air or moisture were carried out under an argon atmosphere in freshly distilled dry solvent under anhydrous conditions, unless, otherwise noted. Sensitive liquids and solutions were transferred by syringe-septum and cannula techniques. All commercially available reagents were used without further purification with the following exceptions. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl under argon. Dichloromethane (CH_2Cl_2) and benzene were distilled from CaH_2 prior to use. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel (SiO_2) plates (Merck, silica gel 60 F_{254}). Plates were visualized by ultraviolet light and by treatment with acidic anisaldehyde or phosphomolybdic acid stain followed by heating. Flash chromatography was performed on YMC Silica Gel 60 (230-400 mesh) as a stationary phase. Melting points were measured on a YANAGIMOTO micro-melting apparatus without calibration. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. Infrared spectra (IR) were measured on a JEOL 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 a JEOL JNM-AL300 (^1H at 300 MHz, ^{13}C at 75 MHz) or a 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) or the residual solvent signal (for example, C_6HD_5 as 7.15 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 doublets; 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 the solvent signal (for example, $^{13}CDCl_3$ as 77.0 ppm; $^{13}C^{12}C_5D_6$ as 128 ppm) as an internal standard. Low and high resolution mass spectra were measured on a JEOL JMS-600H mass spectrometer under electron ionization (EI) condition and a JEOL JMS-SX102A mass spectrometer under field desorption (FD) condition.

Compound 3-12:

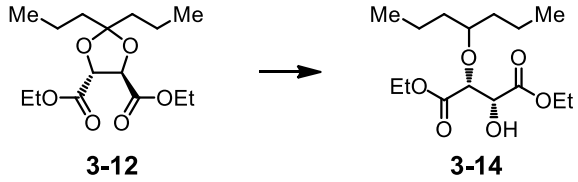
L-(+)-Diethyl tartrate (**3-13**) **3-12**

To a solution of L-(+)-Diethyl tartrate (7.112 g, 34.49 mmol) in benzene (50 ml) were added heptan-4-one (2.40 ml, 17.23 mmol) and PTS·H_2O (327 mg, 1.72 mmol) at 23 °C, and the mixture was stirred and refluxed for 24 h. Then, satd. aq. $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-12** (4.146 g, 13.71 mmol, 80% from heptan-4-one).

3-12: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (6H, t, *J* = 7.3 Hz), 1.31 (6H, t, *J* = 7.1 Hz), 1.35-1.50 (4H , m), 1.63-1.71 (4H, m), 4.27 (4H, q, *J* = 7.1 Hz), 4.69 (2H, s).

Compound 3-14:



3-12 **3-14**

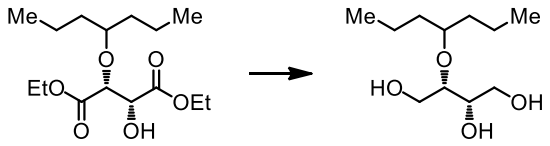
To a solution of **3-12** (4.146 g, 13.71 mmol) in CH_2Cl_2 (100 ml) were added $TiCl_4$ (3.00 ml, 27.4 mmol) and Et_3SiH (4.38 ml, 27.4 mmol) at –78 °C, and the mixture was stirred for 2 h. Then, the mixture was allowed to warm to 23°C and stirred for 15 min. Then, satd. aq. $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-14** (4.048 g, 13.30 mmol, 97%).

3-14: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85-0.93 (6H, m), 1.15-1.54 (8H, m), 1.31 (3H, t, *J* = 7.0 Hz), 1.32 (3H, t, *J* = 7.0 Hz), 3.02 (1H, d, J = 9.2 Hz, OH), 3.33-3.43 (1H, m), 4.14-4.36 (4H, m), 4.37 (1H, d,

J = 1.5 Hz), 4.56 (1H, dd, *J* =1.5, 9.2 Hz).

Compound 3-11:



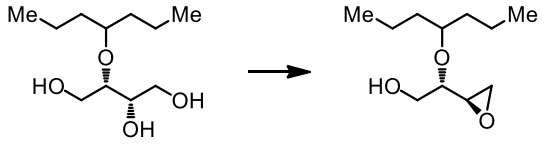
3-14 **3-11**

To a solution of **3-14** (4.048 g, 13.30 mmol) in THF (100 ml) were added $LiAlH_4$ (1.00 g, 26.4 mmol) at –15 °C, and the mixture was stirred for 5 min at –15 °C and then for 15 h at 23 °C. Then, additional $LiAlH_4$ (0.20 g, 5.3 mmol) was added, and stirred for 40 min. Then, satd. aq. Rochelle salt was added, and the mixture was stirred for a while. The mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5 → 1 → EtOAc) to give **3-11** (2.16 g, 9.80 mmol, 74%).

3-11: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (6H, brt, *J* = 7.1 Hz), 1.25-1.60 (8H, m), 2.28 (1H, brs, OH), 2.72 (1H, brs, OH), 2.81 (1H, brs, OH), 3.39-3.49 (1H, m), 3.49-3.55 (1H, m), 3.66-3.85 (2H, m).

Compound 3-10a:



3-11 **3-10a**

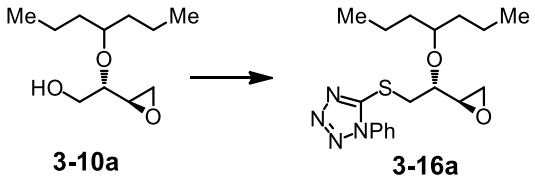
To a solution of **3-11** (254.9 mg, 1.157 mmol) in CH_2Cl_2 (20 ml) were added Et_3N (0.483 ml, 3.47 mmol), DMAP (one crystal), and TBSCl (348.8 mg, 2.314 mmol) at 23 °C, and then the mixture was stirred for 12 h. Then, additional TBSCl (87.2 mg, 0.578 mmol) and Et_3N (0.483 ml, 3.47 mmol) were added, and the mixture was stirred for 6 h. Then, additional TBSCl (52.3 mg, 0.347 mmol) was added, and the mixture was stirred for 2 h. Then, to the resulting mixture was added MsCl (0.0894 ml, 1.16 mmol) at 23 °C, and the mixture was stirred for 30 min. Then, additional MsCl (0.0894 ml,

1.16 mmol) was added, and the mixture was stirred for 30 min. Then, the solution was directly concentrated in vacuo. The resulting residue was roughly purified by column chromatography (silica gel, CH_2Cl_2) to give crude **3-15**. After the crude **3-15** was dissolved in THF (30 ml), TBAF·$3H_2O$ (965 mg, 3.061 mmol) was added to the solution at 23 °C, and the mixture was stirred for 16 h. Then, the solution was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5 → 1) to give **3-10a** (229.0 mg, 1.132 mmol, 98%).

3-10a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (6H, brt, *J* = 7.1 Hz), 1.25-1.57 (8H, m), 2.07 (1H, brs, OH), 2.71 (1H, dd, *J* = 2.7, 5.2 Hz), 2.84 (1H, dd, *J* = 4.1, 5.2 Hz), 2.96 (1H, ddd, *J* = 2.7, 4.1, 6.1 Hz), 3.25 (1H, brdt, *J* = 3.9, 5.8 Hz), 3.38-3.48 (1H, m), 3.62-3.72 (2H, m), 3.73-3.83 (2H, m).

Compound 3-16a:

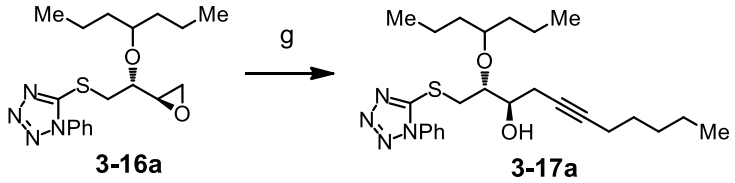


To a solution of **3-10a** (13.3 mg, 0.0657 mmol) in THF (1 ml) were added PPh_3 (24.0 mg, 0.0920 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) (16.4 mg, 0.0920 mmol) at 0 °C, and the mixture was stirred for 5 min. To the mixture was added DIAD (0.0192 ml, 0.0920 mmol) at 0 °C, and the mixture was stirred for 14 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15 → 10) to give **3-16a** (10.6 mg, 0.0292 mmol, 44%).

3-16a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, t, *J* = 7.1 Hz), 0.89 (3H, t, *J* = 7.1 Hz), 1.20-1.53 (8H, m), 2.76 (1H, dd, *J* = 2.6, 5.1 Hz), 2.81 (1H, dd, *J* = 3.9, 5.1 Hz), 3.03 (1H, ddd, *J* = 2.6, 3.9, 5.1 Hz), 3.43-3.50 (1H, m), 3.55 (1H, dd, *J* = 6.4, 12.7 Hz), 3.63-3.70 (1H, m), 3.74 (1H, dd, *J* = 4.4, 12.7 Hz), 7.50-7.65 (5H, m).

Compound 3-17a:



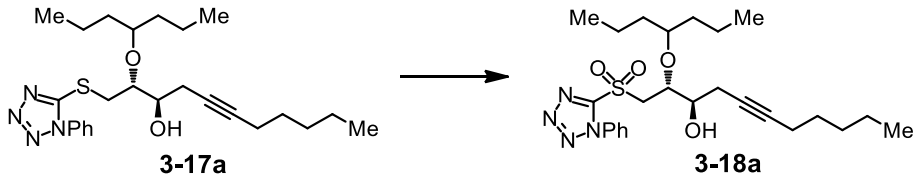
3-16a **3-17a**

To a solution of hept-1-yne (0.0256 ml, 0.197 mmol) in THF (0.4 ml) was added BuLi (1.67 M in hexane, 0.118 ml, 0.197 mmol) at –78 °C, and the mixture was stirred for 35 min. To the mixture was added BF_3•OEt_2 (0.0240 ml, 0.195 mmol) at –78 °C, and the mixture was stirred for 10 min at the same temperature. To the mixture was added a solution of **3-16a** (10.6 mg, 0.0292 mmol**)** in THF (0.3 ml), and the mixture was stirred for 45 min at the same temperature. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with hexane several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15 → 10) to give **3-17a** (9.3 mg, 0.020 mmol, 68%).

3-17a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 7.5 Hz), 0.88 (3H, t, *J* = 7.0 Hz), 0.92 (3H, t, *J* = 7.2 Hz), 1.20-1.60 (14H, m), 2.13-2.20 (2H, m), 2.53-2.59 (2H, m), 3.42-3.52 (2H, m), 3.77-3.88 (3H, m), 7.50-7.65 (5H, m).

Compound 3-18a:



3-17a **3-18a**

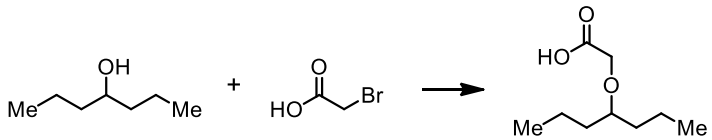
To 30% aq. H_2O_2 (0.050 ml, 0.490 mmol) was added ammonium molybdate hydrate {$Mo_7O_{24}(NH_4)_6$·$4H_2O$} (a catalytic amount) at 0 °C, and the mixture was stirred for 5 min. Then, to a solution of **3-17a** (2.0.mg, 0.0044 mmol) in EtOH (1 ml) was added the above yellow oxidant solution at 0 °C, and the mixture was stirred for 13 h. Then, the reaction was quenched with satd. aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was

purified by column chromatography (silica gel, hexane/EtOAc = 10 → 7 → 5) to give **3-18a** (1.3 mg, 0.0026 mmol, 59%).

3-18a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-0.95 (9H, m), 1.20-1.60 (14H, m), 2.11-2.19 (2H, m), 2.47-2.54 (2H, m), 3.78-3.90 (2H, m), 3.90-4.00 (3H, m), 7.59-7.65 (3H, m), 7.70-7.75 (2H, m).

Compound 3-23:



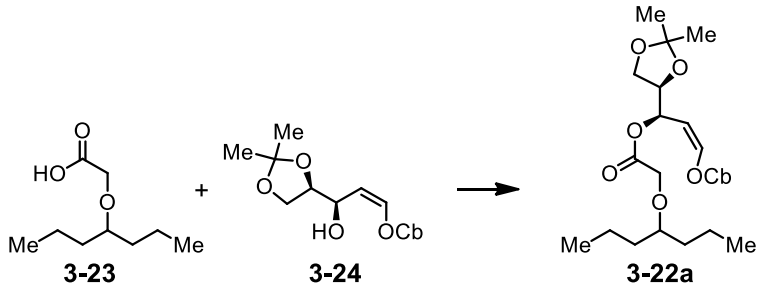
3-23

To a solution of heptan-4-ol (750 mg, 6.45 mmol) in DMF (2 ml) were added NaH (563 mg, 55% in oil, 12.9 mmol) and bromoacetic acid (1.34 g, 9.64 mmol) at 23 °C, and the mixture was stirred for several hours. Although the reaction was exothermal, the reaction was allowed to stand without cooling. During the exothermal reaction, additional DMF (7 ml) was added. Until the end of the reaction (checked by TLC), the solution turned brown. The reaction was quenched with H_2O, and the mixture was acidified and extracted with CH_2Cl_2 and EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, two times, CH_2Cl_2 and EtOAc) to give **3-23** (915 mg, 5.25 mmol, 81%).

3-23: a pale yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (6H, t, *J* = 7.1 Hz), 1.27-1.61 (8H, m), 3.40-3.49 (1H, m), 4.09 (2H, s).

Compound 3-22a:

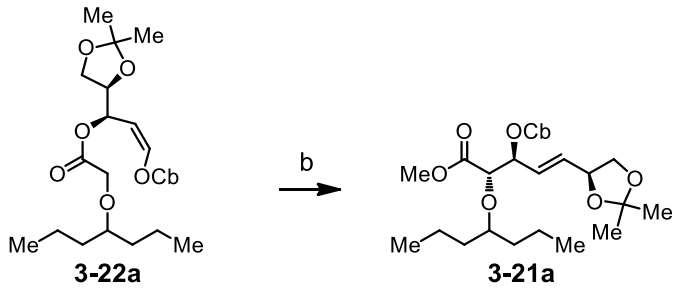


To a solution of **3-24** (165.0 mg, 0.5475 mmol), **3-23** (143.1 mg, 0.8210 mmol), and DMAP (a catalytic amount) in CH_2Cl_2 (8.0 ml) was added EDCI (157.4 mg, 0.8210 mmol) at 23 °C, and the mixture was stirred for 14 h. Then, the mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **3-22a** (240.1 mg, 0.5246 mmol, 96%).

3-22a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-0.97 (6H, m), 1.22-1.60 (20H, m), 1.34 (3H, s), 1.42 (3H, s), 3.31-3.40 (1H, m), 3.79 (1H, dd, *J* = 5.0, 8.8 Hz), 3.99 (1H, dd, *J* = 6.5, 8.8 Hz), 3.90-4.10 (2H, m), 4.06 (1H, d, *J* = 16.3 Hz), 4.14 (1H, d, *J* = 16.3 Hz), 4.16-4.24 (1H, m), 4.70 (1H, dd, J = 6.6, 9.7 Hz), 5.92 (1H, ddd, J = 0.9, 7.6, 9.7 Hz), 7.26 (1H, dd, J = 0.9, 6.6 Hz).

Compound 3-21a:



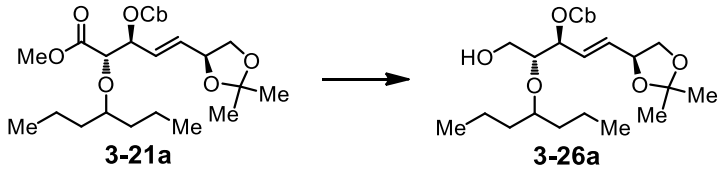
To a solution of **3-22a** (244.7 mg, 0.5347 mmol) in THF (8.0 ml) was added KHMDS (0.5 M in toluene, 3.2 ml, 1.6 mmol) at –78 °C, and the mixture was stirred for 2 min. To the mixture was added TMSCl (0.203 ml, 1.60 mmol) at –78 °C, and the mixture was stirred for 15 min at –78 °C and then for 15 min at 0 °C. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was

extracted with Et_2O, EtOAc and $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was dissolved in MeOH/CH_2Cl_2 (3 ml/1 ml). To the solution was added $TMSCHN_2$ (1.0 M in Et_2O, 1.6 ml, 1.6 mmol) at 23 °C, and the mixture was stirred for 2 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 8 → 1 → EtOAc) to give **3-21a** (118.0 mg, 0.2502 mmol, 47%, ds = 10:1).

3-21a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (6H, t, *J* = 7.0 Hz), 1.21 (12H, d, *J* = 6.5 Hz), 1.22-1.54 (8H, m), 1.38 (3H, s), 1.41 (3H, s), 3.29-3.38 (1H, m), 3.54 (1H, brt, *J* = 7.8 Hz), 3.71 (3H, s), 3.90 (2H, br-sp, *J* = 6.6 Hz), 4.08 (1H, dd, *J* = 6.2, 7.9 Hz), 4.24 (1H, d, *J* = 5.4 Hz), 4.52 (1H, brq, *J* = 6.9 Hz), 5.45 (1H, brt, *J* = 6.9 Hz), 5.71 (1H, dd, *J* = 7.1, 15.7 Hz), 5.91 (1H, dd, *J* = 7.0, 15.7 Hz).

Compound 3-26a:

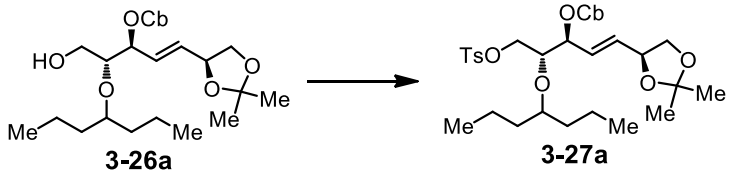


To a solution of **3-21a** (118.0 mg, 0.2502 mmol) in THF (3 ml) was added $LiAlH_4$ (9.5 mg, 0.25 mmol) at –10 °C, and the mixture was stirred for 30 min. Then, the mixture was diluted with Et_2O, and one drop of H_2O was added to the mixture. Then, one drop of 4 M aq. NaOH was added, and additional 10 drops of H_2O was added. The resulting suspension was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5 → 2) to give **3-26a** (114.0. mg, 0.2570 mmol, 100%).

3-26a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86-0.95 (6H, m), 1.17-1.57 (8H, m), 1.22 (12H, d, *J* = 6.7 Hz), 1.39 (3H, s), 1.41 (3H, s), 2.50 (1H, brs), 3.37-3.48 (1H, m), 3.38-3.70 (4H, m), 3.92 (2H, br-sp, *J* = 6.7 Hz), 4.09 (1H, dd, *J* = 6.3, 8.3 Hz), 4.53 (1H, brq, *J* = 6.9 Hz), 5.41 (1H, brt, *J* = 5.3 Hz), 5.70 (1H, brdd, *J* = 6.9, 15.6 Hz), 5.89 (1H, dd, *J* = 5.9, 15.6 Hz).

Compound 3-27a:

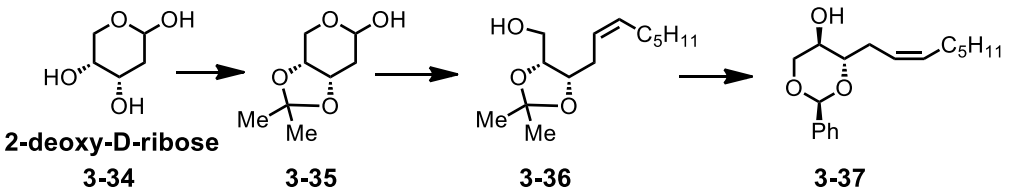


To a solution of **3-26a** (100.0 mg, 0.2254 mmol) in CH_2Cl_2 (4 ml) were added Et_3N (0.127 ml, 0.902 mmol), DMAP (one crystal), and TsCl (64.5 mg, 0.338 mmol) at 0 °C, and the mixture was stirred for 24 h at 23 °C. The reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5 → 2) to give **3-27a** (89.0 mg, 0.149 mmol, 66%).

3-27a: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (6H, brt, *J* = 7.1 Hz), 1.13-1.42 (20H, m), 1.38 (3H, s), 1.40 (3H, s), 2.44 (3H, s), 3.32-3.41 (1H, m), 3.51 (1H, t, *J* = 7.8 Hz), 3.77 (1H, td, J = 4.3, 6.3 Hz), 3.87 (2H, br-sp, *J* = 6.8 Hz), 3.97 (1H, dd, J = 6.5, 10.5 Hz), 4.03-4.10 (2H, m), 4.48 (1H, brq, *J* = 6.8 Hz), 5.28 (1H, brt, *J* = 5.0 Hz), 5.61 (1H, dd, *J* = 6.8, 15.7 Hz), 5.77 (1H, dd, *J* = 6.2, 15.7 Hz), 7.34 (2H, d, *J* = 8.3 Hz), 7.79 (2H, d, *J* = 8.3 Hz).

Compound 3-37:



To a solution of **3-34** (8.21 g, 61.2 mmol) in DMF (100 ml) were added Drierite® (4.0 g), 2-methoxypropene (11.4 ml, 122 mmol), and PTS·H_2O (40.0 mg, 0.210 mmol) at 0 °C, and the mixture was stirred for 3 h. To the mixture was added Na_2CO_3 (100 mg, 0.943 mmol), and the mixture was stirred for a while. Then, the mixture was filtered through a Celite pad, and the pad was washed with acetone. The filtrate was concentrated in vacuo to give crude **3-35**, which was used in the next reaction without further purification.

The same process from **3-34 to **3-35** was performed alternatively with 4.05 g (30.2 mmol) of **3-34**

as the second batch. The resulting crude **3-35** was combined with the above first batch product.**

To a suspension of hexyltriphenylphosphonium bromide (80.3 g, 188 mmol) in THF (400 ml) was added BuLi (1.64 M in hexane, 114.1 ml, 187.1 mmol) at –78 °C, and the mixture was stirred for 1 h. During the reaction, the solution turned red. Then, to the resulting ylide solution was added a solution of the above **combined** crude **3-35** (**the sum of two batches**, <91.4 mmol) in THF (90 ml) at –78 °C, and the mixture was stirred for 17 h at 23 °C. The reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with 3:1 mixture of hexane and Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Then, the resulting residue was suspended in hexane and filtered through a Celite pad. The pad and the residue (Ph_3PO) were washed thoroughly with hexane-EtOAc (4:1), and the filtrate was concentrated in vacuo. This operation, which was carried out to remove the Ph_3PO from **3-36**, was repeated until no white solid (Ph_3PO) was observed in crude **3-36**. The resulting crude **3-36** was used in the next reaction without further purification.

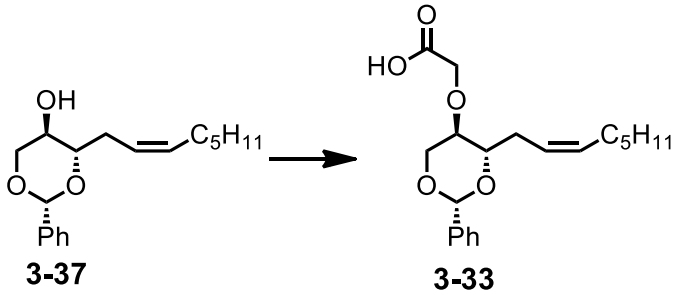
To the above crude **3-36** were added AcOH (140 ml) and H_2O (10 ml), and the mixture was stirred for 1 h at 100°C. Then the mixture was concentrated in vacuo. The residual AcOH was removed by repeated azeotropic removal of acetic acid with toluene. The resulting crude triol was used in the next reaction without further purification.

To a solution of the above crude triol in benzene (200 ml) were added benzaldehyde (12.0 ml, 119 mmol) and $PTS{\cdot}H_2O$ (a catalytic amount), and the mixture was stirred and relfuxed for 1.5 h with azeotropic removal of H_2O (by a Dean-Stark trap). Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc= 5) to give **3-37** (14.26 g, 49.10 mmol, 54% over 4 steps, **sum of two batches**).

3-37: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.6 Hz), 1.23-1.44 (6H, m), 2.05-2.15 (2H , m), 2.38-2.51 (1H, m), 2.60-2.72 (1H, m), 3.55-3.79 (2H, m), 3.58 (1H, brt, *J* = 10.2 Hz), 4.28 (1H, dd, *J*= 4.8, 10.5 Hz), 5.49 (1H, s), 5.51-5.66 (2H, m), 7.30-7.42 (3H, m), 7.45-7.52 (2H, m).

Compound 3-33:



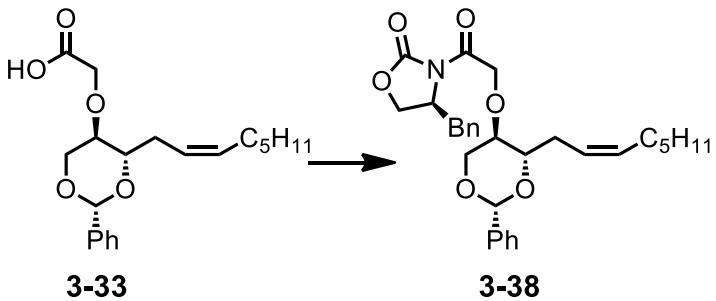
3-37 **3-33**

To a suspension of oil free NaH, which was prepared from commercial NaH in oil (55% in oil, 671.3 mg, 15.38 mmol) by washing with hexane under argon atmosphere, in THF (7 ml) was added a solution of bromoacetic acid (1.12 g, 8.06 mmol) in THF (5 ml) at 0 °C, and the mixture was stirred for 15 min at 0 °C and for 50 min for 23 °C. To the mixture was added a solution of **3-37** (1.12 g, 3.86 mmol) in DMF (7 ml) at 0 °C, and the mixture was stirred for 17 h at 23 °C. The reaction was quenched with 1 M aq. HCl, and the mixture was extracted with Et_2O and $CHCl_3$ several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude **3-33** (1.34 g, 3.84 mmol, 99%), which was used in the next reaction without further purification.

3-33: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 6.8 Hz), 1.24-1.42 (6H, m), 2.00-2.10 (2H, m), 2.41-2.53 (1H, m), 2.60-2.71 (1H, m), 3.46 (1H, ddd, *J* = 5.0, 9.2, 10.0 Hz), 3.68 (1H, brt, *J* = 10.5 Hz), 3.73 (1H, ddd, *J* = 3.8, 7.2, 9.2 Hz), 4.22 (2H, s), 4.45 (1H, dd, J = 5.0, 10.8 Hz), 5.48 (1H, s), 5.48-5.62 (2H, m), 7.31-7.41 (3H, m), 7.43-7.50 (2H, m).

Compound 3-38:



3-33 **3-38**

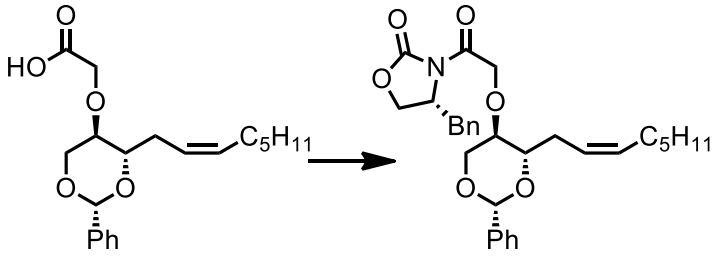
To a solution of carboxylic acid **3-33** (2.91 g, 8.36 mmol) in THF (50 ml) were added Et_3N (3.50 ml,

25.1 mmol) and pivaloyl chloride (2.01 ml, 16.3 mmol) at –20°C, and the mixture was stirred for 1 h at the same temperature. To a solution of (*S*)-4-benzyloxazolidin-2-one (1.91 g, 10.8 mmol) in THF (50 ml) was added BuLi (1.64 M in hexane, 6.12 ml, 10.0 mmol) at –20°C, and the mixture was stirred for 30 min. Then, the solution of lithium (*S*)-4-benzyl-2-oxooxazolidin-3-ide was added to the above mixed anhydride solution at –20°C, and the mixture was stirred for 3 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 8 → 4 → 1 → EtOAc) to give **3-38** (4.29 g, 8.45 mmol, ~100%).

3-38: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.7 Hz), 1.22-1.41 (6H, m), 2.02-2.14 (2H , m), 2.51 (1H, dd, *J* = 7.8, 14.3 Hz), 2.66-2.86 (1H, m), 2.82 (1H, dd, *J* = 9.5, 13.5 Hz), 3.34 (1H, dd, *J* = 3.3, 13.5 Hz), 3.45 (1H, ddd, *J* = 5.0, 9.4, 9.9 Hz), 3.73 (1H, t, *J* = 10.4 Hz), 3.71-3.80 (1H, m), 4.21-4.36 (2H, m), 4.52 (1H, dd, *J* = 5.0, 10.9 Hz), 4.64-4.76 (1H, m), 4.73 (1H, d, *J* = 17.8 Hz), 4.83 (1H, d, *J* = 17.8 Hz), 5.49 (1H, s), 5.48-5.64 (2H, m), 7.18-7.24 (2H, m), 7.27-7.40 (6H, m), 7.45-7.52 (2H, m).

Compound 3-40:



3-33 **3-39**

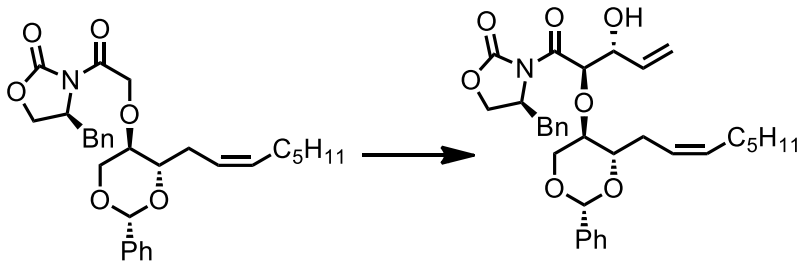
To a solution of carboxylic acid **3-33** (3.16 g, 9.07 mmol) in THF (30 ml) was added Et_3N (3.80 ml, 27.3 mmol) and pivaloyl chloride (2.20 ml, 18.1 mmol) at –20°C, and the mixture was stirred for 1 h at the same temperature. To a solution of (*R*)-4-benzyloxazolidin-2-one (2.41 g, 13.6 mmol) in THF (30 ml) was added BuLi (1.64 M in hexane, 8.29 ml, 13.6 mmol) at –20°C, and the mixture was stirred for 45 min. Then, the solution of lithium (*R*)-4-benzyl-2-oxooxazolidin-3-ide was added to the

above mixed anhydride solution at –20°C, and the mixture was stirred for 2 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 8 → 4 → 2 → EtOAc) to give **3-39** (4.03 g, 7.94 mmol, 88%).

3-39: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.4 Hz), 1.20-1.42 (6H, m), 2.02-2.14 (2H , m), 2.44-2.57 (1H, m), 2.68-2.86 (1H, m), 2.82 (1H, dd, *J* = 9.4, 13.5 Hz), 3.34 (1H, dd, *J* = 3.1, 13.5 Hz), 3.45 (1H, brdt, *J* = 5.1, 9.6 Hz), 3.73 (1H, brt, *J* = 10.4 Hz), 3.71-3.81 (1H, m), 4.20-4.34 (2H, m), 4.53 (1H, dd, *J* = 5.0, 10.7 Hz), 4.63-4.74 (1H, m), 4.75 (1H, d, *J* = 17.9 Hz), 4.80 (1H, d, *J* = 17.9 Hz), 5.49 (1H, s), 5.48-5.65 (2H, m), 7.17-7.24 (2H, m), 7.26-7.40 (6H, m), 7.44-7.53 (2H, m).

Compound 3-40:



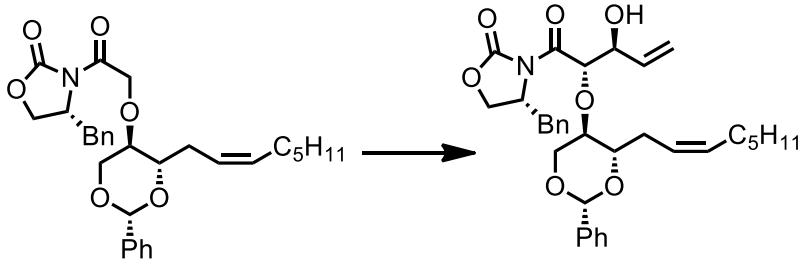
3-38 **3-40**

To a solution of **3-38** (654.8 mg, 1.290 mmol) in toluene (10 ml) was added dropwise LDA [ca. 0.97 M in THF {prepared from diisopropyl amine (1.0 ml, 7.14 mmol) and BuLi (1.65 M in hexane, 3.6 ml, 5.94 mmol) in THF (1.5 ml)}, 2.58 ml, 2.51 mmol] at –78°C, and the mixture was stirred for 5 min at –78°C. To the mixture was added acrolein (0.171 ml, 2.56 mmol) in one portion, and the mixture was stirred for 5 min. The reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 8 → 6 → 3 → EtOAc) to give **3-40** (460.6 mg, 63%).

3-40: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.8 Hz), 1.22-1.40 (6H, m), 2.02-2.12 (2H, m), 2.34-2.45 (1H, m), 2.51 (1H, d, *J* = 8.5 Hz, OH), 2.60-2.76 (1H, m), 2.66 (1H, dd, *J* = 9.9, 13.4 Hz), 3.30-3.44 (2H, m), 3.70-3.79 (1H, m), 3.71 (1H, t, *J* = 10.6 Hz), 4.17-4.36 (3H, m), 4.40-4.48 (1H, m), 4.67-4.77 (1H, m), 5.32 (1H, brd, *J* = 10.5 Hz), 5.38 (1H, d, *J* = 5.7 Hz), 5.43 (1H, brd, *J* = 17.1 Hz), 5.47 (1H, s), 5.48-5.62 (2H, m), 6.06 (1H, ddd, *J* = 5.8, 10.5, 17.1 Hz), 7.21-7.27 (2H, m), 7.27-7.38 (6H, m), 7.44-7.49 (2H, m).

Compound 3-41:



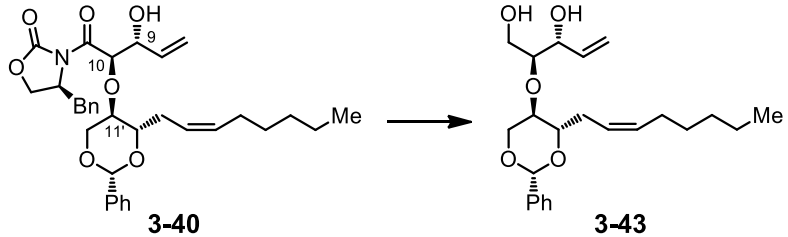
3-39 **3-41**

To a solution of **3-39** (1.35 g, 2.66 mmol) in toluene (25 ml) was added dropwise LDA [ca. 0.98 M in THF {prepared from diisopropyl amine (1.5 ml, 10.7 mmol) and BuLi (1.64 M in hexane, 6.0 ml, 9.84 mmol) in THF (2.5 ml)}, 8.0 ml, 7.84 mmol] at –78°C, and the mixture was stirred for 35 min at –78°C. To the mixture was added acrolein (0.532 ml, 7.98 mmol) in one portion, and the mixture was stirred for 10 min. The reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 8) to give **3-41** (1.14 g, 2.02 mmol, 76%).

3-41: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.5 Hz), 1.20-1.40 (6H, m), 2.04-2.16 (2H, m), 2.26-2.41 (1H, m), 2.49 (1H, d, *J* = 7.7 Hz, OH), 2.66 (1H, dd, *J* = 10.6, 13.6 Hz), 2.75-2.94 (1H, m), 3.23-3.46 (2H, m), 3.54-3.77 (2H, m), 4.18-4.34 (2H, m), 4.45-4.52 (2H, m), 4.68-4.80 (1H, m), 5.31 (1H, brd, *J* = 10.5 Hz), 5.42 (1H, d, *J* = 5.8 Hz), 5.43 (1H, brd, *J* = 17.2 Hz), 5.47 (1H, s), 5.47-5.61 (2H, m), 6.03 (1H, ddd, *J* = 5.7, 10.5, 17.2 Hz), 7.16-7.39 (8H, m), 7.41-7.50 (2H, m).

Compound 3-43:



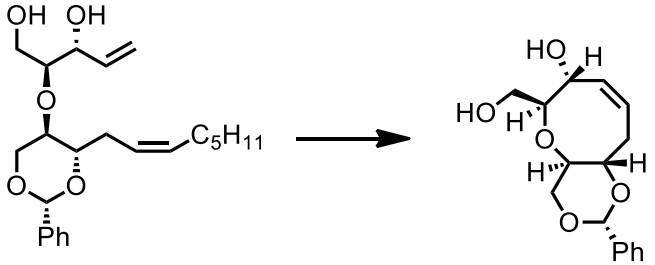
3-40 **3-43**

To a solution of **3-40** (80.3 mg, 0.142 mmol) in THF (1.0 ml) and MeOH (0.5 ml) was added $LiBH_4$ (10 mg, 0.459 mmol) at 23 °C, and the mixture was stirred for 2 h at 70 °C. Then the reaction was quenched with NH_4Cl sat solution and was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 5 → 4→ EtOAc) and HPLC (YMC-Pack SIL-06-5 μm, 500 mm × 20 mmID, hexane/EtOAc) to give **3-43** (32.3 mg, 0.0827 mmol, 58%).

3-43: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.5 Hz), 1.20-1.42 (6H, m), 2.00-2.10 (2H, m), 2.21 (1H, brs, OH), 2.34-2.50 (1H, m), 2.49 (1H, brs, OH), 2.60-2.76 (1H, m), 3.44-3.80 (6H, m), 4.34-4.44 (2H, m), 5.28 (1H, brd, *J* = 10.5 Hz), 5.41 (1H, brd, *J* = 17.2 Hz), 5.48 (1H, s), 5.48-5.64 (2H, m), 5.86-5.99 (1H, m), 7.30-7.40 (3H, m), 7.44-7.52 (2H, m).

Compound 3-45:

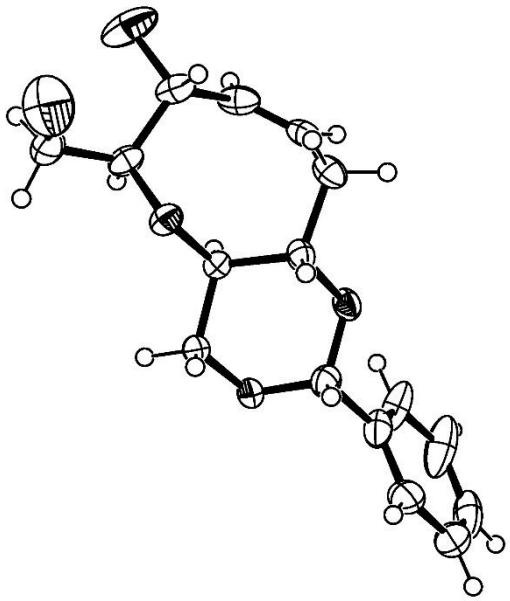


3-43 **3-45**

To a solution of **3-43** (27.3 mg, 0.0699 mol) in CH_2Cl_2 (20 ml) was added Grubbs' second generation catalyst (**3-44**) (1.3 mg, 0.0015 mmol) at 23 °C, and the mixture was stirred and refluxed for 2 h. Then, the reaction was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 4 → 1 → EtOAc) to give **3-45** as a crystalline

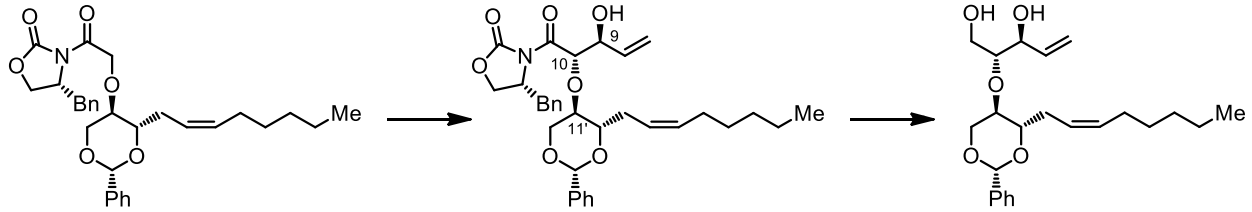
compound. Pure single crystals for X-ray crystallographic analysis were obtained by recrystallization (Et_2O/hexane).

Crystal data for **3-45**: Crystals were obtained by recrystallizing from Et_2O/hexane. $C_{16}H_{20}O_5$, M = 292.33, colorless needle, 0.600 × 0.010 × 0.010 mm^3, monoclinic $P2_1$ (No. 4), a = 8.589(4) Å, b = 4.806(2) Å, c = 17.432(7) Å, β = 98.331(5)°, V = 712.0(5) $Å^3$, D_c (Z = 2) = 1.363 g cm^{-3}. A total 744 unique data ($2\theta_{max}$ = 58.5°) were measured at T = 173 K by Rigaku Mercury CCD apparatus (Mo Kα radiation, λ = 0.71075 Å). Numerical absorption correction was applied (μ = 1.007 cm^{-1}). The structure was solved by the direct method (SIR2004) and refined by the full-matrix least-squares method of F^2 with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located at the calculated positions and refined with riding. The final *R1* and *wR2* values are 0.0882 (all data) and 0.2518 (all data), respectively, for 3032 reflections and 191 parameters. Estimated standard deviations are 0.005–0.011 Å for bond lengths and 0.3–0.6° for bond angles, respectively.



ORTEP diagram of cyclic ether **3-45**.

Compound 3-46:



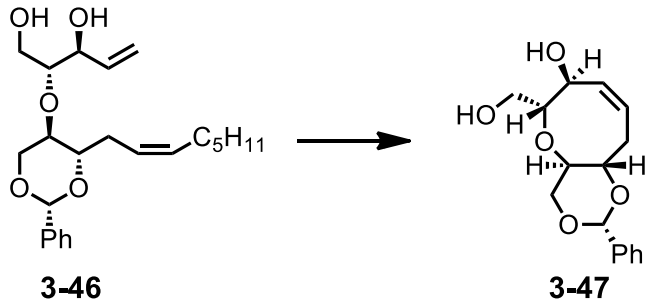
To a solution of **3-39** (92.4 mg, 0.182 mmol) in THF (2 ml) was added dropwise LDA [ca. 0.97 M in THF {prepared from diisopropyl amine (1.0 ml, 7.14 mmol) and BuLi (1.65 M in hexane, 3.6 ml, 5.94 mmol) in THF (1.5 ml)}, 0.546 ml, 0.530 mmol] at –78°C, and the mixture was stirred for 10 min at –78°C. To the mixture was added acrolein (0.10 ml, 1.5 mmol) in one portion, and the mixture was stirred for 15 min. The reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude **3-41**.

To a solution of the above crude **3-41** in THF (1.0 ml) and MeOH (0.5 ml) was added $LiBH_4$ (an excess amount) at 23 °C, and the mixture was stirred for 6 h at the same temperature. Then the reaction was quenched with NH_4Cl sat solution and was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by HPLC (YMC-Pack SIL-06-5 μm, 500 mm × 20 mmID, hexane/EtOAc = 2/3) to give **3-46** (21.3 mg, 0.0545 mmol, 30% over two steps).

3-46: a colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.9 Hz), 1.22-1.40 (6H, m), 2.00-2.10 (2H, m), 2.40-2.50 (1H, m), 2.63-2.71 (1H, m), 3.46 (1H, brq, *J* = 4.5 Hz), 3.51-3.65 (2H, m), 3.65-3.72 (1H, m), 3.74-3.84 (2H, m), 4.25-4.31 (1H, m), 4.36-4.42 (1H, m), 5.27 (1H, brd, *J* = 10.6 Hz), 5.39 (1H, brd, *J* = 17.3 Hz), 5.47 (1H, s), 5.48-5.63 (2H, m), 5.91 (1H, ddd, J = 5.9, 10.6, 17.3 Hz), 7.30-7.40 (3H, m), 7.43-7.50 (2H, m).

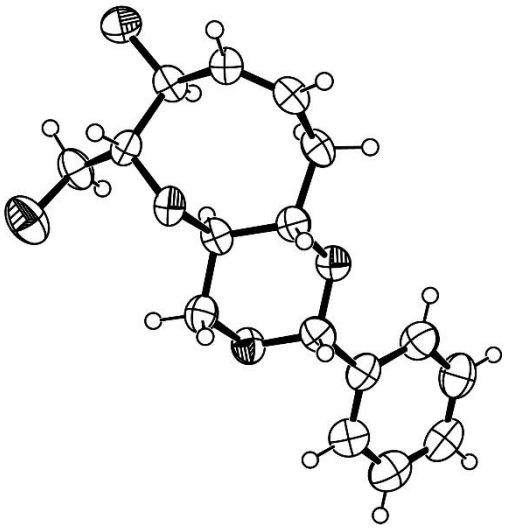
Compound 3-47:



3-46 **3-47**

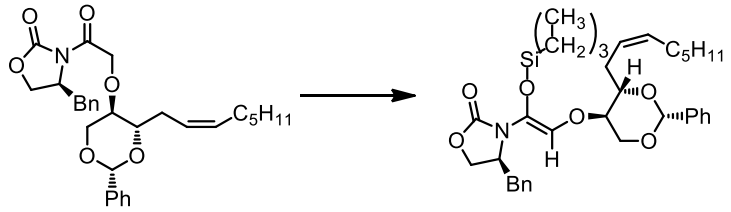
To a solution of **3-46** (21.3 mg, 0.0545 mol) in CH_2Cl_2 (40 ml) was added Grubbs' second generation catalyst (**3-44**) (1.2 mg, 0.0014 mmol) at 23 °C, and the mixture was stirred and refluxed for 4 h. Then, the reaction was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel + florisil, CH_2Cl_2 → hexane/EtOAc = 1 → 1/3) to give **3-47** as a crystalline compound. Pure single crystals for X-ray crystallographic analysis were obtained by recrystallization (Et_2O/hexane).

Crystal data for **3-47**: Crystals were obtained by recrystallizing from Et_2O/hexane. $C_{16}H_{20}O_5$, M = 292.33, colorless needle, 0.400 × 0.200 × 0.010 mm^3, monoclinic $P2_1$ (No. 4), a = 16.487(11) Å, b = 4.461(3) Å, c = 20.93(2) Å, β = 112.934(13)°, V = 1418(2) $Å^3$, D_c (Z = 4) = 1.370 g cm^{-3}. A total 744 unique data ($2\theta_{max}$ = 58.6°) were measured at T = 173 K by Rigaku Mercury CCD apparatus (Mo Kα radiation, λ = 0.71075 Å). Numerical absorption correction was applied (μ = 1.011 cm^{-1}). The structure was solved by the direct method (SIR2004) and refined by the full-matrix least-squares method of F^2 with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located at the calculated positions and refined with riding. The final *R1* and *wR2* values are 0.0856 (all data) and 0.2307 (all data), respectively, for 4898 reflections and 379 parameters. Estimated standard deviations are 0.006–0.012 Å for bond lengths and 0.4–0.7° for bond angles, respectively.



ORTEP diagram of cyclic ether **3-47**. One of two crystallographically independent molecules is shown.

Compound 3-61:



3-38 **3-61**

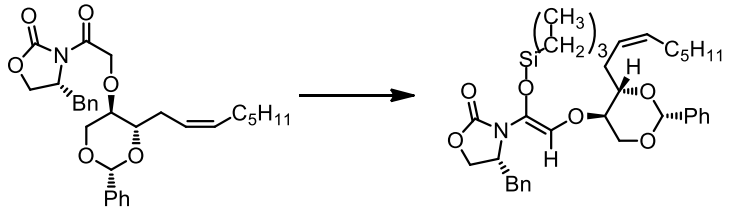
To a solution of **3-38** (85.0 mg, 0.167 mmol) in THF (2 ml) was added dropwise LDA [ca. 0.97 M in THF {prepared from diisopropyl amine (1.0 ml, 7.14 mmol) and BuLi (1.65 M in hexane, 3.6 ml, 5.94 mmol) in THF (1.5 ml)}, 0.502 ml, 0.486 mmol] at –78°C, and the mixture was stirred for 10 min at –78°C. To the mixture was added TESCl (0.084 ml, 0.50 mmol) in one portion, and the mixture was stirred for 2 h. The reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 15 → 10 → 7→ 1→ EtOAc) to give **3-61** (71.8 mg, 0.115 mmol, 69%).

3-61: a colorless oil;

^{1}H NMR (400 MHz, C_6D_6, C_6HD_5 as 7.15 ppm) δ 0.79-0.91 (9H, m, -$SiCH_2$-, H20'), 1.05-1.13 (9H,

m), 1.15-1.24 (4H, m), 1.24-1.34 (2H, m), 2.02-2.14 (2H, m), 2.24 (1H, dd, *J* = 10.2, 13.5 Hz, -CH_2-Ph), 2.47-2.57 (1H, m), 2.70-2.79 (1H, m), 2.98 (1H, dd, *J* = 3.9, 13.5 Hz, -CH_2-Ph), 3.50-3.60 (3H, m), 3.71 (1H, dt, *J* = 3.3, 7.8 Hz, H12'), 3.86-3.96 (2H, m), 4.32-4.44 (1H, m), 5.28 (1H, s), 5.52-5.62 (1H, m), 5.70-5.82 (1H, m), 5.77 (1H, s, H10), 6.82 (2H, d, J = 7.0 Hz), 6.98-7.09 (3H, m), 7.10-7.26 (3H, m), 7.63 (2H, d, J = 7.2 Hz).

Compound 3-63:

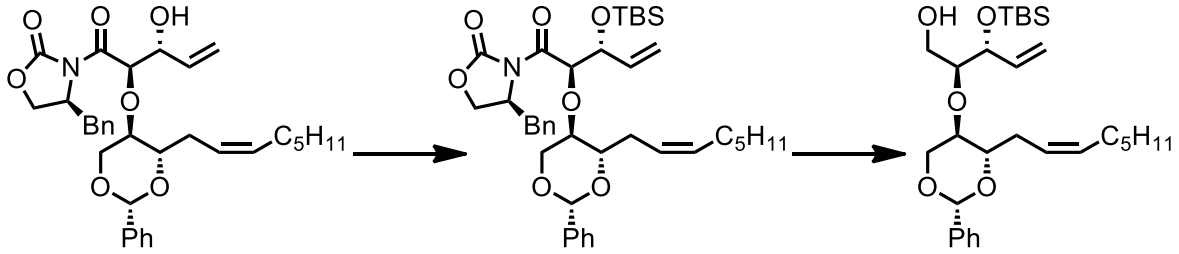


To a solution of **3-39** (60.8 mg, 0.119 mmol) in THF (2 ml) was added dropwise LDA [ca. 0.97 M in THF {prepared from diisopropyl amine (1.0 ml, 7.14 mmol) and BuLi (1.65 M in hexane, 3.6 ml, 5.94 mmol) in THF (1.5 ml)}, 0.359 ml, 0.384 mmol] at –78°C, and the mixture was stirred for 10 min at –78°C. To the mixture was added TESCl (0.060 ml, 0.36 mmol) in one portion, and the mixture was stirred for 2 h. The reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 15 → 10 → 7→ 1→ EtOAc) to give **3-63** (44.5 mg, 0.0716 mmol, 60%).

3-63: a colorless oil;

^{1}H NMR (400 MHz, C_6D_6, C_6HD_5 as 7.15 ppm) δ 0.83-0.93 (9H, m, -$SiCH_2$-, H20'), 1.10 (9H, t, *J* = 7.9 Hz), 1.20-1.47 (6H, m), 2.19 (1H, dd, *J* = 9.9, 13.4 Hz, -CH_2-Ph), 2.20-2.28 (2H, m), 2.56-2.66 (1H, m), 2.80-2.90 (1H, m), 2.91 (1H, dd, *J* = 4.2, 13.4 Hz, -CH_2-Ph), 3.49-3.58 (3H, m), 3.70-3.77 (1H, m, H12'), 3.84-3.95 (2H, m), 4.21-4.26 (1H, m), 5.28 (1H, s), 5.63-5.72 (1H, m), 5.74 (1H, s, H10), 5.79-5.87 (1H, m), 6.77-6.82 (2H, m), 7.00-7.10 (3H, m), 7.10-7.16 (1H, m), 7.18-7.24 (2H, m), 7.62-7.66 (2H, m).

Compound 3-64:



3-40 **3-64** **3-65**

To a solution of **3-40** (323.5 mg, 0.5739 mmol) and 2,6-lutidine (0.163 ml, 1.42 mmol) in CH_2Cl_2 (8 ml) was added TBSOTf (0.198 ml, 0.861 mmol) at 0 °C, and the mixture was stirred for 80 min at the same temperature and then for 2 h at 23 °C. Then, MeOH (an excess amount) was added to the mixture, and the mixture was concentrated in vacuo to give crude **3-64**. [Pure **3-64** was obtained through purification of crude mixture from an alternative batch by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 1). **3-64**: a colorless oil; $[\alpha]_D^{25}$ +1.9 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.13 (3H, s), 0.88 (3H, t, *J* = 6.5 Hz), 0.91 (9H, s), 1.20-1.42 (6H, m), 2.00-2.12 (2H, m), 2.28-2.41 (1H, m), 2.56 (1H, dd, *J* = 11.2, 13.2 Hz), 2.82-2.93 (1H, m), 3.32-3.48 (2H, m), 3.62-3.78 (2H, m), 4.10-4.33 (3H, m), 4.46-4.54 (1H, m), 4.62-4.75 (1H, m), 5.20-5.31 (2H, m), 5.37 (1H, d, *J* = 3.9 Hz), 5.46 (1H, s), 5.45-5.60 (2H, m), 5.92-6.06 (1H, m), 7.19-7.26 (2H, m), 7.26-7.40 (6H, m), 7.40-7.50 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.6 (CH_3), –4.4 (CH_3), 14.1 (CH_3), 18.2 (C), 22.6 (CH_2), 25.8 (CH_3×3), 27.5 (CH_2), 29.3 (CH_2), 29.9 (CH_2), 31.6 (CH_2), 38.3 (CH_2), 55.5 (CH), 66.9 (CH_2), 69.5 (CH_2), 75.2 (CH), 75.6 (CH), 80.6 (CH), 81.9 (CH), 100.7 (CH), 117.5 (CH_2), 124.7 (CH), 126.0 (CH×2), 127.4 (CH), 128.1 (CH×2), 128.7 (C), 129.0 (CH×2), 129.2 (CH×2), 132.3 (CH), 135.2 (CH), 136.6 (C), 137.8 (CH), 153.0 (C), 171.1 (C).]

To a solution of the above crude **3-64** in THF (10 ml) was added $LiBH_4$ (50.0 mg, 2.29 mmol), and the mixture was stirred for 40 min at 60 °C and 10 min at 23 °C. Then, the mixture was diluted with MeOH and 1 M aq. HCl and extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 8) to give **3-65** (205.3 mg, 0.4067 mmol, 71% over 2 steps).

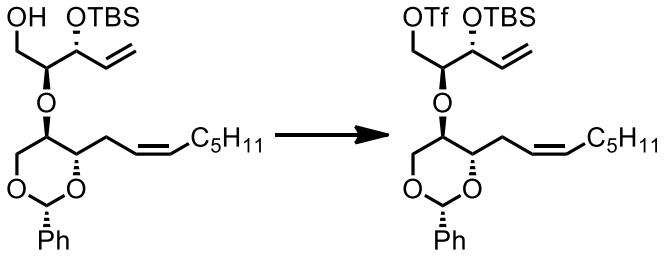
3-65: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.11 (3H, s), 0.88 (3H, t, *J* = 6.5 Hz), 0.92 (9H, s), 1.22-

1.40 (6H, m), 1.99-2.10 (2H, m), 2.22 (1H, t, *J* = 6.0 Hz, OH), 2.23-2.42 (1H, m), 2.68-2.78 (1H, m), 3.41 (1H, brq, *J* = 4.2 Hz), 3.48-3.76 (5H, m), 4.24-4.31 (1H, m), 4.38-4.47 (1H, m), 5.24 (1H, brd, *J* = 10.5 Hz), 5.31 (1H, d, *J* = 17.1 Hz), 5.46 (1H, s), 5.45-5.61 (2H, m), 5.89 (1H, ddd, J = 6.3, 10.5, 17.1 Hz), 7.30-7.40 (3H, m), 7.43-7.51 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$) δ –5.0 (CH_3), –4.4 (CH_3), 14.0 (CH_3), 18.1 (C), 22.5 (CH_2), 25.8 (CH_3×3), 27.5 (CH_2), 29.2 (CH_2), 29.9 (CH_2), 31.5 (CH_2), 62.0 (CH_2), 70.0 (CH_2), 72.7 (CH), 75.6 (CH), 80.9 (CH), 81.9 (CH), 100.7 (CH), 116.9 (CH_2), 124.9 (CH), 126.0 (CH×2), 128.1 (CH×2), 128.7 (CH), 132.0 (CH), 137.8 (C+CH).

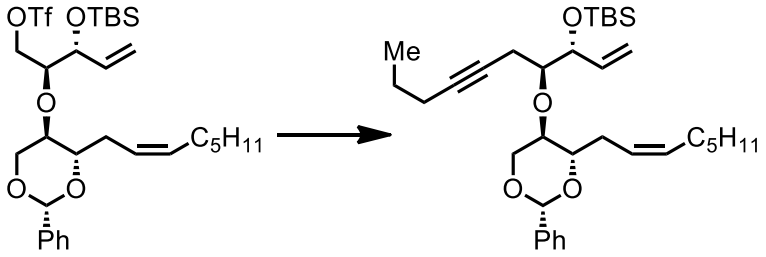
Compound 3-66:



3-65 **3-66**

To a solution of **3-65** (64.0 mg, 0.127 mmol) in CH_2Cl_2 (1.5 ml) were added 2,6-lutidine (0.044 ml, 0.38 mmol), and Tf_2O (0.043 ml, 0.25 mmol) at –78 °C, and the mixture was stirred for 20 min. The reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was roughly purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 1) to give triflate **3-66** (50.9 mg, 0.0799 mmol, 63%, a colorless oil), which was used immediately in the next reaction.

Compound 3-67:



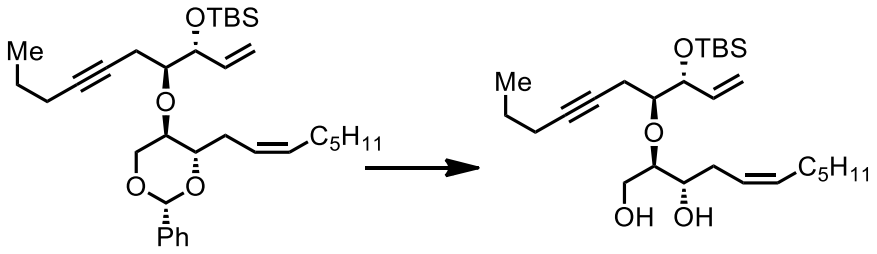
To a solution of pent-1-yne (0.070 ml, 0.71 mmol) in THF (0.8 ml) was added BuLi (1.65 M in hexane, 0.363 ml, 0.599 mmol) at –78 °C, and the mixture was stirred for 1 h. To the solution of pent-1-yn-1-yllithium was added a solution of **3-66** (50.9 mg, 0.0799 mmol) in THF (1.0 ml) at –78 °C, and the mixture was stirred for 6 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with hexane and Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 4 → 1 → 0) to give **3-67** (40.8 mg, 0.0735 mmol, 92%).

3-67: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.09 (3H, s), 0.88 (3H, t, *J* = 6.9 Hz), 0.91 (9H, s), 0.99 (3H, t, *J* = 7.4 Hz), 1.22-1.40 (6H, m), 1.53 (2H, sx, *J* = 7.2 Hz), 1.96-2.10 (2H, m), 2.15 (2H, tt, *J* = 2.4, 7.0 Hz), 2.23-2.38 (1H, m), 2.35 (1H, td, *J* = 2.4, 5.9 Hz), 2.76-2.86 (1H, m), 3.46-3.63 (4H, m), 4.22-4.28 (1H, m), 4.42-4.50 (1H, m), 5.21 (1H, brd, *J* = 10.4 Hz), 5.27 (1H, brd, *J* = 17.3 Hz), 5.44 (1H, s), 5.44-5.61 (2H, m), 5.90 (1H, ddd, J = 6.7, 10.4, 17.3 Hz), 7.28-7.40 (3H, m), 7.43-7.52 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$) δ –4.9 (CH_3), –4.3 (CH_3), 13.6 (CH_3), 14.0 (CH_3), 18.2 (C), 20.8 (CH_2), 22.3 (CH_2), 22.6 (CH_2), 25.9 (CH_3×3), 27.5 (CH_2), 29.3 (CH_2), 29.9 (CH_2), 31.6 (CH_2), 70.2 (CH_2), 73.3 (CH), 75.7 (CH), 76.3 (C), 81.1 (CH), 82.1 (CH), 82.3 (C), 100.7 (CH), 116.9 (CH_2), 125.2 (CH), 126.1 (CH×2), 128.1 (CH×2), 128.6 (CH), 131.9 (CH), 137.6 (CH), 138.1 (C).

Compound 3-68:



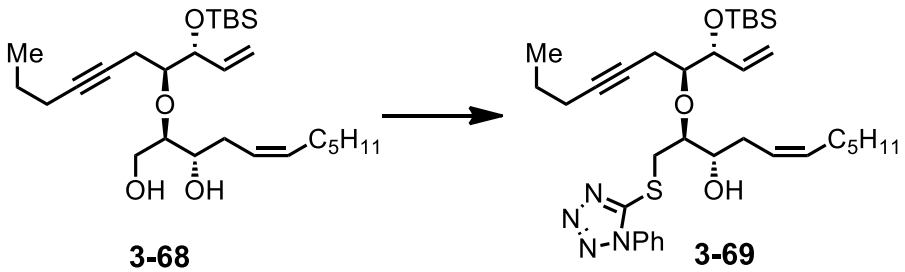
3-67 **3-68**

To a solution of **3-67** (166.2 mg, 0.2995 mmol) in CH_2Cl_2 (30 ml) were added ethanedithiol (0.063 ml, 0.75 mmol) and BF_3·OEt (0.056 ml, 0.45 mmol) at –50 °C, and the mixture was stirred for 35 min. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 20 → 10 → 4 → 1 → EtOAc) to give **3-68** (101.7 mg, 0.2179 mmol, 73%) and a triol (23.0 mg, 0.0652 mmol, 22%).

3-68: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.10 (3H, s), 0.89 (3H, t, *J* = 6.5 Hz), 0.90 (9H, s), 0.97 (3H, t, *J* = 7.4 Hz), 1.22-1.41 (6H, m), 1.52 (2H, sx, *J* = 7.2 Hz), 1.95-2.08 (2H, m), 2.15 (2H, tt, *J* = 2.3, 7.1 Hz), 2.16-2.54 (4H, m), 2.61 (1H, brs, OH), 2.98 (1H, brs, OH), 3.50-3.87 (5H, m), 4.24 (1H, brdd, *J* = 4.6, 7.3 Hz), 5.22-5.30 (2H, m), 5.30-5.58 (2H, m), 5.85-5.96 (1H, m).

Compound 3-69:



3-68 **3-69**

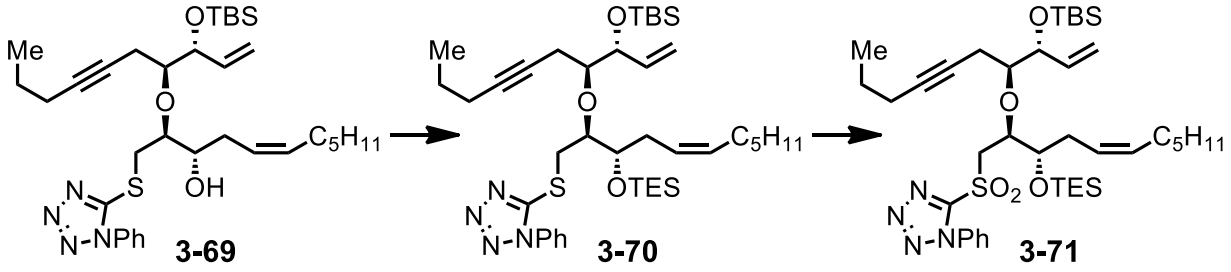
To a solution of **3-68** (10.2 mg, 0.0229 mmol), PPh_3 (6.6 mg, 0.025 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) (12.2 mg, 0.0688 mmol) in THF (0.6 ml) was added DIAD (0.0049 ml, 0.025 mmol) at 0 °C, and the mixture was stirred for 3 h. Then, to the mixture was added an additional

DIAD (0.0025 ml, 0.013 mmol), and the mixture was stirred for 50 min. Then, the mixture was diluted with EtOAc and H_2O and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 20 → 12 → 5) to give **3-69** (11.0 mg, 0.0175 mmol, 76%).

3-69: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.09 (3H, s), 0.88 (3H, t, *J* = 7.2 Hz), 0.90 (9H, s), 0.93 (3H, t, *J* = 7.3 Hz), 1.20-1.51 (8H, m), 1.94-2.12 (4H, m), 2.12-2.54 (4H, m), 3.53 (1H, dd, *J* = 7.7, 13.8 Hz), 3.64 (1H, ddd, *J* = 3.3, 5.5, 8.0 Hz), 3.70 (1H, dd, *J* = 3.4, 13.8 Hz), 3.76-3.94 (3H, m), 4.33 (1H, dd, *J* = 3.3, 7.5 Hz), 5.19-5.27 (2H, m), 5.43-5.58 (2H, m), 5.86 (1H, ddd, J = 7.5, 10.0, 17.7 Hz), 7.50-7.62 (5H, m).

Compound 3-71:



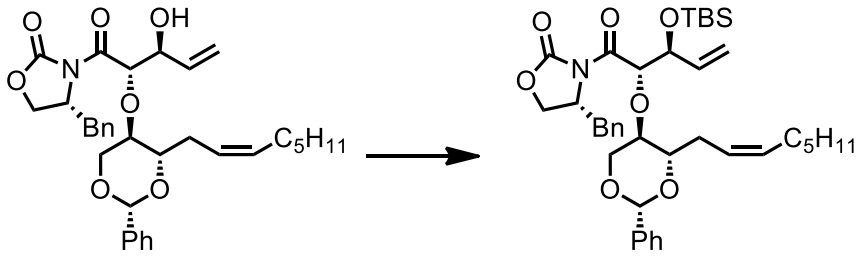
To a solution of **3-69** (11.0 mg, 0.0175 mmol) in CH_2Cl_2 (0.5 ml) were added imidazole (11.9 mg, 0.0175 mmol) and TESCl (0.0079 ml, 0.053 mmol) at 23 °C, and the mixture was stirred for 6 h. Then the mixture was diluted with hexane and filtered through a Celite pad. The residue was washed with hexane several times. The filtrate was concentrated in vacuo to give crude **3-70** [^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.06 (3H, s), 0.59 (6H, q, *J* = 7.9 Hz), 0.87 (9H, s), 0.87-0.96 (15H, m), 1.22-1.38 (6H, m), 1.43 (2H, sx, J = 7.2 Hz), 1.92-2.06 (4H, m), 2.24-2.38 (4H, m), 3.50 (1H, dd, *J* = 6.1, 13.6 Hz), 3.71-3.78 (1H, m), 3.80 (1H, dd, *J* = 4.4, 13.6 Hz), 3.92 (1H, dt, *J* = 2.7, 6.5 Hz), 4.08-4.15 (1H, m), 4.30-4.36 (1H, m), 5.15 (1H, brd, *J* = 10.4 Hz), 5.23 (1H, brd, J = 17.3 Hz), 5.32-5.52 (2H, m), 5.86 (1H, ddd, J = 6.4, 10.4, 17.3 Hz), 7.51-7.63 (5H, m).], which was used to the next reaction without further purification.

To 30% aq. H_2O_2 (0.200 ml, 1.76 mmol) was added ammonium molybdate hydrate $\{Mo_7O_{24}(NH_4)_6 \cdot 4H_2O\}$ (7.9 mg, 0.18 mmol) at 0 °C, and the mixture was stirred for 5 min. Then, to a solution of the above crude **3-70** in EtOH (0.5 ml) was added the above yellow oxidant solution at 0 °C, and the mixture was stirred for 46 h. Then, TBHP (0.9 M in toluene, 2 drops) and MeOH were added to the mixture, and the mixture was stirred for 40 min. Then, the reaction was quenched with satd. aq. $Na_2S_2O_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 30 → 4) to give **3-71** (4.1 mg, 0.0053 mmol, 30% over two steps).

3-71: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.06 (3H, s), 0.61 (6H, q, *J* = 7.7 Hz), 0.88 (9H, s), 0.86-0.98 (15H, m), 1.22-1.38 (6H, m), 1.45 (2H, sx, *J* = 7.2 Hz), 1.94-2.40 (8H, m), 3.79 (1H, dt, *J* = 3.4, 6.5 Hz), 3.98-4.08 (2H, m), 4.16 (1H, dd, *J* = 3.2, 15.6 Hz), 4.25-4.31 (1H, m), 4.35-4.40 (1H, m), 5.12-5.26 (2H, m), 5.26-5.40 (1H, m), 5.42-5.52 (1H, m), 5.78 (1H, ddd, J = 6.6, 10.4, 17.2 Hz), 7.57-7.64 (3H, m), 7.64-7.72 (3H, m).

Compound 3-72:



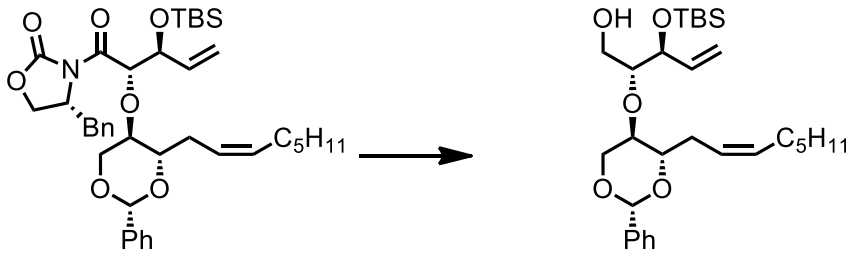
3-41 **3-72**

To a solution of **3-41** (1.14 g, 2.02 mmol) and 2,6-lutidine (0.500 ml, 4.34 mmol) in CH_2Cl_2 (20 ml) was added TBSOTf (0.640 ml, 2.78 mmol) at 0 °C, and the mixture was stirred for 2 h. Then, an additional TBSOTf (0.150 ml, 0.653 mmol) was added, and the mixture was stirred for 4 h. Then, the mixture was diluted with $CHCl_3$ and MeOH and concentrated in vacuo. The resultant residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 6) to give **3-72** (1.09 g, 1.61 mmol, 80%).

3-72: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.13 (3H, s), 0.88 (3H, t, *J* = 6.5 Hz), 0.92 (9H, s), 1.22-1.40 (6H, m), 2.00-2.14 (2H, m), 2.22-2.40 (1H, m), 2.57 (1H, dd, *J* = 10.8, 13.1 Hz), 2.70-2.83 (1H, m), 3.32-3.45 (2H, m), 3.56-3.74 (2H, m), 4.09-4.30 (2H, m), 4.42-4.54 (2H, m), 4.64-4.77 (1H, m), 5.20-5.28 (2H, m), 5.36 (1H, d, *J* = 4.4 Hz), 5.42-5.61 (2H, m), 5.45 (1H, s), 5.94 (1H, ddd, *J* = 7.2, 10.5, 17.1 Hz), 7.19-7.26 (2H, m), 7.26-7.39 (6H, m), 7.42-7.51 (2H, m).

Compound 3-73:



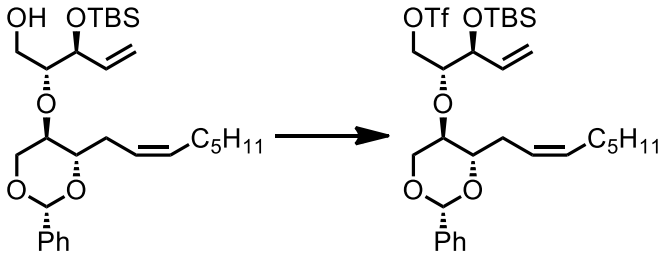
3-72 **3-73**

To a solution of **3-72** (1.09 g, 1.61 mmol) in THF (20 ml) and MeOH (5.0 ml) was added $LiBH_4$ (190.6 mg, 8.75 mmol), and the mixture was stirred for 2 h at 60 °C. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 1) to give **3-73** (651.3 mg, 1.290 mmol, 80%).

3-73: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.11 (3H, s), 0.87 (3H, t, *J* = 6.9 Hz), 0.91 (9H, s), 1.20-1.40 (6H, m), 2.00-2.10 (2H, m), 2.17 (1H, t, *J* = 6.0 Hz, OH), 2.37-2.50 (1H, m), 2.64-2.75 (1H, m), 3.39 (1H, brq, *J* = 4.6 Hz), 3.55 (2H, brd, *J* = 7.2 Hz), 3.57-3.68 (1H, m), 3.73 (2H, dd, *J* = 5.0, 6.0 Hz), 4.19 (1H, brt, *J* = 5.5 Hz), 4.33-4.43 (1H, m), 5.21 (1H, brd, *J* = 10.6 Hz), 5.28 (1H, d, *J* = 17.1 Hz), 5.45 (1H, s), 5.48-5.62 (2H, m), 5.85 (1H, ddd, J = 6.6, 10.6, 17.1 Hz), 7.29-7.38 (3H, m), 7.42-7.50 (2H, m).

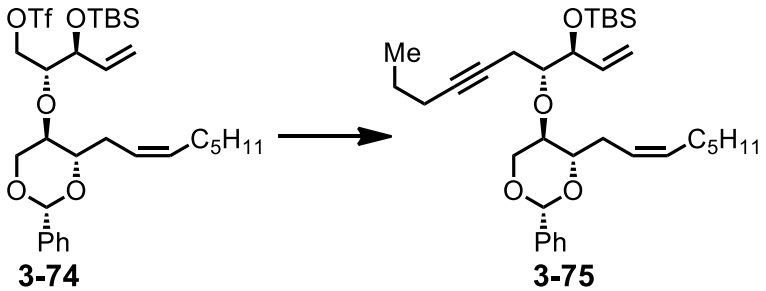
Compound 3-74:



3-73 **3-74**

To a solution of **3-73** (273.3 mg, 0.5414 mmol) in CH_2Cl_2 (8 ml) were added 2,6-lutidine (0.156 ml, 1.35 mmol) and Tf_2O (0.181 ml, 1.08 mmol) at –78 °C, and the mixture was stirred for 15 min at –78 °C and for 40 min at 0 °C. Then, the reaction was quenched with 1 M aq. HCl, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was roughly purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 4) to give triflate **3-74** (306.8 mg, 0.4818 mmol, 89%, a colorless oil), which was used immediately in the next reaction.

Compound 3-75:



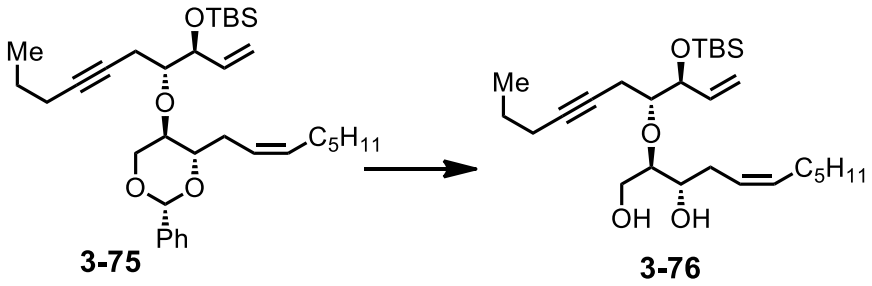
3-74 **3-75**

To a solution of pent-1-yne (0.300 ml, 3.04 mmol) in THF (3 ml) was added BuLi (1.64 M in hexane, 1.52 ml, 2.49 mmol) at –78 °C, and the mixture was stirred for 25 min at –78 °C, 15 min at 0 °C, and 10 min at –78 °C. To the solution of pent-1-yn-1-yllithium was added a solution of **3-74** (306.8 mg, 0.4818 mmol) in THF (3 ml) at –78 °C, and the mixture was stirred for 9 h. Then, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted with hexane and Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 10 → 1) to give **3-75** (235.4 mg, 0.4242 mmol, 88%).

3-75: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.10 (3H, s), 0.88 (3H, t, *J* = 6.7 Hz), 0.92 (9H, s), 0.98 (3H, t, *J* = 7.3 Hz), 1.22-1.40 (6H, m), 1.52 (2H, sx, *J* = 7.4 Hz), 2.00-2.18 (4H, m), 2.28-2.49 (3H, m), 2.68-2.78 (1H, m), 3.44-3.62 (4H, m), 4.21-4.27 (1H, m), 4.38-4.48 (1H, m), 5.16-5.29 (2H, m), 5.43 (1H, s), 5.44-5.60 (2H, m), 5.82 (1H, ddd, J = 6.8, 10.4, 17.3 Hz), 7.29-7.38 (3H, m), 7.42-7.50 (2H, m).

Compound 3-76:

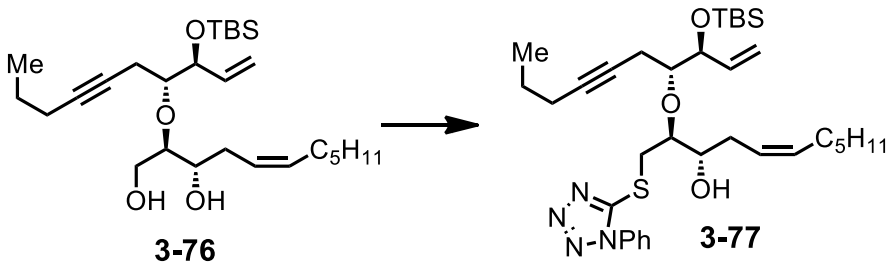


To a solution of **3-75** (200.4 mg, 0.3612 mmol) in CH_2Cl_2 (10 ml) were added ethanedithiol (0.100 ml, 1.31 mmol) and BF_3·OEt (0.100 ml, 0.803 mmol) at –40 °C, and the mixture was stirred for 95 min. Then, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 20 → 4 → EtOAc) to give **3-76** (143.0 mg, 0.3064 mmol, 85%) and a triol (10.3 mg, 0.0292 mmol, 8%).

3-76: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.11 (3H, s), 0.89 (3H, t, *J* = 7.0 Hz), 0.91 (9H, s), 0.97 (3H, t, *J* = 7.4 Hz), 1.20-1.42 (6H, m), 1.51 (2H, sx, *J* = 7.1 Hz), 1.96-2.09 (2H, m), 2.09-2.18 (2H, m), 2.21-2.33 (2H, m), 2.37-2.53 (2H, m), 3.21-3.30 (1H, m), 3.48-3.88 (4H, m), 4.26-4.34 (1H, m), 5.20-5.30 (2H, m), 5.30-5.60 (2H, m), 5.83-5.98 (1H, m).

Compound 3-77:



To a solution of **3-76** (9.0 mg, 0.0193 mmol), PPh_3 (15.2 mg, 0.0579 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) (10.3 mg, 0.0578 mmol) in THF (0.4 ml) was added DIAD (0.0050 ml, 0.025 mmol) at 0 °C, and the mixture was stirred for 25 min. Then, additional DIAD (two drops) was added, and the mixture was stirred for 15 min. Then, the mixture was diluted with Et_2O and MeOH and concentrated in vacuo. The resulting residue was suspended with hexane, and the mixture was filtered through a Celite pad. The residue was washed with hexane several times. The filtrate was concentrated in vacuo to give crude **3-77** (11.1 mg, <0.0177 mmol, <92%).

3-77: a colorless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ –0.02 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 0.88 (3H, t, *J* = 7.6 Hz), 0.96 (3H, t, *J* = 7.3 Hz), 1.20-1.40 (6H, m), 1.51 (2H, sx, *J* = 7.3 Hz), 1.94-2.17 (4H, m), 2.24-2.52 (4H, m), 3.57-3.66 (1H, m), 3.76-3.82 (2H, m), 3.70 (1H, dd, *J* = 3.4, 13.8 Hz), 3.82-3.88 (1H, m), 3.90-3.99 (1H, m), 4.20-4.26 (1H, m), 5.11-5.24 (2H, m), 5.45-5.58 (2H, m), 5.86 (1H, ddd, J = 7.2, 10.3, 17.2 Hz), 7.50-7.62 (5H, m).

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September 2013

Naoto KINASHI