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**Studies toward Convergent Total Synthesis of
Nigricanoside A Dimethyl Ester**

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Dissertation

**Graduate School of Chemical Sciences and Engineering
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Abbreviation

Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
AuNPs	gold nanoparticles
Aux	auxiliary group
Bn	benzyl
Bu	butyl
BRSM	based on recovered starting material
^t Bu	<i>tert</i> -butyl
calcd	calculated
cat.	catalytic
CSA	(±)-10-camphorsulfonic acid
Cy	cyclohexyl
d	day
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Eq	equivalent
Et	ethyl
FD	field desorption ionization
FT	Fourier transform
h	hour
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography

HR	high resolution
IC	inhibitory concentration
IR	infrared absorption spectroscopy
KHMDS	potasium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LR	low resolution
Me	methyl
Mes	mesityl
min	minute
MOM	methoxymethyl
MS	mass spectrometry
Ms	mesyl
MTPA	2-methoxy-2-trifluoromethyl-2-phenylacetyl (or phenylacetic acid)
NHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance
PBB	<i>p</i> -bromobenzyl
Ph	phenyl
Phe	phenylalanine
PMB	<i>p</i> -methoxybenzyl
ⁿ Pr	propyl
ⁱ Pr	isopropyl
PTS	<i>p</i> -toluenesulfonic acid
SEM	β-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBME	<i>tert</i> -butylmethylether
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl

TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin-layer chromatography
TMS	trimethylsilyl / tetramethylsilane
Ts	<i>p</i> -toluenesulfonyl

Chapter 1.

Introduction

1-1. Introduction

Nigricanoside A (**1-1**) (Figure 1-1) is a novel monogalactosyldiacylglycerol (MGDG) isolated from the green alga *Avrainvillea nigricans* by Andersen in 2007.¹ The structure of **1-1** was elucidated by NMR analysis on the dimethyl ester of **1-1** (nigricanoside A dimethyl ester: **1-2**). MGDG **1-1** consists of oxygenated C16 and C20 fatty acids and a galactosylglycerol, which are linked to each other by oxygen atoms to form C10-O-C11' and C8'-O-C6'' ether bonds. The fatty acid chains of **1-1** also have three hydroxy groups at C6, C9, and C12'. However, initial stereochemical information was limited to the relative stereostructure of the galactose moiety. Nigricanoside B (**1-3**), a congener of **1-1**, was also isolated from *A. nigricans*. The spectral data of the dimethyl ester of **1-3** (nigricanoside B dimethyl ester: **1-4**) is quite similar to those of **1-2**, but the spectra show the difference of **1-4** from **1-2** in the number of double bonds of the C20 fatty acid unit.

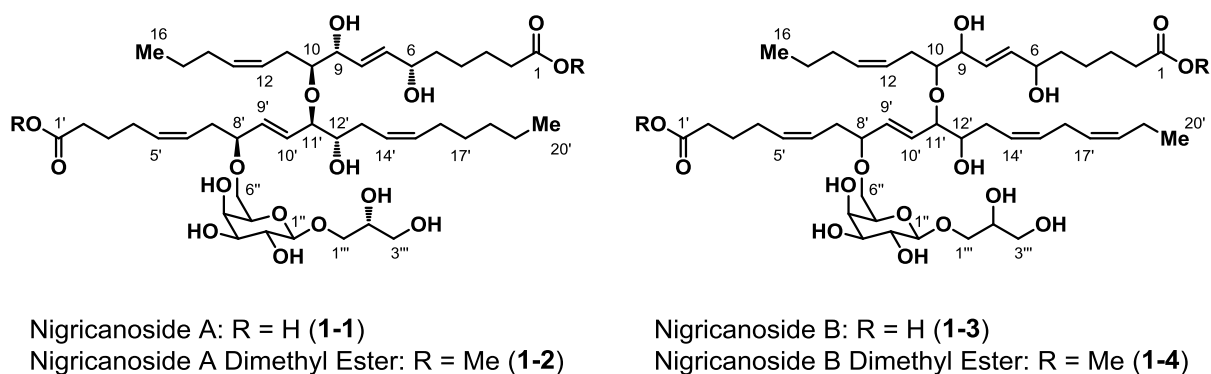


Figure 1-1. Structures of nigricanoside congeners

Andersen initially reported a possible strong cytotoxicity of **1-2** against cancer cells [IC₅₀ of **1-2**: 3 nM against human breast cancer MCF-7 cells and human colon cancer HCT-116 cells] due to its potent antimitotic activity. Therefore, several research groups, including the laboratory to which the author belongs, have paid significant attention to the unique structure and bioactivity of **1-2** and independently started their projects toward total synthesis of **1-2** aiming at the determination of the absolute configuration and demonstration of the cytotoxicity, in spite of the incompletely determined stereochemistry of **1-2**.

As early approaches to **1-2**, the syntheses of the C16 fatty acid unit were independently

reported by MacMillan (2009)² and Kuwahara (2012)³ groups. A model compound corresponding to the galactosylglycerol linked C20 fatty acid unit of **1-2**, including the C8'-O-C6'' ether linkage, was stereoselectively synthesized by Kinashi,⁴ a former member of the laboratory to which the author belongs, in 2013. A biomimetic approach was also planned by Falck in 2014 for the formation of the C10-O-C11' linkage of **1-2** via the connection between allyl monoepoxy alcohols derived from unsaturated fatty acids.⁵ In 2015, Ready achieved the determination of the full absolute configuration of the natural **1-2** by the stereoselective total synthesis and demonstrated the absence of cytotoxicity of **1-2**.⁶ After all, it was clarified that the novel structure of **1-2** causes no antimitotic activity.

The author explored the absolute stereochemistry of **1-2** by comparison between NMR data of natural **1-2** and the synthetic fragments, prepared by the author, during graduate thesis study and master's thesis study. Since Ready reported the total synthesis and absolute configuration of **1-2** just after the master's thesis study, the author started a PhD thesis study toward the development of a new efficient construction process for the established structure of **1-2**.

In this dissertation work, the author has established a new efficient method for the stereoselective construction of the C10-O-C11' ether linkage of **1-2** and synthesized the framework of the right half segment of **1-2**. These details are described in Chapter 2. Furthermore, toward the establishment of the convergent synthesis of **1-2**, several methods for the connection between left- and right-half segments were examined. These results are explained in Chapter 3.

1-2. Synthetic Studies on Nigricanosides by Other Groups

In this section, the total synthesis and the synthetic studies of Nigricanoside congeners by other groups are shown.

1-2-1. The First Appearance of Nigricanoside-related Synthetic C16-Lipid Chain

A model compound (**1-5**) (Figure 1-2) for the C16-lipid chain of **1-2** was first reported by the MacMillan group in 2009 in an article that described a new NMR method, MEDEC (Multi Frequency Homonuclear Decoupling).² However, no synthetic details were reported.

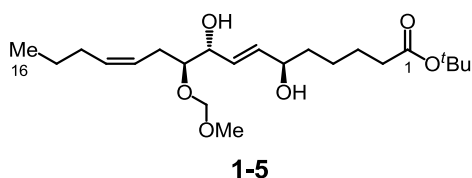
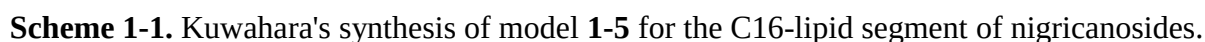


Figure 1-2. MacMillan's model compound **1-5** for the C16-lipid chain of **1-2**.

1-2-2. Synthetic Studies on Nigricanosides by the Kuwahara Group

The Kuwahara group stereoselectively synthesized compound **1-6** as a model for the upper fatty acid segment of nigricanosides in 2012 (Scheme 1-1).³ The synthesis was performed through a convergent route via the connection of C1-C7 segment **1-14** and C8-C16 segment **1-12**. Preparation of **1-12** was based on Evans' asymmetric alkylation of **1-7** with **1-8** to produce **1-9**.¹¹ The counterpart **1-14** was obtained via Sharpless kinetic resolution⁷ of ester **1-13**. Connection between **1-12** and **1-14** using Horner-Wadsworth-Emmons reaction⁸ gave **1-15** in a *trans*-selective manner. Ketone **1-15** was reduced diastereoselectively to afford upper fatty acid model **1-6**. Thus, the Kuwahara group accomplished the stereoselective synthesis of a diastereomer of the upper fatty acid segment of nigricanosides.



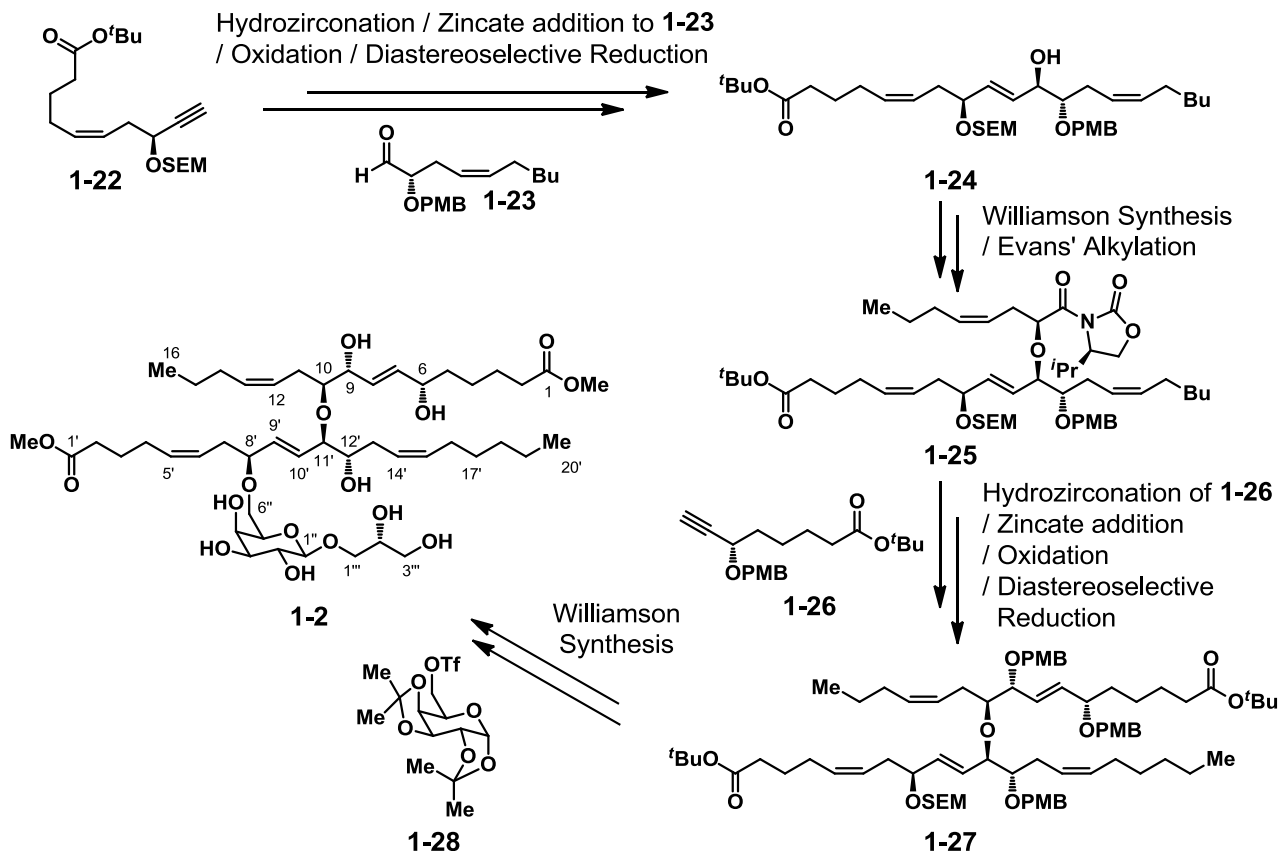
The Falck group reported the regioselective monoepoxidation of diene or triene using methyltrioxorhenium complex in 2014.⁵ The report also mentioned a putative application of the monoepoxidation to a biogenetically inspired total synthesis of nigricanosides (Scheme 1-2).



1-2-4. Total Synthesis of Nigricanoside A Dimethyl Ester by the Ready Group

The Ready group achieved the first total synthesis of **1-2** and the elucidation of absolute configuration of **1-2** in 2015.⁶ The synthesis employed a linear strategy, in which C20 fatty acid **1-24** was first synthesized from C1'-C10' segment **1-22** and C11'-C20' segment **1-23** through a process including hydrozirconation followed by zincate coupling,⁹ oxidation, and diastereoselective reduction. The C10-O-C11' ether bond was constructed from **1-24** by the Williamson ether synthesis¹⁰ and Evans' asymmetric alkylation¹¹ to form **1-25**, which was connected with C1-C8 segment **1-26** to afford **1-27** via the same process as the above. Galactosylglycerol **1-28** was connected with **1-27** via the Williamson synthesis to complete total synthesis of **1-2**. Several diastereomers of **1-2** were also prepared in the same way. Absolute configuration of natural **1-2** was elucidated because NMR and specific rotation of synthetic **1-2** coincided with those of natural **1-2**.

The Ready group also clarified the absence of cytotoxicity of synthetic **1-2**. In their view, the high potency reported for the natural product would require sub-nano molar toxicity for any minor contaminant.⁶



Scheme 1-3. The total synthesis of nigricanoside A dimethyl ester (**1-2**) by the Ready group.

1-3. Previous Work by Kinashi

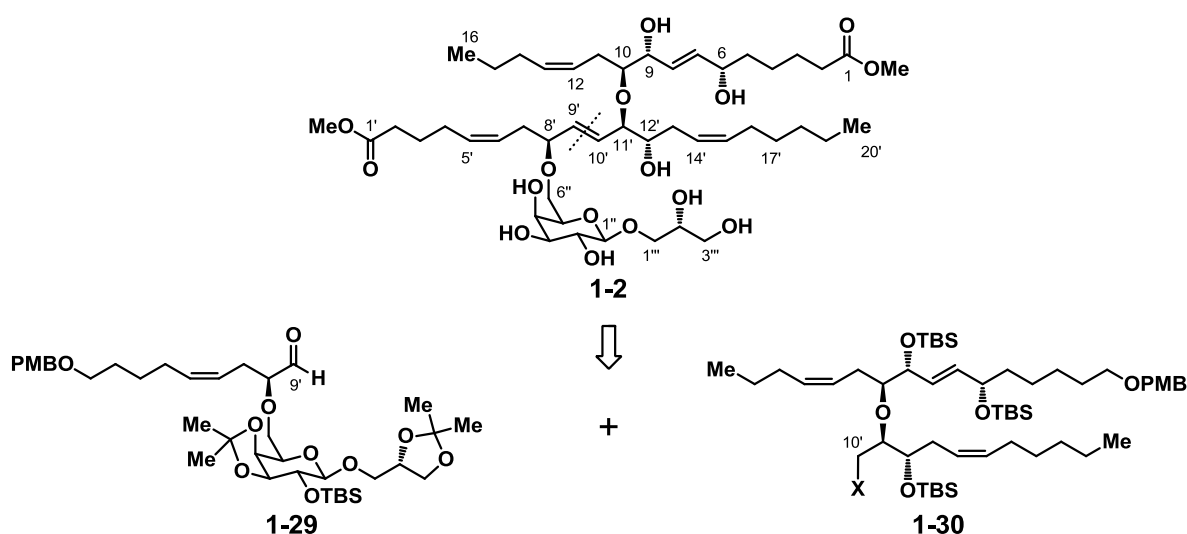
1-3-1. Plan for the Total Synthesis of Nigricanoside A Dimethyl Ester

As described the above, the laboratory to which the author belongs has carried out a project toward the total synthesis of **1-2** according to a synthetic plan, in which **1-2** would be synthesized from the left half segment **1-29** and the right half segment **1-30** by the union at C9'-C10' double bond (Scheme 1-4). To date, a method for the stereoselective construction of **1-29** has been developed based on chirality transferring Ireland-Claisen rearrangement¹² as a key reaction by Kinashi, a former member of our laboratory.⁴

For the next subject of the synthesis of **1-30**, the stereoselective construction of the C10-O-C11' ether bond was a problem. Kinashi also attempted to solve the problem by employing the Evans type asymmetric aldol reaction.⁴ However, because the aldol reaction only reacted with acrolein, the requisite fatty acid chains of **1-30** could not be constructed by the reaction. Therefore, the subject of the synthesis of **1-30** still remained to be solved.

The connection of **1-29** and **1-30** with producing double bond C9'=C10' is also a significant problem. Since the both allylic positions of the double bond C9'=C10' of **1-2** have an alkoxy group, the double bond is difficult to construct. Although the segment connection and the formation of the double bond were attempted by Kinashi, no coupling product was obtained.¹³

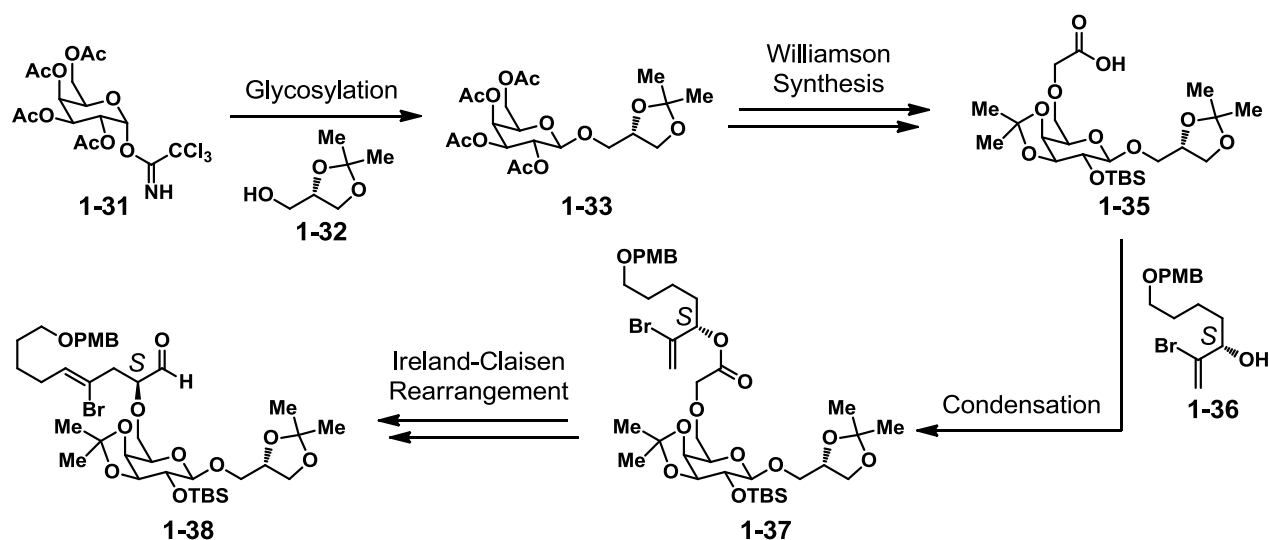
In the following three sections, studies toward the total synthesis of **1-2** by Kinashi are described.



Scheme 1-4. Plan for the total synthesis of **1-2** by the laboratory to which the author belongs.

1-3-2. The Synthesis of the Left-Half Segment of Nigricanoside A Dimethyl Ester

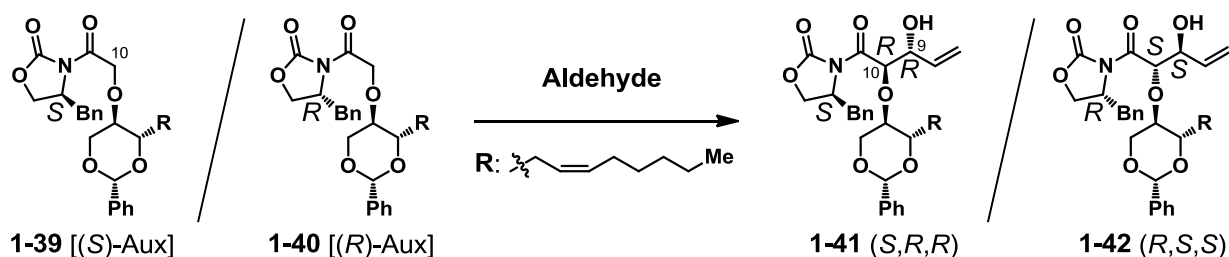
Kinashi has developed a method for the stereoselective construction of left half segment **1-38** (a synthetic equivalent of **1-29**) as shown in Scheme 1-5. Glycerol derivative **1-32** was glycosylated with imidate **1-31**, reported by Schmidt,¹⁴ to give β -glycoside **1-33** selectively.¹⁵ After the conversion of **1-33** to **1-35** through a process including manipulation of protecting groups and Williamson ether synthesis, condensation of **1-35** with chiral bromoallyl alcohol **1-36** produced ester **1-37**. The Ireland-Claisen rearrangement of **1-37** followed by the modification of the degree of oxidation at C9 successfully produced left-half segment **1-38** with high stereoselectivity. Thus, stereoselective construction of left-half segment **1-38** was achieved.



Scheme 1-5. Synthesis of left-half segment **1-38** by Kinashi.

1-3-3. Synthetic Studies on the Right-Half Segment of Nigricanoside A Dimethyl Ester

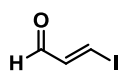
Kinashi attempted to develop a method for the stereoselective synthesis of right-half segment **1-30** using Evans type asymmetric aldol reaction as a key reaction.^{16,17} The method has an advantage that the simultaneous installation of the C1-C9 carbon chain and the stereocenters at C9 and C10 is possible. After preparation of amides **1-39** and **1-40** having Evans' chiral auxiliary, Kinashi attempted aldol reactions of the amides with several aldehydes (Table 1-1). Although amides **1-39** and **1-40** gave only a mixture of complex products under original Evans' boron aldol reaction conditions (entries 1 and 2),¹⁶ treatment of the amides with LDA followed by the reaction with acrolein gave aldol products **1-41** and **1-42** stereoselectively in good yield (entries 3 and 4).¹⁷ However, the amides reacted no other aldehydes than acrolein under the same conditions: neither (*E*)- β -iodoacrolein nor aldehyde **1-43**, corresponding to the C1-C9 segment, reacted with the amides (entries 5 and 6). The strict substrate specificity was a serious problem in the synthesis of right-half segment **1-30**. Therefore, it is necessary to develop a new synthetic strategy for **1-30**.



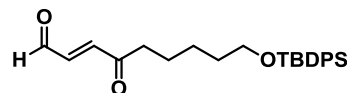
Entry	Substrate	Aldehyde	Conditions	Yield
1	1-39	Acrolein	Bu ₂ BOTf, Et ₃ N, CH ₂ Cl ₂ , -78 °C	Complex mixture
2	1-40	Acrolein	Bu ₂ BOTf, Et ₃ N, CH ₂ Cl ₂ , -78 °C	Complex mixture
3	1-39	Acrolein	LDA, THF-toluene, -78 °C	63% (1-41 ; <i>S,R,R</i>)
4	1-40	Acrolein	LDA, THF-toluene, -78 °C	76% (1-42 ; <i>R,S,S</i>)
5	1-39	(<i>E</i>)- β -Iodoacrolein	LDA, THF-toluene, -78 °C	Complex mixture
6	1-39	1-43	LDA, THF-toluene, -78 °C	Complex mixture



Acrolein



(*E*)- β -Iodoacrolein



1-43

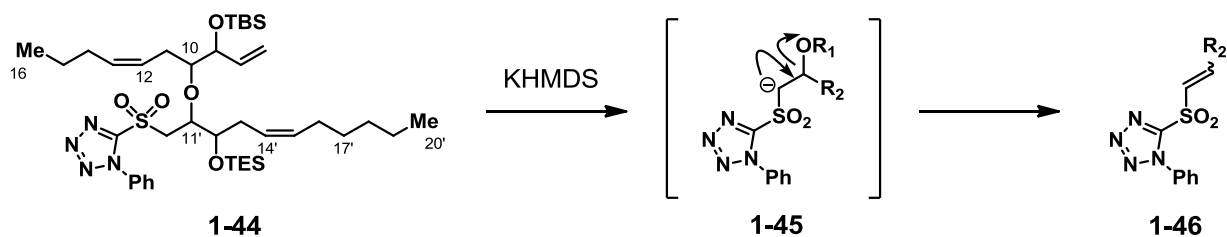
Table 1-1. Evans type asymmetric aldol reactions of **1-39** and **1-40** with several aldehydes.

1-3-4. Exploration of a connecting method between left- and right- half segment

Because the both allylic positions of the double bond C9'=C10' have an alkoxy group of **1-2**, there is few methods for the construction of such double bonds except cross-metathesis. For the synthesis of polyene **1-2**, the cross-metathesis seems ineffective due to suspected ring-closing metathesis as an inevitable side reaction. Therefore, the development of a method based on anion coupling and elimination has been studied as a solution for the segment connection at C9'-C10' double bond of **1-2**.

In this context, Kinashi examined a Julia-Kocienski olefination¹⁸ for the connection of the left- and the right-half segment (**1-44**). However, β -elimination of an alkoxide, corresponding to the C16 fatty acid chain, from the sulfone (right-half) segment (**1-44**) was predominated to give no coupling product (Scheme 1-6).¹³

Thus, the author has explored a new olefination method based on an anion coupling reaction that tolerates the presence of an alkoxy group at β -position of the carbanion.



Scheme 1-6. Mechanism of the undesired β -elimination of the C16 fatty acid chain from **1-44**.

1-4. The Objectives of This Dissertation Work

(i) Development of a stereoselective method for the construction of the C10-O-C11' ether linkage of nigricanoside A dimethyl ester (**1-2**):

As described in chapter 1-3-3, for the synthesis of the right-half segment of nigricanoside-A dimethyl ester **1-2**, the development of a new method for the stereoselective construction of the C10-O-C11' ether linkage is necessary. Therefore, the author examined the application of the chirality transferring Ireland-Claisen rearrangement to the formation of the C10-O-C11' ether linkage. As a result, the rearrangement of the ester, which has C10'-C20' unit as the carboxylate part and C11-C16 unit as the alkenyloxy part, successfully produced the C10-O-C11' ether linkage with high stereoselectivity. The details are described in Chapter 2.

(ii) Stereoselective synthesis of the right-half segment of nigricanoside A dimethyl ester (**1-2**):

Other than the C10-O-C11' ether linkage, the right-half segment of **1-2** has C6 and C9 stereocenters. The author planned to establish the stereocenters during the introduction of the C8-C1 carbon chain. Although the stereocontrol of C9 was yet to be achieved, a chiral C8-C1 unit was successfully introduced to the above rearrangement product to produce the framework of the right-half segment of **1-2**. The details are also explained in Chapter 2.

(iii) Development of a new method for the connection of the left- and the right-half segments of nigricanoside A dimethyl ester (**1-2**):

Toward the convergent total synthesis of **1-2**, the left- and the right-half segments of **1-2** should be connected in a way that forms a double bond between C9' and C10'. However, because the both allylic positions of the double bond have an alkoxy group, there are few methods for the construction of such double bonds except cross-metathesis. For the synthesis of polyene **1-2**, the cross-metathesis seems ineffective due to suspected ring-closing metathesis as an inevitable side reaction. Therefore, the author examined several methods for the segment connection at C9'-C10' double bond of **1-2** based on anion coupling and elimination using a model system. The results are described in Chapter 3.

References

1. Williams, D. E.; Sturgeon, C.M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 5822.
2. Espindola, A. P. D. M.; Crouch, R.; DeBergh, J. R.; Ready, J. M.; MacMillan, J. B. *J. Am. Chem. Soc.* **2009**, *131*, 15994.
3. Kurashina, Y.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 605.
4. Kinashi, N. Ph.D. thesis, Hokkaido University, **2013**.
5. De, S. R.; Kumar, G.; Jat, J. L.; Birudaraju, S.; Lu, B.; Manne, R.; Puli, N.; Adebesin, A. M.; Falck, J. R. *J. Org. Chem.* **2014**, *79*, 10323.
6. Chen, J.; Koswatta, P.; Debergh, J. R.; Fu, P.; Pan, E.; Macmillan, J. B.; Ready, J. M. *Chem. Sci.* **2015**, *6*, 2932.
7. Martin, V.; Woodard, S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
8. For a review: Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
9. Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197.
10. Williamson, W. *Liebigs Ann. Chem.* **1851**, *77*, 37.
11. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
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*, Hierseman, M.; Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, **2007**, p 117.
13. Kinashi, N.; Fujiwara, K.; Suzuki, T. unpublished result.
14. Schmidt, R.R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249.
15. Sias, B.; Ferrato, F.; Grandval, P.; Lafont, D.; Boullanger, P.; De Caro, A.; Leboeuf, B.; Veger, R.; Carrière, F. *Biochemistry* **2004**, *43*, 10138.
16. (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (b) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Evans D. A.; Tedrow J. S.; Shaw J. T.; Downey C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.
17. Stallforth, P.; Adibekian, A.; Seeberger, P. H. *Org. Lett.*, **2008**, *10*, 1573
18. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *9*, 26.

Chapter 2.

Synthetic Studies on the Right-half Segment of Nigricanoside A Dimethyl Ester

2-1. Introduction

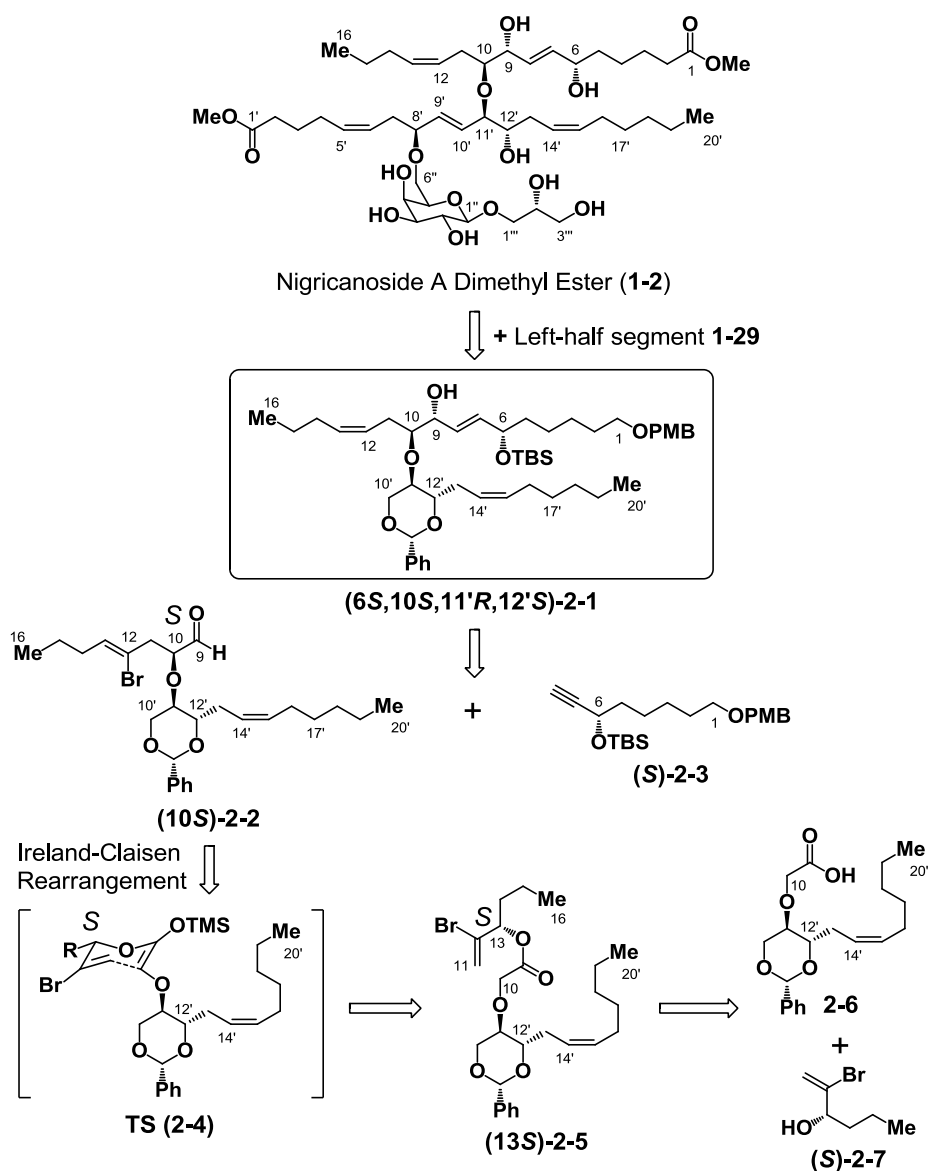
In this chapter, the author describes the studies on the stereoselective synthesis of the right-half segment of nigricanoside A dimethyl ester (**1-2**),¹ of which the absolute configuration was determined by Ready and coworkers.² As described in the chapter 1, the author intended to synthesize **1-2** from left-half segment **1-29**, of which the synthetic methodology was established by Kinashi,³ and right-half segment **2-1** in a convergent way (Scheme 2-1). The synthesis of right-half segment **2-1** involved the following problems: (i) development of an effective method for the stereoselective construction of the C10-O-C11' ether linkage and (ii) development of a method for the extension of the upper fatty acid chain moiety with proper stereochemistry of the C10-C11 double bond and the C6 and C9 stereocenters.

Previously, Kinashi examined the stereoselective formation of the C10-O-C11' ether linkage using Evans-type asymmetric aldol reaction.³ The reaction successfully construct the C9 and C10 stereocenters with (9*S*,10*R*)- or (9*R*,10*S*)-configuration selectively. However, the reaction was not available for the extension of the upper fatty acid chain. Therefore, the author explored a new methodology for the formation of the C10-O-C11' ether linkage compatible with the extension of the fatty acid carbon chain.

The synthetic plan for the right-half segment (**6*S*,10*S*,11'*R*,12'*R***)-**2-1** is outlined in Scheme 2-1. The right-half segment was planned to be synthesized from aldehyde **2-2** and optically active oct-1-yne derivative **2-3**, corresponding to the C1-C8 segment. The stereoselective acetylide coupling between **2-2** and **2-3** followed by *E*-selective reduction (at C7-C8 double bond) of the resulting propargyl alcohol would produce the entire skeleton of the upper fatty acid chain. For the acetylide coupling, the enantioselective method developed by Carreira⁴ may be available. The C10 stereocenter and the C11-C16 carbon chain including the bromoalkene at C12 of aldehyde **2-2** was planned to be introduced by a chirality transferring Ireland-Claisen rearrangement⁵ of the ester (**13*S***)-**2-5**. In the rearrangement, it is predicted that the chirality at C13 of **2-5** is transferred to C10 stereocenter of the product via a stable chair-shaped transition state (**2-4**). Therefore, ester (**13*S***)-**2-5** would produce a carboxylic acid with (10*S*)-configuration and a straight C9-C16 carbon chain. The carboxylic acid would be converted to aldehyde **2-2** in a few steps. The preparation of ester **2-5** relied on the condensation of (*S*)-2-bromohexa-1-en-3-ol ((**5**)-**2-7**) and carboxylic acid **2-6**, which

was previously synthesized from 2-deoxy-D-ribose by Kinashi.

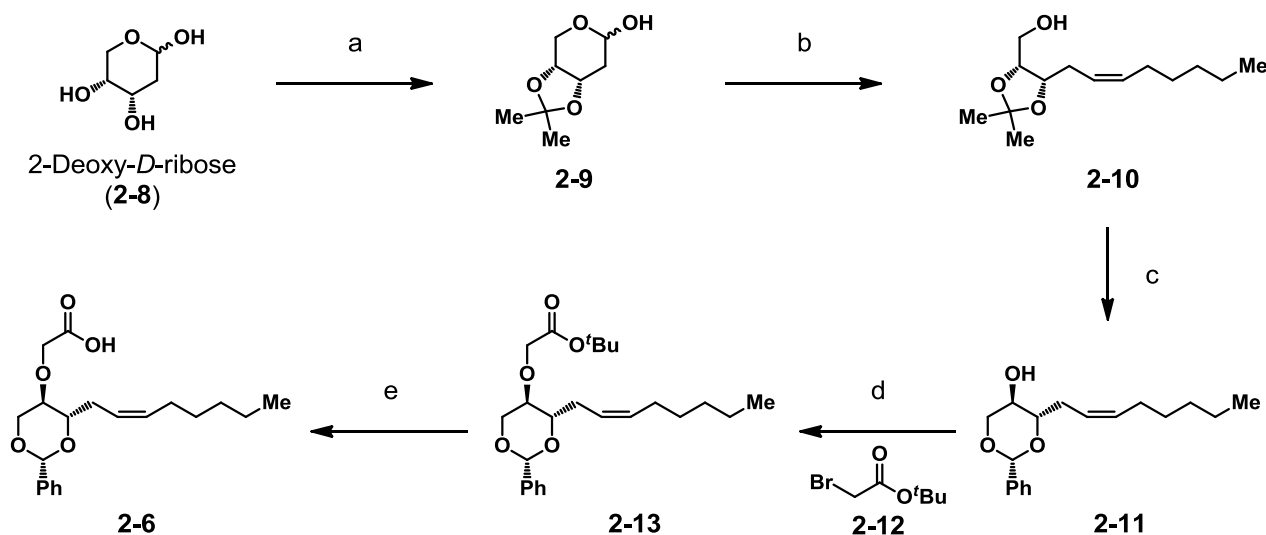
According to the above plan, the author achieved the stereoselective construction of the C10-O-C11' ether linkage. Furthermore, the pilot synthesis of the right-half segment of **1-2** was also accomplished. The successful synthesis of right-half segment **2-1** strongly relied on the preparation of highly enantioenriched alcohol (**S**)-**2-7** and alkyne (**S**)-**2-3**. The author also developed their synthesis based on optical resolution methodology. These details are described in the following sections.



Scheme 2-1. Synthetic plan for right-half segment **2-1**

2-2. Synthesis of the Carboxylic Acid Segment

The carboxylic acid segment **2-6** was prepared according to the procedure reported by Kinashi (Scheme 2-2).³ 2-Deoxy-D-ribose (**2-8**), of which the stereocenters C3 and C4 are identical with the stereocenters C12' and C11' of **1-2**, respectively, was first converted to isopropylidene acetal **2-9** (56%),⁶ which was reacted with hexylidenetriphenylphosphorane to afford *cis*-alkene **2-10** (82%). The hydrolysis of **2-10** followed by acetalization with benzaldehyde gave 6-membered cyclic acetal **2-11** (58% from **2-10**). Treatment of **2-11** with *tert*-butyl bromoacetate (**2-12**) under basic conditions produced **2-13** (99%), which was then subjected to basic hydrolysis to furnish carboxylic acid segment **2-6** (93%).

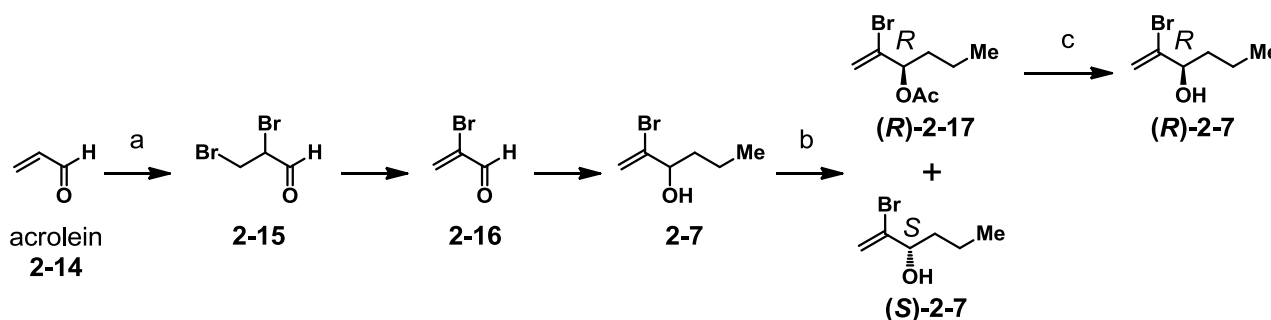


Scheme 2-2. Synthesis of carboxylic acid segment **2-6**. Reagents and conditions: (a) $\text{Me}_2\text{C}(\text{OMe})_2$, CSA, DMF, 23 °C, 4.5 h, 56%; (b) BuLi, $\text{Ph}_3\text{PCH}_2(\text{CH}_2)_4\text{CH}_3\cdot\text{Br}$, THF, -78 °C, then **2-9**, 23 °C, 3 h, 82%; (c) AcOH-H₂O (14:1), 100 °C, 1 h, then evaporation, then PhCHO, CSA, Benzene, reflux, 2.5 h, 58%; (d) NaH, **2-12**, KI, DMF-THF (10:1), 23 °C, 3 h, 99%; (e) 5 M aq. NaOH, MeOH, 23 °C, 24 h, 93% (3cycles).

2-3. Synthesis of Enantioenriched 2-Bromohexa-1-en-3-ol

2-3-1. Synthesis of Enantioenriched 2-Bromohexa-1-en-3-ol

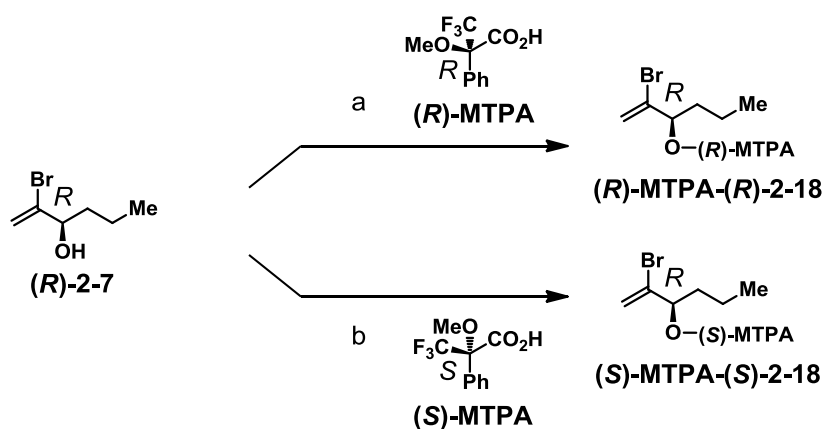
The synthesis of each enantiomer of 2-bromohexa-1-en-3-ol (**2-7**), corresponding to the C11-C16 segment of **1-2**, is illustrated in Scheme 2-3. First, racemic 2-bromohexa-1-en-3-ol (**2-7**) was synthesized from acrolein (**2-14**) by a one-pot process. The reaction of acrolein (**2-14**) with bromine in CH_2Cl_2 followed by the elimination of HBr with triethylamine produced 2-bromoacrolein (**2-16**), which was reacted in situ with propylmagnesium bromide in a 1,2-addition mode to give racemic 2-bromohexa-1-en-3-ol (**2-7**) (40% from **2-14**). Optical resolution of **2-7** was successfully achieved by enzymatic kinetic optical resolution. Although the reaction rate was small, enzymatic acetylation of **2-7** with lipase PS Amano in a blend of vinyl acetate and TBME for 11 days produced acetate (**R**)-**2-17** in 41% yield with high optical purity (93%ee, determined after hydrolysis) along with alcohol (**S**)-**2-7** (54%) with low optical purity (~50%ee). On the other hand, the alcohol (**S**)-**2-7** recovered after the enzymatic acetylation for 60 days exhibited almost complete optical purity. Acetate (**R**)-**2-17** was hydrolyzed to give alcohol (**R**)-**2-7** (96%). The optical purity of (**S**)-**2-7** and (**R**)-**2-7** was determined by NMR analysis after conversion to (*R*)- and (*S*)-MTPA esters. Determination of the absolute configurations of (**S**)-**2-7** and (**R**)-**2-7** is described in the next section.



Scheme 2-3. Synthesis of bromoallyl alcohol **2-7**. Reagents and conditions: (a) Br_2 , CH_2Cl_2 , 0 °C, 10 min, then Et_3N , 26 °C, 1 h, then PrMgBr , -78 °C, 1 h, 40% from **2-14**; (b) i) acetate (**R**)-**2-17**: lipase PS Amano, vinyl acetate, TBME, ambient temperature, 11 d, 41% (NMR yield), 93%ee; ii) alcohol (**S**)-**2-7** lipase PS Amano, vinyl acetate, ambient temperature, 60 d, 41% (NMR yield), > 99%ee; (c) NaOMe , 24 °C, 19 h, 96%.

2-3-2. Determination of Absolute Configuration of 2-Bromohexa-1-en-3-ols

The absolute configuration of alcohol **(R)**-2-7, obtained from acetate **(R)**-2-17 as described in the preceding section, was determined by the Kusumi-Mosher method.⁷ Alcohol **(R)**-2-7 was condensed with (R)-MTPA and (S)-MTPA using EDCI·HCl to give **(R)**-MTPA-**(R)**-2-18 and **(S)**-MTPA-**(R)**-2-18, respectively (Scheme 2-4). According to Kusumi's procedure, the absolute configuration of the alcohol (**(R)**-2-7) which was rapidly acetylated by lipase PS Amano in a blend of vinyl acetate and TBME was determined to be (R) from the pattern of the deviation between the chemical shifts of the MTPA esters (Figure 2-1).



Scheme 2-4. Synthesis of MTPA esters from **(R)**-2-7. Reagents and conditions: (a) (+)-**(R)**-MTPA, EDCI·HCl, DMAP, CH₂Cl₂, 25 °C, 21 h; (b) (-)-**(S)**-MTPA, EDCI·HCl, DMAP, CH₂Cl₂, 24 °C, 7 h.

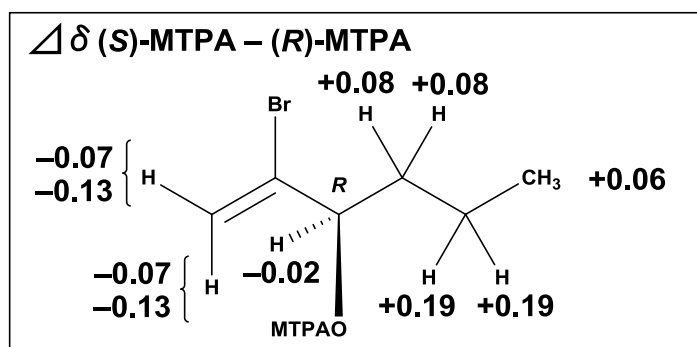
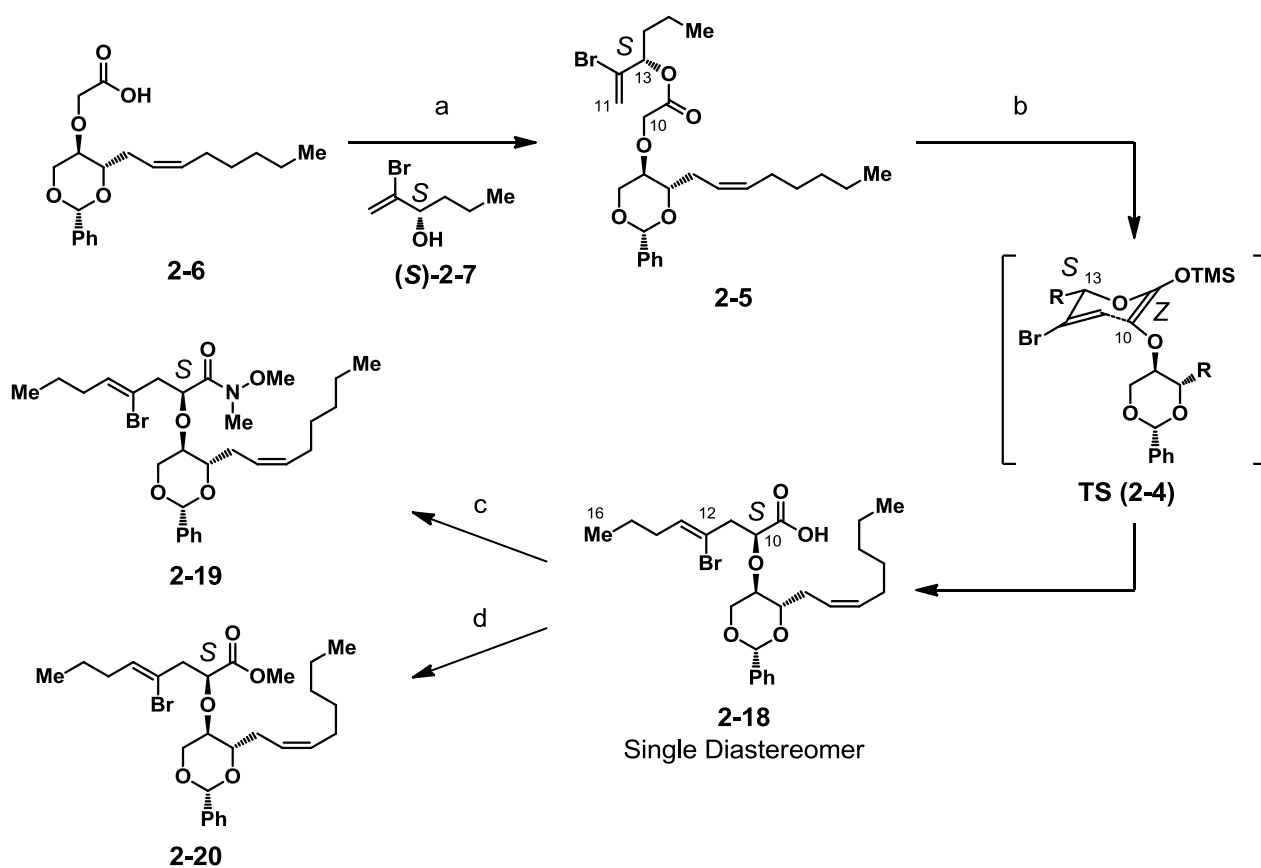


Figure 2-1. Confirmation of stereochemistry of **(R)**-2-7 by the Kusumi-Mosher method.

2-4. Stereoselective Construction of the C10-O-C11' Ether Linkage

2-4-1. Construction of the C10-O-C11' Ether Linkage by Chirality Transferring Ireland-Claisen Rearrangement

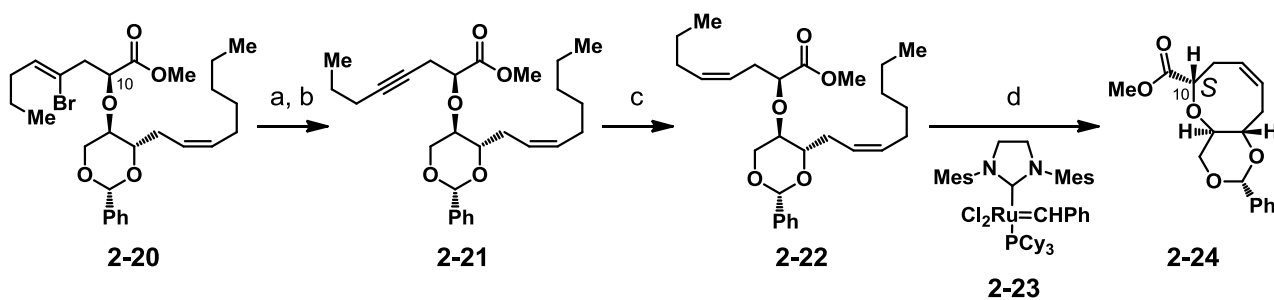
The stereoselective construction of the C10-O-C11' linkage of **1-2** employed a chirality transferring Ireland-Claisen rearrangement according to the plan described in Section 2-1. First, carboxylic acid **2-6** was esterified with alcohol (**S**)-**2-7** to give ester **2-5**. The Ireland-Claisen rearrangement was performed simply as follows: treatment of substrate ester **2-5** with NHMDS in the presence of TMSCl in THF at $-78\text{ }^{\circ}\text{C}$ produced a ketene silyl acetal intermediate, which was then warmed to $0\text{ }^{\circ}\text{C}$ to afford rearranged product **2-18** as a single diastereomer. Carboxylic acid **2-18** was condensed with *N,O*-dimethylhydroxyamine to furnish a Weinreb amide, *N*-methoxy-*N*-methylamide **2-19**. Carboxylic acid **2-18** was also reacted with TMSCHN_2 to afford methyl ester **2-20**. Ester **2-20** was subjected to further derivatization for the determination of absolute configuration of C10, which is described in the next section.



Scheme 2-5. The Ireland-Claisen rearrangement of ester **2-5**. Reagents and conditions: (a) **(S)-2-7**, EDCI·HCl, DMAP, CH₂Cl₂, 26 °C, 5 h, 84%; (b) TMSCl, NHMDS, −78 °C, 5 min, then 0 °C, 1.5 h; (c) MeNH(OMe)·HCl, EDCI·HCl, DMAP, CH₂Cl₂, 26 °C, 1 h, 63% from **2-5**; (d) TMSCHN₂, MeOH, Et₂O, 25 °C, 20 min, 65% from **2-5**.

2-4-2. Confirmation of the C10-Stereochemistry Formed by Ireland-Claisen Rearrangement

The stereochemistry at the C10 stereocenter of **2-18**, obtained by the Ireland-Claisen rearrangement, was confirmed by X-ray crystallographic analysis after the conversion of **2-20** to 8-membered ring ether **2-24** (Scheme 2-6). The reaction of **2-20** with TBAF·3H₂O in DMF at 70 °C, according to Mori's procedure,⁸ followed by the treatment with TMSCHN₂⁹ to esterify the partially hydrolyzed carboxylic acid afforded **2-21**. After Lindlar hydrogenation of **2-21**, the resulting **2-22** was subjected to ring-closing olefin metathesis with Grubbs' second generation catalyst (**2-23**) to produce crystalline 8-membered cyclic ether **2-24**.¹⁰ The X-ray crystallographic analysis on **2-24** confirmed the (10*S*)-configuration based on the (11'*R*,12'*S*)-configuration derived from 2-deoxy-D-ribose (Figure 2-2). Thus, the absolute stereochemistry at C10 stereocenter of rearranged product **2-18** was determined to be (*S*)-configuration as originally assumed.



Scheme 2-6. The preparation of cyclic ether **2-24** for the determination of the configuration at C10 of **2-18**. Reagents and conditions: (a) TBAF·3H₂O, DMF, 70 °C, 6 h; (b) TMSCHN₂, MeOH, Et₂O, 25 °C, 20 min, 80% from **2-20**; (c) H₂, Lindlar cat., 1-hexene, MeOH, 24 °C, 27 h, 93%; (d) **2-23** (cat.), (CH₂Cl)₂, reflux, 11.5 h, 61%.

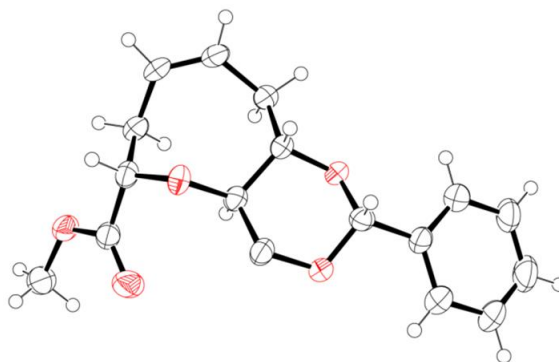
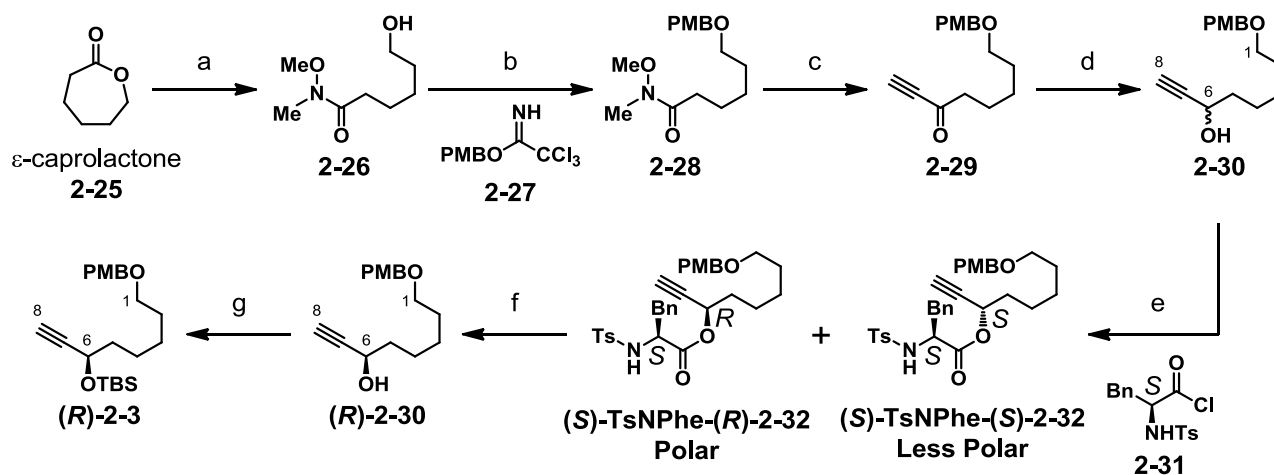


Figure 2-2. ORTEP diagram of cyclic ether **2-24**.

2-5. Synthesis of the C1-C8 Segment in Optically Active Form

Then, alkyne **2-3**, corresponding to the C1-C8 segment of **1-2**, was synthesized in an optically active form for the extension of the upper fatty acid chain of Weinreb amide **2-26** (Scheme 2-7). First, ϵ -caprolactone (**2-25**) was converted to *N*-methoxy-*N*-methylamide **2-26** according to the Sulikowski procedure.¹¹ After the protection of **2-26** with 4-methoxybenzyl 2,2,2-trichloroacetimidate (**2-27**), the resulting **2-28** was reacted with ethynylmagnesium bromide to give ynone **2-29**. Ynone **2-29** was reduced under Luche conditions¹² to afford racemic alcohol **2-30**. The optical resolution of **2-30** was achieved by Ikegami's method.¹³ Racemic alcohol **2-30** was condensed with *N*-tosyl-L-phenylalanine ((*S*)-TsNPhe, (**S**)-**2-31**) to produce a 1:1 mixture of (**S**)-TsNPhe-(**R**)-**2-32** and (**S**)-TsNPhe-(**S**)-**2-32**. Fortunately, these diastereomers were separable by HPLC. Polar diastereomer (**S**)-TsNPhe-(**R**)-**2-32** was obtained in liquid form. On the other hand, less polar diastereomer (**S**)-TsNPhe-(**S**)-**2-32** is crystalline. Therefore, the absolute configuration at C6 was determined to be (*S*) by X-ray crystallographic analysis (Figure 2-3). Ester (**S**)-TsNPhe-(**R**)-**2-32** was then hydrolyzed with NaOH to give optically pure alcohol (**R**)-**2-30**, which was protected with TBSOTf to give (**R**)-**2-3**, the antipode of C1-C8 segment (**S**)-**2-3**. For the pilot synthesis of the right half segment of **1-2**, the author next examined the extension of the upper fatty acid chain of Weinreb amide **2-19** with (**R**)-**2-3**.



Scheme 2-7. Synthesis of alkyne **2-3**. Reagents and conditions: (a) MeNH(OMe)·HCl, EDCI·HCl, Me₃Al, CH₂Cl₂, 0 °C, 17 h, 74%; (b) **2-27**, TMSOTf, CH₂Cl₂, 24 °C, 3 h, 76%; (c) ethynylMgBr, THF, –78 °C, 1 h, 86%; (d) NaBH₄, CeCl₃·7H₂O, CH₂Cl₂, –78 °C, 20 min, 93%; (e) **2-31**, Pyridine, THF, 25 °C, 12 h, then Separation, **(S)-TsNPhe-(S)-2-32**: 25% and **(S)-TsNPhe-(R)-2-32**: 25%; (f) 50% aq. NaOH, MeOH, 26 °C, 19 h, 95%; (g) TBSOTf, 2,6-lutidine, CH₂Cl₂, 24 °C, 12 h, 90%.

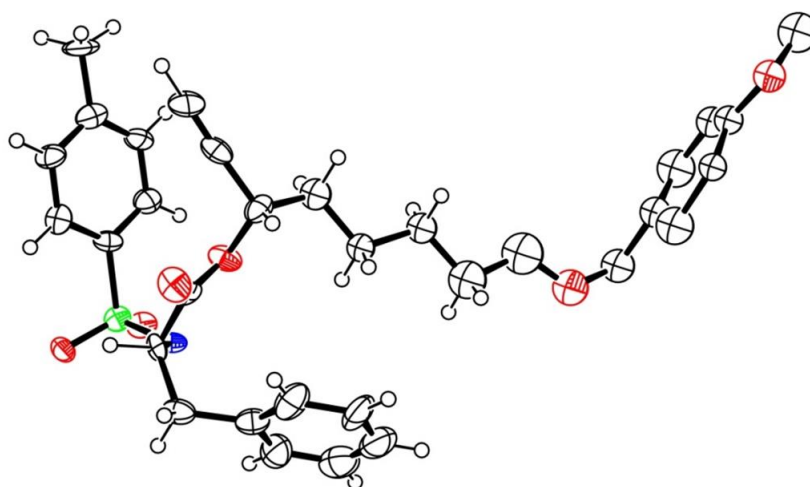
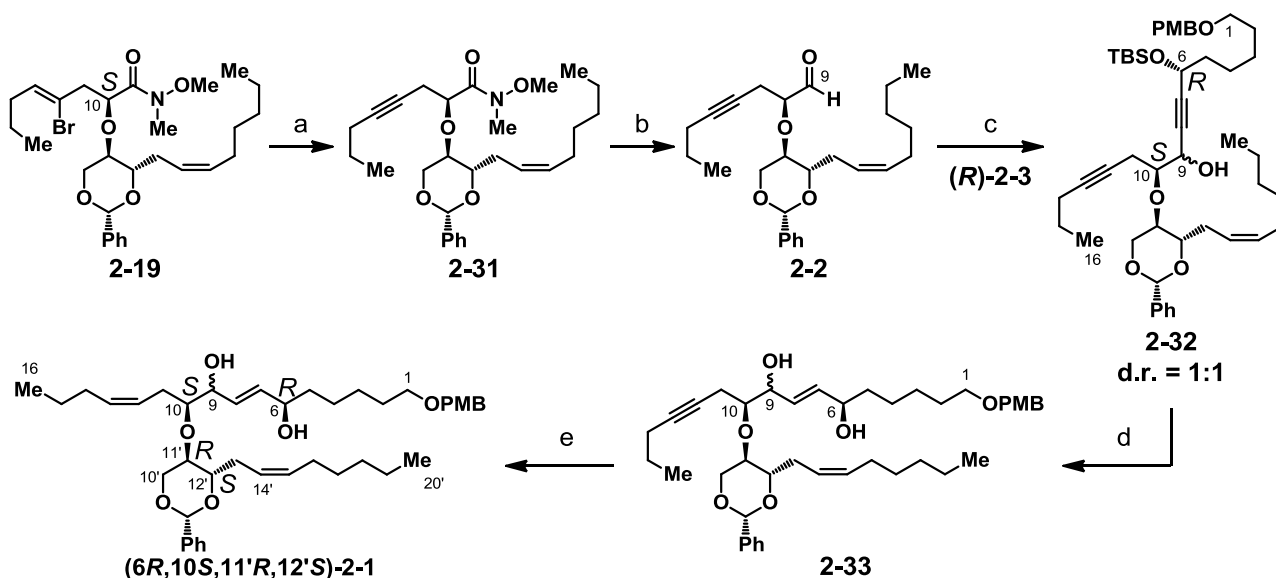


Figure 2-3. ORTEP diagram of ester **(S)-TsNPhe-(S)-2-32**.

2-6. A Pilot Synthesis of the Right Half Segment

As a pilot synthesis of the right-half segment of **1-2**, the extension of the upper fatty acid chain of Weinreb amide **2-19** with (*R*)-**2-3** was performed as shown in Scheme 2-8. Bromoalkene **2-19** was first transformed to **2-31** by Mori's procedure. Reduction of Weinreb amide **2-31** with LiAlH₄ produced aldehyde **2-2**, which was reacted with a lithium acetylide generated from (*R*)-**2-3** to afford **2-32** having a requisite carbon skeleton for the right-half segment as a 1:1 diastereomeric mixture at C9 stereocenter. The formation of an *E*-allylic alcohol from propargyl alcohol **2-32** with LiAlH₄ was accompanied by the removal of the TBS group at the C6 to give diol **2-33**. Finally, Lindlar hydrogenation successfully constructed (**6*R*,10*S*,11'*R*,12'*S***)-**2-1** having all necessary functional groups and framework of the right-half segment of **1-2**. Thus, a pilot synthesis of the right-half segment of **1-2** was achieved. In the future, the right-half segment should be synthesized from (*S*)-**2-3** having proper C6 stereochemistry in a way that controls the C9 configuration to be (*R*).



Scheme 2-8. Synthesis of right-half segment (**6*R*,10*S*,11'*R*,12'*S***)-**2-1**. Reagents and conditions: (a) TBAF·3H₂O, DMF, 70 °C, 6 h, 87%; (b) LiAlH₄, THF, −20 °C, 15 min; (c) (*R*)-**2-3**, BuLi, THF, HMPA, −78 °C, 1 h, then **2-2**, 24 °C, 5.5 h, 59% from **2-31**; (d) LiAlH₄, THF, 23 °C, 24 h, 51%; (e) H₂, Lindlar cat., 1-hexene, MeOH, 26 °C, 26 h, 98%.

2-7. Conclusion

Toward the total synthesis of nigricanoside A dimethyl ester (**1-2**), of which the absolute configuration was determined by Ready et al., the author designed a convergent route that leads to **1-2** from left-half segment **1-29** and right-half segment **2-1**. In this dissertation work, the author studied the stereoselective synthesis of right-half segment **2-1**.

The synthesis included the following problems: (i) development of an effective method for the stereoselective construction of the C10-O-C11' ether linkage and (ii) development of a method for the extension of the upper fatty acid chain moiety with proper stereochemistry of the C10-C11 double bond and the C6 and C9 stereocenters.

The former problem was solved by the application of a chirality transferring Ireland-Claisen rearrangement. The author found that ester **2-5**, which consisted of carboxylic acid segment **2-6** and optically active (*S*)-2-bromohexa-1-en-3-ol (**2-7**), was smoothly rearranged under the Ireland-Claisen conditions to give a sole carboxylic acid **2-18**, which was then converted to Weinreb amide **2-19** for further synthesis.

The latter problem was solved by the use of optically active oct-1-yne derivative **2-3** for the extension of the upper fatty acid chain of **2-2**. The optical resolution of **2-3** was achieved by Ikegami's method. The pilot synthesis of the right-half segment was performed using Weinreb amide **2-19** and alkyne (*R*)-**2-3** to produce (**6*R*,10*S*,11'*R*,12'*S***)-**2-1** having all necessary functional groups and framework of the right-half segment of **1-2**.

The problem of the establishment of the C9 stereochemistry remained to be solved for completing the synthesis of the right-half segment of **1-2**. However, the author hopes that the problem would be solved by the application of the Carreira method,⁴ and that the established right-half segment would be available for the total synthesis of **1-2**.

References

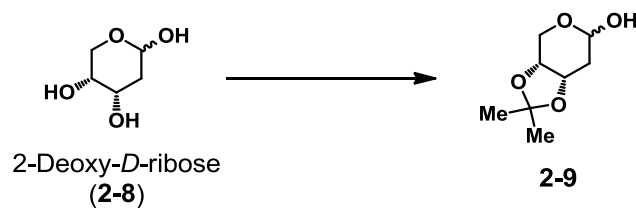
1. Williams, D. E.; Sturgeon, C.M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 5822.
2. Chen, J.; Koswatta, P.; Debergh, J. R.; Fu, P.; Pan, E.; Macmillan, J. B.; Ready, J. M. *Chem. Sci.* **2015**, *6*, 2932.
3. Kinashi, N. Ph.D. thesis, Hokkaido University, **2013**.
4. (a) Franz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807. (b) Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, *43*, 2691-2694.
5. (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.
6. Barbat, J.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1983**, *116*, 312.
7. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
8. Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442.
9. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1457.
10. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
11. Kiewel, K.; Luo, Z.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 5163-5165.
12. Gemal, A. L.; Lucche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
13. Hashimoto, S.; Kase, S.; Suzuki, A.; Yanagiya, Y.; Ikegami, S. *Synth. Commun.* **1991**, *21*, 833-839.

Experimental Section

General Methods

All air sensitive reactions were carried out under argon atmosphere in oven-dried glassware using standard syringe, cannula and septa techniques. THF was prepared by Glass Contour Solvent Dispensing System (Nikko Hansen & Co., Ltd.). Other dry solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel (SiO₂) plates (Merck, silica gel 60 F₂₅₄). Plates were visualized by ultraviolet light and by treatment with acidic anisaldehyde or phosphomolybdic acid stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63–40 µm for flash column chromatography or 63–210 µm for gravity column chromatography) as a stationary phase with indicated eluents. 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 ¹³C NMR spectra were recorded on a Bruker AVANCE III 400 (¹H at 400 MHz, ¹³C at 100 MHz), a JEOL JNM-AL300 (¹H at 300 MHz, ¹³C at 75 MHz) or a JEOL JNM-α-400 (¹H at 400 MHz, ¹³C 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 (C₆HD₅ as 7.15 ppm; CHD₂CN as 1.93 ppm; CHD₂C(O)CD₃ as 2.04 ppm) as an internal standard. The following abbreviations are used to describe spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sext=sextet, 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). ¹³C NMR spectra are reported as chemical shifts (δ) in ppm based on the solvent signal (¹³CDCl₃ as 77.0 ppm; ¹³C¹²C₅D₆ as 128 ppm; CD₃¹³CN as 118.2 ppm; O=C(¹³CD₃)₂ as 29.8 ppm) as an internal standard. Low and high resolution mass spectra were measured on a JEOL JMS-T100GCV (under field desorption [FD] or field ionization (FI) conditions) double focusing magnetic sector mass spectrometer.

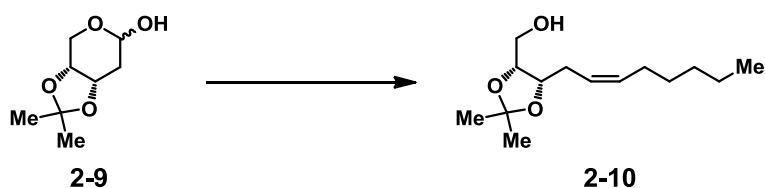
Compound 2-9:



To a solution of **2-8** (500 mg, 3.73 mmol) in DMF (12 mL) were added $\text{Me}_2\text{C}(\text{OMe})_2$ (2.3 mL, 18.6 mmol) and CSA (87.1 mg, 0.373 mmol) at 0 °C, and the mixture was stirred for 4.5 h. The reaction was quenched with Et_3N , and the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 $\rightarrow$ $\text{CHCl}_3/\text{MeOH}$ = 10) to give **2-9** (365.3 mg, 2.10 mmol, 56%).

2-9: an about 4:1 mixture of anomers; a colorless oil;

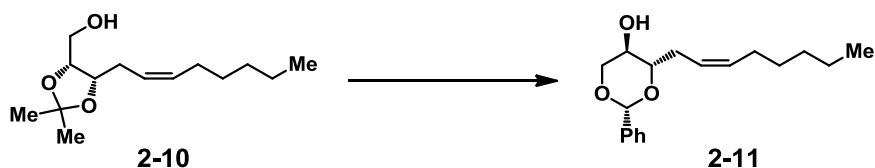
^1H NMR (300 MHz, CDCl_3) (major anomer) δ 1.35 (3H, s), 1.50 (3H, s), 1.78 (1H, ddd, J = 4.2, 7.1, 14.8 Hz), 2.24 (1H, td, 4.2, 14.8 Hz), 3.70 (1H, dd, J = 3.5, 12.7 Hz), 3.95 (1H, dd, J = 3.3, 12.7 Hz), 4.12-4.22 (1H, m), 4.48 (1H, td, J = 4.2, 6.6 Hz), 5.26 (1H, td, J = 4.2, 7.1 Hz).

Compound 2-10:

To a suspension of hexyltriphenylphosphonium bromide (1.61 g, 3.76 mmol) in THF (9 mL) was added BuLi (1.55 mol/L in hexane, 2.4 mL, 3.76 mmol) at $-78\text{ }^{\circ}\text{C}$, and the mixture was stirred for 1 h. Then, to the resulting ylide solution was added a solution of **2-9** (327.6 mg, 1.88 mmol) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$, and the mixture was stirred for 10 min. Then, the mixture was warmed to $23\text{ }^{\circ}\text{C}$ and stirred for further 2.5 h. The reaction was quenched with satd. aq. NH_4Cl , and extracted with EtOAc (10 mL) three 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) to give **2-10** (372.6 mg, 1.54 mmol, 82%).

2-10: a colorless oil;

^1H NMR (300 MHz, CDCl_3) δ 0.88 (3H, t, $J = 6.6\text{ Hz}$), 1.23-1.44 (6H, m), 1.37 (3H, s), 1.49 (3H, s), 1.94-2.12 (2H, m), 2.14-2.48 (2H, m), 3.55-3.76 (3H, m), 4.14-4.28 (1H, m), 5.30-5.61 (2H, m).

Compound 2-11:

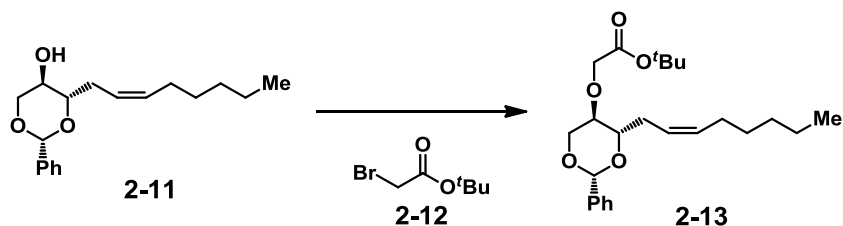
A solution of **2-10** (372.6 mg, 1.54 mmol) and H₂O (500 μ L) in AcOH (7 mL) was warmed to 100 °C and stirred for 1 h. Then, the mixture was concentrated in vacuo. The residual AcOH was removed by repeated azeotropic evaporation with toluene. The resulting residue was used in the next reaction without further purification.

To a solution of the above crude **2-10** in benzene (7.5 mL) were added benzaldehyde (470.6 μ L, 4.61 mmol) and 10-camphorsulfonic acid (71.5 mg, 0.307 mmol) at ambient temperature, and the mixture was refluxed and stirred for 2.5 h. Then, the mixture was cooled to ambient temperature, and the reaction was quenched with satd. aq. NaHCO₃. The mixture was extracted with EtOAc (10 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 30 $\rightarrow$ 10) to give **2-11** (258.8 mg, 0.891 mmol, 58%).

2-11: a colorless oil;

¹H NMR (300 MHz, CDCl₃) 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 2-13:



To a solution of **2-11** (45.3 mg, 0.156 mmol) in a blend of THF (150 μ L) and DMF (1.5 mL) was added NaH (55% in oil, 13.6 mg, 0.320 mmol) at 0 $^{\circ}$ C, and the mixture was stirred for 15 min. Then, the mixture were added KI (2.6 mg, 0.0156 mmol) and *tert*-butyl bromoacetate (**2-12**) (47.3 μ L, 0.320 mmol) at 0 $^{\circ}$ C, and the mixture was stirred for 5 min. Then, the mixture was warmed to 23 $^{\circ}$ C and stirred for further 3 h. The reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three 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 = 50 $\rightarrow$ 10) to give **2-13** (62.8 mg, 0.155 mmol, 99%).

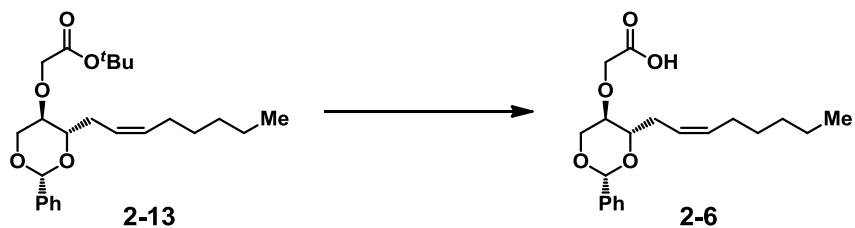
2-13: a colorless oil;

IR (neat) ν 3067, 3006, 2927, 2857, 1749, 1732, 1456, 1393, 1368, 1303, 1228, 1136, 1029, 977, 917, 848, 750, 698, 672, 652 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 0.88 (3H, t, J = 6.8 Hz), 1.22-1.39 (6H, m), 1.49 (9H, s), 2.07 (2H, q, J = 6.9 Hz), 2.46 (1H, td, J = 7.5, 15.2 Hz), 2.63-2.71 (1H, m), 3.39 (1H, ddd, J = 5.1, 9.2, 10.0 Hz), 3.67 (1H, t, J = 10.5 Hz), 3.68-3.73 (1H, m), 4.01 (1H, d, J = 16.2 Hz), 4.08 (1H, d, J = 16.2 Hz), 4.45 (1H, dd, J = 5.1, 10.9 Hz), 5.46 (1H, s), 5.48-5.61 (2H, m), 7.29-7.39 (3H, m), 7.45-7.49 (2H, m);

^{13}C NMR (100 MHz, CDCl_3) δ 14.0 (CH_3), 22.5 (CH_2), 27.4 (CH_2), 28.0 ($\text{CH}_3 \times 3$), 29.3 (CH_2), 29.7 (CH_2), 31.5 (CH_2), 68.5 (CH_2), 69.2 (CH_2), 74.0 (CH), 80.3 (CH), 81.9 (C), 100.8 (CH), 124.5 (CH), 126.1 ($\text{CH} \times 2$), 128.1 ($\text{CH} \times 2$), 128.7 (CH), 132.4 (CH), 137.8 (C), 169.2 (C).

Compound 2-6:

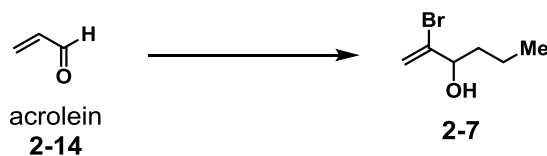


To a solution of **2-13** (33.8 mg, 0.0836 mmol) in MeOH (1 mL) was added 5 mol/L aq. NaOH (1 mL) at 23 °C, and the mixture was stirred for 20 h. The reaction was quenched with satd. aq. HCl. The mixture was extracted with EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The above operations were repeated 3 cycles to give almost pure **2-6** (27.0 mg, 0.775 mmol, 93%).

2-6: a colorless oil;

¹H NMR (300 MHz, CDCl₃) 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 2-7:



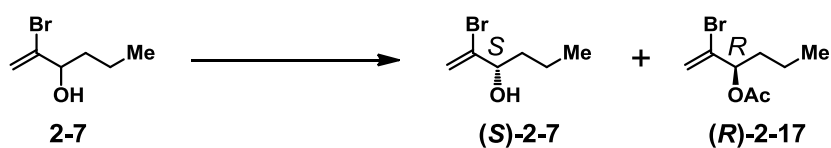
To a solution of acrolein (**2-14**) (1.6 mL, 0.0223 mol) in CH_2Cl_2 (250 mL) was added Br_2 (1.2 mL, 0.0233 mol) at 0 °C, and the mixture was stirred for 10 min. Then, to the mixture was added Et_3N (6.1 mL, 0.0440 mol) at 26 °C, and the mixture was stirred for 1 h. Then, to the mixture was added PrMgBr (1.05 mol/L in THF, 50 mL, 0.0525 mol) at -78 °C, and the mixture was stirred for 1 h. Then, the reaction was quenched with 1 mol/L aq. HCl and satd. aq. NaHSO_3 , and the mixture was extracted with CH_2Cl_2 (30 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo carefully. The resulting residue was purified by column chromatography (silica gel, pentane/ Et_2O = 12 $\rightarrow$ 6) to give racemic **2-7** (1.5826 g, 0.00884 mol, 40% over 3 steps).

2-7: a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 0.95 (3H, t, J = 7.4 Hz), 1.28-1.48 (2H, m), 1.55-1.72 (2H, m), 1.97 (1H, brd, J = 4.5 Hz), 4.10 (1H, q, J = 5.7 Hz), 5.56 (1H, d, J = 1.9 Hz), 5.87 (1H, dd, J = 0.8, 1.9 Hz);

^{13}C NMR (100 MHz, CDCl_3) δ 13.8 (CH_3), 18.4 (CH_2), 37.4 (CH_2), 75.8 (CH), 116.8 (CH_2), 137.6 (C).

Compound (S)-2-7 and (R)-2-17:



For the preparation of acetate (R)-2-17 with high optical purity: To a solution of racemic **2-7** (859.7 mg, 4.80 mmol) in vinyl acetate (4.8 mL) and *tert*-butyl methyl ether (4.8 mL) was added lipase PS Amano (658 mg) at ambient temperature, and the mixture was stirred for 11 d. Then, the mixture was filtered through a Celite pad and concentrated in vacuo carefully. The resulting residue was purified by column chromatography (silica gel, pentane/Et₂O = 12 → 6) to give acetate **(R)-2-17** (233.4 mg, 93 %ee, 41% [NMR yield]) and alcohol **(S)-2-7** (465.4 mg, *R/S* = 1:3).

For the preparation of alcohol (S)-2-7 with high optical purity: To a solution of racemic **2-7** (588.7 mg, 3.29 mmol) in vinyl acetate (6.6 mL) was added lipase PS Amano (658 mg) at ambient temperature, and the mixture was stirred for 60 d. Then, the mixture was filtered through a Celite pad and concentrated in vacuo carefully. The resulting residue was purified by column chromatography (silica gel, pentane/Et₂O = 12 → 6) to give alcohol **(S)-2-7** (142.8 mg, > 99 %ee, 41% [NMR yield]) and acetate **(R)-2-17** (307.4 mg, *R/S* = 3:1).

(S)-2-7: a colorless oil;

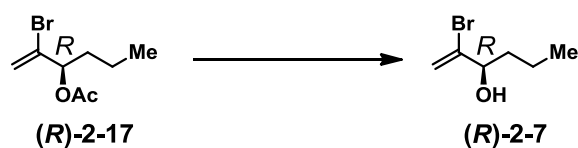
¹H NMR (400 MHz, CDCl₃) δ 0.95 (3H, t, *J* = 7.4 Hz), 1.28-1.48 (2H, m), 1.55-1.72 (2H, m), 1.97 (1H, brd, *J* = 4.5 Hz), 4.10 (1H, q, *J* = 5.7 Hz), 5.56 (1H, d, *J* = 1.9 Hz), 5.87 (1H, dd, *J* = 0.8, 1.9 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 13.8 (CH₃), 18.4 (CH₂), 37.4 (CH₂), 75.8 (CH), 116.8 (CH₂), 137.6 (C).

(R)-2-17: a colorless oil;

¹H NMR (400 MHz, CDCl₃) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.24-1.40 (2H, m), 1.65-1.80 (2H, m), 2.10 (3H, s), 5.23 (1H, t, *J* = 6.7 Hz), 5.62 (1H, d, *J* = 1.9 Hz), 5.89 (1H, dd, *J* = 0.6, 1.9 Hz).

Compound (R)-2-7:



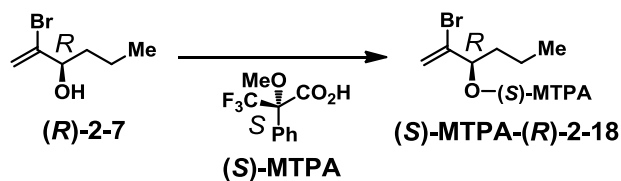
To a solution of acetate **(R)-2-17** (148.7 mg, 0.6726 mmol) in MeOH (7 mL) was added MeONa (a catalytic amount) at 24 °C, and the mixture was stirred for 19 h. Then, to the mixture was added Amberlite IR-120-B (20 mg) at 24 °C, and the mixture was stirred for 4 h. Then, the mixture was filtered and concentrated in vacuo carefully to give almost pure **(R)-2-7** (115.2 mg, 0.6434 mmol, 96%).

(R)-2-7: a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 0.95 (3H, t, $J = 7.4$ Hz), 1.28-1.48 (2H, m), 1.55-1.72 (2H, m), 1.97 (1H, brd, $J = 4.5$ Hz), 4.10 (1H, q, $J = 5.7$ Hz), 5.56 (1H, d, $J = 1.9$ Hz), 5.87 (1H, dd, $J = 0.8, 1.9$ Hz);

^{13}C NMR (100 MHz, CDCl_3) δ 13.8 (CH_3), 18.4 (CH_2), 37.4 (CH_2), 75.8 (CH), 116.8 (CH_2), 137.6 (C).

Compound (S)-MTPA-(R)-2-18:

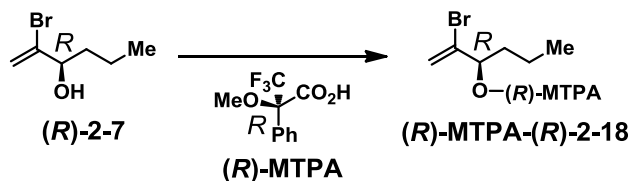


To a solution of **(R)-2-7** (16.5 mg, 0.0922 mmol) in CH_2Cl_2 (1 mL) were added DMAP (1.2 mg, 0.0092 mmol), (–)-(S)-MTPA (25.9 mg, 0.111 mmol), and EDCI·HCl (26.5 mg, 0.138 mmol) at 24 °C and the mixture was stirred for 2.5 h. Then the mixture was added additional DMAP (1.2 mg, 0.0092 mmol), (–)-(S)-MTPA (25.9 mg, 0.111 mmol), and EDCI·HCl (26.5 mg, 0.138 mmol) at 24 °C and the mixture was stirred for 4.5 h. Then, the reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with CH_2Cl_2 (5 mL) three 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) to give **(S)-MTPA-(R)-2-18** (24.3 mg, 0.0615 mmol).

(S)-MTPA-(R)-2-18: a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 0.89 (3H, t, J = 7.4 Hz), 1.30–1.43 (2H, m), 1.66–1.82 (2H, m), 3.58 (3H, q, J = 1.2 Hz), 5.46 (1H, dd, J = 6.2, 7.3 Hz), 5.71 (1H, d, J = 2.1 Hz), 6.00 (1H, dd, J = 0.6, 2.0 Hz), 7.39–7.46 (3H, m), 7.52–7.59 (2H, m).

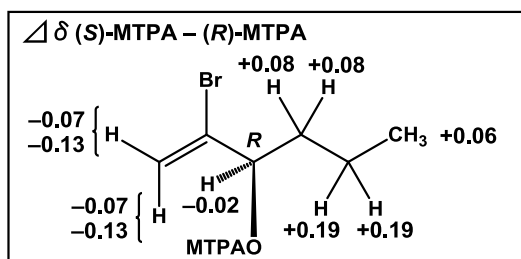
Compound (R)-MTPA-(R)-2-18:



To a solution of **(R)-2-7** (16.9 mg, 0.0944 mmol) in CH_2Cl_2 (1 mL) were added DMAP (1.2 mg, 0.0092 mmol), (+)-**(R)-MTPA** (69.0 mg, 0.295 mmol), and EDCI·HCl (83.2 mg, 0.434 mmol) at 25 °C and the mixture was stirred for 21 h. Then, the reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with CH_2Cl_2 (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo to give crude **(R)-MTPA-(R)-2-18**.

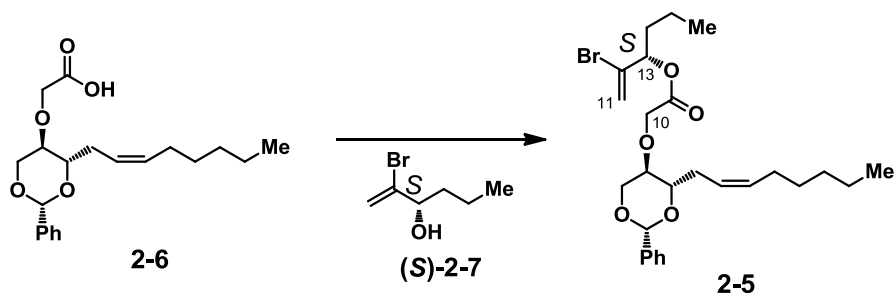
(R)-MTPA-(R)-2-18: a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 0.95 (3H, t, $J = 7.4$ Hz), 1.15-1.29 (2H, m), 1.72-1.86 (2H, m), 3.56 (1H, q, $J = 1.2$ Hz), 5.44 (1H, t, $J = 6.7$ Hz), 5.64 (1H, d, $J = 2.1$ Hz), 5.87 (1H, dd, $J = 0.7, 2.1$ Hz), 7.38-7.44 (3H, m), 7.49-7.56 (2H, m).



The determination of absolute configuration of **(R)-2-7** by modified Mosher's method.

Compound 2-5:

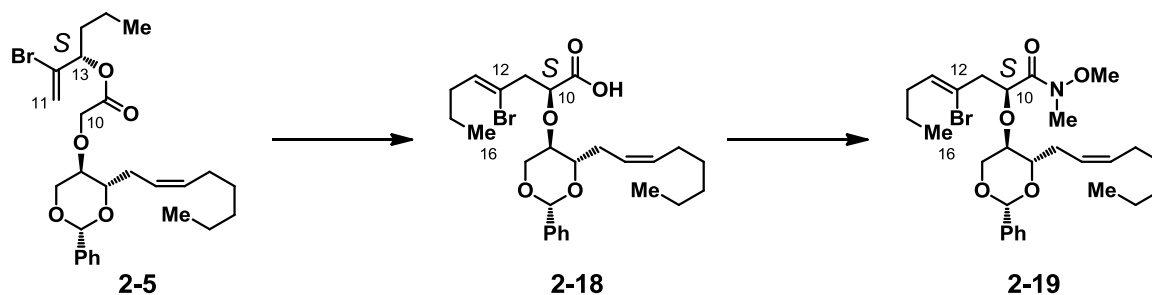


To a solution of **2-6** (80.2 mg, 0.230 mmol) in CH₂Cl₂ (1.5 mL) were added DMAP (1.8 mg, 0.023 mmol), a solution of **(S)-2-7** (27.1 mg, 0.151 mmol) in CH₂Cl₂ (1 mL), and EDCI·HCl (59.1 mg, 0.308 mmol) at 26 °C, and the mixture was stirred for 5 h. Then, the reaction was quenched with satd. aq. NH₄Cl, and the mixture was extracted with CH₂Cl₂ (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give **2-5** (64.8 mg, 0.127 mmol, 84%).

2-5: a colorless oil;

¹H NMR (400 MHz, CDCl₃) δ 0.88 (3H, t, *J* = 6.9 Hz), 0.95 (3H, t, *J* = 7.4 Hz), 1.23-1.41 (8H, m), 1.75 (2H, m), 2.06 (2H, qn, *J* = 7.1 Hz), 2.26-2.52 (2H, m), 2.62-2.74 (1H, m), 3.36-3.47 (1H, m), 3.65-3.74 (1H, m), 3.67 (1H, t, *J* = 10.5 Hz), 4.19 (2H, d, *J* = 14.4 Hz), 4.46 (1H, dd, *J* = 5.1, 10.8 Hz), 5.32 (1H, t, *J* = 6.7 Hz), 5.46 (1H, s), 5.43-5.61 (2H, m), 5.65 (1H, d, *J* = 2.0 Hz), 5.92 (1H, dd, 0.6, 2.0 Hz), 7.29-7.40 (3H, m), 7.43-7.51 (2H, m).

Compound 2-19:



To a solution of **2-5** (32.5 mg, 0.0638 mmol) in THF (3 mL) was added TMSCl (81 μ L, 0.64 mmol) at -78 $^{\circ}$ C, and the mixture was stirred for 3 min. To the mixture was added NHMDs (1.10 mol/L in THF, 580 μ L, 0.638 mmol) at -78 $^{\circ}$ C, and the mixture was stirred for 5 min. Then, the mixture was warmed to 0 $^{\circ}$ C and stirred for 1.5 h. The reaction was quenched with satd. aq. NaHCO_3 , and the mixture was extracted with EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo. The resulting crude carboxylic acid **2-18** was used in the next reaction without further purification.

To a solution of the above crude **2-18** in CH_2Cl_2 (2 mL) were added DMAP (a catalytic amount), $\text{HNMe}(\text{OMe})\cdot\text{HCl}$ (9.3 mg, 0.096 mmol), and EDCI $\cdot\text{HCl}$ (24.5 mg, 0.128 mmol) at 26 $^{\circ}$ C, and the mixture was stirred for 1 h. Then, the reaction was quenched with brine, and the mixture was extracted with CH_2Cl_2 (5 mL) three 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) to give **2-19** (22.2 mg, 0.0402 mmol, 63% for 2 steps).

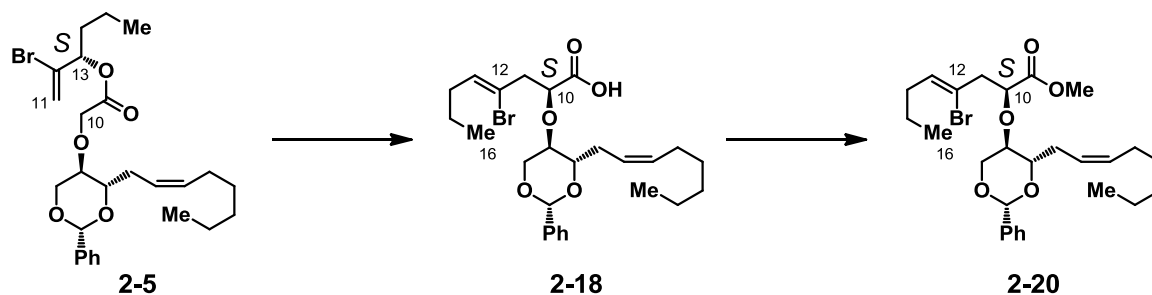
2-19: a colorless oil; $[\alpha]_{\text{D}}^{22} -26.5$ (c 1.00, CHCl_3);

IR (neat) ν 3092, 3066, 3009, 2958, 2929, 2871, 2857, 1725, 1681, 1497, 1460, 1392, 1298, 1252, 1213, 1176, 1115, 1029, 988, 915, 873, 834, 749, 698, 682, 650, 633 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 0.87 (3H, t, J = 6.9 Hz), 0.95 (3H, t, J = 7.4 Hz), 1.20-1.39 (6H, m), 1.45 (2H, sext., J = 7.3 Hz), 2.07 (2H, q, J = 6.8 Hz), 2.16 (2H, dq, J = 2.1, 7.2 Hz), 2.29 (1H, ddd, J = 6.7, 8.6, 15.0 Hz), 2.69-2.78 (2H, m), 2.82 (1H, brddd, J = 2.4, 6.7, 15.0 Hz), 3.21 (3H, s), 3.38 (1H, ddd, J = 5.0, 9.2, 10.0 Hz), 3.55 (1H, t, J = 10.5 Hz), 3.61 (1H, dt, J = 2.6, 8.9 Hz), 3.76 (3H, s), 4.38 (1H, dd, J = 5.0, 10.8 Hz), 4.73 (1H, brt, J = 6.1 Hz), 5.43 (1H, s), 5.44-5.58 (2H, m), 5.80 (1H, t, J = 6.9 Hz), 7.28-7.39 (3H, m), 7.42-7.50 (2H, m);

^{13}C NMR (100 MHz, CDCl_3) δ 13.7 (CH_3), 14.1 (CH_3), 21.6 (CH_2), 22.6 (CH_2), 27.4 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.5 (CH_2), 32.4 (CH_3), 33.4 (CH_2), 45.0 (CH_2), 61.8 (CH_3), 69.3 (CH_2), 72.8 (CH), 72.9 (CH), 80.5 (CH), 100.7 (CH), 122.2 (C), 124.9 (CH), 126.0 ($\text{CH}\times 2$), 128.1 ($\text{CH}\times 2$), 128.7 (CH), 132.3 (CH), 133.2 (CH), 137.9 (C), 171.8 (C).

Compound 2-20:



To a solution of **2-5** (85.1 mg, 0.167 mmol) in THF (8 mL) was added TMSCl (63 μ L, 0.50 mmol) at -78 $^{\circ}$ C, and the mixture was stirred for 3 min. To the mixture was added NHMDs (1.10 mol/L in THF, 456 μ L, 0.501 mmol) at -78 $^{\circ}$ C, and the mixture was stirred for 5 min. Then, the mixture was warmed to 0 $^{\circ}$ C and stirred for 1 h. The reaction was quenched with satd. aq. NaHCO_3 , and the mixture was extracted with EtOAc (5 mL) three 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/Et₂O (1 mL /2 mL), TMSCHN₂ (2 mol/L in Et₂O, 420 μ L, 0.835 mmol) was added to the solution at 25 $^{\circ}$ 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 = 30) to give **2-20** (57.1 mg, 0.109 mmol, 65% over 2 steps).

2-20: a colorless oil; $[\alpha]_D^{23} -57.5$ (c 1.07, CHCl_3);

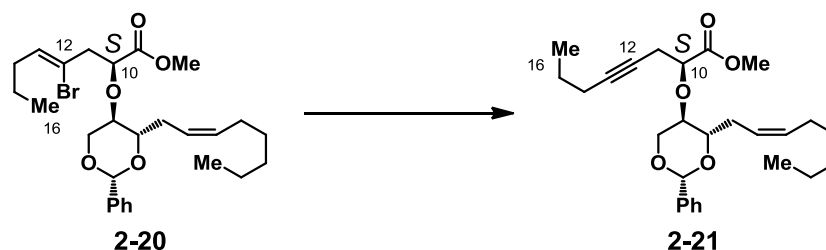
IR (neat) ν 3067, 2957, 2927, 2857, 1754, 1658, 1454, 1434, 1397, 1366, 1276, 1214, 1176, 1116, 1029, 976, 914, 749, 698 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 0.87 (3H, t, J = 6.9 Hz), 0.95 (3H, t, J = 7.4 Hz), 1.23-1.39 (6H, m), 1.45 (2H, sext., J = 7.3 Hz), 2.07 (2H, q, J = 6.8 Hz), 2.16 (2H, q, J = 7.2 Hz), 2.32 (1H, ddd, J = 6.7, 8.6, 15.0 Hz), 2.69-2.87 (3H, m), 3.39-3.54 (2H, m), 3.60 (1H, dt, J = 2.6, 8.5 Hz), 3.77 (3H, s), 4.31 (1H, dd, J = 4.2, 8.9 Hz), 4.34-4.40 (1H, m), 5.43 (1H, s), 5.45-5.60 (2H, m), 5.78 (1H, t, J = 6.9 Hz), 7.29-7.39 (3H, m), 7.43-7.49 (2H, m);

^{13}C NMR (100 MHz, CDCl_3) δ 13.7 (CH_3), 14.1 (CH_3), 21.6 (CH_2), 22.6 (CH_2), 27.4 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.5 (CH_2), 33.4 (CH_2), 45.3 (CH_2), 52.1 (CH_3), 69.0 (CH_2), 72.6 (CH), 75.4 (CH), 80.5 (CH), 100.8 (CH), 121.6 (C), 124.9 (CH), 126.0 ($\text{CH}\times 2$), 128.1 ($\text{CH}\times 2$), 128.8 (CH), 132.2 (CH), 133.2 (CH), 137.8 (C), 171.7 (C);

FD-LRMS m/z 523 (33%, $[\text{M}^+]$), 524 (bp, $[\text{M}+\text{H}^+]$);

FD-HRMS calcd for $\text{C}_{27}\text{H}_{39}\text{BrO}_5$ $[\text{M}^+]$: 522.1981, found: 522.2002.

Compound 2-21:

To a solution of **2-20** (57.1 mg, 0.109 mmol) in DMF (1 mL) was added TBAF·3H₂O (101.2 mg, 0.3207 mmol) at 70 °C, and the mixture was stirred for 6 h. Then, the mixture was acidified with 1 mol/L aq. HCl. The mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. Because partial hydrolysis of the methyl ester was observed, the resulting residue was dissolved in MeOH/Et₂O (1 mL /1 mL), and was treated with TMSCHN₂ (2 mol/L in Et₂O). The reaction mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give **2-21** (26.9 mg, 0.0608 mmol, 80% over 2 steps).

2-21: a colorless oil; $[\alpha]_D^{22}$ -49.3 (c 1.02, CHCl₃);

IR (neat) ν 2958, 2928, 2871, 2857, 2343, 2149, 2019, 1896, 1819, 1755, 1454, 1434, 1397, 1366, 1298, 1204, 1176, 1114, 1029, 977, 915, 749, 698, 679 cm⁻¹;

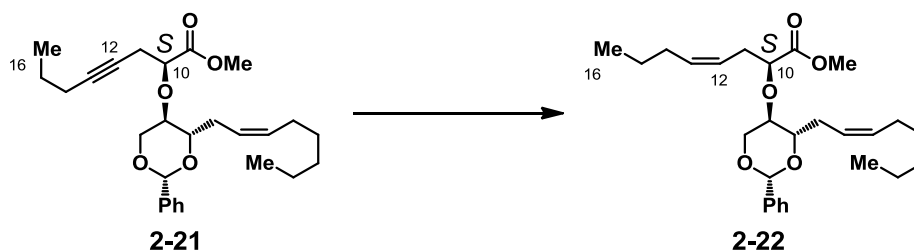
¹H NMR (400 MHz, CDCl₃) δ 0.87 (3H, t, J = 6.9 Hz), 0.97 (3H, t, J = 7.3 Hz), 1.22-1.40 (6H, m), 1.51 (2H, sext., J = 7.3 Hz), 2.06 (2H, q, J = 6.8 Hz), 2.14 (2H, tt, J = 2.4, 7.1 Hz), 2.33 (1H, ddd, J = 6.7, 8.4, 15.0 Hz), 2.51-2.70 (2H, m), 2.79 (1H, m), 3.44-3.4 (1H, m), 3.66 (2H, t, J = 10.5 Hz), 3.78 (3H,s), 4.09 (1H, dd, J = 5.3, 7.5 Hz), 4.43 (1H, dd, J = 4.9, 10.9 Hz), 5.47 (1H, s), 5.46-5.60 (2H, m), 7.29-7.40 (3H, m), 7.43-7.50 (2H, m);

¹³C NMR (100 MHz, CDCl₃) δ 13.5 (CH₃), 14.1 (CH₃), 20.7 (CH₂), 22.2 (CH₂), 22.6 (CH₂), 23.9 (CH₂), 27.4 (CH₂), 29.3 (CH₂), 29.5 (CH₂), 31.6 (CH₂), 52.2 (CH₃), 69.1 (CH₂), 72.9 (CH), 74.6 (C), 77.2 (CH), 80.4 (CH), 83.0 (C), 100.9 (CH), 124.8 (CH), 126.1 (CH×2), 128.2 (CH×2), 128.8 (CH), 132.3 (CH), 137.8 (C), 171.0 (C);

FD-LRMS m/z 442 (bp, [M⁺]), 443 (32%, [M+H⁺]);

FD-HRMS calcd for C₂₇H₃₈O₅ [M⁺]: 442.2719, found: 442.2736.

Compound 2-22:



To a solution of **2-21** (26.9 mg, 0.0608 mmol) and 1-hexene (1.5 mL, 12 mmol) in MeOH (1 mL) was added Lindlar catalyst (3 mg) at 24 °C, and the mixture was stirred for 27 h under H₂ atmosphere. The mixture was filtered through a Celite pad and concentrated in vacuo to give almost pure **2-22** (25.0 mg, 0.0562 mmol, 93%).

2-22: a colorless oil; $[\alpha]_{\text{D}}^{22} -49.8$ (*c* 1.02, CHCl₃);

IR (neat) ν 3067, 3014, 2957, 2927, 2871, 2857, 2341, 1897, 1755, 1497, 1455, 1436, 1397, 1366, 1297, 1200, 1176, 1114, 1030, 977, 914, 749, 698 cm⁻¹;

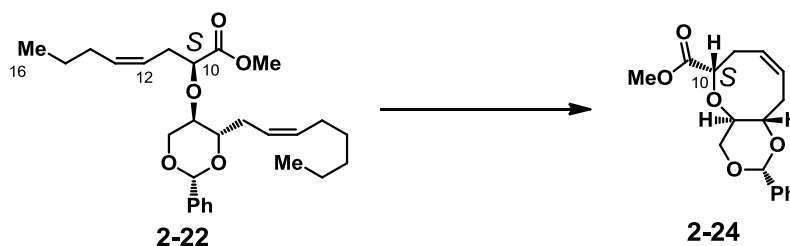
¹H NMR (400 MHz, CDCl₃) δ 0.87 (3H, t, *J* = 6.9 Hz), 0.91 (3H, t, *J* = 7.3 Hz), 1.23-1.43 (8H, m), 2.02 (2H, dq, *J* = 1.2, 7.3 Hz), 2.07 (2H, q, *J* = 6.9 Hz), 2.27-2.38 (1H, m), 2.49 (2H, t, *J* = 6.8 Hz), 2.69-2.88 (1H, m), 3.36-3.48 (1H, m), 3.60 (1H, t, *J* = 10.4 Hz), 3.64 (1H, dt, *J* = 2.8, 8.7 Hz), 3.75 (3H, s), 4.01 (1H, t, *J* = 6.3 Hz), 4.35 (1H, dd, *J* = 4.9, 10.8 Hz), 5.32-5.42 (1H, m), 5.45 (1H, s), 5.45-5.61 (3H, m), 7.29-7.40 (3H, m), 7.43-7.49 (2H, m);

¹³C NMR (100 MHz, CDCl₃) δ 13.8 (CH₃), 14.1 (CH₃), 22.6 (CH₂), 22.6 (CH₂), 27.4 (CH₂), 29.3 (CH₂), 29.4 (CH₂), 29.5 (CH₂), 31.2 (CH₂), 31.5 (CH₂), 51.9 (CH₃), 69.0 (CH₂), 72.3 (CH), 77.5 (CH), 80.6 (CH), 100.9 (CH), 123.1 (CH), 124.9 (CH), 126.0 (CH₂), 128.1 (CH₂), 128.8 (CH), 132.2 (CH), 133.4 (CH), 137.8 (C), 172.0 (C);

FD-LRMS *m/z* 444 (bp, [M⁺]), 445 (31%, [M+H⁺]);

FD-HRMS calcd for C₂₇H₄₀O₅ [M⁺]: 444.2876, found: 444.2878.

Compound 2-24:



To a solution of **2-22** (25.0 mg, 0.0562 mmol) in (CH₂Cl)₂ (12 mL) was added a solution of Grubbs' second generation catalyst (2.1 mg, 0.0025 mmol) in (CH₂Cl)₂ (1 mL) at refluxing temperature, and the mixture was refluxed and stirred for 11.5 h. Then, the mixture was cooled to 23 °C and stirred under air for 2 h. Then, the mixture was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **2-24** (10.5 mg, 0.0345 mmol, 61%).

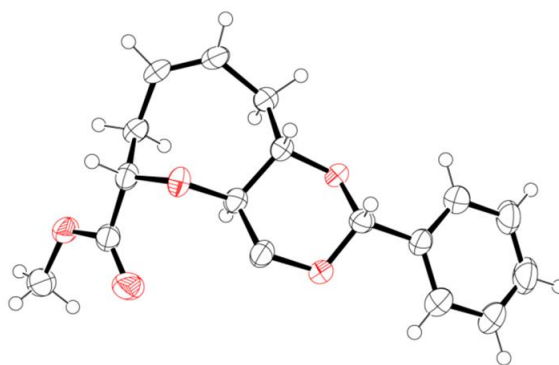
2-24: a colorless needle crystalline ; [α]_D²³ -42.8 (c 0.75, CHCl₃);

IR (KBr) ν 3033, 2936, 2877, 2848, 1741, 1470, 1450, 1439, 1386, 1365, 1282, 1277, 1251, 1231, 1212, 1133, 1034, 1020, 989, 746, 737, 693 cm⁻¹;

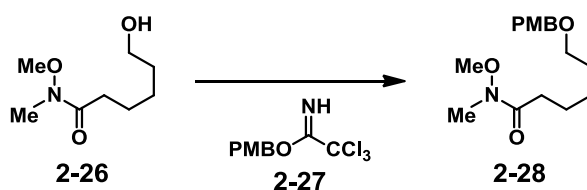
¹H NMR (400 MHz, CDCl₃) δ 2.40-2.58 (3H, m), 2.62-2.73 (1H, m), 3.57 (1H, ddd, J = 3.4, 9.2, 10.3 Hz), 3.61 (1H, dd, J = 10.0, 10.7 Hz), 3.73-3.86 (1H, m), 3.78 (3H, s), 4.15 (1H, dd, J = 3.6, 12.3 Hz), 4.55 (1H, dd, J = 5.4, 10.9 Hz), 5.46 (1H, s), 5.73-5.83 (1H, m), 5.90-6.01 (1H, m), 5.45-5.61 (3H, m), 7.30-7.40 (3H, m), 7.45-7.51 (2H, m);

¹³C NMR (100 MHz, CDCl₃) δ 29.1 (CH₂), 32.7 (CH₂), 52.1 (CH₃), 69.9 (CH₂), 70.7 (CH), 75.2 (CH), 80.4 (CH), 100.9 (CH), 126.1 (CH $\times$ 2), 127.6 (CH), 128.3 (CH $\times$ 2), 128.9 (CH), 128.9 (CH), 137.8 (C), 172.4 (C);

Crystal data of **2-24**: $C_{16}H_{20}O_4$, $M = 276.33$, colorless platelet, $0.60 \times 0.20 \times 0.050 \text{ mm}^3$, monoclinic $P2_1$ (No. 4), $a = 4.489(2) \text{ \AA}$, $b = 10.766(5) \text{ \AA}$, $c = 15.746(8) \text{ \AA}$, $\beta = 95.054(6)^\circ$, $V = 758.0(7) \text{ \AA}^3$, $D_c (Z = 2) = 1.211 \text{ g cm}^{-3}$. A total 2106 unique data ($2\theta_{\text{max}} = 54.9^\circ$) were measured at $T = 293 \text{ K}$ by Rigaku Mercury 70 apparatus (Mo $K\alpha$ radiation, $\lambda = 0.71075 \text{ \AA}$). Numerical absorption correction was applied ($\mu = 0.860 \text{ cm}^{-1}$). The structure was solved by the direct method (SIR2004) and expanded using Fourier techniques. Non-hydrogen atoms were refined by the full-matrix least-squares method of F^2 with anisotropic temperature factors (SHELXL97). Hydrogen atoms were refined using the riding model. The final $wR2$ value is 0.1186 (all data) for 2106 reflections and 199 parameters.



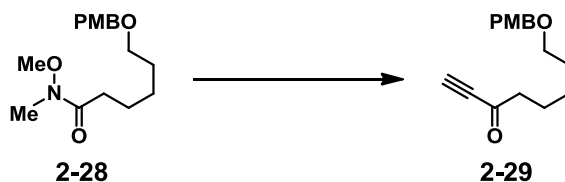
ORTEP diagram of cyclic ether **2-24**.

Compound 2-28:

To a solution of **2-26** (1.1288 g, 6.4418 mmol) in CH_2Cl_2 (65 mL) were added PMB trichloroimidate (**2-27**) (3.65 g, 12.9 mmol) and a solution of TMSOTf (59 μL , 322 μmol) in CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred for 10 min. Then, the mixture was stirred at 24 °C for 3 h. Then, the reaction was quenched with Et_3N (500 μL), and the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 3) to give **2-28** (1.4450 g, 4.8921 mmol, 76%).

2-28: a colorless oil;

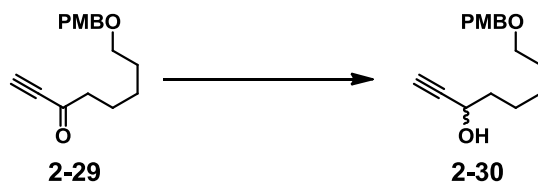
^1H NMR (400 MHz, CDCl_3) δ 1.36-1.46 (2H, m), 1.59-1.70 (4H, m), 2.42 (2H, t, J = 7.5 Hz), 3.17 (3H, s), 3.45 (2H, t, J = 6.6 Hz), 3.67 (3H, s), 3.80 (3H, s), 4.43 (2H, s), 6.87 (2H, td, J = 2.9, 8.7 Hz), 7.26 (2H, td, J = 2.9, 8.7 Hz).

Compound 2-29:

To a solution of **2-28** (597.7 mg, 2.024 mmol) in THF (20 mL) were added ethynyl magnesium bromide (0.5 mol/L in THF, 8.1 mL, 4.048 mmol) at -78°C , and the mixture was stirred for 1 h. Then, the reaction was quenched with satd. aq. NH_4Cl (10 mL), and the mixture was extracted with CH_2Cl_2 (15 mL) three 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) to give **2-29** (455.1 mg, 1.748 mmol, 86%).

2-29: a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 1.35-1.45 (2H, m), 1.57-1.75 (4H, m), 2.59 (2H, t, $J = 7.4$ Hz), 3.20 (1H, s), 3.44 (2H, t, $J = 6.5$ Hz), 3.80 (3H, s), 4.42 (2H, s), 6.88 (2H, td, $J = 2.9, 8.7$ Hz), 7.25 (2H, td, $J = 2.9, 8.7$ Hz).

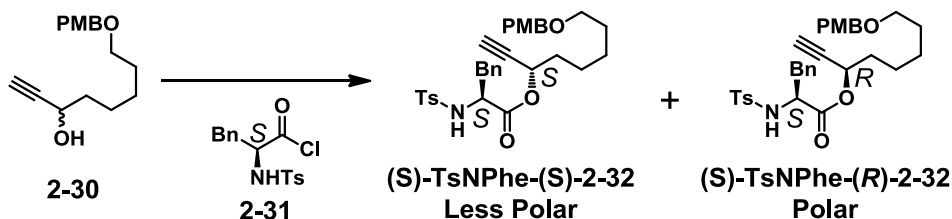
Compound 2-30:

To a solution of **2-29** (462.2 mg, 1.7754 mmol) in MeOH (18 mL) were added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.32 g, 3.55 mmol) and NaBH_4 (134.3 mg, 3.551 mmol) at -78°C , and the mixture was stirred for 20 min. Then, the reaction was quenched with satd. aq. NH_4Cl . The mixture was filtered through a Celite pad, and the filtrate was extracted with CH_2Cl_2 (10 mL) three 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) to give racemic **2-30** (434.9 mg, 1.658 mmol, 93%).

2-30: a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 1.35-1.52 (4H, m), 1.62 (2H, td, $J = 6.6, 14.6$ Hz), 1.67-1.75 (2H, m), 2.11 (1H, brs), 2.45 (1H, d, $J = 2.1$ Hz), 3.44 (2H, t, $J = 6.5$ Hz), 3.80 (3H, s), 4.34 (1H, dt, $J = 2.1, 6.6$ Hz), 4.43 (2H, s), 6.87 (2H, td, $J = 2.9, 8.7$ Hz), 7.26 (2H, td, $J = 2.9, 8.7$ Hz).

Compound (S)-TsNPhe-(S)-2-32 and (S)-TsNPhe-(R)-2-32:



To a solution of **2-30** (255.2 mg, 0.9728 mmol) in THF (10 mL) were added pyridine (236 μ L, 2.92 mmol) and *N*-tosyl-L-phenylalanyl chloride (492.9 mg, 1.459 mmol) at 25 $^{\circ}$ C, and the mixture was stirred for 12 h. Then, the reaction was quenched with 1 mol/L aq. HCl, and the mixture was extracted with EtOAc (10 mL) three times. The combined organic layers were washed with 1 mol/L aq. HCl, H₂O, and brine in this order, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 3) to give a mixture of **(S)-TsNPhe-(S)-2-32** and **(S)-TsNPhe-(R)-2-32**. Then, the mixture was separated by preparative HPLC using a pre-packed column (YMC-Pack SIL-06-5 μ m, 500 mm $\times$ 20 mmID) supplied by YMC Co., Ltd. with hexane-ethyl acetate eluent (flow rate: 20 mL/min) to give colorless solid **(S)-TsNPhe-(S)-2-32** (137.1 mg, 0.2432 mmol, 25%) as a less polar component and **(S)-TsNPhe-(R)-2-32** (138.6 mg, 0.2459 mmol, 25%) as a polar component. Pure single crystals **(S)-TsNPhe-(S)-2-32** were obtained by recrystallization with hexane/MeOH.

(S)-TsNPhe-(S)-2-32: a colorless needle crystal;

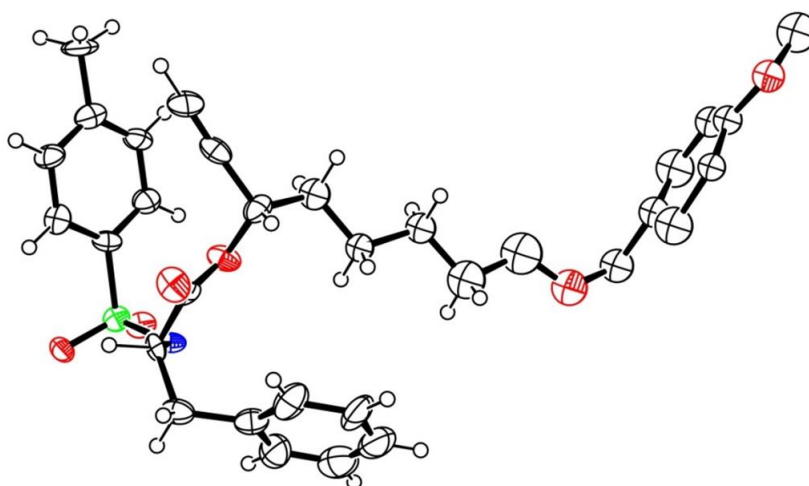
mp 87-89 $^{\circ}$ C; $[\alpha]_D^{22}$ -33.5 (*c* 0.50, CHCl₃);

IR (KBr) ν 3422, 3312, 3270, 3029, 2967, 2935, 2855, 1721, 1611, 1510, 1456, 1439, 1386, 1355, 1334, 1307, 1274, 1257, 1201, 1164, 1090, 1061, 1033, 1020, 1011, 998, 933, 882, 846, 814, 767, 745, 723, 703, 673, 606, 597, 573, 547, 511 cm^{-1} ;

¹H NMR (400 MHz, CDCl₃) δ 1.24-1.40 (4H, m), 1.51-1.66 (4H, m), 2.37 (3H, s), 2.45 (1H, d, *J* = 2.0 Hz), 3.06 (2H, d, *J* = 5.6 Hz), 3.44 (2H, t, *J* = 6.4 Hz), 3.80 (3H, s), 4.21 (1H, td, *J* = 5.6, 9.2 Hz), 4.44 (2H, s), 5.04 (1H, d, *J* = 9.2 Hz), 5.08 (1H, dt, *J* = 2.0, 6.6 Hz), 6.88 (2H, d, *J* = 8.6 Hz), 7.10-7.16 (2H, m), 7.18-7.30 (7H, m), 7.63 (2H, d, *J* = 8.2 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 21.5 (CH₃), 24.5 (CH₂), 25.7 (CH₂), 29.5 (CH₂), 34.2 (CH₂), 39.2 (CH₂), 55.3 (CH₃), 56.2 (CH), 65.3 (CH), 69.8 (CH₂), 72.6 (CH₂), 74.5 (CH), 77.2 (C), 80.0 (CH), 113.7 (CH $\times$ 2), 127.2 (CH $\times$ 2), 127.2 (CH), 128.5 (CH $\times$ 2), 129.2 (CH $\times$ 2), 129.6 (CH $\times$ 2), 129.7 (CH $\times$ 2), 130.6 (C), 134.6 (C), 136.6 (C), 143.5 (C), 159.1 (C), 169.7 (C).

Crystal data of **(S)-TsNPhe-(S)-2-32**: Crystals were obtained by recrystallizing from hexane/MeOH. $C_{32}H_{37}NO_6S$, $M = 563.71$, colorless needle, $0.200 \times 0.020 \times 0.010 \text{ mm}^3$, monoclinic $C2$ (No. 5), $a = 17.416(9) \text{ \AA}$, $b = 5.680(2) \text{ \AA}$, $c = 31.40(2) \text{ \AA}$, $\beta = 105.180(9)^\circ$, $V = 2997(3) \text{ \AA}^3$, D_c ($Z = 4$) = 1.249 g cm^{-3} . A total 3358 unique data ($2\theta_{\text{max}} = 52^\circ$) were measured at $T = 150 \text{ K}$ by Rigaku Mercury 70 apparatus (Mo $K\alpha$ radiation, $\lambda = 0.71075 \text{ \AA}$). Numerical absorption correction was applied ($\mu = 1.517 \text{ cm}^{-1}$). The structure was solved by direct methods (SIR2004) and expanded using Fourier techniques. Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically (SHELXL97). Hydrogen atoms were refined using the riding model. The final $wR2$ value is 0.2398 (all data) for 3358 reflections and 318 parameters.



ORTEP diagram of ester **(S)-TsNPhe-(S)-2-32**.

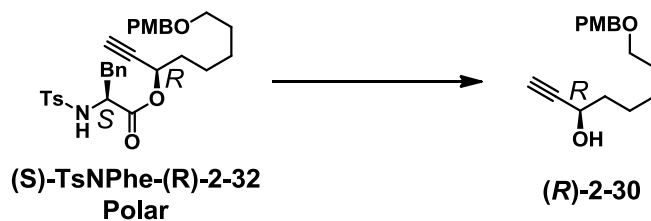
(S)-TsNPhe-(R)-2-32: a colorless oil;

IR (neat) ν 3279, 3088, 3063, 3031, 3004, 2936, 2862, 2794, 2254, 2123, 1885, 1745, 1612, 1586, 1513, 1497, 1456, 1339, 1304, 1248, 1162, 1092, 1034, 909, 815, 742, 702, 663 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 1.24-1.40 (4H, m), 1.49-1.61 (4H, m), 2.38 (3H, s), 2.39 (1H, d, J = 2.1 Hz), 3.02 (2H, d, J = 6.3 Hz), 3.42 (2H, t, J = 6.4 Hz), 3.80 (3H, s), 4.23 (1H, td, J = 6.3, 9.2 Hz), 4.42 (2H, s), 5.03 (1H, d, J = 9.2 Hz), 5.06 (1H, dt, J = 2.1, 6.6 Hz), 6.87 (2H, td, J = 2.8, 8.7 Hz), 7.06-7.11 (2H, m), 7.20-7.28 (7H, m), 7.63 (2H, td, J = 2.1, 8.3 Hz);

^{13}C NMR (100 MHz, CDCl_3) δ 21.5 (CH_3), 24.5 (CH_2), 25.7 (CH_2), 29.5 (CH_2), 34.1 (CH_2), 39.5 (CH_2), 55.3 (CH_3), 56.6 (CH), 65.3 (CH), 69.8 (CH_2), 72.6 (CH_2), 74.3 (CH), 77.2 (C), 80.0 (CH), 113.7 ($\text{CH}\times 2$), 127.1 ($\text{CH}\times 2$), 127.3 (CH), 128.6 ($\text{CH}\times 2$), 129.2 ($\text{CH}\times 2$), 129.5 ($\text{CH}\times 2$), 129.7 ($\text{CH}\times 2$), 130.6 (C), 134.7 (C), 136.7 (C), 143.5 (C), 159.1 (C), 169.8 (C).

Compound (R)-2-30:

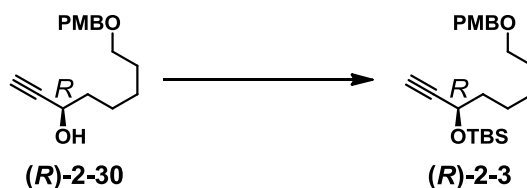


To a solution of **(S)-TsNPhe-(R)-2-32** (86.5 mg, 0.153 mmol) in MeOH (1 mL) was added 50% aq. NaOH (1 ml) at 26 °C, and the mixture was stirred for 19 h. Then, the mixture was extracted with CH₂Cl₂ (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give almost pure **(R)-2-30** (38.1 mg, 0.145 mmol, 95%).

(R)-2-30: a colorless oil;

¹H NMR (400 MHz, CDCl₃) δ 1.35-1.52 (4H, m), 1.62 (2H, td, *J* = 6.6, 14.6 Hz), 1.67-1.75 (2H, m), 2.11 (1H, brs), 2.45 (1H, d, *J* = 2.1 Hz), 3.44 (2H, t, *J* = 6.5 Hz), 3.80 (3H, s), 4.34 (1H, dt, *J* = 2.1, 6.6 Hz), 4.43 (2H, s), 6.87 (2H, td, *J* = 2.9, 8.7 Hz), 7.26 (2H, td, *J* = 2.9, 8.7 Hz).

Compound (R)-2-3:

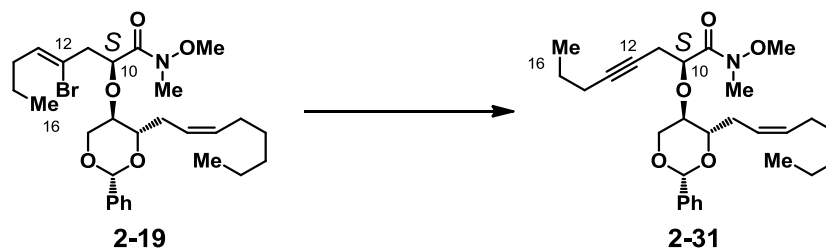


To a solution of **(R)-2-30** (61.1 mg, 0.233 mmol) in CH₂Cl₂ (1 mL) were added 2,6-lutidine (22 μ L, 0.47 mmol) and TBSOTf (26 μ L, 0.28 mmol) at 0°C, and the mixture was stirred for 12 h at 24 °C. Then, the reaction was quenched with 1 mol/L aq. HCl (300 μ L), and the mixture was extracted with EtOAc (10 mL) three times. The combined organic layers were washed with 1 mol/L aq. HCl, H₂O, and brine in this order, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **(R)-2-3** (79.1 mg, 0.210 mmol, 90%).

(R)-2-3: a colorless oil;

¹H NMR (400 MHz, CDCl₃) δ 0.10 (3H, s), 0.13 (3H, s), 0.90 (9H, s), 1.33-1.50 (4H, m), 1.56-1.71 (4H, m), 2.37 (1H, d, J = 2.1 Hz), 3.44 (2H, t, J = 6.6 Hz), 3.80 (3H, s), 4.33 (1H, dt, J = 2.1, 6.5 Hz), 4.43 (2H, s), 6.88 (2H, td, J = 2.8, 8.7 Hz), 7.26 (2H, td, J = 2.8, 8.7 Hz).

Compound 2-19:



To a solution of **2-19** (81.2 mg, 0.147 mmol) in DMF (1.5 mL) was added TBAF·3H₂O (192.7 mg, 0.6107 mmol) at 70 °C, and the mixture was stirred for 7 h. Then, the mixture was acidified with 1 mol/L aq. HCl. The mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **2-31** (60.2 mg, 0.128 mmol, 87%).

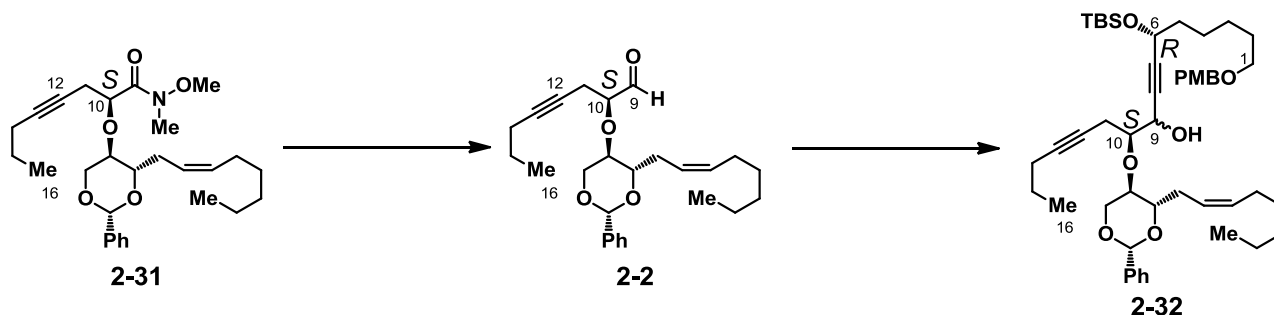
2-31: a colorless oil; $[\alpha]_D^{23}$ -38.2 (c 0.76, CHCl₃);

IR (neat) ν 3066, 2960, 2929, 2957, 1724, 1675, 1456, 1392, 1300, 1277, 1213, 1176, 1103, 1029, 985, 750, 698, 679, 653 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 0.87 (3H, t, J = 6.9 Hz), 0.97 (3H, t, J = 7.4 Hz), 1.22-1.38 (6H, m), 1.51 (2H, sext., J = 7.3 Hz), 2.06 (2H, q, J = 6.8 Hz), 2.13 (2H, tt, J = 2.3, 7.1 Hz), 2.28 (1H, ddd, J = 6.3, 8.6, 14.7 Hz), 2.53 (1H, ddt, J = 2.4, 7.4, 16.4 Hz), 2.64 (1H, ddt, J = 2.4, 6.2, 16.4 Hz), 2.77 (1H, brddd, J = 2.5, 6.5, 14.7 Hz), 3.23 (3H, s), 3.44 (1H, ddd, J = 5.0, 9.3, 9.9 Hz), 3.64 (1H, dt, J = 2.8, 8.9 Hz), 3.67 (1H, t, J = 10.4 Hz), 3.75 (3H, s), 4.46 (1H, dd, J = 5.0, 10.8 Hz), 4.52 (1H, brt, J = 6.7 Hz), 5.44-5.58 (2H, m), 5.46 (1H, s), 7.30-7.37 (3H, m), 7.44-7.50 (2H, m);

¹³C NMR (100 MHz, CDCl₃) δ 13.5 (CH₃), 14.1 (CH₃), 20.7 (CH₂), 22.2 (CH₂), 22.6 (CH₂), 23.4 (CH₂), 27.4 (CH₂), 29.3 (CH₂), 29.5 (CH₂), 31.5 (CH₂), 32.3 (CH₃), 61.7 (CH₃), 69.4 (CH₂), 72.7 (CH), 75.4 (C), 80.4 (CH), 82.5 (C), 100.8 (CH), 124.8 (CH), 126.0 (CH₂), 128.1 (CH₂), 128.7 (CH), 132.3 (CH), 133.2 (CH), 137.9 (C), 171.0 (C).

Compound 2-32:



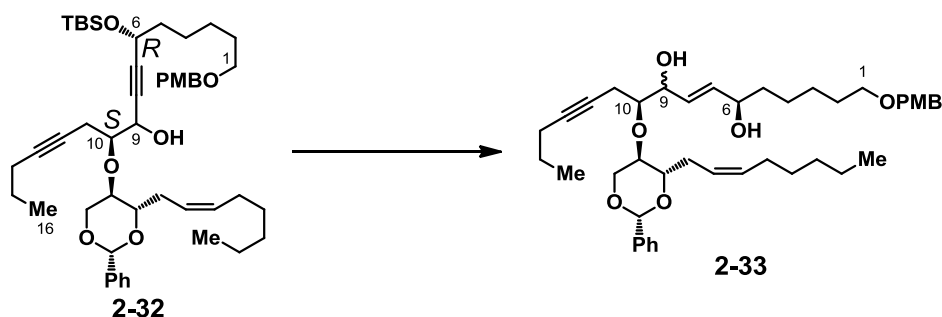
To a solution of **2-31** (20.8 mg, 0.0441 mmol) in THF (1 mL) were added LiAlH_4 (2.2 mg, 0.057 mmol) at $-20\text{ }^\circ\text{C}$, and the mixture was stirred for 15 min. Then, the reaction was quenched with satd. aq. Rochelle salt, and the mixture was extracted with Et_2O (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo. The resulting crude aldehyde **2-2** was immediately used in the next reaction without further purification.

To a solution of (*R*)-**2-3** (83.0 mg, 0.220 mmol) in a 5:1 blend of THF and HMPA (1 mL / 200 μL) was added BuLi (1.55 mol/L in hexane, 0.137 mL, 0.212 mmol) at $-78\text{ }^\circ\text{C}$, and the mixture was stirred for 1 h. To the mixture was added a solution of the above crude aldehyde **2-2** in THF (1 mL) at $-78\text{ }^\circ\text{C}$, and the mixture was stirred for 5.5 h at $25\text{ }^\circ\text{C}$. Then, the reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with EtOAc (5 mL) three times. The combined organic layers were washed with H_2O and brine in this order, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/ EtOAc = 8) to give **2-32** (20.6 mg, 0.0261 mmol, 59% over 2 steps).

2-32: an about 1:1 mixture of two diastereomers at C9; a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 0.10 (3H, s), 0.13 (3H, s), 0.87 (3H, t, J = 6.9 Hz), 0.90 (9H, s), 0.98 (3H, t, J = 7.4 Hz), 1.21-1.47 (10H, m), 1.52 (2H, sext., J = 7.3 Hz), 1.56-1.71 (4H, m), 2.06 (2H, q, J = 6.8 Hz), 2.14 (2H, tt, J = 2.8, 7.0 Hz), 2.24-2.80 (4H, m), 3.43 (2H, q, J = 6.4 Hz), 3.53-3.76 (5H, m), 3.80 (3H, s), 4.37 (1H, t, J = 6.5 Hz), 4.43 (2H, s), 4.46 (1H, dd, J = 4.8, 10.8 Hz), 4.51 (1H $\times$ 1/2, brd, J = 4.9 Hz), 4.59 (1H $\times$ 1/2, brd, J = 1.6 Hz), 5.44-5.63 (2H, m), 5.46 (1H, s), 6.87 (2H, td, J = 2.8, 8.7 Hz), 7.22-7.29 (2H, m), 7.29-7.40 (3H, m), 7.43-7.51 (2H, m).

Compound 2-33:

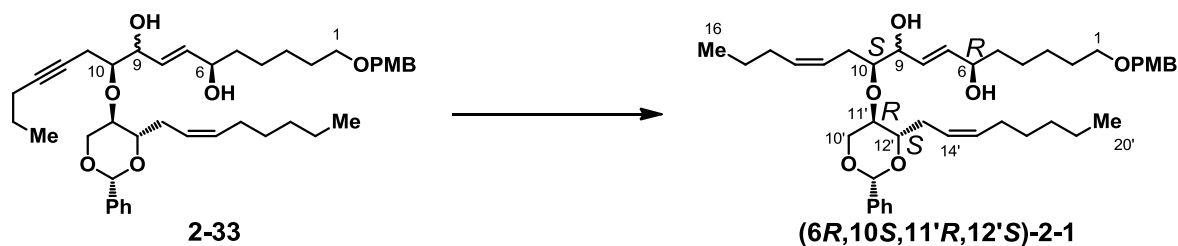


To a solution of **2-32** (12.2 mg, 0.0155 mmol) in THF (1 mL) were added LiAlH_4 (0.7 mg, 0.019 mmol) at 23 °C, and the mixture was stirred for 24 h. Then, the reaction was quenched with satd. aq. Rochelle salt, and the mixture was stirred for 3 h. The mixture was extracted with EtOAc (5 mL) three times. 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 = 4 $\rightarrow$ EtOAc) to give **2-33** (5.3 mg, 0.0078 mmol, 51%).

2-33: an about 1:1 mixture of two diastereomers at C9; a colorless oil;

^1H NMR (400 MHz, CDCl_3) δ 0.87 (3H, t, J = 6.9 Hz), 0.98 (3H, t, J = 7.3 Hz), 1.21-1.68 (14H, m), 1.52 (2H, sext., J = 7.3 Hz), 2.06 (2H, q, J = 6.8 Hz), 2.14 (2H, tt, J = 2.2, 7.1 Hz), 2.24-2.50 (3H, m), 2.62-2.72 (1H, m), 3.44 (2H, q, J = 6.4 Hz), 3.52-3.73 (5H, m), 3.80 (3H, s), 4.06-4.20 (1H, m), 4.36 (1H, brs), 4.39-4.47 (1H, m), 4.43 (2H, s), 5.47 (1H, s), 5.48-5.63 (2H, m), 5.70 (1H, ddd, J = 1.0, 6.0, 15.5 Hz), 5.83 (1H, ddd, J = 1.0, 6.0, 15.5 Hz), 6.88 (2H, td, J = 2.8, 8.7 Hz), 7.26 (2H, td, J = 2.8, 8.7 Hz), 7.30-7.40 (3H, m), 7.43-7.51 (2H, m).

Compound (6*R*,10*S*,11'*R*,12'*S*)-2-1:



To a solution of **2-33** (5.3 mg, 0.0078 mmol) and 1-hexene (1 mL, 0.78 mmol) in MeOH (0.5 mL) was added Lindlar catalyst (9.6 mg) at 26 °C, and the mixture was stirred for 26 h under H₂ atmosphere. The mixture was filtered through a Celite pad and concentrated in vacuo to give almost pure **(6*R*,10*S*,11'*R*,12'*S*)-2-1** (5.2 mg, 0.0077 mmol, 98%).

(6*R*,10*S*,11'*R*,12'*S*)-2-1: an about 1:1 mixture of two diastereomers at C9; a colorless oil;

¹H NMR (400 MHz, CDCl₃) δ 0.84-0.97 (6H, m), 1.20-1.68 (16H, m), 1.93-2.51 (7H, m), 2.63-2.72 (1H, m), 3.38-3.76 (6H, m), 3.44 (2H, t, *J* = 6.4 Hz), 3.80 (3H, s), 4.06-4.34 (3H, m), 4.43 (2H, s), 5.30-5.44 (1H, m), 5.46 (1H, s), 5.44-5.63 (3H, m), 5.63-5.89 (4H, m), 6.88 (2H, brd, *J* = 8.7 Hz), 7.26 (2H, brd, *J* = 8.7 Hz), 7.30-7.39 (3H, m), 7.43-7.50 (2H, m).

Chapter 3.

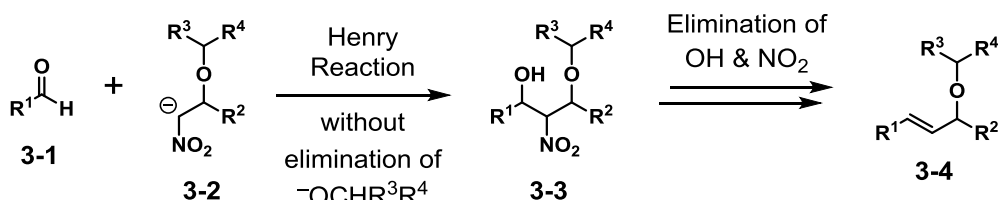
Exploration of a New Method for the Segment Connection at the C9'-C10' Double Bond of Nigricanoside A Dimethyl Ester

3-1. Introduction

In this chapter, the author describes the exploration of a new method for the segment connection at the C9'-C10' double bond aiming at the convergent total synthesis of nigricanoside-A dimethyl ester (**1-2**).¹

As described in the chapter 1, the left- and right-half segments of **1-2** should be connected in a way that forms a double bond between C9' and C10' for the convergent total synthesis of **1-2**. The segment connection at C9'-C10' double bond of **1-2** includes some difficulties due to the presence of ether groups at C8' and C11' and other internal double bonds. Cross-metathesis is a well-known method for the formation of simple ether-group-adjacent double bonds.² However, the C9'-C10' double bond is predicted to react with other internal double bonds at C14'-C15', C7-C8, and C13-C13 by ring-closing olefin metathesis as a side reaction under the cross-metathesis conditions.³ Therefore, the development of a method based on anion coupling and elimination has been studied as a solution for the segment connection at C9'-C10' double bond of **1-2** in our laboratory. In this context, Kinashi examined a Julia-Kocienski olefination⁴ for the connection of the left- and the right-half segment (**1-44**). However, a β -elimination reaction of an alkoxide, corresponding to the C16 fatty acid chain, from the sulfone (right-half) segment (**1-44**) predominated to give no coupling product (Scheme 1-6).⁵

Thus, the author has investigated to develop a new method based on an anion coupling reaction that tolerates the presence of an alkoxy group at the β -position of the carbanion. From the above consideration, the author planned to connect segments **3-1** (corresponding to **1-29**) and **3-2** (corresponding to **1-30**) by a process including Henry (nitroaldol) reaction⁶ to give a nitroaldol and the subsequent elimination of the hydroxy and nitro groups to afford an allyl ether (**3-4**) (Scheme 3-1). Since nitroalkanes generally show smaller values of pK_a than alcohols, the author expected that β -alkoxynitroalkanes would generate stable β -alkoxy- α -nitrocarbanions (**3-2**), which would react with aldehydes (**3-1**) without elimination of the β -alkoxy group to give nitroaldols (**3-3**). The eliminative alkenylation of nitroaldols (**3-3**) would be achievable based on the high radical reactivity of the nitro group.



Scheme 3-1. A plan for the segment connection at a double bond adjacent to an ether group.

The author designed model compounds shown in Figure 3-1 to demonstrate the above segment connection process: a simple nitroalkane **3-5**, a simple β -alkoxynitroalkane **3-6** and advanced β -alkoxynitroalkanes **3-7**. The hept-4-yloxy group at the β -position of nitro group in **3-6** and **3-7a-c** was modeled on the C1-C16 chain of **1-2**. Advanced models **3-7a-c** were prepared as optically active compounds from diethyl-D-tartrate. The preparation of the model compounds is described in Section 3-2.

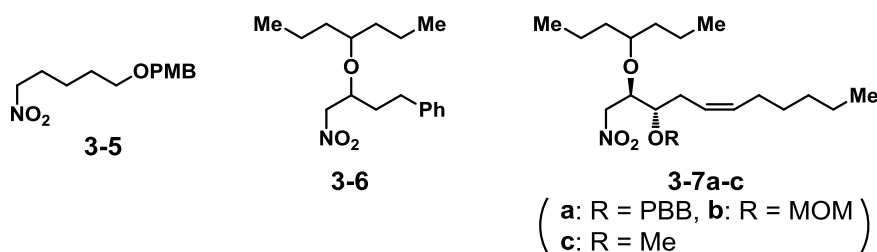


Figure 3-1. Model compounds for the demonstration of the segment connection process.

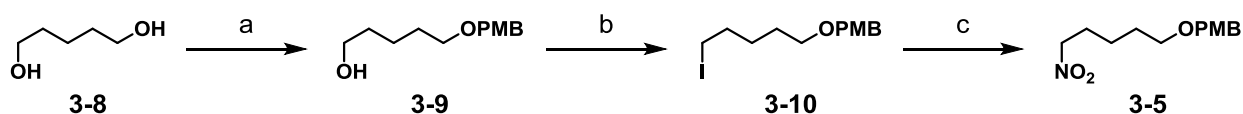
First, the nitroaldol reactions of model nitroalkans **3-5**, **3-6**, and **3-7a-c** with a simple aldehyde, 3-phenylpropanal, were examined. During the examination, it was found that DBN is an effective base for the nitroaldol reaction of β -alkoxynitroalkanes. The results are described in Section 3-3.

Next, the olefin formation from the resulting nitroaldols, namely γ -alkoxy- β -nitroalkanol, was explored. The author planned to transform the nitroaldols to olefins by a stepwise process via the conversion of the hydroxy group to a radical leaving group followed by the simultaneous radical elimination of the leaving group and the nitro group. The demonstration of the olefin formation is described in detail from Section 3-4 to 3-6.

3-2. Preparation of Model Compounds

3-2-1. Preparation of Simple Nitroalkane 3-5

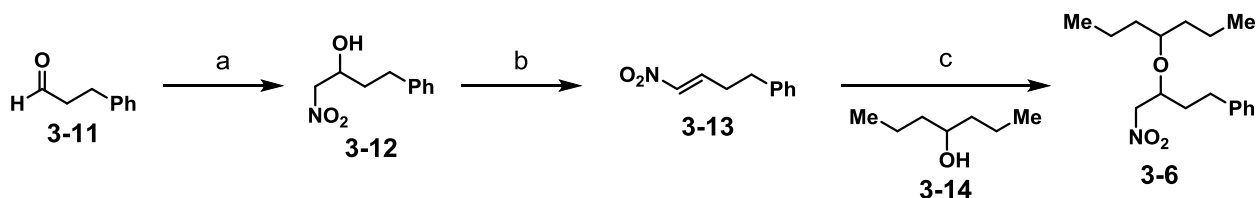
The preparation of simple nitroalkane **3-5** is outlined in Scheme 3-2. First, 1,6-hexanediol (**3-8**) was reacted with PMBCl to afford PMB ether **3-9** (95%). Iodination of **3-9** with iodine and PPh₃ in the presence of imidazole produced iodide **3-10** (77%), which was reacted with NaNO₂ in the presence of urea to give nitroalkane **3-5** (47%).⁷



Scheme 3-2. Preparation of simple nitroalkane **3-5**. Reagents and conditions: (a) PMBCl, NaH, TBAI, THF, 23 °C, 17 h, 95%; (b) I₂, PPh₃, imidazole, CH₂Cl₂, 23 °C, 19 h, 77%; (c) NaNO₂, urea, DMF, 23 °C, 12 h, 47%.

3-2-2. Preparation of Simple Model 3-6

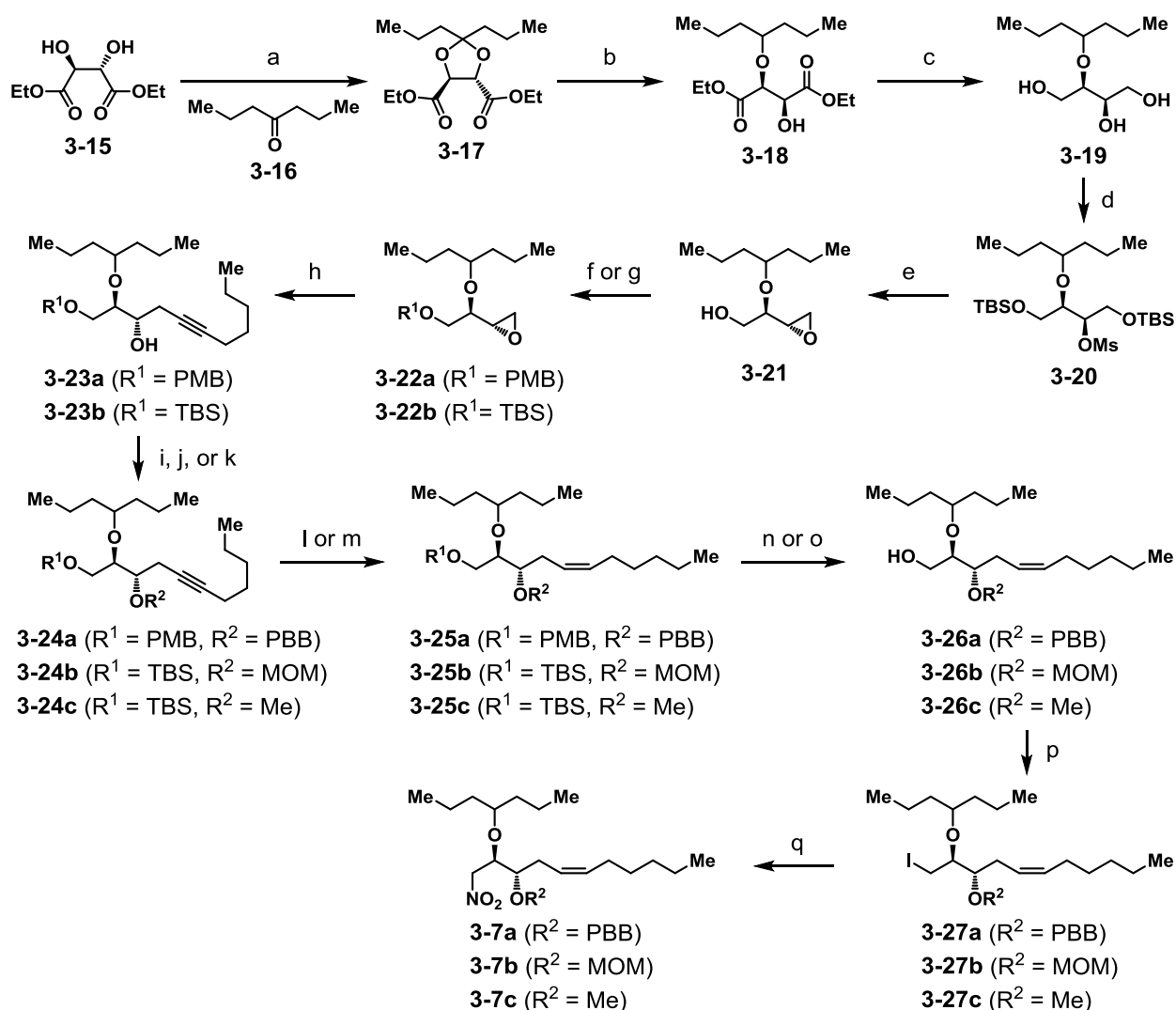
Simple β-alkoxynitroalkane **3-6** was synthesized as shown in Scheme 3-3. The reaction of 3-phenylpropanal (**3-11**) with MeNO₂ was mediated by and KF in EtOH to give nitroaldol **3-12** (81%),⁸ which was converted to **3-13** (82%) on treatment with MsCl and Et₃N. Conjugate addition of potassium heptan-4-olate to **3-13** produced simple model **3-6** (49%).⁹



Scheme 3-3. Preparation of simple model **3-6**. Reagents and conditions: (a) MeNO₂, KF, EtOH, 23 °C, 22 h, 81%; (b) MsCl, Et₃N, CH₂Cl₂, 0 °C, 5 min, 82%; (c) **3-14**, KHMDS, THF, 23 °C, 1.5 h, 49%.

3-2-3. Preparation of Advanced Models 3-7a-c

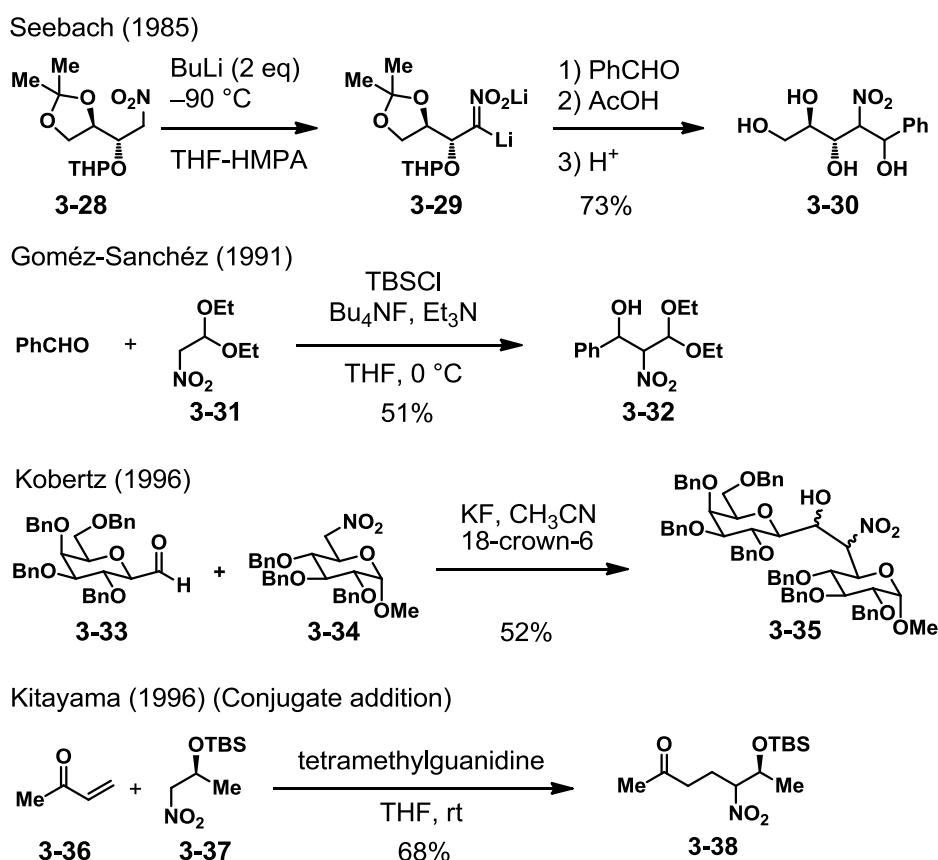
Advanced β -alkoxynitroalkane models **3-7a-c** were prepared from diethyl-D-tartrate (D-DET, **3-15**) (Scheme 3-4). Acetalization of heptan-4-one (**3-16**) with **3-15** gave **3-17** (72%), which was subjected to reductive acetal cleavage to afford **3-18** (81%). After reduction of the ester groups of **3-18** (98%), resulting **3-19** was subjected to one-pot protection of primary hydroxy groups with TBSCl followed by mesylation to produce **3-20**, which was then converted to epoxy alcohol **3-21** (63% from **3-19**) on treatment with TBAF. Protection of **3-21** as PMB ether **3-22a** (94%) or TBS ether **3-22b** (74%) followed by introduction of a heptynyl group under Yamaguchi's conditions produced **3-23a-b** (**3-23a**: 93%, **3-23b**: 73%).¹⁰ Alcohols **3-23a-b** were transformed to PBB ether **3-24a** (94%), MOM ether **3-24b** (69%), and methyl ether **3-24c** (99%). Because **3-24a** resisted being hydrogenated under Lindlar conditions, partial hydrogenation of **3-24a** was achieved by repeated treatment with $\text{Me}_2\text{NH}\cdot\text{BH}_3$ in the presence of Au nano-particles according to Stratakis' procedure¹¹ to give **3-25a** (71%). Alkynes **3-24b** and **3-24c** were hydrogenated by Lindlar hydrogenation to give **3-25b** and **3-25c** (92%), which were desilylated to produce **3-26b** (70% over two steps) and **3-26c** (95%). PMB ether **3-25a** was converted to β -alkoxynitroalkane model **3-7a** (47% over three steps) by a process including removal of the PMB group with DDQ, iodination of the resulting alcohol, nitration with NaNO_2 in the presence of urea.⁷ Alcohols **3-26b** and **3-26c** was iodinated to afford **3-27b** (89%) and **3-27c**, which was reacted with NaNO_2 in the presence of urea⁷ to furnish β -alkoxynitroalkanes **3-7b** (65%) and **3-7c** (67% over 2 steps).



Scheme 3-4. Preparation of advanced models **3-7a-c**. Reagents and conditions: (a) **3-16**, PTS·H₂O (cat.), Benzene, reflux, 25 h, 72%; (b) Et₃SiH, TiCl₄, CH₂Cl₂, -78 °C, 2 h, 81%; (c) LiBH₄, THF, 24 °C, 9.5 h, 98%; (d) TBSCl, Et₃N, DMAP, 24 °C, 9 h, then MsCl, 24 °C, 3 h; (e) TBAF, THF, 25 °C, 1.5 h, 63% from **3-19**; (f) PMBCl, NaH, TBAI, THF, 24 °C, 3 h, then NaH, **3-22a**: 94%; (g) TBSCl, imidazole, DMF, 23 °C, 6 h, **3-22b**: 74%; (h) hept-1-yne, BuLi, BF₃·OEt₂, THF, -78 → 24 °C, 2 h, **3-23a**: 94% from **3-22a**, **3-23b**: 73% from **3-22b**; (i) PBBCl, NaH, TBAI, DMF-THF (10:1), 25 °C, 26 h, **3-24a**: 94% from **3-23a**; (j) MOMCl, DIPEA, KI, THF, reflux, 3.5 h, **3-24b**: 69% from **3-23b**; (k) NaH, MeI, THF, 23 °C, 1 h, **3-24c**: 99% from **3-23b**; (l) Au NPs (cat.), Me₂NH·BH₃, EtOH, 23 °C, 24 h (repeated), **3-25a**: 71% from **3-24a**; (m) H₂, Lindlar cat., 1-hexene, MeOH, 23 °C, 3 d, **3-25c**: 92% from **3-24c**; (n) DDQ, NaHCO₃, CH₂Cl₂-H₂O (3:1), 22 °C, 30 min; (o) TBAF, THF, 23 °C, **3-26b**: 70% from **3-24b**, **3-26c**: 95% from **3-25c**; (p) I₂, PPh₃, imidazole, CH₂Cl₂, **3-27b**: 87% from **3-26b**; (q) NaNO₂, urea, DMF, 23 °C, **3-7a**: 47% from **3-25a**, **3-7b**: 65% from **3-27b**, **3-7c**: 67% from **3-26c**.

3-3. Optimization of Nitroaldol Reaction for the Segment Connection

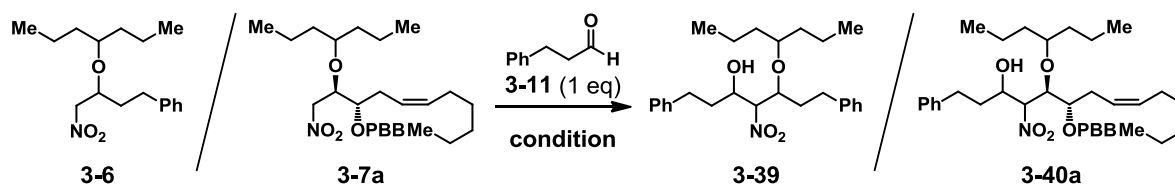
So far, several successful examples have been reported for nitroaldol reactions of β -alkoxynitroalkanes (Scheme 3-5). Seebach connected dianion **3-29**, generated from β -alkoxynitro compound **3-28**, with benzaldehyde to give nitropolyol **3-30** in high yield after hydrolysis.¹² Fluoride ion-promoted nitroaldol reactions using β -alkoxynitro compounds **3-31** and **3-34**, reported by Goméz-Sánchez¹³ and Kobertz,¹⁴ produced nitroaldols **3-32** and **3-35**, respectively, in good yields. The anion generated by β -silyloxynitropropane **3-37** and tetramethylguanidine also reacted with enone **3-36** without elimination of the β -silyloxy group.¹⁵ Thus, encouraged by these successful reports, the author set out to find suitable conditions for the segment connection process using model compounds **3-5**, **3-6** and **3-7a-c**.



Scheme 3-5. Reported nitroaldol-related reactions using β -alkoxynitroalkanes.

3-3-1. Nitroaldol Reaction of Model Compounds **3-6** and **3-7a** under Reported Conditions

The author first explored nitroaldol reactions of model compounds **3-6** and **3-7a** with 3-phenylpropanal (**3-11**). Selected results are shown in Table 3-1. When **3-6** was reacted with **3-11** in the presence of KF and 18-crown-6 in MeCN according to the Kobertz procedure,¹⁴ a complex mixture of unknown products was obtained (entry 1). Under the Gómez-Sánchez conditions,¹³ the simple model **3-6** was treated with Bu₄NF·3H₂O, **3-11**, Et₃N, and TBSCl in the order in THF to produce nitroaldol **3-39** in 55% yield (entry 2). However, the Gómez-Sánchez conditions were ineffective in the reaction of advanced model **3-7a** (entry 3). Thus, the author decided to select an effective base among several conventional bases for the nitroaldol reaction using simple nitroalkane **3-5**.



Entry	SM	Conditions	Results
1	3-6	KF (cat.), 18-crown-6 (cat.), MeCN, 21 °C, 26 h	Complex mixture
2	3-6	Bu ₄ NF·3H ₂ O (0.25 eq), 3-11 (0.67 eq), Et ₃ N, (0.67 eq), TBSCl (1 eq), THF, 0 → 23 °C, 0.5 h	3-39 : 55% (from 3-11)
3	3-7a	Bu ₄ NF·3H ₂ O (0.25 eq), 3-11 (0.67 eq), Et ₃ N, (0.67 eq), TBSCl (1 eq), THF, 0 → 23 °C, 0.5 h	N.R.

Table 3-1. Examination of nitroaldol reactions of the model compounds.

3-3-2. Selection of an Effective Base for Nitroaldol Reaction

Nitroaldol reactions of simple nitroalkane **3-5** and 3-phenylpropanal **3-11** with several bases were examined (Table 3-2). The yield of nitroaldol **3-41** varied with the strength of the base. Strong bases, $\text{NaN}(\text{SiMe}_3)_2$, KO^tBu and BnNMe_3OH , resulted in polymerization of aldehyde **3-11** (Entries 1-3). Relatively strong amine base, DBN and DBU, gave aldol **3-41** in reasonable yield (Entries 4 and 5), while conventional amine base, Et_3N , DMAP and pyridine, produced no aldol **3-41** (Entries 6-8). These results suggested that the pK_a of the conjugate acid of the base is participated to the yield of nitroaldol **3-41**. The no promotion of the nitroaldol reaction by the bases (Et_3N , DMAP and pyridine) having small pK_a (< 12) of the conjugate acids was attributable to difficulty of deprotonation from nitroalkanes by such weak bases. On the other hand, the promotion of the polymerization of aldehyde **3-11** by strong bases ($\text{NaN}(\text{SiMe}_3)_2$, KO^tBu and BnNMe_3OH), of which the conjugate acids have pK_a values larger than 16, may be due to the basic-catalysis-effect of the completely deprotonated nitroalkanes or excessive bases on the aldehyde polymerization under aprotic conditions. The base having the conjugate acid of which the pK_a value positions between those of nitroalkanes and aldehydes (DBU and DBN) would produce a nitroaldol product in good yield under aprotic equilibrium conditions. Thus, the model study suggested DBN-mediated nitroaldol reaction¹⁶ have possibility as the segment connection method between the model compounds and aldehydes.

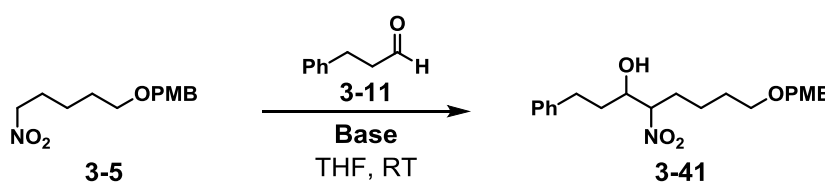
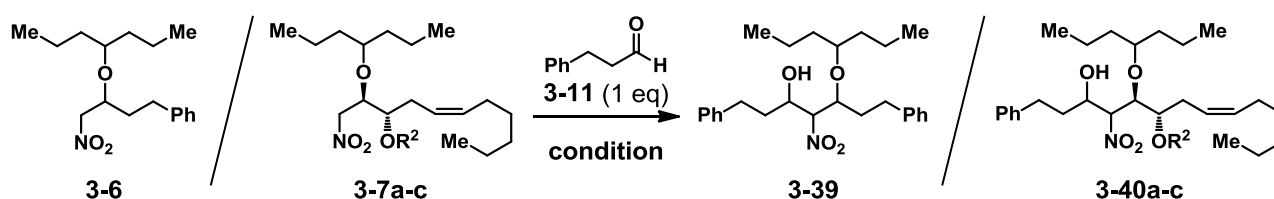
			
Entry	Bases	pK_a	Results
1	$\text{NaN}(\text{SiMe}_3)_2$	~ 26	Aldehyde polymerization
2	KO^tBu	~ 17	Aldehyde polymerization
3	BnNMe_3OH	~ 16	Aldehyde polymerization
4	DBN	~ 13	64%
5	DBU	~ 12 (estimate)	42%
6	Et_3N	~ 11	N.R.
7	DMAP	~ 9	N.R.
8	Pyridine	~ 5	N.R.

Table 3-2. Nitroaldol reactions of simple nitroalkane **3-5** and 3-phenylpropanal **3-11**.

3-3-3. Nitroaldol Reaction of β -Alkoxynitroalkanes

Next, the author examined the nitroaldol reaction of β -alkoxy nitroalkanes **3-6** and **3-7a-c** as shown in Table 3-3. The reaction of simple model **3-6** with **3-11** in the presence of DBN in DMF afforded **3-39** in 53% yield (entry 1).¹⁶ In the reaction, unreacted **3-6** and **3-11** were almost completely recovered, and, therefore, the reaction marked a high yield (81%) based on recovered starting material (BRSM). DBN also mediated the nitroaldol reaction of advanced model **3-7a** with **3-11** to give **3-40a** in 59% yield and 88% BRSM yield (entry 2). Advance models **3-7b,c** also produced the corresponding products **3-40b,c** with high BRSM yield (93% and 86%, respectively) and good reproducibility under the same conditions (entries 3 and 4). Thus, the model study suggested the suitability of the DBN-mediated nitroaldol reaction between the left- and the right-half segments.

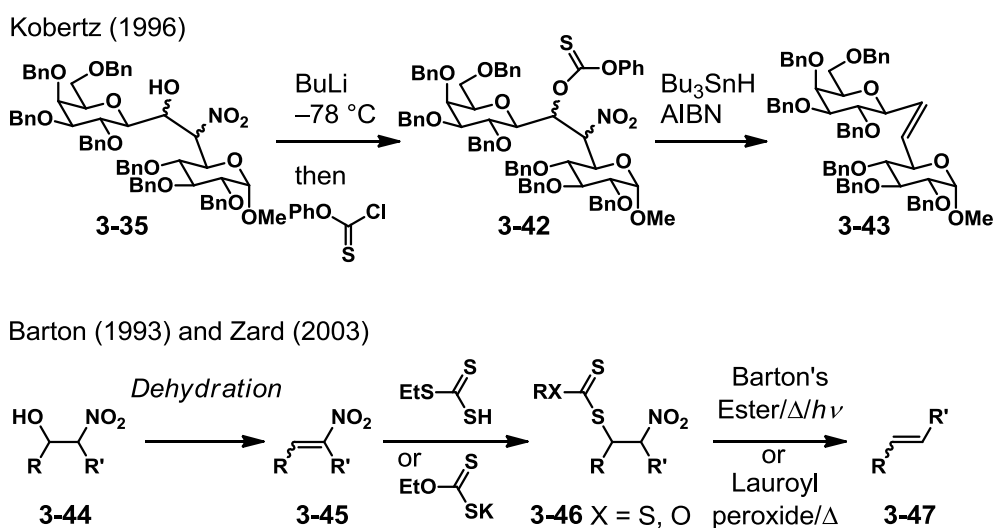


Entry	SM	Conditions	Results
1	3-6 (1 eq)	DBN (3 eq), DMF, 22 °C, 2 h	3-39 : 53% (BRSM 81%)
2	3-7a (1 eq)	DBN (3 eq), DMF, 22 °C, 2 h	3-40a : 59% (BRSM 88%)
3	3-7b (1 eq)	DBN (3 eq), DMF, 22 °C, 2 h	3-40b : 52% (BRSM 93%)
4	3-7c (1 eq)	DBN (3 eq), DMF, 22 °C, 2 h	3-40c : 54% (BRSM 86%)

Table 3-3. DBN-mediated nitroaldol reactions with the model compounds **3-6** and **3-7a-c**.

3-4. Double Bond Formation from a Simple γ -Alkoxy- β -nitroalkanol Model

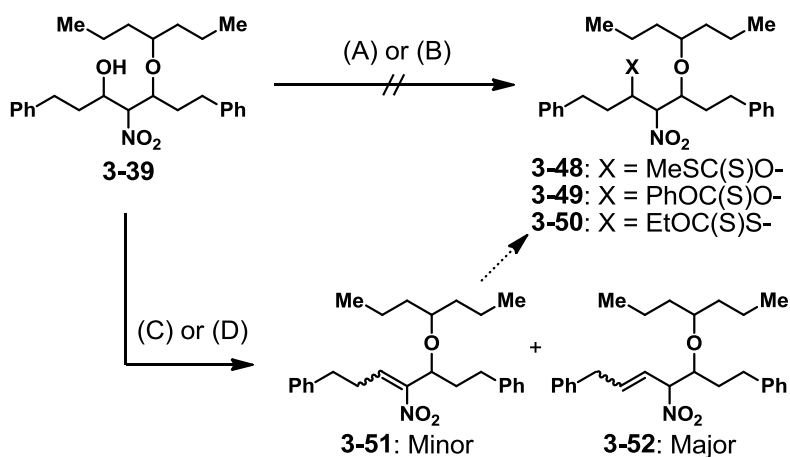
There are only a few examples of the eliminative alkenylation of nitroaldols under radical conditions (Scheme 3-6). However, Kobertz¹⁴ reported a successful application of Robins' procedure¹⁷ to nitroaldol **3-35**, which was subjected to thionocarbonylation under basic conditions followed by radical elimination using AIBN and Bu_3SnH , to produce alkene **3-43** having a 1,4-dialkoxybut-2-ene unit closely related to the C8'-C11' part of **1-2**. For an alternative method, a three-step sequence including dehydration of a nitroaldol to a nitroalkene, conjugate addition of a trithiocarbonic acid or a xanthate to the nitroalkene, and radical elimination to form an alkene was reported by Barton¹⁸ and Zard.¹⁹ The author decided to apply these radical processes for the double bond formation from γ -alkoxy- β -nitroalkanol obtained from the above model experiments.



Scheme 3-6. Reported double bond formation from nitroaldols.

3-4-1. Double Bond Formation via Thionocarbonylation of Nitroaldol 3-39

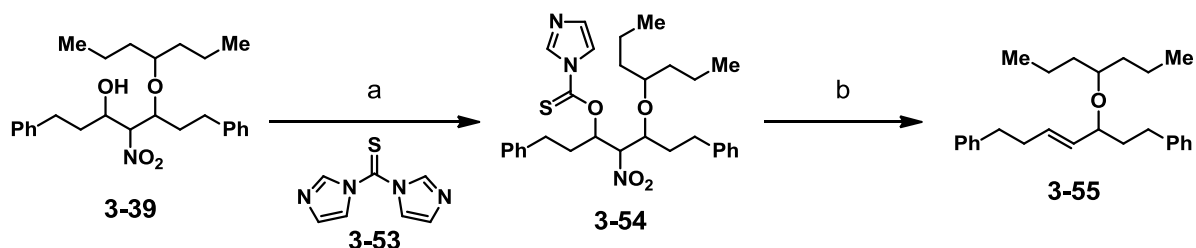
First, conversions of the simple model **3-39** to xanthate **3-48**, thionocarbonate **3-49**, and xanthate **3-50**, which would be transformed to an alkene under radical elimination (Barton-McCombie) conditions,²⁰ were attempted (Scheme 3-7). Although several bases were attempted, standard conditions for xanthate formation resulted in decomposition of **3-39** due to retro-nitroaldol reaction under strong basic conditions (path A). When nitroaldol **3-39** was treated with phenyl chlorothionoformate in the presence of DMAP according to the Robins procedure,¹⁷ no thionocarbonate **3-49** was produced (path B). Then, formation of nitroalkene **3-52** was attempted, because **3-52** was an ideal precursor for xanthate **3-50**.^{18,19} While treatment of **3-39** with TFAA in the presence of 2,6-lutidine and DMAP at $-78\text{ }^{\circ}\text{C}$ promoted dehydration, migration of double bond, however, took place under the reaction conditions to give **3-52** as a major product (path C). After several attempts, a mesylate ester of **3-39** was found to form under standard conditions without elimination. Although elimination of the mesylate with Et_3N at lower temperature was found to show a decreased ratio of double bond migration, migrated alkene **3-52** was still a majority (path D). Thus, no thionocarbonate derivatives **3-48**, **3-49**, and **3-50** were obtained due to instability of nitroaldol **3-39** and nitroalkene **3-51** under basic conditions, which induced the retro-nitroaldol reaction of **3-39** and migration of the double bond of **3-51**.



Scheme 3-7. Attempts of the formation of thionocarbonate derivative from the simple model **3-39**.

Reagents and conditions: (A) Base, CS_2 , $0\text{ }^{\circ}\text{C}$, 30 min, then MeI, $26\text{ }^{\circ}\text{C}$, 1 h; (B) Base, PhOC(S)Cl , $26\text{ }^{\circ}\text{C}$, 1 h; (C) TFAA, 2,6-lutidine, DMAP, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$, 30 min; (D) i) MsCl, Et_3N , CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 2 h; ii) Et_3N , CH_2Cl_2 , $-20\text{ }^{\circ}\text{C}$, 3 h.

Next, the author examined the formation of a thionocarbonate derivative from **3-39** under neutral conditions. As a result, it was found that the treatment of **3-39** with thiocarbonyldiimidazole (**3-53**) in refluxing toluene gave imidazolylthionocarbonate **3-54** (Scheme 3-8). Because of lability, the resulting **3-54** was immediately treated with Bu₃SnH (10 eq) and AIBN (2 eq) in refluxing toluene to produce alkene **3-55** in 25% successfully. Although the author also attempted a tandem one-pot operation for the thionocarbonylation/radical elimination reactions, no alkene **3-55** was obtained. For the successful formation of alkene **3-55**, the removal of thiocarbonyldiimidazole and imidazole by extraction was required in the thionocarbonylation step. Thus, although the reaction proceeded in low yield, an easy access of alkene **3-55** from nitroaldol **3-39** was realized by a simple two-step reaction method.

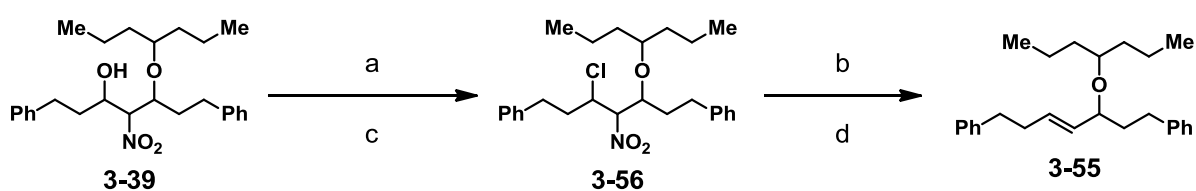


Scheme 3-8. Formation of alkene **3-55** from **3-39** by a thionocarbonylation/radical elimination sequence. Reagents and conditions: (a) **3-53**, toluene, reflux, 2 h; (b) Bu₃SnH, AIBN, toluene, reflux, 3 h, 25% from **3-39**.

3-4-2. Double Bond Formation via Chlorination of Nitroaldol 3-39

During exploration of the reaction conditions for the conversion of **3-39** to **3-55**, the author also found that the treatment of **3-39** (a mixture of diastereomers) with thionyl chloride in DMF at 60 °C for 5 min produced β -chloronitroalkane **3-56** in good yield (62% after purification) without formation of **3-51** (Scheme 3-9: (a) and (b)). The reaction conditions were known for the conversion of simple nitroaldols to β -chloronitroalkanes.²¹ However, the above reaction is a rare preparation of a β -chloro- β' -alkoxynitroalkane from a γ -alkoxy- β -nitroalkanol. Next, the transformation of **3-56** to **3-55** was examined under radical elimination conditions. The treatment of **3-56** with Bu₃SnH and AIBN in refluxing toluene for 2.5 h produced **3-55** along with unreacted **3-56**. Then, the mixture of **3-55** and **3-56** was subjected again to the same reaction conditions to complete the transformation to **3-55** (61%).

Diastereomers of **3-56** exhibited different stabilities. During silica gel chromatography, one of them decomposed, but the rest were fairly stable. Therefore, β -chloro- β' -alkoxynitroalkanes were suggested to be used without purification. When chlorination of **3-39** and radical elimination were performed sequentially without isolation of **3-56**, the two-step yield of **3-55** was markedly improved (83%) as expected (Scheme 3-9: (c) and (d)). Thus, a new method for the conversion of a γ -alkoxy- β -nitroalkanol to a 3-alkoxy-1-alkene has been developed by chlorination followed by radical elimination.



Scheme 3-9. Double bond formation from the simple model **3-6** by a chlorination/ radical elimination sequence. Reagents and conditions: (a) SOCl₂, DMF, 60 °C, 5 min, 62%; (b) Bu₃SnH, AIBN, toluene, reflux, 2.5 h, 61% (2 cycles); (c) SOCl₂, DMF, 60 °C, 5 min; (d) Bu₃SnH, AIBN, benzene, reflux, 2 h, 83% from **3-39**.

3-5. Double Bond Formation from Advanced γ,δ -Dialkoxy- β -nitroalkanol Models

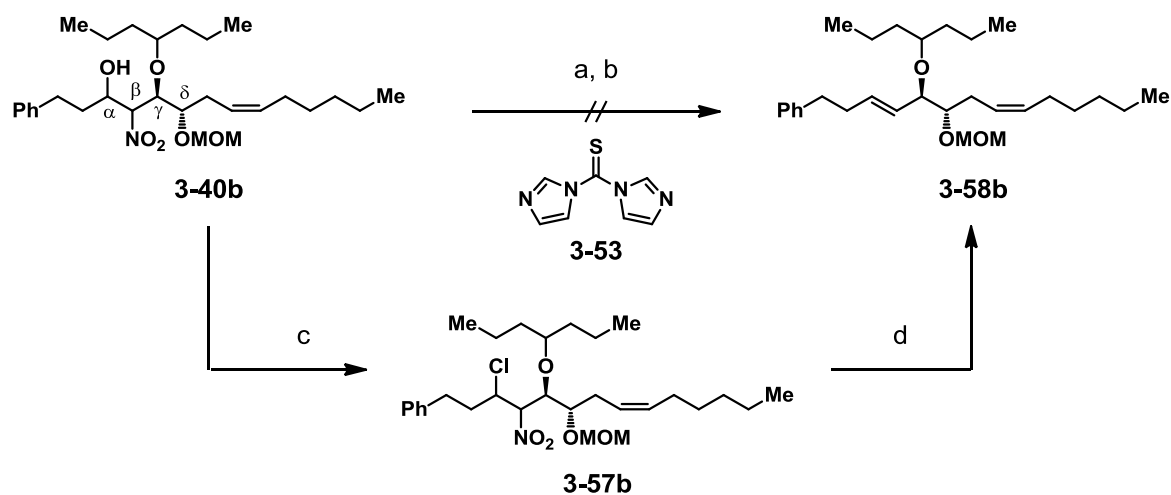
Since the conditions for the conversion of a γ -alkoxy- β -nitroalkanol to a 3-alkoxy-1-alkene was optimized using simple γ -alkoxy- β -nitroalkanol **3-39**, the conditions were applied to advanced γ,δ -Dialkoxy- β -nitroalkanol models **3-7a-c**.

The stepwise treatment of nitroaldol **3-40b** with thiocarbonyldiimidazole and subsequently with Bu_3SnH and AIBN gave a complex mixture of byproducts, and no desired alkene **3-58b** was detected (Scheme 3-10). The disappointing result might be attributable to the steric effect of the protected hydroxy group at the δ -position of the thionocarbonate intermediate, by which the disturbance of radical elimination might enhance undesired radical side reactions or the reverse reaction from the labile thionocarbonate intermediate to afford degradation products.

The alkene formation by chlorination/radical elimination sequence was then applied to **3-40a-c**. The reaction of **3-40a** with thionyl chloride in DMF gave the corresponding chloride in relatively good yield, which was checked by NMR analysis on the crude mixture. Although the reduction of the PBB group to a Bn group was anticipated at the stage of radical elimination, the chloride intermediate with a PBB group was, in fact, unexpectedly damaged and removed under the radical conditions. Therefore, the application of the sequence to **3-40a** did not afford the desired alkene, but gave a complex mixture of byproducts with no PBB or Bn groups. Nitroaldoles **3-40b** and **3-40c** were decomposed in the chlorination step, in which the MOM ether of **3-40b** and even methyl ether of **3-40c** were removed. The addition of pyridine slightly inhibited the removal of MOM group to afford **3-57b** as a minor component (Scheme 3-10). Chloride **3-57b** was reacted with Bu_3SnH and AIBN to produce alkene **3-58b** in total 7.9% yield. The small production of **3-58b** was attributable to the low yield of the chlorination step. The radical elimination of **3-57b** itself proceeded smoothly. Therefore, for the efficient conversion of a γ,δ -dialkoxy- β -nitroalkanol (**3-40**) to a 3,4-dialkoxy-1-alkene (**3-58**) via the chlorination/radical elimination sequence, the suppression of the removal of the protecting group of the oxygen atom at the δ -position of the nitroalkanol is required in the chlorination step.

Since the PBB group of **3-40a** remained intact in the chlorination step, the removal of the methyl group of **3-40c** was unexpected and was difficult to understand. At this stage, the author only speculates that the side reaction may be attributable to the δ -positional relationship between

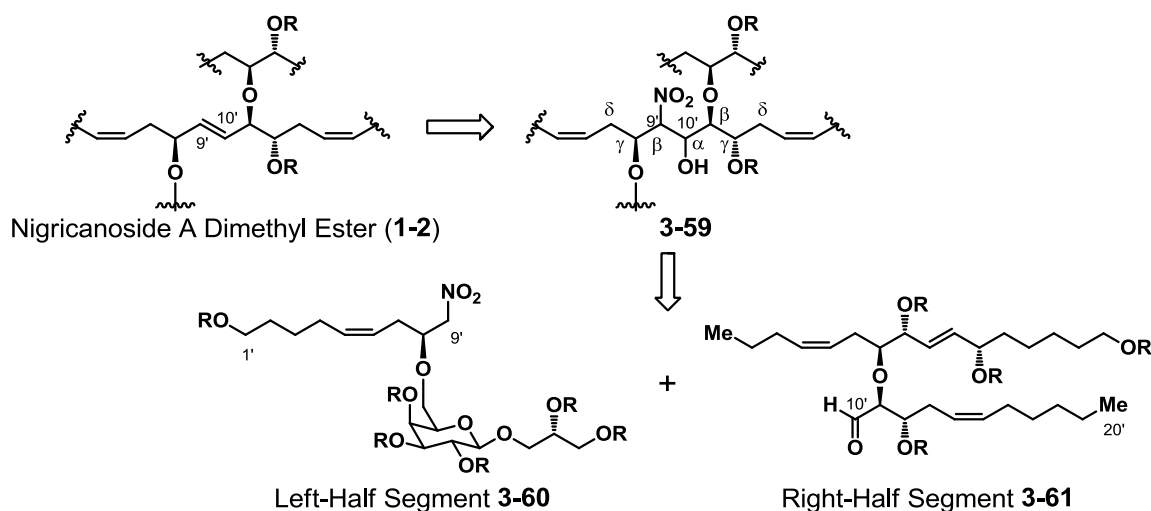
the hydroxy group and the alkoxy group of the nitroaldol intermediates. Based on the speculation, the author designed an alternative synthesis of a 3,4-dialkoxy-1-alkene via a nitroaldol intermediate possessing no δ -alkoxy group. Thus, the alternative synthesis was examined and is described in the next section.



Scheme 3-10. Double bond formation from the advanced model **3-7b**. Reagents and conditions: (a) **3-53**, toluene, reflux, 2 h; (b) Bu₃SnH, AIBN, toluene, reflux, 2 h; (c) SOCl₂, pyridine, DMF, 60 °C, 2 min; (d) Bu₃SnH, AIBN, benzene, reflux, 6 h, 7.9% from **3-40b**.

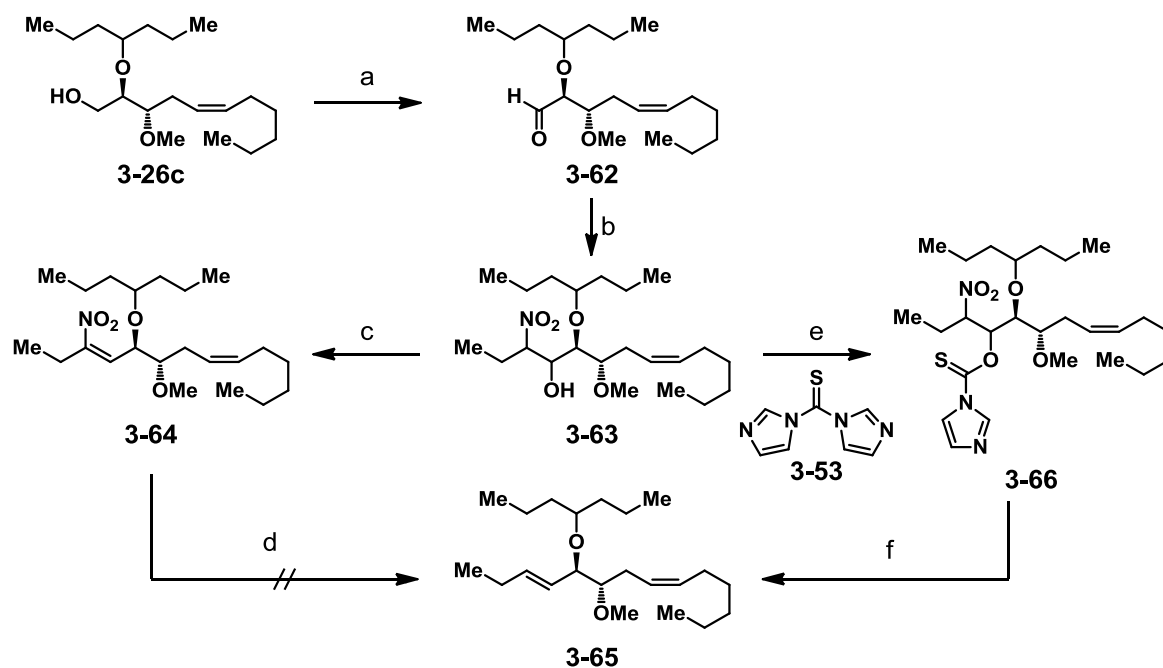
3-6. Exploration of Alternative Olefination Methods with the Advanced Model

The author designed an alternative plan for the union at C9'-C10' double bond of **1-2** (Scheme 3-11). This plan involved the installation of a nitro group to the left segment (**3-60**) and an aldehyde to the right segment (**3-61**), thereby avoiding the presence of a problematic alkoxy group at the δ -position in the β -nitro alcohol intermediate (**3-59**).



Scheme 3-11. An alternative plan for the total synthesis of **1-2**.

The plan was demonstrated by use of model aldehyde **3-62** corresponding to **3-61** and nitropropane corresponding to **3-60** (Scheme 3-12). Aldehyde **3-62** was prepared from alcohol **3-26c** by Swern oxidation.²² The reaction of **3-62** with nitropropane in the presence of DBN in DMF produced nitroaldol **3-63** as a mixture of diastereomers in 84% yield from **3-26c**.¹⁶ Upon treatment with thionyl chloride in DMF, nitroaldol **3-63** was only dehydrated to give nitroalkene **3-64**, while the methyl ether remained intact. The attempted removal of the nitro group from **3-64** under radical conditions with Bu_3SnH and AIBN only resulted in the production of undesired byproducts. On the other hand, reaction of nitroaldol **3-63** with thiocarbonyldiimidazole in 1,2-dichloroethane at 40 °C followed by treatment with Bu_3SnH and AIBN in refluxing toluene furnished alkene **3-65** in 25% yield. Thus, although further optimization is required, the three-step process including a nitroaldol reaction, thionocarbonylation, and radical elimination shows promise for the union at the C9'-C10' double bond of **1**.



Scheme 3-12. Double bond formation from nitroaldol **3-63**. Reagents and conditions: (a) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 20 min, then Et_3N , $0\text{ }^\circ\text{C}$, 10 min; (b) PrNO_2 , DBN, DMF, $22\text{ }^\circ\text{C}$, 2 h, 84% from **3-26c**; (c) SOCl_2 , DMF, $60\text{ }^\circ\text{C}$, 45 min; (d) Bu_3SnH , AIBN, benzene, reflux, 2 h; (e) **3-53**, $(\text{CH}_2\text{Cl})_2$, $40\text{ }^\circ\text{C}$, 16 h; (f) Bu_3SnH , AIBN, benzene, reflux, 2 h, 25% from **3-63**.

3-7. Conclusion

For the convergent total synthesis of nigricanoside A dimethyl ester (**1-2**), the author developed a prototype method for the segment connection at the C9'-C10' double bond of **1-2** using a model system.

In the first stage of the segment connection, the coupling reaction between a β -alkoxycarbanion and an aldehyde was scheduled. For the successful coupling reaction, the suppression of the β -elimination of the β -alkoxy group from the β -alkoxycarbanion is required. The author found that the DBN-mediated nitroaldol reaction of β -alkoxynitroalkanes can avoid the β -elimination and is suitable for the segment connection.

In the double bond formation stage, the elimination of the hydroxy and nitro groups from the nitroaldols, namely γ -alkoxy- β -nitroalkanols or β' -alkoxy- β -nitroalkanols, was a problem to be solved. The author applied a stepwise radical elimination process for the solution. The process, including chlorination or thionocarbonylation of the hydroxy group of the γ -alkoxy- β -nitroalkanols or β' -alkoxy- β -nitroalkanols followed by radical reaction with Bu_3SnH initiated by AIBN, successfully realized the double bond formation from the nitroaldols, although the varied yield, which was dependent on the structure of the nitroaldols, was a problem remained to be solved in future.

Thus, the author developed a prototype method for the segment connection based on three-step process including nitroaldol reaction, chlorination or thionocarbonylation, and radical elimination.

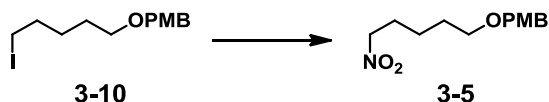
References

1. Williams, D. E.; Sturgeon, C.M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 5822.
2. For a review, see: Chatterjee, A. K. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 246–295.
3. For an example of the coincidence of cross, ring-opening, and ring-closing olefin metathesis reactions, see: Oguri, H.; Sasaki, S.; Oishi, T.; Hiram, M. *Tetrahedron Lett.* **1999**, *40*, 5405.
4. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *9*, 26.
5. Kinashi, N.; Fujiwara, K.; Suzuki, T. unpublished result.
6. (a) Henry, L. *Compt. Rend.* **1895**, *120*, 1265. (b) Henry, L. *Bull. Soc. Chim. France* **1895**, *13*, 999.
7. Kornblum, N.; Larson, H. O.; Blackwood, R. T.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497.
8. Kanbe S.; Yasuda, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1444.
9. cf. Kimimura, A.; Sasatani, H.; Hashimoto, T.; Kawai, T.; Hori, K.; Ono, N. *J. Org. Chem.* **1990**, *55*, 2437.
10. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
11. Vasilikogiannaki, E.; Titilas, I.; Vasilikogiannakis, G.; Stratakis, M. *Chem. Commun.* **2015**, *51*, 2384.
12. Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 3601.
13. Fernández, R.; Gasch, C.; Gómez-Sánchez, A.; Vílchez, J. E. *Tetrahedron Lett.* **1991**, *32*, 3225.
14. Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894.
15. Kitayama, T. *Tetrahedron* **1996**, *52*, 6139.
16. (a) Ono, N.; Katayama, H.; Nisuiyama, S.; Ogawa, T. *J. Heterocycl. Chem.* **1994**, *31*, 707. (b) Kutovaya, I. V.; Shmatova, O. I.; Tkachuk, V. M.; Melnichenko, N. V.; Vovk M. V.; Nenajdenko, V. G. *Eur. J. Org. Chem.*, **2015**, *30*, 6749.
17. Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
18. Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1993**, *34*, 8051.
19. Ouvry, G.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2907.
20. Barton, D. H. R.; McCombie S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
21. (a) Fourneau, J. P. *Bull. Soc. Chim. France* **1940**, *7*, 603. (b) *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl)* **1962**, *11*, 1042. (c) Fukunaga, K.; Okamoto, A.; Kimura, M. *Nippon Kagaku Kaishi* **1983**, 542.
22. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2048.

Experimental Section

General Methods

All air sensitive reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard syringe, cannula and septa techniques. Anhydrous solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel (SiO_2) plates (Merck, silica gel 60 F₂₅₄ or Wako, silica gel 70 F₂₅₄). Plates were visualized by ultraviolet light and by treatment with acidic anisaldehyde or phosphomolybdic acid stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63–40 μm for flash column chromatography or 63–210 μm for gravity column chromatography) as a stationary phase with indicated eluents. 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 JASCO FT/IR-4700 or Thermo Scientific Nicolet iS5 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 400 (^1H at 400 MHz, ^{13}C at 100 MHz), a Bruker DPX 300 (^1H at 300 MHz, ^{13}C at 75 MHz), or a JEOL JNM-ECA500 (^1H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. ^1H NMR spectra are reported as chemical shifts (δ) in parts-per-million (ppm) based on tetramethylsilane (0.00 ppm) as an internal standard. The following abbreviations are used to describe spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet, br=broad, dd=double doublets, dt=double triplets, td=triple doublets, tt=triple triplets 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 ($^{13}\text{CDCl}_3$ as 77.0 ppm) as an internal standard. Low and high resolution mass spectra were measured on a JEOL JMS-T100GCV (under field desorption [FD] or field ionization (FI) conditions) double focusing magnetic sector mass spectrometer.

Compound 3-5:

To a solution of **3-10** (2.7263 g, 8.16 mmol) in DMF (30 mL) were added NaNO₂ (1.1260 g, 16.3 mmol) and urea (980.0 mg, 16.3 mmol) at 23 °C, and the mixture was stirred for 12 h. Then, the reaction was quenched with satd. aq. NH₄Cl, and the mixture was extracted with a 3:1 blend of hexane and EtOAc (30 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-5** (963.0 mg, 3.80 mmol, 47%).

3-5: a colorless oil;

IR (neat) ν 2935, 2861, 1612, 1551, 1513, 1464, 1437, 1384, 1302, 1248, 1174, 1097, 1034, 820 cm⁻¹;

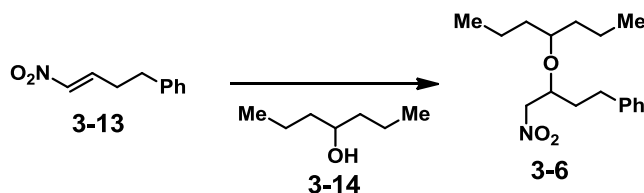
¹H NMR (300 MHz, CDCl₃) δ 1.41-1.55 (2H, m), 1.65 (2H, quin, J = 6.2 Hz), 2.02 (2H, quin, J = 7.1 Hz), 3.45 (2H, t, J = 6.2 Hz), 3.81 (3H, s), 4.37 (2H, t, J = 7.0 Hz), 4.42 (2H, s), 6.88 (2H, td, J = 2.0 8.7 Hz), 7.25 (2H, td, J = 2.0 8.7 Hz);

¹³C NMR (75 MHz, CDCl₃) δ 23.1 (CH₂), 27.2 (CH₂), 29.0 (CH₂), 55.3 (CH₃), 69.3 (CH₂), 72.7 (CH₂), 75.6 (CH₂), 113.8 (CH), 129.2 (CH), 130.5 (C), 159.2 (C);

FD-LRMS m/z 253 (bp, [M⁺]);

FD-HRMS calcd for C₁₃H₁₉NO₄ [M⁺]: 253.1314, found: 253.1326.

Compound 3-6:



To a solution of hept-4-ol (**3-14**) (242.9 μ L, 1.70 mmol) in THF (3.0 mL) was added KHMDS (0.5 mol/L in toluene, 3.39 mL, 1.70 mmol) at 0 °C, and the mixture was stirred for 35 min. Then, to the mixture was added **3-13** (100.4 mg, 0.567 mmol) at 0 °C, and the mixture was stirred for 5 min. Then, the mixture was warmed to room temperature and stirred for 1.5 h. Then, the reaction was quenched with 1 mol/L aq. HCl, and the mixture was extracted with EtOAc (10 mL) three 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) to give **3-6** (81.9 mg, 0.279 mmol, 49%).

3-6: a colorless oil;

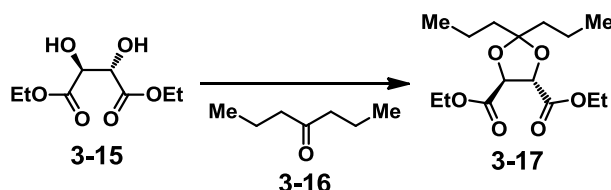
IR (neat) ν 3028, 2959, 2933, 2872, 1603, 1555, 1497, 1456, 1382, 1222, 1091, 1014, 748, 699 cm^{-1} ;

^1H NMR (500 MHz, CDCl_3) δ 0.88 (3H, t, $J = 7.2$ Hz), 0.91 (3H, t, $J = 7.2$ Hz), 1.17-1.50 (8H, m), 1.84-1.96 (2H, m), 2.70 (2H, brt, $J = 8.1$ Hz), 3.34 (1H, qn, $J = 5.6$ Hz), 4.09-4.15 (1H, m), 4.36 (1H, dd, $J = 4.6, 12.0$ Hz), 4.45 (1H, dd, $J = 7.6, 12.0$ Hz), 7.18 (2H, brd, $J = 7.4$ Hz), 7.21 (1H, brt, $J = 7.4$ Hz), 7.30 (2H, brt, $J = 7.4$ Hz);

^{13}C NMR (125 MHz, CDCl_3) δ 14.2 (CH_3), 14.3 (CH_3), 18.2 (CH_2), 18.5 (CH_2), 31.1 (CH_2), 34.4 (CH_2), 35.7 (CH_2), 36.2 (CH_2), 73.6 (CH), 78.5 (CH), 79.1 (CH_2), 126.2 (CH), 128.2 (CH $\times$ 2), 128.6 (CH $\times$ 2), 140.9 (C);

FD-HRMS calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_3$ [M^+]: 293.1991, found: 293.1978.

Compound 3-17:



To a solution of diethyl-D-tartrate (**3-15**) (23.0 mL, 0.135 mol) in benzene (300 mL) were added heptane-4-one (**3-16**) (47.0 mL, 0.337 mol) and PTS·H₂O (2.56 g, 0.0135 mol) at 23 °C, and the mixture was stirred and refluxed for 25 h. Then, the reaction was quenched with satd. aq. NaHCO₃, and the mixture was extracted with EtOAc (100 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **3-17** (29.52 g, 0.0976 mol, 72%).

3-17: a colorless oil; $[\alpha]_D^{24} +16.0$ (c 1.02, CHCl₃);

IR (neat) ν 2963, 2937, 2875, 1759, 1467, 1377, 1273, 1197, 1170, 1116, 1029, 951, 906, 847, 743 cm⁻¹;

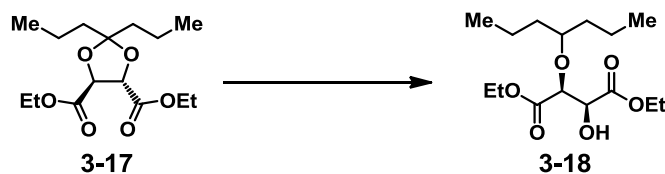
¹H NMR (400 MHz, CDCl₃) δ 0.92 (6H, t, J = 7.3 Hz), 1.32 (6H, t, J = 7.2 Hz), 1.36-1.50 (4H, m), 1.64-1.70 (4H, m), 4.28 (4H, q, J = 7.2 Hz), 4.69 (2H, brs);

¹³C NMR (100 MHz, CDCl₃) δ 14.1 (CH₃), 14.2 (CH₃), 16.8 (CH₂), 39.4 (CH₂), 61.8 (CH₂), 77.2 (CH), 117.0 (C), 169.4 (C);

FD-LRMS m/z 303 (6.6%, [M+H⁺]), 259 (bp);

FD-HRMS calcd for C₁₅H₂₇O₆ [M+H⁺]: 303.1808, found: 303.1804.

Compound 3-18:



To a solution of **3-17** (5.45 g, 18.0 mmol) in CH_2Cl_2 (100 mL) were added TiCl_4 (4.0 mL, 36.0 mmol) and Et_3SiH (5.8 mL, 36.0 mmol) at -78°C , and the mixture was stirred for 2 h. Then, the reaction was quenched with satd. aq. Rochelle salt, and the mixture was filtered through a Celite pad and extracted with CH_2Cl_2 (50 mL) three 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 **3-18** (4.42 g, 14.5 mmol, 81%).

3-18: a colorless oil; $[\alpha]_{\text{D}}^{24} -40.8$ (c 1.15, CHCl_3);

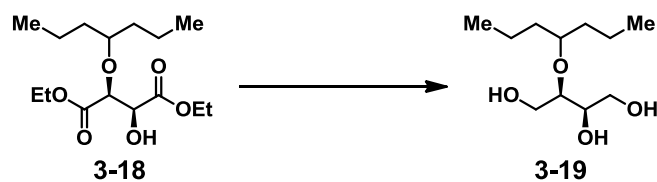
IR (neat) ν 3506, 2960, 2935, 2873, 1759, 1467, 1368, 1259, 1194, 1138, 1096, 1025, 997 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 0.88 (3H, t, J = 6.8 Hz), 0.90 (3H, t, J = 7.2 Hz), 1.16-1.53 (8H, m), 1.31 (3H, t, J = 7.1 Hz), 1.33 (3H, t, J = 7.1 Hz), 3.05 (1H, d, 9.4 Hz), 3.39 (1H, quin, J = 5.4 Hz), 4.15-4.36 (4H, m), 4.37 (1H, d, J = 2.3 Hz), 4.56 (1H, dd, J = 2.3, 9.4 Hz);

^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 14.3 (CH_3), 17.9 (CH_2), 18.3 (CH_2), 34.6 (CH_2), 36.0 (CH_2), 61.3 (CH_2), 61.9 (CH_2), 72.7 (CH), 77.0 (CH), 79.9 (CH), 170.1 (C), 171.2 (C);

FD-LRMS m/z 305 (bp, $[\text{M}+\text{H}^+]$);

FD-HRMS calcd for $\text{C}_{15}\text{H}_{29}\text{O}_6$ $[\text{M}+\text{H}^+]$: 305.1964, found: 305.1979.

Compound 3-19:

To a solution of **3-18** (3.54 g, 11.6 mmol) in CH_2Cl_2 (60 mL) was added LiBH_4 (506.7 mg, 23.3 mmol) at 24 °C, and the mixture was stirred for 9.5 h. Then, the reaction was quenched with MeOH and satd. aq. NH_4Cl , and the mixture was extracted with CH_2Cl_2 (30 mL) three 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 $\rightarrow$ EtOAc) to give **3-19** (2.52 g, 11.4 mmol).

3-19: a colorless oil; $[\alpha]_{\text{D}}^{24} -23.5$ (c 1.04, CHCl_3);

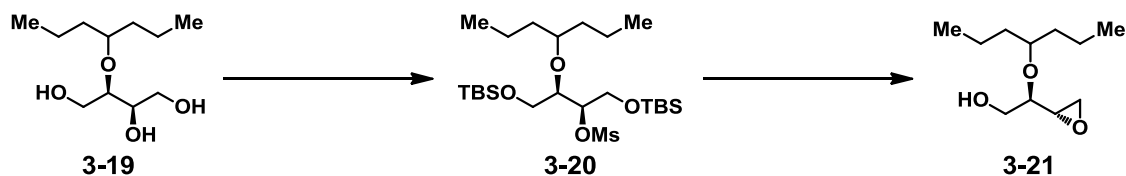
IR (neat) ν 3383, 2958, 2933, 2873, 1466, 1380, 1122, 1082, 1047, 982 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 0.92 (3H, t, $J = 7.2$ Hz), 0.92 (3H, t, $J = 7.2$ Hz), 1.23-1.57 (8H, m), 2.36-2.49 (1H, brs), 2.79-2.94 (1H, brs), 2.91 (1H, d, $J = 5.5$ Hz), 3.44 (1H, quin, $J = 5.6$ Hz), 3.52 (1H, dt, $J = 2.9, 4.9$ Hz), 3.66-3.83 (5H, m);

^{13}C NMR (100 MHz, CDCl_3) δ 14.2 (CH_3), 14.3 (CH_3), 18.5 (CH_2), 18.7 (CH_2), 36.1 (CH_2), 36.5 (CH_2), 61.0 (CH_2), 62.8 (CH_2), 71.3 (CH), 77.1 (CH), 78.7 (CH);

FD-LRMS m/z 221 (bp, $[\text{M}+\text{H}^+]$);

FD-HRMS calcd for $\text{C}_{11}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}^+]$: 221.1753, found: 221.1758.

Compound 3-21:

To a solution of **3-19** (2.52 g, 11.4 mmol) in CH_2Cl_2 (60 mL) were added TBSCl (8.62 g, 5.72 mmol), Et_3N (16 mL, 114 mmol), and DMAP (139.6 mg, 1.14 mmol) at 24 °C, and the mixture was stirred for 9 h. Then, to the mixture was added MsCl (1.8 mL, 22.9 mmol) at 0 °C, and the mixture was warmed at 24 °C and stirred for 3 h. 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 **3-20**. After the crude **3-20** was dissolved in THF (60 mL), Bu_4NF (1 mol/L in THF, 34.3 mL, 34.3 mmol) was added to the solution at 25 °C, and the mixture was stirred for 3.5 h. Then, the solution was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 $\rightarrow$ 3 $\rightarrow$ EtOAc) to give **3-21** (1.45 g, 7.15 mmol, 63% over 2 steps).

3-21: a colorless oil; $[\alpha]_{\text{D}}^{24} +24.1$ (c 1.01, CHCl_3);

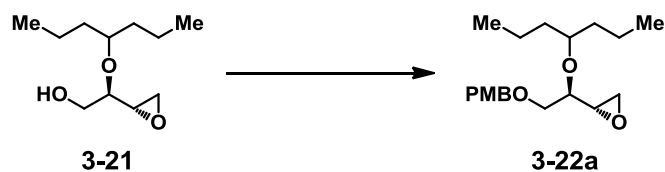
IR (neat) ν 3451, 3049, 2958, 2933, 2873, 1467, 1380, 1330, 1250, 1219, 1159, 1109, 1075, 1006, 957, 927, 890, 858, 838 cm^{-1} ;

^1H NMR (400 MHz, CDCl_3) δ 0.92 (6H, t, $J = 7.2$ Hz), 1.26-1.55 (8H, m), 2.11 (1H, brs), 2.72 (1H, dd, $J = 2.7, 5.3$ Hz), 2.84 (1H, dd, $J = 3.9, 5.3$ Hz), 2.97 (1H, ddd, $J = 2.7, 3.9, 6.1$ Hz), 3.25 (1H, td, $J = 3.9, 5.9$ Hz), 3.43 (1H, quin, $J = 5.6$ Hz), 3.67 (1H, dd, $J = 5.0, 11.0$ Hz), 3.78 (1H, brdd);

^{13}C NMR (100 MHz, CDCl_3) δ 14.2 (CH_3), 14.2 (CH_3), 18.5 (CH_2), 18.6 (CH_2), 36.2 (CH_2), 36.7 (CH_2), 45.9 (CH_2), 51.2 (CH), 63.4 (CH_2), 77.3 (CH), 78.7 (CH);

FD-LRMS m/z 202 (3.5%, $[\text{M}^+]$), 159 (bp);

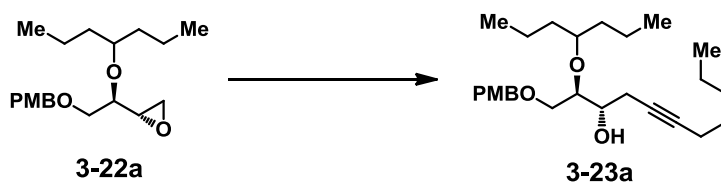
FD-HRMS calcd for $\text{C}_{11}\text{H}_{22}\text{O}_3$ $[\text{M}^+]$: 202.1569, found: 202.2968.

Compound 3-22a:

To a solution of **3-21** (746.8 mg, 3.69 mmol) in THF (20 mL) was added NaH (55% in oil, 162.4 mg, 4.06 mmol) at 0 °C, and the mixture was stirred for 20 min. Then, to the mixture were added PMBCl (1.11 g, 5.54 mmol) and Bu₄NI (68.2 mg, 0.185 mmol) at 0 °C, and the mixture was warmed to 24 °C and stirred for 3 h. The reaction was quenched with 1 mol/L aq. NaOH, and the mixture was extracted with EtOAc (20 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was roughly purified by column chromatography (silica gel, hexane/EtOAc = 10) to give crude **3-22a**. After the crude **3-22a** was dissolved in THF (70 mL), NaH (55% in oil, 162.4 mg, 4.06 mmol) was added to the solution at 0 °C, and the mixture was warmed to 24 °C and stirred for several hours. The reaction was quenched with H₂O, and the mixture was extracted with EtOAc (20 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-22a** (1.12 g, 3.47 mmol, 94% over 2 steps).

3-22a: a colorless oil;

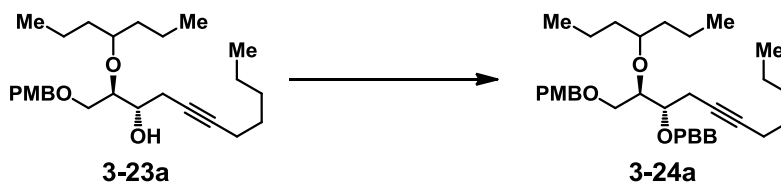
¹H NMR (400 MHz, CDCl₃) δ 0.88 (3H, t, *J* = 7.1 Hz), 0.89 (3H, t, *J* = 7.1 Hz), 1.23-1.52 (8H, m), 2.74 (1H, dd, *J* = 2.7, 5.4 Hz), 2.78 (1H, dd, *J* = 3.9, 5.4 Hz), 3.03 (1H, ddd, *J* = 2.7, 3.9, 5.3 Hz), 3.35-3.41 (1H, m), 3.40 (1H, brq, *J* = 5.1 Hz), 3.56 (2H, dd, *J* = 0.7, 5.1 Hz), 3.81 (3H, s), 4.50 (2H, s), 6.87 (2H, td, *J* = 2.8, 8.7 Hz), 7.26 (2H, td, *J* = 2.8, 8.7 Hz).

Compound 3-23a:

To a solution of hept-1-yne (600 μ L, 4.53 mmol) in THF (23 mL) was added BuLi (1.63 mol/L in hexane, 2.83 mL, 4.53 mmol) at -78 $^{\circ}$ C, and the mixture was stirred for 10 min. Then, to the mixture was added $\text{BF}_3 \cdot \text{OEt}_2$ (568 μ L, 4.53 mmol) at -78 $^{\circ}$ C, and the mixture was stirred for 10 min. Then, to the mixture was added **3-22a** (731.0 mg, 2.27 mmol) at -78 $^{\circ}$ C, and the mixture was stirred for 10 min. Then, the mixture was warmed to 24 $^{\circ}$ C and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with EtOAc (20 mL) three 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) to give **3-23a** (884.0 mg, 2.11 mmol, 93%).

3-23a: a colorless oil;

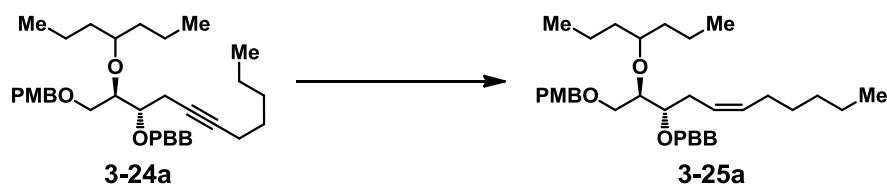
^1H NMR (400 MHz, CDCl_3) δ 0.88 (3H, t, $J = 7.1$ Hz), 0.89 (3H, t, $J = 7.1$ Hz), 0.90 (3H, t, $J = 7.2$ Hz), 1.22-1.56 (14H, m), 2.16 (2H, tt, $J = 2.4, 7.1$ Hz), 2.41-2.54 (2H, m), 2.70 (1H, d, $J = 5.0$ Hz), 3.38-3.47 (1H, m), 3.56 (1H, td, $J = 4.8, 10.2$ Hz), 3.60-3.63 (2H, m), 3.78-3.85 (1H, m), 3.81 (3H, s), 4.47 (2H, s), 6.87 (2H, td, $J = 2.8, 8.7$ Hz), 7.26 (2H, td, $J = 2.8, 8.7$ Hz).

Compound 3-24a:

To a solution of **3-23a** (884.0 mg, 2.11 mmol) in a 10:1 blend of DMF and THF (20 mL / 2 mL) was added NaH (55% in oil, 171.4 mg, 4.22 mmol) at 0 °C, and the mixture was stirred for 20 min. Then, to the mixture were added PBBBr (1.07 g, 4.22 mmol) and Bu₄NI (79.1 mg, 0.211 mmol) at 0 °C, and the mixture was warmed to 25 °C and stirred for 3 h. The reaction was quenched with satd. aq. NaHCO₃, and the mixture was extracted with a 2:1 blend of hexane and EtOAc (20 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give **3-24a** (1.17 g, 1.99 mmol, 94%).

3-24a: a colorless oil;

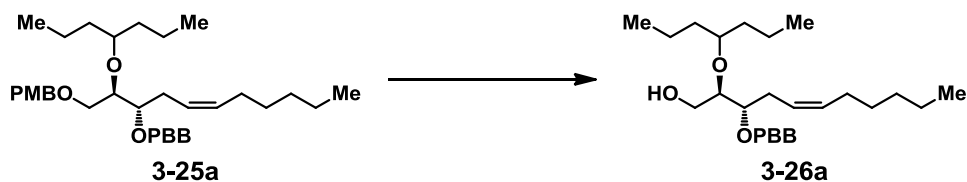
¹H NMR (400 MHz, CDCl₃) δ 0.88 (6H, t, J = 7.1 Hz), 0.88 (3H, t, J = 7.2 Hz), 1.23-1.56 (14H, m), 2.14 (2H, tt, J = 2.4, 7.1 Hz), 2.43-2.59 (2H, m), 3.38-3.49 (1H, m), 3.56 (1H, dd, J = 4.2, 10.0 Hz), 3.59 (1H, dd, J = 3.3, 10.0 Hz), 3.67 (1H, qn, J = 5.5 Hz), 3.80 (3H, s), 4.42 (1H, d, J = 11.7 Hz), 4.46 (1H, d, J = 11.7 Hz), 4.49 (2H, s), 6.84 (2H, td, J = 2.8, 8.7 Hz), 7.17 (2H, td, J = 2.4, 8.4 Hz), 7.24 (2H, td, J = 2.8, 8.7 Hz), 7.41 (2H, td, J = 2.4, 8.4 Hz).

Compound 3-25a:

To a solution of **3-24a** (2.20 g, 3.74 mmol) in EtOH (35 mL) were added gold nano particles (1% on TiO₂, 3.3 g) and Me₂NH·BH₃ (22.0 g, 374 mmol) at 23 °C, and the mixture was stirred for 24 h. The mixture was filtered through a Celite pad, evaporated, diluted with EtOAc. The mixture was washed with H₂O and brine in this order, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The above operations were repeated 6 cycles to give almost pure **3-25a** (1.56 g, 2.65 mmol, 71%).

3-25a: a colorless oil;

¹H NMR (400 MHz, CDCl₃) δ 0.87 (6H, t, J = 7.1 Hz), 0.88 (3H, t, J = 7.2 Hz), 1.21-1.53 (14H, m), 1.95-2.07 (2H, m), 2.28-2.43 (2H, m), 3.38-3.47 (1H, m), 3.52-3.64 (4H, m), 3.80 (3H, s), 4.44 (2H, s), 4.51 (2H, s), 4.49 (2H, s), 5.39-5.50 (2H, m), 6.85 (2H, td, J = 2.8, 8.7 Hz), 7.14 (2H, td, J = 2.4, 8.4 Hz), 7.24 (2H, td, J = 2.8, 8.7 Hz), 7.41 (2H, td, J = 2.4, 8.4 Hz).

Compound 3-26a:

To a solution of **3-25a** (840.1 mg, 1.42 mmol) and H₂O (4 mL) in CH₂Cl₂ (14 mL) were added NaHCO₃ (179.5 mg, 2.14 mmol) and DDQ (970.3 mg, 4.27 mmol) at 23 °C, and the mixture was stirred for 30 min. The reaction was quenched with satd. aq. NaHCO₃, and the mixture was extracted with CH₂Cl₂ (20 mL) three times. The combined organic layers were washed with H₂O and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was roughly purified by column chromatography (silica gel, hexane/EtOAc = 15) to give crude **3-26a**, which was used in the next reaction without further purification.

3-26a: a colorless oil; $[\alpha]_D^{22} +8.1$ (c 1.00, CHCl₃);

IR (neat) ν 3464, 3010, 2957, 2871, 1896, 1653, 1488, 1475, 1379, 1204, 1089, 1012, 876, 803, 734 cm⁻¹;

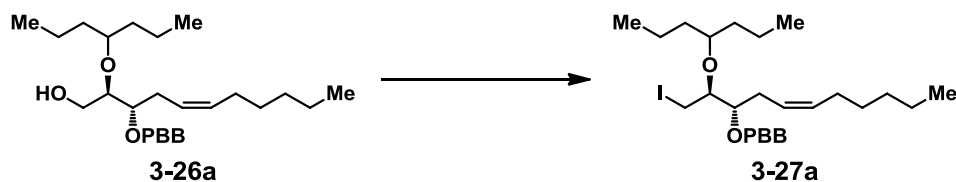
¹H NMR (500 MHz, CDCl₃) δ 0.89 (3H, t, J = 7.1 Hz), 0.90 (3H, t, J = 7.2 Hz), 0.92 (3H, t, J = 7.3 Hz), 1.23-1.52 (14H, m), 1.97-2.10 (2H, m), 2.25 (1H, t, J = 6.2 Hz), 2.33-2.45 (2H, m), 3.40 (1H, quin, J = 5.7 Hz), 3.42 (1H, td, J = 4.3, 5.4 Hz), 3.68-3.79 (2H, m), 4.55 (1H, d, J = 11.6 Hz), 4.59 (1H, d, J = 11.6 Hz), 5.42-5.53 (2H, m), 7.21 (2H, td, J = 1.9, 8.4 Hz), 7.45 (2H, td, J = 1.9, 8.4 Hz);

¹³C NMR (125 MHz, CDCl₃) δ 14.0 (CH₃), 14.3 (CH₃), 14.3 (CH₃), 18.5 (CH₂), 18.6 (CH₂), 22.5 (CH₂), 27.5 (CH₂), 29.2 (CH₂), 31.6 (CH₂), 36.1 (CH₂), 36.2 (CH₂), 61.7 (CH₂), 71.9 (CH₂), 78.0 (CH₂), 78.1 (CH), 80.3 (CH), 121.5 (C), 124.9 (CH), 129.4 (CH), 131.4 (CH), 132.5 (CH), 137.4 (C);

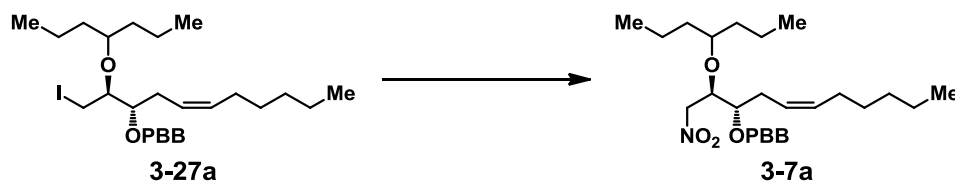
FD-LRMS m/z 468 (91.1%, [M⁺]), 470 (bp, [M+2H⁺]);

FD-HRMS calcd for C₂₅H₄₁BrO₃ [M⁺]: 468.2239, found: 468.2238.

Compound 3-27a:



To a solution of crude **3-26a** in CH_2Cl_2 (14 mL) were added imidazole (290.9 mg, 4.27 mmol), I_2 (542.4 mg, 2.14 mmol), and PPh_3 (560.5 mg, 2.14 mmol) at 0 °C, and the mixture was warmed to 23 °C and stirred for 30 h. The reaction was quenched with satd. aq. NaHCO_3 and satd. aq. $\text{Na}_2\text{S}_2\text{O}_3$, and the mixture was extracted with EtOAc (20 mL) three 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/EtOAc = 50) to give crude **3-27a**, which was immediately used in the next reaction without further purification.

Compound 3-7a:

To a solution of crude **3-27a** in DMF (10 mL) were added NaNO₂ (140.2 mg, 2.85 mmol) and urea (122.0 mg, 2.85 mmol) at 23 °C, and the mixture was stirred for 14 h. Then, the reaction was quenched with satd. aq. NH₄Cl, and the mixture was extracted with a 2:1 blend of hexane and EtOAc (10 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 10) to give **3-7a** (336.8 mg, 0.676 mmol, 47% over 3 steps).

3-7a: a colorless oil; $[\alpha]_D^{22} +8.1$ (c 1.00, CHCl₃);

IR (neat) ν 3010, 2958, 2871, 2733, 1898, 1724, 1594, 1556, 1488, 1474, 1418, 1381, 1352, 1301, 1273, 1221, 1090, 1011, 955, 906, 876, 804, 733 cm⁻¹;

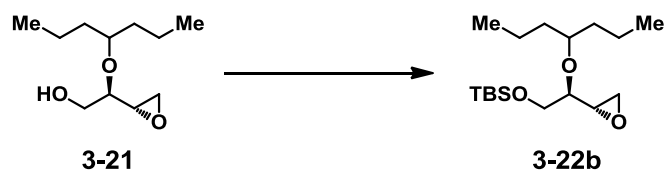
¹H NMR (500 MHz, CDCl₃) δ 0.88 (3H, t, J = 7.2 Hz), 0.88 (3H, t, J = 7.2 Hz), 0.89 (3H, t, J = 7.1 Hz), 1.17-1.49 (14H, m), 2.03 (2H, ddq, J = 1.2, 7.2, 11.5 Hz), 2.28 (1H, td, J = 7.2, 15.0 Hz), 2.36 (1H, td, J = 6.5, 15.0 Hz), 3.35 (1H, quin, J = 5.6 Hz), 3.61 (1H, dt, J = 3.2, 6.4 Hz), 4.14 (1H, td, J = 3.3, 7.8 Hz), 4.52 (1H, dd, J = 3.2, 12.9 Hz), 4.58 (1H, dd, J = 7.8, 12.9 Hz), 4.59 (2H, s), 5.37-5.44 (1H, m), 5.52-5.59 (1H, m), 7.20 (2H, td, J = 1.9, 8.4 Hz), 7.47 (2H, td, J = 1.9, 8.4 Hz);

¹³C NMR (125 MHz, CDCl₃) δ 14.0 (CH₃), 14.2 (CH₃), 14.3 (CH₃), 18.0 (CH₂), 18.4 (CH₂), 22.5 (CH₂), 27.5 (CH₂), 29.1 (CH₂), 29.4 (CH₂), 31.5 (CH₂), 35.3 (CH₂), 35.9 (CH₂), 71.9 (CH), 76.6 (CH₂), 76.7 (CH), 79.1 (CH₂), 80.0 (CH₂), 121.6 (C), 123.6 (CH), 129.3 (CH), 131.5 (CH), 133.6 (CH), 137.1 (C);

FD-LRMS m/z 497 (97.3%, [M⁺]), 499 (bp, [M+2H⁺]);

FD-HRMS calcd for C₂₅H₄₀BrNO₄ [M⁺]: 497.2141, found: 497.2148.

Compound 3-22b:



To a solution of **3-21** (3.63 g, 18.0 mmol) in DMF (45 mL) were added TBSCl (4.06 g, 26.9 mmol) and imidazole (3.67 g, 53.9 mmol) at 23 °C, and the mixture was stirred for 6 h. The reaction was quenched with satd. aq. NaHCO₃, and the mixture was extracted with CH₂Cl₂ (20 mL) three times. The combined organic layers were washed with 1 mol/L aq. HCl, H₂O, and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 50) to give **3-22b** (4.22 g, 13.3 mmol, 74%).

3-22b: a colorless oil; $[\alpha]_D^{22} -15.2$ (c 1.00, CHCl₃);

IR (neat) ν 3047, 2957, 2931, 2859, 1464, 1380, 1362, 1329, 1295, 1255, 1092, 1008, 837, 777, 667 cm⁻¹;

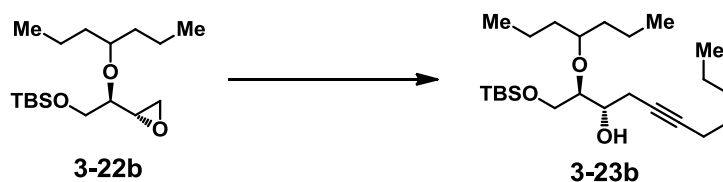
¹H NMR (500 MHz, CDCl₃) δ 0.07 (6H, s), 0.87-0.93 (6H, m), 0.90 (9H, s), 1.24-1.50 (8H, m), 2.75 (1H, dd, J = 2.8, 5.4 Hz), 2.76 (1H, dd, J = 3.8, 5.5 Hz), 3.02 (1H, ddd, J = 2.9, 3.8, 5.0 Hz), 3.31 (1H, q, J = 5.3 Hz), 3.38 (1H, quin, J = 5.4 Hz), 3.69 (1H, dd, J = 5.2, 10.6 Hz), 3.72 (1H, dd, J = 5.6, 10.6 Hz);

¹³C NMR (125 MHz, CDCl₃) δ -5.5 (CH₃), -5.4 (CH₃), 14.3 (CH₃), 14.3 (CH₃), 18.3 (C), 18.5 (CH₂), 18.6 (CH₂), 25.9 (CH₃), 36.5 (CH₂), 36.6 (CH₂), 45.2 (CH₂), 51.7 (CH), 64.2 (CH₂), 77.3 (CH), 79.0 (CH);

FD-LRMS m/z 317 (15.1%, [M+H⁺]), 259 (bp);

FD-HRMS calcd for C₁₇H₃₆O₃Si [M+H⁺]: 317.2512, found: 317.2511.

Compound 3-23b:



To a solution of hept-1-yne (1.5 mL, 11.6 mmol) in THF (60 mL) was added BuLi (1.6 mol/L in hexane, 7.2 mL, 11.6 mmol) at $-78\text{ }^{\circ}\text{C}$, and the mixture was stirred for 10 min. Then, to the mixture was added $\text{BF}_3\cdot\text{OEt}_2$ (1.4 mL, 11.6 mmol) at $-78\text{ }^{\circ}\text{C}$, and the mixture was stirred for 20 min. Then, to the mixture was added **3-22b** (1.83 g, 5.78 mmol) at $-78\text{ }^{\circ}\text{C}$, and the mixture was stirred for 15 min. Then, the mixture was warmed to $26\text{ }^{\circ}\text{C}$ and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with CH_2Cl_2 (50 mL) three 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 **3-23b** (1.75 g, 4.23 mmol, 73%).

3-23b: a colorless oil; $[\alpha]_{\text{D}}^{22} -38.4$ (*c* 1.01, CHCl₃);

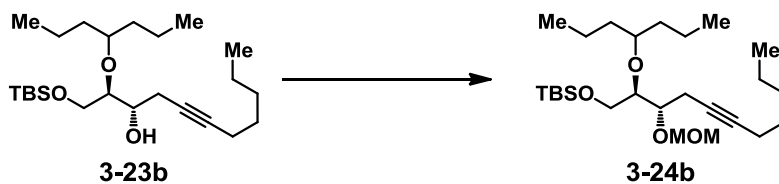
IR (neat) ν 3487, 2957, 2737, 2361, 1464, 1379, 1362, 1329, 1254, 1080, 1006, 939, 837, 777, 668 cm^{-1} ;

¹H NMR (500 MHz, CDCl₃) δ 0.08 (6H, s), 0.88-0.93 (9H, m), 0.90 (9H, s), 1.26-1.54 (14H, m), 2.17 (2H, tt, *J* = 2.4, 7.2 Hz), 2.49 (2H, td, *J* = 2.4, 5.8 Hz), 2.98 (1H, d, *J* = 4.4 Hz), 3.44 (2H, quin, *J* = 5.5 Hz), 3.73-3.84 (3H, m);

¹³C NMR (125 MHz, CDCl₃) δ −5.6 (CH₃), −5.5 (CH₃), 14.0 (CH₃), 14.3 (CH₃), 14.3 (CH₃), 18.2 (C), 18.5 (CH₂), 18.6 (CH₂), 18.8 (CH₂), 22.2 (CH₂), 23.5 (CH₂), 25.8 (CH₃), 28.7 (CH₂), 31.1 (CH₂), 36.2 (CH₂), 36.5 (CH₂), 63.6 (CH₂), 71.8 (CH), 76.3 (C), 77.6 (CH), 78.4 (CH), 82.6 (C);

FD-LRMS m/z 413 (bp, $[M+H]^+$);FD-HRMS calcd for C₂₄H₄₉O₃Si [M+H⁺]: 413.3451, found: 413.3449.

Compound 3-24b:



To a solution of **3-23b** (2.40 g, 5.83 mmol) in THF (30 mL) were added DIPEA (10.0 mL, 58.3 mmol), MOMCl (2.21 mL, 29.1 mmol), and KI (96.7 mg, 0.583 mmol) at 23 °C, and the mixture was refluxed and stirred for 3.5 h. The reaction was quenched with satd. aq. NaHCO₃, and the mixture was extracted with Et₂O (30 mL) three times. The combined organic layers were washed with 1 mol/L aq. HCl, H₂O, and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give **3-24b** (1.84 g, 4.02 mmol, 69%).

3-24b: a colorless oil; $[\alpha]_D^{22}$ -25.1 (c 1.01, CHCl_3);

IR (neat) ν 2957, 2930, 2859, 1465, 1362, 1254, 1151, 1106, 1086, 1041, 919, 837, 814, 776 cm^{-1} ;

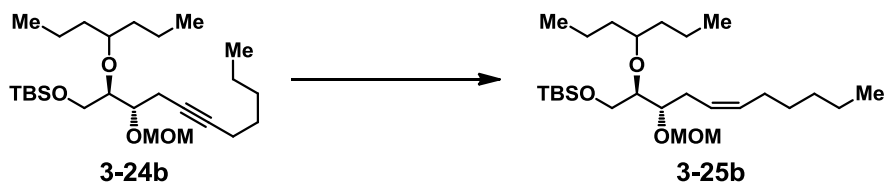
¹H NMR (500 MHz, CDCl₃) δ 0.05 (3H, s), 0.06 (3H, s), 0.86-0.93 (18H, m), 1.25-1.56 (14H, m), 2.15 (2H, tt, *J* = 2.4, 7.2 Hz), 2.48-2.58 (2H, m), 3.41 (3H, s), 3.47 (1H, quin, *J* = 5.6 Hz), 3.61 (1H, q, *J* = 4.6 Hz), 3.66 (1H, dd, *J* = 4.9, 10.7 Hz), 3.75 (1H, dd, *J* = 4.4, 10.7 Hz), 3.79 (1H, td, *J* = 4.7, 5.8 Hz), 4.72 (1H, d, *J* = 6.7 Hz), 4.76 (1H, d, *J* = 6.7 Hz);

¹³C NMR (75 MHz, CDCl₃) δ -5.5 (CH₃), -5.4 (CH₃), 14.0 (CH₃), 14.3 (CH₃), 14.4 (CH₃), 18.3 (C), 18.4 (CH₂), 18.6 (CH₂), 18.8 (CH₂), 21.6 (CH₂), 22.2 (CH₂), 25.9 (CH₃), 28.8 (CH₂), 31.1 (CH₂), 36.1 (CH₂), 36.3 (CH₂), 55.6 (CH₃), 62.4 (CH₂), 76.6 (CH), 76.9 (C), 78.2 (CH), 78.3 (CH), 81.8 (C), 96.6 (CH₂);

FD-LRMS m/z 457 (20.2%, $[M+H^+]$), 399 (bp);

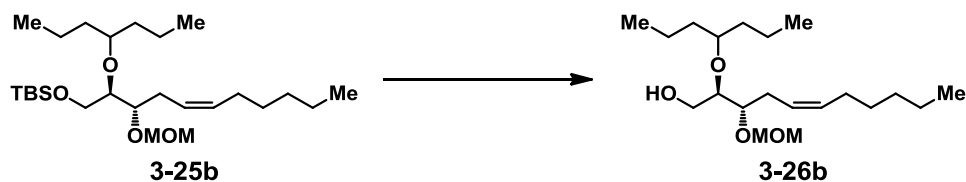
FD-HRMS calcd for C₂₆H₅₂O₄Si [M+H⁺]: 457.3713, found: 457.3701.

Compound 3-25b:



To a solution of **3-24b** (303.9 mg, 0.665 mmol) and 1-hexene (3.3 mL) in MeOH (3.3 mL) was added Lindlar catalyst (455.9 mg) at 23 °C, and the mixture was stirred for 3 d under H₂ atmosphere. The mixture was filtered through a Celite pad and concentrated in vacuo to give almost pure **3-25b** (25.0 mg, 0.0562 mmol, 93%), which was used in the next reaction without further purification.

3-25b: a colorless oil;

Compound 3-26b:

To a solution of crude **3-25b** in THF (3 mL) was added Bu₄NF (1 mol/L in THF, 1.2 mL, 0.998 mmol) at 23 °C, and the mixture was stirred for 9 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 15) to give **3-26b** (160.3 mg, 0.465 mmol, 70% over 2 steps).

3-26b: a colorless oil; $[\alpha]_{\text{D}}^{22} -11.8$ (*c* 0.70, CHCl₃);

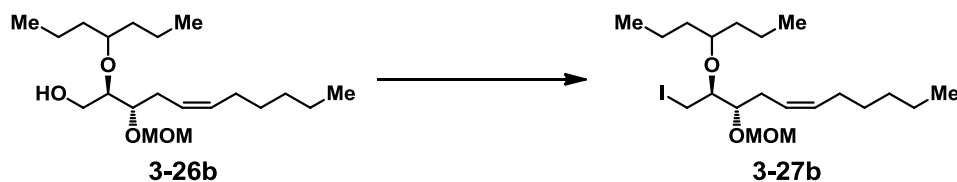
IR (neat) ν 3476, 2957, 2930, 2872, 1466, 1378, 1214, 1152, 1101, 1038, 952, 920, 845, 734 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 0.89 (3H, t, *J* = 7.0 Hz), 0.91 (3H, t, *J* = 7.3 Hz), 0.91 (3H, t, *J* = 7.1 Hz), 1.24-1.54 (14H, m), 2.04 (2H, q, *J* = 7.1 Hz), 2.32-2.43 (3H, m), 3.38-3.42 (2H, m), 3.39 (3H, s), 3.67-3.78 (3H, m), 4.68 (1H, d, *J* = 6.5 Hz), 4.72 (1H, d, *J* = 6.5 Hz), 5.40-5.53 (2H, m);

¹³C NMR (125 MHz, CDCl₃) δ 14.0 (CH₃), 14.3 (CH₃), 14.3 (CH₃), 18.5 (CH₂), 18.5 (CH₂), 22.5 (CH₂), 27.5 (CH₂), 29.2 (CH₂), 29.6 (CH₂), 31.5 (CH₂), 36.1 (CH₂), 36.2 (CH₂), 55.8 (CH₃), 61.4 (CH₂), 78.0 (CH), 78.1 (CH), 78.2 (CH), 96.6 (CH₂), 124.9 (CH), 132.5 (CH);

FD-LRMS *m/z* 344 (68.8%, [M⁺]), 345 (bp, [M+H⁺]);

FD-HRMS calcd for C₂₀H₄₀O₄ [M⁺]: 344.2927, found: 344.2932.

Compound 3-27b:

To a solution of **3-26b** in CH₂Cl₂ (10 mL) were added imidazole (592.9 mg, 8.71 mmol), I₂ (1.11 g, 4.35 mmol), and PPh₃ (1.14 g, 4.35 mmol) at 0 °C, and the mixture was warmed to 23 °C and stirred for 11 h. The reaction was quenched with satd. aq. NaHCO₃ and satd. aq. Na₂S₂O₃, and the mixture was extracted with Et₂O (10 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give **3-27b** (876.5 mg, 1.93 mmol, 89%).

3-27b: a colorless oil; [α]_D²² -33.2 (c 1.00, CHCl₃);

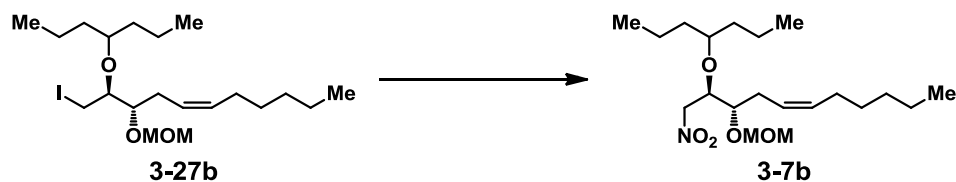
IR (neat) ν 2957, 1465, 1378, 1311, 1253, 1216, 1152, 1103, 1038, 921, 838, 741, 697 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 0.89 (3H, t, J = 7.0 Hz), 0.90 (3H, t, J = 7.3 Hz), 0.92 (3H, t, J = 7.2 Hz), 1.24-1.54 (14H, m), 1.96-2.11 (2H, m), 2.38 (2H, t, J = 5.9 Hz), 3.31-3.39 (3H, m), 3.39 (3H, s), 3.42 (1H, quin, J = 5.7 Hz), 3.73 (1H, td, J = 4.2, 5.8 Hz), 4.67 (1H, d, J = 6.6 Hz), 4.75 (1H, d, J = 6.6 Hz), 5.47 (2H, m);

¹³C NMR (125 MHz, CDCl₃) δ 14.0 (CH₃), 14.3 (CH₃), 14.3 (CH₃), 18.2 (CH₂), 18.6 (CH₂), 22.5 (CH₂), 27.5 (CH₂), 28.6 (CH₂), 29.2 (CH₂), 31.6 (CH₂), 35.6 (CH₂), 36.0 (CH₂), 55.9 (CH₃), 77.0 (CH), 78.0 (CH), 78.6 (CH), 96.4 (CH₂), 124.9 (CH), 132.5 (CH);

FD-LRMS m/z 454 (15.7%, [M⁺]), 185 (bp);

FD-HRMS calcd for C₂₀H₃₉IO₃ [M⁺]: 454.1944, found: 454.1936.

Compound 3-7b:

To a solution of **3-27b** in DMF (1 mL) were added NaNO₂ (22.5 mg, 0.326 mmol) and urea (19.6 mg, 0.326 mmol) at 23 °C, and the mixture was stirred for 17 h. Then, the reaction was quenched with satd. aq. NH₄Cl, and the mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-7b** (15.9 mg, 0.0350 mmol, 65%).

3-7b: a colorless oil; [α]_D²² -11.3 (c 1.00, CHCl₃);

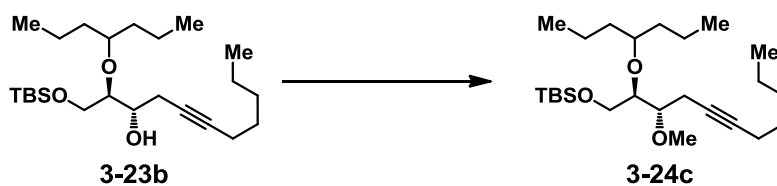
IR (neat) ν 2958, 2931, 2872, 1557, 1466, 1420, 1382, 1212, 1153, 1087, 1034, 921 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 0.87 (3H, t, J = 7.3 Hz), 0.89 (3H, t, J = 7.0 Hz), 0.90 (3H, t, J = 7.3 Hz), 1.16-1.51 (14H, m), 2.05 (2H, tq, J = 2.0, 7.7 Hz), 2.24 (1H, td, J = 7.5, 15.0 Hz), 2.36 (1H, td, J = 6.3, 15.0 Hz), 3.36 (1H, quin, J = 5.6 Hz), 3.38 (3H, s), 3.80 (1H, ddd, J = 2.7, 6.0, 7.6 Hz), 4.15 (1H, td, J = 3.0, 8.0 Hz), 4.51 (1H, dd, J = 3.4, 13.0 Hz), 4.56 (1H, dd, J = 8.1, 13.0 Hz), 4.66 (1H, d, J = 6.7 Hz), 4.75 (1H, d, J = 6.7 Hz), 5.36-5.43 (1H, m), 5.53-5.60 (1H, m);

¹³C NMR (125 MHz, CDCl₃) δ 14.0 (CH₃), 14.2 (CH₃), 14.3 (CH₃), 17.9 (CH₂), 18.3 (CH₂), 22.5 (CH₂), 27.5 (CH₂), 29.1 (CH₂), 29.9 (CH₂), 31.5 (CH₂), 35.1 (CH₂), 35.9 (CH₂), 55.8 (CH₃), 76.4 (CH), 76.8 (CH₂), 77.7 (CH), 79.0 (CH), 96.3 (CH₂), 123.6 (CH), 133.6 (CH);

FD-LRMS m/z 373 (81.2%, [M⁺]), 311 (bp);

FD-HRMS calcd for C₂₀H₃₉NO₅ [M⁺]: 373.2828, found: 373.2846.

Compound 3-24c:

To a solution of **3-23b** (1.11 g, 2.69 mmol) in THF (9 mL) was added NaH (55% in oil, 176.0 mg, 4.03 mmol) at 0 °C, and the mixture was stirred for 15 min. Then, the mixture was added MeI (334.8 μ L, 5.38 mmol) at 0 °C, and the mixture was warmed to 23 °C and stirred for 11 h. The reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with EtOAc (10 mL) three 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 = 30) to give **3-24c** (1.14 g, 2.67 mmol, 99%).

3-24c: a colorless oil; $[\alpha]_{\text{D}}^{22} -14.4$ (c 1.00, CHCl_3);

IR (neat) ν 2931, 1464, 1379, 1362, 1329, 1254, 1217, 1190, 1118, 1006, 940, 837, 776, 668 cm^{-1} ;

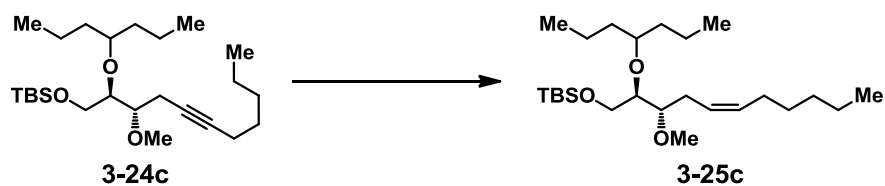
^1H NMR (500 MHz, CDCl_3) δ 0.06 (6H, s), 0.86-0.93 (9H, m), 0.90 (9H, s), 1.26-1.55 (14H, m), 2.15 (2H, tt, $J = 2.4, 7.2$ Hz), 2.43-2.55 (2H, m), 3.37-3.46 (2H, m), 3.42 (3H, s), 3.52 (1H, brtd, $J = 4.5, 5.0$ Hz), 3.68 (1H, dd, $J = 4.5, 10.7$ Hz), 3.74 (1H, dd, $J = 4.1, 10.7$ Hz), ;

^{13}C NMR (75 MHz, CDCl_3) δ -5.5 (CH_3), -5.4 (CH_3), 14.0 (CH_3), 14.3 (CH_3), 14.4 (CH_3), 18.3 (C), 18.5 (CH_2), 18.7 (CH_2), 18.8 (CH_2), 20.2 (CH_2), 22.2 (CH_2), 25.9 (CH_3), 28.8 (CH_2), 31.1 (CH_2), 36.1 (CH_2), 36.5 (CH_2), 58.0 (CH_3), 62.0 (CH_2), 76.9 (C), 78.1 (CH), 78.2 (CH), 79.6 (CH), 81.7(C);

FD-LRMS m/z 427 (20.9%, $[\text{M}+\text{H}^+]$), 369 (bp);

FD-HRMS calcd for $\text{C}_{25}\text{H}_{51}\text{O}_3\text{Si}$ $[\text{M}+\text{H}^+]$: 427.3608, found: 427.3609.

Compound 3-25c:



To a solution of **3-24c** (1.12 g, 2.63 mmol) and 1-hexene (9 mL) in MeOH (9 mL) was added Lindlar catalyst (1.68 g) at 23 °C, and the mixture was stirred for 3 d under H₂ atmosphere. The mixture was filtered through a Celite pad and concentrated in vacuo to give almost pure **3-25c** (1.04 g, 2.42 mmol, 92%), which was used in the next reaction without further purification.

3-25c: a colorless oil; $[\alpha]_D^{22} -15.1$ (c 1.00, CHCl₃);

IR (neat) ν 3006, 2957, 2929, 2858, 1464, 1379, 1362, 1254, 1108, 1006, 837, 814, 776 cm⁻¹;

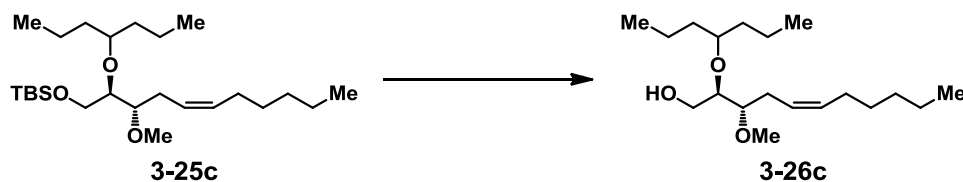
¹H NMR (500 MHz, CDCl₃) δ 0.06 (3H, s), 0.06 (3H, s), 0.86-0.92 (9H, m), 0.90 (9H, s), 1.24-1.52 (14H, m), 2.05 (2H, q, J = 6.9 Hz), 2.31 (2H, td, J = 2.2, 5.2 Hz), 3.29-3.33 (1H, m), 3.38 (3H, s), 3.39-3.46 (2H, m), 3.64 (1H, dd, J = 5.2, 10.6 Hz), 3.68 (1H, dd, J = 5.2, 10.6 Hz), 5.41-5.50 (2H, m);

¹³C NMR (125 MHz, CDCl₃) δ -5.5 (CH₃), -5.4 (CH₃), 14.0 (CH₃), 14.4 (CH₃), 18.3 (C), 18.6 (CH₂), 18.6 (CH₂), 22.6 (CH₂), 25.9 (CH₃), 27.4 (CH₂), 28.2 (CH₂), 29.3 (CH₂), 31.6 (CH₂), 36.3 (CH₂), 36.5 (CH₂), 58.1 (CH₃), 62.6 (CH₂), 78.4 (CH), 78.8 (CH), 81.8 (CH), 126.1 (CH), 131.7 (CH);

FD-LRMS m/z 428 (4.3%, [M⁺]), 371 (bp);

FD-HRMS calcd for C₂₅H₅₂O₃Si [M⁺]: 428.3686, found: 428.3688.

Compound 3-26c:



To a solution of **3-25c** (220.0 mg, 0.513 mmol) in THF (5 mL) was added Bu₄NF (1 mol/L in THF, 770 µL, 0.770 mmol) at 23 °C, and the mixture was stirred for 18 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-26c** (153.2 mg, 0.487 mmol, 95%).

3-26c: a colorless oil; $[\alpha]_D^{22} -4.8$ (c 1.00, CHCl_3);

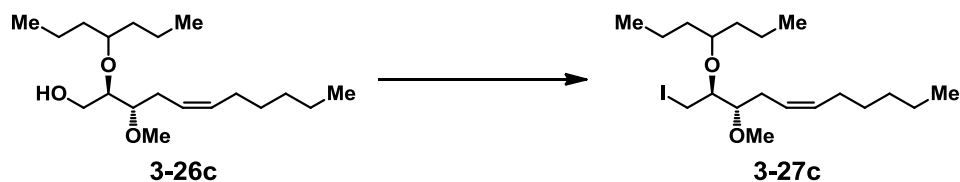
IR (neat) ν 3464, 2957, 2930, 2872, 1465, 1378, 1260, 1191, 1104, 1049, 818, 734 cm^{-1} ;

¹H NMR (500 MHz, CDCl₃) δ 0.89 (3H, t, *J* = 7.1 Hz), 0.91 (3H, t, *J* = 7.2 Hz), 0.91 (3H, t, *J* = 7.1 Hz), 1.23-1.53 (14H, m), 2.05 (2H, q, *J* = 7.1 Hz), 2.25-2.40 (3H, m), 3.32-3.40 (3H, m), 3.42 (3H, s), 3.64-3.76 (2H, m), 5.40-5.53 (2H, m);

¹³C NMR (125 MHz, CDCl₃) δ 14.0 (CH₃), 14.3 (CH₃), 14.3 (CH₃), 18.5 (CH₂), 18.6 (CH₂), 22.5 (CH₂), 27.5 (CH₂), 28.6 (CH₂), 29.2 (CH₂), 31.6 (CH₂), 36.2 (CH₂), 36.3 (CH₂), 58.4 (CH₃), 61.9 (CH₂), 77.8 (CH), 78.1 (CH), 82.4 (CH), 124.9 (CH), 132.3 (CH);

FD-LRMS m/z 314 (58.0%, $[M^+]$), 315 (bp, $[M+H^+]$);

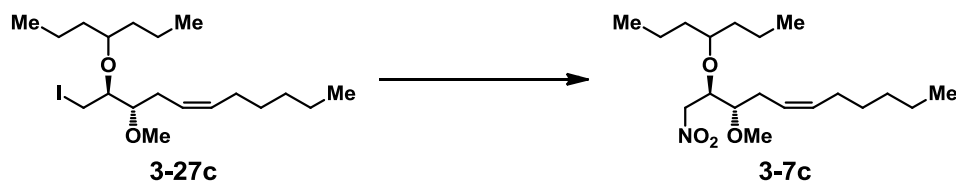
FD-HRMS calcd for $C_{19}H_{38}O_3$ [M^+]: 314.2821, found: 314.2836.

Compound 3-27c:

To a solution of **3-26c** (153.2 mg, 0.487 mmol) in CH_2Cl_2 (5 mL) were added imidazole (99.5 mg, 1.46 mmol), I_2 (185.4 mg, 0.731 mmol), and PPh_3 (191.6 mg, 0.731 mmol) at 0 °C, and the mixture was warmed to 23 °C and stirred for 12 h. The reaction was quenched with satd. aq. NaHCO_3 and satd. aq. $\text{Na}_2\text{S}_2\text{O}_3$, and the mixture was extracted with Et_2O (5 mL) three 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/ EtOAc = 30) to give crude **3-27c**, which was immediately used in the next reaction without further purification.

3-27c: a colorless oil;

Compound 3-7c:



To a solution of crude **3-27c** in DMF (5 mL) were added NaNO₂ (100.8 mg, 1.46 mmol) and urea (87.8 mg, 1.46 mmol) at 23 °C, and the mixture was stirred for 23 h. Then, the reaction was quenched with satd. aq. NH₄Cl, and the mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give **3-7c** (111.6 mg, 0.324 mmol, 67% over 2 steps).

3-7c: a colorless oil; $[\alpha]_{\text{D}}^{22} -12.5$ (c 0.50, CHCl_3);

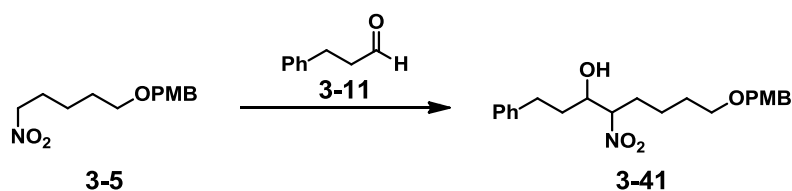
IR (neat) ν 2958, 2931, 2872, 1556, 1465, 1420, 1382, 1363, 1313, 1274, 1222, 1188, 1105, 1002, 731 cm^{-1} ;

¹H NMR (500 MHz, CDCl₃) δ 0.87 (3H, t, *J* = 7.2 Hz), 0.89 (3H, t, *J* = 7.2 Hz), 0.91 (3H, t, 7.2 Hz), 1.16-1.52 (14H, m), 2.05 (2H, quin, *J* = 7.5 Hz), 2.22 (1H, td, *J* = 7.2, 15.1 Hz), 2.33 (1H, td, *J* = 7.2, 15.1 Hz), 3.34 (1H, quin, *J* = 5.6 Hz), 3.36-3.40 (1H, m), 3.43 (3H, s), 4.09 (1H, td, *J* = 3.3, 8.0 Hz), 4.48 (1H, dd, *J* = 3.3, 12.9 Hz), 4.56 (1H, dd, *J* = 8.1, 12.9 Hz), 5.36-5.43 (1H, m), 5.52-5.59 (1H, m);

¹³C NMR (125 MHz, CDCl₃) δ 14.0 (CH₃), 14.2 (CH₃), 14.3 (CH₃), 18.0 (CH₂), 18.4 (CH₂), 22.5 (CH₂), 27.5 (CH₂), 28.8 (CH₂), 29.1 (CH₂), 31.5 (CH₂), 35.3 (CH₂), 35.9 (CH₂), 58.5 (CH₃), 76.4 (CH), 76.6 (CH₂), 79.0 (CH), 81.7 (CH), 123.7 (CH), 133.4 (CH);

FD-LRMS m/z 343 (98.5%, $[M^+]$), 311 (bp);

FD-HRMS calcd for C₁₉H₃₇NO₄ [M⁺]: 343.2723, found: 343.2734.

Compound 3-41:

To a solution of **3-5** (199.7 mg, 0.788 mmol) in DMF (8 mL) were added DBN (290.8 μ L, 2.37 mmol) and 3-phenylpropanal (**3-11**) (115.2 μ L, 0.788 mmol) in this order at 0 °C, and the mixture was warmed to 23 °C and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with EtOAc (10 mL) three 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 $\rightarrow$ 3) to give **3-41** (194.4 mg, 0.502 mmol, 64%).

3-41: an about 1:1 mixture of two diastereomers;* colorless oil;

IR (neat) ν 3417, 3061, 3027, 3002, 2935, 2863, 1612, 1585, 1550, 1513, 1496, 1455, 1363, 1302, 1248, 1095, 925, 822, 751, 701 cm^{-1} ;

^1H NMR (300 MHz, CDCl_3) δ 1.40 (2H $\times$ 4, quin, J = 7.1 Hz), 1.52-1.68 (2H $\times$ 4, m), 1.68-1.90 (2H $\times$ 4 + 1H $\times$ 4, m), 1.95-2.20 (1H $\times$ 4, m), 2.28 (1H $\times$ 2, brt, J = 6.4 Hz), 2.42 (1H $\times$ 2, brs), 2.61-2.78 (1H $\times$ 4, m), 2.79-2.93 (1H $\times$ 4, m), 3.41 (2H $\times$ 2, t, J = 6.2 Hz), 3.42 (2H $\times$ 2, t, J = 6.2 Hz), 3.76-3.90 (1H $\times$ 2, m), 3.79 (3H $\times$ 4, s), 3.94-4.06 (1H $\times$ 2, m), 4.38-4.50 (1H $\times$ 4, m), 4.40 (2H $\times$ 4, s), 6.87 (2H $\times$ 4, td, J = 2.2, 8.6 Hz), 7.13-7.35 (7H $\times$ 4, m);

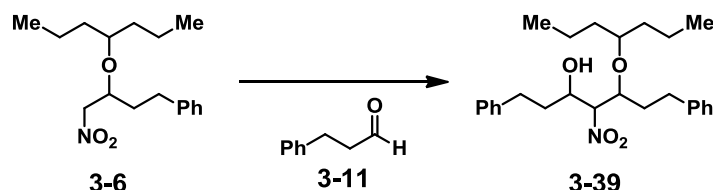
^{13}C NMR (75 MHz, CDCl_3) δ 22.6 (CH_2), 22.9 (CH_2), 27.7 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 30.2 (CH_2), 31.5 (CH_2), 31.8 (CH_2), 34.7 (CH_2), 35.3 (CH_2), 55.3 (CH_3), 69.2 (CH_2), 69.3 (CH_2), 71.2 (CH), 71.4 (CH), 72.6 (CH_2), 92.1 (CH), 92.7 (CH), 113.8 (CH), 126.2 (CH), 128.4 (CH), 128.6 (CH), 129.3 (CH), 130.4 (C), 140.8 (C), 159.1 (C);

FD-LRMS m/z 387 (bp, $[\text{M}^+]$);

FD-HRMS calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_5$ $[\text{M}^+]$: 387.2046, found: 387.2052.

*Two diastereomers were selectively produced from among possible four diastereomers in the nitroaldol reaction.

Compound 3-39:



To a solution of **3-6** (365.2 mg, 1.25 mmol) in DMF (6 mL) were added DBN (459 μ L, 3.74 mmol) and 3-phenylpropanal (**3-11**) (182 μ L, 1.25 mmol) in this order at 0 $^{\circ}$ C, and the mixture was warmed to 23 $^{\circ}$ C and stirred for 2 h. The reaction was quenched with satd. aq. NH_4Cl , and the mixture was extracted with a 2.5:1 blend of hexane and EtOAc (5 mL) three 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 = 50 $\rightarrow$ 30 $\rightarrow$ 10) to give **3-39** (284.2 mg, 0.665 mmol, 53%, BRSM: 81%) and starting material **3-6** (126.0 mg, 0.430 mmol).

3-39: an about 1:1:1:1 mixture of diastereomers; colorless oil;

IR (neat) ν 3551, 3086, 3063, 3027, 2958, 2872, 1603, 1584, 1553, 1496, 1455, 1378, 1260, 1155, 1074, 807, 748, 699 cm^{-1} ;

^1H NMR (500 MHz, CDCl_3) δ 0.85-0.94 (24H/4, m), 1.15-1.58 (32H/4, m), 1.71-1.92 (13H/4, m), 1.93-2.08 (3H/4, m), 2.38 (1H/4, ddd, J = 6.2, 11.3, 13.5 Hz), 2.59 (1H/4, ddd, J = 5.7, 11.1, 13.8 Hz), 2.61-2.93 (14H/4, m), 3.31 (1H/4, qn, J = 5.5 Hz), 3.42 (1H/4, qn, J = 5.7 Hz), 3.44-3.50 (1H/4, m), 3.49 (1H/4, qn, 5.7 Hz), 3.76-3.82 (1H/4, m), 4.03 (1H/4, q, J = 5.5 Hz), 4.07-4.16 (4H/4, m), 4.18 (1H/4, brdt, J = 3.1, 8.4 Hz), 4.22-4.26 (1H/4, m), 4.54-4.60 (3H/4, m), 4.64 (1H/4, t, J = 6.2 Hz), 7.04-7.08 (4H/4, m), 7.11-7.23 (20H/4, m), 7.25-7.32 (16H/4, m);

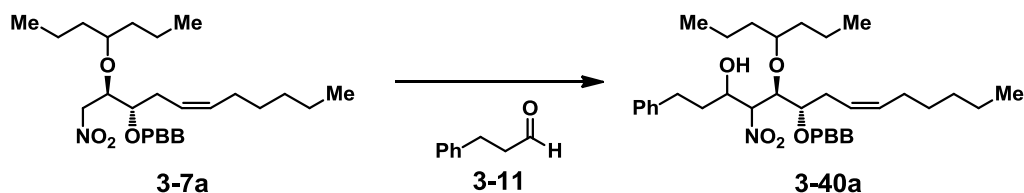
^{13}C NMR (125 MHz, CDCl_3) δ 14.23 ($\text{CH}_3 \times 1/4$), 14.24 ($\text{CH}_3 \times 1/4$), 14.26 ($\text{CH}_3 \times 4/4$), 14.29 ($\text{CH}_3 \times 2/4$), 17.8 ($\text{CH}_2 \times 1/4$), 18.05 ($\text{CH}_2 \times 1/4$), 18.12 ($\text{CH}_2 \times 1/4$), 18.14 ($\text{CH}_2 \times 1/4$), 18.30 ($\text{CH}_2 \times 1/4$), 18.32 ($\text{CH}_2 \times 1/4$), 18.5 ($\text{CH}_2 \times 1/4$), 18.6 ($\text{CH}_2 \times 1/4$), 29.6 ($\text{CH}_2 \times 1/4$), 30.2 ($\text{CH}_2 \times 1/4$), 30.5 ($\text{CH}_2 \times 2/4$), 31.0 ($\text{CH}_2 \times 1/4$), 31.4 ($\text{CH}_2 \times 1/4$), 31.6 ($\text{CH}_2 \times 1/4$), 31.7 ($\text{CH}_2 \times 1/4$), 32.0 ($\text{CH}_2 \times 1/4$), 32.1 ($\text{CH}_2 \times 1/4$), 33.1 ($\text{CH}_2 \times 1/4$), 33.5 ($\text{CH}_2 \times 1/4$), 34.7 ($\text{CH}_2 \times 1/4$), 34.8 ($\text{CH}_2 \times 1/4$), 34.9 ($\text{CH}_2 \times 1/4$), 35.06 ($\text{CH}_2 \times 1/4$), 35.07 ($\text{CH}_2 \times 1/4$), 35.2 ($\text{CH}_2 \times 1/4$), 35.5 ($\text{CH}_2 \times 1/4$), 35.79 ($\text{CH}_2 \times 1/4$), 35.84 ($\text{CH}_2 \times 1/4$), 35.94 ($\text{CH}_2 \times 1/4$), 35.97 ($\text{CH}_2 \times 1/4$), 36.1 ($\text{CH}_2 \times 1/4$), 68.0 ($\text{CH} \times 1/4$), 68.3 ($\text{CH} \times 1/4$), 68.6 ($\text{CH} \times 1/4$), 70.9 ($\text{CH} \times 1/4$), 73.1 ($\text{CH} \times 1/4$), 74.46 ($\text{CH} \times 1/4$), 74.49 ($\text{CH} \times 1/4$), 76.3 ($\text{CH} \times 1/4$),

78.0 (CH $\times$ 1/4), 78.1 (CH $\times$ 1/4), 78.3 (CH $\times$ 1/4), 78.5 (CH $\times$ 1/4), 91.7 (CH $\times$ 1/4), 92.18 (CH $\times$ 1/4), 92.25 (CH $\times$ 1/4), 93.6 (CH $\times$ 1/4), 126.0 (CH $\times$ 1/4), 126.14 (CH $\times$ 1/4), 126.17 (CH $\times$ 1/4), 126.19 (CH $\times$ 1/4), 126.20 (CH $\times$ 1/4), 126.22 (CH $\times$ 1/4), 126.3 (CH $\times$ 1/4), 128.25 (CH $\times$ 2/4), 128.29 (CH $\times$ 6/4), 128.42 (CH $\times$ 2/4), 128.45 (CH $\times$ 2/4), 128.47 (CH $\times$ 4/4), 128.48 (CH $\times$ 2/4), 128.54 (CH $\times$ 8/4), 128.57 (CH $\times$ 2/4), 128.59 (CH $\times$ 2/4), 128.63 (CH $\times$ 2/4), 140.4 (C $\times$ 1/4), 140.75 (C $\times$ 1/4), 140.79 (C $\times$ 1/4), 140.9 (C $\times$ 1/4), 141.0 (C $\times$ 1/4), 141.09 (C $\times$ 1/4), 141.13 (C $\times$ 1/4), 141.3 (C $\times$ 1/4);

FD-LRMS m/z 427 (bp, [M⁺]);

FD-HRMS calcd for C₂₆H₃₇NO₄ [M⁺]: 427.2723, found: 427.2725.

Compound 3-40a:



To a solution of **3-7a** (27.6 mg, 0.0554 mmol) in DMF (1 mL) were added DBN (20.4 μ L, 0.166 mmol) and 3-phenylpropanal (**3-11**) (8.1 μ L, 0.0554 mmol) in this order at 0 $^{\circ}$ C, and the mixture was warmed to 23 $^{\circ}$ C and stirred for 2 h. Then, to the mixture were added a 3:1 blend of hexane and EtOAc and satd. aq. NaHSO₃, and the mixture was stirred for 30 min. The mixture was extracted with a 2.5:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with satd. aq. NaHSO₃, H₂O, and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 $\rightarrow$ 10) to give **3-40a** (20.6 mg, 0.0326 mmol, 59%, BRSM: 88%) and starting material **3-7a** (9.2 mg, 0.00185 mmol).

3-40a: an about 1:1:1:1 mixture of four diastereomers; colorless oil;

IR (neat) ν 3499, 3085, 3062, 3026, 2957, 2929, 2871, 1727, 1594, 1550, 1489, 1455, 1378, 1071, 1012, 943, 804, 747, 700 cm^{-1} ;

¹H NMR (500 MHz, CDCl₃) δ 0.84-0.93 (36H/4, m), 1.12-1.62 (56H/4, m), 1.69-1.90 (8H/4, m), 1.92-2.06 (8H/4, m), 2.21 (1H/4, brtd, J = 7.3, 14.8 Hz), 2.29-2.45 (7H/4, m), 2.58 (1H/4, d, J = 11.3 Hz), 2.59-2.89 (8H/4, m), 2.94 (1H/4, d, J = 6.4 Hz), 3.41 (1H/4, qn, J = 5.6 Hz), 3.47-3.66 (6H/4, m), 3.72 (1H/4, dd, J = 1.2, 2.9 Hz), 3.87-3.94 (1H/4, m), 4.09-4.18 (4H/4, m), 4.21 (1H/4, dd, J = 2.3, 5.1 Hz), 4.22-4.28 (2H/4, m), 4.30 (1H/4, dd, J = 1.6, 8.9 Hz), 4.41-4.59 (8H/4, m), 4.65-4.72 (4H/4, m), 5.26-5.42 (4H/4, m), 5.43-5.55 (4H/4, m), 7.12-7.31 (28H/4, m), 7.43-7.48 (8H/4, m);

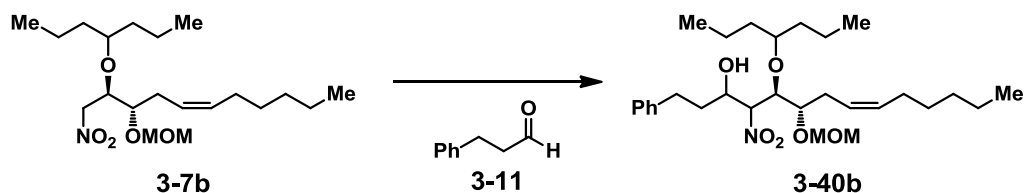
¹³C NMR (125 MHz, CDCl₃) δ 14.02 (CH₃ $\times$ 1/4), 14.03 (CH₃ $\times$ 2/4), 14.05 (CH₃ $\times$ 1/4), 14.24 (CH₃ $\times$ 1/4), 14.26 (CH₃ $\times$ 2/4), 14.27 (CH₃ $\times$ 5/4), 17.7 (CH₂ $\times$ 1/4), 17.85 (CH₂ $\times$ 1/4), 17.92 (CH₂ $\times$ 1/4), 17.97 (CH₂ $\times$ 1/4), 18.17 (CH₂ $\times$ 1/4), 18.21 (CH₂ $\times$ 1/4), 18.26 (CH₂ $\times$ 1/4), 18.4 (CH₂ $\times$ 1/4), 22.53 (CH₂ $\times$ 2/4), 22.55 (CH₂ $\times$ 1/4), 22.56 (CH₂ $\times$ 1/4), 27.4 (CH₂ $\times$ 2/4), 27.50 (CH₂ $\times$ 1/4), 27.53 (CH₂ $\times$ 1/4), 28.2 (CH₂ $\times$ 1/4), 28.7 (CH₂ $\times$ 1/4), 28.8 (CH₂ $\times$ 1/4), 28.9 (CH₂ $\times$ 1/4), 29.11 (CH₂ $\times$ 1/4), 29.12 (CH₂ $\times$ 2/4), 29.2 (CH₂ $\times$ 1/4), 31.0 (CH₂ $\times$ 1/4), 31.50 (CH₂ $\times$ 1/4), 31.53 (CH₂ $\times$ 2/4), 31.55 (CH₂ $\times$ 2/4),

31.7 (CH₂×1/4), 32.0 (CH₂×1/4), 34.1 (CH₂×1/4), 34.57 (CH₂×1/4), 34.64 (CH₂×1/4), 34.87 (CH₂×1/4), 34.88 (CH₂×1/4), 35.27 (CH₂×1/4), 35.30 (CH₂×1/4), 35.4 (CH₂×1/4), 35.5 (CH₂×1/4), 35.7 (CH₂×1/4), 35.8 (CH₂×1/4), 36.3 (CH₂×1/4), 68.2 (CH×1/4), 68.6 (CH×1/4), 68.9 (CH×1/4), 70.0 (CH×1/4), 71.4 (CH₂×1/4), 71.5 (CH₂×1/4), 71.6 (CH₂×1/4), 71.8 (CH₂×1/4), 75.5 (CH×1/4), 75.9 (CH×1/4), 76.1 (CH×1/4), 77.2 (CH×1/4), 79.1 (CH×1/4), 79.2 (CH×1/4), 79.5 (CH×1/4), 79.6 (CH×1/4), 79.9 (CH×1/4), 80.1 (CH×2/4), 80.4 (CH×1/4), 89.8 (CH×1/4), 91.1 (CH×1/4), 91.8 (CH×1/4), 92.9 (CH×1/4), 121.5 (C×1/4), 121.6 (C×1/4), 121.7 (C×1/4), 121.9 (C×1/4), 123.8 (CH×2/4), 124.4 (CH×1/4), 124.7 (CH×1/4), 125.9 (CH×1/4), 126.0 (CH×1/4), 126.21 (CH×1/4), 126.22 (CH×1/4), 128.38 (CH×2/4), 128.40 (CH×2/4), 128.42 (CH×2/4), 128.45 (CH×4/4), 128.47 (CH×2/4), 128.52 (CH×2/4), 128.56 (CH×2/4), 129.2 (CH×2/4), 129.3 (CH×2/4), 129.4 (CH×2/4), 129.5 (CH×2/4), 131.41 (CH×2/4), 131.47 (CH×2/4), 131.48 (CH×2/4), 131.6 (CH×2/4), 133.1 (CH×1/4), 133.3 (CH×1/4), 133.4 (CH×1/4), 133.6 (CH×1/4), 136.4 (C×1/4), 136.8 (C×1/4), 136.9 (C×1/4), 137.1 (C×1/4), 140.6 (C×1/4), 140.8 (C×1/4), 141.1 (C×1/4), 141.2 (C×1/4);

FD-LRMS *m/z* 631 (27.0%, [M⁺]), 632 (bp, [M+H⁺]);

FD-HRMS calcd for C₃₄H₅₀BrNO₅ [M⁺]: 631.2872, found: 631.2878.

Compound 3-40b:



To a solution of **3-7b** (32.7 mg, 0.0875 mmol) in DMF (1 mL) were added DBN (32.3 μ L, 0.263 mmol) and 3-phenylpropanal (**3-11**) (12.8 μ L, 0.0875 mmol) in this order at 0 °C, and the mixture was warmed to 23 °C and stirred for 2 h. Then, to the mixture were added a 3:1 blend of hexane and EtOAc and satd. aq. NaHSO₃, and the mixture was stirred for 30 min. The mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with satd. aq. NaHSO₃, H₂O, and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 $\rightarrow$ 10) to give **3-40b** (22.9 mg, 0.0451 mmol, 52%, BRSM: 93%) and starting material **3-7b** (14.6 mg, 0.0391 mmol).

3-40b: an about 1:1:1:1 mixture of four diastereomers; colorless oil;

IR (neat) ν 3548, 2958, 2930, 2871, 1551, 1455, 1377, 1104, 1073, 699 cm^{-1} ;

¹H NMR (500 MHz, CDCl₃) δ 0.85-0.94 (36H/4, m), 1.13-1.62 (56H/4, m), 1.70-2.12 (16H/4, m), 2.17 (1H/4, brtd, J = 7.8, 14.9 Hz), 2.22-2.46 (7H/4, m), 2.62 (1H/4, d, J = 11.0 Hz), 2.67-2.95 (8H/4, m), 2.70 (1H/4, d, J = 5.0 Hz), 3.11 (1H/4, d, J = 5.7 Hz), 3.28 (3H/4,s), 3.35 (3H/4,s), 3.37 (3H/4,s), 3.38 (3H/4, s), 3.43 (1H/4, qn, J = 5.6 Hz), 3.56 (1H/4, qn, J = 5.6 Hz), 3.61 (1H/4, qn, J = 5.7 Hz), 3.67, (1H/4, qn, J = 5.8 Hz), 3.69-3.80 (4H/4, m), 3.89 (1H/4, dd, J = 1.5, 2.9 Hz), 3.90-3.97 (1H/4, m), 4.05-4.11 (1H/4, m), 4.12 (1H/4, dd, J = 2.5, 7.0 Hz), 4.14-4.20 (1H/4, m), 4.16 (1H/4, dd, J = 3.3, 5.1 Hz), 4.19 (1H/4, dd, J = 1.7, 4.3 Hz), 4.21-4.27 (1H/4, m), 4.26 (1H/4, dd, J = 0.9, 9.2 Hz), 4.48 (1H/4, d, J = 6.8 Hz), 4.56 (1H/4, d, J = 6.8 Hz), 4.619 (1H/4, d, J = 6.7 Hz), 4.623 (1H/4, d, J = 6.7 Hz), 4.66-4.71 (2H/4, m), 4.67 (2H/4, s), 4.699 (1H/4, d, J = 6.7 Hz), 4.705 (1H/4, d, J = 6.7 Hz), 4.74 (1H/4, dd, J = 5.4, 8.5 Hz), 5.27-5.38 (4H/4, m), 5.46-5.55 (4H/4, m), 7.15-7.24 (12H/4, m), 7.24-7.32 (8H/4, m);

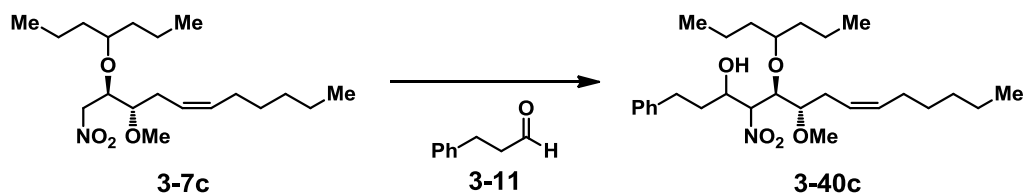
¹³C NMR (125 MHz, CDCl₃) δ 14.01 (CH₃ $\times$ 1/4), 14.02 (CH₃ $\times$ 1/4), 14.03 (CH₃ $\times$ 2/4), 14.23 (CH₃ $\times$ 1/4), 14.26 (CH₃ $\times$ 4/4), 14.28 (CH₃ $\times$ 3/4), 17.7 (CH₂ $\times$ 1/4), 17.8 (CH₂ $\times$ 1/4), 17.9 (CH₂ $\times$ 1/4), 18.0 (CH₂ $\times$ 1/4), 18.10 (CH₂ $\times$ 2/4), 18.11 (CH₂ $\times$ 1/4), 18.3 (CH₂ $\times$ 1/4), 22.51 (CH₂ $\times$ 2/4), 22.54

(CH₂×1/4), 22.55 (CH₂×1/4), 27.33 (CH₂×1/4), 27.38 (CH₂×1/4), 27.40 (CH₂×1/4), 27.46 (CH₂×1/4), 28.8 (CH₂×2/4), 29.10 (CH₂×1/4), 29.13 (CH₂×1/4), 29.2 (CH₂×1/4), 29.3 (CH₂×1/4), 29.4 (CH₂×1/4), 31.0 (CH₂×1/4), 31.47 (CH₂×1/4), 31.50 (CH₂×1/4), 31.53 (CH₂×1/4), 31.55 (CH₂×1/4), 31.63 (CH₂×1/4), 31.84 (CH₂×1/4), 31.89 (CH₂×1/4), 33.9 (CH₂×1/4), 34.29 (CH₂×1/4), 34.35 (CH₂×1/4), 34.71 (CH₂×2/4), 34.76 (CH₂×1/4), 35.3 (CH₂×1/4), 35.4 (CH₂×1/4), 35.5 (CH₂×1/4), 35.7 (CH₂×1/4), 35.8 (CH₂×1/4), 36.4 (CH₂×1/4), 55.73 (CH₃×1/4), 55.76 (CH₃×1/4), 55.96 (CH₃×1/4), 55.99 (CH₃×1/4), 68.2 (CH×1/4), 68.7 (CH×1/4), 68.9 (CH×1/4), 70.0 (CH×1/4), 76.3 (CH×1/4), 76.5 (CH×2/4), 77.7 (CH×1/4), 78.1 (CH×1/4), 78.4 (CH×1/4), 78.5 (CH×1/4), 78.6 (CH×1/4), 78.9 (CH×1/4), 79.0 (CH×1/4), 79.4 (CH×1/4), 79.9 (CH×1/4), 89.2 (CH×1/4), 90.6 (CH×1/4), 92.5 (CH×1/4), 93.0 (CH×1/4), 95.9 (CH₂×1/4), 96.1 (CH₂×1/4), 96.46 (CH₂×1/4), 96.54 (CH₂×1/4), 123.7 (CH), 123.8 (CH×1/4), 124.5 (CH×1/4), 124.7 (CH×1/4), 125.9 (CH×1/4), 126.0 (CH×1/4), 126.2 (CH×2/4), 128.36 (CH×2/4), 128.39 (CH×2/4), 128.40 (CH×2/4), 128.50 (CH×6/4), 128.54 (CH×2/4), 128.58 (CH×2/4), 133.2 (CH×1/4), 133.4 (CH×1/4), 133.5 (CH×1/4), 133.7 (CH×1/4), 140.7 (C×1/4), 140.8 (C×1/4), 141.2 (C×1/4), 141.3 (C×1/4);

FD-LRMS *m/z* 507 (97.7%, [M⁺]);

FD-HRMS calcd for C₂₉H₄₉NO₆ [M⁺]: 507.3560, found: 507.3576.

Compound 3-40c:



To a solution of **3-7c** (43.2 mg, 0.126 mmol) in DMF (1 mL) were added DBN (46.4 μ L, 0.377 mmol) and 3-phenylpropanal (**3-11**) (18.4 μ L, 0.126 mmol) in this order at 0 °C, and the mixture was warmed to 23 °C and stirred for 2 h. Then, to the mixture were added a 3:1 blend of hexane and EtOAc and satd. aq. NaHSO₃, and the solution was stirred for 30 min. The mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with satd. aq. NaHSO₃, H₂O, and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 $\rightarrow$ 10) to give **3-40c** (32.7 mg, 0.0685 mmol, 54%, BRSM: 86%) and starting material **3-7c** (15.7 mg, 0.0457 mmol).

3-40c: an about 1:1 mixture of two diastereomers;* colorless oil;

IR (neat) ν 3482, 2957, 2930, 2872, 1734, 1604, 1550, 1496, 1456, 1377, 1245, 1213, 1152, 1098, 1032, 921, 747, 700 cm^{-1} ;

¹H NMR (500 MHz, CDCl₃) δ 0.85-0.94 (18H/2, m), 1.12-1.51 (28H/2, m), 1.73-1.83 (2H/4, m), 1.84-1.93 (2H/2, m), 1.99 (2H/2, brq, J = 7.3 Hz), 2.01-2.08 (2H/2, m), 2.17 (1H/2, brdt, J = 7.2, 15.0 Hz), 2.31 (1H/2, brtd, J = 6.8, 15.0 Hz), 2.33 (2H/2, brt, J = 6.8 Hz), 2.62 (1H/2, d, J = 10.8 Hz), 2.70-2.88 (4H/2, m), 3.04 (1H/2, d, J = 6.1 Hz), 3.27 (1H/2, dt, J = 2.7, 6.5 Hz), 3.30 (3H/2, s), 3.35 (1H/2, td, J = 2.2, 6.8 Hz), 3.37-3.42 (1H/2, m), 3.39 (3H/2, s), 3.54-3.60 (1H/2, m), 3.88-3.95 (1H/2, m), 4.15 (1H/2, dd, J = 2.8, 4.9 Hz), 4.23 (1H/2, dd, J = 1.9, 8.7 Hz), 4.22-4.27 (1H/2, m), 4.64 (1H/2, dd, J = 2.8, 4.8 Hz), 4.68 (1H/2, dd, J = 3.2, 8.8 Hz), 5.30-5.38 (2H/2, m), 5.45-5.54 (2H/2, m), 7.15-7.24 (6H/2, m), 7.26-7.31 (4H/2, m);

¹³C NMR (125 MHz, CDCl₃) δ 14.01 (CH₃ $\times$ 1/2), 14.03 (CH₃ $\times$ 1/2), 14.23 (CH₃ $\times$ 1/2), 14.25 (CH₃ $\times$ 1/2), 14.27 (CH₃ $\times$ 2/2), 17.8 (CH₂ $\times$ 1/2), 18.0 (CH₂ $\times$ 1/2), 18.3 (CH₂ $\times$ 1/2), 18.4 (CH₂ $\times$ 1/2), 22.53 (CH₂ $\times$ 1/2), 22.56 (CH₂ $\times$ 1/2), 27.40 (CH₂ $\times$ 1/2), 27.42 (CH₂ $\times$ 1/2), 28.3 (CH₂ $\times$ 1/2), 28.6 (CH₂ $\times$ 1/2), 29.1 (CH₂ $\times$ 1/2), 29.2 (CH₂ $\times$ 1/2), 31.5 (CH₂ $\times$ 1/2), 31.6 (CH₂ $\times$ 1/2), 31.8 (CH₂ $\times$ 1/2), 32.0 (CH₂ $\times$ 1/2), 34.3 (CH₂ $\times$ 1/2), 34.8 (CH₂ $\times$ 1/2), 35.4 (CH₂ $\times$ 1/2), 35.79 (CH₂ $\times$ 1/2), 35.82 (CH₂ $\times$ 1/2),

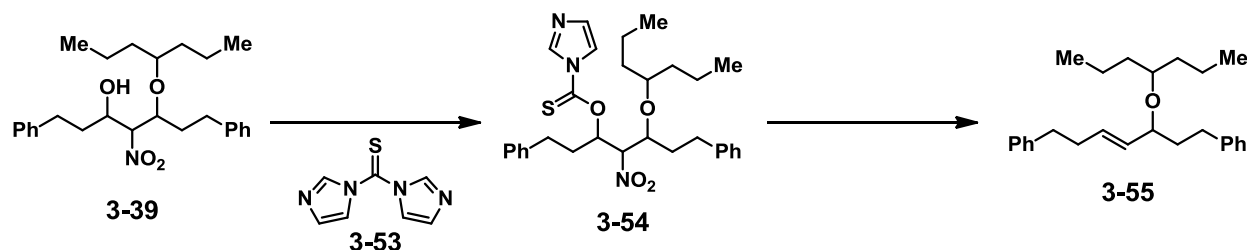
36.4 (CH₂×1/2), 58.1 (CH₃×1/2), 58.3 (CH₃×1/2), 68.3 (CH×1/2), 68.8 (CH×1/2), 75.9 (CH×1/2), 76.0 (CH×1/2), 78.9 (CH×1/2), 79.0 (CH×1/2), 82.0 (CH×1/2), 82.4 (CH×1/2), 89.8 (CH×1/2), 92.8 (CH×1/2), 124.0 (CH×1/2), 124.9 (CH×1/2), 126.0 (CH×1/2), 126.2 (CH×1/2), 128.41 (CH×2/2), 128.43 (CH×2/2), 128.51 (CH×2/2), 128.55 (CH×2/2), 133.1 (CH×1/2), 133.3 (CH×1/2), 140.7 (C×1/2), 141.2 (C×1/2);

FD-LRMS *m/z* 477 (75.1%, [M⁺]), 478 (bp, [M+H⁺]);

FD-HRMS calcd for C₂₈H₄₇NO₅ [M⁺]: 477.3454, found: 477.3464.

*Two diastereomers were selectively produced from among possible four diastereomers in the nitroaldol reaction.

Compound 3-55 (thiocarbonylation/radical elimination sequence):



To a solution of **3-39** (24.4 mg, 0.0571 mmol) in toluene (1 mL) was added thiocarbonyldiimidazole (**3-53**) (33.9 mg, 0.171 mmol) at 23 °C, and the mixture was stirred and refluxed for 2 h. The mixture was cooled to 23 °C and diluted with EtOAc (10 mL). The solution was washed with 1 mol/L aq. HCl, H₂O, and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give crude **3-54**, which was immediately used in the next reaction without further purification.

To a solution of crude **3-54** in toluene (1 mL) were added Bu₃SnH (130.3 μL, 0.571 mmol) and AIBN (15.9 mg, 0.114 mmol) at 23 °C, and the mixture was stirred and refluxed for 3 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give **3-55** (5.1 mg, 0.0140 mmol, 25% over 2 steps).

3-55: a colorless oil;

IR (neat) ν 3085, 3062, 3027, 2956, 2929, 2870, 1734, 1604, 1496, 1454, 1122, 1076, 1036, 971, 745, 698 cm⁻¹;

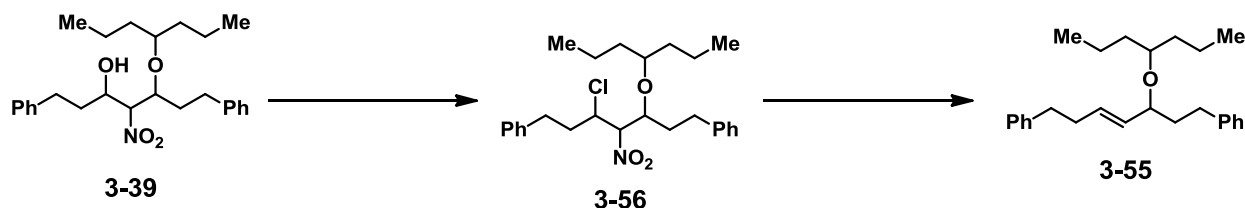
¹H NMR (500 MHz, CDCl₃) δ 0.86 (3H, t, J = 7.2 Hz), 0.89 (3H, t, J = 6.9 Hz), 1.16-1.45 (8H, m), 1.71 (1H, tdd, J = 6.1, 10.1, 13.5 Hz), 1.88 (1H, tdd, J = 6.5, 10.0, 13.5 Hz), 2.35-2.41 (2H, m), 2.57 (1H, ddd, J = 5.9, 10.0, 14.0 Hz), 2.64 (1H, ddd, J = 6.4, 10.1, 14.0 Hz), 2.71 (2H, t, J = 7.7 Hz), 3.23-3.29 (1H, m), 3.65 (1H, td, J = 6.5, 8.2 Hz), 5.34 (1H, tdd, J = 1.4, 8.2, 15.4 Hz), 5.56 (1H, td, J = 6.7, 15.4 Hz), 7.14-7.20 (6H, m), 7.24-7.30 (4H, m);

¹³C NMR (125 MHz, CDCl₃) δ 14.2 (CH₃), 14.4 (CH₃), 18.3 (CH₂), 18.8 (CH₂), 31.7 (CH₂), 34.0 (CH₂), 35.7 (CH₂), 36.1 (CH₂), 37.0 (CH₂), 37.4 (CH₂), 75.4 (CH), 78.0 (CH), 125.6 (CH), 125.8 (CH), 128.2 (CH $\times$ 2), 128.30 (CH $\times$ 2), 128.38 (CH $\times$ 2), 128.44 (CH $\times$ 2), 132.1 (CH), 132.7 (CH), 141.7 (C), 142.4 (C);

FD-LRMS m/z 364 (bp, [M⁺]);

FD-HRMS calcd for C₂₆H₃₆O [M⁺]: 364.2766, found: 364.2776.

Compound 3-55 (chlorination/radical elimination sequence):



Method I: To a solution of **3-39** (31.5 mg, 0.0737 mmol) in DMF (1 mL) was added SOCl₂ (53.4 μ L, 0.737 mmol) at 23 °C, and the mixture was warmed to 60 °C and stirred for 5 min. The mixture was cooled to 23 °C and quenched with H₂O. The mixture was extracted with a 2.5:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc = 50) to give **3-56** (20.5 mg, 0.0460 mmol, 62%).

To a solution of **3-56** (20.5 mg, 0.0460 mmol) in toluene (1 mL) were added Bu₃SnH (24.8 μ L, 0.0919 mmol) and AIBN (7.5 mg, 0.0460 mmol) at 23 °C, and the mixture was stirred and refluxed for 2 h. Then, the mixture was directly concentrated in vacuo. Because the resulting residue included unreacted **3-56**, the residue was treated again with Bu₃SnH and AIBN under the same conditions as above. After concentration of the mixture, the resulting residue was purified by column chromatography (silica gel, hexane $\rightarrow$ hexane/EtOAc = 100) to give **3-55** (10.3 mg, 0.0283 mmol, 61%).

Method II: To a solution of **3-39** (10.1 mg, 0.0236 mmol) in DMF (1 mL) was added SOCl₂ (17.1 μ L, 0.236 mmol) at 23 °C, and the mixture was warmed to 60 °C and stirred for 5 min. The mixture was cooled to 23 °C and quenched with satd. aq. NaHCO₃. The mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give crude **3-56**, which was immediately used in the next reaction without further purification.

To a solution of crude **3-56** in benzene (1 mL) were added Bu₃SnH (63.7 μ L, 0.236 mmol) and AIBN (3.9 mg, 0.0236 mmol) at 23 °C, and the mixture was stirred and refluxed for 2 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane $\rightarrow$ hexane/EtOAc = 100) to give **3-55** (7.1 mg, 0.0195 mmol,

83% over 2 steps).

Chemical reaction scheme showing the conversion of compound **3-40b** to compound **3-58b** via intermediate **3-57b**.

Structure **3-40b** is a complex molecule featuring a central carbon atom bonded to a phenyl group, a nitro group, a methoxy group, and a methoxy-methyl ether. It also has a side chain with a double bond and a methyl group.

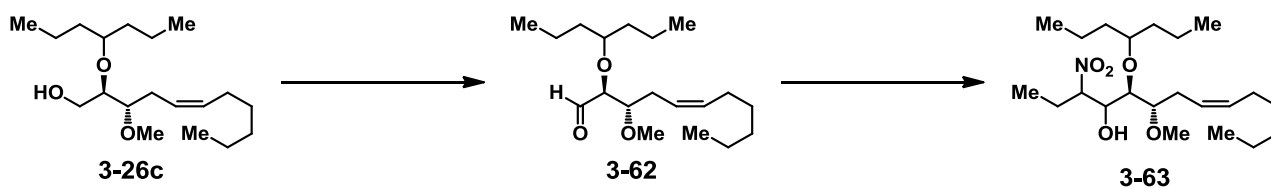
Structure **3-57b** is the intermediate product, showing modifications to the side chain.

Structure **3-58b** is the final product, showing further modifications to the side chain.

To a solution of crude **3-57b** in benzene (1 mL) were added Bu₃SnH (76.3 μL, 0.284 mmol) and AIBN (9.3 mg, 0.0567 mmol) at 23 °C, and the mixture was stirred and refluxed for 6 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give **3-58b** (1.0 mg, 0.00225 mmol, 8% over 2 steps).

¹H NMR (500 MHz, CDCl₃) δ 0.83-0.93 (9H, m), 1.12-1.52 (14H, m), 1.96-2.05 (2H, m), 2.24 (2H, brt, *J* = 6.3 Hz), 2.41 (2H, brtd, *J* = 6.9, 7.9 Hz), 2.71 (2H, t, *J* = 7.8 Hz), 3.24-3.31 (1H, m), 3.37 (3H, s), 3.60-3.66 (1H, m), 3.70 (1H, dd, *J* = 3.5, 8.2 Hz), 4.63 (1H, d, *J* = 6.6 Hz), 4.77 (1H, d, *J* = 6.6 Hz), 5.33-5.48 (3H, m), 5.62 (1H, td, *J* = 6.5, 15.5 Hz), 7.15-7.21 (3H, m), 7.24-7.30 (2H, m);

FD-HRMS calcd for C₂₉H₄₈O₃ [M⁺]: 444.3603, found: 444.3597.

Compound 3-63:

To a solution of $(\text{COCl})_2$ (54.8 μL , 0.639 mmol) in CH_2Cl_2 (1 mL) was added DMSO (91.6 μL , 1.28 mmol) at -78°C , and the mixture was stirred for 10 min. Then, to the mixture was added a solution of **3-26c** (40.2 mg, 0.128 mmol) in CH_2Cl_2 (1 mL) at -78°C , and the mixture was stirred for 15 min. Then, to the mixture was added Et_3N (215.6 μL , 1.53 mmol) at -78°C , and the mixture was stirred for 5 min. The mixture was warmed to 0°C , and the reaction was quenched with 1 mol/L aq. HCl. Then, the mixture was diluted with a 2:1 blend of hexane and CH_2Cl_2 (15 mL) and washed with 1 mol/L aq. HCl, H_2O , and brine. The resulting organic layer was dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo to give crude **3-62**, which was immediately used in the next reaction without further purification.

To a solution of PrNO_2 (11.4 μL , 0.128 mmol) in DMF (1 mL) were added DBN (46.4 μL , 0.377 mmol) and a solution of crude **3-62** (47.2 μL , 0.383 mmol) in DMF (1 mL) at 0°C , and the mixture was warmed to 23°C and stirred for 2 h. Then, to the mixture were added a 3:1 blend of hexane and EtOAc and aq. NaHSO_3 , and the mixture was stirred for 30 min. The mixture was extracted with a 3:1 blend of hexane and EtOAc (5 mL) three times. The combined organic layers were washed with satd. aq. NaHSO_3 , H_2O , and brine, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane/ EtOAc = 30 $\rightarrow$ 10) to give **3-63** (43.0 mg, 0.107 mmol, 84%).

3-63: an about 1:1 mixture of two diastereomers;* colorless oil;

IR (neat) ν 3520, 2958, 2931, 2873, 1732, 1550, 1464, 1377, 1254, 1104, 809, 735 cm^{-1} ;

^1H NMR (500 MHz, CDCl_3) δ 0.87-0.94 (18H/2, m), 0.98 (3H/2, t, J = 7.4 Hz), 0.99 (3H/2, J = 7.4 Hz), 1.24-1.51 (28H/2, m), 1.88-2.19 (8H/2, m), 2.29-2.47 (4H/2, m), 2.78 (1H/2, dd, J = 4.3 Hz), 2.88 (1H/2, d, J = 6.4 Hz), 3.38-3.52 (6H/2, m), 3.39 (3H/2, s), 3.40 (3H/2, s), 4.04 (1H/2, brdt, J = 5.1, 6.1 Hz), 4.23 (1H/2, brdt, J = 4.3, 6.3 Hz), 4.66-4.74 (2H/2, m) 5.34-5.57 (4H/2, m);

^{13}C NMR (125 MHz, CDCl_3) δ 10.3 ($\text{CH}_3 \times 1/2$), 10.4 ($\text{CH}_3 \times 1/2$), 14.0 ($\text{CH}_3 \times 2/2$), 14.21 ($\text{CH}_3 \times 1/2$), 14.26 ($\text{CH}_3 \times 1/2$), 14.27 ($\text{CH}_3 \times 1/2$), 14.30 ($\text{CH}_3 \times 1/2$), 18.27 ($\text{CH}_2 \times 1/2$), 18.32 ($\text{CH}_2 \times 1/2$), 18.4 ($\text{CH}_2 \times 2/2$), 21.7 ($\text{CH}_2 \times 1/2$), 22.6 ($\text{CH}_2 \times 2/2$), 24.1 ($\text{CH}_2 \times 1/2$), 27.50 ($\text{CH}_2 \times 1/2$), 27.53 ($\text{CH}_2 \times 1/2$),

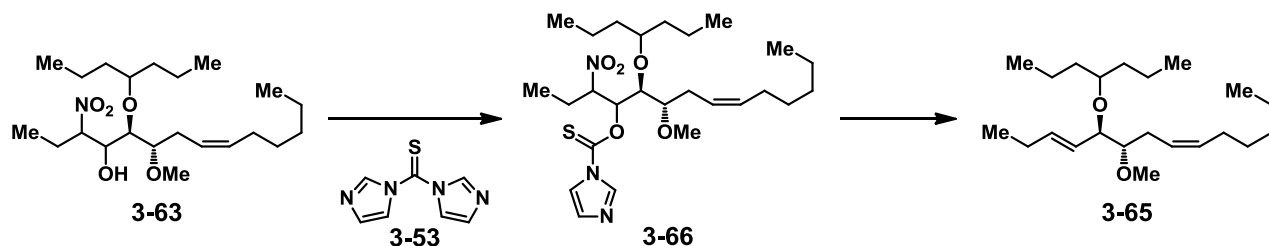
28.3 (CH₂×1/2), 28.7 (CH₂×1/2), 29.18 (CH₂×1/2), 29.21 (CH₂×1/2), 31.6 (CH₂×2/2), 35.05 (CH₂×1/2), 35.10 (CH₂×1/2), 35.81 (CH₂×1/2), 36.03 (CH₂×1/2), 57.9 (CH×1/2), 58.1 (CH×1/2), 72.33 (CH×1/2), 72.37 (CH×1/2), 76.1 (CH×1/2), 76.7 (CH), 77.8 (CH×1/2), 78.0 (CH×1/2), 80.7 (CH×1/2), 82.1 (CH×1/2), 90.6 (CH×1/2), 90.8 (CH×1/2), 124.7 (CH×1/2), 125.0 (CH×1/2), 132.57 (CH×1/2), 132.62 (CH×1/2);

FD-LRMS *m/z* 401 (bp, [M⁺]);

FD-HRMS calcd for C₂₂H₄₃NO₅ [M⁺]: 401.3141, found: 401.3128.

*Two diastereomers were selectively produced from among possible four diastereomers in the nitroaldol reaction.

Compound 3-65:



To a solution of **3-63** (32.9 mg, 0.0819 mmol) in (CH₂Cl)₂ (1 mL) was added thiocarbonyldiimidazole (**3-53**) (162.2 mg, 0.819 mmol) at 23 °C, and the mixture was warmed to 40 °C and stirred for 16 h. The mixture was cooled to 23 °C and diluted with Et₂O (10 mL). The solution was washed with 1 mol/L aq. HCl, H₂O, and brine, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give crude **3-66**, which was immediately used in the next reaction without further purification.

To a solution of crude **3-66** in toluene (1 mL) were added Bu₃SnH (221.2 μL, 0.819 mmol) and AIBN (27.0 mg, 0.164 mmol) at 23 °C, and the mixture was stirred and refluxed for 2 h. Then, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give **3-65** (7.0 mg, 0.0207 mmol, 25% over 2 steps).

3-65: a colorless oil; $[\alpha]_D^{22} -70.8$ (*c* 0.15, CHCl₃);

IR (neat) ν 2958, 2927, 2872, 1739, 1463, 1377, 1261, 1111, 1048, 972, 736 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 0.87 (3H, t, *J* = 7.1 Hz), 0.89 (3H, t, *J* = 7.2 Hz), 0.90 (3H, t, *J* = 6.9 Hz), 1.01 (3H, t, *J* = 7.4 Hz), 1.24-1.47 (14H, m), 2.03 (2H, q, *J* = 6.9 Hz), 2.09 (2H, ddq, *J* = 1.5, 6.3, 7.4 Hz), 2.17-2.30 (2H, m), 3.20 (1H, ddd, 3.9, 5.9, 6.8 Hz), 3.30-3.36 (1H, m), 3.42 (3H, s), 3.69 (1H, dd, *J* = 3.9, 8.5 Hz), 5.37-5.48 (3H, m), 5.63 (1H, td, *J* = 6.3, 15.5 Hz);

¹³C NMR (125 MHz, CDCl₃) δ 13.6 (CH₃), 14.0 (CH₃), 14.2 (CH₃), 14.4 (CH₃), 18.4 (CH₂), 18.7 (CH₂), 22.6 (CH₂), 25.5 (CH₂), 27.5 (CH₂), 29.0 (CH₂), 29.3 (CH₂), 31.6 (CH₂), 35.8 (CH₂), 36.8 (CH₂), 58.6 (CH), 75.6 (CH), 80.3 (CH), 84.3 (CH), 125.9 (CH), 127.2 (CH), 131.6 (CH), 136.5 (CH);

FD-LRMS *m/z* 338 (0.4%, [M⁺]), 339 (2.2%, [M+H⁺]), 183 (bp);

FD-HRMS calcd for C₂₂H₄₂O₂ [M⁺]: 338.3185, found: 338.3197.

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