Synthesis of the cyclohexene segment of portimine

(ポーチミンのシクロヘキセンセグメントの合成)

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Contents

Abbreviations

Ac	acetyl
Alloc	allyloxycarbonyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxylcarbonyl
Bu	butyl
i-Bu, ^{i}Bu	*iso*-butyl
t-Bu, ^{t}Bu	*tert*-butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBALH	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPI	Dess-Martin-periodinane
DMSO	dimethyl sulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
epi	epimer
eq, equiv	equivalent
Et	ethyl
HMPA	hexamethylphophoramide
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
Me	methyl
MOM	methoxymethyl
Ms	methansulfonyl
MS4A	molecular sieves 4 angstrom

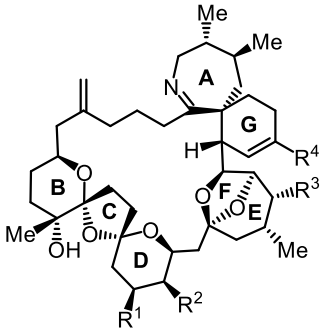
MVK	methyl vinyl ketone
NHMDS	sodium hexamethyldisilazide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
PBB	4-bromobenzyl
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PMB	4-methoxybenzyl
PPTS	pyridinium 4-toluenesuflonate
PTS	4-toluenesufonic acid
i-Pr, iPr	isopropyl
RCM	ring-closing metathesis
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Teoc	2-(trimethylsilyl)ehoxylcarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

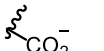
Chapter 1
Introduction

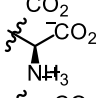
1-1. Spirocyclic Imine Toxins

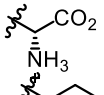
In late 20th century, food poisoning due to ingestion of the common edible bivalve *Pinna* sp. frequently broke out in the coastal regions of East Asia.[1,2] From the predominant symptoms of the patients of the poisoning accidents by the bivalve at Guangdong, China, in 1980 and 1989, Chinese researchers deduced that the poisoning may be attributable to neurotoxins and reported that the toxic extract from *Pinna attenuata* acts as a Ca^{2+} channel activator.[2]

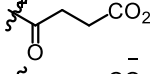
In 1995, Uemura and co-workers first isolated pinnatoxin A (PnTX A [**1-1**], Figure 1-1) from the viscera of *Pinna muricata*and as a causative toxin of the food poisoning, and determined the gross structure of the compound, consisting of a 27-membered carbocycle including a spirocyclic imine (A,G-ring), a spirotricyclic bis-acetal (B,C,D-ring) and a bicyclic acetal (E,F-ring).[3] In 1996, the relative stereochemistry of **1-1** was determined by extensive NMR analysis by them.[4] The absolute configuration of **1-1** was finally confirmed by total synthesis by the Kishi group in 1998.[5] To date, many spirocyclic imine toxins, having similar structure to PnTX A, were discovered and classified by the size of the spirocyclic imine: (i) 6,7-spirocyclic imines: pinnatoxins (PnTXs, **1-1**–**8**, Figure 1-1),[3,6] pteriatoxins (PtTXs, **1-9**–**11**, Figure 1-1),[7] spirolides (SPXs, **1-12**–**24**, Figure 1-2),[8] (ii) 6,6-spirocyclic imines: gymnodimines (GYMs, **1-25**–**30**, Figure 1-2),[9] spiro-prorocentrimine (**1-31**, Figure 1-2),[10] and (iii) a 5,6-spirocyclic imine: portimine (**1-32**, Figure 1-2).[11] The spirocyclic imine toxins were found to be specifically produced by dinoflagellates, such as *Volcanodinium rugosum*[11,12], *Alexandrium ostenfeldii*,[13] *Gymnodinium sp.*,[9] and *Prorocentrum lima.*[10]

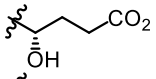


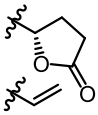
pinnatoxin A (**1-1**) : R^1 = H, R^2 = H, R^3 = OH, R^4 = 

pinnatoxin B (**1-2**) : R^1 = H, R^2 = H, R^3 = OH, R^4 = 

pinnatoxin C (**1-3**) : R^1 = H, R^2 = H, R^3 = OH, R^4 = 

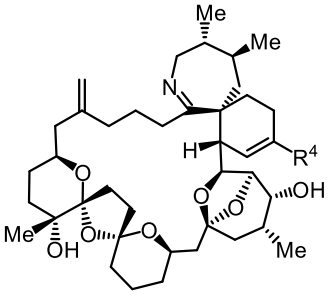
pinnatoxin D (**1-4**) : R^1 = Me, R^2 = OH, R^3 = H, R^4 = 

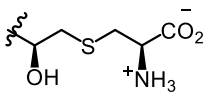
pinnatoxin E (**1-5**) : R^1 = Me, R^2 = OH, R^3 = H, R^4 = 

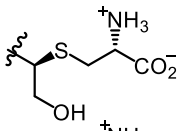
pinnatoxin F (**1-6**) : R^1 = Me, R^2 = OH, R^3 = H, R^4 = 

pinnatoxin G (**1-7**) : R^1 = H, R^2 = H, R^3 = OH, R^4 = 

pinnatoxin H (**1-8**) : R^1 = Me, R^2 = OH, R^3 = H, R^4 = 



pteriatoxin A (**1-9**) : R^4 = 

pteriatoxin B (**1-10**) : R^4 = 

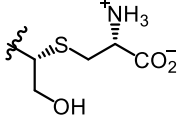
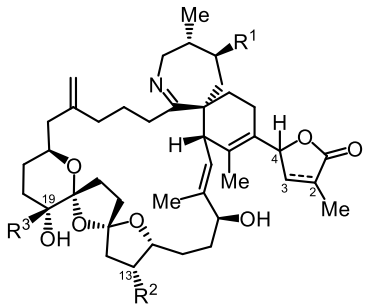
pteriatoxin C (**1-11**) : R^4 = 

Figure 1-1. Pinnatoxins and pteriatoxins.



spirolide A (**1-12**) : R^1 = H, R^2 = Me, R^3 = Me, $\Delta^{2,3}$

spirolide B (**1-13**) : R^1 = H, R^2 = Me, R^3 = Me

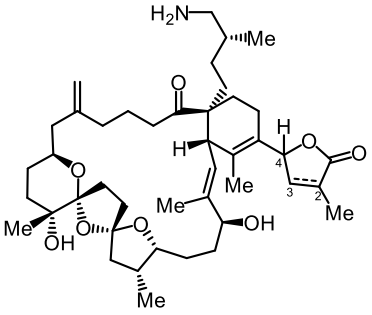
spirolide C (**1-14**) : R^1 = Me, R^2 = Me, R^3 = Me, $\Delta^{2,3}$

spirolide D (**1-15**) : R^1 = Me, R^2 = Me, R^3 = Me

13-desmethyl spirolide C (**1-16**) : R^1 = Me, R^2 = H, R^3 = Me, $\Delta^{2,3}$

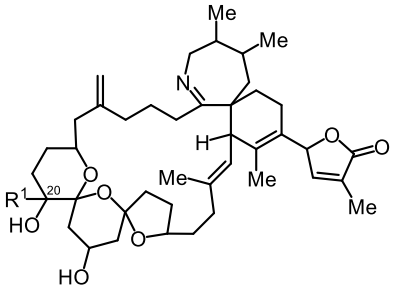
13-desmethyl spirolide D (**1-17**) : R^1 = Me, R^2 = H, R^3 = Me

13, 19-didesmethyl spirolide C (**1-18**) : R^1 = H, R^2 = H, R^3 = Me, $\Delta^{2,3}$



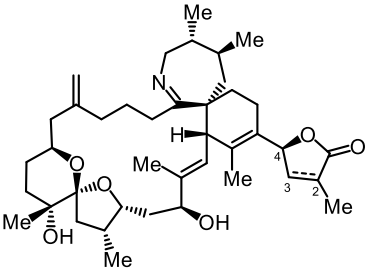
spirolide E (**1-19**) : $\Delta^{2,3}$

spirolide F (**1-20**) :



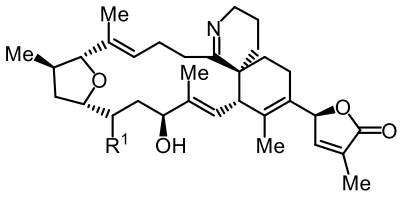
spirolide G (**1-21**) : R^1 = H

20-methyl spirolide G (**1-22**) : R^1 = Me



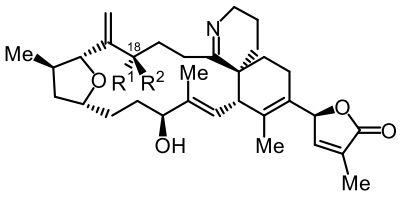
spirolide H (**1-23**) : $\Delta^{2,3}$

spirolide I (**1-24**) :



gymnodimine A (**1-25**) : R^1 = H

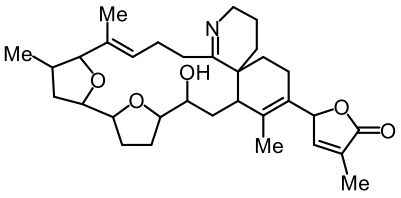
12-methylgymnodimine A (**1-26**) : R^1 = Me



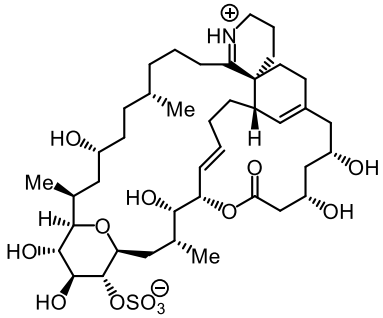
gymnodimine B (**1-27**) : R^1 = OH, R^2 = H

gymnodimine C (**1-28**) : R^1 = H, R^2 = OH

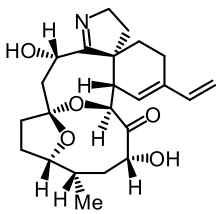
18-deoxygymnodimine B (**1-29**) : R^1 = H, R^2 = H



gymnodimine D (**1-30**)



spiro-prorocentrimine (**1-31**)



portimine (**1-32**)

Figure 1-2. Spirolides, gymnodimines, spiro-prorocentrimine and portimine.

The presence of acute lethal toxicities of the spirocyclic imine toxins to mice was confirmed via intraperitoneal (ip) and gavage (oral) administrations by many research groups (Table 1-1).[3,5,6,7,8,9,10,11,14] Most of the spirocyclic imine toxins show acute toxicities at a dose of <100 μg/kg. In particular, SPX D (**1-14**), 13-desmethyl SPX C (**1-16**) and 20-methyl SPX G (**1-22**) display high acute toxicities to mice (LD_{50} <10 μg/kg). It was clarified that the spirocyclic imine toxins act as antagonists of both muscle- and neuronal-types of nicotinic and muscarinic acetylcholine receptors (nAChRs and mAChRs, respectively).[15] The cyclic imine moiety, a common feature of this toxin family, was thought to be a main structural requirement for toxicity based on a series of biological studies.[15,16,23b]

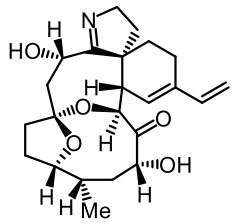
	acute toxicity to mice	
	i.p. injection	gavage administration
PnTX A (**1-1**) (+)-natural (**1-33**) (–)-synthetic	180 μg/kg (LD_{99})[3] inactive (>100 μg/kg in mouse assay)[5]	— —
PnTX B (**1-2**) PnTX C (**1-3**)	22 μg/kg (LD_{50})*, [6a]	—
PnTX D (**1-4**)	400 μg/kg (LD_{50})[6b]	—
PnTX E (**1-5**)	45, 57 μg/kg (LD_{50})[6c, 14a]	2,800 μg/kg (LD_{50})[14a]
PnTX F (**1-6**)	12.7, 16 μg/kg (LD_{50})[6c, 14a]	25.0 μg/kg (LD_{50})[14a]
PnTX G (**1-7**)	48, 50 μg/kg (LD_{50})[6c, 14a]	150 μg/kg (LD_{50})[14a]
PnTX H (**1-8**)	67 μg/kg (LD_{50})[6d]	—
PtTX A (**1-9**)	100 μg/kg (LD_{50})[7]	—
PtTX B (**1-10**) PtTX C (**1-11**)	8 μg/kg (LD_{50})**, [7]	—
SPX A (**1-12**)	35-44 μg/kg (LD_{50})[14b]	430-690 μg/kg (LD_{50})[14b]
SPX B (**1-13**)	99, 250 μg/kg (LD_{50})[8b, 14b]	320-500 μg/kg (LD_{50})[14b]
SPX C (**1-14**)	4.6-16 μg/kg (LD_{50})[14b]	180 μg/kg (LD_{50})[14b]
SPX D (**1-15**)	250 μg/kg (LD_{50})[8b]	—
13-desMeSPX C (**1-16**)	6.9, 27.9 μg/kg (LD_{50})[14b,c]	123-198 μg/kg (LD_{50})[14b]
13,19-desMeSPX C (**1-18**)	32.2 μg/kg (LD_{50})[14c]	—
SPX E (**1-19**)	inactive [8c]	—
SPX F (**1-20**)	inactive [8c]	—
20-MeSPX G (**1-22**)	8 μg/kg (LD_{50})[14b]	160 μg/kg (LD_{50})[14b]
SPX H (**1-23**)	>2000 μg/kg (LD_{50})[8f]	—
GYM A (**1-25**)	80, 96, 450, 700 μg/kg (LD_{50})[9a,14d,e,f]	755 μg/kg (LD_{50})[14e]
GYM B (**1-26**)	800 μg/kg (LD_{50})[14f]	—
spiro-prorocentrimine (**1-31**)	2500 μg/kg (LD_{99})[10]	—
portimine (**1-32**)	1570 μg/kg (LD_{50})[11]	—

* : 1:1 ratio of PnTX B (**1-2**) and C (**1-3**). ** : 1:1 ratio of PtTX B (**1-9**) and C (**1-10**).

Table 1-1. Acute toxicity of spirocyclic imine toxin family

1-2. Portimine

Portimine (**1-32**, Figure 1-3), isolated as a cytotoxin from the benthic dinoflagellate *Vulcanodinium rugosum* by the Selwood group in 2015, has a unique pentacyclic skeleton including a five-membered cyclic imine, connected with a cyclohexene to form a spirocycle, and a dioxatricyclo[7.5.1.^{11,4}]hexadecane.[11] Selwood and co-workers determined the relative configuration of portimine by extensive NMR experiments. The determination of the absolute configuration of **1-32**, however, has yet to be reported. Although most of the spirocyclic imine toxins, such as pinnatoxins, pteriatoxins, spirolides, gymnodimines and spiro-prorocentrimine, show strong acute neurotoxicity as described above, portimine is unusual in displaying low acute toxicity (LD_{50} 1570 μg/kg, Table 1-1) but exhibiting high cytotoxicity to cultured cells due to apoptosis inducing activity (LC_{50} 2.7, 3.0 and 6.0 nmol/L for P388, Vero and human Jurkat T-lymphoma cells, respectively).[17] In contrast, highly acutely toxic PnTX F is far less toxic to P388 cells in vitro (LC_{50} >1 μmol/L) than portimine. To date, the total synthesis and the synthetic studies of portimine (**1-32**) have yet to be reported.



portimine (**1-32**)

Figure 1-3. Portimine

Because of strong interest in the relationship between the unique structure and the unusual bioactivity of portimine, which has yet to be elucidated, the author decided to develop an efficient synthesis of portimine (**1-32)** to obtain sufficient quantities for biological studies.

In the dissertation, the author describes the synthesis of the cyclohexene segment of portimine (**1-32**) toward the convergent total synthesis.

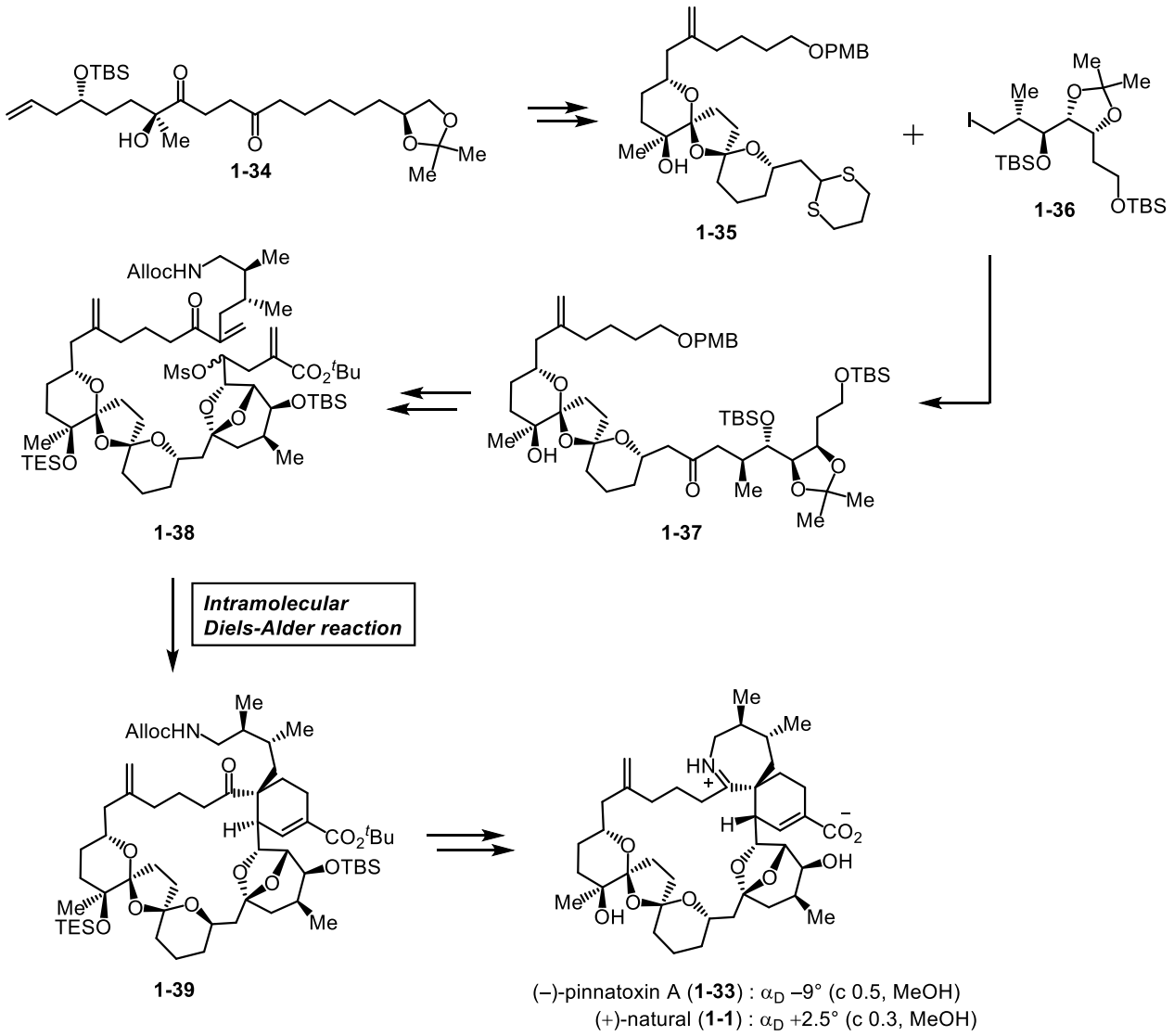
1-3. Total Synthesis and Synthetic Studies of Spirocyclic Imine Toxins by Other Research Groups

In this section, the total synthesis and the synthetic studies of spirocyclic imine toxins by other groups are outlined with focusing on the construction of the cyclohexene moieties.

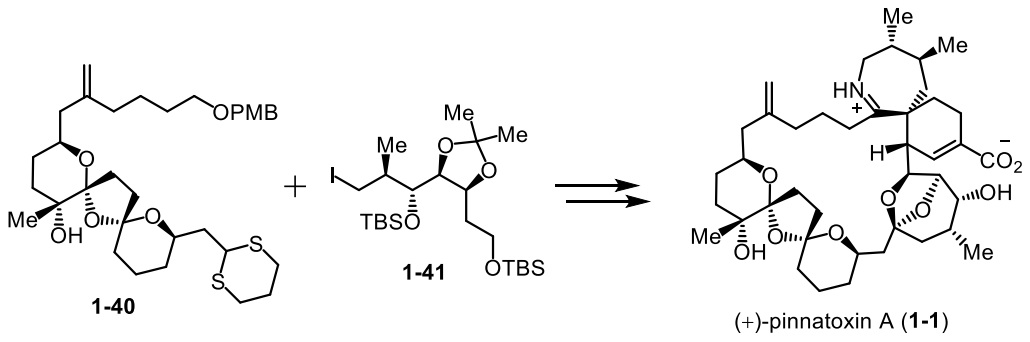
1-3-1. Total Syntheses of PnTX A, B, C and PtTX A, B, C by the Kishi Group

As mentioned in the preceding section, Kishi and co-workers reported first total synthesis of (-)-PnTX A, the enantiomer of the natural product, in 1998 (Scheme 1-1).[5] The Kishi group took a synthetic route that mimicked the biogenesis reported by Uemura[3] including a macrocycle-forming Diels-Alder reaction at the final stage of the synthesis. Treatment of Diketone **1-34**, prepared from 4-pentyn-1-ol over 12 steps, with CSA followed by interconversion of functional groups afforded bis-spiroacetal **1-35**, which was subjected to a 11 step process involving the coupling reaction with iodide **1-36** and the subsequent carbon-chain-extension using Nozaki-Hiyama-Kishi reaction[18] to give **1-38**. Intramolecular Diels-Alder reaction of a diene-enone substrate, derived from **1-38** by an elimination reaction, provided a 1:1.3 mixture of the desired *exo*-cyclic product **1-39** and the diastereomers in 78% combined yield. Finally, although the spirocyclic imine formation required severe conditions (200 °C, 1-2 Torr) to complete, the synthesis of the antipode of natural PnTX A (**1-33**) was successfully achieved. Interestingly, the unnatural PnTX A (**1-33**) was found to be non-toxic to mice (Table 1-1). Later, the accomplishment of the total synthesis of (+)-PnTX (**1-1**) by the Kishi group via the same synthetic route using bis-spiroacetal **1-40** and iodide **1-41**, enantiomers of **1-35** and **1-36**, respectively, was disclosed in a review by Nagasawa (Scheme 1-2).[19]

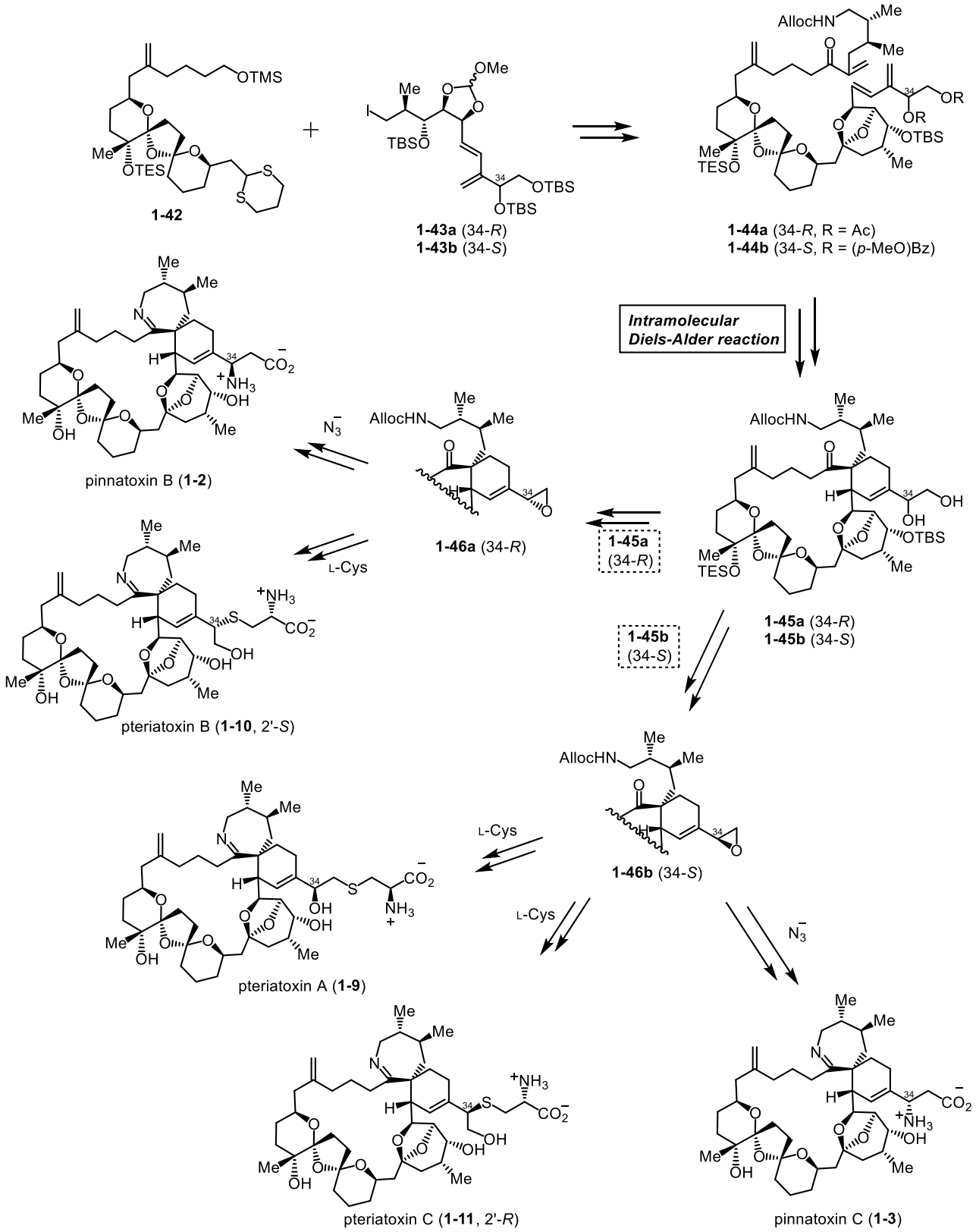
The Kishi group applied the above strategy to the synthesis of PnTX and PtTX family compounds (Scheme 1-3).[20] The reaction of dithiane **1-42** with C34-diastereomeric dienes **1-43a** and **b** and the subsequent several steps produced diene-enone **1-44a** and **b**. A process including the intramolecular Diels-Alder reaction of **1-44a** furnished cyclohexene **1-45a**. After the conversion of **1-45a** to epoxide **1-46b**, PnTX B (**1-2**) and PtTX B (**1-10**) were synthesized from **1-46a** by a sequence involving an azide-substitution and by a transformation using a L-cysteine derivative, respectively. On the other hand, cyclohexene **1-45b**, similarly obtained from **1-44b**, was epoxidized to produce **1-46b**, which was transformed to PnTX C (**1-3**), PtTX A (**1-9**) and PtTX C (**1-11**). The total synthesis unambiguously assigned the relative and absolute configurations of PnTX B (**1-2**), PtTX B (**1-10**), PnTX C (**1-3**), PtTX A (**1-9**) and PtTX C (**1-11**).



Scheme 1-1. Total synthesis of (-)-PnTX A by the Kishi group.



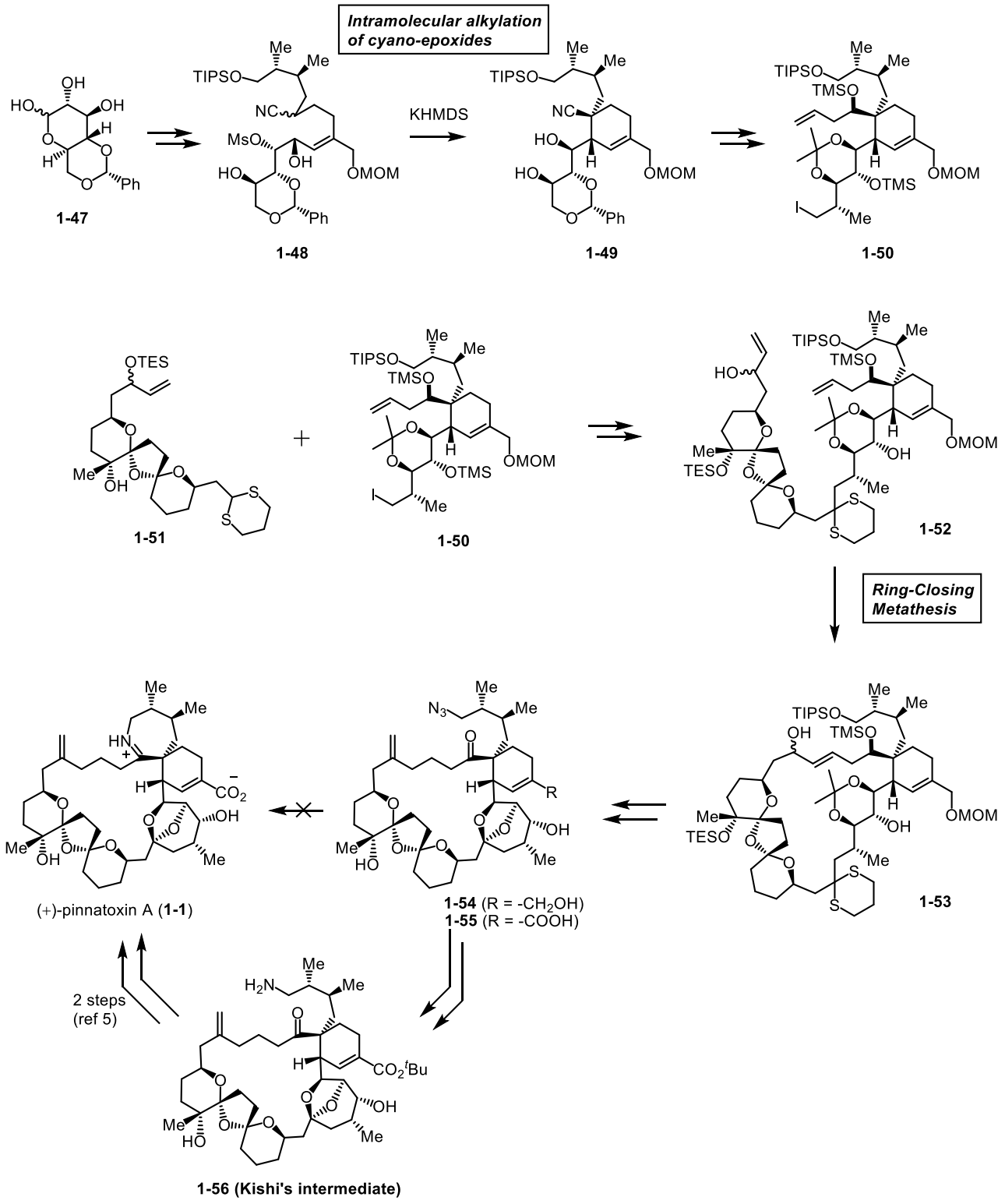
Scheme 1-2. Total synthesis of (+)-PnTX A by the Kishi group.



Scheme 1-3. Total synthesis of PnTX B and C and PtTX family compounds by the Kishi group.

1-3-2. A Formal Total Synthesis of PnTX A by Hirama group

The Hirama group has achieved the formal total synthesis of PnTX A using intramolecular alkylation and ring-closing metathesis as key reactions (Scheme 1-4)[21]. Exposure of mesylate **1-48**, prepared from glucose derivative **1-47** over 13 steps, with KHMDS generated in situ a cyano-epoxide, which was deprotonated with additional KHMDS and cyclized to give cyclohexene **1-49** as a sole isomer. After the conversion of **1-49** to iodide **1-50** over 8 steps, the dithiane coupling between cyclic acetal **1-51** and **1-50** afforded **1-52**. Construction of macrocyclic compound **1-53** was performed via a ring closing metathesis reaction. The Hirama group found that the direct cyclization of azide **1-55**, derived from **1-53**, to PnTX A (**1-1**) was difficult. Therefore, they applied the procedure developed by the Kishi group to the final conversion. Thus, alcohol **1-54** was transformed to aminoketone **1-56**, which was converted to PnTX A (**1-1**) by Kishi's procedure, thereby achieving the formal total synthesis of **1-1**.

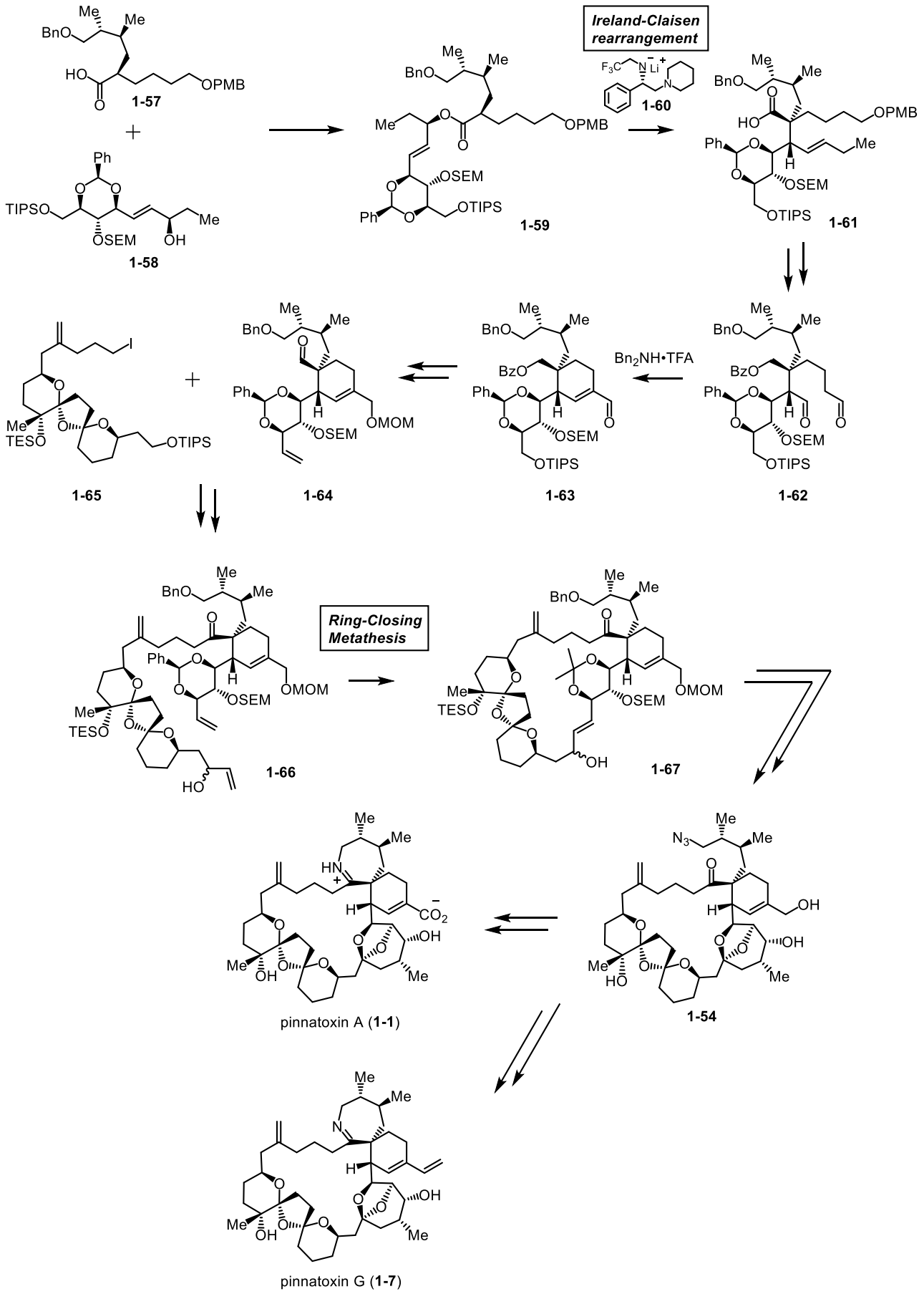


Scheme 1-4. The formal total synthesis of PnTX A by the Hirama group.

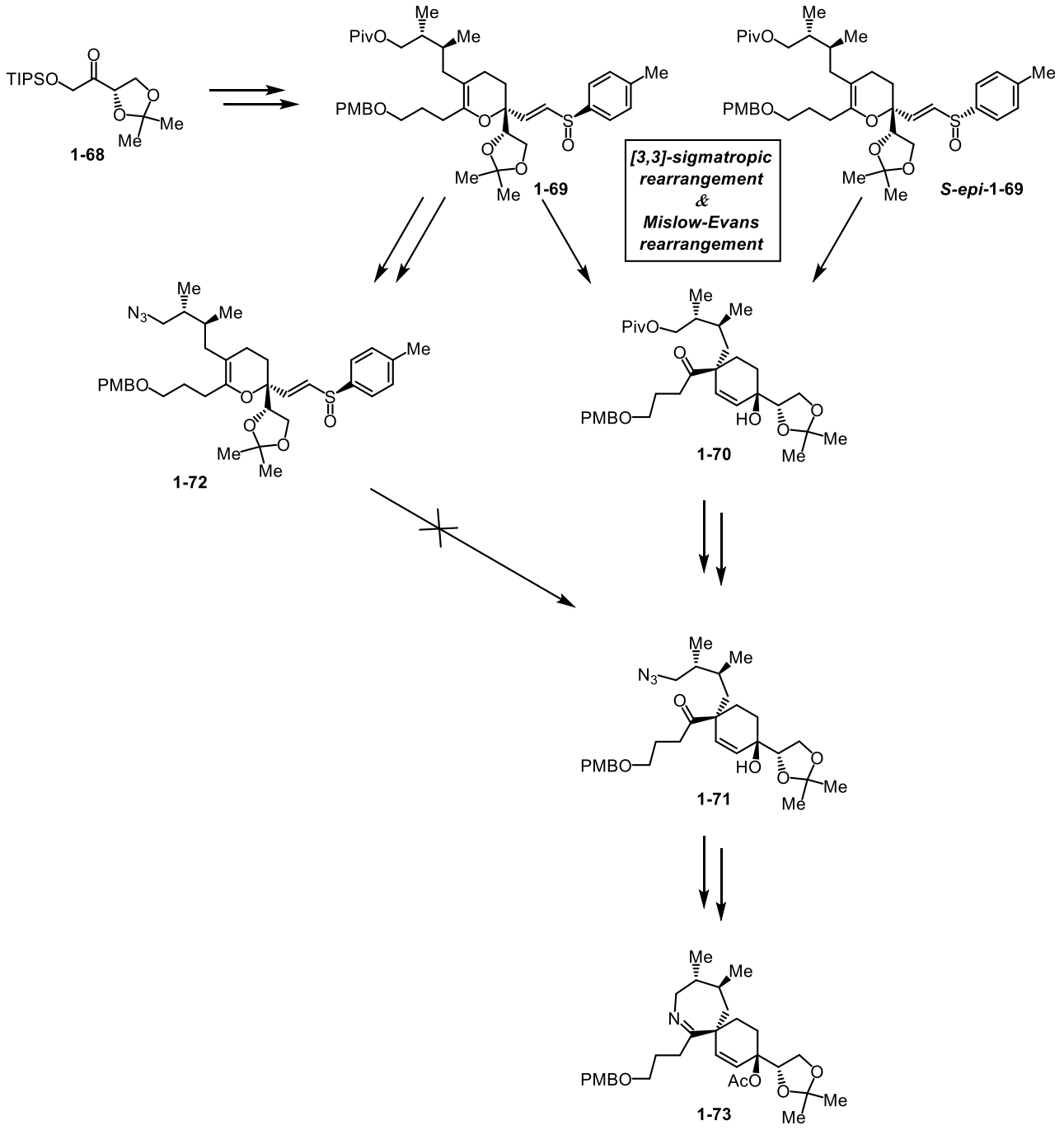
1-3-3. Total Synthesis of PnTX A and G by the Zakarian group

The Zakarian group has established the total syntheses of PnTX A (**1-1**) and PnTX G (**1-7**) using the Ireland-Claisen rearrangement[22] as a key reaction (Scheme 1-5).[23] The allylic ester **1-59** was first constructed from carboxylic acid **1-57** and allylic alcohol **1-58** by condensation reaction. Ester **1-59** was subjected to stereoselective enolization using chiral lithium amide **1-60**, and the resulting ketene silyl acetal underwent a diastereoselective Ireland-Claisen rearrangement to give carboxylic acid **1-61** selectively. After oxidation of **1-61** under Swern conditions to provide dialdehyde **1-62**, intramolecular aldol cyclization of **1-62** with $BnNH_2$·TFA afforded the cyclohexene **1-63** in 80% over 2 steps. The coupling between aldehyde **1-64** and an anion, derived from iodide **1-65** and ^{t}BuLi, followed by ring closing olefin metathesis constructed macrocyclic alkene **1-67**, which was then converted to Hirama's intermediate **1-54**. After conversion of **1-54** to a methyl ester, the application of Kishi's procedure completed the total synthesis of PnTX A. They also accomplished the synthesis of PnTX G from **1-54** in 4 steps.

The Zakarian group also reported an alternative [3,3]-sigmatropic rearrangement approach to construct the spirocyclic imine moiety (Scheme 1-6).[23d] After the preparation of vinyl sulfoxide **1-69** and ***S-epi*-1-69** from optically active ketone **1-68**, heating of each sulfoxide in an alcohol of high-boiling point induced tandem reactions of Claisen rearrangement and Mislow-Evans rearrangement[24] to give the desired cyclohexene **1-70**. After installation of an azide group, 6,7-spirocyclic imine **1-73** was successfully synthesized using Staudinger reaction[25]. Zakarian noted that the azide installation before rearrangement was unsuccessful.



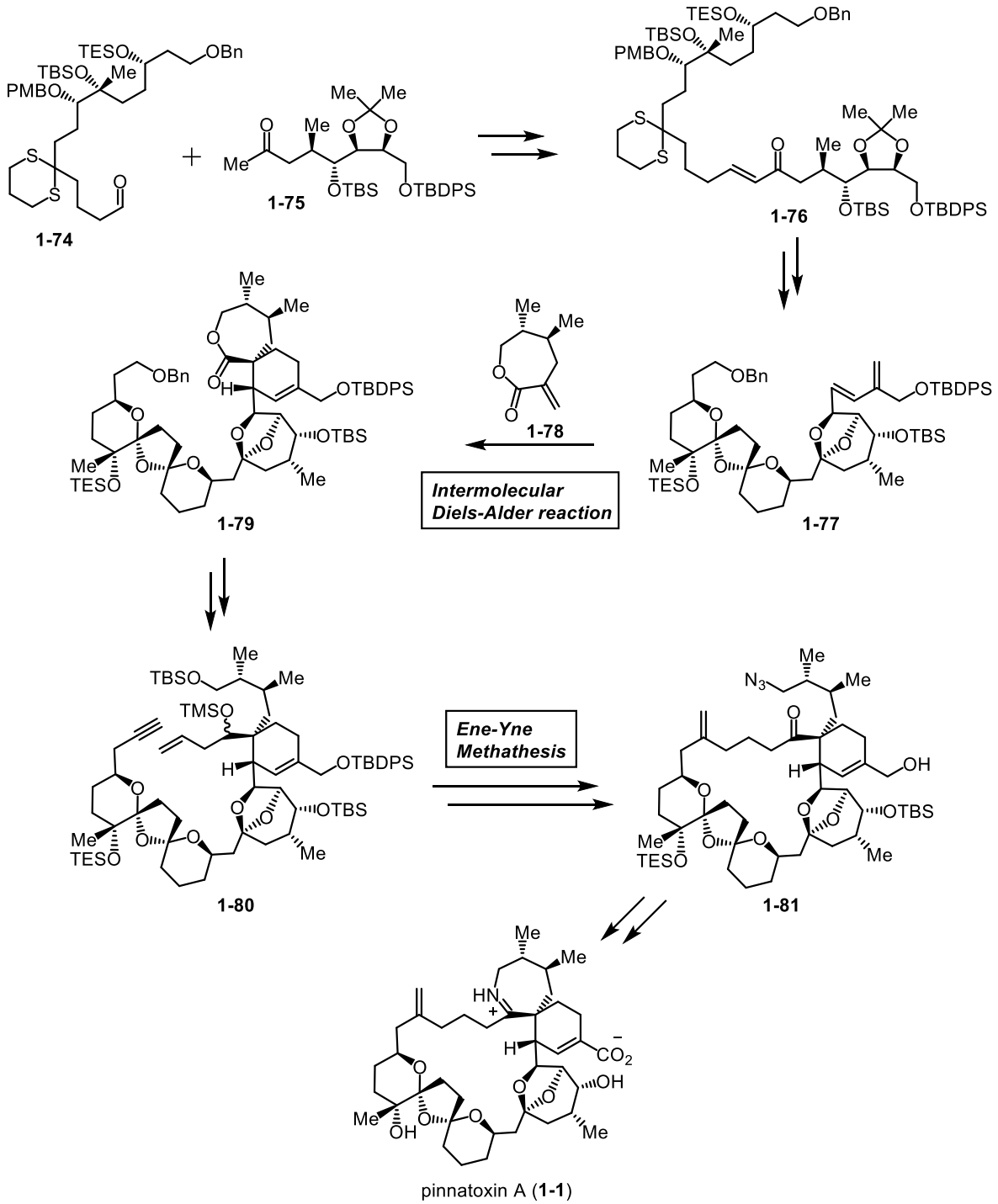
Scheme 1-5. Total synthesis of PnTX A and G by the Zakarian group.



Scheme 1-6. 6,7-Spirocyclic imine formation using [3,3]-sigmatropic rearrangement by the Zakarian group.

1-3-4. Total Synthesis of PnTX A by the Hashimoto group

The Hashimoto group has achieved the total synthesis of PnTX A (**1-1**) using Diels-Alder reaction and ene-yne metathesis as key reactions (Scheme 1-7).[26] Aldol condensation between aldehyde **1-74** and ketone **1-75** produced enone **1-76**. After the formation of a spirocyclic acetal, diene **1-77** was reacted with α-methylene lactone **1-78** in xylene at 160 °C in a sealed tube to provide *exo*-adduct **1-79** in 35% yield. After eneyne **1-80** was derived from **1-79**, an ene-yne metathesis successfully gave macrocycle **1-81**. The spirocyclic imine formation of **1-81** by Kishi's procedure completed the total synthesis of PnTX A (**1-1**).

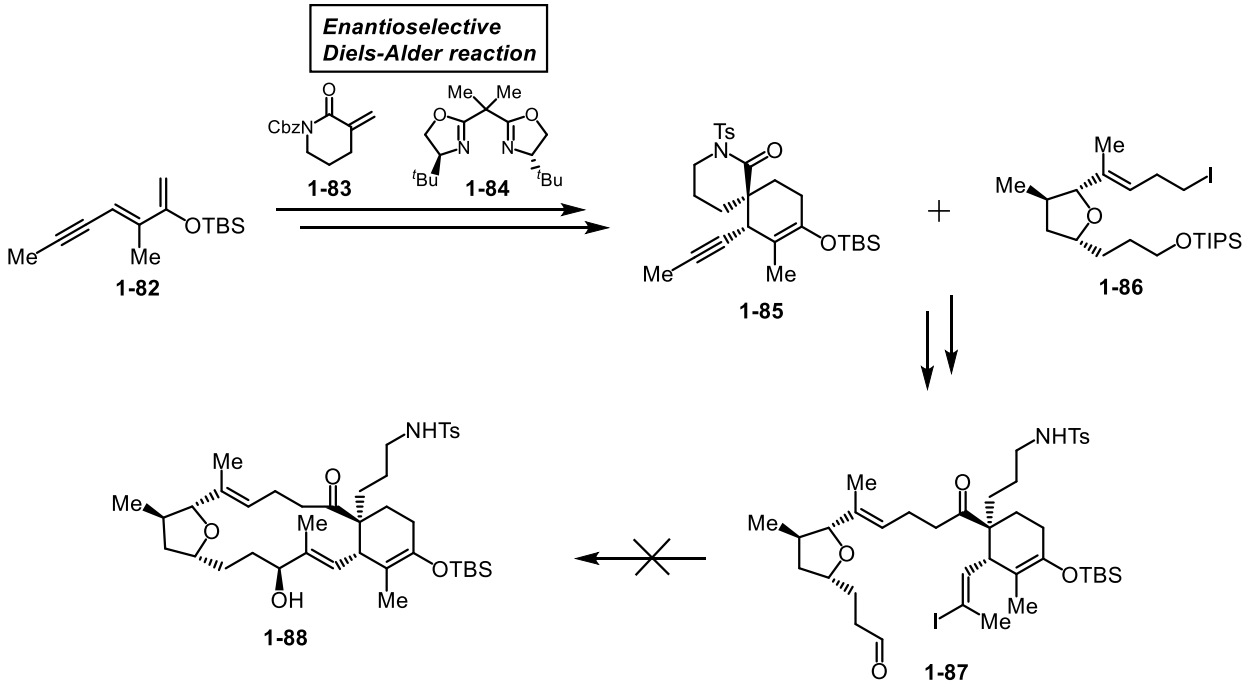


Scheme 1-7. Total synthesis of PnTX A by the Hashimoto group.

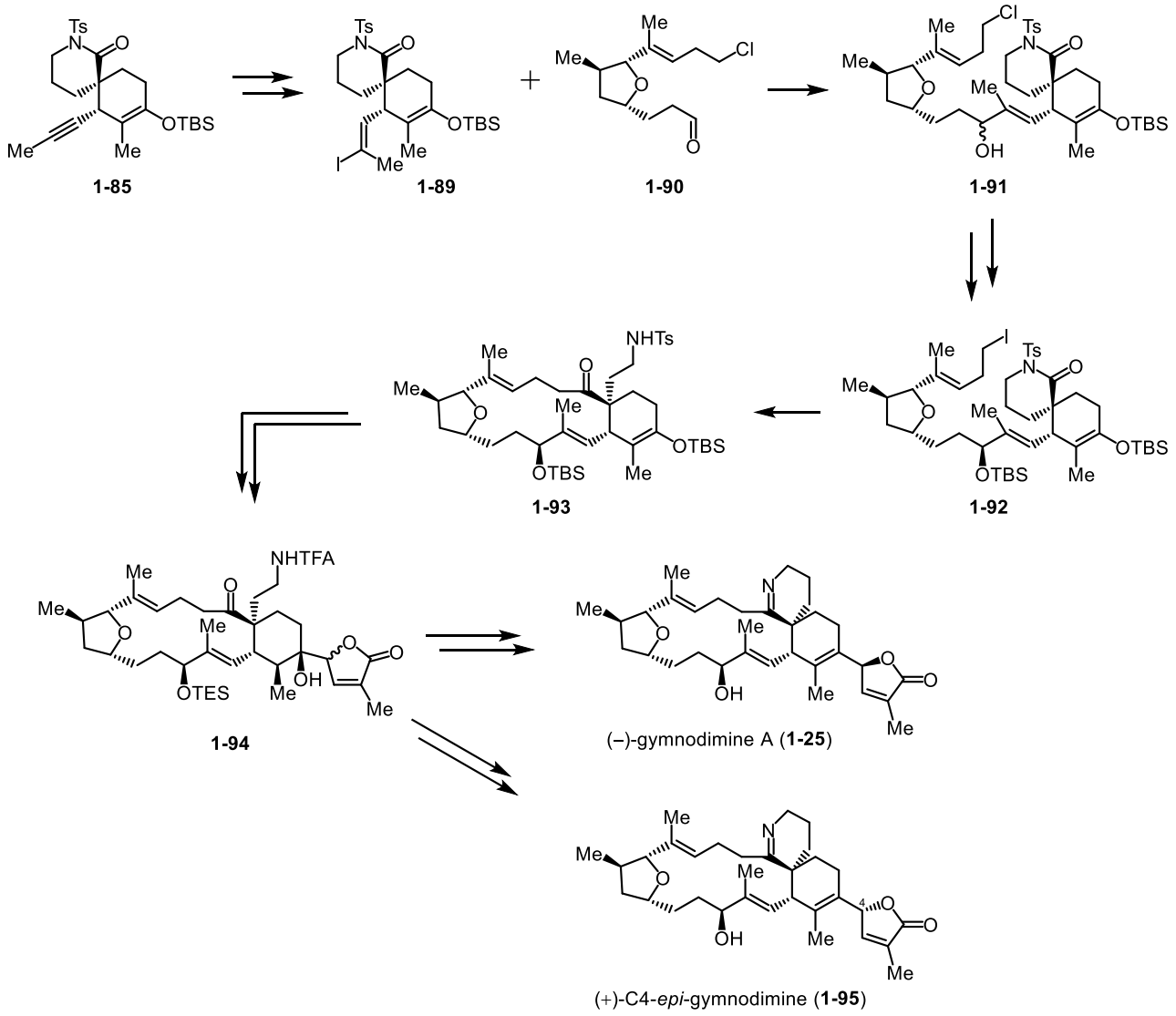
1-3-5. Total Synthesis of Gymnodimine A by the Romo group

To date, the total synthesis of gymnodimine A (**1-25**) was only achieved by the Romo group (Scheme 1-8).[27] The key reactions were the Diels-Alder reaction to form the spirocyclic imine and macrocyclization using NHK coupling. Diene **1-82** was reacted with α-methylene lactam **1-83** in the presence of chiral ligand **1-84** and a copper catalyst to produce Diels-Alder cycloadduct **1-85** in an enantioselective manner. Fragment coupling between spirolactam **1-85** and iodide **1-86** via a Barbier reaction followed by functional-group-inter-conversion afforded **1-87** in 92% yield. However, numerous attempts toward macrocyclization of **1-85** gave no cyclic product.

Based on the above results, they re-designed the approach for the macrocyclization (Scheme 1-9). First, the intermolecular NHK reaction connected between **1-89**, derived from **1-85**, and **1-90** to produce allylic alcohol **1-91** in 97% yield. Barbier-type macrocyclization of iodide **1-92**, prepared from **1-91**, gave **1-93** (~60% yield), which was converted to **1-94** via several steps. Common intermediate **1-94** was finally transformed to gymnodimine A (**1-25**) and C4-*epi*-gymnodimine A (**1-95**), thereby completing the first total synthesis of gymnodimine A and the derivative.



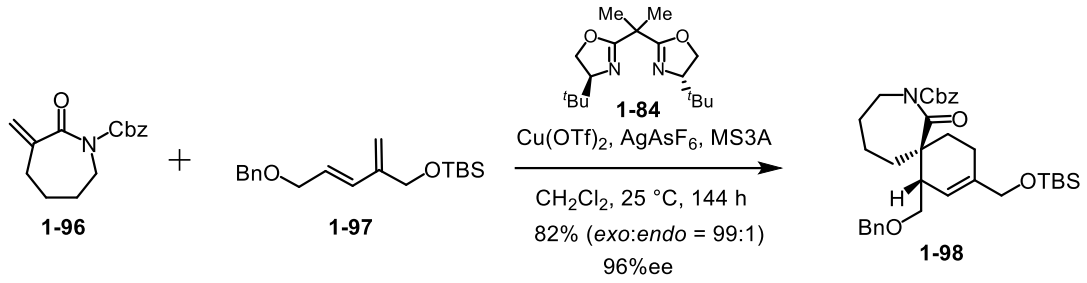
Scheme 1-8. Spirocyclic imine formation via asymmetric Diels-Alder reaction by the Romo group.



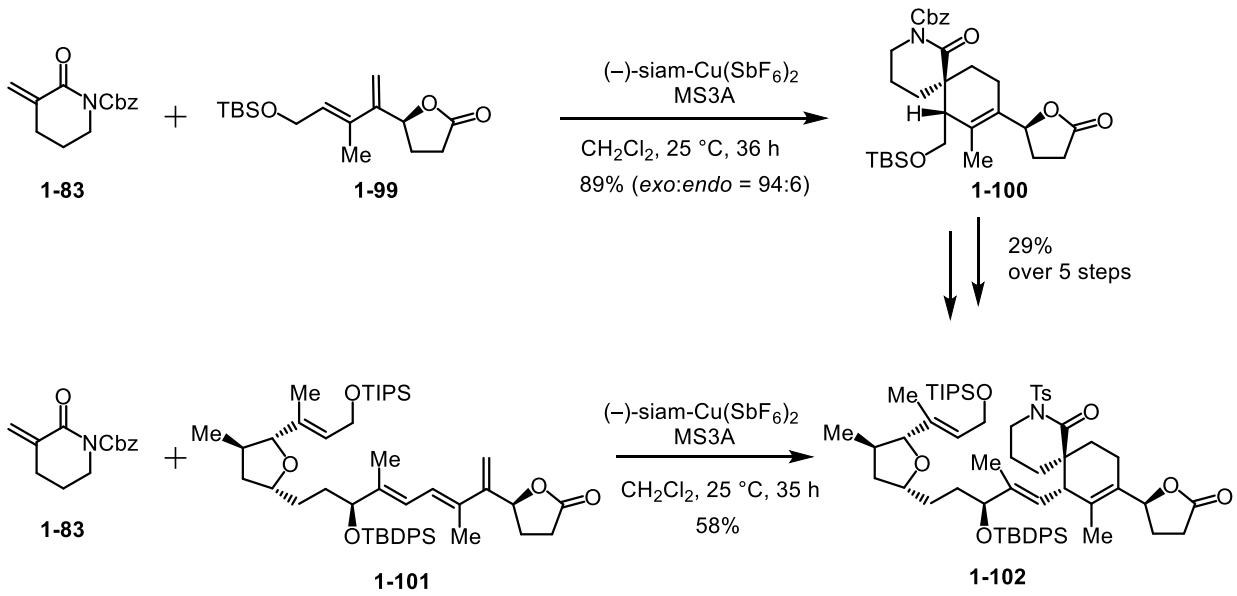
Scheme 1-9. Total synthesis of gymnodimine A by the Romo group.

1-3-6. Synthetic Studies of PnTXs and GYMs by the Ishihara and Murai group

The Ishihara and Murai group extensively studied toward the total synthesis of spirocyclic imine toxins containing 6,7- or 6,6-spirocyclic imine unit.[28] They developed an enantio-/diastereoselective Diels-Alder reaction of an α-methylene lactam with an acyclic di- or trisubstituted diene using a chiral Lewis acid catalyst for the construction of the 6,7- or 6,6-spirocyclic imine unit (Scheme 1-10, 1-11). The high *exo*-selectivity was rationalized by the steric repulsion between the bulky ligand and the dienes.



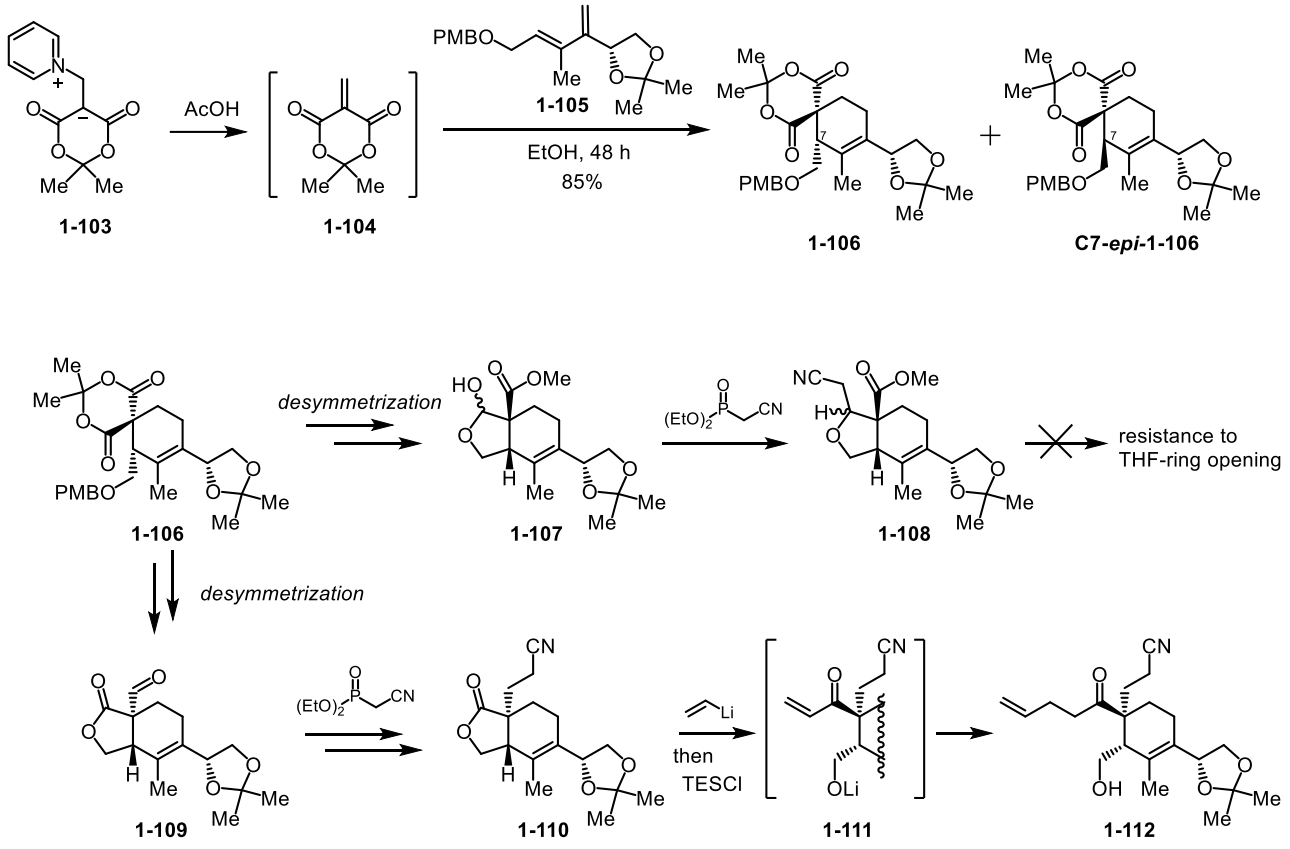
Scheme 1-10. Enantioselective Diels-Alder reaction by the Ishihara and Murai group.



Scheme 1-11. Synthetic studies of gymnodimines by the Ishihara and Murai group.

1-3-7. Synthetic Studies of GYMs by the White group

The White group reported the construction of the spirocyclic imine moiety of gymnodimines by a process including a Diels-Alder reaction followed by desymmetrization (Scheme 1-12).[29] The Diels-Alder reaction of unstable methylene derivative **1-104**, prepared from zwitterion **1-103** in situ, with diene **1-105** gave adducts **1-106** and **C7-*epi*-1-106** in a 1.2:1 ratio. According to their initial desymmetrization strategy, lactol **1-107** was successfully obtained from **1-106** in 3 steps. After Horner-Emmons reaction, however, intramolecular Michael addition was occurred to give tetrahydrofuran **1-108**, which showed low reactivity under THF-ring-opening conditions. Therefore, they employed an alternative desymmetrization process to form lactone **1-109**, which was subjected to a Horner-Emmons reaction and the subsequent reduction to produce **1-110**. The vinylation of the lactone followed by a conjugate addition of vinyllithium to the intermediate **1-111** produced cyanoketone **1-112**.



Scheme 1-12. Synthetic studies of gymnodimines by the White group.

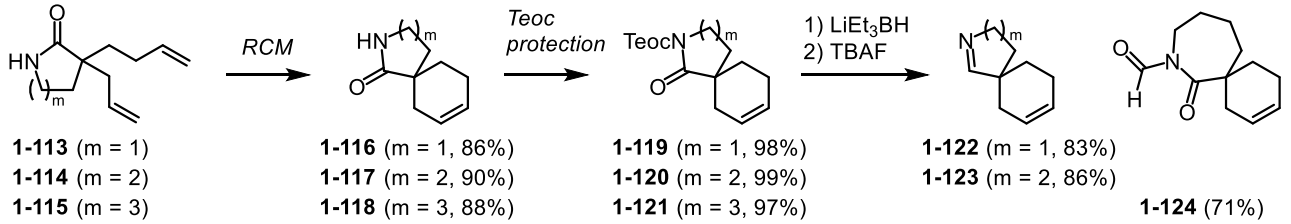
1-3-8. Synthetic Studies for Spirocyclic Imine Structure by the Brimble group

The Brimble group reported several methods for the preparation of spirocyclic imine moieties.[30]

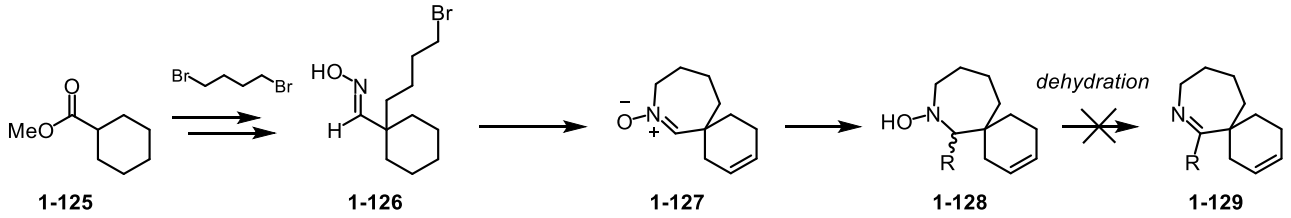
First, simple spirocyclic imines **1-122**–**124** were prepared from double alkylated lactams **1-113**–**115** using a process including ring-closing metathesis/lactam reduction (Scheme 1-13). It was noted that the carbonyl group of Teoc-protected 7-membered lactam **1-121** showed low reactivity in hydride reduction to give only *N*-formyl lactam **1-124**, which was rationalized by the steric hindrance due to the transannular interactions of the 7-memberd ring.

The Brimble group also attempted to form a cyclic imine via cyclic hydroxylamine **1-128** (Scheme 1-14). Treatment of **1-126** with K_2CO_3 in aqueous acetone under microwave-irradiated conditions gave unstable spironitron **1-127**, which was highly reactive to Grignard reagents and organolithium reagents to give adducts (**1-128**) in good yields. However, the dehydration of **1-128** was difficult to give none of **1-129**.

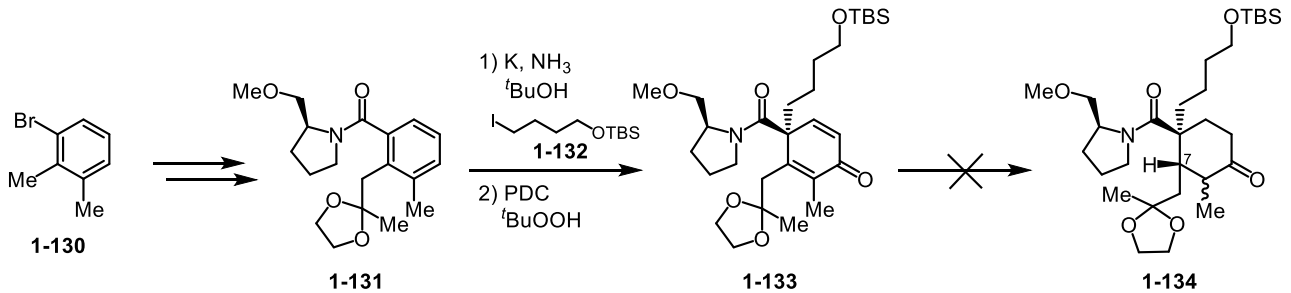
The Brimble group attempted to construct a cyclohexene framework related to spirolide using a Birch reduction strategy (Scheme 1-15). Reduction of chiral benzamide **1-131** under Birch conditions and the subsequent substitution of **1-132** constructed a quaternary center diastereoselectively. Then, allylic oxidation with PDC/^{t}BuOOH afforded enone **1-133**. However, the stereoselective hydrogenation of **1-133** was unsuccessful to give none of **1-134**.



Scheme 1-13. Synthesis of spirocyclic imines using RCM/reduction strategy by Brimble.

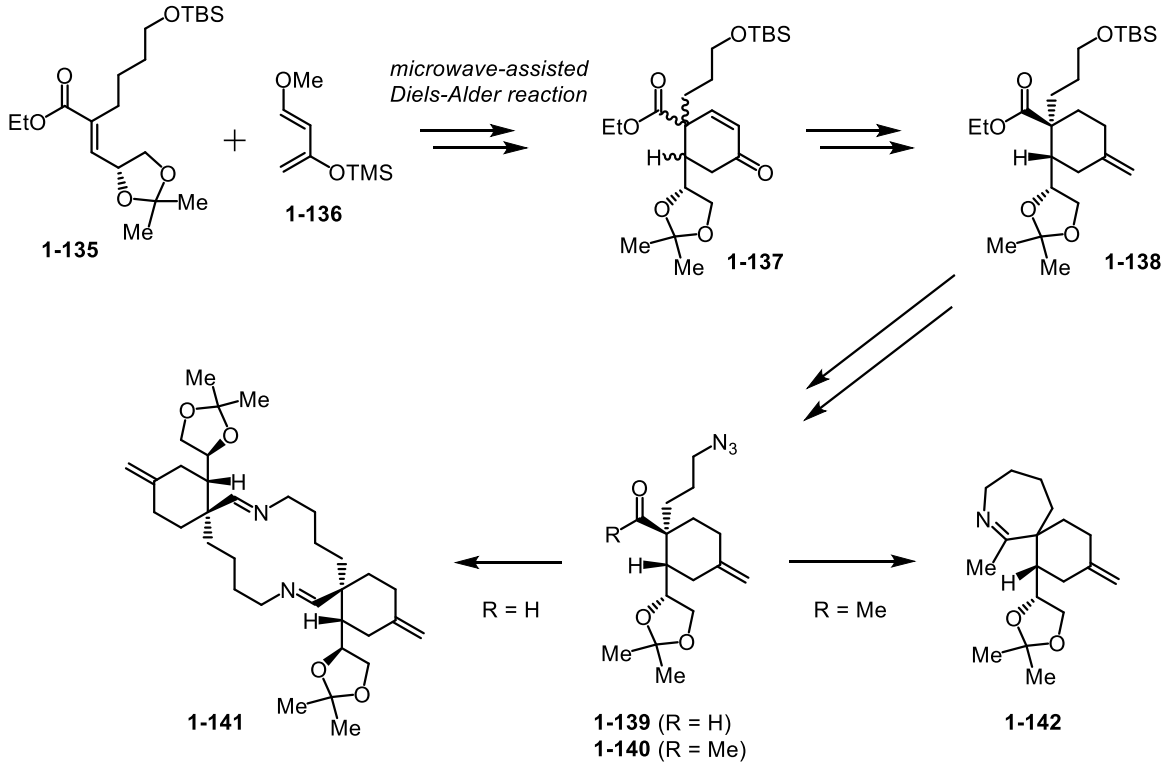


Scheme 1-14. Attempted synthesis of spirocyclic imines using a hydroxylamine strategy by Brimble.



Scheme 1-15. Synthetic studies of spirocyclic imines using Birch reduction by Brimble.

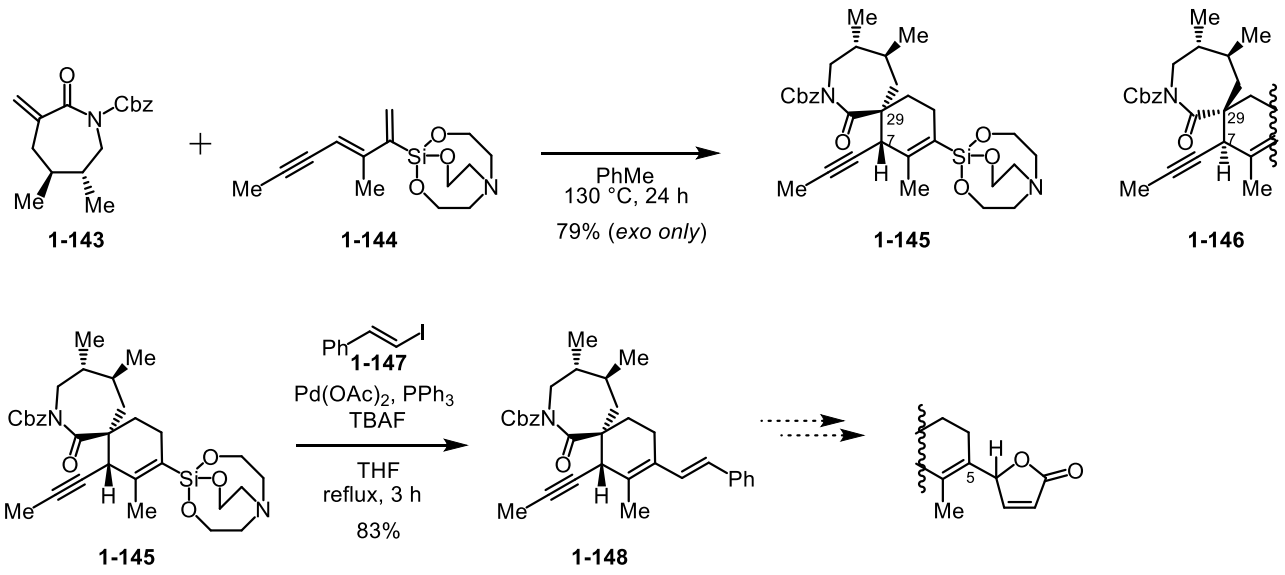
In 2011, Brimble and co-workers reported a Diels-Alder reaction strategy (Scheme 1-16). Microwave-assisted Diels-Alder reaction of dienophile **1-135** and diene **1-136** produced a 5:2:1 diastereomeric mixture of **1-137**, which was transformed to **1-38** (22% from **1-135**) via several steps including separation from diastereomers. Cyclohexane **1-138** has the desired three contiguous stereocenters corresponding to natural spirocyclic imine toxins. Interestingly, when they examined to construct 6,7-spirocyclic imine from aldehyde **1-139** using Staudinger reaction, dimeric product **1-141** was only produced. On the other hand, ketone **1-140** gave 6,7-spirocyclic imine **1-142** in good yield.



Scheme 1-16. Synthetic studies of spirocyclic imines using a Diels-Alder reaction strategy by Brimble.

1-3-9. Synthetic Studies for Gymnodimines by Murata group

The Murata group has studied toward the total synthesis of spirolides. In the course of the study, they reported the diastereoselective construction of the spirocyclic imine unit by Diels-Alder reaction using sterically hindered diene **1-144** (Scheme 1-17).[31] The bulky silatrane substituted diene **1-144** was reacted with **1-143** in toluene at 130 °C to provide desired cycloadduct **1-145** and the isomer **1-146** in a ratio of 10:3 with exclusive *exo*-selectivity. Cycloadduct **1-145** has an advantage that it is directly available as a Hiyama coupling substrate. Indeed, the coupling between vinylsilane **1-145** and vinyliodide **1-147** under general Hiyama coupling conditions produced conjugated diene **1-148** in good yield.

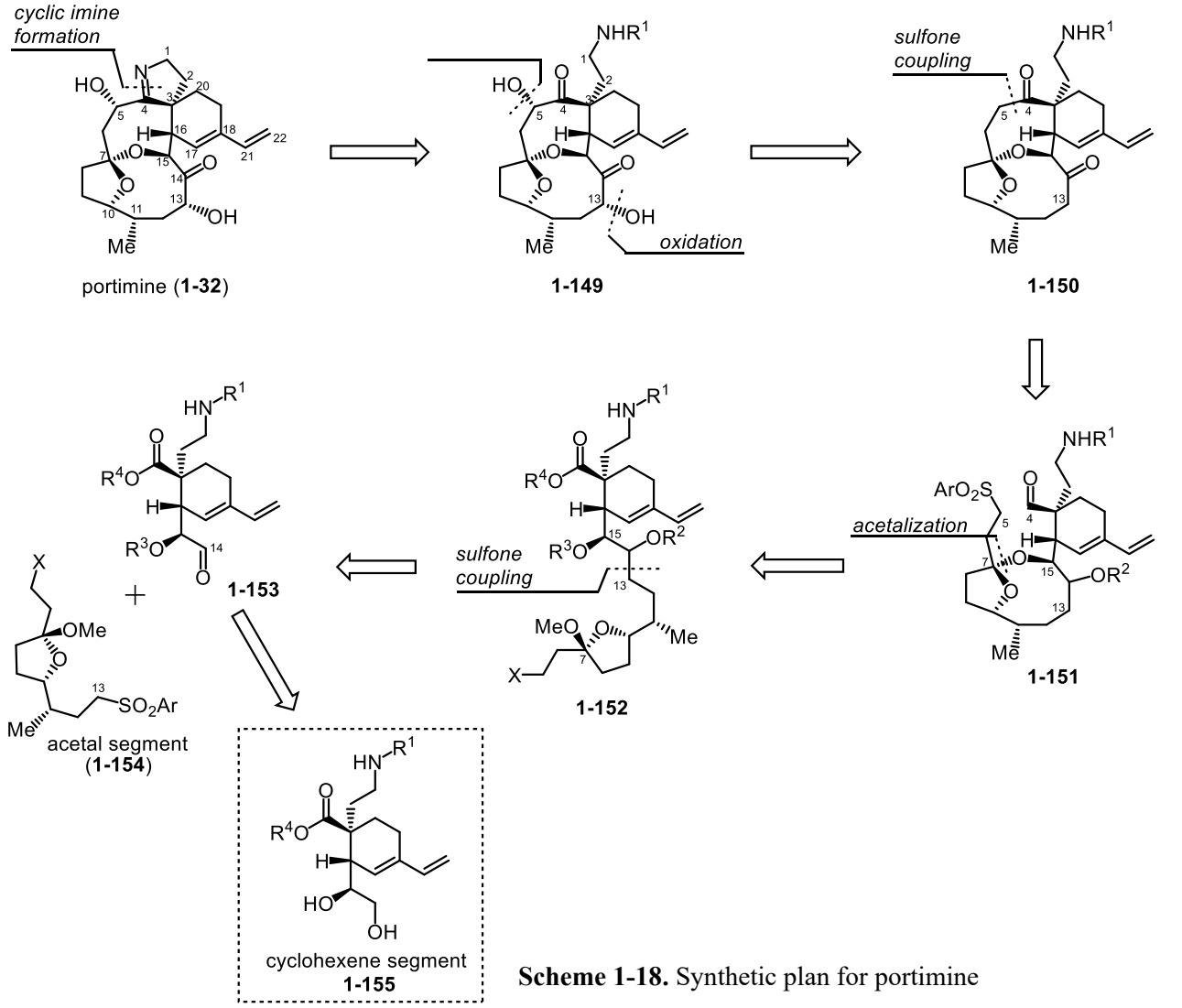


Scheme 1-17. Synthetic studies of gymnodimines using a Diels-Alder reaction strategy by the Murata group.

1-4. Plan for the Total Synthesis of Portimine

As described above, prompted by the unique structure and the unusual bioactivity of portimine (**1-32**), which has yet to be elucidated, the author decided to develop an efficient synthesis of portimine (**1-32**) to obtain sufficient quantities for biological studies.

First, the author planned to synthesize **1-32** from cyclohexene segment **1-155** and acetal segment **1-154** by a convergent route, illustrated in Scheme 1-18. The cyclic imine moiety of **1-32** was scheduled to be formed from **1-149** at the final stage of the synthesis. Two hydroxy groups at C5 and C13 of **1-149** would be installed by the stereoselective α-oxidation of diketone **1-150**. The dioxatricyclo[7.5.1.^{11,4}]hexadecane framework was planned to construct as follows: (i) formation of the C4-C5 bond of **1-51** by intramolecular sulfone coupling, (ii) acetal formation between C7 and the hydroxy group at C15 of **1-152**, and (iii) formation of the C13-C14 bond by the sulfone coupling between **1-153** and **1-154**. Aldehyde **1-154** would be prepared from cyclohexene segment **1-155**, of which the three contiguous stereocenters at C-3, C15 and C16 include synthetic challenges in their construction.



Scheme 1-18. Synthetic plan for portimine

1-5. The Objective of the Dissertation Work

In the dissertation work, the author has studied the development of an efficient synthetic route to portimine, a cytotoxic marine natural product isolated from the dinoflagellate *Vulcanodinium rugosum*. The objective of the work was the establishment of the synthesis of the cyclohexene segment (**1-155)** of portimine, and the synthesis was achieved by a new methodology developed by the author.

As detailed in Section 1-3, successful synthesis of related cyclohexene moieties of other spirocyclic imine toxins have been reported by many research groups to date. The key reactions for the cyclohexene ring construction are mainly classified into four types: (i) Diels-Alder reaction,[5,19,20,26,28,29,30,31d] (ii) ring-closing olefin metathesis (RCM),[30b] (iii) Claisen rearrangement/aldol cyclization[23] and (iv) intramolecular alkylation of cyano-epoxides.[21] However, for the construction of 5,6-spirocyclic imine moieties, corresponding to the key structure of portimine, few method was reported except the RCM approach.

Thus, the author designed cyclohexene segment **1-155** as a synthetic intermediate appropriate for the connection with acetal segment **1-154** as well as for the 5,6-spirocyclic imine formation (Figure 1-1). In contrast to the above described known approaches, cyclohexene segment **1-155** was planned to be synthesized from a simple cyclohexene derivative by a new strategy that achieves a facile construction of the three contiguous stereocenters at C-3, C15 and C16.

In Chapter 2, efforts toward the discovery of an effective route to **1-155** is described. Chapter 3 describes the details of the development of the synthetic route to **1-155** based on conjugate addition, dihydroxylation and reductive amination.

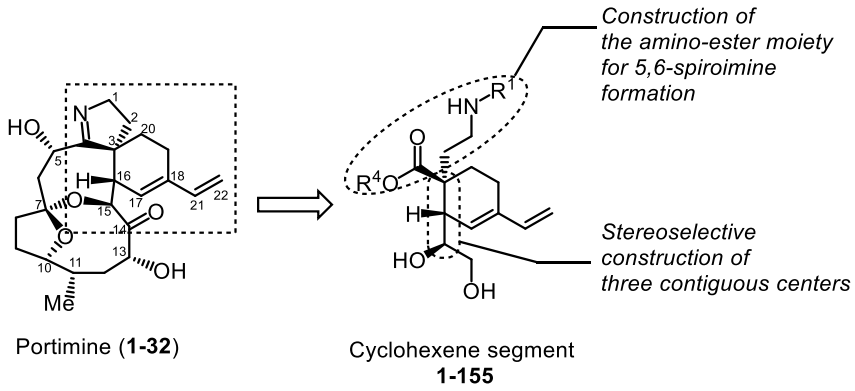


Figure 1-4. The challenges in the cyclohexene segment of portimine.

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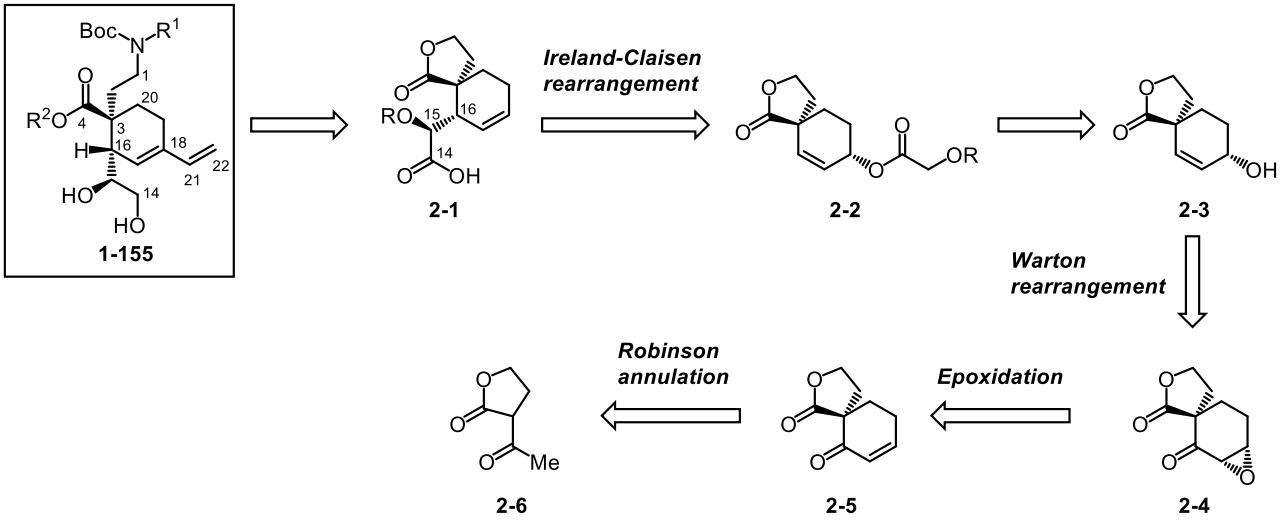
Chapter 2
First Generation Synthetic Approach for the Cyclohexene Segment

2-1. Initial Plan for the Synthesis of the Cyclohexene Segment from Cyclohexenone 2-5

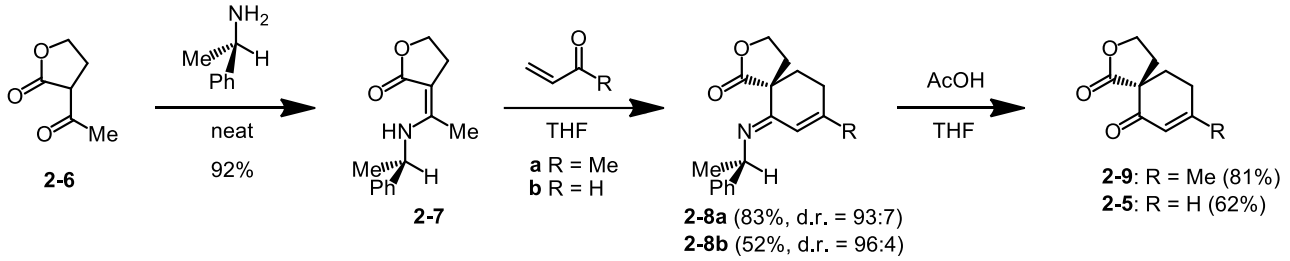
As described in Chapter 1, the author first intended to synthesize cyclohexene segment **1-155** having three contiguous stereogenic centers including a quaternary carbon. Although several successful syntheses of the corresponding cyclohexene region were reported, the author decided to explore a new synthetic route to the segment with the goal of high efficiency in my mind.

In the initial synthetic plan (Scheme 2-1), segment **1-155** would be derived from cyclohexene **2-1** via the attachment of an amino group at C1 and a vinyl group at C18. The C14-C15 unit of **2-1** was designed to be installed stereoselectively by the Ireland-Claisen rearrangement[1] of α-alkoxy ester **2-2**. The ester would be derived from alcohol **2-3**, which was expected to be produced from epoxyketone **2-4** by Warton rearrangement. The synthesis of **2-4** relied on epoxidation of cyclohexenone **2-5**, which would be accessible from easily available keto-lactone **2-6** by Robinson annulation.[2] Thus, the author envisaged an early-stage construction of the cyclohexene framework of **1-155** with expecting a stereoselective installation of the C14-C15 unit within the cyclic framework at later stage.

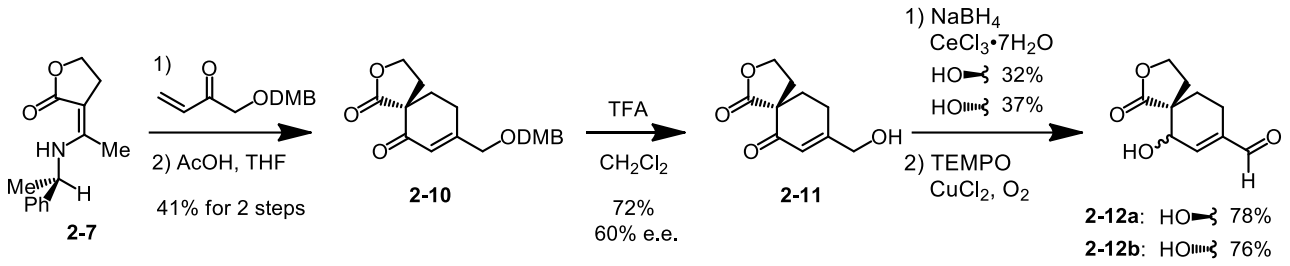


Scheme 2-1. Initial synthetic plan for cyclohexene segment **1-155**

It should be noted that the asymmetric synthesis of **2-5** using enantioselective Robinson annulation has already been reported by Felk (Scheme 2-2).[3] Furthermore, Christoffers[4] reported an advanced synthesis of compound **2-11** using the same methodology as that of Felk and a few derivatizations from **2-11** using Luche reduction[5] and TEMPO oxidation[6] (Scheme 2-3). Since the enantioselective preparation of **2-5** has thus been established, the author decided to focus on the diastereoselective construction of C15 and C16 based on the C3 stereochemistry using racemic **2-5**.



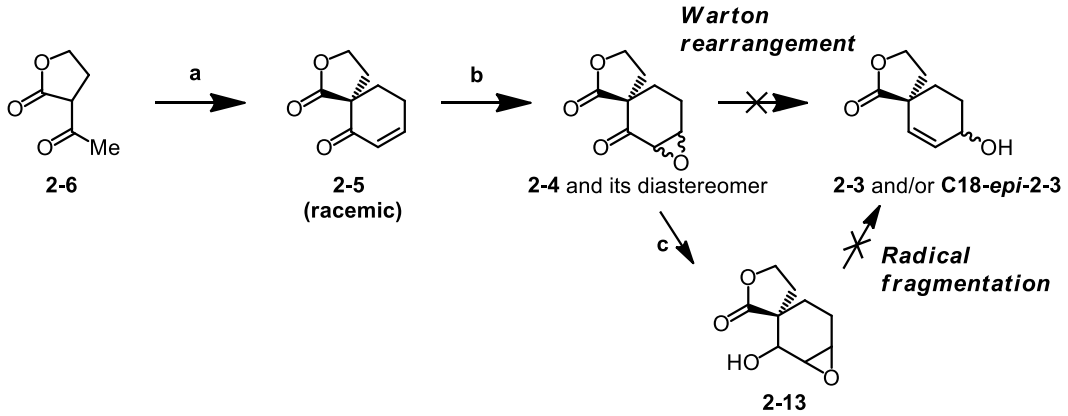
Scheme 2-2. Asymmetric synthesis of cyclohexenones **2-5** and **2-9** by the Felk group



Scheme 2-3. Asymmetric synthesis of cyclohexenone **2-10** and its derivatization by the Christoffers group

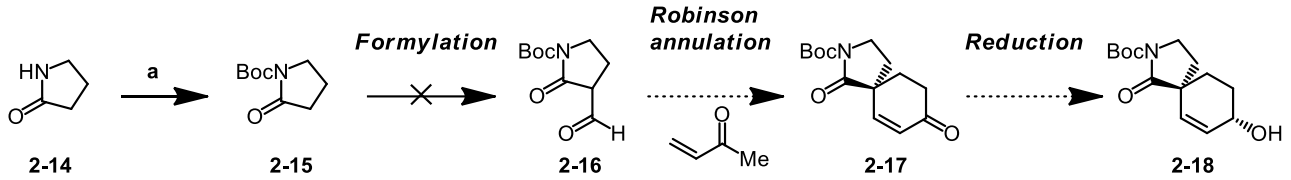
2-2. Synthesis of Cyclohexenone 2-5 and Its Attempted Conversion to Alcohol 2-3

According to the above plan, cyclohexenone **2-5** was first prepared in racemic form from **2-6** by the one-pot Robinson annulation with acrolein in the presence of DBU (62%) (Scheme 2-3). Exposure of **2-5** to *t*-BuOOH and DBU smoothly produced a mixture of α,β-epoxyketone **2-4** and its diastereomer (75%). Although one of the epoxyketones was given as a major product (7:1), the stereochemistry was unknown. The major and minor epoxyketones were separately reacted with hydrazine monohydrate to afford highly polar intermediates, which were then treated with AcOH-MeOH under reflux conditions. As a result, a trace amount of the rearranged product (**2-3** and/or its C18 epimer) was obtained from the major epoxyketone, while no rearranged product was detected from the minor epoxyketone. The low yield of the Warton rearrangement was rationalized by the suspected formation of a stable *N*-*N* bridge between the two carbonyl groups of the substrates. To improve the yield of the desired **2-3**, the radical fragmentation of epoxyalcohol **2-13** was then planned. After the reduction of the above major epoxyketone under the Luche conditions,[5] the resulting **2-13** was subjected to thionoesterification. However, due to lability of **2-13** against strong basic conditions, no thionoester of **2-13** was produced, and only a complex mixture was obtained. Therefore, the radical fragmentation of **2-13** was abandoned.



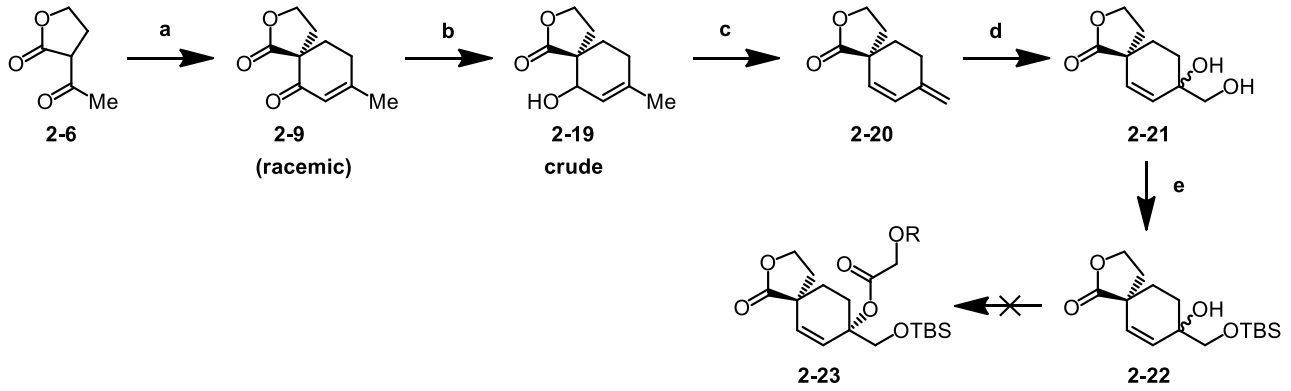
Scheme 2-4. An attempt to prepare allylic alcohol **2-3**. Reagents and conditions: (a) acrolein, DBU, PhH, 80 °C, 30 min then MsCl, 24 °C, 10 h, 62%; (b) *t*-BuOOH, DBU, CH_2Cl_2, 21 °C, 1.5 h, 75% (d.r. = 7:1); (c) $NaBH_4$, MeOH, 0 °C, 1 h

The author also attempted to prepare cyclohexenol **2-18** from formate **2-16** via Robinson annulation followed by reduction (Scheme 2-5). Cyclohexenol **2-18** was expected to be an alternative intermediate having the same function as that of **2-3** for **1-155**. However, the formylation of *N*-Boc-γ-lactam **2-15**, prepared from 2-pyrrolidinone **2-14** (91%), was failed due to the instability of formate **2-16** produced even under milder conditions.



Scheme 2-5. An attempt to construct cyclohexenol **2-18** via Robinson annulation followed by reduction. Reagents and conditions: (a) Boc_2O, DMAP, CH_3CN, 21 °C, 2 h, 91%.

Next, the author envisioned that methyl-substituted cyclohexenone **2-9** may be converted to diene **2-20** via the 1,4-elimination of allylic alcohol **2-19** and that the diene would undergo dihydroxylation at the exomethylene group to give diol **2-21**, which would be transformed to glycolate **2-23**, a substrate ester for the next Ireland-Claisen rearrangement step (Scheme 2-6).



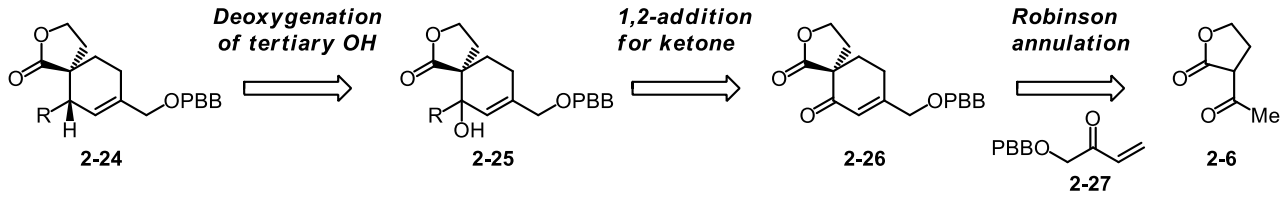
Scheme 2-6. Attempt to synthesize glycolate ester **2-23**. Reagents and conditions: (a) MVK, DBU, toluene, 80 °C, 1 h, then MsCl, 21 °C, 71%; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, -78 to -10 °C, 30 min; (c) MsCl, Et_3N, CH_2Cl_2, 21 °C, 8% isolated yield from **2-9**; (d) OsO_4, NMO, acetone-H_2O, 21 °C, 24 h, 80%, (a 1:1 mixture of diastereomer); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 21 °C. 30 min, quant.

Racemic **2-9** was prepared from **2-6** and methyl vinyl ketone by a one-pot procedure (71%). Enone **2-9** was reduced under Luche conditions[5] to give **2-19**. The dehydration of **2-19** by 1,4-elimination was extensively examined with several sulfonylation reagents (MsCl, TsCl, TfCl and Tf_2O). Although most of the sulfonylation reagents produced only a complex mixture including regioisomers of **2-20** and no detectable amount of **2-20**, only a combination of MsCl and Et_3N provided **2-20** in low overall yield (8% over 2 steps). Dihydroxylation of **2-20** was regioselectively afforded **2-21** (80%), which was protected as TBS ether **2-22**

(~100%). However, the sterically hindered tertiary hydroxyl group of **2-22** was inert under esterification conditions to give no **2-23**. Due to the difficulty in esterification/sulfonilation of cyclohexenol intermediates, the author abandoned the initial route based on the Ireland-Claisen rearrangement using a cyclohexenyl glycolate ester, and, therefore, revised the approach to **1-155** as described in the next section.

2-3. Alternative Plan for the Synthesis of the Cyclohexene Segment using Cyclohexenone 2-26

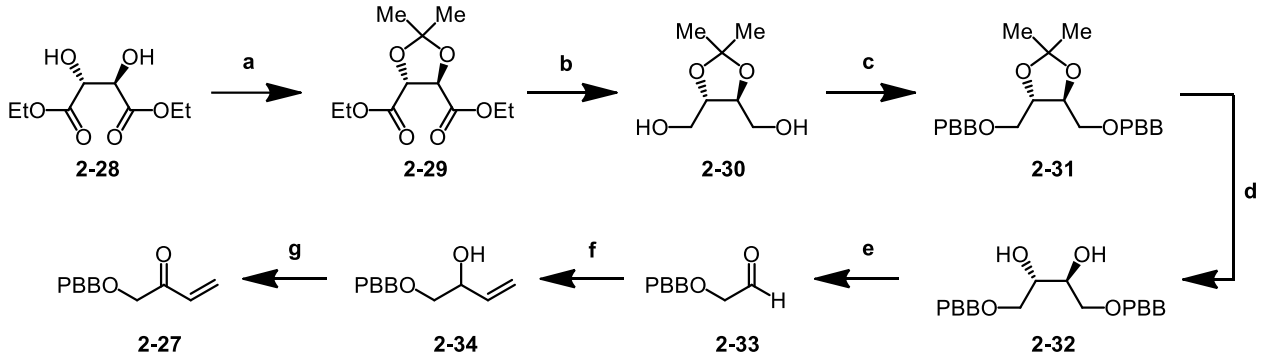
As an alternative plan for the construction of cyclohexene segment **1-155**, the author employed a process including the formation of advanced cyclohexenone intermediate **2-26**, the 1,2-addition of an appropriate C14-C15 unit to **2-26** and the deoxygenation/reduction of the resulting tertiary alcohol **2-25** to give key intermediate **2-24** (Scheme 2-7). The successful formation of **2-24** strongly depended on the regio- and stereo-selectivity of the latter reaction step. Cyclohexenone intermediate **2-26** would be prepared from **2-6** and **2-27** by Robinson annulation in expecting the future chiral synthesis by Christoffers' procedure.[4]



Scheme 2-7. Plan for the construction of key intermediate **2-24** via a 1,2-addition/deoxygenation process.

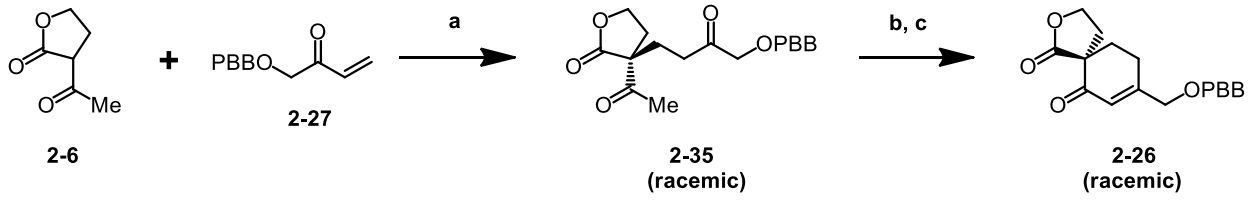
2-4. Synthesis of Cyclohexenone 2-26 and Its Attempted Conversion to 2-24.

The preparation of Michael acceptor **2-27** is shown in Scheme 2-8. Diethyl-L-tartrate **2-28** was first converted to isopropylidene acetal **2-29**, which was reduced with $LiAlH_4$ to give diol **2-30**. Protection of the resulting alcohol with 4-bromobenzyl bromide (86% for 3 steps) followed by removal of isopropylidene acetal under acidic condition produced diol **2-32** (84%). The diol moiety of **2-32** was oxidatively cleaved with $NaIO_4$ to afford aldehyde **2-33**, which was reacted with vinyl magnesium chloride to form allyl alcohol **2-34** (43% for 2 steps; conversion yield). After oxidation of alcohol **2-34** with DMPI, the resulting vinyl ketone **2-27** was used in the next reaction without purification due to the instability of **2-27**.



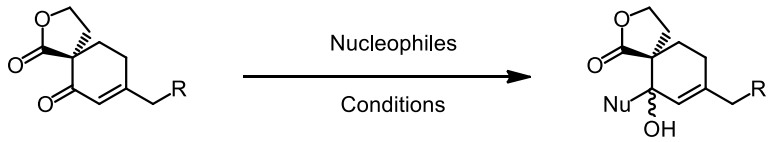
Scheme 2-8. Preparation of Michael acceptor **2-27**. Reagents and conditions: (a) 2,2-dimethoxypropane, PTS·H_2O, PhH, reflux, 4 h; (b) $LiAlH_4$, THF, 40 °C, 5 h; (c) PBBBr, NaH, KI, THF-DMF, 21 °C, overnight, 86% from **2-28**; (d) THF-2 mol/L HCl, 40 °C, overnight, 84%; (e) $NaIO_4$, THF-H_2O, 21 °C, 2.5 h; (f) vinyl magnesium chloride, THF, -78 °C, 2 h, 43% from **2-32**; (g) DMPI, $NaHCO_3$, CH_2Cl_2, 21 °C, 1 h.

The synthesis of β-alkoxymethyl cyclohexenone **2-26** in racemic form was achieved from **2-6** and **2-27** by a stepwise Robinson annulation (Scheme 2-9): (i) Michael addition of **2-6** to vinyl ketone **2-27** gave diketone **2-35** (76% from **2-34**), which was subjected to (ii) an intramolecular aldol reaction with DBU followed by (iii) dehydration with TFAA in pyridine to produce cyclohexenone **2-26** (78% from **2-35**).



Scheme 2-9. Synthesis of cyclohexenone **2-26**. Reagents and conditions: (a) Et_3N, $(CH_2Cl)_2$, 40 °C, 1 h, 76% from **2-34**; (b) DBU, PhH, reflux, 10 min; (c) TFAA, pyridine, 100 °C, 4 h, 78% from **2-35**.

With the desired advanced cyclohexenone **2-26** in hand, the author next examined the 1,2-addition reaction of the enone system with several nucleophiles (Table 2-1). After extensive investigations using **2-26** and the above described **2-9**, it was found that reactive organolitium or Grignard reagents were smoothly added to the sterically hindered ketone groups of the subtrates (Entry 1-3). On the other hand, a methylene Wittig reagent and a Horner-Wadsworth-Emmons reagent induced no reaction, which was attributable to the low reactivity of these phosphonium ylide and phoshonate anion (Entry 4,5). Interestingly, the lithium acetylide derived from *tert*-butyldiphenylsilyl 2-propynyl ether or vinyl magnesium bromide produced an adduct as a single diastereomer, of which the stereochemistry was unknown, in moderate yield (Entry 2,3), while the reaction of **2-26** with lithium enolate from ethyl acetate afforded a 1:1 diastereomeric mixture of adduct **2-36a** (Entry 1).



2-9 : R = -H
2-26 : R = -OPBB

2-35 : R = -H
2-36 : R = -OPBB

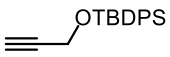
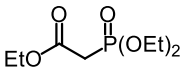
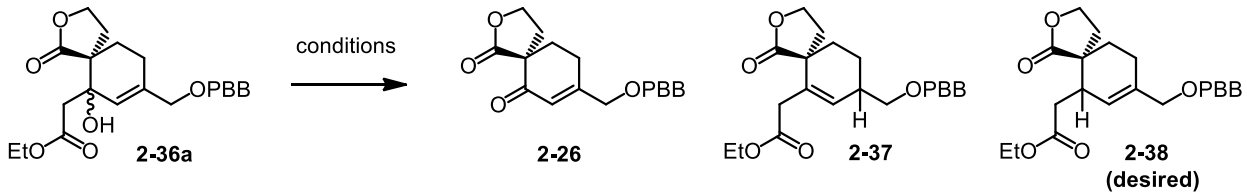
Entry	R	Nucleophiles	Conditions	Yield
1	-OPBB	EtOAc	LDA, THF, -78 °C	**2-36a** crude (d.r. = 1:1)
2	-OPBB		BuLi, THF, -78 °C	**2-36b** 47% (a single isomer)
3	-H		THF, -10 °C	**2-35c** 40% (a single isomer)
4	-H	CH_3PPh_3Br	*t*-BuOK, THF, 21 °C	N.R.
5	-H		NaH, THF, 21 °C	N.R.

Table 2-1. The 1,2-addition of **2-9** and **2-26** with several nucleophiles.

The subsequent deoxygenation step was examined with **2-36a**, because the γ,δ-unsaturated ester was expected to generate an α,β,γ,δ-unsaturated ester, of which the α,β-unsaturated bond could undergo a conjugate reduction to give the desired **2-38** (Table 2-2). Therefore, adduct **2-36a** was first treated with NaOEt in EtOH in expectation of E1cb reaction. However, the reaction only gave enone **2-26** due to retroaldol reaction (Entry 1). The standard mesylation/elimination process of **2-36a** resulted in no reaction, which was similar to the result of the above mentioned attempted esterification of **2-22**. The author next applied a Lewis acid-mediated organosilane reduction. When alcohol **2-36a** was treated with Et_3SiH in the presence of BF_3•OEt_2, the reduction smoothly proceeded. However, the reduction was found to give only a regioisomer (**2-37**) of the desired **2-38** (Entry 3). The disappointing regioselectivity of the hydride addition may be attributable to the steric hindrance around C16. Since the C18 center, the other reactive site of the

allyl cation generated from **2-36a** with BF_3•OEt_2, has no significant substituent around it, relatively hindered Et_3SiH is accessible to C18 rather than to C16.



Entry	Conditions	Yield
1	NaOEt, EtOH, 21 °C	only **2-26**
2	MsCl, Et_3N or NHMDS	N.R.
3	Et_3SiH, BF_3•OEt_2, CH_2Cl_2	only **2-37**

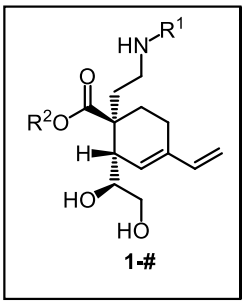


Table 2-2. Attemption of removal tertiary hydroxyl group.

2-5. Conclusion

The author initially planned to construct cyclohexene segment **1-155** of portimine **1-32** from α-acetyl-γ-butyrolactone **2-6** by a process including Robinson annulation to form the cyclohexene ring and Ireland-Claisen rearrangement or 1,2-addition to the enone system for the installation of C14-C15 unit at C16. In Ireland-Claisen route, however, the difficulty in the conversion of cyclohexenones **2-5** and **2-9** to esters **2-3** and **2-23**, respectively, was found. On the other hand, the 1,2-addition approach provided an easy introduction of nucleophiles to ketone at C16 of **2-9** and **2-26** even in moderate yields. However, the subsequent deoxygenation of tertiary hydroxyl group at C16 gave only unsatisfactory results. The difficulties may be attributable to the instability or uncontrollable reactivity of the cyclohexenol unit embedded in the spirolactone framework, which included in the routes the author examined. Thus, the author decided to design a new synthetic route to cyclohexene segment **1-155** from a different starting material excluding the generation of the problematic cyclohexenol moiety. The synthesis of **1-155** based on the new route is described in the next chapter.

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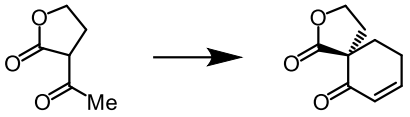
Experimental sections

General methods

All air sensitive reactions were carried out under argon in oven-dried glassware using standard syringe, cannula and septa techniques. Dry solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F254, 0.25 mm in thickness or Wako, silica gel 70 F254, 0.25 mm in thickness). 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) as a stationary phase. Melting points were measured on an ASONE ATM-02 without calibration. Infrared spectra (IR) were measured on a JASCO FT/IR-4700 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) or a JEOL JNM-ECA 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of tetramethylsilane (0 ppm for ^{1}H NMR in $CDCl_3$) or the respective solvent (^{1}H NMR: 7.26 ppm in $CDCl_3$; ^{13}C NMR: 77.0 ppm in $CDCl_3$) as the internal standard. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Coupling constants (J) are reported in Hz. High resolution mass spectra (HRMS) were measured on a JEOL JMS-T100GCV (under field desorption [FD] conditions) double focusing magnetic sector mass spectrometer.

Compound 2-5

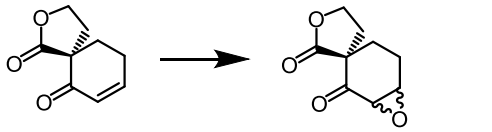


2-6 **2-5 (racemic)**

To a solution of **2-6** (302.3 mg, 2.36 mmol) in benzene (15.0 mL) was added DBU (0.352 mL, 2.36 mmol) and acrolein (90% monomer, 0.262 mL, 3.54 mmol) at 0 °C, and the mixture was stirred for 15 min at 24 °C. Then, the mixture was warmed to 80 °C and the mixture was stirred for 30 min. To the mixture was added MsCl (0.365 mL, 4.72 mmol) at 24 °C, and the mixture was stirred for 10 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (30 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2.5) to give **2-5** (241.3 mg, 1.45 mmol, 62%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (1H, ddd, *J* = 5.2, 7.0, 13.6 Hz), 2.14 (1H, td, *J* = 8.6, 12.9 Hz), 2.33-2.43 (1H, m), 2.47 (1H, ddd, *J* = 5.2, 6.8, 13.7 Hz), 2.72 (1H, ddd, *J* = 4.1, 6.8, 12.9 Hz), 2.76-2.85 (1H, m), 4.33-4.43 (2H, m), 6.07 (1H, td, *J* = 2.0, 10.2 Hz), 7.10 (1H, td, *J* = 4.1, 10.2 Hz).

Compound 2-4 and its diastereomer



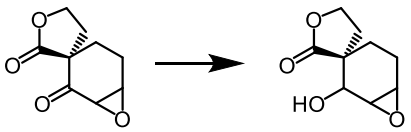
2-5 **2-4** and its diastereomer

To a solution of **2-5** (106.6 mg, 0.6415 mmol) in CH_2Cl_2 (6.4 mL) was added DBU (0.144 mL, 1.92 mmol) and *t*-BuOOH (5.5 mol/L in decane, 0.350 mL, 3.85 mmol) at 0 °C, and the mixture was stirred for 1.5 h at 21 °C. The reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2.5 : 1) to give **2-4** as a major diastereomer (77.4 mg, 0.4249 mmol, 66%) and its minor diastereomer (10.6 mg, 0.05819 mmol, 9%) as a colorless oil.

2-4 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49-1.61 (1H, m), 1.93 (1H, dddd, *J* = 0.7, 4.5, 13.7, 15.2 Hz), 2.11 (1H, td, *J* = 8.6, 13.1 Hz), 2.38-2.52 (2H, m), 2.59 (1H, dt, *J* = 4.4, 13.7 Hz), 3.32 (1H, d, *J* = 3.7 Hz), 3.65 (1H, d, *J* = 3.3 Hz), 4.36 (1H, d, *J* = 8.7 Hz), 4.38 (1H, dd, *J* = 1.6, 8.6 Hz).

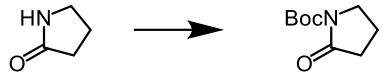
Its diastereomer : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (1H, ddd, *J* = 2.9, 5.3, 13.9 Hz), 2.00-2.14 (2H, m), 2.26 (1H, tdd, *J* = 3.0, 4.6, 15.2 Hz), 2.55 (1H, dddd, *J* = 0.9, 5.4, 12.5, 15.2 Hz), 2.86 (1H, ddd, *J* = 6.0, 8.0, 13.1 Hz), 3.40 (1H, d, *J* = 3.9 Hz), 3.71 (1H, t, *J* = 3.3 Hz), 4.32 (1H, ddd, *J* = 6.1, 8.0, 8.9 Hz), 4.45 (1H, ddd, *J* = 6.4, 8.1, 8.9 Hz).

Compound 2-13



To a solution of **2-4** (13.8 mg, 0.04906 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (2.2 mg, 0.05887 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (5 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product, which was used in the next reaction without purification.

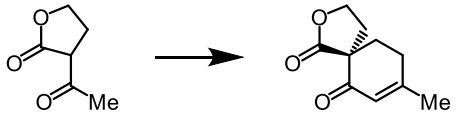
Compound 2-15



To a solution of **2-14** (989.6 mg, 11.63 mmol) in CH_3CN (5.3 mL) was added DMAP (142.1 mg, 1.16 mmol) and ta solution of Boc_2O (3.05 g, 13.95 mmol) in CH3CN (18 mL) at 21 °C, and the mixture was stirred for 2 h at 21 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (5 mL × 3). The mixture was evaporated and the residue was dissolved in EtOAc. The mixture was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2) to give **2-15** (1.97 g, 10.61 mmol, 91%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (9H, s), 1.99 (2H, quintet, J = 7.7 Hz), 2.50 (2H, t, J = 8.1 Hz), 3.74 (2H, t, J = 7.2 Hz).

Compound 2-5

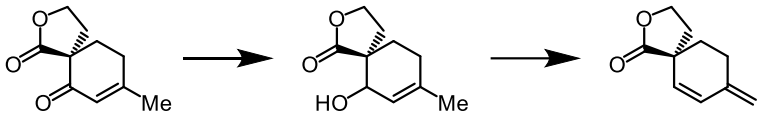


2-6 **2-9 (racemic)**

To a solution of **2-6** (205.7 mg, 1.61 mmol) in toluene (16.0 mL) was added DBU (0.359 mL, 2.41 mmol) and methyl vinyl ketone (0.200 mL, 2.41 mmol) at 0 °C, and the mixture was stirred for 50 min at 21 °C. Then, the mixture was warmed to 80 °C and the mixture was stirred for 30 min. To the mixture was added an excess amounts of MsCl at 24 °C, and the mixture was stirred for 10 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3.5) to give **2-9** (206.1 mg, 1.14 mmol, 71%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97-2.07 (1H, m, *J* = 4.9, 7.1 Hz), 2.02 (3H, s), 2.10 (1H, td, *J* = 8.6, 12.9 Hz), 2.29 (1H, td, *J* = 6.0, 19.2 Hz), 2.44 (1H, ddd, *J* = 5.0, 6.6, 13.6 Hz), 2.71 (1H, ddd, *J* = 3.9, 7.1, 12.8 Hz), 2.69-2.83 (1H, m), 4.30-4.47 (2H, m), 5.92 (1H, br-s).

Compound 2-20



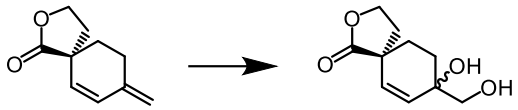
2-9 **2-19** **2-20**

To a solution of **2-9** (217.8 mg, 0.7798 mmol) in EtOH (7.8 mL) was added $NaBH_4$ (44.2 mg, 1.17 mmol) and $CeCl_3 \cdot 7H_2O$ (435.8 mg, 1.17 mmol) at −20 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (20 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product, which was used in the next reaction without purification.

To a solution of the above crude product in $(CH_2Cl)_2$ (7.8 mL) was added Et_3N (0.652 mL, 4.68 mmol) and TsCl (446.0 mg, 2.34 mmol) at 21 °C, and the mixture was warmed to reflux conditions and stirred for 12 h. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 30 → 20) to give **2-20** (19.8 mg, 0.06238 mmol, 8% from **2-9**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48-1.61 (1H, m), 1.81 (1H, ddd, *J* = 4.3, 8.9, 13.0 Hz), 1.93-2.13 (2H, m), 2.19-2.32 (1H, m), 2.52-2.64 (1H, m), 3.77-3.95 (2H, m), 4.85-4.92 (2H, m), 5.38 (1H, d, *J* = 9.8 Hz), 6.25 (1H, d, *J* = 9.8 Hz).

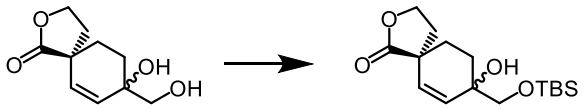
Compound 2-21



2-20 **2-21**

To a solution of **2-21** (5.0 mg, 0.01575 mmol) in acetone-H_2O (10:1, 7.8 mL) was added NMO (1.8 mg, 0.01575 mmol) and OsO_4 (0.01636 mol/L in H_2O, 96 μL, 1.58 μmol) at 0 °C, and the mixture was stirred for 4.5 h at 21 °C. The reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2) to give a 1:1 mixture of **2-21** (4.4 mg, 0.01252 mmol, 80%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-1.89 (6H/2, m), 1.89-2.14 (6H/2, m), 3.44 (2H/2, t, *J* = 6.2 Hz), 3.52 (2H/2, br-s), 3.78-3.86 (4H/2, m), 3.86-3.98 (4H/2, m).

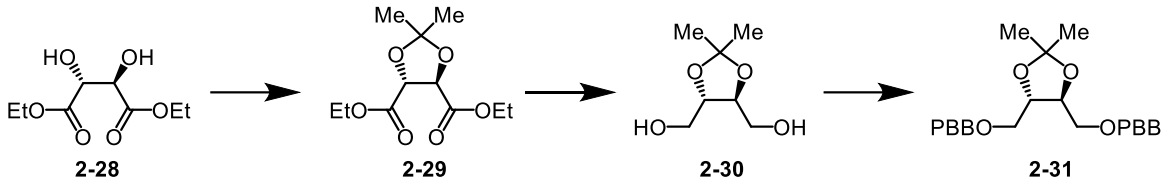
Compound 2-22



2-21 **2-22**

To a solution of **2-21** (2.4 mg, 6.82 μmol) in CH_2Cl_2 (0.4 mL) was added 2,6-lutidine (8 μL, 0.06825 mmol) and TBSOTf (8 μL, 0.03415 mmol) at 0 °C, and the mixture was stirred for 30 min at 21 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3 → 1) to give **2-22** (2.0 mg, quant.) and its diastereomer (2.4 mg, quant.) as a colorless oil.
2-22 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 1.39-1.69 (2H, m), 1.71-1.86 (1H, m), 1.87-2.06 (3H, m), 3.39 (1H, d, *J* = 9.7 Hz), 3.44 (1H, d, *J* = 9.6 Hz), 3.61-3.94 (2H, m), 5.48 (1H, d, *J* = 10.0 Hz), 5.80 (1H, d, *J* = 10.0 Hz).
Its diastereomer : ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 1.50-1.62 (1H, m), 1.67-1.76 (2H, m), 1.89 (1H, ddd, *J* = 3.9, 9.4, 14.3 Hz), 1.96-2.15 (2H, m), 2.83 (1H, s), 3.44 (1H, d, *J* = 9.8 Hz), 3.49 (1H, d, *J* = 9.8 Hz), 3.78-3.95 (2H, m), 5.44 (1H, d, *J* = 10.1 Hz), 5.80 (1H, d, *J* = 10.0 Hz).

Compound 2-31



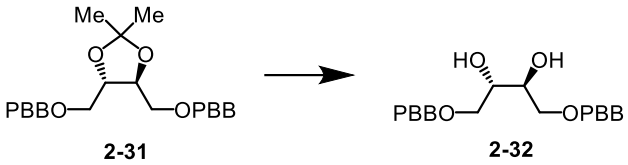
To a solution of **2-28** (2.00 g, 9.70 mmol) in benzene (24.2 mL) was added 2,2-dimethoxypropane (1.78 mL, 14.54 mmol) and PTS·H_2O (18.6 mg, 0.09700 mmol) at 21 °C, and the mixture was stirred and heated to reflux with removal of water by Dean-Stark apparatus. After 4 h from the start of the reaction, the mixture was cooled to 21 °C, and the reaction was quenched with saturated aq. $NaHCO_3$, and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **2-29**, which was used in the next reaction without purification.

To a solution of the $LiAlH_4$ (736.2 mg, 19.40 mmol) in THF (14.2 mL) was added a solution of the above crude **2-29** in THF (10.0 mL) at 0 °C, and the mixture was warmed to 40 °C and stirred for 5 h. The reaction was quenched with H_2O (3.2 mL) and 2.0 mol/L aq. NaOH (0.8 mL), and the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to give crude product **2-30**, which was used in the next reaction without purification.

To a solution of the above crude **2-30** in THF-DMF (10:1, 19.3 mL) was added KI (161.0 mg, 0.9700 mmol), PBBBr (4.85 g, 19.40 mmol) and NaH (55% in oil, 888.5 mg, 20.37 mmol) at 0 °C, and the mixture was stirred 17 h at 21 °C. The reaction was quenched with MeOH and 2.0 mol/L aq. NaOH, and the mixture was extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10) to give **2-31** (4.19 g, 8.38 mmol, 86% from **2-28**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (6H, s), 3.59 (4H, dd, *J* = 1.5, 3.0 Hz), 4.02 (2H, br-s), 4.51 (4H, s), 7.18 (4H, d, *J* = 8.3 Hz), 7.46 (4H, d, *J* = 8.3 Hz).

Compound 2-32

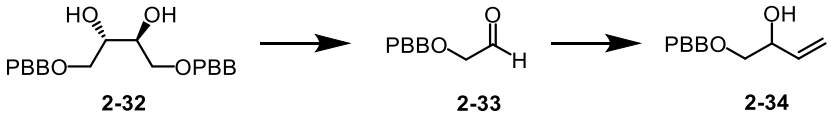


2-31 **2-32**

To a solution of **2-31** (4.19 g, 8.38 mmol) in THF (18.6 mL) was added 2.0 mol/L aq. HCl (9.3 mL) at 0 °C, and the mixture was stirred for 30 min at 40 °C. The reaction was quenched with H_2O, and the mixture was extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3 → A) to give **2-32** (3.22 g, 7.008 mmol, 84%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (2H, d, *J* = 4.4 Hz), 3.50-3.68 (2H, m), 3.79-3.92 (1H, m), 4.50 (2H, s), 7.18 (2H, d, *J* = 8.3 Hz), 7.47 (1H, d, *J* = 8.3 Hz).

Compound 2-34



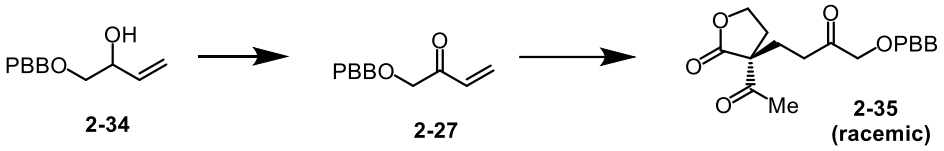
2-32 **2-33** **2-34**

To a solution of **2-32** (3.50 g, 7.62 mmol) in THF-H_2O (1:1, 25.4 mL) was added $NaIO_4$ (1.79 g, 8.38 mmol) at 0 °C, and the mixture was stirred for 2.5 h at 21 °C. The reaction was quenched with H_2O, and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **2-33**, which was used in the next reaction without purification.

To a solution of the above crude **2-33** in THF (30.5 mL) was added vinyl magnesium chloride (1.42 mol/L in THF, 16.1 mL, 22.85 mmol) at -78 °C, and the mixture was stirred 2 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8) to give **2-34** (1.69 g, 6.59 mmol, 43% from **2-32**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (1H, d, *J* = 3.6 Hz), 3.37 (1H, dd, *J* = 7.9, 9.6 Hz), 3.54 (1H, dd, *J* = 3.3, 9.6 Hz), 4.29-4.42 (1H, m), 4.53 (2H, s), 5.21 (1H, td, *J* = 1.4, 10.6 Hz), 5.36 (1H, td, *J* = 1.5, 17.3 Hz), 5.84 (1H, ddd, *J* = 5.6, 10.6, 17.3 Hz), 7.22 (2H, d, *J* = 8.3 Hz), 7.49 (1H, d, *J* = 8.4 Hz).

Compound 2-35

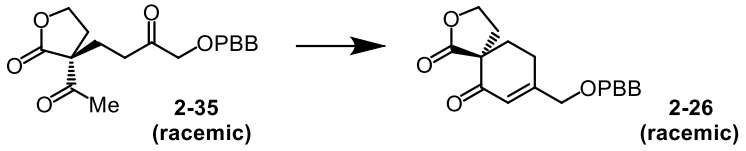


To a solution of **2-34** (838.9 mg, 3.26 mmol) in CH_2Cl_2 (32.6 mL) was added $NaHCO_3$ (1.64 g, 19.58 mmol) and DMPI (2.77 g, 6.53 mmol) at 21 °C, and the mixture was stirred for 25 min at 21 °C. The reaction was quenched with saturated aq. $NaHCO_3$ and $Na_2S_2O_3$, and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **2-27**, which was used in the next reaction without purification.

To a solution of **2-6** (836.1 mg, 6.53 mmol) in $(CH_2Cl)_2$ (25.0 mL) was added Et_3N (0.905 mL, 6.53 mmol) and a solution of the above crude **2-27** in $(CH_2Cl)_2$ (7.6 mL) at 21 °C, and the mixture was stirred 1 h at 40 °C. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 2.5) to give **2-35** (951.2 mg, 2.48 mmol, 76% from **2-34**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (1H, td, *J* = 8.5, 12.9 Hz), 2.16 (1H, ddd, *J* = 4.8, 8.1, 13.8 Hz), 2.27-2.42 (1H, m), 2.31 (3H, s), 2.42-2.53 (2H, m), 2.81 (1H, ddd, *J* = 3.8, 7.2, 13.0 Hz), 4.03 (2H, s), 4.17 (1H, ddd, *J* = 7.2, 8.5, 9.0 Hz), 4.32 (1H, ddd, *J* = 3.8, 8.6, 9.0 Hz), 4.52 (2H, s), 7.22 (2H, d, *J* = 8.3 Hz), 7.50 (2H, d, *J* = 8.4 Hz).

Compound 2-26

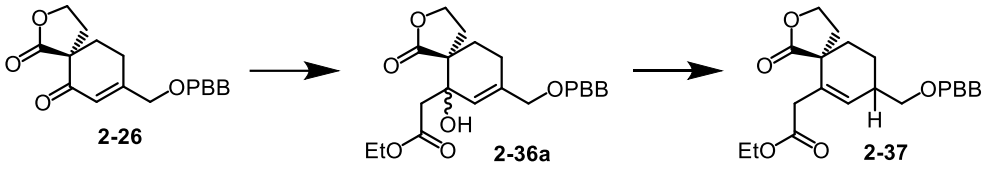


To a solution of **2-35** (94.0 mg, 0.2453 mmol) in benzene (2.5 mL) was added DBU (55 μL, 0.3680 mmol) at 21 °C, and the mixture was heated to reflux condtion and stirred for 20 min. The reaction mixture was evaporated to give crude product, which was used in the next reaction without purification.

To a solution of above crude product in pyridine (2.5 mL) was added TFAA (0.103 mL, 0.7359 mmol) and at 0 °C, and the mixture was stirred 4 h at 100 °C. The reaction mixture was quenched with H_2O, and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2.5to give **2-26 (**70.6 mg, 0.1865 mmol, 76% from **2-35**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00-2.18 (2H, m), 2.28 (1H, td, *J* = 5.8, 18.3 Hz), 2.46 (1H, ddd, *J* = 5.1, 6.3, 13.7 Hz), 2.68-2.83 (2H, m), 4.13 (2H, s), 4.31-4.45 (2H, m), 4.52 (2H, s), 6.19 (1H, t, *J* = 1.6 Hz), 7.22 (2H, d, *J* = 8.3 Hz), 7.49 (2H, d, *J* = 8.4 Hz).

Compound 2-37

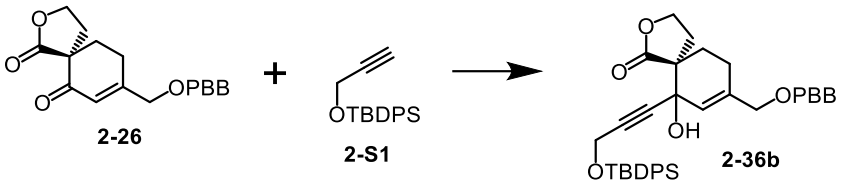


To a solution of EtOAc (63 μL, 0.6407 mmol) in THF (1.0 mL) was added NHMDS (1.10 mol/L in THF, 0.582 mL, 0.6407 mmol) at -78 °C, and the mixture was stirred for 5 min. Then, to the mixture was added a solution of **2-26** (23.4 mg, 0.06407 mmol) in THF (1.0 mL) at -78 °C, and the mixture was stirred for 30 min. The reaction mixture was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **2-36a**, which was used in the next reaction without purification.

To a solution of above crude **2-36a** in CH_2Cl_2-Et_3SiH (2:1, 1.2 mL) was added $BF_3 \cdot OEt_2$ (0.103 mL, 0.7359 mmol) and at 0 °C, and the mixture was stirred 10 min at 0 °C. The reaction mixture was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (6 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6) to give **2-37** **(**16.5 mg, 0.03773 mmol, 59% from **2-26**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, *J* = 7.1 Hz), 1.83-2.03 (2H, m), 2.08 (1H, ddd, *J* = 2.4, 7.1, 13.3 Hz), 2.50 (1H, td, *J* = 9.5, 13.3 Hz), 2.53-2.69 (1H, m), 2.81 (1H, d, *J* = 15.5 Hz), 3.12 (1H, td, *J* = 1.7, 15.5 Hz), 3.32 (1H, dd, *J* = 7.1, 9.0 Hz), 3.39 (1H, dd, *J* = 6.3, 9.0 Hz), 4.12 (2H, q, *J* = 7.1 Hz), 4.26 (1H, dt, *J* = 7.0, 9.6 Hz), 4.37 (1H, dt, *J* = 2.4, 9.2 Hz), 4.45 (2H, s), 5.86 (1H, s), 7.19 (2H, d, *J* = 8.3 Hz), 7.46 (2H, d, *J* = 8.3 Hz).

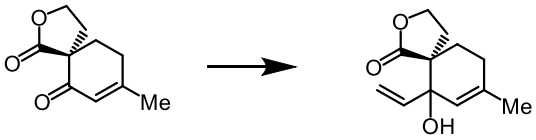
Compound 2-36b



To a solution of **2-S1** (202.2 mg, 0.6868 mmol) in THF (2.0 mL) was added BuLi (0.443 mL, 0.6868 mmol) at -78 °C, and the mixture was stirred for 5 min. Then, to the mixture was added a solution of 2-26 (125.4 mg, 0.3434 mmol) in THF (1.4 mL) at -78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4) to give **2-36b** (105.8 mg, 0.1604 mmol, 47%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.71-1.84 (1H, m), 1.99 (1H, ddd, *J* = 4.0, 7.6, 13.3 Hz), 2.13 (1H, t, *J* = 7.9 Hz), 2.22 (1H, dt, *J* = 1.6, 6.0 Hz), 2.29 (1H, ddd, *J* = 4.0, 6.1, 8.6 Hz), 2.51 (1H, td, *J* = 8.8, 13.3 Hz), 3.79 (1H, s), 3.93 (2H, s), 4.22 (1H, td, *J* = 7.8, 8.7 Hz), 4.28-4.34 (1H, m, *J* = 3.9 Hz), 4.36 (1H, d, *J* = 5.0 Hz), 4.38 (1H, d, *J* = 5.0 Hz), 4.41 (1H, d, *J* = 12.0 Hz), 4.46 (1H, d, *J* = 12.0 Hz), 5.71 (1H, s), 7.22 (2H, d, *J* = 8.3 Hz), 7.33-7.44 (6H, m), 7.46 (2H, d, *J* = 8.3 Hz), 7.60-7.75 (4H, m).

Compound 2-35c



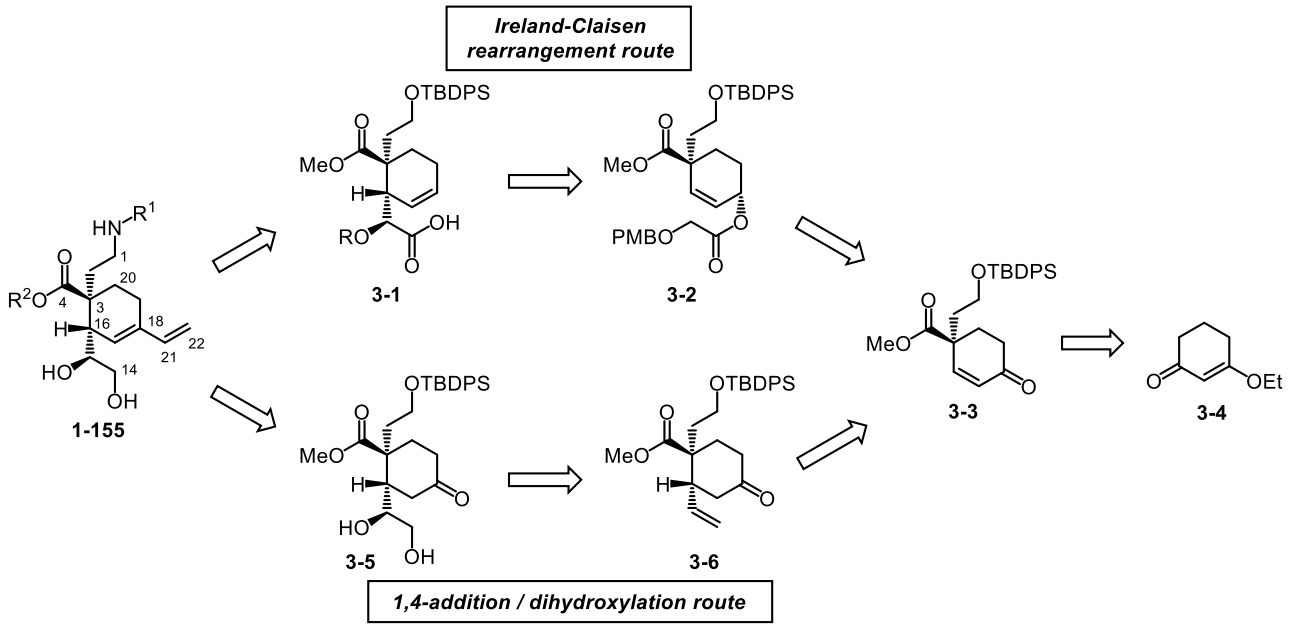
To a solution of **2-9** (11.7 mg, 0.06493 mmol) in THF (0.6 mL) was added vinyl magnesium bromide (1.0 mol/L in THF, 0.195 mL, 0.1947 mmol) at -10 °C, and the mixture was stirred for 15 min. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **2-35c** (5.4 mg, 0.02593 mmol, 40%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (3H, s), 1.72-1.86 (1H, m), 1.92-2.10 (3H, m), 2.62 (1H, ddd, *J* = 5.5, 8.2, 13.1 Hz), 4.23 (1H, dt, *J* = 5.5, 8.5 Hz), 4.33 (1H, dt, *J* = 6.9, 8.3 Hz), 5.21 (1H, q, *J* = 1.5 Hz), 5.25 (1H, dd, *J* = 1.5, 10.6 Hz), 5.32 (1H, dd, *J* = 1.5, 17.1 Hz), 6.08 (1H, dd, *J* = 10.6, 17.1 Hz).

Chapter 3
Synthesis of the Cyclohexene Segment of Portimine

3-1. New Two Routes to the Cyclohexene Segment via Cyclohexenone 3-3

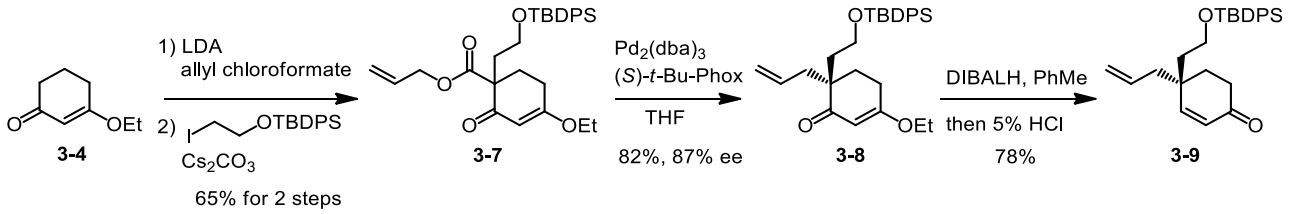
As shown in latter half of Chapter 2, it was difficult for the intermediates (**2-5**, **2-9** and **2-26**) having a 2-oxaspiro[4.5]dec-7-ene-1,6-dione framework to undergo an installation of C14-C15 unit at C16 as well as establishment of the stereocenters at C15 and C16 in the route to cyclohexene segment **1-155** of portimine (**1-32**). Therefore, the author re-designed the synthesis of **1-155** using a 4,4-disubstututed cyclohex-2-enone (**3-3**) as a key intermediate, which was expected to facilitate the installation of C14-C15 unit at C16 by a 1,4-addition reaction (a process form **3-3** to **3-6**) (Scheme 3-1). The intermediate may also be usable for an Ireland-Claisen rearrangement route (a process form **3-2** to **3-1**) that could not be realized in the above described work, although the re-designed route includes a difficult cyclohexenonl intermediate. The 4,4-disubstututed cyclohex-2-enone intermediate (**3-3**) would be prepared from easily available 3-ethoxycyclohex-2-enone (**3-4**) without employing Robinson annulation reaction.



Scheme 3-1. Two routes to cyclohexene segment **1-155** from **3-4** via **3-3**.

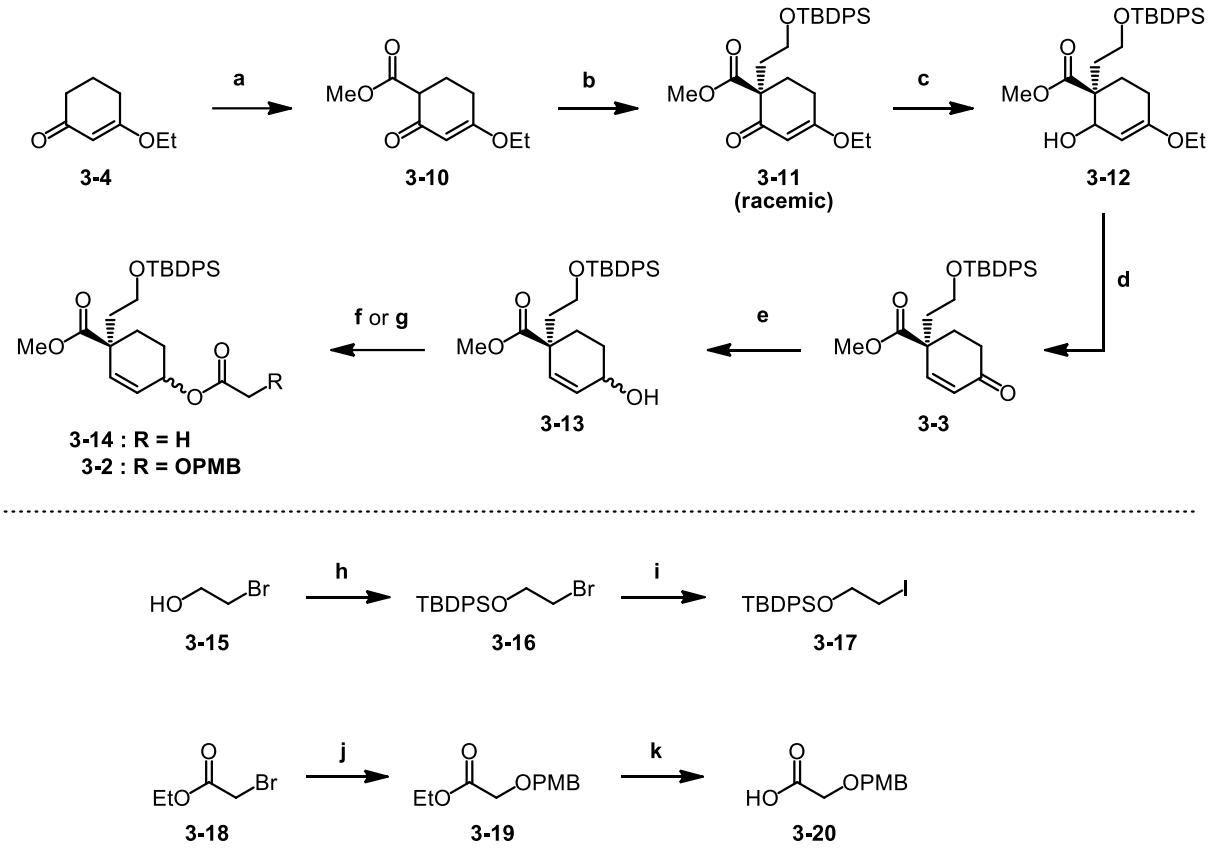
3-2. The First Route Based on Ireland-Claisen Rearrangement

The preparation of **3-3**, described in detail in Section 3-2, relied on the procedure reported by Ma's group. In their total synthesis of Lungshengenin D and the derivative,[1] 4-quaternary-substituted cyclohex-2-enone **3-9** was prepared from **3-4** via a process including acylation/alkylation giving **3-7** and Trost asymmetric allylation[2] providing **3-8** followed by reduction and hydrolysis (Scheme 3-2). The author noted a reduction/hydrolysis sequence would transform **3-7** to an enone-ester close similar to **3-3**. Therefore, the new synthetic route employed Ma's protocol for the preparation of **3-3** from **3-4**.



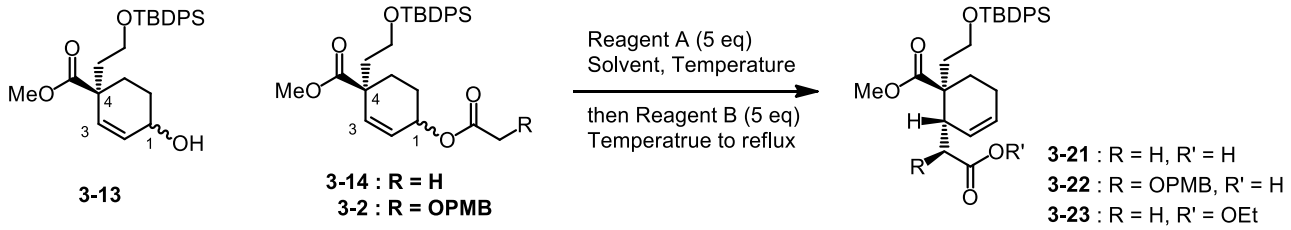
Scheme 3-2. Preparation of cyclohexenone **3-9** from **3-4** by Ma.

Preparation of allylic ester **3-2** starting from enone **3-4** is shown in Scheme 3-3. Enone **3-4** was deprotonated with LDA, and the resulting lithium enolate was reacted with methyl chloroformate to produce β-ketoester **3-10** (97%). Alkylation of **3-10** with TBDPS protected 2-iodoethanol **3-17**, prepared from 2-bromoethanol via protection with TBDPSCl (87%) followed by the substitution of I for Br (90%), in the presence of cesium carbonate provided racemic **3-11**. Enone **3-11** was subjected to Luche reduction[3] at –40 °C followed by the hydrolysis of the enol ether moiety to give the desired cyclohexenone **3-3**. It should be noted that the Luche 1,2-reduction was required a strict temperature-control to obtain an allylic alcohol in good yield: while low temperature around –78 °C retarded the reduction, higher temperature more than –20 °C induced a significant decarboxylation as a side-reaction to decrease the yield of the allylic alcohol. Enone **3-3** was reduced under Luche conditions to afford alcohol **3-12** (d.r. = 1:1). Acetylation of **3-12** under standard conditions produced **3-14** (76% over 4 steps). Condensation of **3-12** and carboxylic acid **3-20**, prepared via S_N2 reaction of 4-methoxyl benzylalcohol with ethyl bromoacetate (**3-18**) followed by hydrolysis, furnished β-hydroxy ester **3-2** (75% over 4 steps). Thus, the requisite substrate for the next Ireland-Claisen rearrangement step was successfully obtained.



Scheme 3-3. Preparation of allylic ester **3-2** and **3-14**. Reagents and conditions: (a) LDA, methyl chloroformate, THF, –78 °C, 30 min then 0 °C, 10 min, 88%; (b) **3-17**, Cs_2CO_3, CH_3CN, 65 °C, 15 h, 48%; (c) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH, –40 °C; (d) PTS•H_2O, CH_2Cl_2-MeOH-H_2O, 21 °C, 3 h; (e) $NaBH_4$, $CeCl_3$•$7H_2O$, EtOH-THF, –20 °C, 30 min; (f) Ac_2O, CH_2Cl_2-pyridine, 21 °C, 19 h, 76% from **3-11,** d.r. =1:1; (g) **3-20**, EDCI•HCl, DMAP, CH_2Cl_2, 21 °C, 1 h, 75% from **3-11**, d.r. =1:1; (h) TBDPSCl, Imidazole, DMF, 21 °C, 22 h, 87%; (i) NaI, acetone, 40 °C, 16 h, 90%; (j) 4-methoxybenzylalcohol, NaH, THF-DMF, 21 °C, 2.5 h, 81%; (k) THF-aq. NaOH, 21 °C, 1 h.

With allylic esters **3-2** and **3-14** in hand, the author next examined the Ireland-Claisen rearrangement. It is notable that, to the best of the author's knowledge, there are only a few applications[4] of Claisen/Ireland-Claisen rearrangement of esters or vinyl ethers having 4,4-disubstituted cyclohex-2-en-1-yl moiety[5]. Therefore, the author carefully explored the reaction conditions for the Ireland-Claisen rearrangement[6] of substrates **3-2** and **3-14**. However, the examined rearrangement conditions resulted in only recovery (Table 3-1, Entries 1-4 and 6) or decomposition (Entry 5) of the substrate. Since the allylic esters were used as a 1:1 diastereomeric mixture, the stereochemistry of the substrates was thought to be independent of the inactivity. Therefore, the inactivity would be attributable to an unstable (high-energy) transition state, consists of a ketene silyl acetal from **3-2** or **3-14**, in the rearrangement step. In the transition state, a sever steric hindrance by the substituents at C4 would disturb the approach of the ketene silyl acetal moiety to the reaction center at C3. The Ireland-Claisen rearrangement of less hindered acetate **3-14** also recovered the starting material (Entry 6). As an alternative attempt, the Johnson-Claisen rearrangement[7] of allylic alcohol **3-13**, however, gave no rearrangement product (Entry 7).

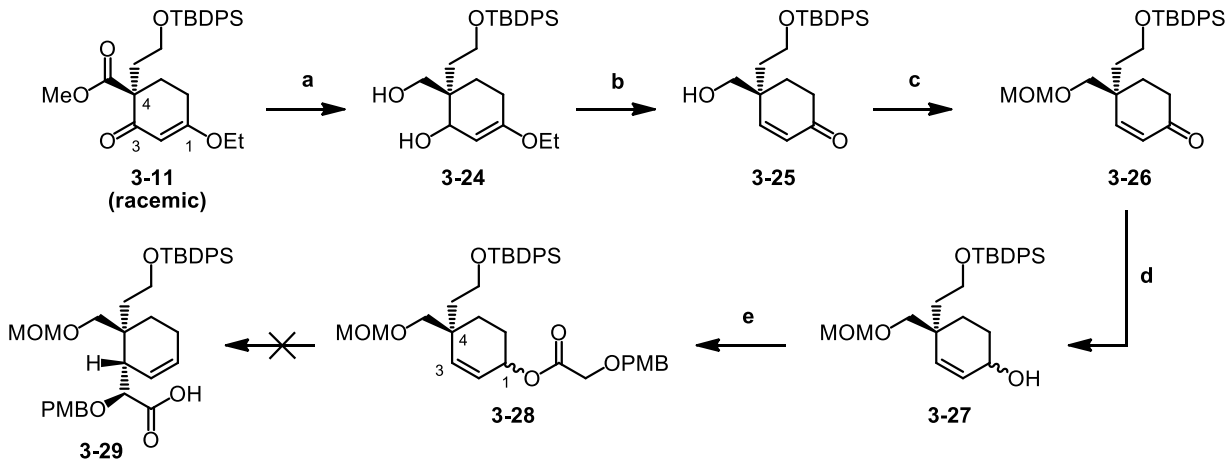


	Substrate[a]	Reagent A	Solvent	Reagent B	Temperature	Result
Entry 1	**3-2**	TMSCl	THF	LDA	-78 °C	**3-22** : N.R.
Entry 2	**3-2**	TMSCl	THF	NHMDS	-78 °C	**3-22** : N.R.
Entry 3	**3-2**	TMSCl	THF-PhMe	KHMDS	-78 °C	**3-22** : N.R.
Entry 4	**3-2**	TMSCl	THF-PhMe-HMPA	KHMDS	-78 °C	**3-22** : N.R.
Entry 5	**3-2**	KHMDS	THF-PhMe	TMSCl	-78 °C	Decomposition
Entry 6	**3-14**	TMSCl	THF-PhMe	KHMDS	-78 °C	**3-21** : N.R
Entry 7	**3-13**	AcOH	$MeCH(OEt)_2$	——	21 °C	**3-23** : N.R

a) Each substrate was 1:1 diastereomeric mixture

Table 3-1. Attempt to perform the Ireland-Claisen or Johnson-Claisen rearrangement

To decrease the steric hindrance around the C3 center of the Ireland-Claisen rearrangement substrate, the ester group at C4 was transformed to a $MOMOCH_2$- group as shown in Scheme 3-4. Racemic **3-11** was reduced by $LiAlH_4$, and the resulting diol **3-24** underwent acidic hydrolysis to afford cyclohexenone **3-25**. The MOM protection of **3-25** using sodium hydride led to decomposition and byproduction of aromatic compounds. Therefore, optimization of the reaction conditions was required. As a result, it was found that the conditions using MOMCl and DIPEA successfully produced MOM ether **3-26** without decomposition. The 1,2-reduction of **3-26** under Luche conditions and the condensation of the resulting **3-27** with **3-20** furnished allylic ester **3-28** (55% for 5 steps, d.r. = 1:1). However, the Ireland-Claisen rearrangement of **3-28** resulted in no reaction even after extensive optimization.



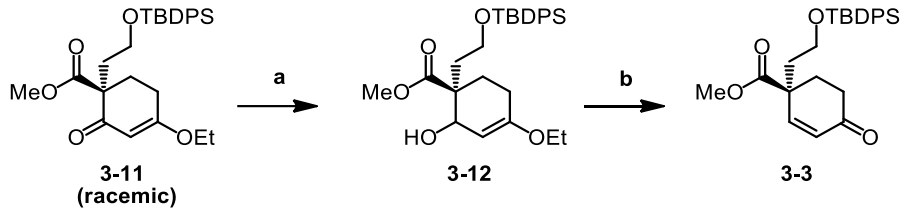
Scheme 3-4 Preparation of allylic ester **3-28** and an attempt to perform Ireland-Claisen rearrangement. Reagents and conditions: (a) $LiAlH_4$, 21 °C, 2 h; (b) PTS•H_2O, CH_2Cl_2-MeOH-H_2O, 21 °C, 1 h; (c) MOMCl, DIPEA, 21 °C, 18.5 h; (d) $NaBH_4$, $CeCl_3$•$7H_2O$, EtOH-THF, –78 °C, 20 min then 0 °C, 10 min; (e) **3-20**, EDCI•HCl, DMAP, CH_2Cl_2, 21 °C, 1 h, 55% from **3-11**, d.r. =1:1.

Thus, the author found the difficulty of the approach using Ireland-Claisen rearrangement for the installation of a substituent at C16 (portimine numbering), and decided to examine the second route using 1,4-addition to enone **3-3** for setting up a C14-C15 unit at C16.

3-3. The Second Route Based on 1,4-Addition to a Cyclohex-2-enon Intermediate

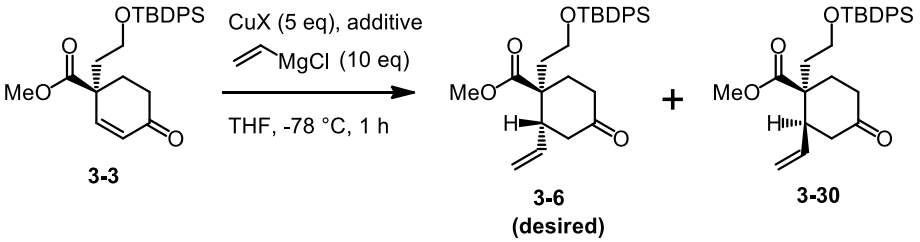
As described in Section 3-1, the author designed two synthetic route to **1-155** via a 4,4-disubstututed cyclohex-2-enone (**3-3**) as a key intermediate. Since the first route based on Ireland-Claisen rearrangement was found to be difficult to realize, the second route, expected to facilitate the installation of C14-C15 unit at C16 by a 1,4-addition reaction, was next examined.

Cyclohexenone **3-3** was prepared from **3-11** according to the procedure described in Section 3-2 (85% over 2 steps, Scheme 3-5).



Scheme 3-5. Preparation of **3-3**. Reagents and conditions: (a) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH-THF, –40 °C; (d) PTS•H_2O, CH_2Cl_2-MeOH-H_2O, 21 °C, 4.5 h, 85% from **3-11**.

In the 1,4-addition step, a vinyl group was selected as the C14-C15 unit. Several vinyl copper reagents, prepared *in situ* from vinylmagnesium chloride and CuI-Me_2S or CuCN, were examined (Table 3-2). Treatment of **3-3** with vinylmagnesium chloride-CuI-Me_2S provided an inseparable 1:>10 mixture of the desired **3-6** and diastereomeric **3-30** in 34% yield (Entry 1). When HMPA was used as an additive, the yield and the selectivity of **3-6** to **3-30** were retained (Entry 2). The use of BF_3•OEt_2 as an additive in the CuI-Me_2S system (Entry 3) or the use of a cyanocuprate (Entry 4) increased the yield and the ratio of **3-6**. However, the production of the desired **3-6** was still smaller than that of **3-30**.

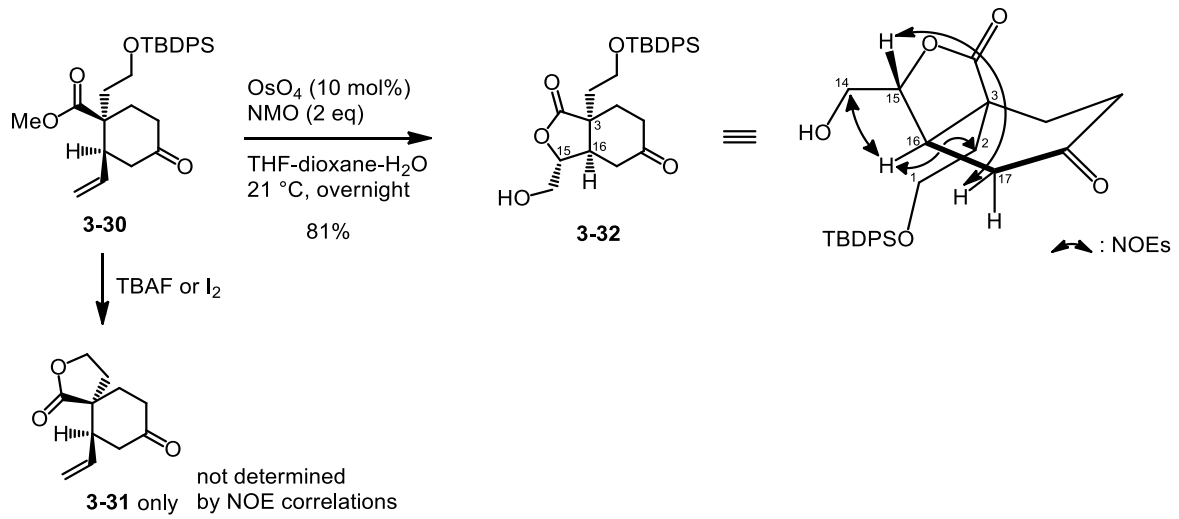


	CuX	Additive	Yield (**3-6** : **3-30**)
Entry 1	CuI	Me_2S	34% (1 : >10)
Entry 2	CuI	Me_2S, HMPA	31% (1 : >10)
Entry 3	CuI	Me_2S, BF_3•OEt_2	50% (1 : 2.5)
Entry 4	CuCN	—	49% (1 : 3)

Table 3-2. The 1,4-addition of several vinyl cuprate reagents to cyclohexenone **3-3**

In order to confirm the relative stereochemistry at C3 and C16 centers, major product **3-30** was derivatized (Scheme 3-6). The iodo-etherification or the iodo-lactonization of **3-30** was first attempted to construct a fused-ring structure. When the TBDPS group of **3-30** was removed with TBAF, spirolactone **3-31** was produced instead of a primary alcohol. Treatment of **3-30** with iodine also gave **3-31** without formation of an iodolactone. The facilely constructed **3-31** having 2-oxaspiro[4.5]decane structure, however, only showed unclear NOE correlations even after extensive NOE experiments. Therefore, the relative stereochemistry at C3 and C16 centers could not be determined by NMR analysis of **3-31**.

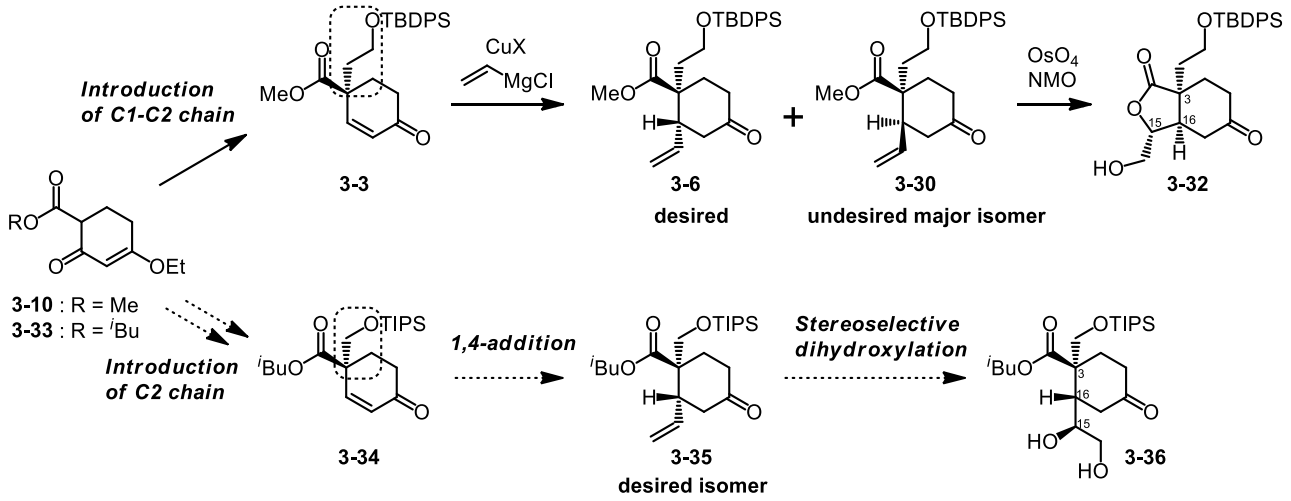
Next, the dihydroxylation of the vinyl group of **3-30** was examined. When alkene **3-30** was subjected to OsO_4-catalysed dihydroxylation, unexpected lactonization concomitant with the dihydroxylation proceeded to afford fused bicyclic lactone **3-32** as an almost single isomer in 81% yield.[8] The relative stereochemistry of **3-32** was confirmed by NMR analysis. The presence of NOE between H2 and H16 confirmed the *cis*-relationship between H16 and 2-TBDPSoxyethyl group. The NOE correlation between H15 and one of the protons at C17 indicated the *trans*-relationship between H15 and H16. The NOE enhancement between H14 and H16 also supported the *trans*-orientation between H15 and H16. Thus, the relative configurations at C3, C16 and C15 centers of **3-32** were determined to be (3*R**,15*R**,16*R**), which was corresponding to the diastereomer of **1-155** at C15 and C16, as shown in Scheme 3-6. Although the stereochemistry of the 1,4-addition and dihydroxylation steps was undesirable, high diastereoselectivity of the dihydroxylation step was remarkable.



Scheme 3-6. Determination of relative configurations at C3, C15 and C16 stereocenters.

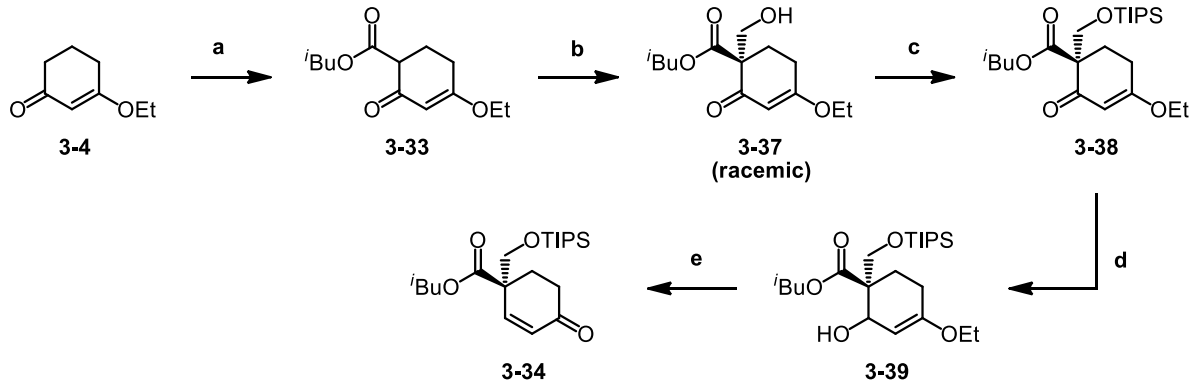
3-4. Optimization of the Second Route

The initial investigation of the second route via cyclohexenone **3-3** showed undesired diastereoselectivity in the 1,4-addition step to give **3-30** as a major product as described in Section 3-3 (Scheme 3-7). On the other hand, the OsO_4-catalyzed dihydroxylation of **3-30** proceeded with high diastereoselectivity to produce **3-32**. The diastereoselection of the dihydroxylation would be attributable to the stereochemical effect of the substituents at C16 adjacent to the vinyl group. The stereoselection was supported by the report by Vandewalle, in which the similar diastereoselection in the dihydroxylation of 4,4-dimethyl-3-vinylcyclohexenone was described.[8] The diastereoselection was favorable for the second route synthesis of **1-155**. Therefore, improvement of the stereoselectivity in the 1,4-addition of a vinyl group to a 4,4-disubstituted cyclohex-2-enone system is an important problem to be solved. As a solution of the problem, the author undertook to optimize the effect of the substituent at C4 on the improvement of the diastereoselectivity in the 1,4-addition step. Thus, instead of the TBDPSoxyethyl group, a protected alkoxymethyl group was employed at C4 of the cyclohex-2-enone system (**3-34**). Using the cyclohex-2-enone substrates, the reaction conditions of the 1,4-addition of vinyl cuprate reagents were optimized (**3-34** → **3-35**).



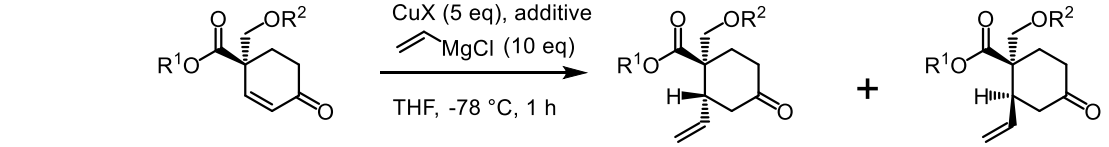
Scheme 3-7. An alternative approach to the construction of C3-C16-C15 stereocenters.

Cyclohexenone **3-34** was first prepared from 3-ethoxycyclohex-2-enone (**3-4**) through a five-step process shown in Scheme 3-8. Deprotonation of **3-4** with LDA followed by the reaction of isobutyl chloroformate gave β-ketoester **3-33** (95%), which was subjected to an aldol reaction with formaldehyde and the subsequent protection with TIPSOTf to produce enone **3-38** in racemic form (99% over 2 steps). Luche reduction followed by acidic hydrolysis of the enol ether moiety furnished cyclohexenone **3-34** in 93% for 2 steps. Using the similar processes, several variants of **3-34** having different ester and silyl ether groups were synthesized (**3-40**: 62% overall yield, **3-41**: 47% overall yield, **3-42**: 64% overall yield, **3-43**: 68% overall yield, **3-44**: 14% overall yield; *vide infra*).



Scheme 3-8. Preparation of cyclohexenone **3-34**. Reagents and conditions: (a) LDA, isobutyl chloroformate, THF, –78 °C, 30 min then 0 °C, 30 min, 95%; (b) KOH, 13 mol/L aq. HCHO, EtOH, –20 °C, 1 h; (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 99% from **3-33**; (d) $NaBH_4$, $CeCl_3$•$7H_2O$, EtOH, –40 °C, 1 h; (e) PTS•H_2O, CH_2Cl_2-MeOH-H_2O, 0 °C, 1 h, 93% from **3-38**.

The 1,4-addition reactions of cyclohexenones **3-34** and **3-40–44** with vinyl cuprate reagents are summarized in Table 3-3. As described in Section 3-3 (Table 3-2), the combination of vinylmagnesium chloride and CuCN provided an increased ratio of *anti*-adduct rather than that of the combination of vinylmagnesium chloride and CuI. Therefore, the author first employed the vinylcyanocuprate for the 1,4-addition reactions. Treatment of enone **3-40** (R^1 = Me, R^2 = TBS) with CuCN and vinylmagnesium chloride in THF at –78 °C gave a 1:1 diastereomeric mixture of adducts in 49% yield (Entry 1). When R^2 was changed to a bulky TBDPS group (**3-41**; R^1 = Me, R^2 = TBDPS), the ratio of the desired *anti*-adduct was decreased (*anti*:*syn* = 1:1.8; Entry 2). Isobutyl esters **3-42** (R^1 = ^{i}Bu, R^2 = TBS) and **3-43** (R^1 = ^{i}Bu, R^2 = TBDPS) showed a similar tendency of the diastereoselectivity and the yield (49%, *anti*:*syn* = 1:1, Entry 3; 56%, *anti*:*syn* = 1:2.5, Entry 4; respectively) to the corresponding methyl esters **3-41** and **3-42**. *tert*-Butyl ester **3-44** having a TBDPS ether also examined with vinylcyanocuprate to give adducts in moderate yield with slight *syn*-selectivity (*anti*:*syn* = 1:1.3, 60% combined yield; Entry 7). While the low yields of adducts were observed in the reactions using the vinylcyanocuprate, the combination of vinylmagnesium chloride and CuI [CuI (5.5 eq), vinyl magnesium chloride (11 eq), Me_2S (22 eq), 100–300 mg substrate scale] was found to induce a clean 1,4-addition to **3-43** in high yield (92%) with a moderate *syn*-selectivity (*anti*:*syn* = 1:3.4, Entry 5). The reaction of TIPS ether **3-34** under the same conditions gave the best production of *anti*-adduct **3-35-*anti*** (*anti*:*syn* = 1:1, 94% combined yield; Entry 6). Due to inseparability, the diastereomeric mixture of **3-35-*anti*** and **-*syn*** was used in the next reaction as it stands.



3-40 (R^1 = Me, R^2 = TBS) **3-43** (R^1 = ^{i}Bu, R^2 = TBDPS)
3-41 (R^1 = Me, R^2 = TBDPS) **3-34** (R^1 = ^{i}Bu, R^2 = TIPS)
3-42 (R^1 = ^{i}Bu, R^2 = TBS) **3-44** (R^1 = ^{t}Bu, R^2 = TBDPS)

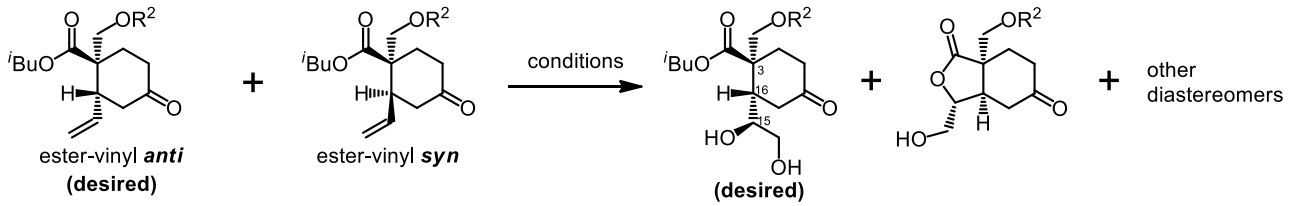
anti* (desired)** **3-45-*anti (R^1 = ^{i}Bu, R^2 = TBDPS) **3-35-*anti*** (R^1 = ^{i}Bu, R^2 = TIPS)

syn **3-45-*syn*** **3-35-*syn***

	Substrate	R^1	R^2	CuX	additive	Yield (***anti*** : ***syn***)
Entry 1	**3-40**	Me	TBS	CuCN	——	49% (1 : 1)
Entry 2	**3-41**	Me	TBDPS	CuCN	——	58% (1 : 1.8)
Entry 3	**3-42**	^{i}Bu	TBS	CuCN	——	49% (1 : 1)
Entry 4	**3-43**	^{i}Bu	TBDPS	CuCN	——	56% (1 : 2.5)
Entry 5	**3-43**	^{i}Bu	TBDPS	CuI	Me_2S	92% (1 : 3.4)
Entry 6	**3-34**	^{i}Bu	TIPS	CuI	Me_2S	94% (1 : 1)
Entry 7	**3-44**	^{t}Bu	TBDPS	CuCN	——	60% (1 : 1.3)

Table 3-3. Optimization of the 1,4-addition step.

Subsequently, the author examined the stereoselective dihydroxylation of **3-45** and **3-35** (Table 3-4). In a preliminary examination using a mixture of **3-45-*anti*** and **-*syn***, the dihydroxylation was found to be accompanied by the lactonization of one of the diastereomers of product diols. It was also found that the dihydroxylation reaction of **3-45** proceeded slower with lower yield rather than that of **3-30**. In addition, the lactonization reaction was much slower than the dihydroxylation, and the end point of the lactonization was difficult to recognize due to the messy reaction mixture including two starting materials, four diols, a lactone and unknown byproducts. Therefore, optimization of the reaction conditions that should enhance the dihydroxylation and the lactonization was required. After extensive screening of reaction conditions including solvents (acetone, CH_3CN, THF, ^{t}BuOH, dioxane, H_2O) and additives (citric acid, DABCO, $PhB(OH)_2$), it was found that lactone **3-47** was obtained from the mixture of **3-45-*anti*** and **-*syn*** (1:2.8) in good yield (55%) by dihydroxylation, using a catalytic amount of OsO_4 in the presence of NMO in a 2:1:1 blend of THF-H_2O-dioxane as a solvent with heating at 40 °C for 2 days, followed by an additional acidic treatment (2 mol/L aq. HCl, 21 °C, 10 h) to stimulate lactonization of the leftover diol. Although the desired diol **3-46** was produced as a major diol, it was not separable from other diol isomers. Therefore, the dihydroxylation of TIPS ether **3-35** was next examined in expecting facile separation of the desired diol. Under the optimized conditions [OsO_4 (cat.), NMO (2 eq), THF-H_2O-dioxane (2:2:1), 40 °C, 19 h], TIPS ether **3-35** stereoselectively provided the desired diol **3-36** and lactone **3-48**. Due to instability of TIPS ether under acidic conditions, the additional treatment with aq. HCl for lactonization was avoided. Thus, thanks to the tandem reactions, diol **3-36** (41%) having the desired stereochemistry was facilely separated from the less polar lactone **3-18** (20%) and other minor diastereomers by silica gel column chromatography.

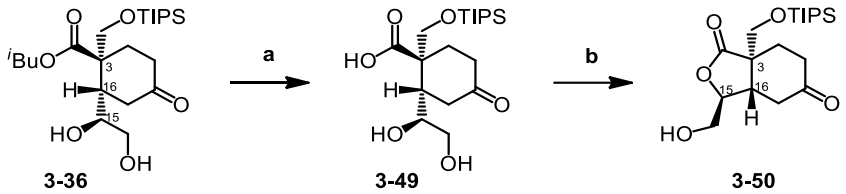


3-45-*anti* (R^2 = TBDPS) **3-45-*syn*** (R^2 = TBDPS) **3-46** (R^2 = TBDPS) **3-47** (R^2 = TBDPS)
3-35-*anti* (R^2 = TIPS) **3-35-*syn*** (R^2 = TIPS) **3-36** (R^2 = TIPS) **3-48** (R^2 = TIPS)

	Substrate	*anti* : *syn*	Conditions	Yields
Entry 1	**3-45** (R^2 = TBDPS)	1 : 2.8	OsO_4 (3 mol% in ^{t}BuOH), NMO (2 eq) THF-H_2O-dioxane (2:1:1), 40 °C, 2 days then 2 mol/L aq. HCl, 21 °C, 10 h	**3-46** : inseparable, not determined **3-47** : 55% (ca. 71% from **3-45-*syn***)
Entry 2	**3-35** (R^2 = TIPS)	1 : 1	OsO_4 (3 mol% in ^{t}BuOH), NMO (2 eq) THF-H_2O-dioxane (2:2:1), 40 °C, 19 h	**3-36** : 41% (ca. 81% from **3-35-*anti***) **3-48** : 20% (ca. 39% from **3-35-*syn***)

Table 3-4. Optimized conditions for stereoselective dihydroxylation/lactonization

The relative stereochemistry at C3, C16 and C15 of **3-36** was confirmed by X-ray analysis of lactone **3-50**, derived from **3-36** (Scheme 3-9). After the hydrolysis of the isobutyl ester moiety of **3-36** under basic conditions, the resulting carboxylic acid was rapidly treated with EDCI•HCl to give crystalline lactone **3-50** (62% over 2 steps). The single crystal X-ray crystallographic analysis of **3-50** demonstrated the stereostructure (Figure 3-1). Thus, the author achieved the synthesis of diol **3-36** including stereocenters at C3, C16 and C15 of portimine **1-32** via a 1,4-addition/diastereoselective dihydroxylation process.



3-36 3-49 3-50

Scheme 3-9. Preparation of crystalline lactone **3-50**. Reagents and conditions: (a) 2 mol/L aq. NaOH, 30% aq. H_2O_2, THF, 21 °C, 47 h; (b) EDCI・HCl, CH_2Cl_2, 21 °C, 2 min, 62% from **3-36**.

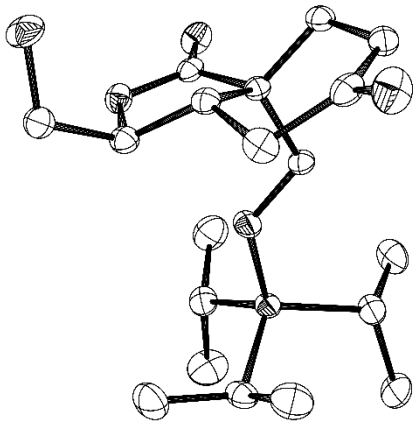
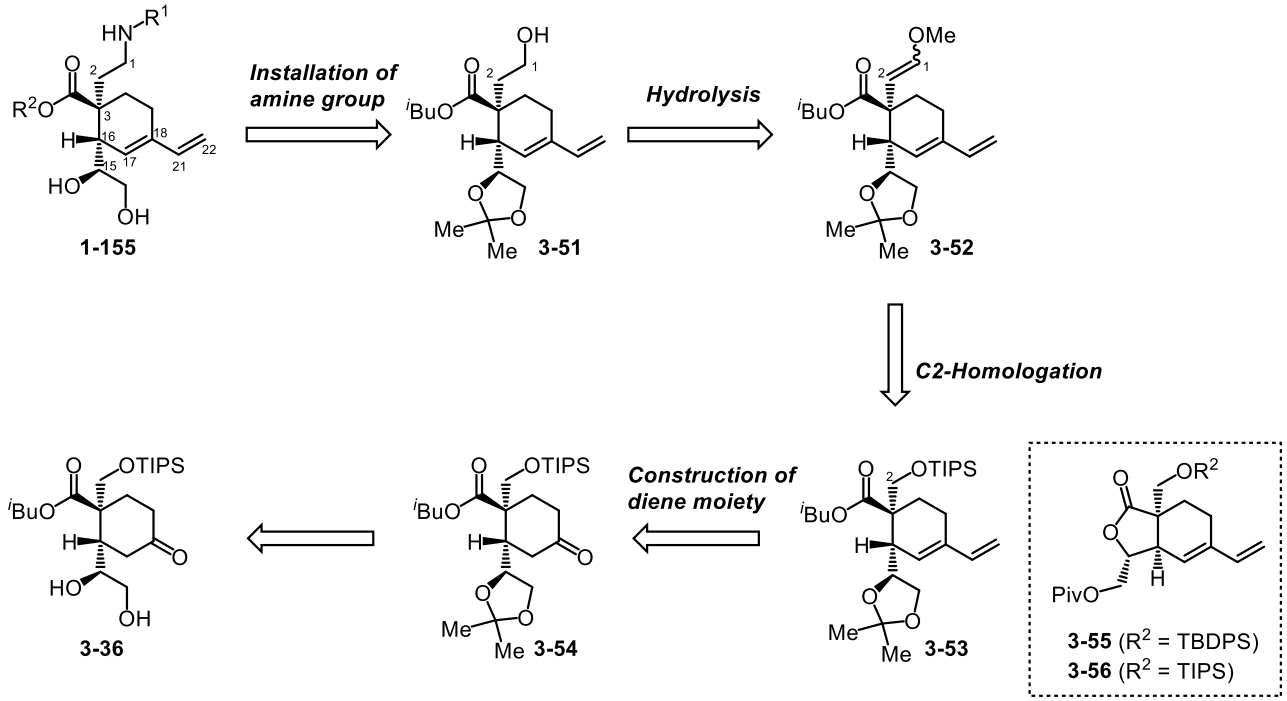


Figure 3-1. ORTEP diagram of **3-50**. Hydrogen atoms are omitted for clarity.

3-5. Construction of the Diene Moiety of the Cyclohexene Segment

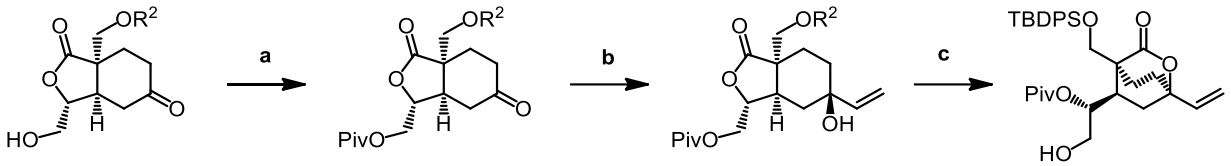
According to the second route, described in Section 3-1, diol **3-36** was planned to be converted to cyclohexene segment **1-155**. The latter half of the synthesis of **1-155** includes the formation of the conjugated diene moiety and the installation of an aminomethyl group, corresponding to the C1-N segment, at C2. The author designed a process toward the goal as shown in Scheme 3-10. The amino group at C1 would be installed by a substitution reaction from primary alcohol **3-51**, which would be prepared from enol ether **3-52**. The enol ether was expected to be synthesized from **3-53** via homologation at C2 including a Wittig reaction. Diene **3-53** would be constructed from cyclohexanone **3-54**, which would be prepared from diol **3-36**.



Scheme 3-10. Plan for the synthesis of cyclohexene segment **1-155** from **3-36**.

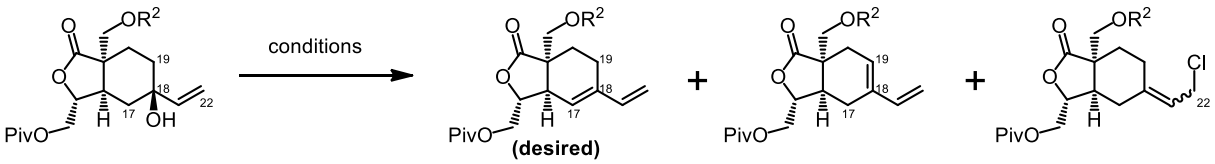
First, in order to find appropriate reaction conditions for the diene-formation, the author undertook the synthesis of dienes **3-55** and **3-56** from above described **3-47** and **3-48**, respectively, as a model study.

The diene formation relied on an addition/elimination process. The C21-C22 unit was introduced as vinylmagnesium chloride at C18 of model compounds **3-47** and **3-48** (Scheme 3-11). After the protection of the primary alcohols of **3-47** and **3-48** as pivalate esters,[9] the resulting **3-57** (91%) and **3-58** (84%) were reacted with vinylmagnesium chloride to afford **3-59** (87%, a 10:1 mixture of diastereomers) and **3-60** (87%, a 9:1 mixture of diastereomers), respectively. It should be noted that the vinylation reaction required an excess amount of vinylmagnesium chloride (3 to 5 eq) at a high concentration (> 0.2 mol/L) to complete the reaction. When allylic alcohol **3-59** was treated with vinylmagnesium chloride at 40 °C, bicyclic lactone **3-61** was produced as a major product, thereby determining the relative stereochemistry of newly generated stereocenter.



Scheme 3-11. Preparation of allylic alcohols **3-59** and **3-60**. Reagents and conditions: (a) PivCl, DIPEA, DMAP, CH_2Cl_2, 21 °C, 2 h, **3-57**: 91%, **3-58**: 84%; (b) vinylmagnesium chloride, THF, –78 °C, 1 h, **3-59**: 87% (d.r. = 10:1), **3-60**: 87% (d.r. = 9:1). (c) vinyl magnesium chloride, THF, 40 °C, 3 h, 55%.

Next, dehydration of allylic alcohols **3-59** and **3-60** was examined to construct the diene moiety (Table 3-5). When alcohol **3-59** was treated with mesyl chloride and Et_3N at 40 °C, tertiary hydroxyl group was eliminated to give a 2:1 mixture of the desired diene **3-55** and regioisomeric diene **3-62** along with unidentified, aromatized byproducts (Entry 1). The author extensively explored effective conditions for the sulfonylation/elimination process. However, the exploration resulted in only enhancement of the aromatization, and no improvement was observed. The reaction of **3-59** with $SOCl_2$ in pyridine at 0 °C for 40 min produced only a small amount of allylic chloride **3-64** (Entry 2). This result suggested the use of more reactive sulfoxide or sulfonium reagents, which were expected to be reacted even with the hindered tertiary hydroxyl group at C18. Thus, allylic alcohol **3-60** was reacted with chlorodimethylsulfonium chloride, generated under Swern oxidation conditions[10], to produce a 1.1:1 inseparable mixture of dienes **3-56** and **3-63** (52% combined yield) and chloride **3-65** (10%) without aromatized byproduct (Entry 3). The change of base to more bulky DIPEA increased the ratio of the desired diene **3-56** (Entry 4). Finally, the use of THF as a solvent, instead of CH_2Cl_2, resulted in the best production of **3-56** (Entry 5). The attempts to suppress the chlorination, such as the use of DMSO-TFAA or DMSO-Tf_2O, resulted in no reaction.

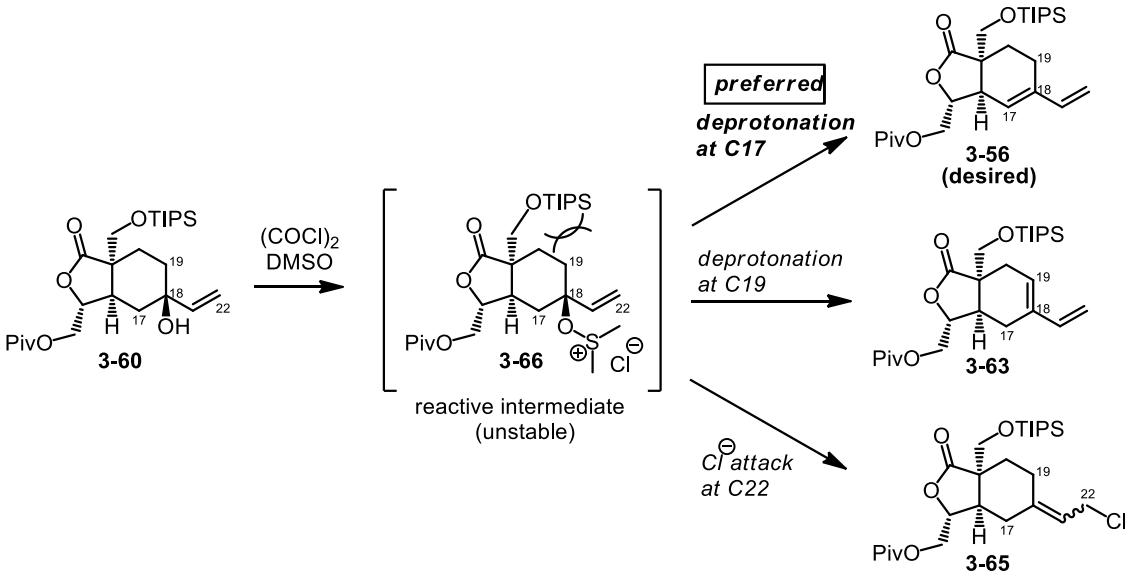


3-59 (R^2 = TBDPS, d.r. = 10:1 at C18)
3-60 (R^2 = TIPS, d.r. = 9:1 at C18)
3-55 (R^2 = TBDPS)
3-56 (R^2 = TIPS)
3-62 (R^2 = TBDPS)
3-63 (R^2 = TIPS)
3-64 (R^2 = TBDPS)
3-65 (R^2 = TIPS)

	Substrate	Conditions	Yields
Entry 1	**3-59** (R^2 = TBDPS)	MsCl, Et_3N, $(CH_2Cl)_2$, 40 °C, overnight	**3-55**+**3-62** : ~50% (2 : 1)
Entry 2	**3-59** (R^2 = TBDPS)	$SOCl_2$, pyridine, 0 °C, 40 min	**3-64** : 25%
Entry 3	**3-60** (R^2 = TIPS)	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C to 21 °C, 18 h	**3-56**+**3-63** : 52% (1.1 : 1), **3-65** : 10%
Entry 4	**3-60** (R^2 = TIPS)	$(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, -60 °C to 21 °C, 25 h	**3-56**+**3-63** : 70% (2.6 : 1), **3-65** : 11%
Entry 5	**3-60** (R^2 = TIPS)	$(COCl)_2$, DMSO, DIPEA, THF, -60 °C to 21 °C, 1.5 h	**3-56**+**3-63** : 84% (4.0 : 1), **3-65** : 8%

Table 3-5. Optimization of elimination conditions for the diene formation using model compounds.

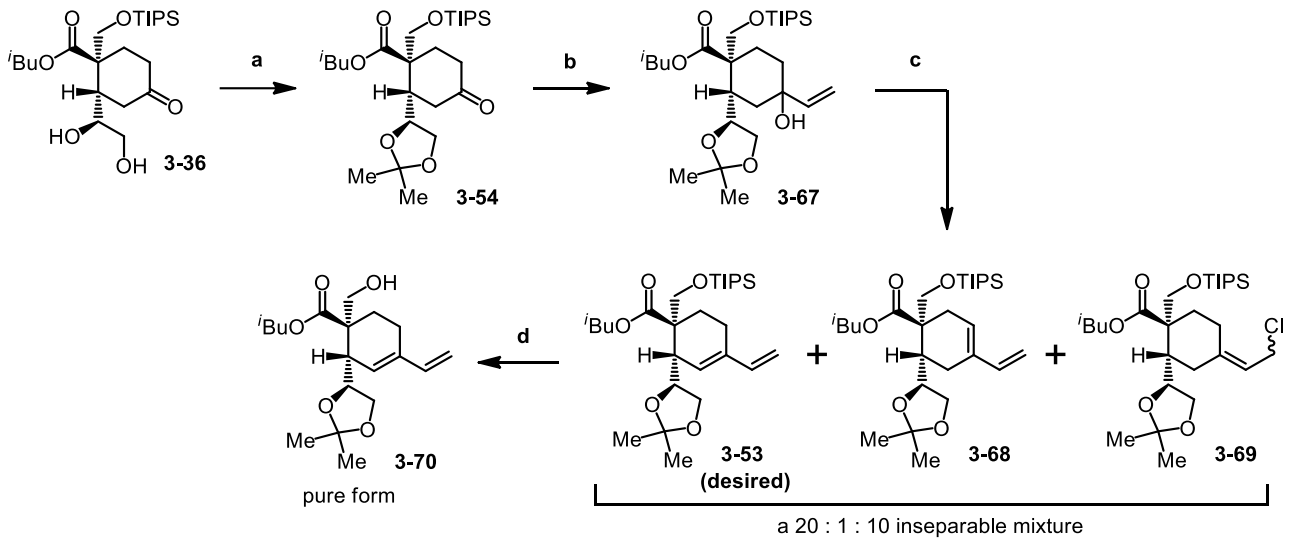
The improved regioselective production of **3-56** in the elimination reaction of **3-60** was rationalized as follows (Scheme 3-12): (i) Although similar degrees of the steric hindrance around H17 and H19, which would be caused by the TIPSoxymethyl group at C3, are anticipated due to the similar distances of C3-C17 and C3-C19, the fact of the improved selectivity by bulky DIEPA instead of compact TEA suggested that the steric effect of the TIPSoxymethyl group might control the regio selectivity in E2 type deprotonation. (ii) Because THF, more polar than CH_2Cl_2, would stabilize ionic intermediate **3-66**, the side reactions, caused by the instability of **3-66**, would be inhibited, thereby enhancing the desired elimination reaction.



Scheme 3-12. Plausible reaction pathway for the elimination reaction.

The diene formation from **3-36** was then examined (Scheme 3-13). After diol **3-36** was protected as an isopropylidene acetal (87%), the resulting ketone **3-54** was reacted with vinylmagnesium chloride to give allylic alcohol **3-67** as a 4:1 mixture of diastereomers (97%). Next, the diastereomers of **3-67** were separately dehydrated under the optimized conditions as a preliminary study. The major isomer was converted to an inseparable 10:1:10 mixture of the desired diene **3-53**, regioisomeric diene **3-68** and allylic chloride **3-69**, while the minor isomer provided a 10:1:3 mixture of **3-53**, **3-68** and **3-69**. It is notable that allylic alcohol **3-67** showed higher selectivity of C17-C18 double bond than model **3-60** in the dehydration reaction. Since both diastereomers of **3-67** showed the preference of **3-53**, the 4:1 mixture of **3-67** was dehydrated without separation as a practical synthesis. As a result, an inseparable 20:1:10 mixture of **3-53**, **3-68** and **3-69** was obtained. Treatment of the mixture with TBAF followed by separation by SiO_2 column chromatography gave the desired alcohol **3-70** in pure form.

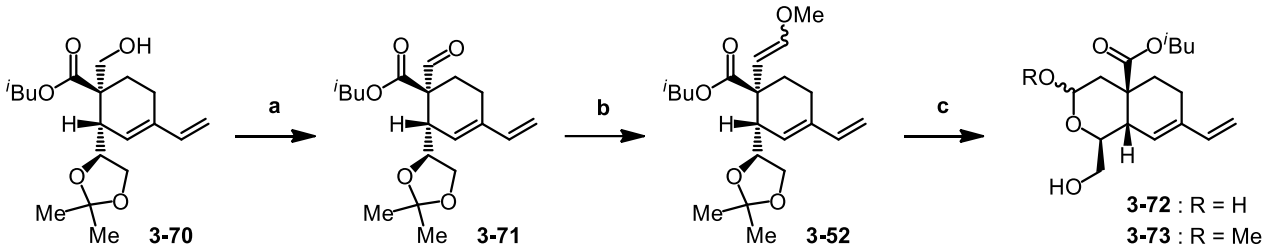
Thus, the author achieved the construction of the diene moiety of cyclohexene segment **1-155** via a process including the installation of a vinyl group followed by the elimination under the modified Swern oxidation conditions.



Scheme 3-13. Synthesis of **3-70**. Reagents and conditions: (a) 2,2-dimethoxypropane, PPTS, acetone, 21 °C, 21 h, then H_2O, 21 °C, 14 h, 87%; (b) vinyl magnesium chloride, THF, –78 °C, 30 min, 97% (a 4:1 mixture of diastereomers); (c) $(COCl)_2$, DMSO, THF, –60 °C, 10 min, then , –60 °C, 30 min, then DIPEA, –60 °C to 0 °C, 1 h, then 21 °C, 17.5 h; (d) TBAF, THF, 21 °C, 13 h, then separation, 63% from **3-67**.

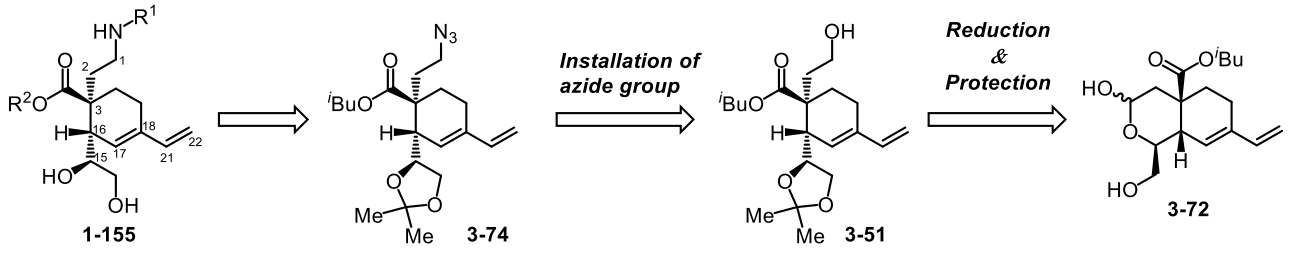
3-6. Completion of the Synthesis of the Cyclohexene Segment

Toward the completion of the synthesis of cyclohexene segment **1-155**, the author examined the homologation at C2 (Scheme 3-14). Alcohol **3-70** was oxidized with DMPI[11] to give aldehyde **3-71**. Wittig reaction of aldehyde **3-71** produced a 1:1 mixture of **(*E*)-** and **(*Z*)-3-52** in 71% for 2 steps. Treatment of the mixture of **3-52** with aq. HCl promoted the hydrolysis of the methyl enol ether and the acetonide group to produce cyclic hemiacetal **3-72** (64%) and **3-73** (23%). Efforts to convert **3-73** to **3-72** under various acidic conditions, however, resulted in no reaction or decomposition of substrate.



Scheme 3-14. Synthesis of **3-72**. Reagents and conditions: (a) DMPI, $NaHCO_3$, CH_2Cl_2, 21 °C, 1 h; (b) $CH_3OCH_2PPh_3Cl$, NHMDS, THF, 0 °C, 15 min, then **3-71**, –78 °C to 21 °C, 19 h, 71% from **3-70**; (c) 2 mol/L aq. HCl, THF, 21 °C, 12.5 h, **3-72**: 64%, **3-73**: 23%.

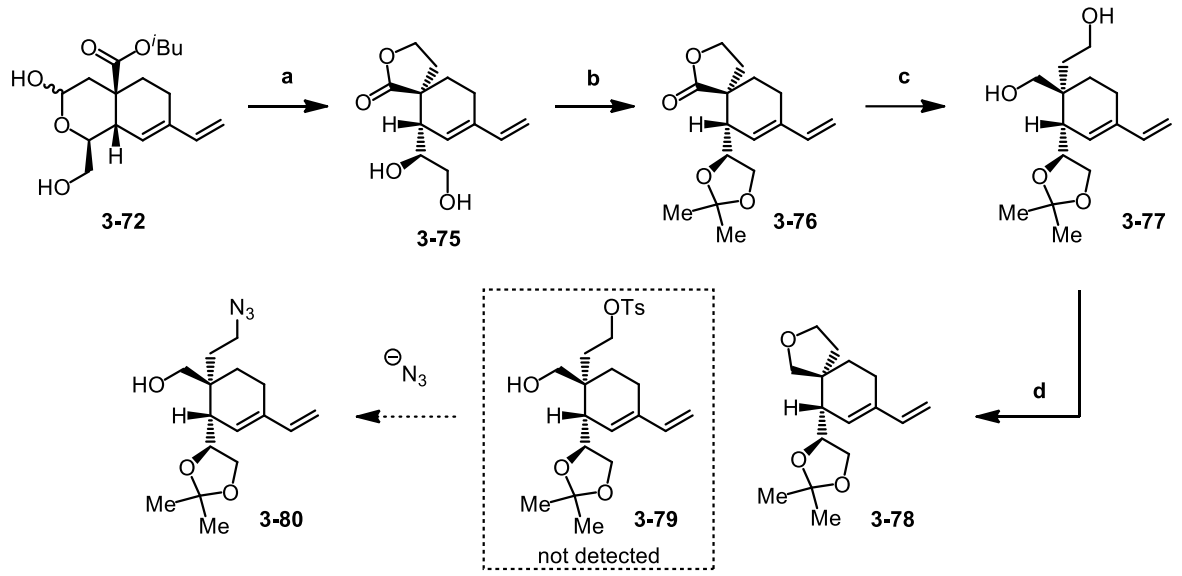
At this stage, the transformation of **3-72** to **1-155**, corresponding to the rest of the second route, was designed to employ a sequence involving reduction of C1, protection of O14 and O15, substitution of an azide group at C1 followed by reduction to an amino group and deprotection (Scheme 3-15).



Scheme 3-15. A plan for the installation of an amino group at C1.

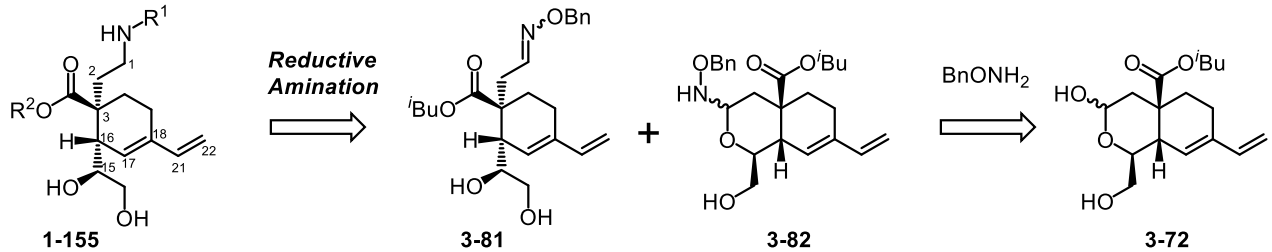
The reduction of cyclic acetal **3-72** with $NaBH_4$, contrary to the expectation, produced spirolactone **3-75**, which was quantitatively isolated as acetonide **3-76** after protection (Scheme 3-16). Lactone **3-76** was reduced with $LiAlH_4$ to produce 1,4-diol **3-77** (66%). In expectation of the selective tosylation of the sterically less-hindered primary alcohol at C1, diol **3-77** was then treated with TsCl. However, concomitant

with the tosylation, an intramolecular cyclic etherification took place to give spirocyclic ether **3-78**. The introduction of a leaving group at C1 would be possible but would require a roundabout multistep route including a protection/deprotection sequence. Therefore, the author decided to take an alternative short-step process from **3-72** to **1-155**.

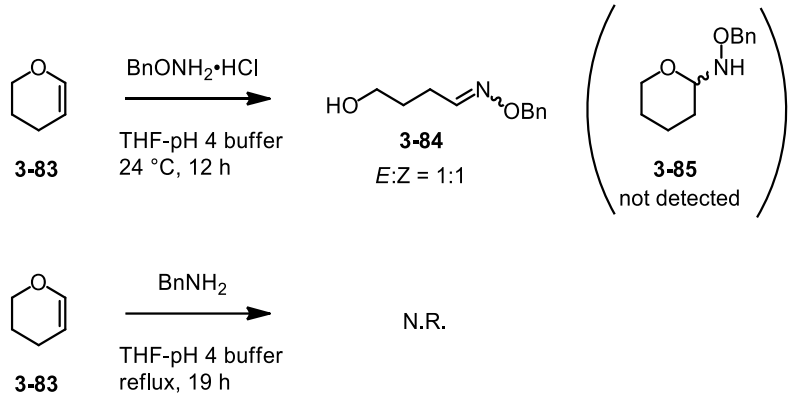


Scheme 3-16. Attempted transformation of **3-72** for the installation of azide group at C1. Reagents and conditions: (a) $NaBH_4$, EtOH-H_2O, 21 °C, 1 h; (b) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 21 °C, 2 h, quant.; (c) $LiAlH_4$, THF, 21 °C, 30 min, 66%; (d) TsCl, Et_3N, CH_2Cl_2, 21 °C, 12 h, **3-78**:77%.

The short-step process for the installation of an amino group at C1 included a reductive amination using $BnONH_2$ as an ammonia equivalent (Scheme 3-17). Hydroxylamines are known to have higher nucleophilicity due to α-effect and, therefore, have greater tendency of imine formation over general amines. In order to know the difference of reactivity, $BnONH_2$ and benzylamine were treated with dihydropyran (**3-83**) in actual practice (Scheme 3-18). As a result, benzylamine was not reacted with dihydropyran in the presence of pH4 buffer even under reflux condition. On the contrary, $BnONH_2$ was completely reacted with dihydropyran at room temperature to produce exclusively a 1:1 mixture of (*E*)- and (*Z*)-oxime **3-84**. Thus, $BnONH_2$ was employed as an ammonia equivalent for the process.

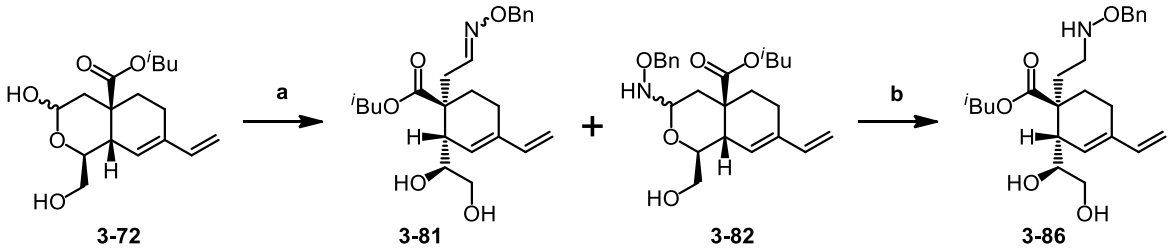


Scheme 3-17. The second plan for the installation of amino group at C1.



Scheme 3-18. Comparison of reactivity between *O*-benzylhydroxylamine and benzylamine.

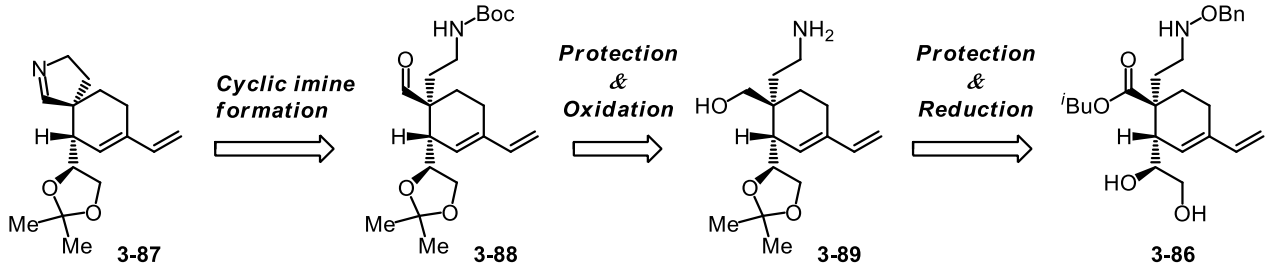
Finally, cyclohexene segment **3-86** was synthesized from cyclic acetal **3-72** (Scheme 3-19). Upon treatment with $BnONH_2$ under acidic condition, hemiacetal **3-72** produced a mixture of oxime **3-81** and cyclic aminal **3-82**, which was reduced with $NaBH_3CN$ to afford **3-86** corresponding to cyclohexene segment **1-155** in 75% for 2 steps, thereby completing the installation of an amino group at C1. Thus, the author achieved the synthesis of cyclohexene segment **3-86** of portimine in 6.5% overall yield over 16 steps from 3-ethoxycyclohex-2-enone (**3-4**).



Scheme 3-19. Synthesis of cyclohexene segment of portimine. Reagents and conditions: (a) $BnONH_2$・HCl, THF-pH 4 buffer, 21 °C, 24.5 h; (b) $NaBH_3CN$, 1 mol/L methanolic HCl, EtOH, 21 °C, 30 min, 75% from **3-72**.

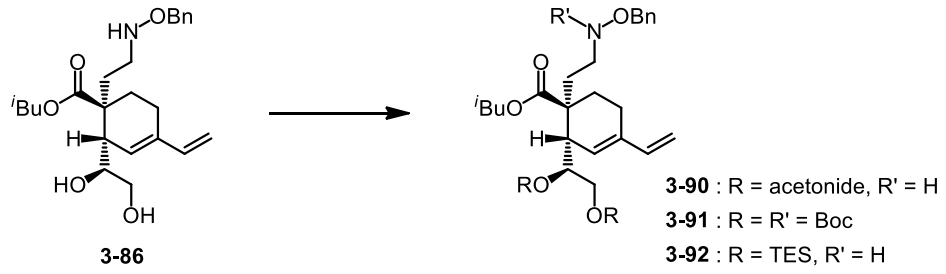
3-7. Further Conversion of the Cyclohexene Segment

With the desired cyclohexene segment **3-86** in hand, the author next focused on the development of further conversion process from **3-86** for total synthesis of portimine. Accordingly, a preliminary process for the transformation of **3-86** to model imine **3-87** was investigated via a route including the protection of the diol group of **3-86** as an isopropylidene acetal, the reduction of the ester and alkoxyamine groups to form **3-89**, the protection of the amino group followed by oxidation to aldehyde **3-88**, and cyclic imine formation to afford **3-87** (Scheme 3-20).



Scheme 3-20. A plan for the synthesis of cyclic imine **3-87** from **3-86**.

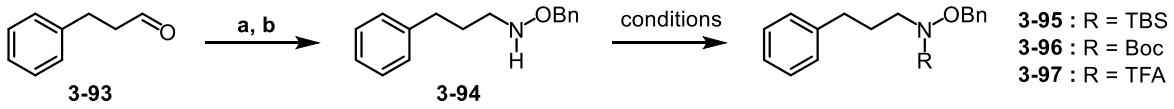
The selective protection of the 1,2-diol moiety of **3-86** required repeated trial and error (Table 3-6). Treatment of **3-86** with 2,2-dimethoxypropane in the presence of PPTS resulted in decomposition to give a complex mixture, which unexpectedly lost the benzyloxy group (Entry 1). The protection of the alkoxyamine with Boc_2O before the acetonization, however, afforded only a complex mixture (Entry 2). The reaction of **3-86** with TESOTf produced no desired **3-92** but a complex mixture (Entry 3).



	Conditions	Results
Entry 1	2,2-dimethoxypropane, PPTS, CH_2Cl_2, 21 °C	decomposition
Entry 2	Boc_2O, DMAP, CH_3CN, 21 °C	complex mixture
Entry 3	TESOTf, 2,6-lutidine,CH_2Cl_2, -60 °C	complex mixture

Table 3-6. Attempts to protect 1,2-diol moiety of **3-86**.

The above results suggested the lability of the alkoxyamine moiety of **3-86** under acidic or basic conditions. Therefore, the author investigated the conditions for the reliable protection of an alkoxyamine group without decomposition using simple model compound **3-94**, prepared from 3-phenylpropanal (**3-93**) (Scheme 3-21). Although the treatment of **3-94** with PPTS under the above acetonization conditions recovered **3-94** (Entry 1), the use of PTS under reflux conditions induced decomposition accompanied by the loss of the benzyloxy group (Entry 2). Since it was suggested that the alkoxyamine group would be decomposed via an enamine intermediate, the protection of the alkoxyamine group which reduce nucleophilicity would inhibit the decomposition under acetonization conditions. Therefore, the author next searched for an appropriate protection for the alkoxyamine group. However, the reaction with TBSOTf or Boc_2O gave only unsatisfactory results (Entries 3 and 4). Finally, it was found that the treatment of **3-94** with TFAA and pyridine at 24 °C produced amide **3-97** in 90% yield (Entry 5).

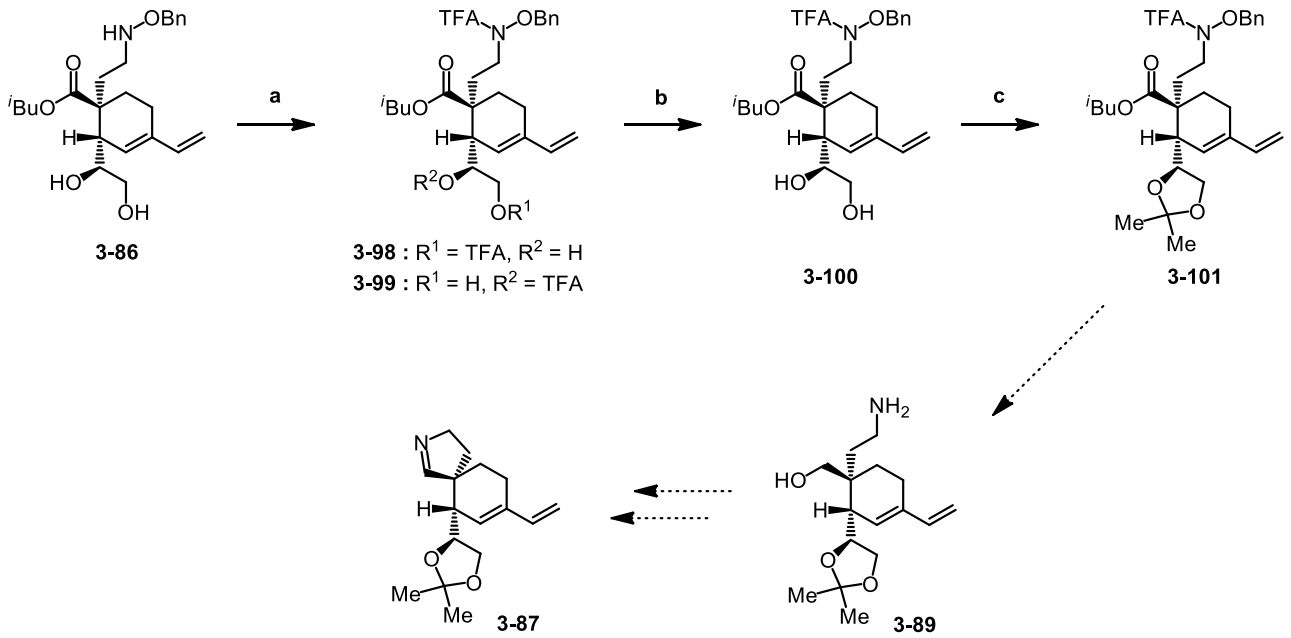


	conditions	results
Entry 1	2,2-dimethoxypropane, PPTS, $(CH_2Cl)_2$, 21-40 °C	No reaction
Entry 2	2,2-dimethoxypropane, PTS, $(CH_2Cl)_2$, reflux	decomposition
Entry 3	TBSOTf, 2,6-lutidine,CH_2Cl_2, 24 °C, 11 h	No reaction
Entry 4	Boc_2O, DMAP, CH_3CN, 24 °C, 1 week	ca. 50% conversion[a]
Entry 5	TFAA, pyridine, CH_2Cl_2, 24 °C, 19 h	**3-97** : 90%

a) The conversion yield was calculated by the ^1H NMR spectra.

Scheme 3-21. Investigation of the protection conditions for alkoxyamine **3-94**. Reagents and conditions: (a) $BnONH_2 \cdot HCl$, CH_2Cl_2, MS4A, 25 °C, 2 days; (b) $NaBH_3CN$, 1 mol/L methanolic HCl, EtOH, 21 °C, 40 min, 43% from **3-93**.

The author next studied the selective protection of the diol group of **3-86** based on the above result (Scheme 3-22). Treatment of **3-86** with TFAA and pyridine afforded a mixture of **3-98** and **3-99**, which have a TFA amide and a mono TFA ester. After several examinations, the selective hydrolysis of the TFA ester groups of **3-98** and **3-99** was accomplished by using 5% aq. NH_3-MeOH solution (24% over 2 steps). Finally, the resulting diol **3-100** was successfully protected as isopropylidene acetal **3-101** (98%). In the future, TFA amide **3-100** would be transformed to aminoalcohol **3-89**, which would also be convertible to cyclic imine **3-87**. Although the demonstration of the route shown in Scheme 3-22 was incomplete, the author hoped that this route would provide useful knowledge for the total synthesis of portimine.



Scheme 3-22. Reagents and conditions: (a) TFAA, pyridine, CH_2Cl_2, 24 °C, 1 h; (b) 5% aq. NH_3-MeOH-CH_2Cl_2, 0 °C, 12 min, 24% from **3-86**; (c) 2,2-dimethyxpropane, PPTS, CH_2Cl_2, 24 °C, 20 min, 98%.

3-8. Conclusion

For the second plan for the construction of cyclohexene segment **1-155** of portimine (**1-32**), the author designed two routes to the cyclohexene segment via cyclohexenone **3-3**.

In the first route, the Ireland-Claisen rearrangement of cyclohexenyl esters **3-14** and **3-2**, prepared from 3-ethoxy-cyclohex-2-enone (**3-4**) via cyclohexenone **3-3**, were attempted to install a C14-C15 unit to C16 center. However, despite extensive investigations of reaction conditions, no rearranged product was obtained.

Then, the author examined the second route, which employed a 1,4-addition of vinyl cuprate to cyclohexenone **3-3** for the installation of a C14-C15 unit at C16. The 1,4-addition, however, afforded the desired adduct **3-6** in low yield and diastereoselectivity. To improve the ratio of the desired diastereomer, the author synthesized cyclohexenone **3-34**, which had a truncated side chain corresponding to the C2 unit at C3, a TIPSO group at C2 and isobutyl ester at C3, as a substrate for the 1,4-addition. As a result, the diastereoselectivity of the 1,4-addition exhibited an increased ratio of the desired *anti*-adduct **3-35-*anti*** to *syn*-adduct **3-35-*syn*** up to 1:1. The mixture of **3-35-*anti*** and **3-35-*syn*** was subjected to a dihydroxylation/lactonization sequence to afford the desired diol **3-36** selectively after separation form lactone **3-48** and other diastereomer diols. The relative configurations of C3, C16 and C15 centers were unambiguously determined by X-ray crystallographic analysis of lactone **3-50** derived from **3-36**.

Next, the diene moiety of the C17-C18-C21-C22 region was constructed by the addition of a vinyl Grignard reagent followed by elimination. Although the optimization of the elimination required trial and error using a model compound, a chlorodimethylsulfonium chloride-mediated elimination reaction was found to work out well. Thus, a 1,2-addition of a vinyl Grignard reagent to ketone **3-67**, derived from **3-36**, and the subsequent elimination under Swern conditions provided desired diene **3-53** in high regioselectivity. After homologation at C2 of **3-70**, derived from **3-36**, via a process including oxidation/Wittig reaction followed by hydrolysis, the resulting cyclic acetal **3-72** was reacted with $BnONH_2$ and subsequently with $NaBH_3CN$ to provide the desired cyclohexene segment **3-86** successfully. Thus, the author achieved the synthesis of the core structure of portimine in 6.5% yield over 16 steps from **3-4**.

The reactivity of cyclohexene segment **3-86** was then investigated under several conditions in order to access cyclic imine **3-87**. However, it found that benzylhydroxylamine moiety in **3-86** was unstable even under mild acidic/basic conditions. After several investigations, the author found that TFA amide **3-100** was stable under acetonide-protection conditions. In the future, TFA amide **3-100** would be transformed to aminoalcohol **3-89**, which is expected to be used for the total synthesis of portimine.

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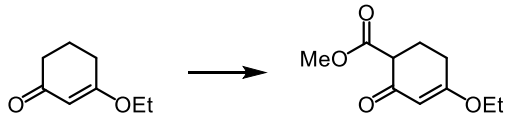
Experimental sections

General methods

All air sensitive reactions were carried out under argon in oven-dried glassware using standard syringe, cannula and septa techniques. Dry solvents were purchased from commercial sources. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F254, 0.25 mm in thickness or Wako, silica gel 70 F254, 0.25 mm in thickness). 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) as a stationary phase. Melting points were measured on an ASONE ATM-02 without calibration. Infrared spectra (IR) were measured on a JASCO FT/IR-4700 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) or a JEOL JNM-ECA 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of tetramethylsilane (0 ppm for ^{1}H NMR in $CDCl_3$) or the respective solvent (^{1}H NMR: 7.26 ppm in $CDCl_3$; ^{13}C NMR: 77.0 ppm in $CDCl_3$) as the internal standard. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Coupling constants (J) are reported in Hz. High resolution mass spectra (HRMS) were measured on a JEOL JMS-T100GCV (under field desorption [FD] conditions) double focusing magnetic sector mass spectrometer.

Compound 3-10

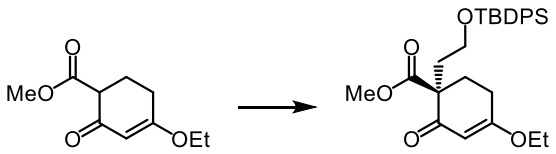


3-4 **3-10**

To a solution of *N*,*N*-diisopropylamine (1.04 mL, 7.39 mmol) in THF (7.4 mL) was added BuLi (1.55 mol/L in Hexane, 4.77 mL, 7.39 mmol) at -78 °C, and the mixture was stirred for 5 min. Then, to the mixture was added a solution of **3-4** (414.2 mg, 2.95 mmol) in THF (2.4 mL) at -78 °C, and the mixture was stirred for 20 min. Then, to the mixture was added methyl chloroformate (0.275 mL, 3.55 mmol) at -78 °C, and the mixture was stirred for 20 min. After the reaction mixture was warmed to 24 °C, the mixture was stirred for 3 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (30 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4) to give **3-10** (515.7 mg, 2.60 mmol, 88%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* = 7.0 Hz), 2.16 (1H, tdd, *J* = 5.1, 13.4 Hz), 2.35 (1H, dtd, *J* = 4.6, 8.6, 13.3 Hz), 2.42 (1H, ddd, *J* = 5.1, 8.3, 17.5 Hz), 2.57 (1H, ddd, *J* = 5.1, 8.3, 17.5 Hz), 3.34 (1H, dd, *J* = 5.0, 9.0 Hz), 3.75 (3H, s), 3.91 (2H, dq, *J* = 2.9, 7.0 Hz), 5.38 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (CH_3), 23.9 (CH_2), 27.2 (CH_2), 52.0 (CH), 52.1 (CH_3), 64.4 (CH_2), 101.9 (CH), 170.7 (C), 177.6 (C), 193.5 (C).

Compound 3-11

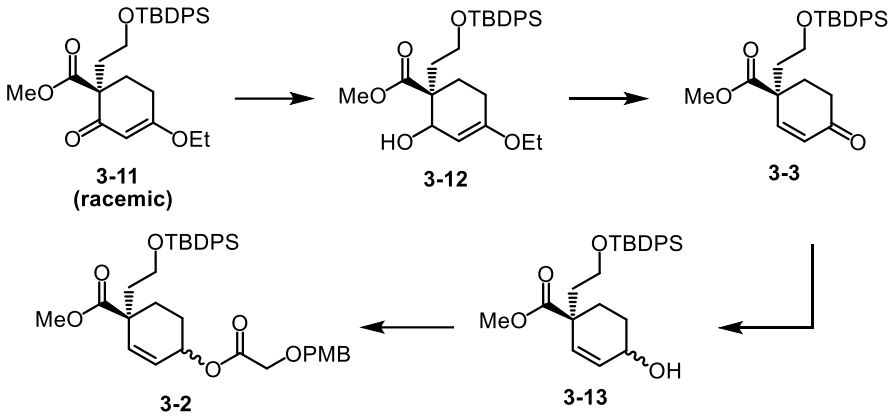


3-10 **3-11 (racemic)**

To a solution of **3-10** (515.7 mg, 2.60 mmol) in CH_3CN (3.0 mL) was added Cs_2CO_3 (1.70 g, 5.20 mmol) and a solution of **3-17** (2.26 g, 5.50 mmol) at 21 °C, and the mixture was stirred for 15 h at 65 °C. The reaction mixture was filtered through a Celite pad and the filterate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 30 → 4) to give **3-11** (598.9 mg, 1.2460 mmol, 48%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.36 (3H, t, *J* = 7.0 Hz), 1.98 (1H, ddd, *J* = 5.3, 9.0, 13.6 Hz), 2.03 (1H, td, *J* = 6.6, 14.2 Hz), 2.29-2.38 (2H, m), 2.47 (1H, td, *J* = 5.3, 13.6 Hz), 2.59 (1H, br-ddd, *J* = 5.1, 9.0, 17.8 Hz), 3.63 (3H, s), 3.74 (2H, t, *J* = 6.7 Hz), 3.88 (2H, q, *J* = 7.0 Hz), 5.31 (1H, s), 7.34-7.44 (6H, m), 7.61-7.68 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (CH_3), 19.1 (C), 26.4 (CH_2), 26.8 (CH_3×3), 28.4 (CH_2), 36.2 (CH_2), 52.4 (CH_3), 54.8 (C), 60.7 (CH_2), 64.4 (CH_2), 101.7 (CH), 127.6 (CH×4), 129.6 (CH×2), 133.5 (C), 133.6 (C), 135.5 (CH×4), 172.0 (C), 176.8 (C), 195.6 (C).

Compound 3-2



To a solution of **3-11** (40.6 mg, 0.08446 mmol) in MeOH (0.8 mL) was added $NaBH_4$ (9.6 mg, 0.2534 mmol) and $CeCl_3 \cdot 7H_2O$ (94.4 mg, 0.2534 mmol) at -40 °C, and the mixture was stirred for 30 min at -40 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-12**, which was used in the next reaction without purification.

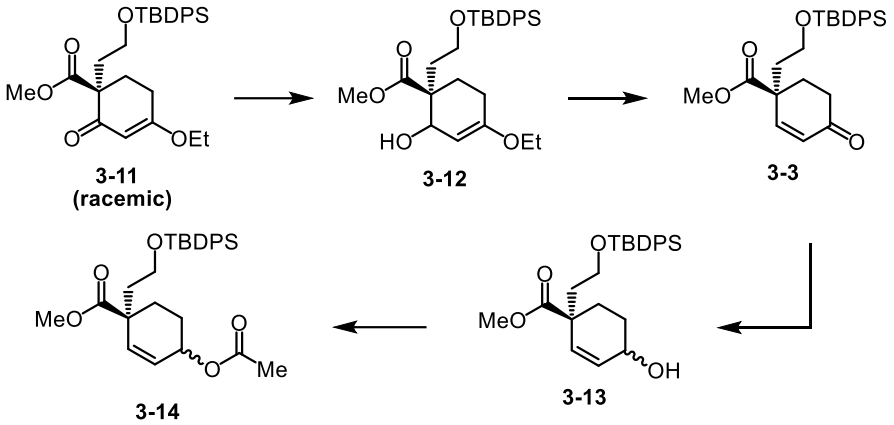
To a solution of the above crude **3-12** in CH_2Cl_2-MeOH-H_2O (2:2:1, 0.8 mL) was added a small amount of PTS·H_2O at 24 °C, and the mixture was stirred for 3 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-3**, which was used in the next reaction without purification.

To a solution of the above crude **3-3** in EtOH-THF (5:1, 0.8 mL) was added $NaBH_4$ (9.6 mg, 0.2534 mmol) and $CeCl_3 \cdot 7H_2O$ (94.4 mg, 0.2534 mmol) at -20 °C, and the mixture was stirred for 15 min at -20 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-13**, which was used in the next reaction without purification.

To a solution of above crude **3-13** in CH_2Cl_2 (0.5 mL) was added a solution of crude **3-20** (0.2074 mmol), EDCI·HCl (42.1 mg, 0.2196 mmol) and an small amount of DMAP at 0 °C, and the mixture was stirred for 40 min at 24 °C. The reaction was quenched with H_2O, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. NaOH and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give a 1:1 mixture of **3-2** (39.0 mg, 0.06323 mmol, 75% from **3-11**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (27/3H, s), 1.20-1.33 (3/3H, m), 1.49-2.15 (13/3H, m), 2.22 (2/3H, dd, *J* = 8.0, 13.0 Hz), 3.58 (3/3H, s), 3.59 (6/3H, s), 3.65 (6/3H, dt, *J* = 6.4, 6.6 Hz), 3.81 (9/3H, br-s), 4.00-4.09 (6/3H, m), 4.55 (6/3H, s), 5.29-5.35 (3/3H, m), 5.71 (2/3H, dd, *J* = 2.8, 10.2 Hz), 5.79 (1/3H, dd, 4.0, 10.2 Hz), 5.94 (2/3H, d, 10.3 Hz), 6.00 (1/3H, d, *J* = 10.3 Hz), 6.88 (6/3H, d, *J* = 8.4 Hz), 7.21-7.49 (24/3H, m), 7.59-7.71 (12/3H, m, *J* = 7.8 Hz)

Compound 3-14



To a solution of **3-11** (46.6 mg, 0.09695 mmol) in MeOH-THF (10:1, 1.0 mL) was added $NaBH_4$ (11.0 mg, 0.2909 mmol) and $CeCl_3 \cdot 7H_2O$ (108.4 mg, 0.2909 mmol) at -40 °C, and the mixture was stirred for 20 min at -40 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-12**, which was used in the next reaction without purification.

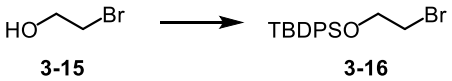
To a solution of the above crude **3-12** in CH_2Cl_2-MeOH-H_2O (2:2:1, 1.0 mL) was added a small amount of PTS·H_2O at 24 °C, and the mixture was stirred for 3 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-3**, which was used in the next reaction without purification.

To a solution of the above crude **3-3** in MeOH-THF (5:1, 1.0 mL) was added $NaBH_4$ (11.0 mg, 0.2909 mmol) and $CeCl_3 \cdot 7H_2O$ (108.4 mg, 0.2909 mmol) at -20 °C, and the mixture was stirred for 30 min at -20 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-13**, which was used in the next reaction without purification.

To a solution of above crude **3-13** in CH_2Cl_2-pyridine (1:1, 1.0 mL) was added an excess amount of Ac_2O at 0 °C, and the mixture was stirred for 19 h at 24 °C. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc (7 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give a 1:1 mixture of **3-14** (35.2 mg, 0.07323 mmol, 76% from **3-11**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (27/3H, s), 1.47-2.11 (16/3H, m), 2.04 (9/3H, s), 2.23 (2/3H, dd, *J* = 7.1, 12.3 Hz), 3.61-3.74 (6/3H, m), 3.58 (3/3H, s), 3.60 (6/3H, s), 5.11-5.30 (3/3H, m), 5.71 (2/3H, dd, *J* = 2.8, 10.3 Hz), 5.79 (1/3H, dd, 3.9, 10.2 Hz), 5.92 (2/3H, d, 10.2 Hz), 5.98 (1/3H, d, *J* = 10.3 Hz), 7.33-7.54 (18/3H, m), 7.59-7.79 (12/3H, m)

Compound 3-16

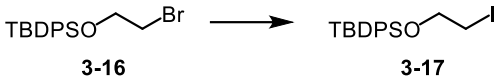


3-15 **3-16**

To a solution of imidazole (686.4 mg, 10.08 mmol) in DMF (5.6 mL) was added TBDPSCl (1.74 mL, 6.72 mmol) and a solution of **3-15** (0.400 mL, 5.60 mmol) at 0 °C, and the mixture was stirred for 22 h at 24 °C. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O (40 mL × 3). The combined organic layers were washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/benzene = 10) to give **3-16** (1.76 g, 4.85 mmol, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s), 3.42 (2H, t, *J* = 6.4 Hz), 3.92 (2H, t, *J* = 6.4 Hz), 7.35-7.51 (6H, m), 7.64-7.75 (4H, m)

Compound 3-17

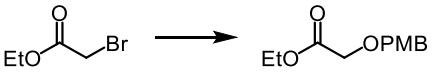


3-16 **3-17**

To a solution of **3-16** (1.76 g, 4.85 mmol) in acetone (16.2 mL) was added NaI (1.45 g, 9.70 mmol) at 24 °C, and the mixture was stirred for 16 h at 40 °C. The reaction mixture was filtered through a Celite pad and the filterate was concentrated under reduced pressure to give crude product **3-17** (1.80 g, 4.80 mmol, 90%) as an yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s), 3.22 (2H, t, *J* = 6.4 Hz), 3.86 (2H, t, *J* = 6.4 Hz), 7.34-7.51 (6H, m), 7.63-7.75 (4H, m)

Compound 3-19

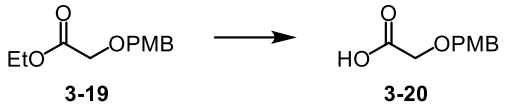


3-18 **3-19**

To a solution of 4-methoxybenzyl alcohol (687.1 mg, 4.97 mmol) in THF-DMF (10:1, 9.0 mL) was added a catalytic amount of KI, NaH (60% in oil, 180.8 mg, 4.75 mmol) and **3-18** (0.500 mL, 4.52 mmol) at 0 °C, and the mixture was stirred for 2.5 h at 24 °C. The reaction was quenched with saturated aq. $NaHCO_3$ and $Na_2S_2O_3$, and the mixture was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/benzene = 9) to give **3-19** (824.8 mg, 3.68 mmol, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* = 7.2 Hz), 3.80 (3H, s), 4.05 (2H, s), 4.22 (2H, q, *J* = 7.2 Hz), 4.56 (2H, s), 6.88 (2H, d, *J* = 8.7 Hz), 7.30 (2H, d, *J* = 8.6 Hz)

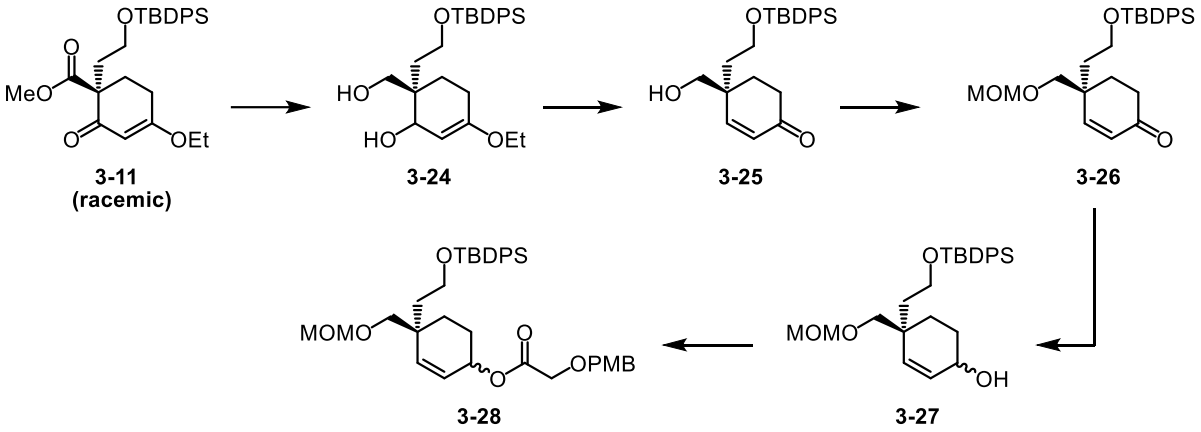
Compound 3-20



3-19 3-20

To a solution of **3-19** (202.9 mg, 0.9048 mmol) in THF (0.9 mL) was added 2.0 mol/L aq. NaOH (0.9 mL) at 0 °C, and the mixture was stirred for 1 h at 24 °C. The reaction was quenched with H_2O, and the mixture was washed with Et_2O (10 mL × 1). After neutralization of the mixture with aq. HCl to pH 1, the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4) to give crude product **3-20**, which was used in the next reaction without purification.

Compound 3-28



3-11 (racemic) 3-24 3-25 3-26 3-27 3-28

To a solution of **3-11** (25.5 mg, 0.05305 mmol) in THF (0.6 mL) was added $LiAlH_4$ (10.1 mg, 0.2653 mmol) at 0 °C, and the mixture was stirred for 2 h at 21 °C. The reaction was quenched with saturated aq. Roschell's salt, and the mixture was extracted with EtOAc (8 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-24**, which was used in the next reaction without purification.

To a solution of the above crude **3-24** in CH_2Cl_2-MeOH-H_2O (2:2:1, 0.7 mL) was added a small amount of PTS·H_2O at 21 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-25**, which was used in the next reaction without purification.

To a solution of the above crude **3-25** in CH_2Cl_2 (0.5 mL) was added DIPEA (44 μL, 0.2496 mmol) and MOMCl (19 μL, 0.2496 mmol) at 0 °C, and the mixture was stirred for 2 h at 24 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (6 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under

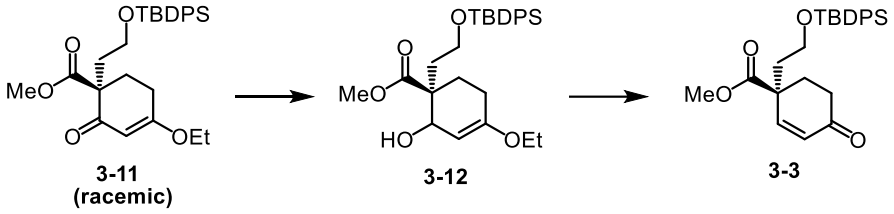
reduced pressure to give crude product **3-26**, which was used in the next reaction without purification.

To a solution of the above crude **3-26** in EtOH-THF (5:1, 0.5 mL) was added $NaBH_4$ (4.7 mg, 0.1248 mmol) and $CeCl_3 \cdot 7H_2O$ (46.5 mg, 0.1248 mmol) at -78 °C, and the mixture was stirred for 10 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-27**, which was used in the next reaction without purification.

To a solution of above crude **3-27** in CH_2Cl_2 (0.5 mL) was added a solution of crude **3-20** (0.05058 mmol), EDCI·HCl (10.5 mg, 0.05491 mmol) and an small amount of DMAP at 0 °C, and the mixture was stirred for 1 h at 21 °C. The reaction was quenched with H_2O, and the mixture was extracted with $CHCl_3$ (5 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. NaOH and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8) to give a 1:1 mixture of **3-28** (8.7 mg, 0.01375 mmol, 55% from **3-11**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (27/3H, s), 1.46-2.02 (18/3H, m), 3.24-3.39 (6/3H, m), 3.28 (9/3H, s), 3.62-3.78 (6/3H, m), 3.81 (9/3H, s), 3.99-4.09 (6/3H, m, *J* = 9.0, 11.4 Hz), 4.51-4.58 (6/3H, d, *J* = 9.8 Hz), 5.23-5.37 (3/3H, m), 5.64-5.76 (6/3H, m), 6.81-7.00 (6/3H, m), 7.18-7.54 (24/3H, m), 7.59-7.79 (12/3H, m)

Compound 3-14

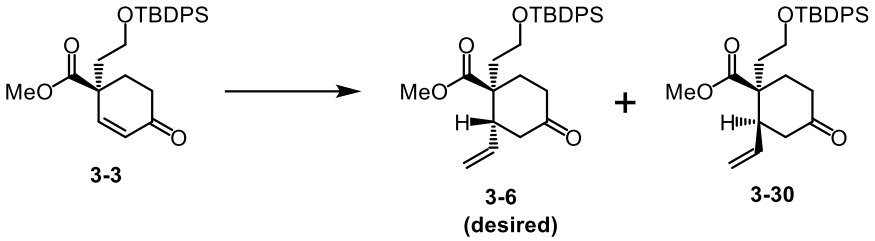


To a solution of **3-11** (63.6 mg, 0.1323 mmol) in MeOH-THF (10:1, 1.3 mL) was added $NaBH_4$ (15.0 mg, 0.3969 mmol) and $CeCl_3 \cdot 7H_2O$ (147.9 mg, 0.3969 mmol) at -40 °C, and the mixture was stirred for 20 min at -40 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-12**, which was used in the next reaction without purification.

To a solution of the above crude **3-12** in CH_2Cl_2-MeOH-H_2O (2:2:1, 1.3 mL) was added a small amount of PTS·H_2O at 24 °C, and the mixture was stirred for 3.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-3**, which was used in the next reaction without purification. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-3** (48.8 mg, 0.1118 mmol, 85% from **3-11**) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.97-2.22 (4H, m), 2.32-2.63 (4H, m), 2.63 (3H, s), 3.70 (2H, t, *J* = 6.4 Hz), 5.97 (1H, d, *J* = 10.3 Hz), 7.00 (1H, d, *J* = 10.3 Hz), 7.34-7.51 (6H, m), 7.60-7.75 (4H, m)

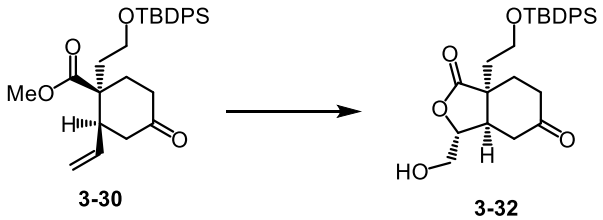
Compound 3-6 and 3-30



To a solution of CuCN (14.1 mg, 0.1569 mmol) in THF (0.8 mL) was added vinyl magnesium chloride (1.42 mol/L in THF, 0.221 mL, 0.3138 mmol) at -78 °C, and the mixture was stirred for 30 min at -78 °C. Then, to the mixture was added a solution of **3-3** (13.7 mg, 0.03138 mmol) in THF (0.3 mL) at -78 °C, and the mixture was stirred for 55 min at -78 °C. The reaction was quenched with 10% aq. NH_3, and the mixture was filtered through the Celite pad. The firterate was extracted with $CHCl_3$ (5 mL × 3) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 13 → 5) to give a 1:3 mixture of **3-6** and **3-30** (7.2 mg, 0.01549 mmol, 49%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (27/3H, s), 1.68-1.91 (3/3H, m), 1.97 (3/3H, quin, *J* = 6.8 Hz), 2.15-2.59 (18/3H, m), 2.66 (2/3H, brdt, *J* = 6.3, 7.1 Hz), 3.08 (1/3H, td, *J* = 4.4, 9.1 Hz), 3.60 (6/3H, s), 3.62-3.80 (6/3H, m), 3.63 (3/3H, s), 4.90-5.22 (6/3H, m), 5.63 (1/3H, ddd, *J* = 8.6, 10.4, 17.0 Hz), 5.77 (2/3H, ddd, *J* = 8.3, 10.4, 17.0 Hz), 7.33-7.52 (18/3H, m), 7.58-7.74 (12/3H, m).

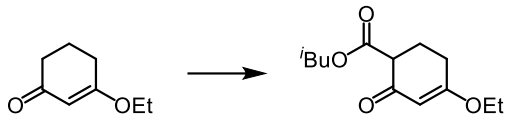
Compound 3-32



To a solution of **3-30** (19.5 mg, 0.04197 mmol) in THF-dioxane-H_2O (1:2:1, 0.4 mL) was added NMO (9.8 mg, 0.08394 mmol) and OsO_4 (0.0197 mol/L in *t*-BuOH, 0.213 mL, 4.20 μmol) at 21 °C, and the mixture was stirred for overnight. The reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc (6 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 1) to give **3-32** (15.8 mg, 0.03386 mmol, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.84 (1H, t, *J* = 6.4 Hz), 1.90 (1H, td, *J* = 5.3, 14.5 Hz), 2.02 (1H, ddd, *J* = 3.4, 10.3, 14.8 Hz), 2.08-2.25 (3H, m), 2.32 (1H, dd, *J* = 2.6, 16.5 Hz), 2.40-2.51 (1H, m), 2.57 (1H, dd, *J* = 6.2, 16.4 Hz), 3.09 (1H, ddd, *J* = 2.6, 6.1, 8.0 Hz), 3.59 (1H, ddd, *J* = 4.0, 7.1, 12.7 Hz), 3.78-3.98 (3H, m), 4.02 (1H, ddd, *J* = 3.0, 4.0, 8.0 Hz), 7.35-7.50 (6H, m), 7.60-7.73 (4H, m).

Compound 3-33

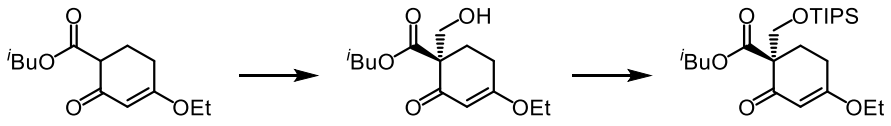


3-4 3-33

To a solution of DIPEA (3.76 mL, 26.75 mmol) in THF (26.8 mL) was added BuLi (1.57 mol/L in hexane, 17.0 mL, 26.75 mmol) at −78 °C, and the mixture was stirred for 8 min. Then, to the mixture was added a solution of **3-4** (1.50 g, 10.70 mmol) in THF (8.9 mL) at −78 °C, and the mixture was stirred for 30 min. Then, to the mixture was added chloro isobutylformate (1.67 mL, 12.84 mmol) at −78 °C, and the mixture was stirred for 30 min. The mixture was warmed to 0 °C, and stirred for 30 min. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (70 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8 → 4) to give **3-33** (2.45 g, 10.17 mmol, 95%) as a colorless solid.

m.p. 67-68°C ; IR (neat) ν 3053, 2966, 2903, 1734, 1650, 1604, 1470, 1383, 1314, 1253, 1206, 1172, 1152, 1114, 1085, 1049, 1015, 913, 867, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (6H, d, J = 6.7 Hz), 1.35 (3H, t, J = 7.0 Hz), 1.95 (1H, nonet, J = 6.7 Hz), 2.17 (1H, tdd, J = 5.1, 6.6, 13.3 Hz), 2.33 (1H, dtd, J = 4.8, 8.5, 13.4 Hz), 2.42 (1H, ddd, J = 5.1, 8.2, 17.4 Hz), 2.54 (1H, ddd, J = 5.2, 6.5, 17.5 Hz), 3.32 (1H, dd, J = 5.1, 8.8 Hz), 3.87-3.93 (2H, m), 3.90 (1H, dd, J = 6.7, 10.4 Hz), 3.95 (1H, dd, J = 6.7, 10.6 Hz), 5.37 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (CH_3), 19.0 (CH_3×2), 24.2 (CH_2), 27.3 (CH_2), 27.7 (CH), 52.3 (CH), 64.4 (CH_2), 71.1 (CH_2), 102.1 (CH), 170.4 (C), 177.4 (C), 193.7 (C); FD-HRMS (*m/z*) calcd for $C_{13}H_{20}O_4$ [M^+]: 240.13616, found: 240.13626.

Compound 3-38



3-33 3-37 (racemic) 3-38

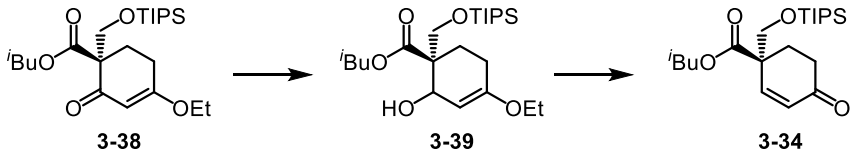
To a solution of **3-33** (459.4 mg, 1.91 mmol) in EtOH (15 mL) was added aq. HCHO (ca. 13 mol/L, 1.47 mL, 19.1 mmol) and KOH (536.4 mg, 9.56 mmol) in EtOH (4.1 mL) at −15 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-37**, which was used in the next reaction without purification.

To a solution of the above crude product **3-37** in CH_2Cl_2 (9.6 mL) was added 2,6-lutidine (0.528 mL, 4.59 mmol) and TIPSOTf (0.617 mL, 2.29 mmol) at 0 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (15 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$,

filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 30) to give **3-38** (807.9 mg, 1.8935 mmol, 99% from **3-33**) as a colorless oil.

IR (neat) ν 2943, 2892, 2867, 1732, 1660, 1608, 1466, 1426, 1405, 1380, 1316, 1289, 1241, 1191, 1157, 1116, 1068, 1029, 1015, 995, 946, 920, 882, 843, 820, 804, 770, 747, 683, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (6H, d, J = 6.7 Hz), 1.01-1.12 (21H, m), 1.36 (3H, t, J = 7.0 Hz), 1.92 (1H, nonet, J = 6.7 Hz), 2.18 (1H, ddd, J = 5.5, 10.2, 15.7 Hz), 2.43 (1H, td, J = 4.9, 17.8 Hz), 2.54 (1H, td, J = 4.8, 13.7 Hz), 2.73 (1H, ddd, J = 5.4, 10.2, 17.8 Hz), 3.82 (1H, dd, J = 6.5, 10.6 Hz), 3.86-3.91 (1H, m), 3.89 (1H, dd, J = 4.8, 7.0 Hz), 3.92 (1H, dd, J = 6.7, 10.6 Hz), 4.04 (1H, d, J = 9.5 Hz), 4.24 (1H, d, J = 9.5 Hz), 5.36 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9 (CH×3), 14.1 (CH_3), 17.9 (CH_3×6), 19.0 (CH_3), 19.0 (CH_3), 26.5 (CH_2), 26.6 (CH_2), 27.7 (CH), 58.2 (C), 64.3 (CH_2), 66.2 (CH_2), 71.1 (CH_2), 102.4 (CH), 170.2 (C), 177.4 (C), 194.0 (C); FD-HRMS (*m/z*) calcd for $C_{23}H_{43}O_5Si$ $[M+H]^+$: 427.28797, found: 427.28776.

Compound 3-34

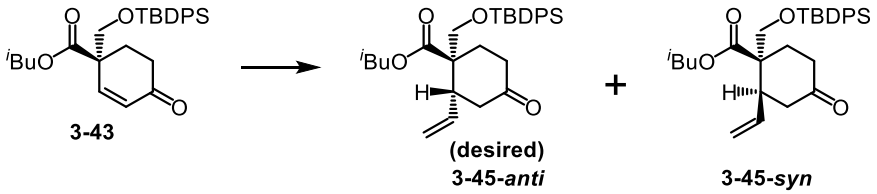


To a solution of **3-38** (3.11 g, 7.29 mmol) in MeOH-THF (2:1, 36.5 mL) was added $CeCl_3 \cdot 7H_2O$ (3.53 g, 9.48 mmol) and $NaBH_4$ (358.6 mg, 9.48 mmol) in EtOH at −40 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was filtered through a Celite pad. The filtrate was extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product **3-39**, which was used in the next reaction without purification.

To a solution of the above crude product **3-39** in CH_2Cl_2-MeOH-H_2O (53:26:1, 72.9 mL) was added PTS·H_2O (138.7 mg, 0.7292 mmol) at 0 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (60 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-34** (2.59 g, 6.77 mmol, 93% from **3-38**) as a colorless oil.

IR (neat) ν 3041, 2944, 2893, 2868, 2727, 1733, 1692, 1465, 1419, 1386, 1331, 1301, 1240, 1206, 1178, 1117, 1068, 1013, 994, 947, 919, 882, 810, 776, 753, 740, 684, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (6H, d, J = 6.7 Hz), 1.01-1.14 (21H, m), 1.94 (1H, nonet, J = 6.7 Hz), 2.06 (1H, m), 2.38-2.55 (3H, m), 3.87 (1H, d, J = 9.1 Hz), 3.89 (1H, dd, J = 6.6, 10.6 Hz), 3.94 (1H, dd, J = 6.6, 10.6 Hz), 3.96 (1H, d, J = 9.1 Hz), 6.08 (1H, d, J = 10.2 Hz), 7.02 (1H, dd, J = 1.0, 10.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (CH×3), 17.8 (CH_3×6), 19.0 (CH_3×2), 27.7 (CH), 27.8 (CH_2), 34.5 (CH_2), 50.9 (C), 68.8 (CH_2), 71.4 (CH_2), 130.0 (CH), 148.7 (CH), 172.2 (C), 198.6 (C); FD-HRMS (*m/z*) calcd for $C_{21}H_{39}O_4Si$ $[M+H]^+$: 383.26176, found:383.26130

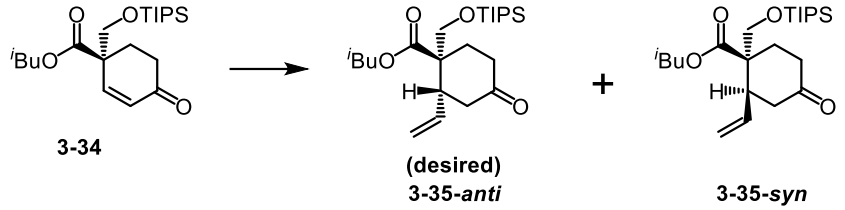
Compound 3-45-*anti/syn*



To a solution of CuI (233.6 mg, 1.23 mmol) and Me_2S (0.3 mL) in THF (4.1 mL) was added vinyl magnesium chloride (1.42 mol/L in THF, 1.73 mL, 2.45 mmol) at −78 °C, and the mixture was stirred for 30 min at −78 °C. Then, to the mixture was added a solution of **3-43** (172.7 mg, 0.3717 mmol) in THF (1.9 mL) at −78 °C, and the mixture was stirred for 35 min. The reaction was quenched with saturated aq. NH_4Cl and 5% aq. NH_3, the mixture was extracted with $CHCl_3$ (20 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give a 1:3.4 mixture of **3-45-*anti*** and **3-45-*syn*** (158.5 mg, 0.3217 mmol, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (18/4H, d, *J* = 6.7 Hz), 0.95 (6/4H, d, *J* = 6.7 Hz), 1.04 (9/4H, s), 1.05 (27/4H, s), 1.91 (3/4H, nonet, *J* = 6.7 Hz), 1.94 (1/4H, nonet, *J* = 6.8 Hz), 2.07-2.39 (15/4H, m), 2.42-2.71 (9/4H, m), 2.84 (3/4H, dt, *J* = 4.9, 8.7 Hz), 3.40 (1/4H, s), 3.64 (1/4H, d, *J* = 9.8 Hz), 3.76-4.04 (15/4H, m), 4.96-5.15 (8/4H, m), 5.59 (1/4H, ddd, *J* = 8.6, 10.4, 17.1 Hz), 5.79 (3/4H, ddd, *J* = 8.2, 10.5, 16.9 Hz), 7.32-7.51 (24/4H, m), 7.55-7.72 (16/4H, m).

Compound 3-35-*anti/syn*

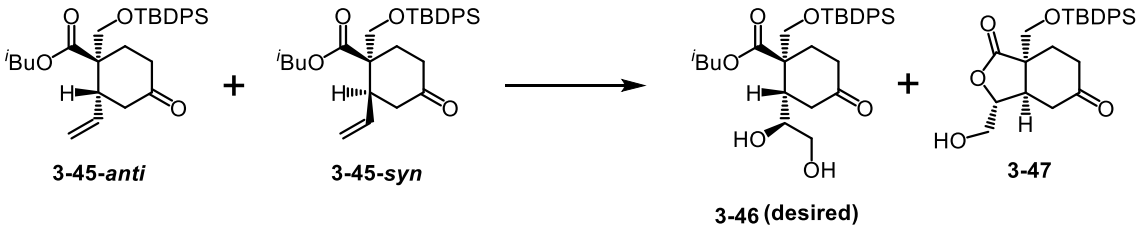


To a solution of CuI (694.8 mg, 3.65 mmol) and Me_2S (1.08 mL, 14.59 mmol) in THF (12.1 mL) was added vinyl magnesium chloride (1.35 mol/L in THF, 5.40 mL, 7.30 mmol) at −78 °C, and the mixture was stirred for 30 min. Then, to the mixture was added a solution of **3-34** (253.8 mg, 0.6633 mmol) in THF (2.2 mL) at −78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aq. NH_4Cl and 5% aq. NH_3, the mixture was extracted with $CHCl_3$ (20 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give a 1:1 mixture of **3-35-*anti*** and **3-35-*syn*** (256.7 mg, 0.6251 mmol, 94%) as a yellow oil.

IR (neat) ν 3080, 2960, 2868, 2756, 2726, 1723, 1638, 1466, 1422, 1383, 1369, 1340, 1304, 1223,1116,1068, 1012, 995, 921, 882, 849, 804, 767, 717, 684, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (6H/2, d, *J* = 6.8 Hz), 0.97 (6H/2, d, *J* = 6.7 Hz), 1.00-1.14 (42H/2, m), 1.73 (1H/2, dt, *J* = 5.1, 13.0 Hz), 1,96 (2H/2, nonet, *J* = 6.7 Hz), 2.14 (1H/2, ddd, *J* = 5.6, 10.7, 14.0 Hz), 2.26 (1H/2, td, *J* = 5.9, 14.0 Hz), 2.32-2.46 (5H/2, m),

2.51 (1H/2, ddd, J = 6.4, 12.7, 15.3 Hz), 2.57-2.70 (3H/2, m), 2.84 (1H/2, ddd, J = 4.8, 8.4, 10.6 Hz), 3.35 (1H/2, br-s), 3.71 (1H/2, d, J = 9.4 Hz), 3.85 (1H/2, d, J = 9.4 Hz), 3.85-3.97 (2H/2, m), 3.90 (2H/2, t, J = 6.7 Hz), 3.92 (1H/2, d, J = 9.5 Hz), 3.94 (1H/2, dd, J = 4.6, 6.6 Hz), 3.99 (1H/2, d, J = 9.5 Hz), 5.07 (1H/2, J = 17.5 Hz), 5.09 (1H/2, d, J = 9.5 Hz), 5.15 (1H/2, d, J = 11.7 Hz), 5.16 (1H/2, d, J = 15.6 Hz), 5.71 (1H/2, ddd, J = 8.7, 10.0, 17.3 Hz), 5.85 (1H/2, ddd, J = 8.4, 10.4, 16.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (CH×6/2), 17.8 (CH_3×6/2), 17.9 (CH_3×6/2), 19.2 (CH_3×4/2), 19.2 (CH_3×4/2), 26.8 (CH_2×1/2), 27.6 (CH×1/2), 27.7 (CH×1/2), 28.9 (CH_2×1/2), 37.8 (CH_2×1/2), 38.1 (CH_2×1/2), 43.4 (CH_2×1/2), 43.5 (CH×1/2), 44.0 (CH_2×1/2), 44.4 (CH×1/2), 51.1 (C×1/2), 51.4 (C×1/2), 66.2 (CH_2×1/2), 68.7 (CH_2×1/2), 70.9 (CH_2×1/2), 71.2 (CH_2×1/2), 117.1 (CH_2×1/2), 118.2 (CH_2×1/2), 135.9 (CH×1/2), 137.1 (CH×1/2), 173.3 (C×1/2), 174.1 (C×1/2), 210.2 (C×1/2), 210.7 (C×1/2); FD-HRMS (*m/z*) calcd for $C_{23}H_{43}O_4Si$ $[M+H]^+$: 411.29306, found: 411.29149.

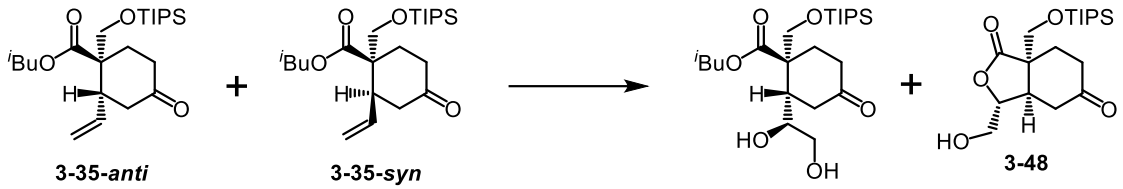
Compound 3-46 and 3-47



To a solution of a 1:2.8 mixture of **3-45-*anti*** and **3-45-*syn*** (40.4 mg, 0.08199 mmol) in THF-1,4-dioxane-H_2O (1:2:1, 0.8 mL) was added NMO (19.2 mg, 0.1640 mmol) and OsO_4 (0.0197 mol/L in ^{t}BuOH, 0.416 mL, 8.20 μmol) at 21 °C, and the mixture was stirred for 2 days at 40 °C. Then, to the mixture was added 2.0 mol/L aq. HCl (0.4 mL) at 21 °C, and the mixture was stirred for 10 h at 21 °C. The reaction was quenched with 2.0 mol/L aq. NaOH and saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc (8 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4 → 3→ 2) to give **3-47** (19.6 mg, 0.04330 mmol, 53%) as a colorless oil and other inseparable diastereomers including desired **3-46**.

3-47 : ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.20 (9H, s), 1.85-2.00 (1H, m), 2.03-2.24 (2H, m, J = 4.6 Hz), 2.37-2.51 (1H, m), 2.43 (1H, dd, J = 2.9, 16.7 Hz), 2.54 (1H, dd, J = 5.8, 16.7 Hz), 2.90 (1H, dddd, J = 2.9, 6.0, 7.0, 12.9 Hz), 3.64 (1H, dd, J = 9.9 Hz), 3.92 (1H, dd, J = 9.9 Hz), 4.08-4.24 (3H, m), 7.36-7.51 (6H, m), 7.59-7.68 (4H, m).

Compound 3-36 and 3-48

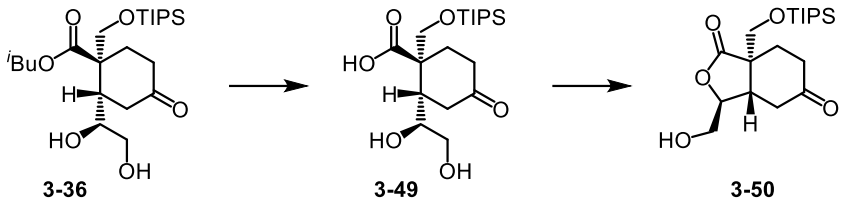


To a solution of OsO_4 (0.0197 mol/L in ^{t}BuOH, 3.50 mL, 0.06886 mmol) and NMO (537.8 mg 4.59 mmol) in 1,4-dioxane-H_2O (1:2, 13.8 mL) was added a 1:1 mixture of **3-35-*anti*** and **3-35-*syn*** (942.6 mg, 2.2953 mmol) in THF (9.2 mL) at 0 °C, and the mixture was stirred for 19 h at 40 °C. After the mixture was cooled to 21 °C, the reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with 0.2 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4 → 3→ 2) to give lactone **3-48** (167.5 mg, 0.4520 mmol, 20%) as a colorless oil and diol **3-36** (412.9 mg, 0.9285 mmol, 41%) as a colorless oil

3-48 : IR (neat) ν 3452, 2944, 2867, 2727, 1769, 1717, 1463, 1415, 1384, 1366, 1333, 1300, 1245, 1201, 1095, 999, 963, 917, 882, 797, 750, 684, 661 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98-1.21 (21H, m), 1.93 (1H, br-s), 2.03 (1H, ddd, *J* = 4.4, 12.9, 14.1 Hz), 2.12 (1H, td, J = 4.8, 14.1 Hz), 2.19 (1H, ddd, *J* = 4.18, 12.8, 18.3 Hz), 2.44 (1H, dd, *J* = 2.7, 16.7 Hz), 2.51 (1H, td, *J* = 4.4, 18.3 Hz), 2.63 (1H, dd, *J* = 6.0, 16.7 Hz), 3.11 (1H, ddd, *J* = 2.7, 6.0, 7.8 Hz), 3.71 (1H, dd, *J* = 5.2, 12.5 Hz), 3.74 (1H, d, *J* = 9.5 Hz), 3.87 (1H, dd, *J* = 3.1, 12.5 Hz), 3.98 (1H, d, *J* = 9.5 Hz), 4.03 (1H, ddd, *J* = 3.2, 5.1, 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (CH×3), 17.9 (CH_3×3), 17.9 (CH_3×3), 26.1 (CH_2), 36.1 (CH), 36.2 (CH_2), 39.5 (CH_2), 49.5 (C), 63.1 (CH_2), 67.0 (CH_2), 83.0 (CH), 178.9 (C), 209.7 (C); FD-HRMS (*m/z*) calcd for $C_{19}H_{35}O_5Si$ $[M+H]^+$: 371.22537, found: 371.22446.

3-36 : IR (neat) ν 3416, 2943, 2892, 2867, 1721, 1465, 1383, 1368, 1342, 1218, 1106, 996, 920, 882, 830, 806, 764, 683, 660, 412 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (6H, d, *J* = 6.7 Hz), 1.00-1.21 (21H, m), 1.96 (1H, nonet, *J* = 6.7 Hz), 2.03 (1H, ddd, *J* = 5.7, 8.3, 14.0 Hz), 2.10 (1H, dd, *J* = 5.2, 6.4 Hz), 2.21 (1H, ddd, *J* = 6.2, 8.0, 14.0 Hz), 2.34 (1H, br-dd, *J* = 5.2, 15.5 Hz), 2.37-2.52 (3H, m), 2.87 (1H, dt, *J* = 5.1, 9.5 Hz), 3.51 (1H, ddd, *J* = 4.8, 7.0, 12.0 Hz), 3.66 (1H, d, *J* = 4.4 Hz), 3.69-3.75 (2H, m), 3.92 (2H, dd, *J* = 1.2, 6.7 Hz), 4.14 (1H, d, *J* = 10.4 Hz), 4.27 (1H, d, *J* = 10.4 Hz),; ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (CH×3), 17.9 (CH_3×6), 19.2 (CH_3×2), 27.6 (CH), 30.1 (CH_2), 37.1 (CH_2), 40.9 (CH_2), 42.9 (CH), 49.5 (C), 64.4 (CH_2), 65.7 (CH_2), 71.3 (CH_2), 72.1 (CH), 175.4 (C), 210.2 (C); FD-HRMS (*m/z*) calcd for $C_{23}H_{45}O_6Si$ $[M+H]^+$: 445.29854, found: 445.29833

Compound 3-50



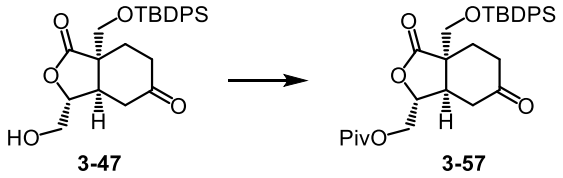
To a solution of **3-36** (14.4 mg, 0.03238 mmol) in THF (0.3 mL) was added 1:1 mol/mol mixture of 2.0 mol/L aq. NaOH and 30% aq. H_2O_2 (ca. 1.6 mol/L, 20 μL, 0.032 mmol) at 0 °C, and the mixture was stirred for 2 days at 21 °C. The reaction was quenched with saturated aq. $NaHSO_3$, and the mixture was extracted with Et_2O 5 mL in several times. After 0.1 mol/L aq. HCl was added to the water layer to adjust pH <4, the acidified solution was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude carboxylic acid **3-49**, which was used in the next reaction without purification.

To a solution of the above crude carboxylic acid **3-49** in CH_2Cl_2 (1.0 mL) was added EDCI·HCl (18.6 mg, 0.09714 mmol) at 21 °C, and the mixture was stirred for 2 min at 21 °C. The reaction was quenched with H_2O, and the mixture was extracted with $CHCl_3$ (5 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3 → 11) to give **3-50** (7.4 mg, 0.01997 mmol, 62% from **3-36**) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97-1.18 (21H, m), 1.84 (1H, t, J = 6.2 Hz), 1.94-2.06 (2H, m), 2.43 (1H, td, J = 8.7, 17.9 Hz), 2.55 (1H, ddd, J = 4.1, 7.9, 17.9 Hz), 2.63 (1H, t, J = 16.7 Hz), 2.64 (1H, td, J = 16.8, 19.2 Hz), 2.85 (1H, ddd, J = 6.0, 10.6, 13.2 Hz), 3.64 (1H, ddd, J = 3.7, 7.0, 13.0 Hz), 3.97 (1H, dtd, J = 2.0, 2.9, 12.8 Hz), 4.79 (1H, td, J = 3.3, 10.6 Hz).

Crystal data of **3-50**: Crystals were obtained by recrystallizing from CH_2Cl_2-Et_2O. $C_{19}H_{34}O_5Si$, M = 370.56, colorless block, mp 112-114 °C, monoclinic $C2/c$ (No. 15), a = 40.6195(5) Å, b = 7.95745(14) Å, c = 12.65312(18) Å, β = 94.1851(12)°, V = 4078.93(11) Å^3, D_c (Z = 8) = 1.207 g cm^{-3}. A total 4044 unique data ($2\theta_{max}$ = 151.5°) were measured at T = 296 K by Rigaku XtaLAB Synergy apparatus (Cu Kα radiation, λ = 1.54184 Å). The linear absorption coefficient, μ, for Cu-Kα radiation is 12.217 cm-1. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.503 to 1.000. The data were corrected for Lorentz and polarization effects. The structure was solved by the direct method (SIR92) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final wR value of full-matrix least-squares refinement on F is 0.0509 (all data) for 4044 reflections and 259 parameters. CCDC 1879128.

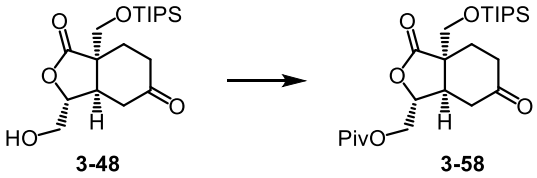
Compound 3-57



To a solution of **3-47** (94.8 mg, 0.2095 mmol) in CH_2Cl_2 (2.1 mL) was added DMAP (2.6 mg, 0.02095 mmol), DIPEA (0.146 mL, 0.8380 mmol) and PivCl (52 μL, 0.4190 mmol) at 0 °C, and the mixture was stirred for 1.5 h at 21 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. NaOH, 0.1 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 7) to give **3-57** (105.4 mg, 0.1964 mmol, 94%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.20 (9H, s), 1.85-2.00 (1H, m), 2.03-2.24 (2H, m, *J* = 4.6 Hz), 2.37-2.51 (1H, m), 2.43 (1H, dd, *J* = 2.9, 16.7 Hz), 2.54 (1H, dd, *J* = 5.8, 16.7 Hz), 2.90 (1H, dddd, *J* = 2.9, 6.0, 7.0, 12.9 Hz), 3.64 (1H, d, *J* = 9.9 Hz), 3.92 (1H, d, *J* = 9.9 Hz), 4.08-4.24 (3H, m), 7.36-7.51 (6H, m), 7.59-7.68 (4H, m).

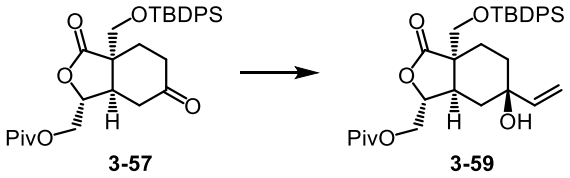
Compound 3-58



To a solution of **3-48** (21.3 mg, 0.05748 mmol) in CH_2Cl_2 (0.6 mL) was added DMAP (0.7 mg, 5.75 μmol), DIPEA (40 μL, 0.2299 mmol) and PivCl (14 μL, 0.1149 mmol) at 0 °C, and the mixture was stirred for 1 h at 21 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with 0.1 mol/L aq. NaOH, 0.1 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6) to give **3-58** (22.0 mg, 0.04839 mmol, 84%) as a colorless oil.

^{1}H NMR(300 MHz, $CDCl_3$) δ 0.98-1.35 (21H, m), 1.21 (9H, s), 1.93-2.07 (1H, m, *J* = 3.7, 4.8 Hz), 2.08-2.27 (2H, m), 2.47 (1H, dd, *J* = 2.9, 16.6 Hz), 2.51 (1H, td, *J* = 4.5, 18.3 Hz), 2.66 (1H, dd, *J* = 6.0, 16.6 Hz), 2.96 (1H, dt, *J* = 2.9, 6.5 Hz), 3.74 (1H, d, *J* = 9.5 Hz), 3.98 (1H, d, *J* = 9.5 Hz), 4.08-4.26 (3H, m).

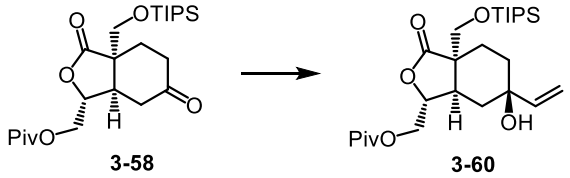
Compound 3-59



To a solution of **3-57** (30.1 mg, 0.06620 mmol) in THF (0.22 mL) was added vinyl magnesium chloride (1.42 mol/L in THF, 0.140 mL, 0.1986 mmol) at -78 °C, and the mixture was stirred for 1 h at -78 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8) to give a 10:1 mixture of **3-59** and its diastereomer at C18 (27.8 mg, 0.05759 mmol, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.21 (9H, s), 1.14-1.73 (5H, m), 1.95-2.13 (1H, m), 2.68 (1H, dd, *J* = 6.0, 10.9 Hz), 3.66 (1H, d, *J* = 10.3 Hz), 3.97 (1H, d, 10.2 Hz), 4.02 (1H, dd, *J* = 7.1, 12.3 Hz), 4.43 (1H, dd, *J* = 2.4, 12.3 Hz), 5.04 (1H, d, *J* = 10.7 Hz), 5.18 (1H, d, *J* = 17.3 Hz), 5.23 (1H, ddd, *J* = 2.2, 7.1, 11.0 Hz), 5.78 (1H, dd, *J* = 10.7, 17.3 Hz), 7.34-7.50 (6H, m), 7.59-7.72 (4H, m).

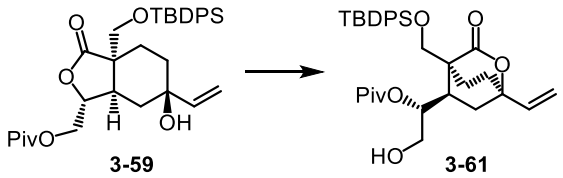
Compound 3-60



To a solution of **3-58** (345.7 mg, 0.7603 mmol) in THF (2.53 mL) was added vinyl magnesium chloride (1.35 mol/L in THF, 1.69 mL, 2.28 mmol) at -78 °C, and the mixture was stirred for 1 h at -78 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 7) to give a 9:1 mixture of **3-60** and its diastereomer at C18 (320.0 mg, 0.6629 mmol, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94-1.37 (21H, m), 1.22 (9H, s), 1.46-1.84 (5H, m), 2.09 (1H, ddd, *J* = 5.3, 12.5, 13.8 Hz), 2.71 (1H, dd, *J* = 5.3, 10.4 Hz), 3.79 (1H, d, *J* = 9.8 Hz), 3.98 (1H, d, *J* = 9.8 Hz), 4.01 (1H ,dd, *J* = 6.9, 12.4 Hz), 4.43 (1H, dd, *J* = 2.4, 12.3 Hz), 5.10 (1H, dd, *J* = 0.7, 10.7 Hz), 5.23 (1H, ddd, *J* = 2.3, 6.8, 10.9 Hz), 5.27 (1H, dd, *J* = 0.7, 17.3 Hz), 5.93 (1H, dd, *J* = 10.7, 17.3 Hz)

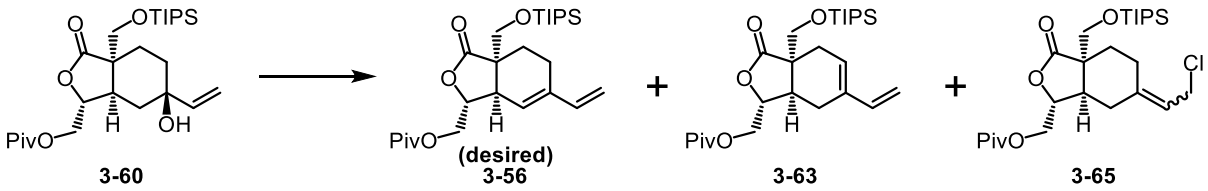
Compound 3-61



To a solution of **3-59** (117.1 mg, 0.2073 mmol) in THF (2.0 mL) was added vinyl magnesium chloride (1.42 mol/L in THF, 0.290 mL, 0.4118 mmol) at 0 °C, and the mixture was stirred for 3 h at 40 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (10 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8) to give **3-61** (54.8 mg, 0.1140 mmol, 55%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (9H, s), 1.18 (9H, s), 1.36-1.52 (1H, m), 1.75 (1H, dd, *J* = 7.2, 13.5 Hz), 1.85 (2H, t, *J* = 8.1 Hz), 2.10 (1H, dd, *J* = 11.0, 14.4 Hz), 2.19 (1H, dt, *J* = 1.8, 6.5 Hz), 2.26 (1H, t, *J* = 6.4 Hz), 2.73 (1H, ddd, *J* = 3.6, 7.4, 10.7 Hz), 3.62 (1H, dt, *J* = 6.5, 12.5 Hz), 3.73 (1H, ddd, *J* = 4.3, 6.7, 12.3 Hz), 3.87 (1H, d, *J* = 11.3 Hz), 4.05 (1H, d, *J* = 11.3 Hz), 4.98 (1H, td, *J* = 3.9, 6.8 Hz), 5.19 (1H, d, *J* = 11.2 Hz), 5.33 (1H, d, *J* = 17.5 Hz), 5.91 (1H, dd, *J* = 6.7 Hz), 7.33-7.50 (6H, m), 7.59-7.74 (4H, m).

Compound 3-56 and regioisomer 3-63

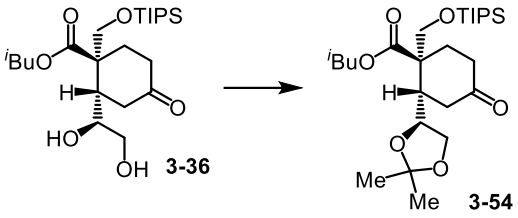


To a solution of $(COCl)_2$ (0.173 mL, 1.99 mmol) in THF (4.4 mL) was added a solution of DMSO (0.235 mL, 3.31 mmol) in THF (2.2 mL) dropwise at −60 °C, and the mixture was stirred for 10 min. Then, to the mixture was added a solution of **3-60** (320.0 mg, 0.6629 mmol) in THF (2.2 mL) at −60 °C, and the mixture was stirred for 45 min. To the mixture was added DIPEA (1.16 mL, 6.63 mmol) at −60 °C, and the mixture was stirred for 1 h. Then, the mixture was warmed to 21 °C and stirred for 1.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with 0.2 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give a 4:1 inseparable mixture of **3-56** and **3-63** (258.3 mg, 0.5558 mmol, 84%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96-1.17 (105/5H, m), 1.22 (9/5H, s), 1.23 (36/5H, s), 1.72-1.84 (8/5H, m), 2.01-2.18 (5/5H, m), 2.20-2.29 (1/5H, m), 2.29 (4/5H, td, *J* = 4.4, 17.4 Hz), 2.35-2.45 (2/5H, m), 2.94 (1/5H, dt, *J* = 1.7, 6.4 Hz), 3.14 (4/5H, dd, *J* = 4.8, 9.2 Hz), 3.61 (1/5H, d, *J* = 9.6 Hz), 3.66 (4/5H, d, *J* = 9.6 Hz), 3.96 (1/5H, d, *J* = 9.6 Hz), 3.98 (4/5H, d, *J* = 9.6 Hz), 4.10-4.17 (2/5H, m), 4.16 (4/5H, dd, *J* = 7.4, 12.0 Hz),

4.28 (4/5H, ddd, *J* = 3.4, 7.4, 9.3 Hz), 4.32-4.38 (1/5H, m), 4.43 (4/5H, dd, *J* = 3.4, 12.0 Hz), 5.04 (1/5H, d, *J* = 10.7 Hz), 5.09 (4/5H, d, *J* = 10.8 Hz), 5.16 (1/5H, d, *J* = 17.5 Hz), 5.20 (4/5H, d, *J* = 17.5 Hz), 5.71 (4/5H, d, *J* = 4.8 Hz), 5.83 (1/5H, brs), 6.37 (4/5H, dd, *J* = 10.8, 17.5 Hz), 6.36-6.43 (1/5H, m)

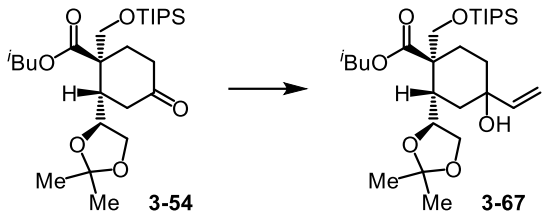
Compound 3-54



To a solution of **3-36** (273.9 mg, 0.6159 mmol) in acetone (5.7 mL) were added 2,2-dimethoxypropane (0.113 mL, 0.9239 mmol) and PPTS (15.5 mg, 0.06159 mmol) at 21 °C, and the mixture was stirred for 21 h. Then, to the mixture was added H_2O (0.5 mL) at 21 °C, and the mixture was stirred for 14 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6) to give **3-54** (260.8 mg, 0.5380 mmol, 87%) as a colorless oil.

IR (neat) ν 2943, 2891, 2868, 1722, 1465, 1380, 1370, 1340, 1324, 1303, 1246, 1217, 1154, 1123, 1101, 1069, 10131, 995, 945, 918, 882, 860, 806, 766, 683, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (6H, d, *J* = 6.7 Hz), 1.03-1.21 (21H, m), 1.31 (3H, s), 1.33 (3H, s), 1.97 (1H, nonet, *J* = 6.7 Hz), 2.06 (1H, ddd, *J* = 4.9, 11.0, 14.0 Hz), 2.21 (1H, dd, *J* = 4.9, 15.5 Hz), 2.34-2.52 (3H, m), 2.65 (1H, ddd, *J* = 6.0, 11.3, 15.5 Hz), 2.77 (1H, dt, *J* = 4.9, 8.4 Hz), 3.51 (1H, m, *J* = 3.5, 5.8 Hz), 3.83 (1H, dd, *J* = 6.6, 10.7 Hz), 3.96 (1H, dd, *J* = 6.6, 10.7 Hz), 4.05-4.13 (3H, m), 4.20 (1H, d, *J* = 10.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9 (CH×3), 18.0 (CH_3×6), 19.2 (CH_3), 19.3 (CH_3), 25.9 (CH_3), 26.4 (CH_3), 27.7 (CH), 28.7 (CH_2), 37.5 (CH_2), 40.8 (CH_2), 44.0 (CH), 50.1 (C), 67.7 (CH_2), 68.6 (CH_2), 71.1 (CH_2), 75.5 (CH), 109.2 (C), 174.8 (C), 210.8 (C); FD-HRMS (*m/z*) calcd for $C_{26}H_{49}O_6Si$ [$M+H^+$]: 485.3298, found: 485.3286.

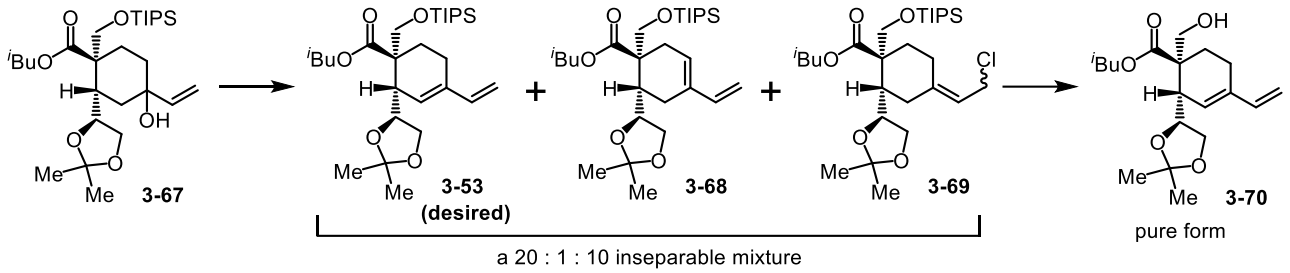
Compound 3-67



To a solution of **3-54** (260.8 mg, 0.5380 mmol) in THF (1.6 mL) was added vinyl magnesium chloride (1.5 mol/L, 1.09 mL, 1.45 mmol) at −78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 12 → 5) to give a 4:1 diastereomeric mixture of **3-67** (267.3 mg, 0.5213 mmol, 97%) as a colorless oil.

IR (neat) ν 3492, 3086, 2943, 2892, 2867, 1722, 1465, 1379, 1369, 1244, 1223, 1160, 1097, 1060, 997, 945, 919, 882, 864, 807, 765, 682, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (24H/5, d, J = 6.7 Hz), 0.94 (6H/5, d, J = 6.7 Hz), 1.00-1.19 (210H/5, m), 1.28 (3H/5, s), 1.30 (15H/5, s), 1.33 (12H/5, s), 1.45-1.57 (8H/5, m), 1.58-1.73 (7H/5, m), 1.89-2.01 (15H/5, m, J = 3.2, 6.7, 8.8 Hz), 2.09-2.19 (4H/5, m), 2.21 (1H/5, dt, J = 4.7, 13.9 Hz), 2.43 (4H/5, ddd, J = 5.4, 6.6, 8.3 Hz), 2.76 (1H/5, ddd, J = 4.3, 8.4, 13.0 Hz), 3.51 (5H/5, t, J = 8.1 Hz), 3.73 (1H/5, dd, J = 6.4, 10.5 Hz), 3.81 (4H/5, dd, J = 6.6, 10.6 Hz), 3.86 (4H/5, dd, J = 6.7, 10.7 Hz), 3.86-3.93 (5H/5, m, J = 9.8 Hz), 3.98-4.09 (2H/5, m), 4.08-4.15 (9H/5, m), 4.18 (1H/5, d, J = 10.2 Hz), 4.30 (4H/5, dt, J = 5.8, 8.5 Hz), 5.04 (1H/5, dd, J = 1.1, 10.7 Hz), 5.09 (1H/5, brd, J = 10.7 Hz), 5.25 (4H/5, dd, J = 0.9, 17.4 Hz), 5.26 (1H/5, dd, J = 1.2, 17.3 Hz), 5.92 (1H/5, dd, J = 10.7, 17.3 Hz), 5.98 (4H/5, dd, J = 10.7, 17.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9 (CH×12/5), 12.0 (CH×3/5), 18.0 (CH_3×24/5), 18.1 (CH_3×6/5), 19.2 (CH_3×2/5), 19.3 (CH_3×8/5), 25.5 (CH_3×1/5), 25.9 (CH_3×4/5), 26.3 (CH_3×1/5), 26.7 (CH_3×4/5), 27.6 (CH×1/5), 27.7 (CH_2×4/5), 28.2 (CH_2×4/5), 29.7 (CH_2×1/5), 32.8 (CH_2×1/5), 34.5 (CH_2×4/5), 35.4 (CH_2×1/5), 36.3 (CH_2×4/5), 40.1 (CH×1/5), 41.7 (CH×4/5), 48.1 (C×1/5), 51.1 (C×4/5), 63.7 (CH_2×1/5), 67.3 (CH_2×4/5), 68.7 (CH_2×1/5), 68.9 (CH_2×4/5), 70.6 (CH_2×1/5), 70.7 (CH_2×4/5), 70.9 (C×1/5), 71.5 (C×4/5), 76.2 (CH×4/5), 76.5 (CH×1/5), 108.5 (C×4/5), 108.6 (C×1/5), 111.6 (CH_2×1/5), 112.8 (CH_2×4/5), 144.7 (CH×4/5), 146.0 (CH×1/5), 175.4 (C×4/5), 176.3 (C×1/5); FD-HRMS (*m/z*) calcd for $C_{28}H_{53}O_6Si$ [$M+H^+$]: 513.3611, found: 513.3619.

Compound 3-70

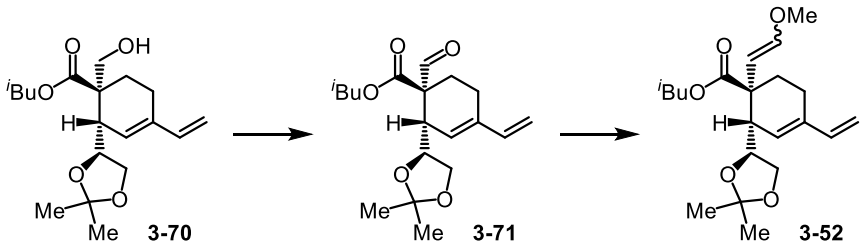


To a solution of $(COCl)_2$ (0.179 mL, 2.06 mmol) in THF (4.9 mL) was added a solution of DMSO (0.244 mL, 3.43 mmol) in THF (2.0 mL) dropwise at −60 °C, and the mixture was stirred for 10 min. Then, to the mixture was added a solution of **3-67** (352.0 mg, 0.6864 mmol) in THF (2.3 mL) at −60 °C, and the mixture was stirred for 30 min. To the mixture was added DIPEA (1.20 mL, 6.86 mmol) at −60 °C, and the mixture was stirred for 1 h. Then, the mixture was warmed to 0 °C and stirred for 1 h. Then, the mixture was warmed to 21 °C, the mixture was stirred for 17.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with 0.2 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give a 20:1:10 inseparable mixture of **3-53** and **3-68** and **3-69** (332.7 mg) as a yellow oil.

To the above mixture was added TBAF (1.0 mol/L in THF, 1.97 mL, 1.97 mmol) at 0 °C, and the mixture was stirred for 13 h at 21 °C. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10) to give **3-70** (146.3 mg, 0.4323 mmol, 63% from **3-67**) as a colorless oil.

IR (neat) ν 3533, 3088, 3042, 2961, 2875, 2727, 1723, 1645, 1607, 1470, 1371, 1349, 1304, 1247, 1211, 1162, 1125, 1067, 988, 947, 890, 860, 797, 777, 749, 738, 721, 704, 639, 434 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (6H, d, J = 6.7 Hz), 1.36 (3H, s), 1.40 (3H, s), 1.82 (1H, ddd, J = 6.2, 8.0, 13.4 Hz), 1.89-1.95 (1H, m), 1.95 (1H, nonet, J = 6.7 Hz), 2.13 (1H, td, J = 7.0, 17.8 Hz), 2.23 (1H, td, J = 5.8, 17.8 Hz), 3.19 (1H, dd, J = 4.2, 9.2 Hz), 3.23 (1H, dd, J = 4.8, 10.6 Hz), 3.69 (1H, dd, J = 10.8, 11.7 Hz), 3.75 (1H, t, J = 8.3 Hz), 3.82 (1H, dd, J = 6.5, 10.6 Hz), 3.89 (1H, dd, J = 4.8, 11.8 Hz), 3.94 (1H, ddd, J = 5.6, 8.6, 9.2 Hz), 3.98 (1H, dd, J = 6.5, 10.6 Hz), 4.09 (1H, dd, J = 5.6, 8.1 Hz), 4.99 (1H, d, J = 10.7 Hz), 5.12 (1H, d, J = 17.5 Hz), 5.39 (1H, d, J = 4.3 Hz), 6.28 (1H, dd, J = 10.7, 17.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1 (CH_3×2), 24.9 (CH_2), 25.9 (CH_3), 26.5 (CH_3), 27.7 (CH), 42.5 (CH), 50.3 (C), 65.1 (CH_2), 68.9 (CH_2), 70.9 (CH_2), 75.8 (CH), 109.4 (C), 112.3 (CH_2), 125.5 (CH), 137.7 (C), 138.7 (CH), 175.7 (C); FD-HRMS (*m/z*) calcd for $C_{29}H_{30}O_5$ [M^+]: 338.2093, found: 338.2100.

Compound 3-52

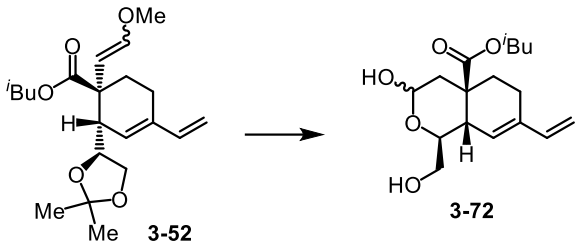


To a solution of **3-70** (92.8 mg, 0.2742 mmol) in CH_2Cl_2 (2.7 mL) were added $NaHCO_3$ (483.7 mg, 5.76 mmol) and DMPI (349.6 mg, 0.8226 mmol) in THF (2.0 mL) at 0 °C, and the mixture was stirred for 1 h at 21 °C. The reaction was quenched with saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$, and extracted with CH_2Cl_2 (8 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude aldehyde, which was used in the next reaction without purification.

To the suspension of (methoxymethyl)triphenylphosphonium chloride (939.9 mg, 2.74 mmol) in THF (13.7 mL) was added NHMDS (1.14 mol/L in THF, 2.41 mL, 2.74 mmol) at 0 °C, and the mixture was stirred for 15 min. Then, to the mixture was added a solution of the above crude aldehyde in THF (2.7 mL) at −78 °C, and the mixture was stirred for 19 h at 21 °C. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with $CHCl_3$ (10 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 30 → 10) to give a 1:1 *E*/*Z*-isomeric mixture of **3-52** (70.8 mg, 0.1942 mmol, 75% from **3-70**) as a yellow oil.

3-52: a 1:1 mixture of *E*/*Z*-isomers; IR (neat) ν 3087, 3042, 2959, 2934, 2874, 1727, 1659, 1607, 1469, 1455, 1378, 1369, 1234, 1218, 1161, 1114, 1056, 991, 940, 898, 865, 796, 741, 712, 427 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H/2, d, *J* = 6.7 Hz), 0.94 (3H/2, d, *J* = 6.7 Hz), 1.33 (6H/2, s), 1.38 (3H/2, s), 1.42 (3H/2, s), 1.66 (1H/2, td, *J* = 6.5, 13.8 Hz), 1.88-2.02 (3H/2, m), 2.10 (1H/2, td, *J* = 5.1, 13.2 Hz), 2.17-2.38 (5H/2, m), 3.30 (1H/2, brs), 3.33 (1H/2, brs), 3.53 (3H/2, s), 3.55 (3H/2, s), 3.58 (1H/2, m, *J* = 4.4 Hz), 3.60 (1H/2, m, *J* = 5.2 Hz), 3.82 (1H/2, dd, *J* = 6.5, 8.6 Hz), 3.84 (1H/2, dd, *J* = 6.5, 8.6 Hz), 3.86-3.93 (4H/2, m), 4.19 (1H/2, td, *J* = 5.9, 8.4 Hz), 4.23 (1H/2, d, *J* = 6.7 Hz), 4.48 (1H/2, ddd, *J* = 4.5, 6.5, 7.5 Hz), 4.88 (1H/2, d, *J* = 13.1 Hz), 4.97 (1H/2, dd, *J* = 8.0, 10.6 Hz), 5.10 (1H/2, dd, *J* = 6.7, 17.4 Hz), 5.62 (2H/2, brs), 5.89 (1H/2, d, *J* = 6.7 Hz), 6.33 (1H/2, dd, *J* = 10.8, 17.5 Hz), 6.37 (1H/2, dd, *J* = 10.7, 17.5 Hz), 6.44 (1H/2, d, *J* = 13.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1 (CH_3×2/2), 19.2 (CH_3×2/2), 21.3 (CH_2×1/2), 25.0 (CH_3×1/2), 25.7 (CH_3×1/2), 26.4 (CH_3×1/2), 26.5 (CH_3×1/2), 27.6 (CH_2×1/2), 27.8 (CH×2/2), 29.7 (CH_2×1/2), 30.5 (CH_2×1/2), 44.2 (CH×1/2), 45.2 (CH×1/2), 46.5 (C×1/2), 47.1 (C×1/2), 55.9 (CH_3×1/2), 59.9 (CH_3×1/2), 66.5 (CH_2×1/2), 67.0 (CH_2×1/2), 71.0 (CH_2×1/2), 71.1 (CH_2×1/2), 75.6 (CH×1/2), 76.4 (CH×1/2), 103.5 (CH×1/2), 103.9 (CH×1/2), 107.4 (C×1/2), 108.0 (C×1/2), 111.2 (CH_2×1/2), 111.8 (CH_2×1/2), 126.5 (CH×1/2), 126.6 (CH×1/2), 136.6 (C×1/2), 137.0 (C×1/2), 139.0 (CH×1/2), 139.2 (CH×1/2), 147.7 (CH×1/2), 148.5 (CH×1/2), 175.0 (C×1/2), 175.4 (C×1/2); FD-HRMS (*m/z*) calcd for $C_{21}H_{32}O_5$ [M^+]: 364.2250, found: 364.2261

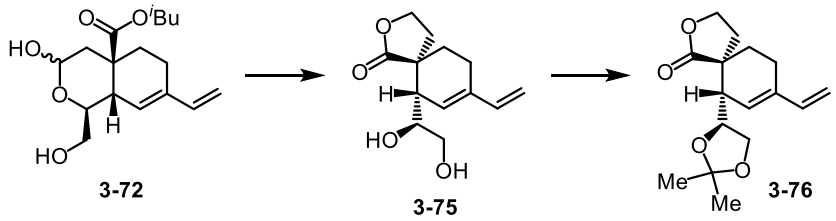
Compound 3-72



To a solution of **3-52** (70.8 mg, 0.1942 mmol) in THF (2.3 mL) was added 2.0 mol/L aq. HCl (1.5 mL) at 21 °C, and the mixture was stirred for 12.5 h. The reaction was quenched with 2.0 mol/L aq. NaOH and saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc (8 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4 → 1) to give a 1:1 diastereomeric mixture of acetal **3-72** (38.8 mg, 0.1250 mmol, 64%) as a colorless oil.

3-72: a 1:1 mixture of diastereomers; IR (neat) ν 3408, 3088, 3040, 2958, 2925, 2874, 2850, 1727, 1644, 1606, 1469, 1371, 1329, 1251, 1225, 1178, 1139, 1096, 1062, 1032, 991, 973, 941, 901, 869, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H/2, d, J = 6.7 Hz), 0.92 (3H/2, d, J = 6.7 Hz), 1.71 (1H/2, dd, J = 9.2, 13.2 Hz), 1.85 (1H/2, dd, J = 3.2, 14.0 Hz), 1.91 (1H/2, nonet, J = 6.7 Hz), 1.92 (1H/2, nonet, J = 6.7 Hz), 1.97-2.10 (4H/2, m), 2.10-2.36 (6H/2, m), 2.71 (1H/2, brs), 2.87 (1H/2, dd, J = 5.6, 10.5 Hz), 2.96 (1H/2, dd, J = 4.5, 9.7 Hz), 3.23 (1H/2, brs), 3.49 (1H/2, ddd, J = 2.5, 6.2, 10.4 Hz), 3.68-3.76 (2H/2, m), 3.79-3.86 (5H/2, m), 3.88 (1H/2, dd, J = 6.6, 10.6 Hz), 3.90 (1H/2, dd, J = 6.6, 10.6 Hz), 4.98 (2H/2, d, J = 10.7 Hz), 5.04 (1H/2, brs), 5.10 (1H/2, d, J = 17.5 Hz), 5.11 (1H/2, d, J = 17.5 Hz), 5.43 (1H/2, brs), 5.57 (1H/2, d, J = 4.6 Hz), 5.59 (1H/2, d, J = 5.5 Hz), 6.28 (1H/2, dd, J = 10.7, 17.4 Hz), 6.31 (1H/2, dd, J = 10.7, 17.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0 (CH_3×4/2), 21.6 (CH_2×1/2), 21.8 (CH_2×1/2), 25.3 (CH_2×2/2), 27.7 (CH×2/2), 36.1 (CH_2×1/2), 36.7 (CH×1/2), 37.3 (CH×1/2), 41.1 (CH_2×1/2), 42.9 (C×1/2), 45.0 (C×1/2), 63.6 (CH_2×1/2), 63.9 (CH_2×1/2), 71.0 (CH×1/2), 71.0 (CH_2×1/2), 71.1 (CH_2×1/2), 77.6 (CH×1/2), 91.7 (CH×1/2), 92.6 (CH×1/2), 111.9 (CH_2×1/2), 112.2 (CH_2×1/2), 126.1 (CH×1/2), 127.0 (CH×1/2), 136.6 (C×1/2), 137.1 (C×1/2), 138.8 (CH×1/2), 139.0 (CH×1/2), 175.0 (C×1/2), 176.1 (C×1/2); FD-HRMS (*m/z*) calcd for $C_{17}H_{26}O_5$ [M^+]: 310.1780, found: 310.1789

Compound 3-76

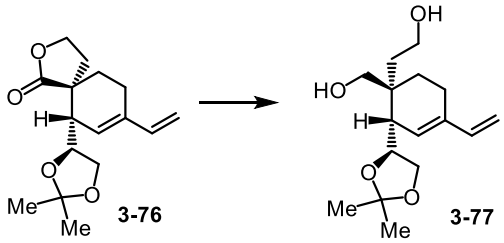


To a solution of **3-72** (2.7 mg, 8.70 μmol) in EtOH-H_2O (2:1, 0.3 mL) was added $NaBH_4$ (6.6 mg, 0.1740 mmol) at 0 °C, and the mixture was stirred for 1 h at 21 °C. The reaction was quenched with saturated aq. NH_4Cl and extracted with EtOAc (4 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product **3-75**, which was used in the next reaction without purification.

To a solution of the above crude **3-75** in CH_2Cl_2 (87 μL) was added an excess amount of 2,2-dimethoxypropane and an excess amount of PPTS at 21 °C, and the mixture was stirred for 2 h. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc (4 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 11 → 6) to give **3-76** (2.7 mg, quantitative yield from **3-72**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.38 (3H, s), 1.75-2.21 (4H, m), 2.28 (1H, ddd, *J* = 5.7, 8.4, 13.2 Hz), 2.39 (1H, brd, *J* = 17.9 Hz), 2.89 (1H, brd, *J* = 10.5 Hz), 3.80 (1H, dd, *J* = 6.8, 7.7 Hz), 3.88 (1H, ddd, *J* = 5.7, 6.5, 10.3 Hz), 4.24 (1H, dd, *J* = 5.7, 7.7 Hz), 4.31 (1H, dd, *J* = 5.6, 8.8 Hz), 4.38 (1H, dt, *J* = 6.8, 8.5 Hz), 5.05 (1H, d, *J* = 10.9 Hz), 5.13-5.23 (2H, m), 6.31 (1H, dd, *J* = 10.9, 17.5 Hz).

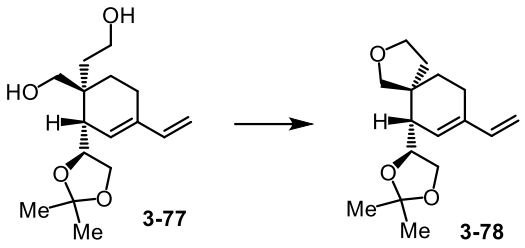
Compound 3-77



To a solution of **3-76** (2.7 mg, 9.70 μmol) in CH_2Cl_2 (0.32 mL) was added $LiAlH_4$ (7.4 mg, 0.1940 mmol) at 0 °C, and the mixture was stirred for 30 min at 21 °C. The reaction was quenched with saturated aq. Roschell's salt, and the mixture was extracted with EtOAc (4 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2 → EtOAc only) to give **3-77** (1.8 mg, 6.37 μmol, 66%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (3H, s), 1.44 (3H, s), 1.74 (1H, ddd, *J* = 3.3, 5.7,13.8 Hz), 1.80-1.98 (1H, m), 1.86 (1H, ddd, *J* = 5.2, 8.2, 14.8 Hz), 1.98-2.15 (1H, m), 2.23 (1H, d, *J* = 17.9 Hz), 2.36 (1H, d, *J* = 9.1 Hz), 3.41-3.92 (5H, m), 4.05 (1H, ddd, *J* = 5.8, 8.2, 9.5 Hz), 4.23 (1H, dd, *J* = 5.8, 8.0 Hz), 5.01 (1H, d, *J* = 10.6 Hz), 5.13 (1H, s), 5.14 (1H, d, *J* = 17.3 Hz), 6.30 (1H, dd, *J* = 10.7, 17.4 Hz).

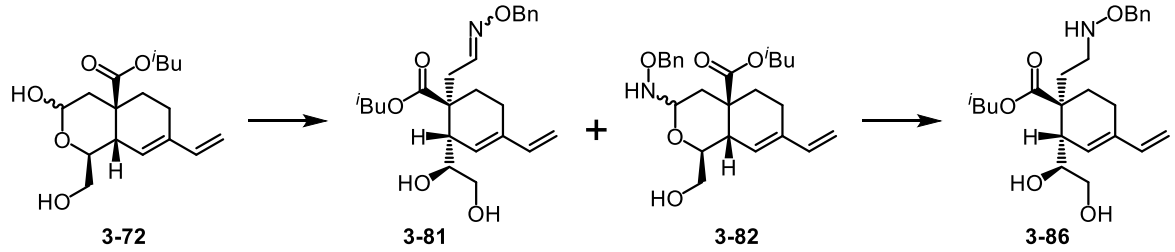
Compound 3-78



To a solution of **3-77** (1.8 mg, 6.37 μmol) in CH_2Cl_2 (0.13 mL) was added Et_3N (3 μL, 0.01912 mmol) and TsCl (1.8 mg, 9.56 μmol) at 0 °C, and the mixture was stirred for 12 h at 21 °C. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc (4 mL × 3). The combined organic layers were washed with 0.2 mol/L aq. HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-78** (1.3 mg, 6.37 μmol, 77%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.39 (3H, s), 1.49-1.74 (4H, m), 2.07-2.26 (2H, m), 2.38-2.49 (1H, m), 3.56 (2H, dt, *J* = 6.6, 8.4 Hz), 3.66 (1H, t, *J* = 8.2 Hz), 3.90 (1H, t, *J* = 7.1 Hz), 3.92 (1H, dd, *J* = 5.5, 8.5 Hz), 3.97 (1H, dd, *J* = 5.9, 7.8 Hz), 4.13 (1H, td, *J* = 6.4, 8.2 Hz), 4.99 (1H, d, *J* = 10.8 Hz), 5.14 (1H, d, *J* = 17.5 Hz), 5.56 (1H, d, *J* = 5.0 Hz), 6.33 (1H, dd, *J* = 10.7, 17.4 Hz)

Compound 3-86



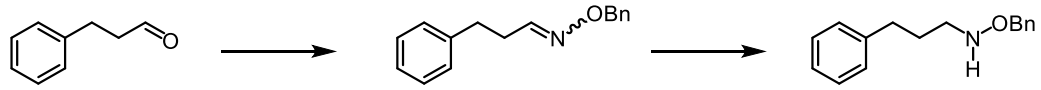
To a solution of **3-72** (19.1 mg, 0.06163 mmol) in THF-pH 4 buffer (1:1, 0.62 mL) was added $BnONH_2$·HCl (99.0 mg, 0.62 mmol) at 21 °C, and the mixture was stirred for 24.5 h. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3) to give a mixture of hydrazon derivatives **3-81** and **3-82** (20.6 mg) as a colorless oil.

To the above mixture in EtOH (0.5 mL) was added methyl orange (pH indicator: a small amount), $NaBH_3CN$ (15.6 mg, 0.2479 mmol) and 1.0 mol/L methanolic HCl (freshly prepared from AcCl and MeOH) in alternating portions until the mixture became cloudy and pink at 21 °C, and the mixture was stirred for 30 min. The reaction was quenched with 2.0 mol/L aq. HCl (5 drops), 2.0 mol/L aq. NaOH (4 drops) and saturated aq. $NaHCO_3$ in order. The mixture was extracted with EtOAc (8 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3) to give **3-86**

(19.3 mg, 0.04622 mmol, 75% from **3-72**) as a colorless oil.

3-86: IR (neat) ν 3438, 3087, 3062, 3032, 2958, 2931, 2873, 1721, 1469, 1455, 1368, 1227, 1186, 1086, 1027, 907, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (6H, d, *J* = 6.7 Hz), 1.72 (1H, ddd, *J* = 5.4, 9.9, 13.9 Hz), 1.84 (1H, brtd, *J* = 5.6, 13.6 Hz), 1.92 (1H, nonet, *J* = 6.7 Hz), 1.95-2.16 (3H, m), 2.22 (1H, brtd, *J* = 5.8, 17.7 Hz), 2.98 (1H, ddd, *J* = 5.3, 9.7, 12.2 Hz), 3.04 (1H, brd, *J* = 6.7), 3.26 (1H, ddd, *J* = 5.0, 9.8, 12.2 Hz), 3.55-3.61 (2H, m), 3.74-3.80 (1H, m), 3.83 (1H, dd, *J* = 6.5, 10.6 Hz), 3.85 (1H, dd, *J* = 6.5, 10.6 Hz), 4.70 (2H, s), 4.99 (1H, d, *J* = 10.8 Hz), 5.09 (1H, d, *J* = 17.5 Hz), 5.47 (1H, brs), 6.31 (1H, dd, *J* = 10.8, 17.5 Hz) 7.27-7.36 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.16 (CH_3), 19.17 (CH_3), 21.1 (CH_2), 27.6 (CH), 28.2 (CH_2), 28.9 (CH_2), 45.0 (CH), 46.1 (C), 48.0 (CH_2), 65.0 (CH_2), 71.0 (CH_2), 71.8 (CH), 76.1 (CH_2), 111.8 (CH_2), 126.8 (CH), 127.8 (CH), 128.37 (CH×2), 128.43 (CH×2), 136.4 (C), 137.7 (C), 138.9 (CH), 177.6 (C); FD-HRMS (*m/z*) calcd for $C_{24}H_{35}NO_5$ [M^+]: 417.2515, found: 417.2518.

Compound 3-94



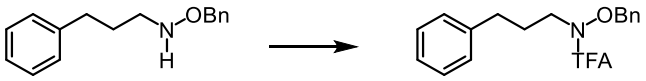
3-93 **3-S2** **3-94**

To a solution of **3-93** (1.00 g, 7.45 mmol) in CH_2Cl_2 (7.45 mL) was added $BnONH_2$·HCl (1.43 g, 8.94 mmol) and MS4A (1.0 g) at 21 °C, and the mixture was stirred for 19 h. The reaction mixture was filtered through the Celite pad and the filterate was concentrated under reduced pressure to give a crude product **3-S2**, which was used in the next reaction without purification.

To the above crude **3-S2** in EtOH (7.45 mL) was added methyl orange (pH indicator: a small amount), $NaBH_3CN$ (468.3 mg, 7.45 mmol) and 1.0 mol/L methanolic HCl (freshly prepared from AcCl and MeOH) in alternating portions until the mixture became cloudy and pink at 21 °C, and the mixture was stirred for 40 min. The reaction was quenched with 2.0 mol/L aq. HCl (0.5 mL), 2.0 mol/L aq. NaOH (0.5 mL) and saturated aq. $NaHCO_3$ in order. The mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-94** (850.0 mg, 3.52 mmol, 47% from **3-93**) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$) δ 1.86 (2H, quin, *J* = 7.5 Hz), 2.66 (2H, t, *J* = 7.7 Hz), 2.97 (2H, t, *J* = 7.1 Hz), 4.71 (2H, s), 5.57 (1H, brs), 7.14-7.21 (3H, m), 7.25-7.38 (7H, m).

Compound 3-97

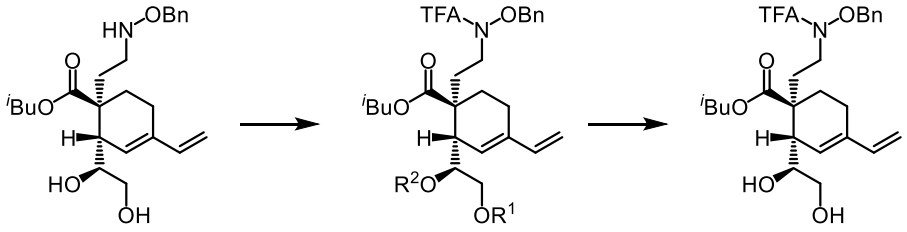


3-94 **3-97**

To a solution of **3-94** (35.9 mg, 0.1488 mmol) in CH_2Cl_2 (1.5 mL) was added TFAA (31 μL, 0.2232 mmol) and pyridine (36 μL, 0.4464 mmol) at 0 °C, and the mixture was stirred for 19 h. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-97** (45.1 mg, 0.1337 mmol, 90%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (2H, quin, *J* = 7.4 Hz), 2.63 (2H, t, *J* = 7.6 Hz), 3.73 (2H, t, *J* = 6.9 Hz), 4.85 (2H, s), 7.16 (2H, d, *J* = 7.5 Hz), 7.21 (1H, t, *J* = 7.2 Hz), 7.27 (2H, t, *J* = 7.3 Hz), 7.34 (2H, brs), 7.36-7.42 (3H, m).

Compound 3-100



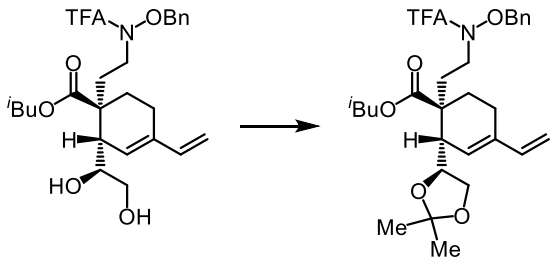
3-86 **3-98** : R^1 = TFA, R^2 = H
3-99 : R^1 = H, R^2 = TFA **3-100**

To a solution of **3-86** (4.2 mg, 0.01006 mmol) in CH_2Cl_2 (0.2 mL) was added pyridine (16 μL, 0.2012 mmol) and TFAA (14 μL, 0.1006 mmol) at 0 °C, and the mixture was stirred for 1.5 h. The reaction was quenched with saturated aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude mixture of **3-98** and **3-99**, which was used in the next reaction without purification.

To a solution of the above crude mixture in MeOH (0.19 mL) was added 5% aq. NH_3 (20 μL) at 0 °C, and the mixture was stirred for 12 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl and the mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2.5) to give **3-100** (1.24 mg, 2.37 μmol, 24% from **3-86**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (6H, d, *J* = 6.7 Hz), 1.78 (1H, dt, *J* = 4.1, 12.5 Hz), 1.83 (1H, brs), 1.91 (1H, td, *J* = 5.1, 13.5 Hz), 1.91-2.07 (2H, m, *J* = 6.7 Hz), 2.16-2.48 (3H, m), 3.15 (1H, d, *J* = 9.3 Hz), 3.44 (1H, t, *J* = 7.5 Hz), 3.48-3.75 (6H, m), 3.79-4.00 (4H, m), 4.24 (1H, dt, *J* = 4.0, 12.8 Hz), 4.88 (1H, d, *J* = 9.0 Hz), 5.01 (1H, d, *J* = 8.9 Hz), 5.02 (1H, d, *J* = 10.8 Hz), 5.13 (1H, d, *J* = 17.6 Hz), 5.39 (1H, s), 6.29 (1H, dd, *J* = 10.7, 17.4 Hz), 7.36-7.43 (5H, m).

Compound 3-101



3-100 **3-101**

To a solution of **3-100** (0.8 mg, 1.56 μmol) in CH_2Cl_2 (52 μL) was added 2,2-dimethoxypropane (4 μL, 0.03116 mmol) and PPTS (1.2 mg, 4.67 μmol) at 0 °C, and the mixture was stirred for 20 min at 24 °C. The reaction was quenched with saturated aq. $NaHCO_3$ and the mixture was extracted with $CHCl_3$ (3 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-101** (0.81 mg, 1.52 μmol, 98%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (6H, d, *J* = 6.7 Hz), 1.30 (3H, s), 1.37 (3H, s), 1.50-1.67 (1H, m), 1.72 (1H, dt, *J* = 3.2, 12.2 Hz), 1.82-1.92 (1H, m), 1.95 (1H, nonet, *J* = 6.7 Hz), 2.02-2.12 (1H, ddd, *J* = 6.4, 9.5, 13.4 Hz), 2.13-2.24 (1H, brd, *J* = 15.7 Hz), 2.25-2.38 (2H, m), 3.11 (1H, d, *J* = 8.0 Hz), 3.67 (1H, t, *J* = 7.8 Hz), 3.81 (1H, dd, *J* = 6.6, 10.5 Hz), 3.87-4.00 (2H, m), 4.08 (1H, dd, *J* = 6.0, 7.8 Hz), 4.11-4.20 (1H, m, *J* = 4.7 Hz), 4.86 (1H, d, *J* = 8.7 Hz), 5.02 (1H, d, *J* = 10.8 Hz), 5.03 (1H, d, *J* = 9.0 Hz), 5.13 (1H, d, *J* = 17.5 Hz), 5.26 (1H, s), 6.29 (1H, dd, *J* = 10.7, 17.5 Hz), 7.33-7.45 (5H, m).

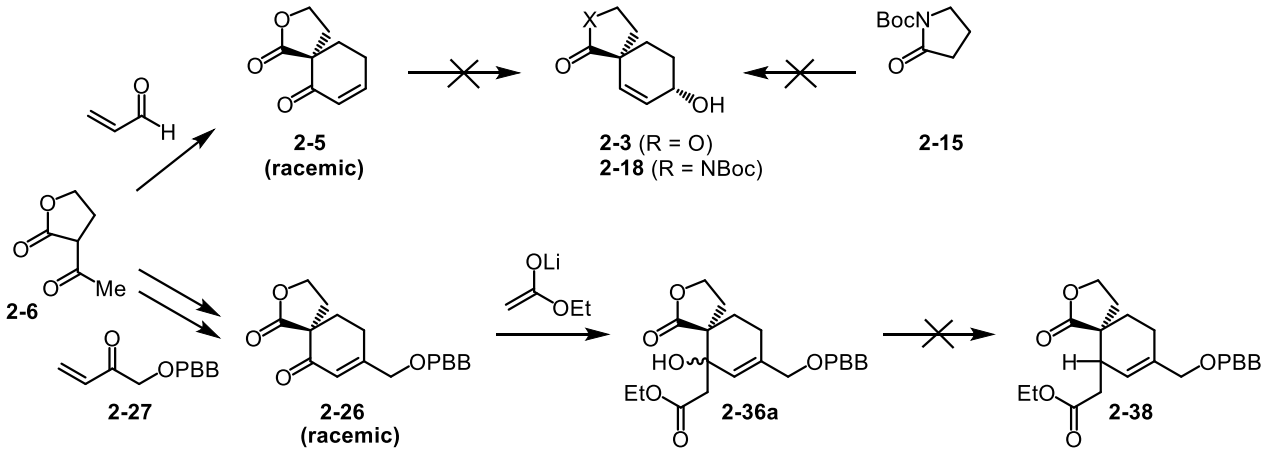
Chapter 4
Coclusion and Scope for Future Work

4-1. Conclusion

The author studied the synthesis of the cyclohexene segment of portimine, isolated from the dinoflagellate *Vulcanodinium rugosum* as an unprecedented highly active cytotoxin in a series of spirocyclic imine toxins. In this dissertation work, (i) an effective synthetic route to cyclohexene segment **1-155** was investigated (Chapter 2), and (ii) the synthesis of cyclohexene segment **1-155** was accomplished using a conjugate addition, dihydroxylation and reductive amination (Chapter 3).

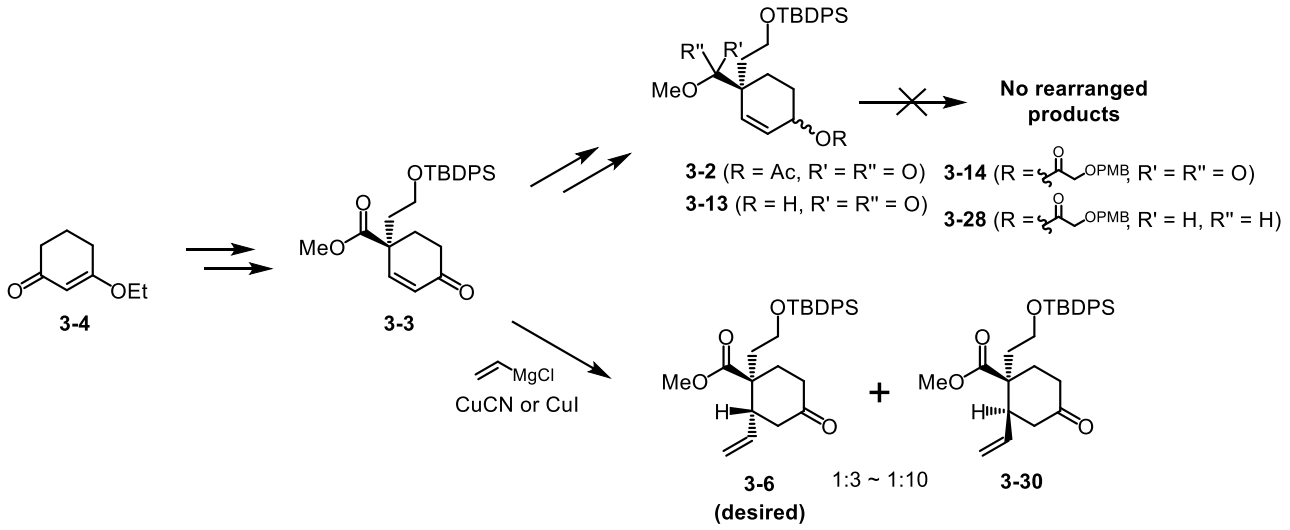
In previous synthetic studies of other spirocyclic imine toxins by other research groups, the key reactions for the cyclohexene ring construction are mainly classified into four types: (i) Diels-Alder reaction, (ii) ring-closing olefin metathesis (RCM), (iii) Claisen rearrangement/aldol cyclization and (iv) intramolecular alkylation of cyano-epoxides. In contrast, the author planned to develop a new process for the cyclohexene segment of portimine.

First, the possibility of a sequential transformation including Robinson annulation and Ireland-Claisen rearrangement as a new method for the cyclohexene ring formation was examined (Scheme 4-1). Although the formation of spirocyclic cyclohexenone **2-5** was found to be synthesized easily from α-acetyl-γ-butyrolactone (**2-6**) by Robinson annulation, the difficulty in the preparation of the cyclohexanols **2-3** and **2-18** prevented the application of Ireland-Claisen rearrangement for the installation of C14-C15 unit. Next, an alternative process including 1,2-addition of an ester enolate to β-(alkoxymethyl)cyclohexenone **2-26** followed by the deoxygenation of the resulting **2-36a** was examined. However, the process was fruitless due to the problem of unfavorable double bond migration in the deoxygenation step. Thus, the author decided to re-design the new synthetic route for the desired cyclohexene framework from a different starting material.



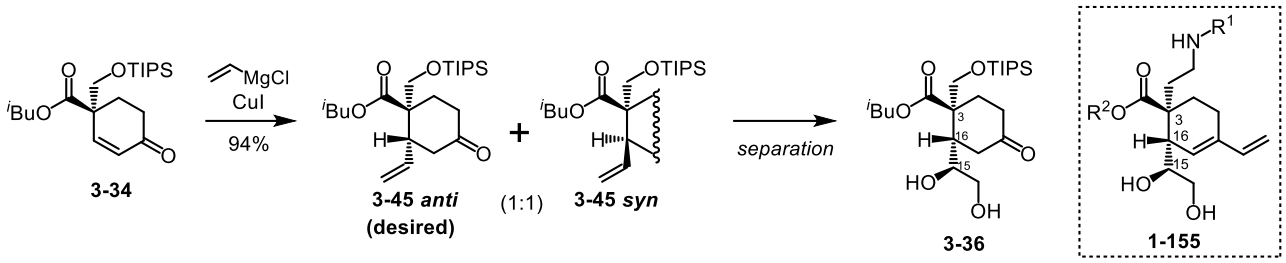
Scheme 4-1. Outline of the attempts for the preparation of the cyclohexene framework in Chapter 2.

Next, the author planned to synthesize the cyclohexene segment **1-155** from 3-ethoxy-cyclohex-2-enone (**3-4**) via cyclohexenone **3-3** (Scheme 6-2). Initially, the Ireland-Claisen rearrangement of allylic esters **3-2**, **3-14** and **3-28** and the Johnson-Claisen rearrangement of allylic alcohol **3-13** were attempted to install a C14-C15 unit to C16 center. However, the desired rearranged products were not produced. Then, the conjugate addition of vinylcuprate to enone **3-3** was alternatively examined for the C14-C15 unit installation. However, the desired 1,4-adduct **3-6**, produced from **3-3** with vinylmagnesium chloride and CuI or CuCN, only obtained as a minor component.



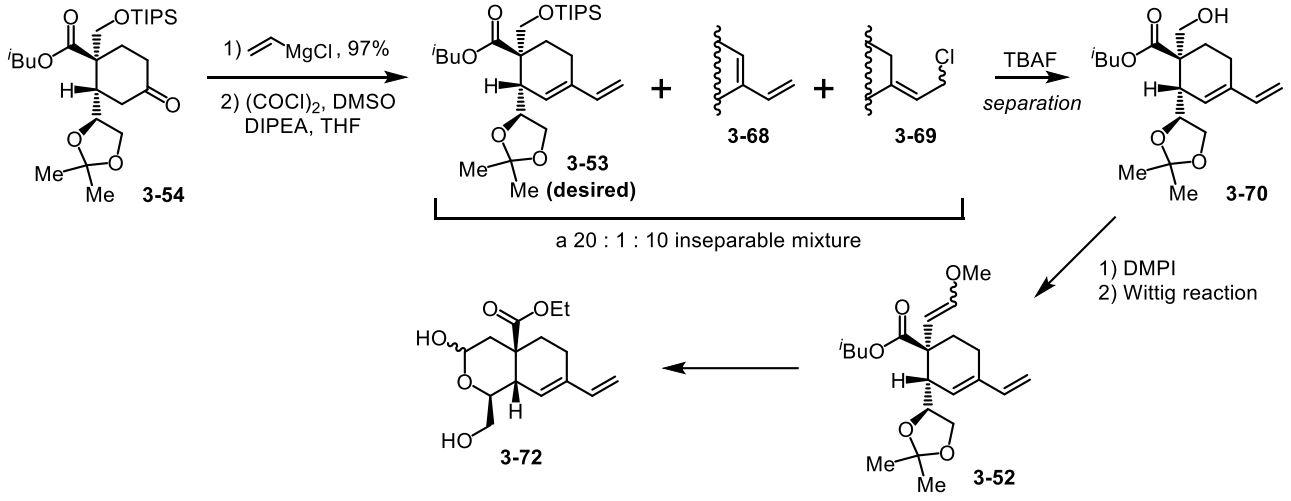
Scheme 4-2. Attempts to install substituents at C6 of cyclohexenone **3-3**.

The author further revised the synthetic route to cyclohexene segment **1-155** in a way that the diastereoselectivity of the 1,4-addition was raised by the improvement of the steric environment around C3 of the substrate. Thus, the cyclohexenone **3-34** was reacted with a vinyl cuprate, and the resulting vinyl compounds were dihydroxylated to produce *anti*-diol **3-36** having the desired three contiguous stereocenters at C3, C16 and C15 as a major product.



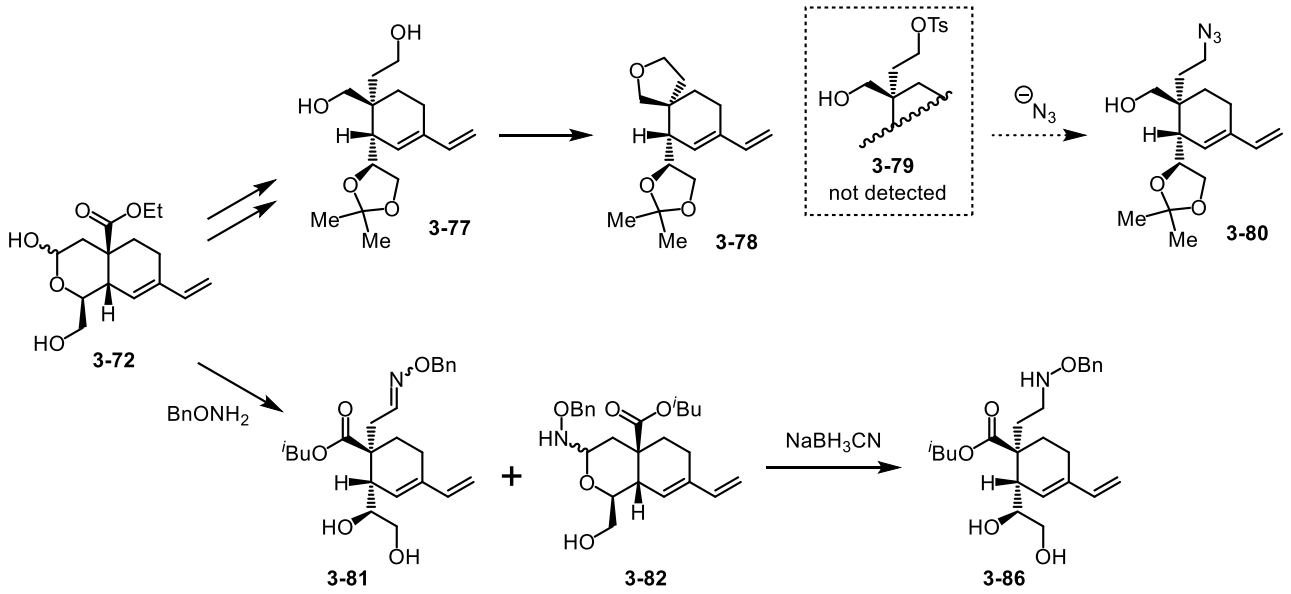
Scheme 4-3. The construction of three contiguous stereocenters of the cyclohexene segment.

The following construction of the diene moiety at C17-C18-C21-C22 region of the cyclohexene segment employed a process including vinylation followed dehydration under Swern conditions, which transformed **3-54** to **3-53** facilely. The subsequent homologation at C2 was achieved in high yield from alcohol **3-70** by a Dess-Martin oxidation/Wittig reaction/hydrolysis sequence to give **3-72**.



Scheme 4-4. The construction of the diene moiety and the homologation at C2.

Since the derivatization to azide **3-80** from **3-72** failed due to the instability of intermediate **3-79**, a supposed substrate for **3-80**, cyclic acetal **3-72** was finally reacted with $BnONH_2$ and subsequently with $NaBH_3CN$ to produce the desired **3-86** corresponding to cyclohexene segment **1-155**. Thus, the author established the synthesis of the cyclohexene segment of portimine in 6.5% yield over 16 steps from **3-4**.



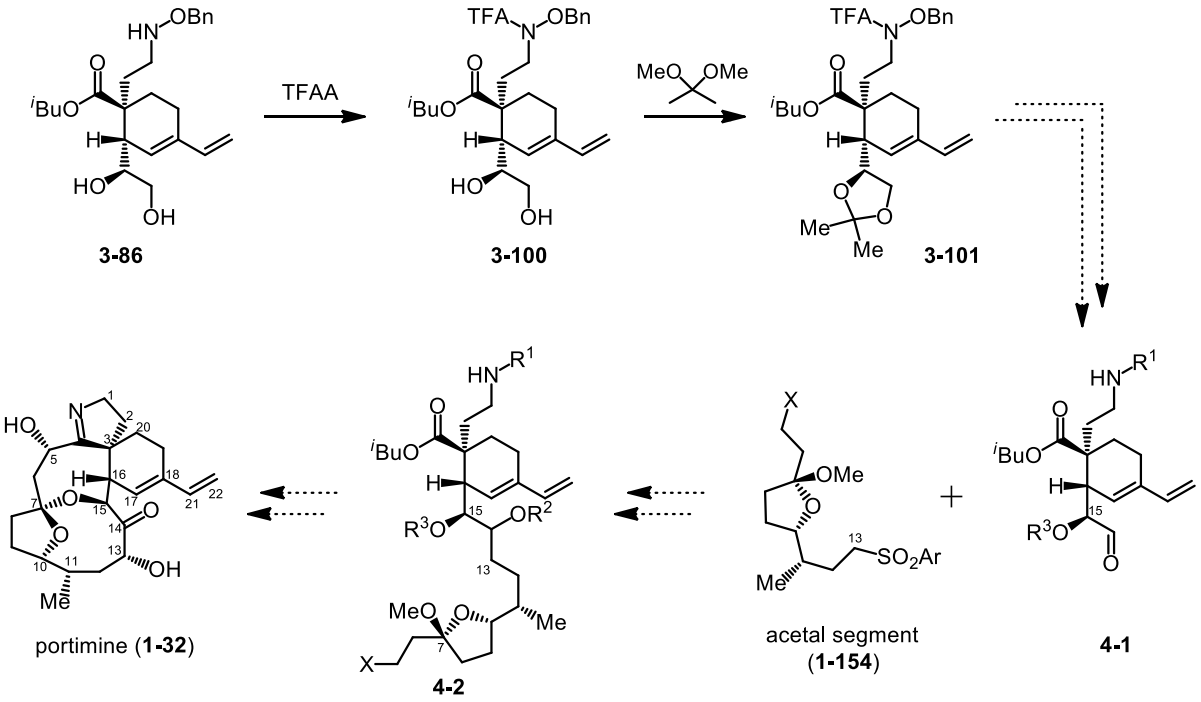
Scheme 4-5. The synthesis of cyclohexene segment **3-86** of portimine.

4-2. Scope for Future Work

The author further investigated the derivatization of cyclohexene segment **3-86** and found that the treatment of **3-86** with TFAA followed by partial hydrolysis produced TFA amide **3-100,** which was easily converted to **3-101** under acidic conditions (Scheme 4-6). Intermediate **3-101** would be useful for the preparation of aldehyde **4-1**.

After establishment of the enantioselective synthesis of cyclohexene **4-1** and acetal segment **1-154**, a sequence of transformations will be scheduled for the total synthesis of portimine as follows: the sulfone coupling between **4-1** and **1-154**, acetal cyclization at C7, formation of the macrocycle at C4-C5, hydroxylation at C13 and C5 and formation of the spirocyclic imine.

Finally, the author hopes that the dissertation work will be useful for the future studies of total synthesis and biological evaluation of portimine.



Scheme 4-6. Synthesis of **3-101** and a future plan for the total synthesis of portimine.

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