Total Synthesis of Spiro-Heterocyclic γ-Lactam Natural Products

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Doctor of Philosophy

by
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List of Abbreviations

Ac	acetyl
bipy	2,2’-bipyridine
Bn	benzyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
ca.	circa
CAN	ammonium cerium(IV) nitrate
CSA	(±)-camphorsulfonic acid
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron impact ionization
Et	ethyl
HRMS	high-resolution mass spectroscopy
IBX	1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide
i-Pr	isopropyl
IR	infrared absorption spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
MMTr	(4-methoxyphenyl)diphenylmethyl
MOM	methoxymethyl
mp	melting point
MPM	(4-methoxyphenyl)methyl

MS4A	molecular sieves 4A powder
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
R_f	retention factor (in chromatography)
rt	room temperature
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tr	triphenylmethyl (trityl)

Chapter 1

Introduction

1.1 Isolation, Structure Determination and Biological Activity

Over the past three decades, structurally as well as biologically intriguing hetero-spirocyclic γ-lactam-type antibiotics have been found in nature. Pseurotin A (**1**) (Figure 1), isolated from the culture filtrate of *Pseudeurotium ovalis* (Ascomycetes) by Tamm et al. in 1976,[1a] is a representative example of these class of secondary microbial metabolites. The structure of pseurotin A (**1**), including its relative and absolute stereochemistries, was determined by a combination of spectroscopic data analysis and chemical modification,[1a] and finally by a single-crystal X-ray analysis of its 12,13-dibromo derivative.[1b] In 1981, Tamm and co-workers also reported on the isolation and structural determination of four additional metabolites, pseurotins B (**2**), C (**3**), D (**4**), and E (**5**), from culture filtrates of the same microorganism.[1e] Pseurotin F_2 (8-*O*-demethylpseurotin A) (**6**) was first isolated from *Aspergillus fumigatus* DSM 6598 as an antagonist of apomorphine.[2] Compound **6** was also isolated from *A. fumigatus* strain HA 57-88 as an inhibitor of both the solubilized and membrane-bound forms of chitin synthase, along with **1**.[3] Later, compound **1** was reported as a novel neurite-forming substance for rat PC12 pheochromocytoma cells, and was thus expected to be a useful tool for investigating the mechanism of neurite formation of neuronal cells.[4] Some other hetero-spirocyclic γ-lactams related to pseurotins were reported. Synerazol (**7**) was isolated from a cultured broth of *A. fumigatus* SANK 10588 as an antifungal antibiotic.[5] FD-838 (**8**) was isolated from *A. fumigatus fresenius* F-838, which induces the differentiation of leukemia in culture and inhibits the growth of

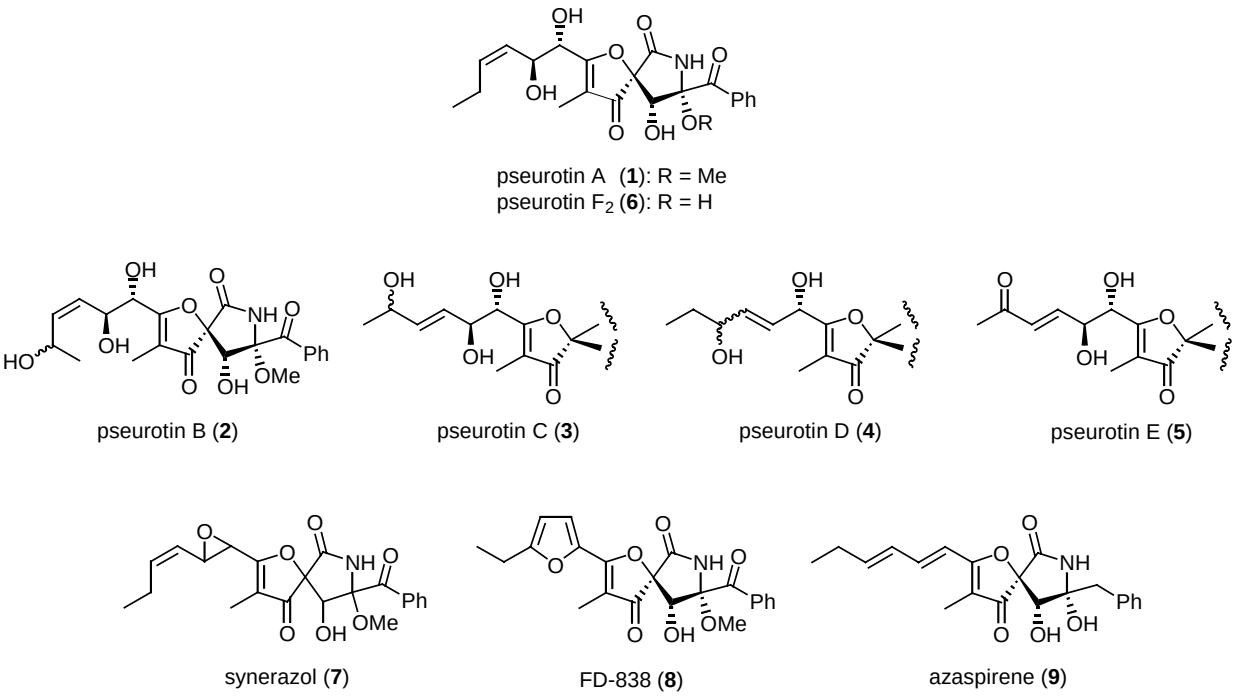


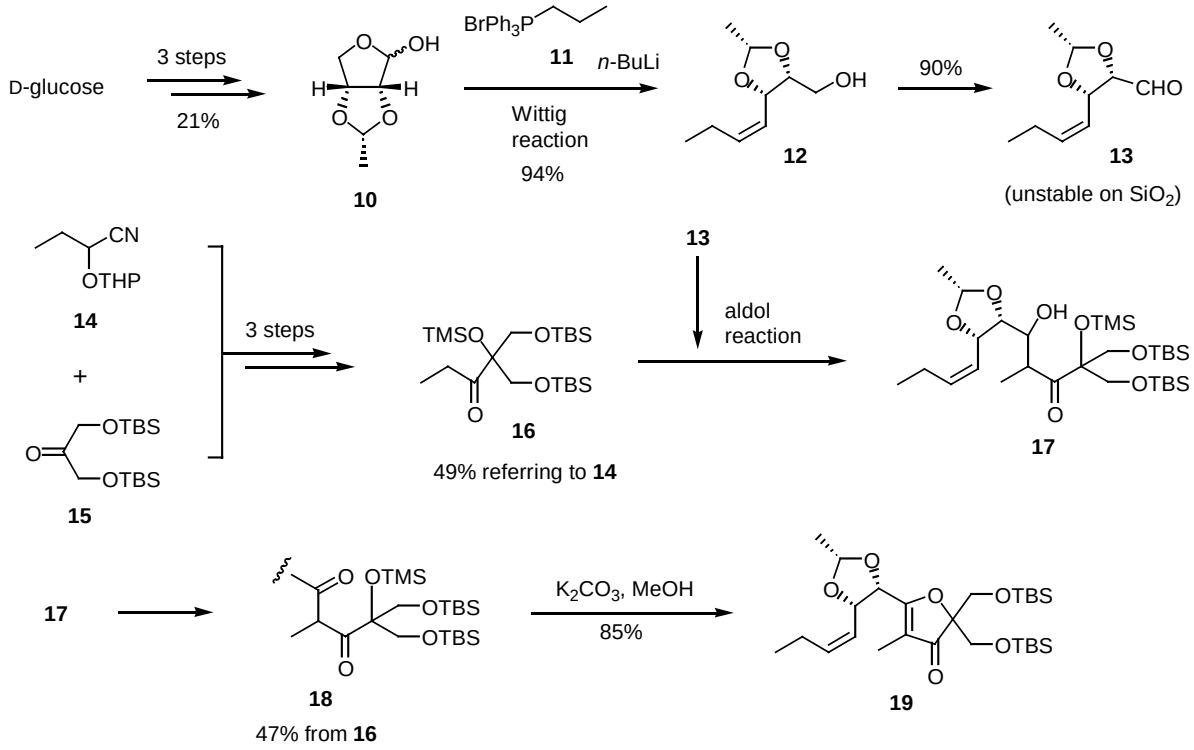
Figure 1. Structures of the spiro-heterocyclic γ-lactam natural products.

certain Gram–positive bacteria and fungi.[6] All of these natural products, **1**–**8**, were characterized structurally by their unusual 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione core skeleton, including three contiguous stereogenic centers, in addition to an oxygenated olefinic side chain (for **1**–**7**) or a furan ring (for **8**) at C2 and a benzoyl group at C8 (for **1**–**8**). Recently, azaspirene (**9**) was isolated from the fungus *Neosartorya* sp. by Osada and co-workers as a novel angiogenesis inhibitor of the endothelial migration induced by a vascular endothelial growth factor.[7] Although the core framework of **9** is similar to those of **1**–**8**, the structure of **9** is characterized by an *E*,*E*-conjugate hexadiene side chain at C2 and a benzyl group instead of the benzoyl group at C8.

1.2 Previous Synthetic Studies of Pseurotin A (**1**) and Related Compounds

The first report on the synthetic study of pseurotin A (**1**) was disclosed by the Tamm's group in 1990 (Scheme 1).[8a,b] They synthesized a model substance **19** for the left part in **1** using the aldol reaction as a key transformation. The construction of the substituted 3(2*H*)-furanone structure was achieved by the ring-closure of an open-chain β-diketone **18** under basic conditions. First D-glucose was converted to 2,3-(ethylidenedioxy)-D-erythrofuranose (**10**) via three steps including glycol cleavage with $NaIO_4$. Chain extension involving introduction of a *Z*-olefinic double bond was carried out by a Wittig reaction using 2.0

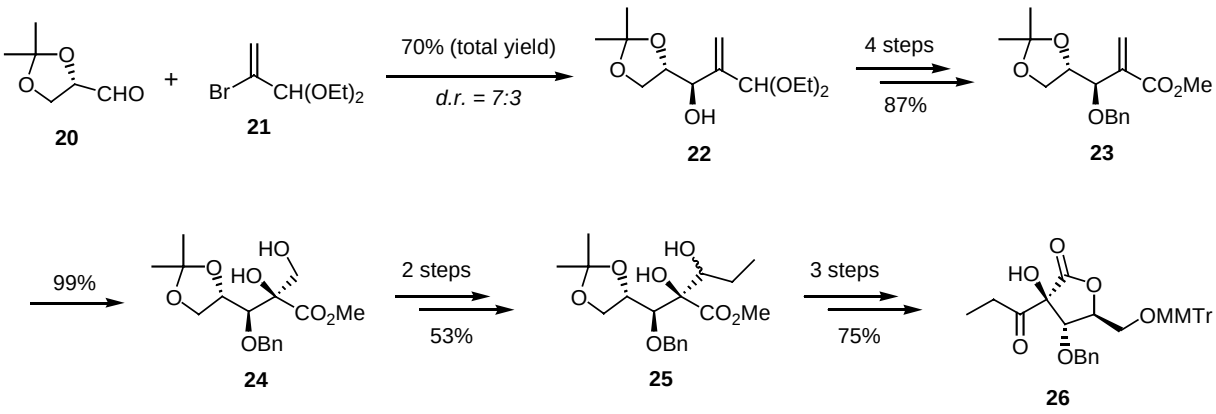
Scheme 1. Tamm's First Synthetic Study of Pseurotin A (**1**)



molar amounts of the ylide prepared from (*n*-propyl)triphenylphosphonium bromide (**11**) and *n*-butyllithium (*n*-BuLi). The oxidation of **12** gave an aldehyde **13**. On the other hand, coupling of the cyanohydrin **14** and the dihydroxyacetone derivative **15**, followed by retrocyanohydrin reaction of the resulting adducts and protection with trimethylsilyl (TMS) group provided the ethyl ketone **16**. Aldol reaction of **16** with the aldehyde **13**, and subsequent oxidation of the resulting adducts **17** gave β-diketone **18**. By removal of TMS group followed by dehydration, the 3(2*H*)-furanone **19** was synthesized.

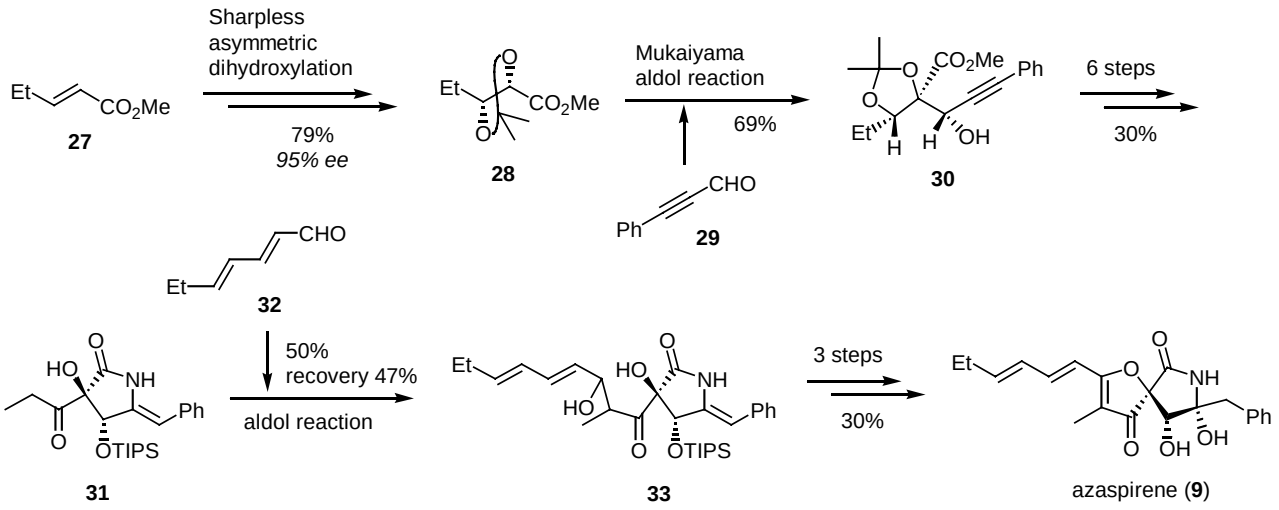
The same group reported the other concept for the synthetic study of pseurotin A (**1**) (Scheme 2).[8c,d] A functionalized γ-lactone **26** was synthesized from (*S*)-*O*-isopropylideneglyceraldehyde (**20**) and 2-bromo-3,3-diethoxypropene (**21**). Coupling reaction of **20** with 2-lithio-3,3-diethoxypropene, generated from **21** and *n*-BuLi, gave **22**, which was transformed into ester **23** in four steps. Dihydroxylation of **23** with OsO_4 provided exclusively the diol **24**. An extension of the chain by two-carbon and subsequent γ-lactonization produced the γ-lactone **26**.

Scheme 2. Tamm's Second Synthetic Study of Pseurotin A (**1**)



In 2002, Hayashi's group disclosed the first total synthesis of azaspirene (**9**) and established its absolute configuration (Scheme 3).[9] The synthesis started with the Sharpless dihydroxylation of methyl 2-pentenoate (**27**). Acetalization of the resulting diol gave acetal **28** in 95% ee. The $MgBr_2 \cdot OEt_2$-mediated Mukaiyama aldol reaction of the ketene silyl acetal, prepared from **28**, with phenylpropargyl aldehyde (**29**) proceeded stereoselectively, giving the desired aldol adduct **30**. γ-Lactam **31** was prepared via several steps including a NaH-promoted intramolecular cyclization of alkynylamide derivative. The aldol reaction of **31** with (2*E*,4*E*)-2,4-heptadienal (**32**) gave adducts **33** as a 3.8:1 diastereomeric mixture, which was oxidized to form spiro-fused 3(2*H*)-furanone structure. By removal of the triisopropylsilyl (TIPS) group, the total synthesis of natural azaspirene (**9**) was achieved.

Scheme 3. Hayashi's Total Synthesis of Azaspirene (**9**)

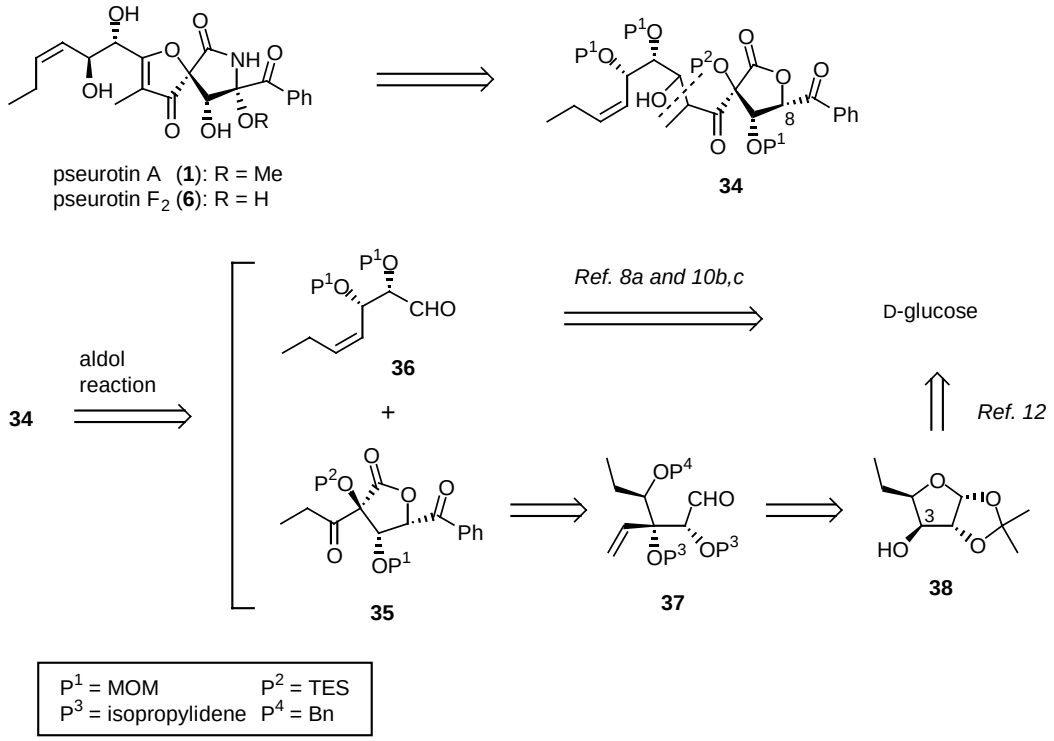


In the same time of my total syntheses of pseurotins A (**1**), F_2 (**6**) and azaspirene (**9**),[10] Hayashi and co-workers also established total syntheses of pseurotins **1** and **6** by the same strategy to their total synthesis of **9**.[11]

1.3 Retrosynthetic Analysis

My initial synthetic approach to **1** and **6** is outlined in Scheme 4. I envisioned that the pseurotins **1** and **6** would be obtained from γ-benzoylated γ-lactone **34**, which contains all the requisite carbon skeleton with correct stereogenic centers, via construction of the spiro-3(2*H*)-furanone substructure, transformation of the γ-lactone to a γ-lactam, and final adjustment of the oxidation level at C8. This advanced intermediate **34** would be prepared by the aldol-type connection of a γ-lactone **35** equipped with an ethyl ketone moiety to a seven-carbon olefinic aldehyde **36** corresponding to the left-side chain. The preparation of the side-chain equivalent **36** was originally reported by the Tamm group.[8a] The aldol partner **35** could be obtained from an acyclic hexose derivative **37** via the installation of a benzoyl group, followed by formation of the γ-lactone via an oxidative cleavage of the vinyl group. This functionalized branched deoxy hexose **37** could be prepared via the stereoselective introduction of a vinyl group at C3 in the 3-ulose prepared from known 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**38**), in turn prepared from D-glucose in six convenient steps.[12]

Scheme 4. Retrosynthetic Analysis of Pseurotins **1** and **6**



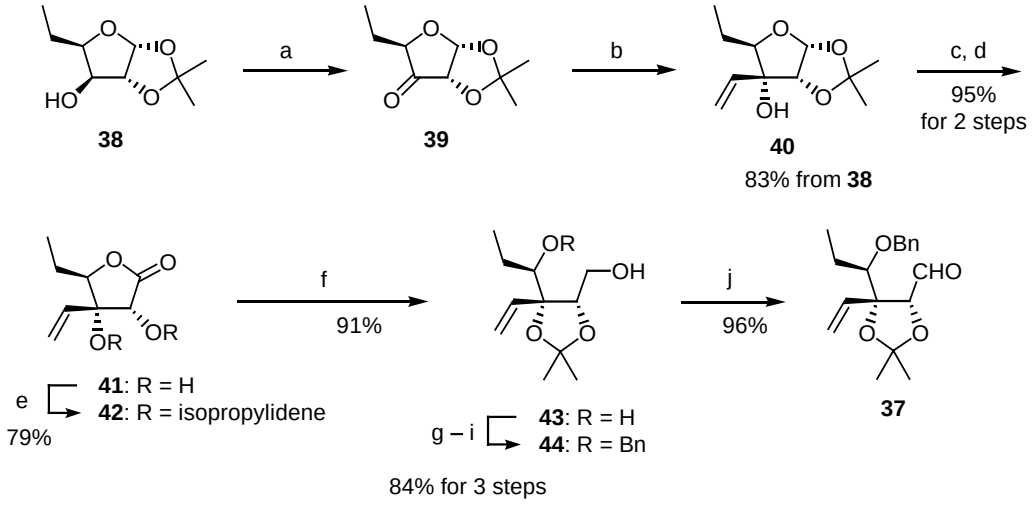
Chapter 2

The First-Generation Approach

2.1 Construction of the Quaternary Carbon Center

The synthesis of **37** from 5-deoxy-aldohexose **38** is summarized in Scheme 5. The oxidation of **38** with pyridinium chlorochromate (PCC),[13] followed by the vinyl Grignard addition to the resultant 3-ulose **39**, provided the adduct **40** as a single diastereoisomer. The vinyl nucleophile attacked exclusively from the convex face of the trioxabicyclo[3.3.0]octane structure of **39** (Figure 2). The acidic hydrolysis of the acetal moiety in **40** and subsequent chemoselective oxidation of the hemiacetal carbon with *N*-iodosuccinimide (NIS) in the presence of *n*-Bu_4NI[14] provided γ-lactone-α,β-diol **41**. The *cis*-diol in **41** was protected as an isopropylidene acetal **42**, which was treated with $LiAlH_4$ to provide a ring-opened diol **43**. A three-step protection/deprotection process from **43** via a trityl ether provided an acyclic suitably protected intermediate **44**. Dess−Martin oxidation[15] of **44** produced the aldehyde **37**.

Scheme 5. Synthesis of the Aldehyde **37**



Reagents and conditions: (a) PCC, MS4A, CH_2Cl_2; (b) CH_2=CHMgBr, THF, −18 °C; (c) 80% aqueous AcOH, 80 °C; (d) NIS, *n*-Bu_4NI, CH_2Cl_2; (e) CSA, $Me_2C(OMe)_2$, Me_2CO, reduced pressure (*ca.* 300 hPa), 40 °C; (f) $LiAlH_4$, THF, 0 °C; (g) TrCl, DMAP, pyr, reflux; (h) BnBr, NaH, DMF; (i) CSA, MeOH; (j) Dess−Martin periodinane, CH_2Cl_2.

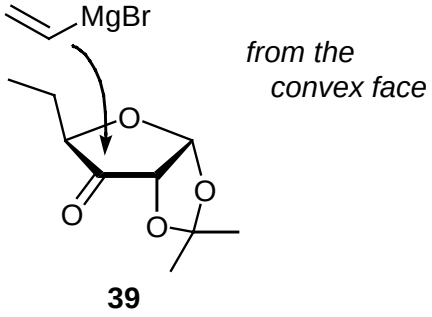
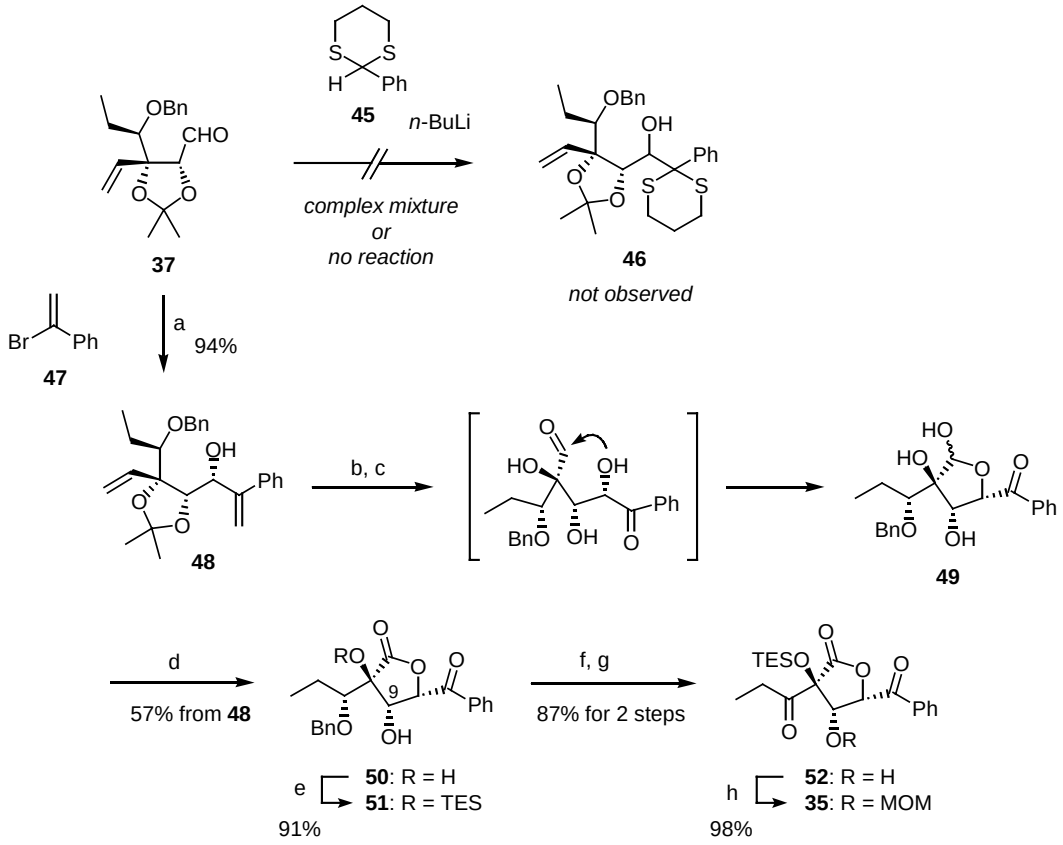


Figure 2. Plausible mechanism for the stereoselectivity in the Grignard reaction of **39**.

2.2 Synthesis of the Right Part Precursor **35**

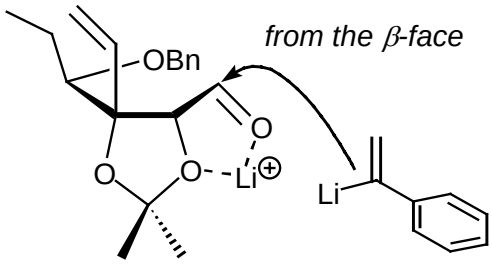
The introduction of a benzoyl equivalent into **37** was next investigated (Scheme 6). First, I chose 2-phenyl-1,3-dithiane (**45**) as a benzoyl equivalent. However, the addition of the 2-lithio-1,3-dithiane generated from **45** to **37** did not occur cleanly. On the other hand, the reaction of **37** with 1-lithiated-1-phenylethene, prepared from 1-bromo-1-phenylethene (**47**) and *tert*-butyllithium (*t*-BuLi) (2 molar amounts) in Et_2O at −78 °C, proceeded smoothly to produce the 2-phenylallyl alcohol **48** as a single stereoisomer. The introduced (*R*)-stereogenic center in **48** was determined by NOE experiments of **50**. This diastereoselective nucleophilic addition of 1-lithiated 1-phenylethene to **37** can be explained by the fact that the lithium-ion-associated five-membered chelate formation occurs between the aldehyde oxygen and one of the acetal oxygens in **37**, to which the nucleophile attacks from the less-hindered β-side leading to **48** (Figure 3). Simultaneous ozonolytic cleavage of the two carbon–carbon double bonds in **48**, followed by acidic hydrolysis of the acetal moiety, spontaneously formed a five-membered hemiacetal **49**, which was oxidized

Scheme 6. Synthesis of the γ-Lactone **35**



Reagents and conditions: (a) **47** (2.0 mol. amt.), *t*-BuLi (4.0 mol. amt.), Et_2O, −78 °C; then **37**; (b) O_3, CH_2Cl_2, −78 °C; Ph_3P; (c) 60% aqueous TFA; (d) NIS, *n*-Bu_4NI, CH_2Cl_2; (e) TESOTf, pyr; (f) H_2, 10% Pd on C, EtOAc; (g) IBX, DMSO; (h) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2.

with NIS to γ-benzoyl-γ-lactone-α,β-diol **50**. The tertiary hydroxy group in **50** could be selectively protected as a triethylsilyl (TES) ether to provide **51**. The signal for H-9 of **51** (δ 4.70) was shifted to lower field (δ 5.30) by acetylation. I suppose that this selective protection of the tertiary hydroxy group may be attributable to the electric effect of the benzoyl carbonyl, although a steric reason cannot be excluded. Hydrogenolysis of the benzyl group in **51**, accompanied by the reduction of the benzoyl carbonyl, followed by oxidation using 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX)[16] in DMSO, provided **52**. Then the secondary hydroxy group in **52** was protected as a methoxymethyl (MOM) ether to give **35**, the substrate for the aldol reaction.



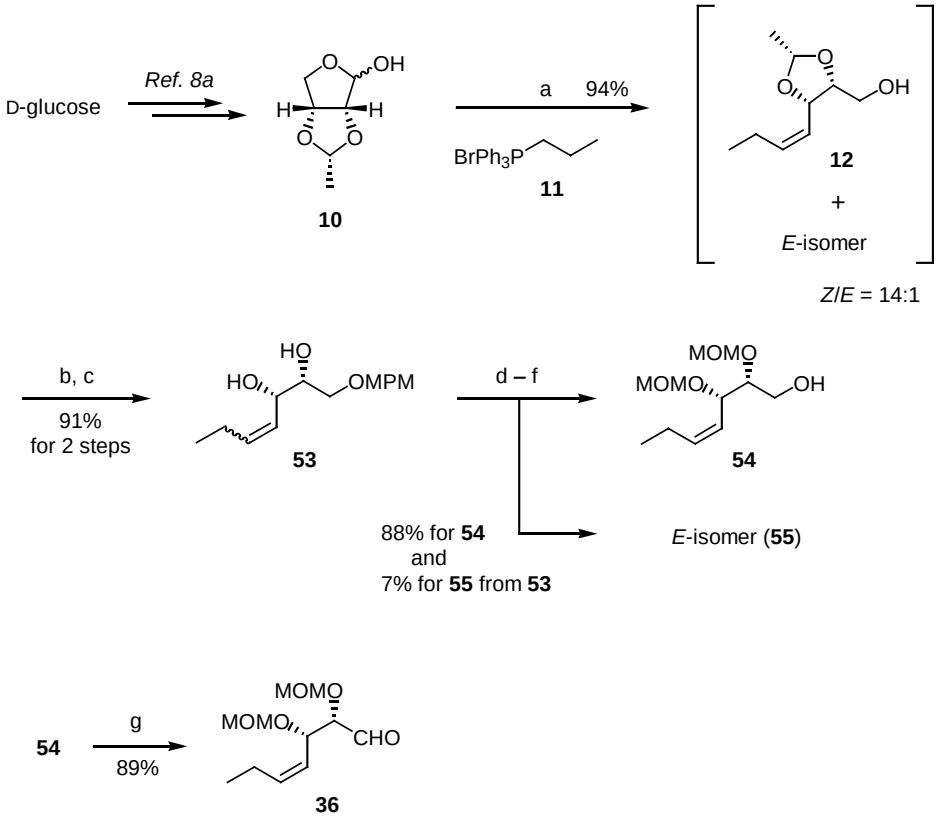
37

Figure 3. Plausible mechanism for the stereoselectivity in the coupling reaction of **37**.

2.3 Synthesis of the Left-Side Chain Equivalent **36**

The coupling partner for the aldol reaction of **35**, aldehyde **36** was synthesized from D-glucose according to the reported procedure[8a] with improvement of the *Z*-olefin introduction (Scheme 7). For the preparation of the known compound **12**, I first used *n*-BuLi as a base for the Wittig olefination of the intermediary aldehyde **10** to introduce the carbon–carbon double bond, but the disappointingly low stereoselectivity was observed (*Z*:*E* = 6:1). Therefore, I chose potassium bis(trimethylsilyl)amide (KHMDS) as a base. Under my conditions, the selectivity was significantly improved (*Z*:*E* = 14:1). Transformation of **12** to di-*O*-MOM ether **54** via *O*-*p*-methoxyphenylmethyl (MPM) ether **53** was conducted straightforwardly. At this stage the *E*-geometrical isomer **55** was cleanly removed. Swern oxidation[17] of the *Z*-isomer **54** provided **36**.

Scheme 7. Synthesis of the Aldehyde **36**

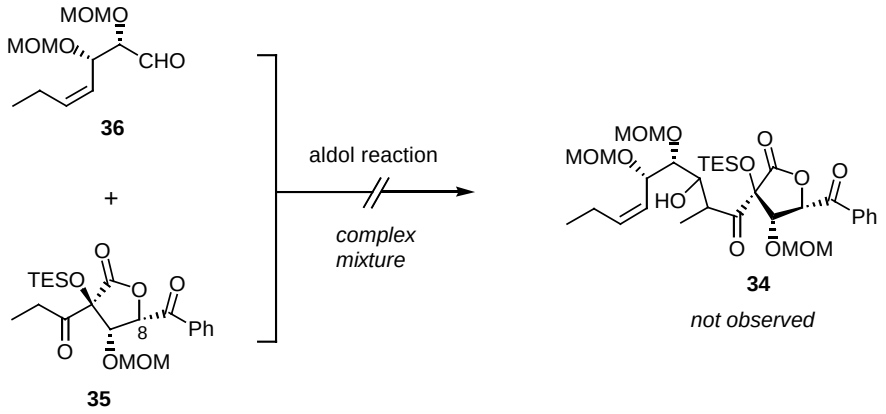


Reagents and conditions: (a) **11** (2.5 mol. amt.), KHMDS (2.5 mol. amt.), THF, rt; (b) MPMCl, NaH, DMF; (c) Amberlyst 15 (H^+), MeOH; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (e) DDQ, CH_2Cl_2 / H_2O (15:1, v/v); (f) separation of the geometrical isomers on silica gel; (g) $(COCl)_2$, DMSO, CH_2Cl_2; then Et_3N, −78 °C to rt.

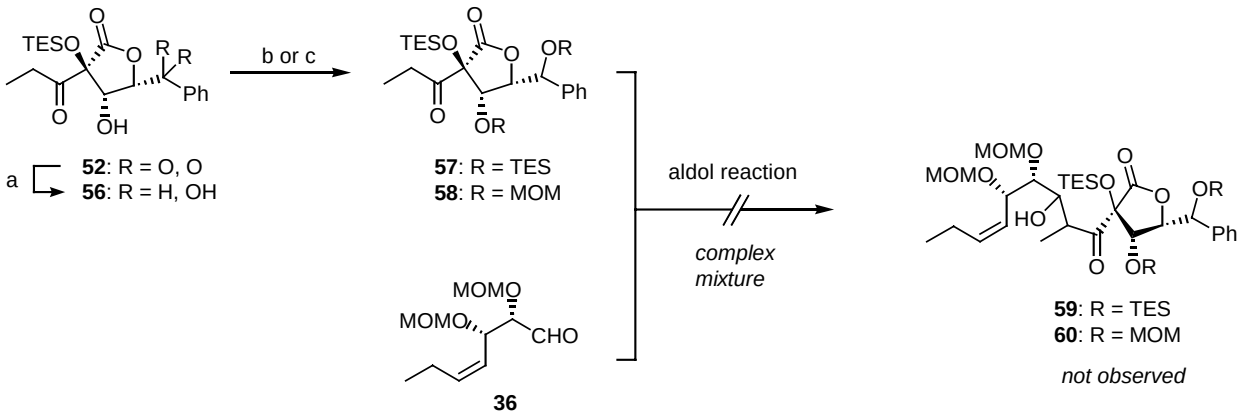
2.4 Attempted Aldol Reaction

I attempted the aldol connection of **35** with **36** under a variety of reaction conditions (LDA, LiHMDS or KHMDS in THF or THF/toluene at −78 °C). Unfortunately, all cases examined resulted in the formation of a complex mixture of products or the decomposition of **35** (Scheme 8). It is reasonable to suggest that the key aldol reaction giving rise to none desired products caused by the benzoyl group at C8, so the benzoate **52** was hydrogenated with catalytic palladium under atmospheric hydrogen to give benzylic alcohol **56** as a single stereoisomer (Scheme 9). The benzylic hydroxy group was protected as an *O*-TES ether to afford **57**, or as an *O*-MOM ether **58**, but the aldol reaction of **57** or **58** with **36** was not successful. Since all attempts at the reaction in the advanced intermediates **57** and **58** failed, recourse was made to alternative precursor for a benzoyl group at C8 in pseurotins.

Scheme 8. Attempted Carbon–Carbon Connection by Aldol Reaction of **35**



Scheme 9. Attempted Carbon–Carbon Connection by Aldol Reaction of **57** or **58**



Reagents and conditions: (a) H_2, 10% Pd on C, EtOAc / MeOH (3:1, v/v) (82%); (b) TESOTf, pyr (**57**: 100%); (c) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, 0 °C (**58**: 98%).

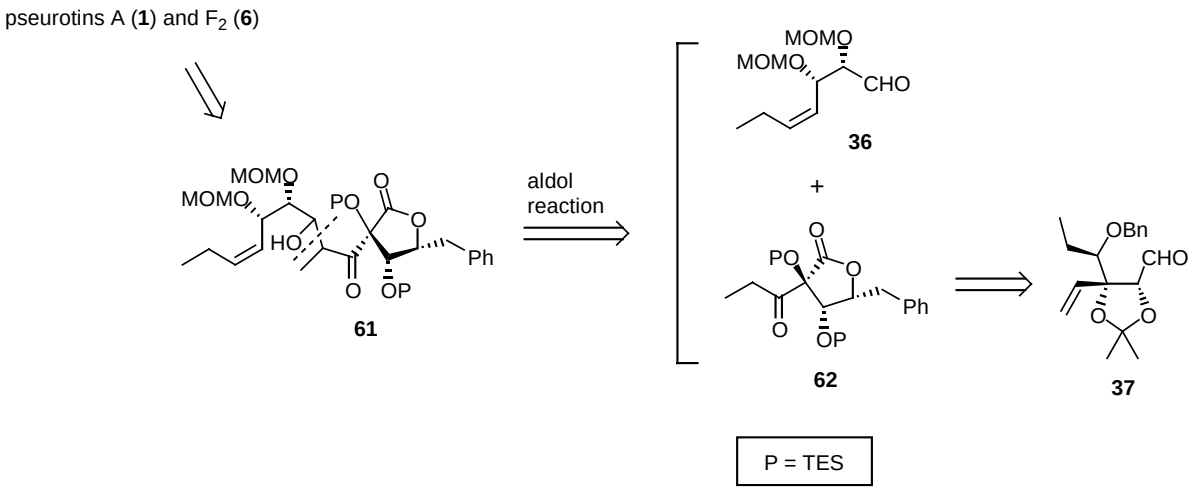
Chapter 3

The Second-Generation Approach

3.1 Revised Retrosynthetic Analysis

After all, I chose a benzyl group as a synthetic precursor for a benzoyl moiety in pseurotins. The alternative retrosynthetic analysis is outlined in Scheme 10. In this analysis, I considered that the γ-benzyl-γ-lactone **61**, instead of the γ-benzoyl-γ-lactone **34**, would be an advanced synthetic intermediate. For the construction of **61**, the aldol reaction of a keto γ-lactone **62**, having a benzyl moiety as a benzoyl precursor, with the aldehyde **36** was anticipated. Then, the γ-lactone **62** would be obtained from aldehyde **37** via benzyl Grignard addition followed by the same reaction sequence used for the conversion of **48** into **35**.

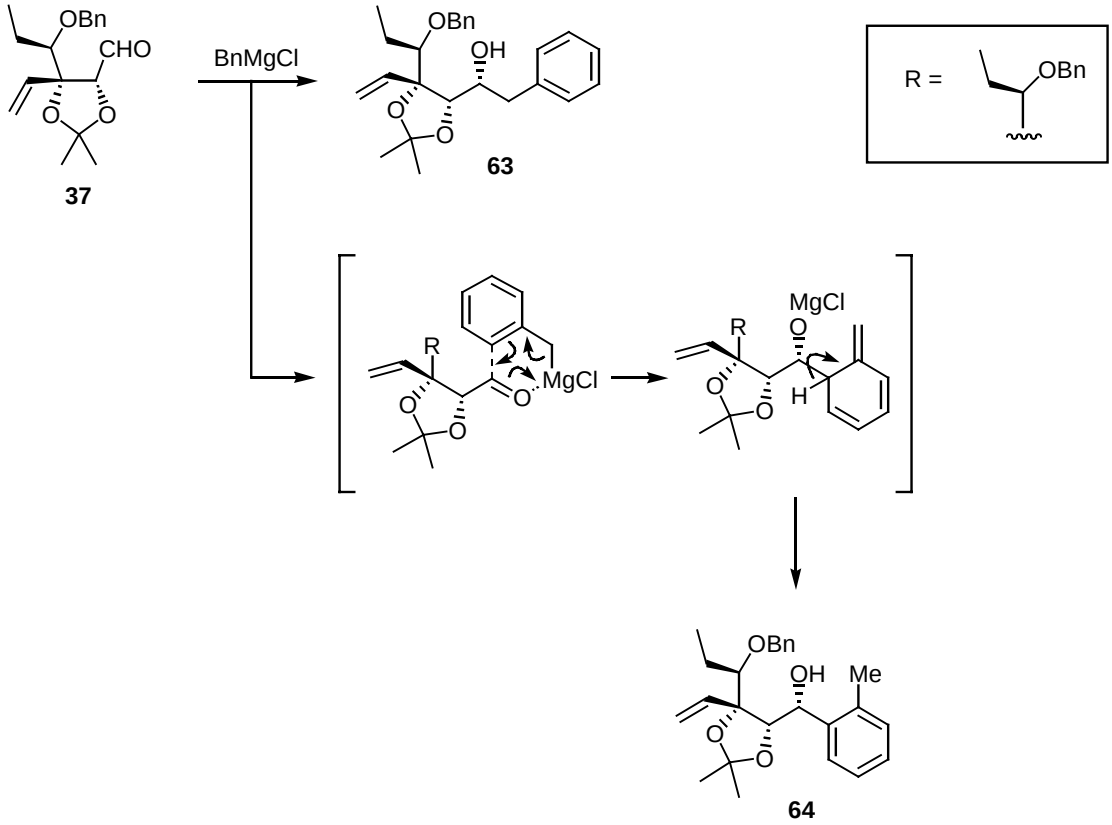
Scheme 10. Revised Retrosynthetic Analysis



3.2 Benzyl Grignard Addition to Aldehyde **37**

For the introduction of a benzyl group as a synthetic precursor of a benzoyl group, I investigated the benzyl Grignard addition to aldehyde **37** (Scheme 11). Using excess benzylmagnesium chloride in THF at room temperature, I obtained a mixture of the desired benzyl adduct **63** and the undesired and abnormal 2-methylphenyl (*ortho*-tolyl) adduct **64** along with a 9% recovery of **37** (entry 1, Table 1). As shown, the 2-methylphenyl adduct **64** was formed via a Mg(II)-mediated six-membered transition state, in which the *ortho*-carbon of the benzyl Grignard reagent attacked the aldehyde, as previously proposed.[18] The formation of the desired adduct **63** was slightly improved by the addition of an equal amount of $CeCl_3$[19] in the reaction mixture (entry 2, Table 1). I was pleased to find that the addition of $CuBr \cdot Me_2S$ in a mixed solution of THF and Me_2S[20] dramatically increased the yield of **63**. As a result, the benzyl adduct **63** was isolated in 89% yield along with a small amount (2%) of **64** (entry 3, Table 1). It was considered that the addition of the

Scheme 11. Benzyl Grignard Addition to Aldehyde **37**



Cu(I) salt suppressed the formation of the six-membered transition state; thus, the expected "*normal*" addition occurred preferentially. Similar to the case involving the formation of **48**, the configuration of a newly introduced secondary alcohol carbons in **63** and **64** were determined, after converting to the γ-lactone **66** and **69**, respectively.

Table 1. Benzyl Grignard Addition to Aldehyde **37**

		yield (%)[a]		
entry	conditions (mol. amt.)	**37**	**63**	**64**
1	BnMgCl (12), THF, rt	9	14	51
2	BnMgCl (10), $CeCl_3$ (10), THF, rt	22	26	36
3	BnMgCl (10), $CuBr{\cdot}Me_2S$ (5), THF / Me_2S, 0 °C	–	89	2

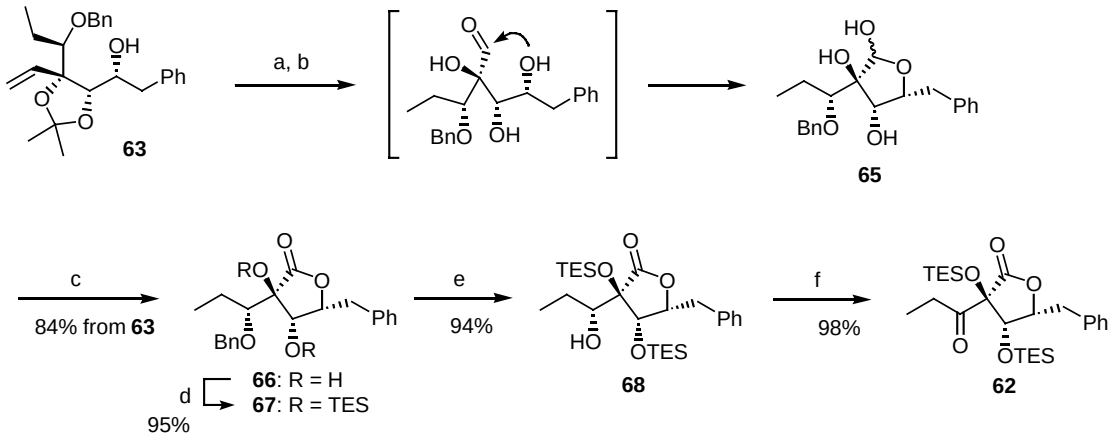
[a] Isolated yield of chromatographically pure compound.

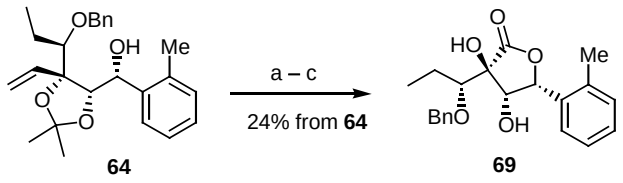
3.3 Synthesis of the Right Part Precursor **62**

The successive ozonolysis and hydrolytic removal of the acetal of **63**, followed by the chemoselective oxidation of the resultant γ-lactol **65** with NIS, eventually provided γ-lactone **66** (Scheme 12). Two hydroxy groups in **66** were then protected as a vicinal di-*O*-TES derivative to provide **67**. Deprotection of the benzyl group in **67** by hydrogenolysis, followed by Dess−Martin oxidation of the resultant **68**, provided ethyl ketone **62**.

To assign to the configuration of the secondary alcohol carbon in **64**, methylphenylated γ-lactone **69** was derived via the same reaction sequence used for the transformation of **63** to **66**, similarly.

Scheme 12. Synthesis of the Right Part Precursor **62**





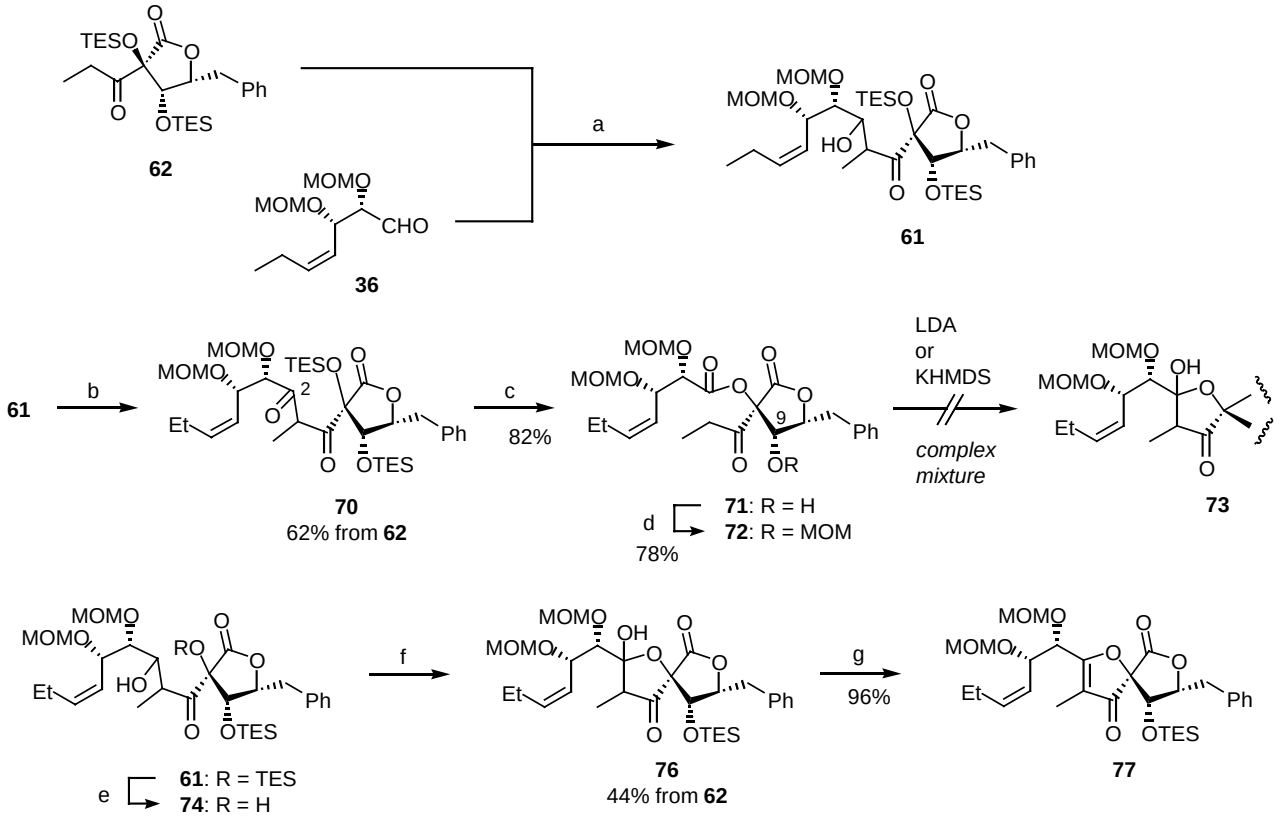
Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C; Ph_3P; (b) 60% aqueous TFA; (c) NIS, *n*-Bu_4NI, CH_2Cl_2; (d) TESOTf, pyr, 50 °C; (e) H_2, 10% Pd on C, EtOH; (f) Dess−Martin periodinane, CH_2Cl_2.

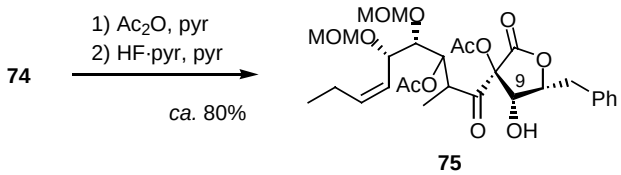
3.4 Aldol Reaction, and 3(2*H*)-Furanone Formation

The coupling reaction of **62** and aldehyde **36** was best achieved using 1.0 molar amount of KHMDS as the base in THF at −78 °C to produce the aldol product **61** with a high level of diastereoselectivity. I did not determine the stereochemistry of the aldol adduct. Dess−Martin oxidation of the aldol hydroxy group in

61 gave β-diketone **70**. Treatment of **70** with a hydrogen fluoride–pyridine complex (HF·pyridine) in pyridine[21] caused the desilylation and spontaneous acetal formation of the tertiary alcohol with carbonyl at C2 as well as retro-Dieckmann-type reaction, providing the unexpected product **71**. The signal for H-9 of **71** (δ 5.46) was shifted to lower field (δ 6.02) by acetylation. Then secondary alcohol in **71** was protected as an *O*-MOM ether to give **72**. Treatment of **72** with a variety of base, such as LDA and KHMDS, did not give the desired acetal compound **73**. Therefore, exposure of **61** to a HF·pyridine in pyridine selectively cleaved the *O*-TES group attached to the tertiary alcohol giving **74**. The chemoselectivity of this de-*O*-silylation was

Scheme 13. Construction of the 3(2*H*)-Furanone Structure





Reagents and conditions: (a) KHMDS (1.0 mol. amt.), THF, −78 °C; then **36** (3.0 mol. amt.); (b) Dess–Martin periodinane, CH_2Cl_2; (c) HF·pyr, pyr, THF; (d) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, 0 °C; (e) HF·pyr, pyr, THF; (f) Dess–Martin periodinane, CH_2Cl_2; (g) $SOCl_2$, pyr, 0 °C.

determined from the $^{3}J_{\text{H-9,OH}}$ (6.1 Hz) in ^{1}H NMR spectrum of di-*O*-acetylated γ-lactone **75**, which was prepared from **74** by the two-step acetylation/de-*O*-silylation sequence. At last, Dess−Martin oxidation of **74**, followed by dehydration of the resultant spirocyclic five-membered hemiketal γ-lactone **76** with thionyl chloride, provided the desired spirocyclic 3(2*H*)-furanone **77**.

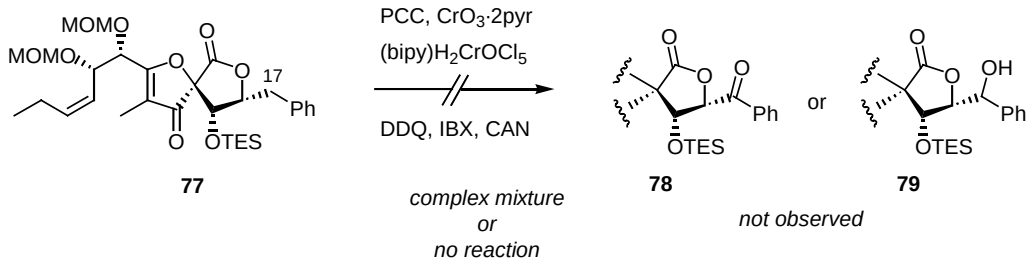
Chapter 4

Completion of the Total Syntheses of Pseurotins A and F_2

4.1 Attempted Benzylic Oxidation

I attempted the benzylic (C17) oxidation of spirocyclic γ-lactone **77** (Scheme 14). A variety of six- or five-valent chromium complexes were examined. PCC reagent, Collins' reagent (CrO_3·2pyridine)[22] or treatment with 2,2'-bipyridyl complex of oxochromium(V) [(bypy)H_2CrOCl_5][23] did not work. Treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or IBX[16c] in DMSO also failed, and the starting material was recovered. Oxidation with ammonium cerium(IV) nitrate (CAN) resulted in the decomposition of **77**.

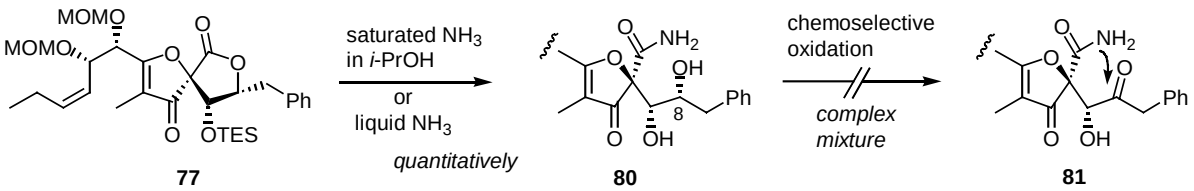
Scheme 14. Attempted Benzylic Oxidation of **77**



4.2 Attempted γ-Lactam Formation

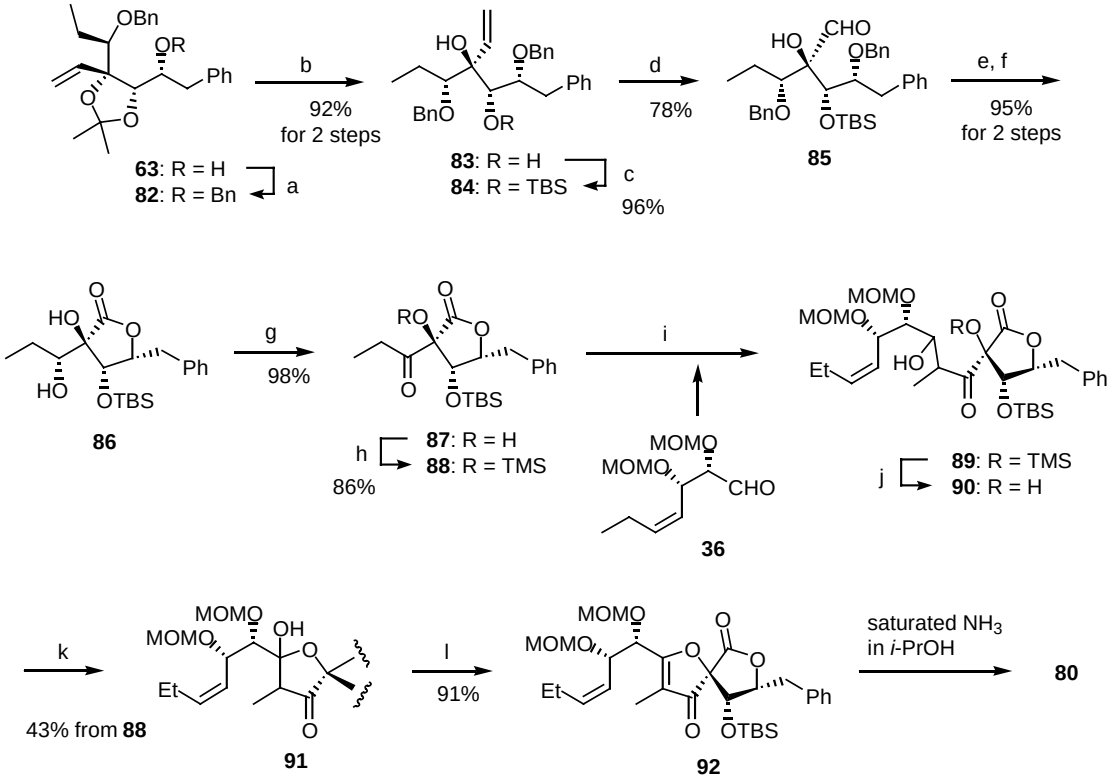
Therefore, I examined the installation of a γ-lactam nitrogen atom to **77** by a variety of reagents, such as ammonium hydroxide, ammonium acetate with catalytic sodium cyanide,[24] or 1,1,1,3,3,3-hexamethyldisilazane.[25] None of these conditions gave useful results. Finally, I found that treatment of **77** with saturated NH_3 in *i*-PrOH, or liquid NH_3 resulted in a γ-lactone ring-opened amidation accompanied by the cleavage of the *O*-TES group in **77** to give amide vicinal alcohol **80**, quantitatively (Scheme 15). However, chemoselective oxidation of C8 carbon in **80** using di-*n*-butyltin oxide−NBS,[26] $RuCl_3$−NMO reagents,[27] or Dess−Martin reagent afforded none of the desired amide ketone **81** or ring-closed γ-lactam.

Scheme 15. Attempted γ-Lactamization



Scheme 16 depicted the route leading to an alternative substance, *tert*-butyldimethylsilyl (TBS) ether **92**, for the introduction of amide-nitrogen atom. (Direct silylation of two hydroxy groups in **66** using TBSOTf was unsuccessful). Treatment of **63** with benzyl bromide and NaH afforded benzyl ether **82**. Acidic hydrolytic removal of the acetal provided diol **83**. The secondary hydroxy group in **83** was protected as an *O*-TBS ether to give **84**. The ozonolysis of **84** give α-hydroxy aldehyde **85**. Deprotection of the benzyl groups in **85** by hydrogenolysis, followed by oxidation of the resultant γ-lactol with NIS, eventually provided γ-lactone **86**. Oxidation of **86** with the Dess−Martin periodinane in the presence of water according to Schreiber's modified conditions[15d] gave ethyl ketone **87** in 98% yield. The coupling reaction of **87** and aldehyde **36** using 2.0 molar amounts of KHMDS as the base in THF at −78 °C afforded the aldol product, but the yield was only 8%. Therefore, the tertiary hydroxy group in **87** was protected as a trimethylsilyl (TMS) ether to provide **88**. The coupling reaction of **88** and **36** was examined under the same reaction conditions to produce the aldol product **89** as a single stereoisomer. I did not determine the stereochemistry

Scheme 16. Synthesis of the Spiro-Fused γ-Lactone **92**

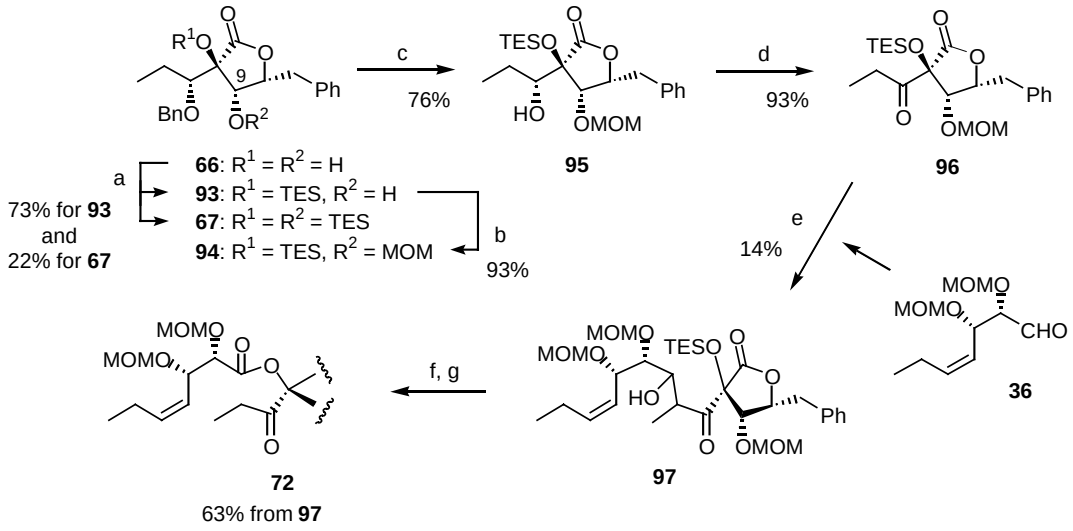


Reagents and Conditions: (a) BnBr, NaH, DMF; (b) 60% aqueous TFA; (c) TBSOTf, pyr, 50 °C; (d) O_3, CH_2Cl_2, −78 °C; PPh_3; (e) Pd on C, H_2, EtOAc; (f) NIS, *n*-Bu_4NI, CH_2Cl_2; (g) Dess−Martin periodinane, H_2O, CH_2Cl_2; (h) TMSCl, pyr; (i) KHMDS (1.0 mol. amt.), THF, −78 °C; then **36** (3.0 mol. amt.); (j) HF·pyr, pyr, THF; (k) Dess−Martin periodinane, CH_2Cl_2; (l) $SOCl_2$, pyr, 0 °C.

of the aldol adduct. Then, the desired 3(2*H*)-furanone **92** was obtained from **89** via the same reaction sequence used for the conversion of **61** into **77**. However, treatment of **92** with saturated NH_3 in *i*-PrOH caused a removal of *O*-TBS group to give the amide vicinal alcohol **80**.

On the other hand, I prepared an alternative aldol substrate **96** (Scheme 17). Although I examined the selective protection of the tertiary hydroxy group in **66**, attempts to protect as *O*-TBS, *O*-TMS, *O*-MOM or *O*-THP failed. In the case of the *O*-TES protection, effective differentiation of the hydroxy groups in **66** was achieved with carefull addition of triethylsilyl trifluoromethanesulfonate at 0 °C to provide predominantly the desired mono-*O*-TES ether **93** in 73% yield along with the di-*O*-TES ether **67** in 22%. The signal for H-9 of **93** (δ 4.33) was shifted to lower field (δ 4.98) by acetylation. The secondary hydroxy group in **93** was protected as an *O*-MOM ether under acidic conditions to give **94**. The resulting **94** was converted into the ethyl ketone **96** via secondary alcohol **95** by the two-step hydrogenolysis/oxidation sequence used for the conversion of **67** into **62**. Contrary to my expectation, the coupling reaction of **96** and aldehyde **36** using KHMDS as the base in THF at −78 °C gave little amount of the aldol product **97** (14%). Unfortunately, I could not find any reliable conditions for deprotonation of **96** for the subsequent aldol reactions. The practical yield for **97** was not obtained on these conditions, such as LDA, LiHMDS or NaHMDS in THF or THF/toluene at −78 °C. Furthermore, Dess−Martin oxidation of the aldol hydroxy group in **97**, followed by desilylation of resulting β-diketone provided the unexpected product **72**.

Scheme 17. Synthesis of the γ-Lactone **96**, and Aldol Reaction

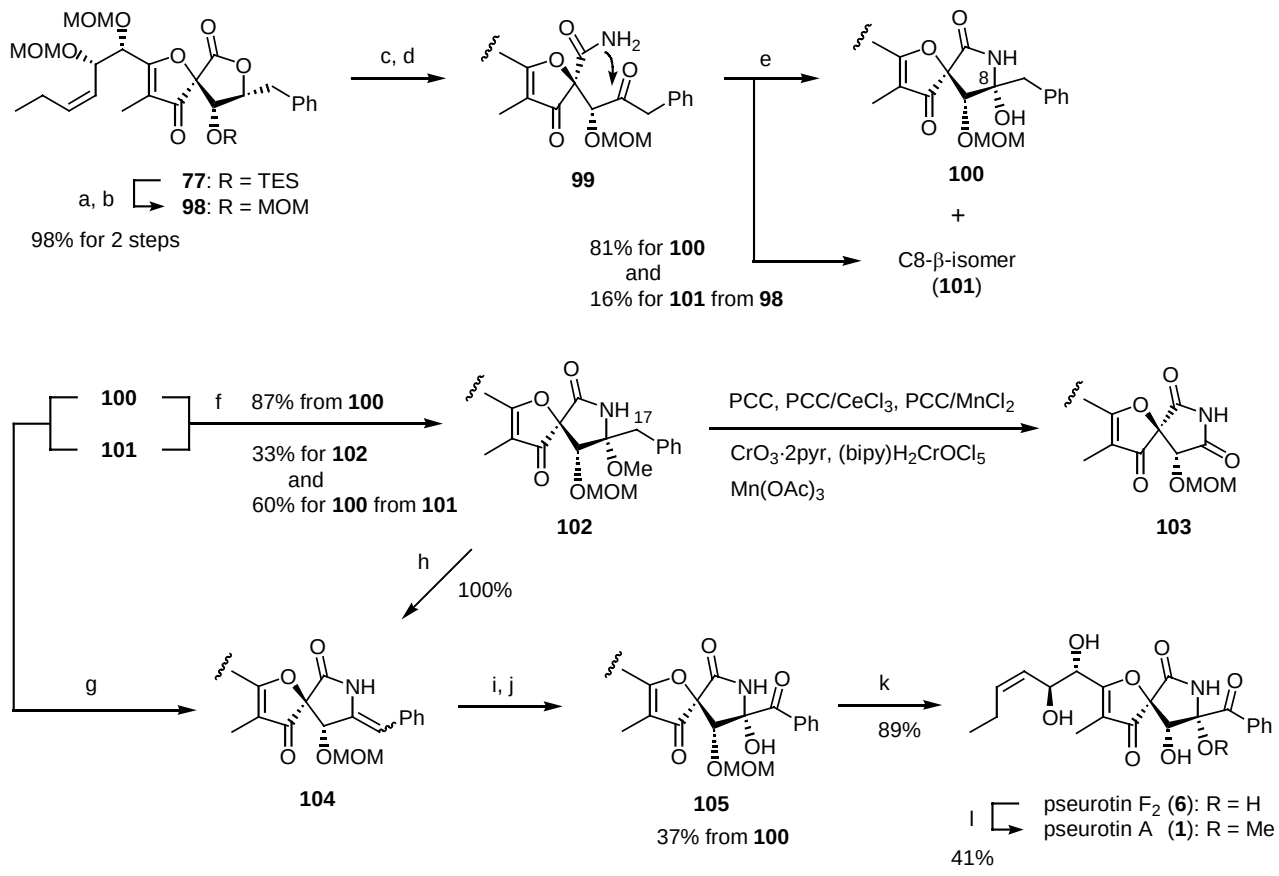


Reagents and conditions: (a) TESOTf, pyr, 0 °C; (b) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, 0 °C; (c) H_2, 10% Pd on C, EtOAc; (d) Dess–Martin periodinane, CH_2Cl_2; (e) KHMDS (1.0 mol. amt.), THF, −78 °C; then **36** (3.7 mol. amt.); (f) Dess–Martin periodinane, CH_2Cl_2; (g) HF·pyr, pyr.

4.3 Total Syntheses of Pseurotins A and F_2

Therefore, the *O*-TES group in **77** was replaced with the MOM group prior to ammonolysis (Scheme 18). De-*O*-silylation of **77** followed by etherification under acidic conditions provided the MOM ether **98** in good yield. The ammonolysis of **98** with saturated NH_3 in *i*-PrOH, followed by Dess–Martin oxidation, provided the ring-opened amide ketone **99**. By the brief exposure of **99** to saturated aqueous Na_2CO_3, the intramolecular attack of the amide-nitrogen to the carbonyl occurred to form the aminal **100** (a γ-hydroxy-γ-lactam) as the predominant α-anomer along with the β-anomer **101** in a ratio of approximately 5:1. The anomers were separable by column chromatography on silica gel. The stereochemistry of the α-anomeric carbon (C8) in **100** was determined by NOE experiments.

Scheme 18. Total Syntheses of Pseurotins A (**1**) and F_2 (**6**)



Reagents and conditions: (a) HF·pyr, pyr, THF; (b) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, 0 °C; (c) saturated NH_3 in *i*-PrOH; (d) Dess–Martin periodinane, CH_2Cl_2; (e) saturated aqueous Na_2CO_3; (f) MeOH, 60 °C; (g) 5% AcOH in *i*-PrOH, 70 °C; (h) pyr, 80 °C; (i) mCPBA, $NaHCO_3$, CH_2Cl_2; (j) Dess–Martin periodinane, CH_2Cl_2; (k) 6 M HCl / MeOH (v/v, 1:1); (l) CSA, MeOH, 40 °C.

I explored attempts to protect of aminal alcohol in **100**. Treatment of the α-anomer **100** with hot MeOH afforded C8-α-8-*O*-methylated intermediate **102** in good yield. On the other hand, the ketalization of the β-anomer **101** under the same reaction conditions gave the same α-product **102** along with a large amount of the recovered **100**. To achieve the crucial benzylic (C17) oxidation, a variety of six- or five-valent chromium complexes were examined. PCC oxidation of **102** afforded undesired spirocyclic imide **103**. The presence of additives[28] such as $MnCl_3$ or $CeCl_3$ had no effect against the oxidative cleavage of C8−C17 bond. Collins' reagent or treatment with (bypy)H_2CrOCl_5 gave also **103**. Oxidation with manganic(III) acetate[29] also failed.

After some experimentation, I found that the dehydrated enamide **104** was formed as an inseparable *E,Z*-mixture by heating **100** in 5% acetic acid in *i*-PrOH. The β-isomer **101** also provided the mixture of *E,Z*-enamides **104** under similar acidic conditions. Approximately, the geometrical ratios of these mixtures were both 5:4, determined by ^{1}H NMR at 300 MHz. At preliminary experiment,[10a,b] I used the following conditions for the conversion of hemiaminal **100** into enamide **104**: heating in MeOH at 60 °C for 158 hours, then heating in pyridine at 80 °C for 8 hours. Under these conditions, the ovarall yield of **105** was 31%. Therefore, I could achieve the improvement of the ovarall yield (37% yield of **105** from **100**) by the present modification,[10c] and also could shorten the reaction time significantly (66 hours).

To my delight, the formation of the desired γ-hydroxy-γ-lactam, carrying a benzoyl side-chain was successfully achieved by the regioselective epoxidation of the enamide double bond in **104** with mCPBA,[30] followed by Dess−Martin oxidation of the resulting benzylic alcohols, which were presumably formed by the ring-opening of the intermediary epoxide by the attack of water. I could not isolate the intermediary epoxide. On the other hand, treatment of **104** with dimethyldioxirane[31] gave undesired overoxidation products. In this case, epoxidation of the left-hand side-chain double bond was observed. Osmium tetroxide in alcoholic solvents[32] provided a mixture of degradation products. Singlet oxygen[33] provided **100** via the hydration of the enamide moiety. Heterogeneous potassium permanganate in the presence of $CuSO_4 \cdot 5H_2O$[34] did not work. Removal of all the *O*-MOM groups in **105** by acidic hydrolysis completed the total sysnthesis of natural pseurotin F_2 (**6**). The spectroscopic data of synthetic **6** matched well with those reported for natural **6**.[3] Furthermore, methyl acetalization of **6** with CSA in MeOH provided natural pseurotin A (**1**). Synthetic **1** was identical to an authentic sample of natural **1** in all respects (mp, $[\alpha]_D$, IR, ^{1}H and ^{13}C NMR, HRMS, TLC).

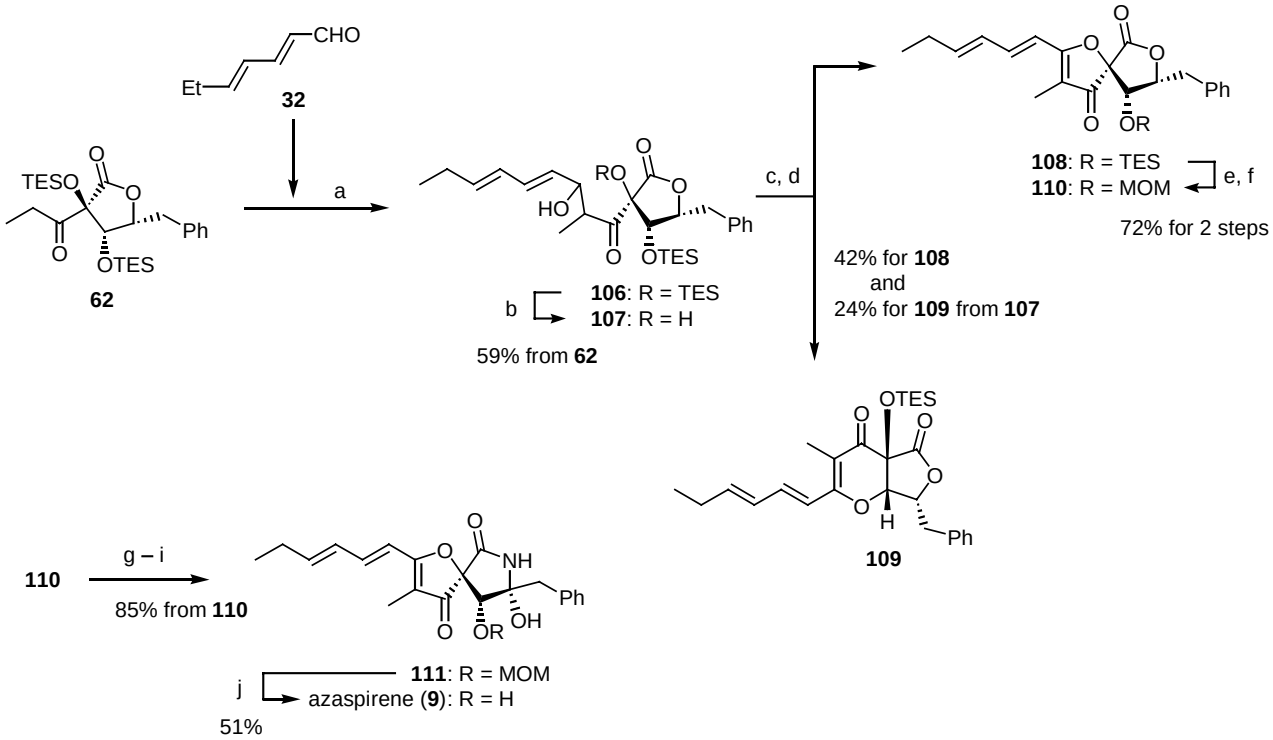
Chapter 5

Completion of the Total Synthesis of Azaspirene

5.1 Total Synthesis of Azaspirene

My next concern focused on the total synthesis of azaspirene (**9**). The total synthesis was accomplished starting from the union of the intermediate **62** and commercially available (2*E*,4*E*)-2,4-heptadienal (**32**) (Scheme 19). Deprotonation of **62** with KHMDS in THF at −78 °C, followed by the addition of **32** in the presence of 5.0 molar amounts of LiBr,[35a] provided the aldol adduct **106** as a sole product. The stereochemistry of **106** was not determined. When the reaction was conducted in the absence of LiBr, **106** was not obtained. I also explored the following reaction conditions[35b,c] for this aldol coupling. After treating **62** with 1.0 molar amount of KHMDS, 5.0 molar amounts of **32** were added with 5.0 molar amounts of chlorotriethylsilane in THF or THF/toluene (1:1, v/v) at −78 °C. Under these conditions, the silylated ether derived from **62** was only an obtainable product, whose geometrical stereochemistry was not determined.

Scheme 19. Total Synthesis of Azaspirene (**9**)

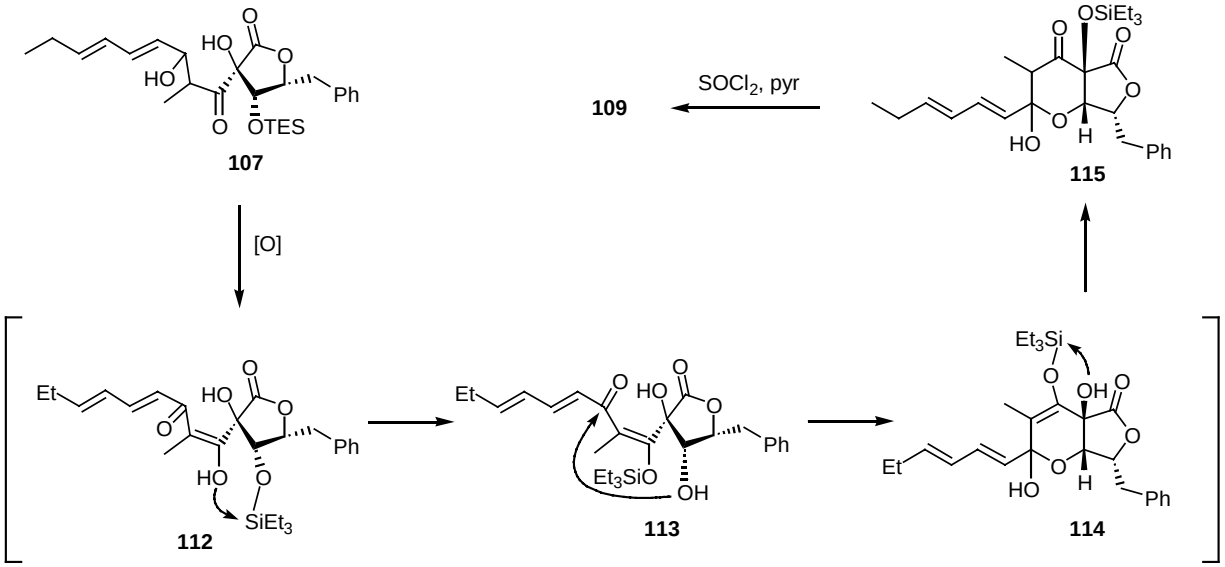


Reagents and conditions: (a) KHMDS (1.0 mol. amt.), THF, −78 °C; then **32** (5.0 mol. amt.), LiBr (5.0 mol. amt.); (b) HF·pyr, pyr, THF; (c) Dess−Martin periodinane, CH_2Cl_2; (d) $SOCl_2$, pyr, 0 °C; (e) HF·pyr, pyr, THF; (f) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, 0 °C; (g) saturated NH_3 in *i*-PrOH; (h) Dess–Martin periodinane, CH_2Cl_2; (i) saturated aqueous Na_2CO_3; (j) 6 M HCl / MeOH (1:1, v/v).

Exposure of **106** to HF·pyridine complex in pyridine cleaved selectively the *O*-TES group on the tertiary alcohol to provide **107**. Dess−Martin oxidation of **107**, followed by dehydration of the resultant γ-lactone hemiketal with thionyl chloride, provided the desired 1,7-dioxaspiro[4.4]non-2-ene-4,6-dione **108**, along with a 2,8-dioxabicyclo[4.3.0]non-3-ene-5,7-dione **109**. I explain that the *O*-TES group in **107** migrated to the tertiary hydroxy group in the oxidation step (Scheme 20). Then the liberated secondary hydroxy group in **113** attacked to the formed carbonyl, producing **109** after dehydration. To suppress the formation of **109**, I examined a variety of oxidation conditions. Initially, manganese dioxide was examined, since the aldol hydroxy group in **107** was dienylic, but the oxidant was unsuccessful (ratio of **108** to **109** was approximately 2:1). Oxidation using Dess−Martin reagent with catalytic pyridine, and IBX gave similar results. Treatment with sodium acetate buffered PCC led to degradation.

The spirocyclic γ-lactone **108** was converted into the aminal **111** (a γ-oxgenated-γ-lactam) via the *O*-MOM ether **110** by the same reaction sequence used for the conversion of **77** into **100**. The stereochemistry of the α-anomeric carbon in **111** was determined by NOE experiments. Hydrolysis of the *O*-MOM group in **111** completed the total synthesis of azaspirene (**9**). Synthetic **9** was identical to an authentic sample of natural **9** in all respects (mp, $[\alpha]_D$, IR, ^{1}H and ^{13}C NMR, HRMS, TLC).[7]

Scheme 20. Plausible mechanism for the formation of 2,8-dioxabicyclo[4.3.0]non-3-ene-5,7-dione **109**



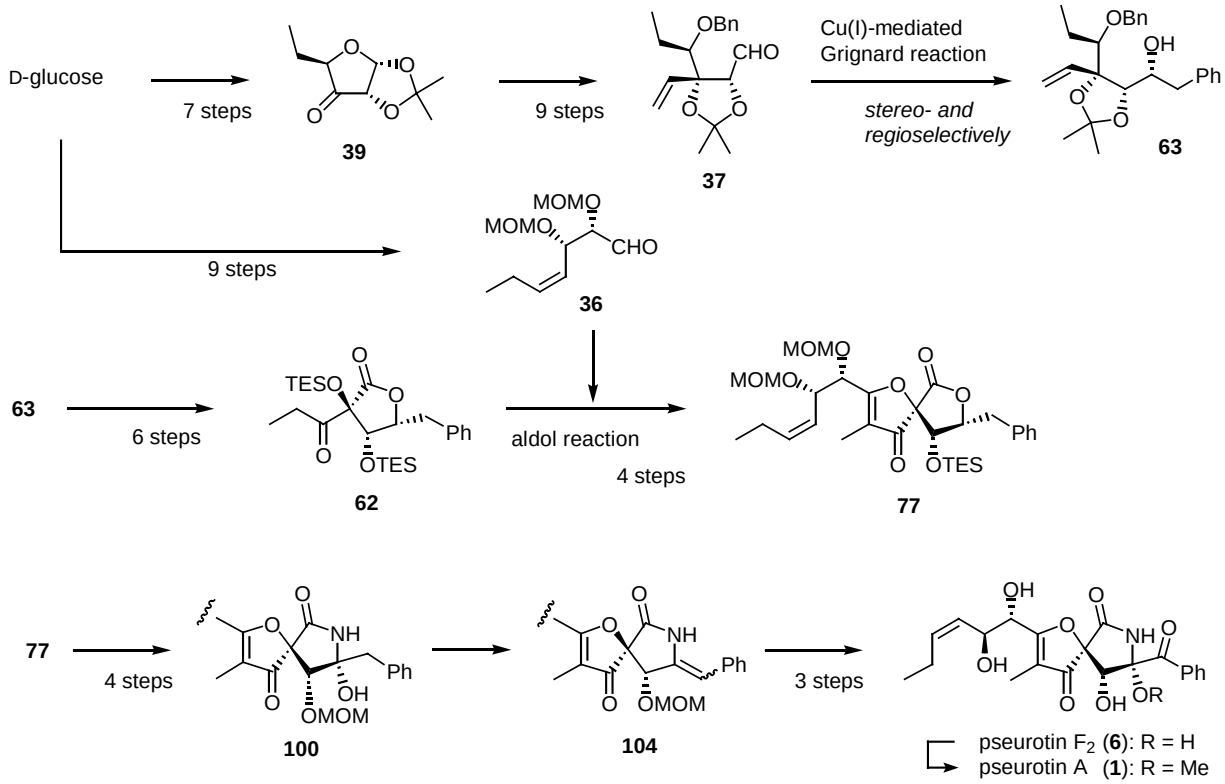
Chapter 6

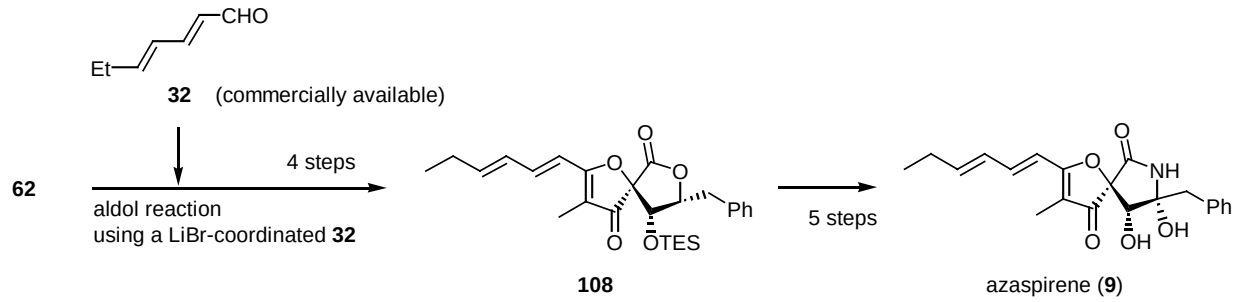
Conclusion

I describe the total syntheses of natural pseurotins A (**1**) and F_2 (**6**), inhibitors of chitin synthase, which possess an unusual 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione ring system (Scheme 21). The total syntheses of these spiro-heterocyclic natural products feature: 1) a stereoselective preparation of two segments, i.e., a 2,3-dihydroxylated heptenal **36** and a highly functionalized γ-lactone **62**, each from D-glucose, 2) the connection of two segments via an aldol-type carbon–carbon bond formation, 3) spirocyclic ring formation from the aldol adduct through convenient 3(2*H*)-furanone formation, 4) the transformation of a spirocyclic γ-lactone **77** into a γ-lactam hemiaminal **100**, and 5) conversion of the benzyl substituent in the γ-lactam ring into a benzoyl group via a cyclic emanide **104** followed by sodium hydrogencarbonate buffered mCPBA oxidation in the final stage of the total synthesis. In the initial stage, the quaternary spiro-carbon center in the target molecules, pseurotins **1** and **6**, was efficiently constructed by a stereochemically exclusive vinyl Grignard addition to the D-glucose derived 3-ulose **39**. Furthermore, the preparation of the γ-lactone **62** included a stereo- and regioselective Cu(I)-mediated benzyl Grignard addition to aldehyde **37**.

I have also completed the total synthesis of a structurally related novel angiogenesis inhibitor, azaspirene (**9**), using the analogous reaction sequence. The left-part in the antibiotic was introduced by the aldol reaction of the common potassium-enolate generated from ethyl ketone **62** with LiBr-coordinated (2*E*,4*E*)-2,4-heptadienal (**32**). By a similar synthetic pathway, the total synthesis of azaspirene (**9**) was completed.

Scheme 21. Summary





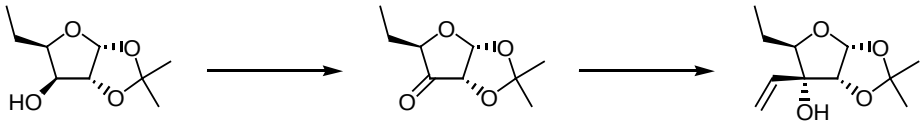
Experimental Section

General Remarks

Melting points are uncorrected. Specific rotations were measured in a 10 mm cell. ^{1}H NMR spectra were recorded at 270 MHz or at 300 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ solution. All spectra were recorded in $CDCl_3$ as solvent unless otherwise noted. High-resolution mass spectra (HRMS) were measured by the EI method (70 eV) unless otherwise noted. Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 F_{254} (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on silica gel Daisogel IR-60 (Daiso Co., Ltd.) or Wakogel C300 (Wako Pure Chemical Industries). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from reaction mixture or combined organic extracts by concentration under reduced pressure using an evaporator with a water bath at 35−45 °C.

Experimental Procedures for Chapter 2

(2*R*,3*R*,4*R*,5*R*)-5-Ethyl-4-hydroxy-2,3-isopropylidenedioxy-4-vinyltetrahydrofuran (40).



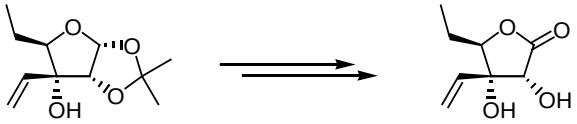
38 **39** **40**

To a cooled (0 °C) stirred solution of **38**[12] (14.4 g, 76.6 mmol) in CH_2Cl_2 (300 mL) were added PCC (67.4 g, 313 mmol) and molecular sieves 4A (67.6 g). The mixture was stirred at rt for 10 h followed by elution through a short column of silica gel to remove inorganic salts. The column was eluted with excess Et_2O. The combined eluates were concentrated in vacuo to give crude 3-ulose **39** (14.6 g), which was used directry in the next step.

The following reaction was carried out under Ar. To a cooled (−18 °C) stirred solution of crude 3-ulose **39** (14.6 g) in THF (100 mL) was added dropwise vinylmagnesium bromide (1.0 M solution in THF, 121 mL, 121 mmol). After being stirred for 1 h at −18 °C, the solution was quenched with saturated aqueous NH_4Cl (50 mL), diluted with EtOAc (1 L) and washed with saturated aqueous NH_4Cl (300 mL) and saturated brine (300 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 13.6 g (83% from **38**) of **40** as colorless crystals: mp 59.6−60.7 °C; TLC R_f 0.35 (EtOAc/hexane, 1:10); $[\alpha]_D^{23}$ +54.6 (*c* 1.32, $CHCl_3$); IR (neat) 3480 cm^{-1}; ^1H NMR (300 MHz) δ 0.98 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.36, 1.60 (2 s, each 3 H, isopropylidene), 1.49 (quint, 2 H, *J* = 7.3 Hz, $C\underline{H}_2CH_3$), 2.68 (s, 1 H, O<u>H</u>), 3.70 (t, 1 H, *J* = 7.3 Hz, H-5), 4.20 (d, 1 H, *J* = 3.9 Hz, H-3), 5.28 (dd, 1 H, *J* = 1.7, 11.0 Hz, CH=C<u>H</u>H), 5.49 (dd, 1 H, *J* = 1.7, 17.3 Hz, CH=CH<u>H</u>), 5.75 (dd, 1 H, *J* = 11.0, 17.3 Hz, C<u>H</u>=CHH), 5.80 (d, 1 H, *J* = 3.9 Hz, H-2); ^{13}C NMR (75 MHz)

δ 10.5, 21.8, 26.4, 26.5, 80.1, 83.5 × 2, 103.3, 112.3, 115.5, 134.4; HRMS calcd for $C_{11}H_{18}O_4$ (M^+) *m/z* 214.1205, found 214.1198. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%. Found: C, 61.53; H, 8.58%.

(2*R*,3*S*,4*R*)-4-Ethyl-2,3-dihydroxy-3-vinyl-4-butanolide (41).

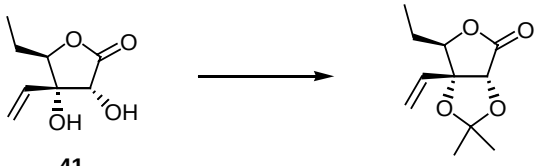


40 **41**

Compound **40** (7.32 g, 34.2 mmol) was dissolved in 80% aqueous AcOH (120 mL). The solution was stirred at 80 °C for 11 h and concentrated in vacuo with the aid of EtOH and toluene to give crude γ-lactol derivative (6.99 g), which was used in the next step without further purification.

The following reaction was carried out in the dark. To a cooled (0 °C) stirred solution of crude γ-lactol derivative (6.99 g) in CH_2Cl_2 (100 mL) were added tetra-*n*-butylammonium iodide (18.9 g, 51.2 mmol) and NIS (19.2 g, 85.4 mmol). The mixture was stirred at rt for 20 h, diluted with EtOAc (800 mL), and washed with saturated aqueous $Na_2S_2O_3$ (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and saturated brine (300 mL). The organic layer was dried and concentrated in vacuo followed by elution through a short column of silica gel. The column was eluted with EtOAc/hexane (1:2). The combined eluates were concentrated in vacuo and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 5.60 g (95% from **40**) of **41** as colorless crystals: mp 71.0−72.1 °C; TLC R_f 0.39 (EtOAc/hexane, 1:1); $[\alpha]_D^{21}$ +106 (*c* 1.07, $CHCl_3$); IR (neat) 3440, 1780, 1640 cm^{-1}; ^1H NMR (300 MHz) δ 1.03 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.42−1.57, 1.64−1.77 (2 m, each 1 H, $C\underline{H}_2CH_3$), 3.60 (br s, 2 H, O<u>H</u> × 2), 4.30 (dd, 1 H, *J* = 3.7, 10.7 Hz, H-4), 4.56 (s, 1 H, H-2), 5.42 (dd, 1 H, *J* = 0.7, 10.7 Hz, CH=C<u>H</u>H), 5.60 (dd, 1 H, *J* = 0.7, 17.1 Hz, CH=CH<u>H</u>), 5.93 (dd, 1 H, *J* = 10.7, 17.1 Hz, C<u>H</u>=CHH); ^{13}C NMR (75 MHz) δ 10.4, 25.0, 71.7, 78.6, 88.6, 118.8, 134.5, 175.2; HRMS calcd for $C_8H_{12}O_4$ (M^+) *m/z* 172.0736, found 172.0736. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02%. Found: C, 55.74; H, 7.03%.

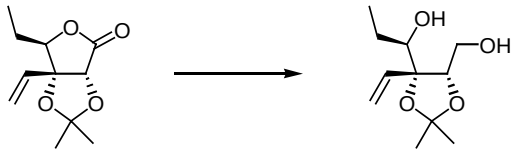
(2*R*,3*S*,4*R*)-4-Ethyl-2,3-isopropylidenedioxy-3-vinyl-4-butanolide (42).



41 **42**

To a stirred solution of **41** (5.40 g, 31.4 mmol) in acetone/$Me_2C(OMe)_2$ (1:1, v/v, 100 mL) was added CSA (2.19 g, 9.41 mmol). After being stirred for 6 h at 40 °C under reducing pressure (300 hPa), the solution was neutralized with saturated aqueous $NaHCO_3$ at 0 °C, diluted with EtOAc (500 mL), and washed with saturated aqueous $NaHCO_3$ (200 mL × 2) and saturated brine (200 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 5.25 g (79%) of **42** as a colorless oil: TLC R_f 0.53 (EtOAc/hexane, 1:3); $[\alpha]_D^{27}$ +6.5 (*c* 2.72, $CHCl_3$); IR (neat) 1790 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.31−1.48, 1.65−1.81 (2 m, each 1 H, $C\underline{H}_2CH_3$), 1.42, 1.44 (2 s, each 3 H, isopropylidene), 4.44 (dd, 1 H, *J* = 3.7, 9.8 Hz, H-4), 4.66 (s, 1 H, H-2), 5.42 (dd, 1 H, *J* = 1.1, 10.7 Hz, CH=C$\underline{H}$H), 5.58 (dd, 1 H, *J* = 1.1, 17.1 Hz, CH=CH$\underline{H}$), 5.98 (dd, 1 H, *J* = 10.7, 17.1 Hz, C$\underline{H}$=CHH); ^{13}C NMR (75 MHz) δ 9.8, 26.1, 27.7, 27.9, 78.0, 87.0, 88.3, 114.2, 118.3, 133.3, 173.7; HRMS calcd for $C_{11}H_{16}O_4$ (M^+) *m/z* 212.1049, found 212.1064.

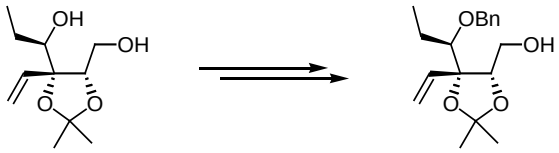
(2*S*,3*R*,4*R*)-2,3-Isopropylidenedioxy-3-vinylhexane-1,4-diol (43).



42 **43**

To a cooled (0 °C) stirred solution of **42** (2.99 g, 14.1 mmol) in THF (60 mL) was added $LiAlH_4$ (1.61 g, 42.4 mmol). After being stirred for 2 h at 0 °C, the mixture was quenched with H_2O (5 mL). The resulting gels were removed by filtration through a Celite-pad and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 2.77 g (91%) of **43** as colorless crystals: mp 80.1−80.3 °C; TLC R_f 0.20 (EtOAc/hexane, 1:3); $[\alpha]_D^{27}$ +86.0 (*c* 2.53, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^1H NMR (270 MHz) δ 0.99 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.18−1.30, 1.74−1.88 (2 m, each 1 H, $C\underline{H}_2CH_3$), 1.39, 1.44 (2 s, each 3 H, isopropylidene), 2.54 (br s, 1 H, O$\underline{H}$), 3.67 (dd, 1 H, *J* = 2.2, 10.3 Hz, H-4), 3.92−4.06 (m, 3 H, H-1, 1', 2), 5.26 (dd, 1 H, *J* = 2.0, 11.0 Hz, CH=C$\underline{H}$H), 5.49 (dd, 1 H, *J* = 2.0, 17.2 Hz, CH=CH$\underline{H}$), 6.14 (dd, 1 H, *J* = 11.0, 17.2 Hz, C$\underline{H}$=CHH); ^{13}C NMR (75 MHz) δ 10.7, 24.1, 26.0, 28.3, 60.1, 73.7, 82.9, 85.8, 107.8, 115.6, 136.0; HRMS calcd for $C_{10}H_{13}O_4$ ($M^+ - CH_3$) *m/z* 201.1127, found 201.1130.

(2*S*,3*R*,4*R*)-4-Benzyloxy-2,3-isopropylidenedioxy-3-vinylhexan-1-ol (44).



43 **44**

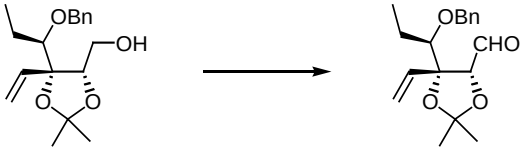
To a stirred solution of **43** (5.55 g, 25.7 mmol) in pyridine (100 mL) were added DMAP (6.27 g, 51.3 mmol) and trityl chloride (14.3 g, 51.3 mmol). The solution was refluxed for 4 h, diluted with EtOAc (500 mL), and washed with saturated aqueous $NaHCO_3$ (200 mL), saturated aqueous NH_4Cl (200 mL), and saturated brine (200 mL). The organic layer was dried and concentrated in vacuo followed by elution through a short column of silica gel. The column was eluted with EtOAc/hexane (1:15, containing 1 v/v% Et_3N). The combined eluates were concentrated in vacuo to give crude secondary alcohol (17.8 g), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude trityl ether (17.8 g) in DMF (50 mL) were added NaH (60% emulsion in mineral oil, 10.3 g, 257 mmol) and benzyl bromide (15.3 mL, 129 mmol). After being stirred for 8 h at rt, the mixture was quenched with H_2O (30 mL) at 0 °C, diluted with EtOAc (500 mL), and washed with saturated aqueous $NaHCO_3$ (300 mL), saturated aqueous NH_4Cl (300 mL), and saturated brine (300 mL). The organic layer was dried and concentrated in vacuo followed by elution through a short column of silica gel. The column was eluted with EtOAc/hexane (1:20, containing 1 v/v% Et_3N). The combined eluates were concentrated in vacuo to give crude benzyl ether (22.6 g), which was used in the next step without further purification.

To a stirred solution of crude benzyl ether (22.6 g) in MeOH (100 mL) was added CSA (59.6 mg, 0.257 mmol). The solution was stirred for 2 days, diluted with EtOAc (500 mL), and washed with saturated aqueous $NaHCO_3$ (200 mL × 2) and sturated brine (200 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8 to 1:6) to provide 6.59 g (84% from **43**) of **44** as a colorless oil: TLC R_f 0.28 (EtOAc/hexane, 1:6); $[\alpha]_D^{29}$ +64.2 (*c* 2.18, $CHCl_3$); IR (neat) 3500 cm^{-1}; ^1H NMR (300 MHz) δ 1.03 (t, 3 H, *J* = 7.7 Hz, $CH_2C\underline{H}_3$), 1.41, 1.47 (2 s, each 3 H, isopropylidene), 1.60−1.74, 1.84−1.99 (2 m, each 1 H, $C\underline{H}_2CH_3$), 2.37 (br s, 1 H, O<u>H</u>), 3.57 (dd, 1 H, *J* = 3.7, 5.1 Hz, H-4), 3.79 (d, 2 H, *J* = 6.6 Hz, H-1, 1'), 3.98 (t, 1 H, *J* = 6.6 Hz, H-2), 4.37, 4.69 (AB q, each 1 H, *J* = 10.7 Hz, $OC\underline{H}_2Ph$), 5.19 (dd, 1 H, *J* = 2.0, 10.7 Hz, CH=C<u>H</u>H), 5.53 (dd, 1 H, *J* = 2.0, 17.1 Hz, CH=CH<u>H</u>), 6.17 (dd, 1 H, *J* = 10.7, 17.1 Hz, C<u>H</u>=CHH), 7.25−7.38 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ

11.9, 22.2, 25.9, 28.2, 60.6, 71.0, 80.8, 84.2, 85.8, 108.1, 114.7, 127.8 × 2, 127.9, 128.5 × 2, 137.1, 137.4; HRMS calcd for $C_{18}H_{26}O_4$ (M^+) *m/z* 306.1831, found 306.1833.

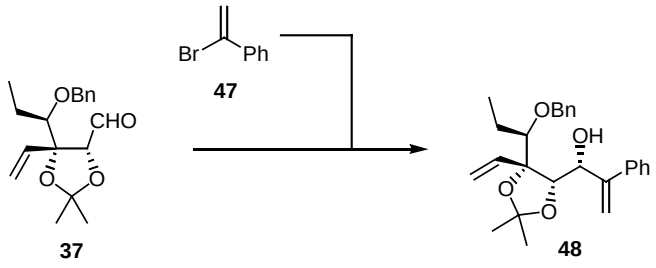
(2*R*,3*R*,4*R*)-4-Benzyloxy-2,3-isopropylidenedioxy-3-vinylhexan-1-al (37).



44 **37**

To a cooled (0 °C) stirred solution of **44** (6.50 g, 21.2 mmol) in CH_2Cl_2 (100 mL) was added Dess−Martin periodinane (9.90 g, 23.3 mmol). The mixture was stirred for 3 h at rt, diluted with EtOAc (500 mL), and washed with saturated aqueous $Na_2S_2O_3$ (300 mL) and saturated aqueous Na_2CO_3 (300 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide 6.17 g (96%) of **37** as a colorless oil: TLC R_f 0.48 (EtOAc/hexane, 1:6); $[\alpha]_D^{28}$ −17.5 (*c* 1.76, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (300 MHz) δ 1.01 (t, 3 H, *J* = 7.7 Hz, $CH_2C\underline{H}_3$), 1.42, 1.59 (2 s, each 3 H, isopropylidene), 1.53−1.67, 1.71−1.85 (2 m, each 1 H, $C\underline{H}_2CH_3$), 3.40 (t, 1 H, *J* = 5.1 Hz, H-4), 4.19, 4.50 (AB q, each 1 H, *J* = 11.0 Hz, $OC\underline{H}_2Ph$), 4.35 (s, 1 H, H-2), 5.31 (dd, 1 H, *J* = 1.7, 11.0 Hz, CH=C<u>H</u>H), 5.61 (dd, 1 H, *J* = 1.7, 17.3 Hz, CH=CH<u>H</u>), 6.27 (dd, 1 H, *J* = 11.0, 17.3 Hz, C<u>H</u>=CHH), 7.24−7.37 (m, 5 H, $C_6\underline{H}_5$), 9.51 (s, 1 H, H-1); ^{13}C NMR (75 MHz) δ 11.6, 22.3, 26.0, 28.1, 71.0, 80.4, 87.8, 88.9, 110.2, 115.9, 127.6, 127.8 × 2, 128.3 × 2, 135.7, 137.7, 192.5; HRMS calcd for $C_{18}H_{24}O_4$ (M^+) *m/z* 304.1675, found 304.1676.

(3*R*,4*S*,5*R*,6*R*)-6-Benzyloxy-4,5-isopropylidenedioxy-2-phenyl-5-vinyloct-1-en-3-ol (48).

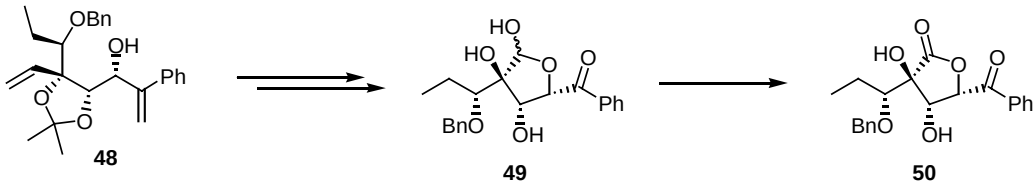


37 **48**

The following reaction was carried out under Ar. To a cooled (−78 °C) solution of 1-bromo-1-phenylethene (**47**) (0.48 mL, 3.70 mmol) in Et_2O (10 mL) was added dropwise *tert*-butyllithium (1.57 M solution in pentane, 4.71 mL, 7.39 mmol). The solution was stirred at −78 °C for 30 min, and a solution of **37** (566 mg, 1.86 mmol) in Et_2O (0.5 mL) was added. After being stirred at −78 °C for 30 min, the solution was

quenched with H_2O (1 mL), diluted with Et_2O (100 mL), and washed with saturated brine (80 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 715 mg (94%) of **48** as a colorless oil: TLC R_f 0.55 (EtOAc/hexane, 1:6); $[\alpha]_D^{18}$ +82.2 (*c* 0.720, $CHCl_3$); IR (neat) 3540 cm^{-1}; ^1H NMR (300 MHz) δ 1.01 (t, 3 H, *J* = 7.6 Hz, H-8, 8', 8"), 1.29, 1.52 (2 s, each 3 H, isopropylidene), 1.56−1.70, 1.75−1.90 (2 m, each 1 H, H-7, 7'), 3.16 (br s, 1 H, OH), 3.93 (t, 1 H, *J* = 5.0 Hz, H-6), 3.84 (d, 1 H, *J* = 1.5 Hz, H-4), 4.66 (s, 2 H, OCH_2Ph), 5.07 (dd, 1 H, *J* = 1.7 Hz, 11.0 Hz, CH=CHH), 5.24 (br s, 1 H, H-3), 5.33 (dd, 1 H, *J* = 1.7, 17.3 Hz, CH=CHH), 5.35−5.37 (m, 1 H, H-1), 5.44 (d, 1 H, *J* = 1.2 Hz, H-1'), 6.13 (dd, 1 H, *J* = 11.0, 17.3 Hz, CH=CHH), 7.18−7.43 (m, 10 H, C_6H_5 × 2); ^{13}C NMR (75 MHz) δ 12.2, 23.2, 26.2, 28.0, 68.2, 71.6, 81.4, 83.0, 86.0, 108.1, 113.1, 114.4, 126.7 × 2, 127.3, 127.4 × 2, 127.6, 128.27 × 2, 128.34 × 2, 137.9, 139.0, 139.9, 150.0; HRMS calcd for $C_{26}H_{32}O_4$ (M^+) *m/z* 408.2301, found 408.2302.

(2*S*,3*S*,4*S*)-4-Benzoyl-2-[(1*R*)-1-(benzyloxy)propyl]-2,3-dihydroxy-4-butanolide (50).



48 **49** **50**

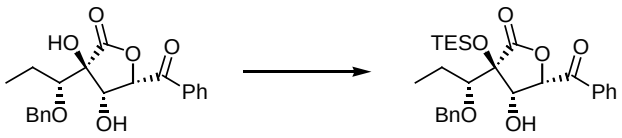
To a cooled (−78 °C) stirred solution of **48** (686 mg, 1.68 mmol) in CH_2Cl_2 (10 mL) was bubbled ozone (O_2 containing *ca.* 3% O_3) for 15 min to a persistent light bluecolor. To this solution was added Ph_3P (1.10 g, 4.19 mmol), and the solution was stirred for 30 min at −78 °C and for additional 1 h warming to rt. The solvent was removed by evaporation in vacuo to provide crude aldehyde (2.03 g), which was used directly in the next step.

The crude aldehyde (2.03 g) was dissolved in 60% aqueous CF_3CO_2H (20 mL). After being stirred for 10 h at rt, the solution was neutralized with 5 M (1 M = 1 mol·dm^{-1}) aqueous NaOH, diluted with EtOAc (200 mL), and washed with saturated brine (80 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:2), and the combined eluates were cncentrated in vacuo to provide crude γ-lactol **49** (890 mg), which was used in the next step without further purification.

The following reaction was carried out in the dark. To a cooled (0 °C) stirred solution of crude γ-lactol **49** (890 mg) in CH_2Cl_2 (10 mL) were added tetra-*n*-butylammonium iodide (620 mg, 1.68 mmol) and NIS (633 mg, 2.81 mmol). The solution was stirred at rt for 24 h, and additional NIS (633 mg × 2, 2.81

mmol × 2) was added every 12 h. The solution was stirred for total 48 h, diluted with Et_2O (200 mL), and washed with saturated aqueous $Na_2S_2O_3$ (80 mL) and saturated aqueous $NaHCO_3$ (80 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3 to 1:2) to give 352 mg (57% from **48**) of **50** as a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:1); $[\alpha]_D^{25}$ +31.6 (*c* 1.18, $CHCl_3$); IR (neat) 3450, 1790, 1695 cm^{-1}; ^1H NMR (300 MHz) δ 1.07 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.67−1.95 (m, 2 H, $C\underline{H}_2CH_3$), 3.87 (dd, 1 H, *J* = 3.9, 8.5 Hz, H-1 of the side chain at C-2), 4.58 (d, 1 H, *J* = 2.8 Hz, H-3), 4.70, 5.15 (AB q, each 1 H, *J* = 10.0 Hz, $OC\underline{H}_2Ph$), 5.76 (d, 1 H, *J* = 2.8 Hz, H-4), 7.26−7.40, 7.42−7.47 (2 m, 3 H + 2 H, $OCH_2C_6\underline{H}_5$), 7.52 (t, 2 H, *J* = 7.1 Hz, H-3, 5 of C(O)Ph), 7.67 (t, 1 H, *J* = 7.1 Hz, H-4 of C(O)Ph), 8.07 (d, 2 H, *J* = 7.1 Hz, H-2, 6 of C(O)Ph); ^{13}C NMR (75 MHz) δ 10.2, 23.4, 75.0, 75.4, 78.3, 78.8, 80.7, 127.9, 128.4 × 2, 128.5 × 2, 128.9 × 2, 129.3 × 2, 134.6, 134.7, 138.1, 174.2, 195.2; HRMS calcd for $C_{21}H_{22}O_6$ (M^+) *m/z* 370.1416, found 370.1418. NOE experiment; 10.2% enhancement of the H-4 (δ 5.76) was observed when H-3 (δ 4.58) was irradiated, and 8.0% enhancement of H-3 (δ 4.58) was observed when H-4 (δ 5.76) was irradiated.

(2*S*,3*S*,4*S*)-4-Benzoyl-2-[(1*R*)-1-(benzyloxy)propyl]-3-hydroxy-2-triethylsilyloxy-4-butanolide (51).

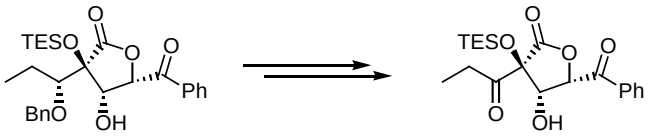


50 **51**

The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **50** (198 mg, 0.535 mmol) in pyridine (10 mL) was added dropwise triethylsilyl trifluoromethanesulfonate (0.18 mL, 0.80 mmol). After being stirred for 2 h at rt, the solution was quenched with saturated aqueous $NaHCO_3$ (1 mL) at 0 °C, diluted with EtOAc (50 mL), and washed with saturated aqueous $NaHCO_3$ (30 mL), saturated aqueous NH_4Cl (30 mL), and saturated brine (30 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to give 236 mg (91%) of **51** as a colorless oil: TLC R_f 0.45 (EtOAc/hexane, 1:3); $[\alpha]_D^{20}$ +16.2 (*c* 1.40, $CHCl_3$); IR (neat) 3460, 1790, 1700 cm^{-1}; ^1H NMR (300 MHz) δ 0.33−0.43 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 0.79 (t, 9 H, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.06 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.49−1.61, 1.69−1.82 (2 m, each 1 H, $C\underline{H}_2CH_3$), 3.79 (dd, 1 H, *J* = 2.4, 9.7 Hz, H-1 of the side chain at C-2), 4.66, 5.17 (AB q, each 1 H, *J* = 10.0 Hz, $OC\underline{H}_2Ph$), 4.70 (d, 1 H, *J* = 3.4 Hz, H-3), 5.85 (d, 1 H, *J* = 3.4 Hz, H-4), 7.28−7.39, 7.44−7.49 (2 m, 3 H + 2 H, $OCH_2C_6\underline{H}_5$), 7.51 (t, 2 H, *J* = 7.3 Hz, H-3, 5 of C(O)Ph), 7.63 (t, 1 H, *J* = 7.3 Hz, H-4 of C(O)Ph), 8.04 (d, 2 H, *J* = 7.3 Hz, H-2, 6 of

C(O)Ph); ^{13}C NMR (75 MHz) δ 5.0 × 3, 6.6 × 3, 10.1, 23.6, 75.7, 77.8, 78.6, 79.2, 83.3, 127.9, 128.4 × 2, 128.6 × 2, 128.7 × 2, 129.0 × 2, 134.1, 135.2, 138.1, 174.2, 193.4; HRMS calcd for $C_{25}H_{31}O_6Si$ ($M^+ - CH_2CH_3$) *m/z* 455.1890, found 455.1891. NOE experiment; 14.0% enhancement of the H-4 (δ 5.85) was observed when H-3 (δ 4.70) was irradiated, and 9.7% enhancement of the H-3 (δ 4.70) was observed when H-4 (δ 5.85) was irradiated.

(2*S*,3*S*,4*S*)-4-Benzoyl-3-hydroxy-2-(1-propanoyl)-2-triethylsilyloxy-4-butanolide (52).

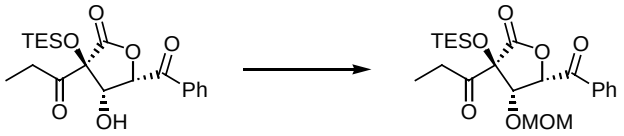


51 **52**

A solution of **51** (231 mg, 476 μmol) in EtOAc (5 mL) was stirred under atmospheric H_2 gas in the presence of 10% Pd on charcoal (41.0 mg) for 1 day, and additional 10% Pd on charcoal (41.0 mg × 2) was added every 1 day. The mixture was stirred for total 3 days, and the catalyst was removed by filtration through a Celite-pad and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo to give crude triol (201 mg), which was used in the next step without further purification.

To a solution of crude triol (201 mg) in DMSO (5 mL) was added 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) (399 mg, 1.42 mmol). The solution was stirred for 12 h, and additional IBX (399 mg, 1.42 mmol) was added. The solution was stirred for 11 h at rt, diluted with EtOAc (100 mL), and washed with saturated aqueous $Na_2S_2O_3$ (40 mL) and saturated aqueous Na_2CO_3 (40 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 194 mg (87%) of **52** as colorless crystals: mp 114.8–115.0 °C; TLC R_f 0.62 (EtOAc/hexane, 1:5); $[\alpha]_D^{20}$ +64.5 (*c* 2.02, $CHCl_3$); IR (neat) 3440, 1790, 1715, 1700 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.09–0.31 (m, 6 H, Si(C$\underline{H}_2$CH$_3$)$_3$), 0.69 (t, 9 H, *J* = 7.8 Hz, Si(CH$_2$C$\underline{H}_3$)$_3$), 1.13 (t, 3 H, *J* = 7.1 Hz, CH$_2$C$\underline{H}_3$), 2.79, 2.84 (2 dq, each 1 H, *J* = 15.4, 7.1 Hz, C$\underline{H}_2$CH$_3$), 4.84 (br s, 1 H, O$\underline{H}$), 5.03 (d, 1 H, *J* = 7.6 Hz, H-3), 6.14 (d, 1 H, *J* = 7.6 Hz, H-4), 7.53 (t, 2 H, *J* = 7.8 Hz, H-3, 5 of Ph), 7.66 (t, 1 H, *J* = 7.8 Hz, H-4 of Ph), 7.96 (d, 2 H, *J* = 7.8 Hz, H-2, 6 of Ph); ^{13}C NMR (75 MHz) δ 4.1 × 3, 6.4 × 3, 7.2, 33.4, 79.4, 80.5, 83.0, 128.5 × 2, 128.9 × 2, 134.3, 135.7, 171.9, 192.5, 204.2; HRMS calcd for $C_{20}H_{28}O_6Si$ (M^+) *m/z* 392.1655, found 392.1653. NOE experiment; 10.8% enhancement of the H-4 (δ 6.14) was observed when H-3 (δ 5.03) was irradiated, and 13.4% enhancement of the H-3 (δ 5.03) was observed when H-4 (δ 6.14) was irradiated.

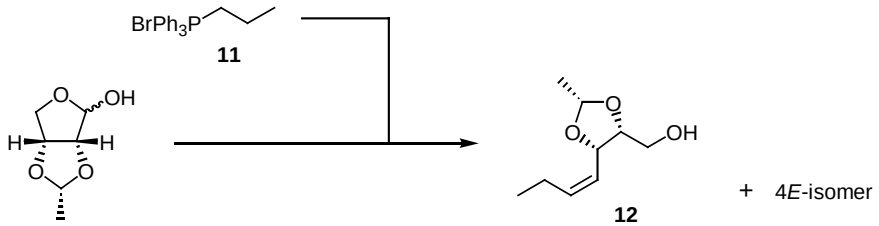
(2*S*,3*S*,4*S*)-4-Benzoyl-3-methoxymethoxy-2-(1-propanoyl)-2-triethylsilyloxy-4-butanolide (35).



52 **35**

To a cooled (0 °C) stirred suspension of P_2O_5 (185 mg, 1.30 mmol) in $CH_2(OMe)_2$ (5 mL) was added a solution of **52** (139 mg, 0.354 mmol) in CH_2Cl_2 (1 mL). After being stirred at 0 °C for 1.5 h, the mixture was quenched with saturated aqueous Na_2CO_3 (5 mL), diluted with EtOAc (50 mL), and washed with saturated aqueous Na_2CO_3 (20 mL) and saturated brine (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 131 mg (98%) of **35** as a colorless oil: TLC R_f 0.64 (EtOAc/hexane, 1:5); $[\alpha]_D^{17}$ +74.7 (*c* 0.385, $CHCl_3$); IR (neat) 1790, 1720, 1705 cm^{-1}; ^1H NMR (300 MHz) δ 0.15–0.36 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 0.73 (t, 9 H, *J* = 8.1 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.09 (t, 3 H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.56, 3.21 (2 dq, each 1 H, *J* = 20.0, 7.1 Hz, $C\underline{H}_2CH_3$), 3.36 (s, 3 H, $OC\underline{H}_3$), 4.70, 4.94 (AB q, each 1 H, *J* = 6.8 Hz, $OC\underline{H}_2O$), 4.98 (d, 1 H, *J* = 3.7 Hz, H-3), 5.81 (d, 1 H, *J* = 3.7 Hz, H-4), 7.52 (t, 2 H, *J* = 7.3 Hz, H-3, 5 of Ph), 7.65 (t, 1 H, *J* = 7.3 Hz, H-4 of Ph), 8.02 (d, 2 H, *J* = 7.3 Hz, H-2, 6 of Ph); ^{13}C NMR (75 MHz) δ 4.4 × 3, 6.5 × 3, 6.9, 36.0, 56.9, 79.3, 83.9, 84.0, 94.4, 128.8 × 2, 129.0 × 2, 134.2, 134.9, 169.9, 192.0, 204.0; HRMS calcd for $C_{22}H_{32}O_7Si$ (M^+) *m/z* 436.1917, found 436.1912. NOE experiment; 16.4% enhancement of the H-4 (δ 5.81) was observed when H-3 (δ 4.98) was irradiated, and 15.8% enhancement of the H-3 (δ 4.98) was observed when H-4 (δ 5.81) was irradiated.

(2*R*,3*S*,4*Z*)-2,3-(Ethylidenedioxy)hept-4-en-1-ol (12) and 4*E*-Isomer.

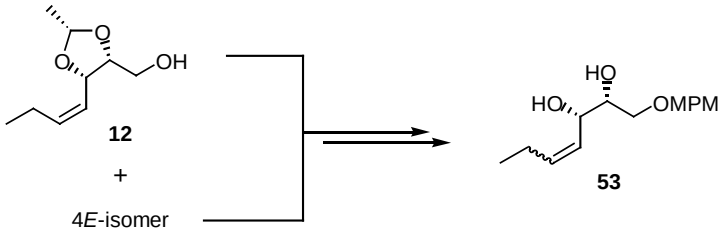


10 **12**

The following reaction was carried out under Ar. To a stirred suspension of *n*-propyltriphenylphosphonium bromide (**11**) (33.0 g, 85.7 mmol) in THF (100 mL) was added dropwise potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution in toluene, 171 mL, 85.5 mmol). The mixture was stirred at rt for 1.5 h, and 2,3-(ethylidenedioxy)-D-erythrofuranose (**10**)[8a] (5.01 g, 34.3 mmol) was added directly. After being

stirred at rt for 1.5 h, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, diluted EtOAc (300 mL), and washed with saturated aqueous NH_4Cl (70 mL), saturated aqueous $NaHCO_3$ (70 mL), and saturated brine (70 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 5.56 g (94%) of **12** (*Z*/*E* = *ca.* 14:1, determined by ^{1}H NMR analysis) as a colorless oil. Spectroscopic data for **12**; see Ref. 8a.

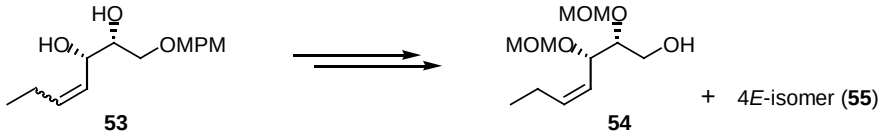
(2*R*,3*S*,4*Z*)-1-(4-Methoxybenzyloxy)hept-4-ene-2,3-diol (53) and 4*E*-Isomer.



To a cooled (0 °C) stirred solution of **12** (*Z*/*E* = *ca.* 14:1, determined by ^{1}H NMR analysis) (4.12 g, 23.9 mmol) in DMF (10 mL) were added NaH (60% emulsion in mineral oil, 2.30 g, 57.4 mmol) and 4-methoxybenzyl chloride (3.89 mL, 28.7 mmol). After being stirred for 5 h at rt, the mixture was quenched with H_2O (5 mL) at 0 °C, diluted with EtOAc (100 mL), and washed with saturated aqueous $NaHCO_3$ (70 mL), saturated aqueous NH_4Cl (70 mL), and saturated brine (70 mL). The organic layer was dried and concentrated in vacuo to give crude 4-methoxybenzyl ether (10.3 g), which was used directly in the next step.

To a stirred solution of crude 4-methoxybenzyl ether (10.3 g) in MeOH (15 mL) was added Amberlite IR-120 (H^+) (1.10 g). The mixture was stirred for 20 h, and the resin was removed by filtration and washed well with MeOH. The combined filtrate and washings were concentrated in vacuo, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to provide 5.80 g (91% for 2 steps) of **53** (*Z*/*E* = *ca.* 14:1, determined by ^{1}H NMR analysis) as colorless crystals: mp 54.3–55.7 °C; TLC R_f 0.33 (EtOAc/hexane, 1:1); $[\alpha]_D^{22}$ +26.6 (*c* 1.38, $CHCl_3$); IR (neat) 3290, 1615 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.98 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.96–2.23 (m, 2 H, $C\underline{H}_2CH_3$), 2.59 (br s, 2 H, O<u>H</u> × 2), 3.56 (dd, 1 H, *J* = 4.2, 9.8 Hz, H-1), 3.60 (dd, 1 H, *J* = 5.9, 9.8 Hz, H-1'), 3.74 (dt, 1 H, *J* = 5.9, 4.2 Hz, H-2), 3.80 (s, 3 H, $OC\underline{H}_3$), 4.47 (s, 2 H, $C\underline{H}_2C_6H_4OMe$), 4.53 (dd, 1 H, *J* = 4.2, 9.3 Hz, H-3), 5.36 (dd, 1 H, *J* = 9.3, 11.0 Hz, H-4), 5.60 (dt, 1 H, *J* = 11.0, 7.6 Hz, H-5), 6.85–6.91, 7.22–7.28 (2 m, 2 H + 2 H, $C_6\underline{H}_4OMe$); ^{13}C NMR (75 MHz) δ 14.2, 21.2, 55.2, 69.3, 70.9, 72.5, 73.3, 113.8 × 2, 127.1, 129.5 × 2, 129.7, 136.1, 159.3; HRMS calcd for $C_{15}H_{22}O_4$ (M^+) *m/z* 266.1518, found 266.1518.

(2*R*,3*S*,4*Z*)-2,3-Bis(methoxymethoxy)hept-4-en-1-ol (54) and 4*E*-Isomer (55).

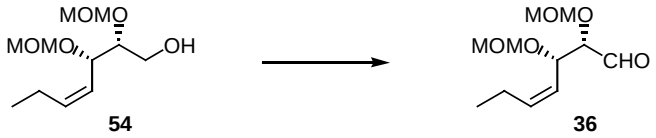


53 **54**

To a cooled (0 °C) stirred solution of **53** (4.25 g, 15.9 mmo) in CH_2Cl_2 (15 mL) were added *i*-Pr_2NEt (11.7 mL, 67.2 mmol) and chloromethyl methyl ether (2.54 mL, 33.4 mmol). The solution was stirred for 8 h at rt, diluted with EtOAc (250 mL), and washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated brine (100 mL × 2). The organic layer was dried and concentrated in vacuo to give crude bis(methoxymethyl) ether (5.78 g), which was used directly in the next step.

To a cooled (0 °C) stirred suspension of crude bis(methoxymethyl) ether (5.78 g) in CH_2Cl_2/H_2O (15:1, v/v, 16 mL) was added DDQ (4.34 g, 19.1 mmol). After being stirred for 12 h at rt, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and diluted with saturated aqeous $NaHCO_3$ (300 mL). The whole was extracted with CH_2Cl_2 (150 mL × 4), and the combined extracts layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 3.29 g (88% from **53**) of **54** and 260 mg (7% from **53**) of **55**. Compound **54** was obtained as a colorless oil: TLC R_f 0.30 (EtOAc/hexane, 1:1); $[\alpha]_D^{23}$ +162 (*c* 1.14, $CHCl_3$); IR (neat) 3480 cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 2.04−2.22 (m, 2 H, $C\underline{H}_2CH_3$), 3.38, 3.43 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 3.64 (dt, 1 H, *J* = 9.5, 4.9 Hz, H-2), 3.69−3.74 (m, 2 H, H-1, 1'), 4.50−4.57 (m, 1 H, H-3), 4.53, 4.67 (AB q, each 1 H, *J* = 6.6 Hz, $OC\underline{H}_2O$), 4.73, 4.75 (AB q, each 1 H, *J* = 6.8 Hz, $OC\underline{H}_2O$), 5.25−5.34 (m, 1 H, H-4), 5.73 (dt, 1 H, *J* = 10.7, 7.6 Hz, H-5); ^{13}C NMR (75 MHz) δ 14.1, 21.1, 55.4, 55.7, 62.7, 70.9, 82.1, 93.3, 97.0, 125.1, 137.8; HRMS calcd for $C_{11}H_{22}O_5$ (M^+) *m/z* 234.1467, found 234.1454. Compound **55** was obtained as a colorless oil: TLC R_f 0.29 (EtOAc/hexane, 1:1); $[\alpha]_D^{23}$ +168 (*c* 1.00, $CHCl_3$); IR (neat) 3460, 1730 cm^{-1}; ^1H NMR (300 MHz) δ 1.01 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 2.04−2.15 (m, 2 H, $C\underline{H}_2CH_3$), 3.38, 3.43 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 3.61−3.66, 3.69−3.72 (2 m, 1 H + 2 H, H-1, 1', 2), 4.11 (dd, 1 H, *J* = 4.4, 8.3 Hz, H-3), 4.54, 4.71 (AB q, each 1 H, *J* = 6.6 Hz, $OC\underline{H}_2O$), 4.73, 4.76 (AB q, each 1 H, *J* = 6.8 Hz, $OC\underline{H}_2O$), 5.32−5.41 (m, 1 H, H-4), 5.79 (dt, 1 H, *J* = 15.6, 6.3 Hz, H-5); ^{13}C NMR (75 MHz) δ 13.3, 25.3, 55.5, 55.7, 62.7, 76.8, 82.1, 93.3, 96.9, 124.8, 138.5; HRMS calcd for $C_{11}H_{21}O_4$ (M^+ − OH) *m/z* 217.1440, found 217.1439.

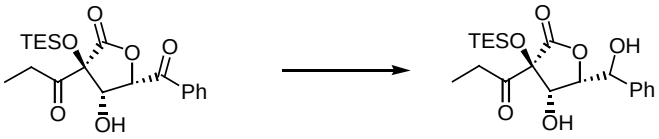
(2*S*,3*S*,4*Z*)-2,3-Bis(methoxymethoxy)hept-4-en-1-al (36).



54 **36**

The following reaction was carried out under Ar. To a coold (−78 °C) solution of oxalyl chloride (0.60 mL, 6.88 mmol) in CH_2Cl_2 (5 mL) was added dropwise DMSO (0.98 mL, 13.8 mmol) slowly. The solution was stirred at −78 °C for 1 h, and a solution of **54** (539 mg, 2.30 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After being stirred at −78 °C for 1 h, Et_3N (2.89 mL, 20.7 mmol) was added dropwise to the mixture, which was then warmed to rt. The mixture was stirred for an additional 30 min, diluted with EtOAc (100 mL), and washed with saturated brine (50 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 474 mg (89%) of **36** as a colorless oil: TLC R_f 0.39 (EtOAc/hexane, 1:3); $[\alpha]_D^{22}$ +125 (*c* 3.18, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.98 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.98−2.22 (m, 2 H, $C\underline{H}_2CH_3$), 3.36, 3.42 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 4.04 (dd, 1 H, *J* = 2.0, 4.6 Hz, H-2), 4.53, 4.67 (AB q, each 1 H, *J* = 6.8 Hz, $OC\underline{H}_2O$), 4.74, 4.78 (AB q, each 1 H, *J* = 6.6 Hz, $OC\underline{H}_2O$), 4.73−4.77 (m, 1 H, H-3), 5.34−5.43 (m, 1 H, H-4), 5.76 (dt, 1 H, *J* = 11.0, 7.3 Hz, H-5), 9.67 (d, 1 H, *J* = 2.0 Hz, H-1); ^{13}C NMR (75 MHz) δ 14.0, 21.1, 55.5, 55.9, 70.5, 83.6, 93.2, 96.9, 123.7, 138.5, 201.3; HRMS calcd for $C_{10}H_{17}O_5$ ($M^+ - CH_3$) *m/z* 217.1076, found 217.1080.

(2*S*,3*S*,4*R*)-3-Hydroxy-4-(1-hydroxy-1-phenylmethyl)-2-(1-propanoyl)-2-triethylsilyloxy-4-butanolide (56).

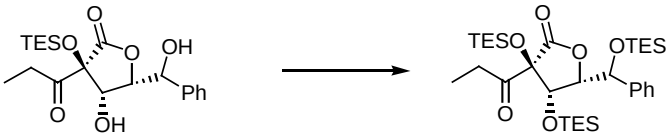


52 **56**

A solution of **52** (42.7 mg, 109 μmol) in EtOAc/MeOH (3:1, v/v, 4 mL) was stirred under atmospheric H_2 gas in the presence of 10% Pd on charcoal (46.0 mg) for 6 h, and the catalyst was removed by filtration through a Celite-pad and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give 35.1 mg (82%) of **56** as a colorless oil: TLC R_f 0.52 (EtOAc/hexane, 1:3); $[\alpha]_D^{22}$ +101 (*c* 0.305, $CHCl_3$); IR (neat) 3440, 1790, 1715 cm^{-1}; ^1H NMR (300 MHz) δ 0.66−0.78 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 1.00 (t,

9 H, *J* = 7.6 Hz, Si($CH_2C\underline{H}_3$)$_3$), 1.15 (t, 3 H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.34 (br s, 1 H, O<u>H</u>), 2.80, 2.88 (2 dq, each 1 H, *J* = 19.3, 7.1 Hz, $C\underline{H}_2CH_3$), 4.12 (br s, 1 H, O<u>H</u>), 4.67 (d, 1 H, *J* = 8.3 Hz, H-4), 4.68 (s, 1 H, H-3), 5.07 (d, 1 H, *J* = 8.3 Hz, H-1 of the side chain at C-4), 7.33−7.48 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.5 × 3, 6.6 × 3, 7.0, 34.0, 70.4, 78.7, 82.8, 83.4, 125.0, 127.1 × 2, 128.6 × 2, 139.9, 172.3, 207.5; HRMS calcd for $C_{20}H_{30}O_6Si$ (M^+) *m/z* 394.1812, found 394.1801.

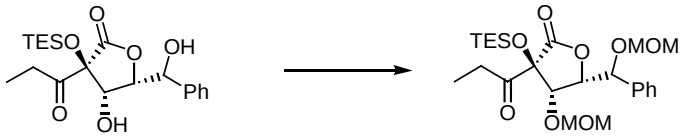
(2*S*,3*S*,4*R*)-4-[1-Phenyl-1-(triethylsilyloxy)methyl]-2-(1-propanoyl)-2,3-bis(triethylsilyloxy)-4-butanolide (57).



56 **57**

The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **56** (35.1 mg, 89.0 μmol) in pyridine (2 mL) was added dropwise triethylsilyl trifluoromethanesulfonate (50 μL, 0.22 mmol). After being stirred for 3 h at rt, the solution was quenched with saturated aqueous $NaHCO_3$ (1 mL) at 0 °C, diluted with EtOAc (40 mL), and washed with saturated aqueous $NaHCO_3$ (30 mL), saturated aqueous NH_4Cl (30 mL), and saturated brine (30 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100 to 1:10) to give 55.3 mg (100%) of **57** as a colorless oil: TLC R_f 0.49 (EtOAc/hexane, 1:15); $[\alpha]_D^{22}$ +58.8 (*c* 1.31, $CHCl_3$); IR (neat) 1790, 1720 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.31−0.39, 0.48−0.75 (2 m, 6 H + 12 H, Si($C\underline{H}_2CH_3$)$_3$ × 3), 0.82, 0.92 (2 t, each 9 H, *J* = 7.8 Hz, Si($CH_2C\underline{H}_3$)$_3$ × 2), 0.96−1.06 (m, 9 H, Si($CH_2C\underline{H}_3$)$_3$), 1.26 (t, 3 H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.52, 2.82 (2 dq, each 1 H, *J* = 19.8, 7.1 Hz, $C\underline{H}_2CH_3$), 4.58 (d, 1 H, *J* = 5.6 Hz, H-3), 4.70 (dd, 1 H, *J* = 5.6, 8.3 Hz, H-4), 5.00 (d, 1 H, *J* = 8.3 Hz, H-1 of the side chain at C-4), 7.26−7.41 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.8 × 3, 5.2 × 3, 5.7 × 3, 6.78 × 3, 6.81 × 7, 34.2, 71.6, 79.4, 83.0, 84.6, 128.1 × 2, 128.3 × 2, 128.5, 140.2, 172.0, 208.0; HRMS calcd for $C_{32}H_{58}O_6Si_3$ (M^+) *m/z* 622.3541, found 622.3542.

(2*S*,3*S*,4*R*)-3-Methoxymethoxy-4-[1-methoxymethoy-1-phenylmethyl]-2-(1-propanoyl)-2-triethylsilyloxy-4-butanolide (58).

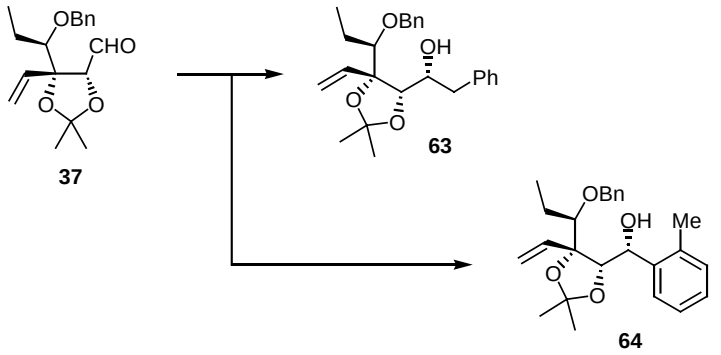


56 **58**

To a cooled (0 °C) stirred suspension of P_2O_5 (27.3 mg, 192 μmol) in $CH_2(OMe)_2$ (3 mL) was added a solution of **56** (15.2 mg, 38.5 μmol) in CH_2Cl_2 (1 mL). After being stirred at 0 °C for 1.5 h, the mixture was quenched with saturated aqueous Na_2CO_3 (5 mL), diluted with EtOAc (50 mL), and washed with saturated aqueous Na_2CO_3 (20 mL) and saturated brine (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 18.2 mg (98%) of **58** as a colorless oil: TLC R_f 0.48 (EtOAc/hexane, 1:3); $[\alpha]_D^{21}$ +102 (*c* 0.500, $CHCl_3$); IR (neat) 1790, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.66–0.74 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 1.01 (t, 9 H, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.07 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 2.52, 3.03 (2 dq, each 1 H, *J* = 19.8, 7.3 Hz, $C\underline{H}_2CH_3$), 3.20, 3.33 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 4.53, 4.55 (AB q, each 1 H, *J* = 5.9 Hz, $OC\underline{H}_2O$), 4.67, 4.87 (AB q, each 1 H, *J* = 6.8 Hz, $OC\underline{H}_2O$), 4.73 (dd, 1 H, *J* = 4.4, 8.8 Hz, H-4), 4.80 (d, 1 H, *J* = 8.8 Hz, H-1 of the side chain at C-4), 4.83 (d, 1 H, *J* = 4.4 Hz, H-3), 7.29–7.43 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.6 × 3, 6.8 × 3, 6.9, 35.3, 56.3, 56.8, 75.5, 76.7, 82.2, 85.2, 94.2, 95.1, 128.2 × 2, 128.4 × 2, 128.5, 137.7, 170.0, 205.9; HRMS calcd for $C_{24}H_{38}O_8Si$ (M^+) *m/z* 482.2336, found 482.2335.

Experimental Procedures for Chapter 3

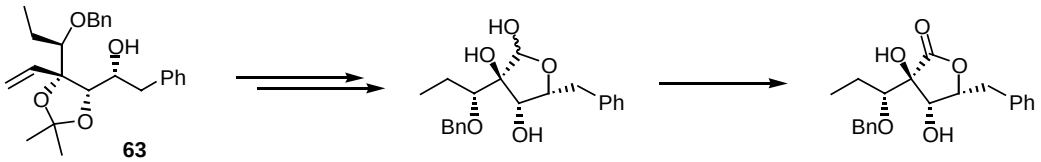
(2*R*,3*S*,4*R*,5*R*)-5-Benzyloxy-3,4-isopropylidenedioxy-1-phenyl-4-vinylheptan-2-ol (63) and (1*R*,2*S*,3*R*,4*R*)-4-Benzyloxy-2,3-isopropylidenedioxy-1-(2-methylphenyl)-3-vinylhexan-1-ol (64).



The following reaction was carried out under Ar. To a cooled (0 °C) solution of **37** (6.17 g, 20.3 mmol) and CuBr·Me_2S (20.8 g, 101 mmol) in THF/Me_2S (2:1, v/v, 300 mL) was added dropwise benzylmagnesium chloride (2.0 M solution in THF, 101 mL, 202 mmol). After being stirred for 30 min at 0 °C, the mixture was quenched with saturated aqueous NH_4Cl (50 mL). The resulting mixture was diluted with EtOAc (500 mL), and washed with saturated aqueous NH_4Cl (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and saturated brine (300 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30 to 1:20) to provide 7.12 g (89%) of **63** and 125 mg (2%) of **64**. Compound **63** was obtained as a colorless oil: TLC R_f 0.27 (EtOAc/hexane, 1:15); $[\alpha]_D^{22}$ +35.5 (*c* 1.53, $CHCl_3$); IR (neat) 3500 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.41, 1.54 (2 s, each 3 H, isopropylidene), 1.56–1.72, 1.77–1.91 (2 m, each 1 H, $C\underline{H}_2CH_3$), 2.78 (dd, 1 H, *J* = 8.3, 13.7 Hz, H-1), 2.90 (dd, 1 H, *J* = 5.4, 13.7 Hz, H-1'), 3.74 (d, 1 H, *J* = 3.9 Hz, H-3), 3.78 (t, 1 H, *J* = 4.9 Hz, H-5), 4.26 (ddd, 1 H, *J* = 3.9, 5.4, 8.3 Hz, H-2), 4.56, 4.66 (AB q, each 1 H, *J* = 11.2 Hz,

OC$\underline{H}_2$Ph), 5.17 (dd, 1 H, *J* = 2.0, 11.0 Hz, CH=C$\underline{H}$H), 5.45 (dd, 1 H, *J* = 2.0, 17.2 Hz, CH=CH$\underline{H}$), 6.19 (dd, 1 H, *J* = 11.0, 17.2 Hz, C$\underline{H}$=CHH), 7.16−7.31, (m, 10 H, $C_6\underline{H}_5$ × 2); ^{13}C NMR (75 MHz) δ 11.9, 22.7, 26.1, 28.1, 41.5, 68.8, 71.5, 81.2, 85.6, 85.7, 107.6, 114.8, 126.1, 127.4 × 2, 128.2 × 2, 128.3 × 2, 129.3 × 3, 137.7, 138.2, 138.5; HRMS calcd for $C_{25}H_{32}O_4$ (M^+) *m/z* 396.2301, found 396.2305. Compound **64** was obtained as a colorless oil: TLC R_f 0.41 (EtOAc/hexane, 1:15); $[\alpha]_D^{24}$ −10.7 (*c* 1.20, $CHCl_3$); IR (neat) 3440 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.05 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.37, 1.59 (2 s, each 3 H, isopropylidene), 1.60−1.75, 1.80−1.96 (2 m, each 1 H, $C\underline{H}_2CH_3$), 2.12 (s, 3 H, $C\underline{H}_3$-2 of the 2-methylpheny), 3.28 (br s, 1 H, O$\underline{H}$), 3.96 (s, 1 H, H-2), 3.98 (t, 1 H, *J* = 4.9 Hz, H-4), 4.71 (s, 2 H, OC$\underline{H}_2$Ph), 5.20 (dd, 1 H, *J* = 2.0, 11.0 Hz, CH=C$\underline{H}$H), 5.49 (dd, 1 H, *J* = 2.0, 17.2 Hz, CH=CH$\underline{H}$), 5.53 (s, 1 H, H-1), 6.31 (dd, 1 H, *J* = 11.0, 17.2 Hz, C$\underline{H}$=CHH), 7.05−7.37, 7.45−7.48 (2 m, 8 H + 1 H, 2-Me$C_6\underline{H}_4$, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 12.1, 19.1, 23.2, 26.5, 28.1, 65.7, 71.6, 81.1, 85.2, 86.3, 108.4, 114.5, 125.8, 126.0, 127.19, 127.24, 127.3 × 2, 128.2 × 2, 130.3, 134.7, 138.1, 139.0, 141.5; HRMS calcd for $C_{25}H_{32}O_4$ (M^+) *m/z* 396.2301, found 396.2305. NOE experiment; 10.7% enhancement of the H-1 (δ 5.53) and 6.7% enhancement of the H-2 (δ 3.96) were observed when C$\underline{H}_3$-2 (δ 2.12) was irradiated.

(2*S*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(benzyloxy)propyl]-2,3-dihydroxy-4-butanolide (66).



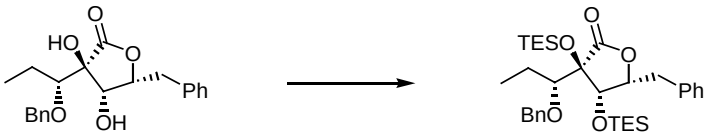
63 **65** **66**

To a cooled (−78 °C) stirred solution of **63** (1.47 g, 3.70 mmol) in CH_2Cl_2 (15 mL) was bubbled ozone (O_2 containing *ca.* 3% O_3) for 1 h to a persistent light bluecolor. To this solution was added Ph_3P (971 mg, 3.70 mmol), and the solution was stirred for 30 min at −78 °C and for additional 1 h warming to rt. The solvent was removed by evaporation in vacuo to provide crude aldehyde (2.76 g), which was used directly in the next step.

The crude aldehyde (2.76 g) was dissolved in 60% aqueous CF_3CO_2H (15 mL). After being stirred for 9 h at rt, the solution was neutralized with 5 M (1 M = 1 mol·dm^{-1}) aqueous NaOH, diluted with EtOAc (200 mL), and washed with saturated brine (50 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:2), and the combined eluates were concentrated in vacuo to provide crude γ-lactol **65** (1.21 g), which was used in the next step without further purification.

The following reaction was carried out in the dark. To a cooled (0 °C) stirred solution of crude γ-lactol **65** (1.21 g) in CH_2Cl_2 (20 mL) were added tetra-*n*-butylammonium iodide (2.05 g, 5.55 mmol) and NIS (2.08 g, 9.24 mmol). The solution was stirred at rt for 24 h, and additional NIS (416 mg × 2, 1.85 mmol × 2) was added every 24 h. The solution was stirred for total 72 h, diluted with EtOAc (200 mL), and washed with saturated aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give 1.11 g (84% from **63**) of **66** as a colorless oil: TLC R_f 0.34 (EtOAc/hexane, 1:3); $[\alpha]_D^{22}$ +76.1 (*c* 2.89, $CHCl_3$); IR (neat) 3440, 1780 cm^{-1}; ^1H NMR (300 MHz) δ 1.03 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.64−1.75 (m, 2 H, $C\underline{H}_2CH_3$), 2.61, 3.63 (2 br s, each 1 H, O<u>H</u> × 2), 2.99 (dd, 1 H, *J* = 7.3, 13.9 Hz, C<u>H</u>HPh at C-4), 3.17 (dd, 1 H, *J* = 7.3, 13.9 Hz, CH<u>H</u>Ph at C-4), 3.78 (t, 1 H, *J* = 6.3 Hz, H-1 of the side chain at C-2), 3.97 (br d, 1 H, *J* = 2.9 Hz, H-3), 4.64, 5.08 (AB q, each 1 H, *J* = 10.3 Hz, $OC\underline{H}_2Ph$), 4.92 (dt, 1 H, *J* = 2.9, 7.3 Hz, H-4), 7.20−7.42 (m, 10 H, $C_6\underline{H}_5$ × 2); ^{13}C NMR (75 MHz) δ 10.4, 23.7, 34.1, 74.5, 75.4, 79.4, 79.7, 82.4, 126.9, 127.9, 128.39 × 2, 128.44 × 2, 128.8 × 2, 129.1 × 2, 135.9, 138.0, 175.5; HRMS calcd for $C_{21}H_{25}O_5$ (M^+ + H) *m/z* 357.1702, found 357.1707. NOE experiment; 9.6% enhancement of the H-4 (δ 4.92) was observed when H-3 (δ 3.97) was irradiated, and 7.5% enhancement of the H-3 (δ 3.97) was observed when H-4 (δ 4.92) was irradiated.

(2*R*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(benzyloxy)propyl]-2,3-bis(triethylsilyloxy)-4-butanolide (67).

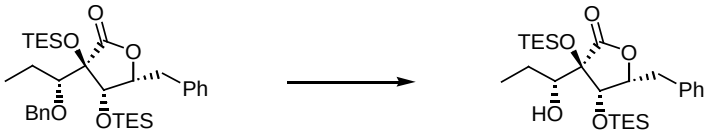


66 **67**

The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **66** (3.03 g, 8.50 mmol) in pyridine (100 mL) was added dropwise triethylsilyl trifluoromethanesulfonate (4.04 mL, 17.9 mmol). After being stirred at 50 °C for 12 h, the solution was quenched with saturated aqueous $NaHCO_3$ (50 mL) at 0 °C. The resulting mixture was diluted with EtOAc (300 mL), and washed with saturated aqueous $NaHCO_3$ (200 mL × 2) and saturated brine (200 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 4.70 g (95%) of **67** as a colorless oil: TLC R_f 0.69 (EtOAc/hexane, 1:15); $[\alpha]_D^{20}$ +81.1 (*c* 1.87, $CHCl_3$); IR (neat) 1780 cm^{-1}; ^1H NMR (300 MHz) δ 0.60−0.77 (m, 12 H, $Si(C\underline{H}_2CH_3)_3$ × 2), 0.91 (t, 9 H, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.03 (t, 9 H, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.06 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.78−1.89, 1.90−

2.06 (2 m, each 1 H, C<u>H</u>$_2$CH$_3$), 2.80 (dd, 1 H, *J* = 3.2, 15.1 Hz, C<u>H</u>HPh at C-4), 2.90 (dd, 1 H, *J* = 10.3, 15.1 Hz, CH<u>H</u>Ph at C-4), 3.72 (dd, 1 H, *J* = 4.2, 7.6 Hz, H-1 of the side chain at C-2), 4.56 (d, 1 H, *J* = 7.1 Hz, H-3), 4.65, 4.82 (AB q, each 1 H, *J* = 11.2 Hz, OC<u>H</u>$_2$Ph), 4.75 (ddd, 1 H, *J* = 3.2, 7.1, 10.3 Hz, H-4), 6.97−7.01, 7.17−7.45 (2 m, 2 H + 8 H, C$_6$<u>H</u>$_5$ × 2); ^{13}C NMR (75 MHz) δ 4.9 × 3, 5.8 × 3, 6.9 × 3, 6.9 × 3, 12.0, 23.0, 35.5, 73.2, 79.8, 80.9, 81.2, 82.1, 126.3, 127.3 × 2, 127.6 × 2, 128.1 × 2, 128.3 × 2, 129.1, 138.2, 138.5, 174.3; HRMS calcd for $C_{33}H_{52}O_5Si_2$ (M^+) *m/z* 584.3353, found 584.3353.

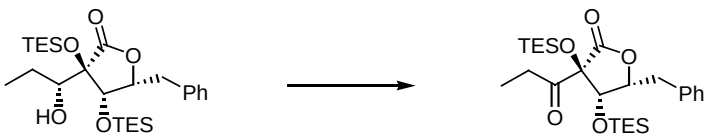
(2*R*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(hydroxy)propyl]-2,3-bis(triethylsilyloxy)-4-butanolide (68).



67 **68**

A solution of **67** (2.20 g, 3.76 mmol) in EtOH (100 mL) was stirred under atmospheric H_2 gas in the presence of 10% Pd on charcoal (220 mg) for 3 days, and the catalyst was removed by filtration through a Celite-pad and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:30) to provide 1.75 g (94%) of **68** as a colorless oil: TLC R_f 0.54 (EtOAc/hexane, 1:15); $[\alpha]_D^{20}$ +74.8 (*c* 1.44, $CHCl_3$); IR (neat) 3540, 1770 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.57−0.74 (m, 12 H, Si(C<u>H</u>$_2$CH$_3$)$_3$ × 2), 0.90 (t, 9 H, *J* = 7.6 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 1.02 (t, 9 H, *J* = 7.8 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 1.05 (t, 3 H, *J* = 7.3 Hz, CH$_2$C<u>H</u>$_3$), 1.46−1.77 (m, 2 H, C<u>H</u>$_2$CH$_3$), 2.85 (dd, 1 H, *J* = 2.4, 14.9 Hz, C<u>H</u>HPh), 3.03 (dd, 1 H, *J* = 10.5, 14.9 Hz, CH<u>H</u>Ph), 3.35 (br s, 1 H, O<u>H</u>), 3.88 (dd, 1 H, *J* = 1.5, 10.7 Hz, H-1 of the side chain at C-2), 4.27 (d, 1 H, *J* = 4.6 Hz, H-3), 4.87 (ddd, 1 H, *J* = 2.4, 4.6, 10.5 Hz, H-4), 7.21−7.35 (m, 5 H, C$_6$<u>H</u>$_5$); ^{13}C NMR (75 MHz) δ 5.1 × 3, 5.8 × 3, 6.9 × 6, 10.4, 22.4, 35.9, 72.9, 79.6, 80.9, 83.0, 126.7, 128.6 × 2, 129.0 × 2, 137.4, 176.1; HRMS calcd for $C_{26}H_{46}O_5Si_2$ (M^+) *m/z* 494.2884, found 494.2883.

(2*S*,3*S*,4*R*)-4-Benzyl-2-(1-propanoyl)-2,3-bis(triethylsilyloxy)-4-butanolide (62).

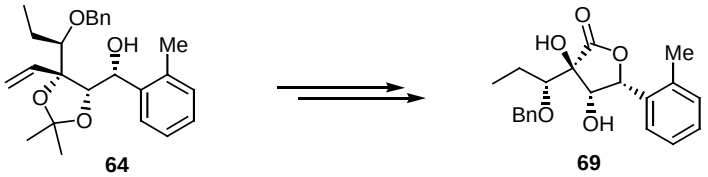


68 **62**

To a cooled (0 °C) solution of **68** (3.25 g, 6.57 mmol) in CH_2Cl_2 (50 mL) was added Dess−Martin periodinane (3.34 g, 7.87 mmol). The mixture was stirred for 9 h at rt, diluted with EtOAc (300 mL), and

washed with saturated aqueous $Na_2S_2O_3$ (200 mL) and saturated aqueous Na_2CO_3 (200 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:30) to provide 3.17 g (98%) of **62** as a colorless oil: TLC R_f 0.56 (EtOAc/hexane, 1:15); $[\alpha]_D^{23}$ +104 (*c* 2.11, $CHCl_3$); IR (neat) 1790, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.57–0.78 (m, 12 H, $Si(C\underline{H}_2CH_3)_3$ × 2), 0.94 (t, 9 H, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.00 (t, 9 H, *J* = 8.3 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.09 (t, 3 H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.71, 2.82 (2 dq, each 1 H, *J* = 19.3, 7.1 Hz, $C\underline{H}_2CH_3$), 2.85 (dd, 1 H, *J* = 2.5, 14.9 Hz, C<u>H</u>HPh), 3.08 (dd, 1 H, *J* = 11.0, 14.9 Hz, CH<u>H</u>Ph), 4.52 (d, 1 H, *J* = 6.8 Hz, H-3), 4.74 (ddd, 1 H, *J* = 2.5, 6.8, 11.0 Hz, H-4), 7.20–7.35 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.7 × 3, 5.8 × 3, 6.6 × 3, 6.9 × 3, 7.0, 33.5, 35.0, 80.0, 82.4, 85.6, 126.6, 128.5 × 2, 129.2 × 2, 137.7, 172.3, 209.0; HRMS calcd for $C_{26}H_{44}O_5Si_2$ (M^+) *m/z* 492.2727, found 492.2713.

(2*S*,3*S*,4*R*)-[(1*R*)-1-(Benzyloxy)propyl]-2,3-dihydroxy-4-(2-methylphenyl)-4-butanolide (69).



64 **69**

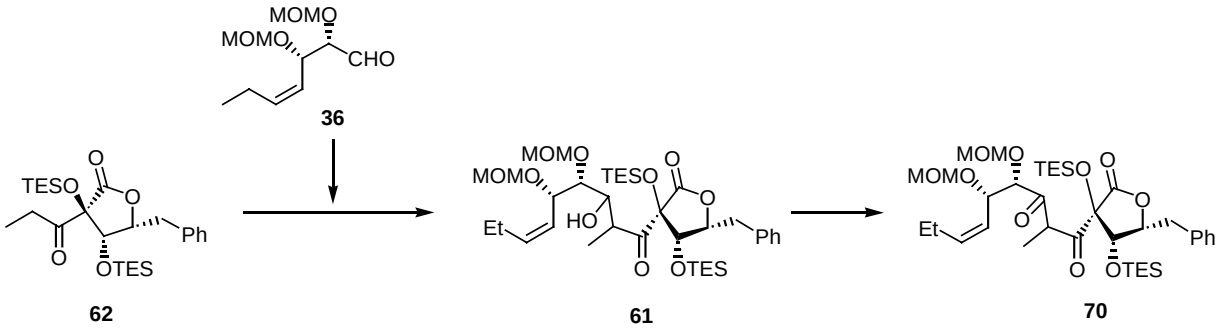
To a cooled (−78 °C) stirred solution of **64** (296 mg, 0.746 mmol) in CH_2Cl_2 (10 mL) was bubbled ozone (O_2 containing *ca.* 3% O_3) for 1 h to a persistent light bluecolor. To this solution was added Ph_3P (215 mg, 0.820 mmol), and the solution was stirred for 30 min at −78 °C and for additional 1 h warming to rt. The solvent was removed by evaporation in vacuo to provide crude aldehyde (709 mg), which was used directly in the next step.

The crude aldehyde (709 mg) was dissolved in 60% aqueous CF_3CO_2H (10 mL). After being stirred for 14 h at rt, the solution was neutralized with 5 M (1 M = 1 mol·dm^{-1}) aqueous NaOH, diluted with EtOAc (100 mL), and washed with saturated brine (50 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:2), and the combined eluates were concentrated in vacuo to provide crude γ-lactol (113 mg), which was used in the next step without further purification.

The following reaction was carried out in the dark. To a cooled (0 °C) stirred solution of crude γ-lactol (113 mg) in CH_2Cl_2 (10 mL) were added tetra-*n*-butylammonium iodide (414 mg, 1.12 mmol) and NIS (420 mg, 1.87 mmol). The solution was stirred at rt for 18 h, diluted with EtOAc (100 mL), and washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried

and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give 63.4 mg (24% from **64**) of **69** as a colorless oil: TLC R_f 0.18 (EtOAc/hexane, 1:3); $[\alpha]_D^{24}$ −7.2 (*c* 1.52, $CHCl_3$); IR (neat) 3460, 1790 cm^{-1}; ^1H NMR (300 MHz) δ 1.06 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.76 (quint, 2 H, *J* = 7.3 Hz, $C\underline{H}_2CH_3$), 2.36 (s, 3 H, $C\underline{H}_3$-2 of the 2-methylphenyl), 3.78 (s, 1 H, O<u>H</u>), 3.85 (t, 1 H, *J* = 7.3 Hz, H-1 of the side chain at C-2), 4.20 (dd, 1 H, *J* = 1.5, 2.3 Hz, H-3), 4.70, 5.21 (AB q, each 1 H, *J* = 10.0 Hz, $OC\underline{H}_2Ph$), 6.04 (d, 1 H, *J* = 2.3 Hz, H-4), 7.20−7.40, 7.45−7.53 (2 m, 6 H + 3 H, 2-$MeC_6\underline{H}_4$, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 10.2, 19.1, 23.5, 73.6, 75.5, 78.3, 79.6, 80.0, 126.5, 126.9, 127.9, 128.4 × 2, 128.6 × 2, 129.0, 130.4, 130.9, 134.6, 138.2, 175.2; HRMS calcd for $C_{21}H_{24}O_5$ (M^+) *m/z* 356.1624, found 356.1619. NOE experiment; 10.6% (for H-4, δ 6.04) and 4.8% (for $C\underline{H}_3$-2, δ 2.36) enhancements were observed when H-3 (δ 4.20) was irradiated. 7.8% (for H-3, δ 4.20) and 10.0% (for $C\underline{H}_3$-2, δ 2.36) enhancements were observed when H-4 (δ 6.04) was irradiated.

(2*S*,3*S*,4*R*)-4-Benzyl-2-[(4*S*,5*S*,6*Z*)-4,5-bis(methoxymethoxy)-2-methyl-1,3-dioxonon-6-enyl]-2,3-bis(triethylsilyloxy)-4-butanolide (70).

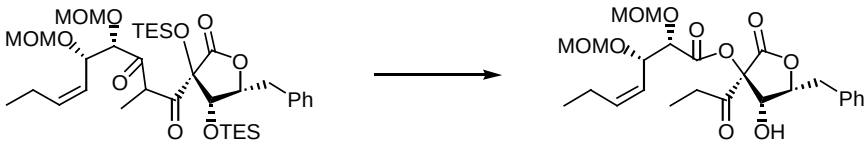


The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **62** (42.0 mg, 85.2 μmol) in THF (2 mL) was added dropwise potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution in toluene, 0.18 mL, 89 μmol). The solution was stirred at −78 °C for 1 h, and a solution of **36** (68.2 mg, 0.294 mmol) in THF (0.5 mL) was added. After being stirred at −78 °C for 1 h, the solution was quenched with CSA (47.7 mg, 0.205 mmol) and saturated aqueous $NaHCO_3$ (1.5 mL), diluted with EtOAc (50 mL), and washed with saturated brine (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:8), and the combined eluates were concentrated in vacuo to provide crude **61** (77.4 mg), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude **61** (77.4 mg) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (87.3 mg, 0.206 mmol). The mixture was stirred for 21 h at rt, diluted with EtOAc (50 mL), and

washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous Na_2CO_3 (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 38.2 mg (62% from **62**) of **70** as a colorless oil: TLC R_f 0.62 (EtOAc/hexane, 1:4); $[\alpha]_D^{21}$ +153 (*c* 1.77, $CHCl_3$); IR (neat) 1790, 1740, 1710 cm^{-1}; ^1H NMR (300 MHz) δ 0.64−0.82 (m, 12 H, $Si(C\underline{H}_2CH_3)_3$ × 2), 0.95−1.05 (m, 21 H, $Si(CH_2C\underline{H}_3)_3$ × 2, $CH_2C\underline{H}_3$), 1.35 (d, 3 H, *J* = 7.1 Hz, $C\underline{H}_3$-2 of the side chain at C-2), 2.15 (quint, 2 H, *J* = 7.6 Hz, $C\underline{H}_2CH_3$), 2.91 (dd, 1 H, *J* = 1.7, 15.4 Hz, C<u>H</u>HPh), 3.26, 3.32 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 3.34 (dd, 1 H, *J* = 10.5, 15.4 Hz, CH<u>H</u>Ph), 4.24 (d, 1 H, *J* = 6.6 Hz, H-4 of the side chain at C-2), 4.42 (d, 1 H, *J* = 6.8 Hz, OC<u>H</u>HO), 4.59−4.76 (m, 7 H, H-3, 4, H-2, 5 of the side chain at C-2, OCH<u>H</u>O, $OC\underline{H}_2O$), 5.27−5.37 (m, 1 H, H-6 of the side chain at C-2), 5.77 (dt, 1 H, *J* = 7.6, 10.7 Hz, H-7 of the side chain at C-2), 7.19−7.33 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.8 × 3, 6.0 × 3, 6.7 × 3, 7.0 × 3, 11.9, 14.1, 21.1, 35.0, 54.9, 55.5, 55.8, 71.9, 79.8, 82.0, 82.4, 87.1, 92.8, 96.3, 125.0, 126.6, 128.5 × 2, 129.3 × 2, 137.9, 139.1, 171.3, 204.2, 205.2; HRMS calcd for $C_{35}H_{57}O_{10}Si_2$ ($M^+ - C_2H_5$) *m/z* 693.3491, found 693.3500.

(2*S*,3*S*,4*R*)-4-Benzyl-3-hydroxy-2-[(2*S*,3*S*,4*Z*)-2,3-bis(methoxymethoxy)hept-4-enoyloxy]-2-(1-propanoyl)-4-butanolide (71).

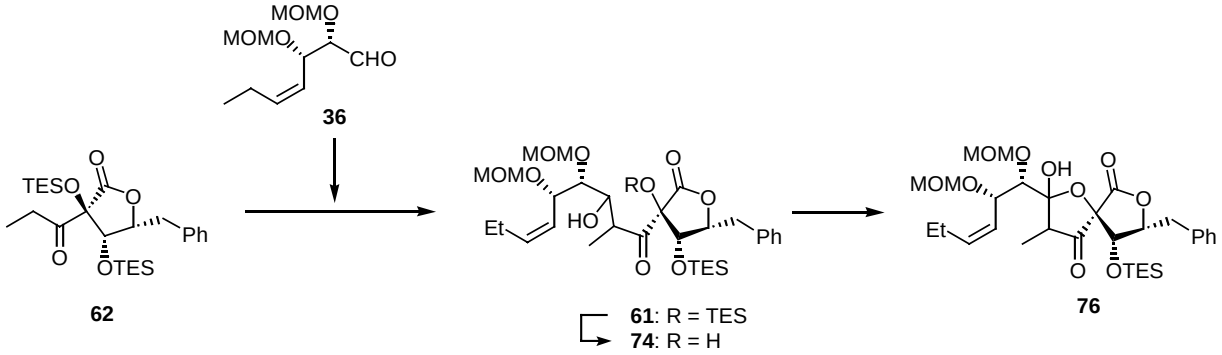


70 **71**

To a cooled (0 °C) stirred solution of **70** (12.8 mg, 17.7 μmol) in pyridine (1 mL) was added dropwise HF·pyridine complex (1 mL). After being stirred at rt for 13 h, the solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), diluted with EtOAc (20 mL), and washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated brine (10 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 7.2 mg (82%) of **71** as a colorless oil: TLC R_f 0.53 (EtOAc/hexane, 1:2); $[\alpha]_D^{24}$ +162 (*c* 0.130, $CHCl_3$); IR (neat) 3420, 1790, 1765, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (t, 3 H, *J* = 7.6 Hz, $CH{=}CHCH_2C\underline{H}_3$), 1.15 (t, 3 H, *J* = 7.1 Hz, $C(O)CH_2C\underline{H}_3$), 2.09−2.21 (m, 2 H, $CH{=}CHC\underline{H}_2CH_3$), 2.888, 2.894 (2 dq, each 1 H, *J* = 2.0, 7.1 Hz, $C(O)C\underline{H}_2CH_3$), 2.95 (dd, 1 H, *J* = 2.9, 14.9 Hz, C<u>H</u>HPh), 3.12 (dd, 1 H, *J* = 10.7, 14.9 Hz, CH<u>H</u>Ph), 3.25, 3.34 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 4.02 (d, 1 H, *J* = 7.3 Hz, H-2 of the heptenoyloxy), 4.37−4.41 (m, 2 H, H-3 of the heptenoyloxy, O<u>H</u>), 4.61−4.72 (m, 4 H, $OC\underline{H}_2O$ × 2), 5.10 (ddd, 1 H, *J* = 2.9, 4.9, 10.7 Hz, H-4),

5.15−5.24 (m, 1 H, C<u>H</u>=CHCH$_2$CH$_3$), 5.46 (d, 1 H, *J* = 4.9 Hz, H-3), 5.84 (dt, 1 H, *J* = 11.0, 7.8 Hz, CH=C<u>H</u>CH$_2$CH$_3$), 7.21−7.36 (m, 5 H, C$_6$<u>H</u>$_5$); ^{13}C NMR (75 MHz) δ 7.3, 14.1, 21.2, 33.7, 34.7, 55.7, 56.3, 70.6, 78.6, 79.4, 81.8, 82.4, 92.8, 97.4, 124.3, 127.1, 128.7 × 2, 129.2 × 2, 136.2, 140.3, 170.5, 171.4, 205.7; HRMS calcd for $C_{25}H_{34}O_{10}$ (M^+) *m/z* 494.2152, found 494.2155.

(5*S*,8*R*,9*S*)-8-Benzyl-2-[(1*S*,2*S*,3*Z*)-1,2-bis(methoxymethoxy)-3-hexenyl]-2-hydroxy-3-methyl-9-triethylsilyloxy-1,7-dioxaspiro[4.4]nonane-4,6-dione (76).



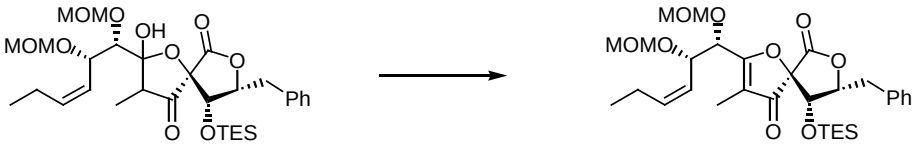
The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **62** (43.5 mg, 88.3 μmol) in THF (2 mL) was added dropwise potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution in toluene, 0.19 mL, 95 μmol). The solution was stirred at −78 °C for 1 h, and a solution of **36** (80.3 mg, 0.346 mmol) in THF (0.5 mL) was added. After being stirred at −78 °C for 1 h, the solution was quenched with CSA (33.1 mg, 0.143 mmol) and H_2O (1.5 mL), diluted with EtOAc (50 mL), and washed with saturated brine (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:8), and the combined eluates were concentrated in vacuo to provide crude **61** (65.7 mg), which was used in the next step without further purification.

To a coold (0 °C) stirred solution of crude **61** (65.7 mg) in pyridine (2 mL) was added a dilute solution of HF·pyridine complex in pyridine (1:25, v/v, 2 mL). The solution was stirred for 30 min at rt, and additional solution of HF·pyridine complex in pyridine (1:25, v/v, 2 mL × 4) was added every 30 min. The solution was stirred for total 2.5 h, and quenched with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C. The resulting mixture was diluted with EtOAc (50 mL), and washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated brine (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:3), and the eluates were

concentrated in vacuo to provide crude **74** (32.4 mg), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude **74** (32.4 mg) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (33.7 mg, 79.5 μmol). The mixture was stirred for 6 h at rt, diluted with EtOAc (50 mL), and washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous Na_2CO_3 (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to provide 23.6 mg (44% from **62**) of **76** as white crystals: mp 77.5−78.1 °C; TLC R_f 0.41 (EtOAc/hexane, 1:3); $[\alpha]_D^{21}$ +45.9 (*c* 1.45, $CHCl_3$); IR (neat) 3440, 1800, 1770 cm^{-1}; ^1H NMR (300 MHz) δ 0.64−0.73 (m, 6 H, Si($C\underline{H}_2CH_3$)$_3$), 0.96−1.02 (m, 12 H, Si($CH_2C\underline{H}_3$)$_3$, $CH_2C\underline{H}_3$), 1.18 (d, 3 H, *J* = 6.8 Hz, $C\underline{H}_3$ at C-3), 2.08−2.28 (m, 2 H, $C\underline{H}_2CH_3$), 3.03−3.10 (m, 1 H, C<u>H</u>HPh), 3.19 (dq, 1 H, *J* = 1.5, 6.8 Hz, H-3), 3.36, 3.40 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 3.41−3.51 (m, 1 H, CH<u>H</u>Ph), 3.74 (d, 1 H, *J* = 8.3 Hz, H-1 of the side chain at C-2), 4.51, 4.53 (2 d, each 1 H, *J* = 6.8 Hz, $OC\underline{H}_2O$), 4.69−4.80 (m, 4 H, H-8, 9, $OC\underline{H}_2O$), 5.07−5.14 (m, 1 H, H-2 of the side chain at C-2), 5.24−5.33 (m, 1 H, H-3 of the side chain at C-2), 5.62 (d, 1 H, *J* = 1.5 Hz, O<u>H</u>), 5.83 (dt, 1 H, *J* = 11.0, 7.3 Hz, H-4 of the side chain at C-2), 7.20−7.34 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.6 × 3, 6.7 × 4, 14.0, 21.1, 35.7, 49.1, 56.5, 56.6, 69.8, 75.2, 77.7, 82.2, 86.0, 92.7, 98.1, 106.5, 125.3, 126.5, 128.5 × 2, 129.3 × 2, 137.8, 139.5, 170.0, 206.5; HRMS calcd for $C_{31}H_{48}O_{10}Si$ (M^+) *m/z* 608.3017, found 608.3017. NOE experiment; 4.3% enhancement of the H-1 of the side chain at C-2 (δ 3.74) was observed when $C\underline{H}_3$ at C-3 (δ 1.18) was irradiated.

(5*S*,8*R*,9*S*)-8-Benzyl-2-[(1*S*,2*S*,3*Z*)-1,2-bis(methoxymethoxy)-3-hexenyl]-3-methyl-9-triethylsilyloxy-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (77).



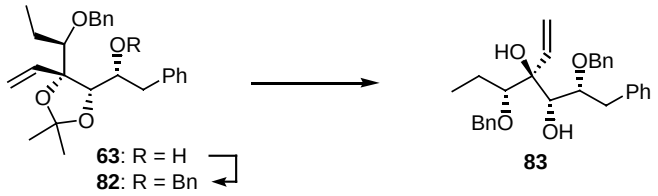
76 **77**

To a cooled (0 °C) sttired solution of **76** (996 mg, 1.64 mmol) in pyridine (50 mL) was added thionyl chloride (0.24 mL, 3.3 mmol). After being stirred at 0 °C for 10 min, the solution was quenched with saturated aqueous $NaHCO_3$ (10 mL), diluted with EtOAc (200 mL), and washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated brine (100 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 954 mg (99%) of **77** as colorless crystals: mp 56.0−56.3 °C; TLC R_f 0.20 (EtOAc/hexane, 1:5); $[\alpha]_D^{21}$ +23.0 (*c* 2.09,

$CHCl_3$); IR (neat) 1790, 1715, 1640 cm^{-1}; ^1H NMR (300 MHz) δ 0.51−0.69 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 0.94, (t, 9 H, *J* = 8.1 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.01 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.79 (s, 3 H, $C\underline{H}_3$ at C-3), 2.09−2.27 (m, 2 H, $C\underline{H}_2CH_3$), 3.19 (dd, 1 H, *J* = 2.7, 15.4 Hz, C<u>H</u>HPh), 3.31, 3.39 (2 s, each 3 H, $OC\underline{H}_3$ × 2), 3.65 (dd, 1 H, *J* = 11.0, 15.4 Hz, CH<u>H</u>Ph), 4.57−4.68 (m, 5 H, H-9, $OC\underline{H}_2O$ × 2), 4.71−4.78 (m, 1 H, H-2 of the side chain at C-2), 4.83 (ddd, 1 H, *J* = 2.7, 7.3, 11.0 Hz, H-8), 5.00 (d, 1 H, *J* = 7.3 Hz, H-1 of the side chain at C-2), 5.35 (dd, 1 H, *J* = 9.5, 11.0 Hz, H-3 of the side chain at C-2), 5.78 (dt, 1 H, *J* = 11.0, 7.3 Hz, H-4 of the side chain at C-2), 7.21−7.35 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.5 × 3, 5.7, 6.6 × 3, 14.0, 21.2, 36.3, 55.8, 56.0, 71.1, 72.7, 74.2, 82.7, 89.1, 94.5, 95.1, 114.9, 125.5, 126.6, 128.5 × 2, 129.3 × 2, 137.6, 138.6, 166.3, 183.4, 195.4; HRMS calcd for $C_{30}H_{43}O_8Si$ ($M^+ - OCH_3$) *m/z* 559.2727, found 559.2722.

Experimental Procedures for Chapter 4

(2*R*,3*S*,4*S*,5*R*)-2,5-Bis(benzyloxy)-1-phenyl-4-vinylheptane-3,4-diol (83).

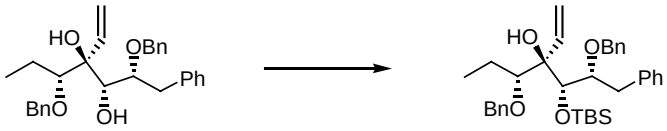


To a cooled (0 °C) solution of **63** (232 mg, 0.586 mmol) in DMF (5 mL) were added NaH (60% emulsion in mineral oil, 234 mg, 5.86 mmol) and benzyl bromide (0.35 mL, 2.94 mmol). After being stirred for 3 h at rt, the mixture was quenched with H_2O (3 mL) at 0 °C, diluted with EtOAc (50 mL), and washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NH_4Cl (50 mL), and saturated brine (50 mL). The organic layer was dried and concentrated in vacuo to give crude **82** (624 mg), which was used directly in the next step.

The crude **82** (624 mg) was dissolved in 60% aqueous CF_3CO_2H (10 mL). After being stirred for 3 h at rt, the solution was neutralized with 5 M (1 M = 1 mol·dm^{-1}) aqueous NaOH, diluted with EtOAc (50 mL), and washed with saturated brine (25 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 247 mg (94%) of **83** as a colorless oil: TLC R_f 0.16 (EtOAc/hexane, 1:8); $[\alpha]_D^{24}$ −28.5 (*c* 4.50, $CHCl_3$); IR (neat) 3460 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.94 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.34−1.50, 1.57−1.75 (2 m, each 1 H, $C\underline{H}_2CH_3$), 2.53 (d, 1 H, *J* = 7.3 Hz, O<u>H</u> at C-3), 3.04 (dd, 1 H, *J* = 6.2, 13.4 Hz, C<u>H</u>HPh), 3.12 (dd, 1 H, *J* = 7.7, 13.4 Hz, CH<u>H</u>Ph), 3.25 (dd, 1 H, *J* = 4.0, 7.3 Hz, H-3), 3.59 (dd, 1 H, *J* = 2.0, 7.1 Hz, H-5), 3.65 (s, 1 H, O<u>H</u> at C-4), 3.98 (ddd, 1 H, *J* = 4.0, 6.2, 7.7 Hz, H-2), 4.25, 4.47 (AB q, each 1 H, *J* = 11.0 Hz, OC$\underline{H}_2$Ph), 4.33, 4.43 (AB q, each 1 H, *J* = 11.0 Hz, OC$\underline{H}_2$Ph), 5.27 (dd, 1 H, *J* = 1.8, 10.6 Hz, CH=C<u>H</u>H), 5.45 (dd, 1 H, *J* = 1.8,

17.2 Hz, CH=CHH), 5.98 (dd, 1 H, *J* = 10.6, 17.2 Hz, CH=CHH), 7.06–7.11, 7.17–7.37 (2 m, 2 H + 13 H, C_6H_5 × 3); ^{13}C NMR (75 MHz) δ 11.6, 22.9, 36.9, 71.2, 71.4, 73.6, 79.5, 79.7, 84.2, 115.4, 126.3, 127.48, 127.53, 128.1, 128.2 × 3, 128.41 × 2, 128.44, 128.5 × 3, 129.6 × 2, 137.2, 138.0, 138.2, 138.9; HRMS calcd for $C_{29}H_{35}O_4$ (M^+ + H) *m/z* 447.2535, found 447.2544.

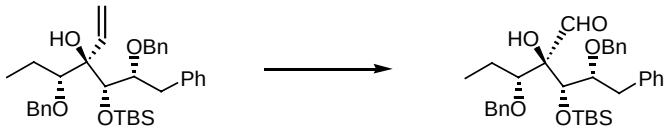
(2*R*,3*S*,4*R*,5*R*)-2,5-Bis(benzyloxy)-3-*tert*-butyldimethylsilyloxy-1-phenyl-4-vinylheptan-4-ol (84).



83 **84**

The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **83** (206 mg, 0.462 mmol) in pyridine (5 mL) was added dropwise trifluoromethanesulfonic acid *tert*-butyldimethylsilyl ester (0.42 mL, 1.83 mmol). After being stirred for 8 h at 50 °C, the solution was quenched with saturated aqueous $NaHCO_3$ (3 mL) at 0 °C, diluted with EtOAc (50 mL), and washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NH_4Cl (50 mL), and saturated brine (50 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to give 248 mg (96%) of **84** as white crystals: mp 88.0–88.1 °C; TLC R_f 0.57 (EtOAc/hexane, 1:8); $[\alpha]_D^{22}$ +29.0 (*c* 1.93, $CHCl_3$); IR (neat) 3460 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.02, 0.06 (2 s, each 3 H, *tert*-BuSi(C$\underline{H}_3$)$_2$), 0.94 (s, 9 H, $Me_2SiC(C\underline{H}_3)_3$), 0.99 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.65 (quint, 2 H, *J* = 7.3 Hz, $C\underline{H}_2CH_3$), 2.95 (dd, 1 H, *J* = 3.4, 14.2 Hz, C$\underline{H}$HPh), 3.05 (dd, 1 H, *J* = 9.8, 14.2 Hz, CH$\underline{H}$Ph), 3.50 (t, 1 H, *J* = 7.3 Hz, H-5), 3.72 (s, 1 H, O$\underline{H}$), 3.76 (dt, 1 H, *J* = 9.8, 3.4 Hz, H-2), 4.16, 4.28 (AB q, each 1 H, *J* = 11.6 Hz, OC$\underline{H}_2$Ph), 4.19 (d, 1 H, *J* = 3.4 Hz, H-3), 4.55, 4.64 (AB q, each 1 H, *J* = 11.5 Hz, OC$\underline{H}_2$Ph), 5.25 (dd, 1 H, *J* = 2.0, 10.7 Hz, CH=C$\underline{H}$H), 5.51 (dd, 1 H, *J* = 2.0, 17.3 Hz, CH=CH$\underline{H}$), 6.29 (dd, 1 H, *J* = 10.7, 17.3 Hz, C$\underline{H}$=CHH), 6.94–6.98, 7.14–7.34 (2 m, 2 H + 13 H, $C_6\underline{H}_5$ × 3); ^{13}C NMR (75 MHz) δ −4.2, −3.2, 11.7, 18.3, 23.2, 26.1 × 3, 38.1, 72.1, 72.9, 73.5, 80.8, 83.3, 85.2, 114.6, 126.0, 127.1, 127.3 × 3, 127.5, 127.9 × 2, 128.08, 128.11, 128.2 × 3, 129.4 × 2, 137.2, 138.0, 138.2, 138.9; HRMS calcd for $C_{35}H_{48}O_4Si$ (M^+) *m/z* 560.3322, found 560.3319.

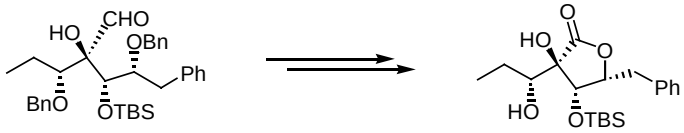
(2*R*,3*S*,4*R*,5*R*)-2,5-Bis(benzyloxy)-3-*tert*-butyldimethylsilyloxy-4-formyl-1-phenylheptan-4-ol (85).



84 **85**

To a cooled (−78 °C) stirred solution of **84** (165 mg, 0.294 mmol) in CH_2Cl_2 (20 mL) was bubbled ozone (O_2 containing *ca.* 3% O_3) for 15 min to a persistent light bluecolor. To this solution was added Ph_3P (84.9 mg, 0.324 mmol), and the solution was stirred for 30 min at −78 °C and for additional 1 h warming to rt. The solvent was removed by evaporation in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide 136 mg (82%) of **85** as a colorless oil: TLC R_f 0.42 (EtOAc/hexane, 1:8); $[\alpha]_D^{22}$ +46.0 (*c* 1.85, $CHCl_3$); IR (neat) 3480, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.14, 0.16 (2 s, each 3 H, *tert*-BuSi(C<u>H</u>$_3$)$_2$), 0.98 (s, 9 H, $Me_2SiC(C\underline{H}_3)_3$), 1.05 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.62−1.74, 1.75−1.88 (2 m, each 1 H, $C\underline{H}_2CH_3$), 2.91 (dd, 1 H, *J* = 4.2, 13.9 Hz, C<u>H</u>HPh), 3.02 (dd, 1 H, *J* = 9.3, 13.9 Hz, CH<u>H</u>Ph), 3.77 (s, 1 H, O<u>H</u>), 3.86, 3.99 (AB q, each 1 H, *J* = 11.4 Hz, $OC\underline{H}_2Ph$), 3.87−3.93 (m, 1 H, H-2), 4.11 (s, 1 H, H-3), 4.09−4.15 (m, 1 H, H-5), 4.36, 4.49 (AB q, each 1 H, *J* = 11.0 Hz, $OC\underline{H}_2Ph$), 7.03−7.07, 7.17−7.34 (2 m, 2 H + 13 H, $C_6\underline{H}_5$ × 3), 9.82 (s, 1 H, C<u>H</u>O); ^{13}C NMR (75 MHz) δ −3.7, −3.5, 10.1, 18.6, 21.7, 26.1 × 3, 38.6, 71.8, 72.9, 78.9, 79.0 × 2, 83.4, 126.3, 127.1, 127.3 × 2, 127.8, 127.9 × 3, 128.3 × 2, 128.5 × 2, 129.2 × 3, 137.7, 138.1, 139.0, 201.1; HRMS calcd for $C_{33}H_{45}O_4Si$ (M^+ − CHO) *m/z* 533.3087, found 533.3087.

(2*R*,3*S*,4*R*)-4-Benzyl-3-*tert*-butyldimethylsilyloxy-2-hydroxy-2-[(1*R*)-1-(hydroxy)propyl]-4-butanolide (86).

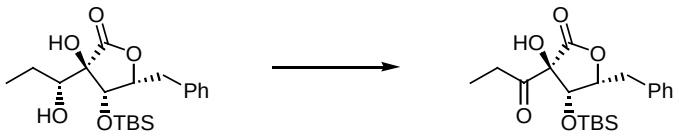


85 **86**

A solution of **85** (135 mg, 0.240 mmol) in EtOAc (10 mL) was stirred under atmospheric H_2 gas in the presence of 10% Pd on charcoal (50.4 mg) for 10 h, and the catalyst was removed by filtration through a Celite-pad, and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo to provide crude γ-lactol (95.2 mg), which was used in the next step without further purification.

The following reaction was carried out in the dark. To a cooled (0 °C) stirred solution of crude γ-lactol (95.2 mg) in CH_2Cl_2 (10 mL) were added tetra-*n*-butylammonium iodide (132.9 mg, 0.360 mmol) and NIS (134.9 mg, 0.600 mmol). After being stirred at rt for 18 h, the solution was diluted with EtOAc (50 mL), and washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give 70.6 mg (77% from **85**) of **86** as white crystals: mp 142.0−142.4 °C; TLC R_f 0.38 (EtOAc/hexane, 1:3); $[\alpha]_D^{24}$ +122.3 (*c* 1.45, $CHCl_3$); IR (neat) 3370, 1750 cm^{-1}; ^1H NMR (300 MHz) δ 0.17, 0.19 (2 s, each 3 H, *tert*-BuSi($C\underline{H}_3)_2$), 0.96 (s, 9 H, $Me_2SiC(C\underline{H}_3)_3$), 1.06 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.46−1.71 (m, 2 H, $C\underline{H}_2CH_3$), 2.81 (dd, 1 H, *J* = 2.2, 14.6 Hz, C<u>H</u>HPh), 3.06 (dd, 1 H, *J* = 11.0, 14.6 Hz, CH<u>H</u>Ph), 3.44, 3.66 (2 br s, each 1 H, O<u>H</u> × 2), 3.98−4.04 (m, 1 H, H-1 of the side chain at C-2), 4.30 (d, 1 H, *J* = 2.2 Hz, H-3), 4.94 (dt, 1 H, *J* = 11.0, 2.0 Hz, H-4), 7.23−7.36 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ −4.1, −3.1, 10.1, 18.4, 22.4, 26.0 × 3, 36.1, 71.8, 78.8, 83.9 × 2, 126.8, 128.6 × 2, 129.1 × 2, 137.2, 177.2; HRMS calcd for $C_{20}H_{32}O_5Si$ (M^+) *m/z* 380.2019, found 380.2008.

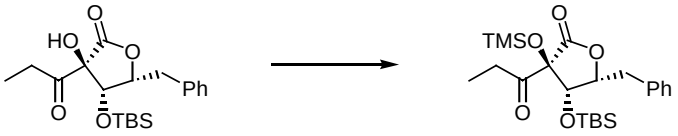
(2*S*,3*S*,4*R*)-4-Benzyl-3-*tert*-butyldimethylsilyloxy-2-hydroxy-2-(1-propanoyl)-4-butanolide (87).



86 **87**

To a cooled (0 °C) solution of **86** (66.8 mg, 0.176 mmol) in saturated aqueous CH_2Cl_2 (4 mL) was added Dess−Martin periodinane (149 mg, 0.351 mmol). The mixture was stirred for 26 h at rt, diluted with EtOAc (50 mL), and washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous Na_2CO_3 (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 66.0 mg (99%) of **87** as white crystals: mp 61.8−62.0 °C; TLC R_f 0.36 (EtOAc/hexane, 1:2); $[\alpha]_D^{20}$ +133.1 (*c* 3.30, $CHCl_3$); IR (neat) 3430, 1770, 1715 cm^{-1}; ^1H NMR (300 MHz) δ 0.08, 0.14 (2 s, each 3 H, *tert*-BuSi($C\underline{H}_3)_2$), 0.94 (s, 9 H, $Me_2SiC(C\underline{H}_3)_3$), 1.13 (t, 3 H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.78, 2.89 (2 dq, each 1 H, *J* = 19.2, 7.1 Hz, $C\underline{H}_2CH_3$), 2.92 (dd, 1 H, *J* = 2.2, 15.4 Hz, C<u>H</u>HPh), 3.15 (dd, 1 H, *J* = 11.2, 15.4 Hz, CH<u>H</u>Ph), 4.38 (s, 1 H, O<u>H</u>), 4.56 (d, 1 H, *J* = 6.6 Hz, H-3), 4.88 (ddd, 1 H, *J* = 2.2, 6.6, 11.2 Hz, H-4), 7.22−7.35 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ −4.9, −4.8, 6.9, 18.0, 25.7 × 3, 33.6, 35.3, 78.4, 83.3, 83.8, 126.7, 128.6 × 2, 129.1 × 2, 137.2, 173.3, 207.5; HRMS calcd for $C_{20}H_{30}O_5Si$ (M^+) *m/z* 378.1863, found 378.1866.

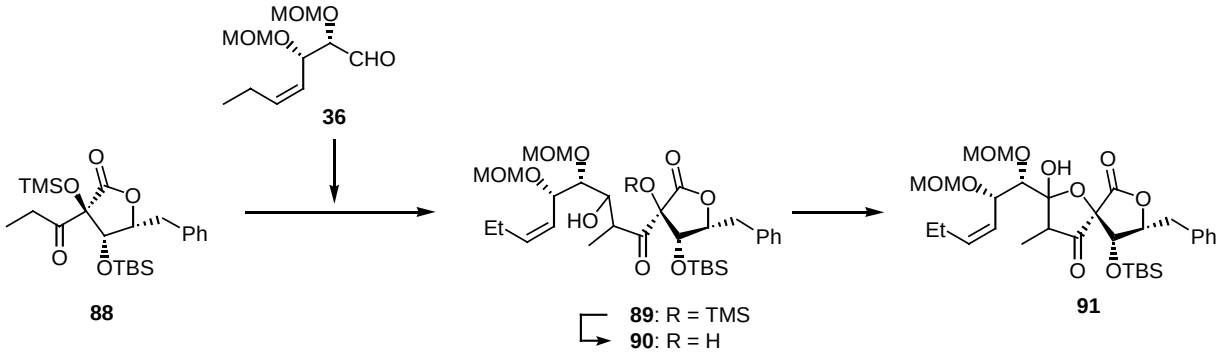
(2*S*,3*S*,4*R*)-4-Benzyl-3-*tert*-butyldimethylsilyloxy-2-(1-propanoyl)-2-trimethylsilyloxy-4-butanolide (88).



87 **88**

The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **87** (55.9 mg, 0.148 mmol) in pyridine (2 mL) was added dropwise chlorotrimethylsilane (93.7 μL, 0.738 mmol). After being stirred for 8 h at rt, the solution was quenched with saturated aqueous $NaHCO_3$ (1 mL) at 0 °C, diluted with EtOAc (10 mL), and washed with saturated aqueous $NaHCO_3$ (5 mL), saturated aqueous NH_4Cl (5 mL), and saturated brine (5 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:25) to give 57.0 mg (86%) of **88** as colorless crystals: mp 55.1−56.0 °C; TLC R_f 0.59 (EtOAc/hexane, 1:5); $[\alpha]_D^{20}$ +99.0 (*c* 2.75, $CHCl_3$); IR (neat) 1790, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.14, 0.16 (2 s, each 3 H, *tert*-BuSi($C\underline{H}_3$)$_2$), 0.20 (s, 9 H, Si($C\underline{H}_3$)$_3$), 0.95 (s, 9 H, $Me_2SiC(C\underline{H}_3)_3$), 1.09 (t, 3 H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.73, 2.81 (2 dq, each 1 H, *J* = 19.3, 7.1 Hz, $C\underline{H}_2CH_3$), 2.86 (dd, 1 H, *J* = 2.0, 14.9 Hz, C<u>H</u>HPh), 3.12 (dd, 1 H, *J* = 11.2, 14.9 Hz, CH<u>H</u>Ph), 4.52 (d, 1 H, *J* = 7.1 Hz, H-3), 4.75 (ddd, 1 H, *J* = 2.0, 7.1, 11.2 Hz, H-4), 7.21−7.34 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ −4.8, −4.6, 1.4 × 3, 7.0, 18.1, 25.7 × 3, 33.6, 35.0, 79.9, 82.4, 85.7, 126.6, 128.5 × 2, 129.2 × 2, 137.7, 172.2, 208.8; HRMS calcd for $C_{23}H_{38}O_5Si_2$ (M^+) *m/z* 450.2258, found 450.2257.

(5*S*,8*R*,9*S*)-8-Benzyl-9-*tert*-butyldimethylsilyloxy-2-hydroxy-2-[(1*S*,2*S*,3*Z*)-1,2-bis(methoxymethoxy)-3-hexenyl]-3-methyl-1,7-dioxaspiro[4.4]nonane-4,6-dione (91).



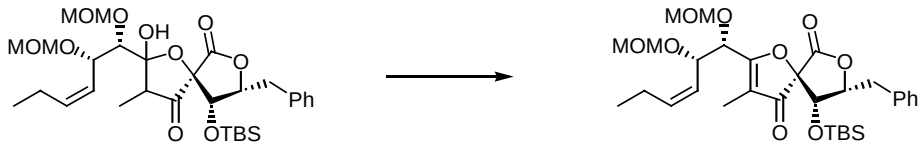
The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **88** (45.7 mg, 0.101 mmol) in THF (2 mL) was added dropwise potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution in toluene, 0.20 mL, 0.10 mmol). The solution was stirred at −78 °C for 30 min, and a solution of **36** (70.4 mg, 0.303 mmol) in THF (0.5 mL) was added. After being stirred at −78 °C for 1 h, the solution was

quenched with CSA (45.0 mg, 0.194 mmol) and H_2O (1.5 mL), diluted with EtOAc (50 mL), and washed with saturated brine (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:10), and the combined eluates were concentrated in vacuo to provide crude **89** (37.3 mg), which was used in the next step without further purification.

To a coold (0 °C) stirred solution of crude **89** (37.3 mg) in pyridine (2 mL) was added a dilute solution of HF·pyridine complex in pyridine (1:25, v/v, 2 mL). The solution was stirred for 30 min at 0 °C, and additional solution of HF·pyridine complex in pyridine (1:25, v/v, 2 mL × 4) was added every 30 min. The solution was stirred for total 2.5 h, and quenched with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C. The resulting mixture was diluted with EtOAc (50 mL), and washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated brine (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (2:5), and the eluates were concentrated in vacuo to provide crude **90** (28.1 mg), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude **90** (28.1 mg) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (38.1 mg, 89.8 μmol). The mixture was stirred for 2 h at rt, diluted with EtOAc (50 mL), and washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous Na_2CO_3 (20 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to provide 26.5 mg (43% from **88**) of **91** as white crystals: mp 133.6−140.0 °C; TLC R_f 0.50 (EtOAc/hexane, 1:3); $[\alpha]_D^{20}$ +52.2 (*c* 1.30, $CHCl_3$); IR (neat) 3440, 1800, 1765 cm^{-1}; ^1H NMR (300 MHz) δ 0.18, 0.20 (2 s, each 3 H, *tert*-BuSi(C$\underline{H}_3$)$_2$), 0.93 (s, 9 H, $Me_2SiC(C\underline{H}_3)_3$), 0.99 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.18 (d, 3 H, *J* = 6.8 Hz, C$\underline{H}_3$ at C-3), 2.09−2.25 (m, 2 H, C$\underline{H}_2CH_3$), 3.05 (d, 1 H, *J* = 14.6 Hz, C$\underline{H}$HPh), 3.12 (dq, 1 H, *J* = 1.5, 6.8 Hz, H-3), 3.34, 3.40 (2 s, each 3 H, OC$\underline{H}_3$ × 2), 3.41−3.54 (m, 1 H, CH$\underline{H}$Ph), 3.75 (d, 1 H, *J* = 8.3 Hz, H-1 of the side chain at C-2), 4.50, 4.53 (2 d, each 1 H, *J* = 6.7 Hz, OC$\underline{H}_2$O), 4.71−4.79 (m, 4 H, H-8, 9, OC$\underline{H}_2$O), 5.12 (dd, 1 H, *J* = 8.3, 9.8 Hz, H-2 of the side chain at C-2), 5.28 (dd, 1 H, *J* = 9.8, 10.7 Hz, H-3 of the side chain at C-2), 5.58 (d, 1 H, *J* = 1.5 Hz, O$\underline{H}$), 5.83 (dt, 1 H, *J* = 10.7, 7.6 Hz, H-4 of the side chain at C-2), 7.20−7.35 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ −5.3, −4.7, 6.8, 14.0, 17.9, 21.2, 25.6 × 3, 35.8, 49.1, 56.5, 56.6, 69.8, 75.1, 77.5, 82.2, 86.0, 92.7, 97.9, 106.5, 125.3, 126.6, 128.5 × 2, 129.3 × 2, 137.8, 139.5, 170.0, 206.5; HRMS calcd for $C_{31}H_{48}O_{10}Si$ (M^+) *m/z* 608.3017, found 608.3002.

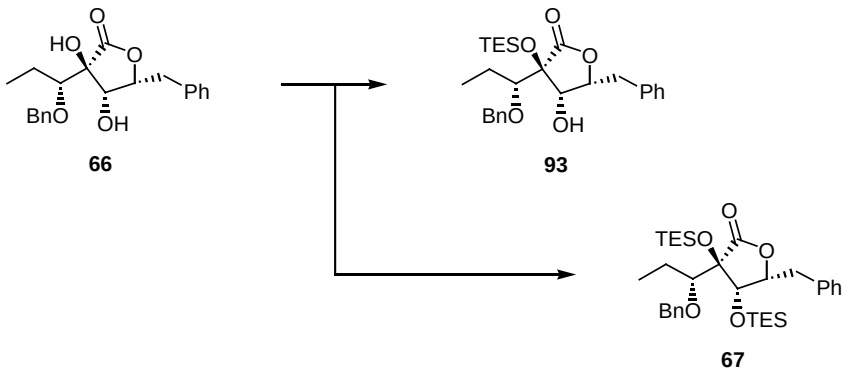
(5*S*,8*R*,9*S*)-8-Benzyl-9-*tert*-butyldimethylsilyloxy-2-[(1*S*,2*S*,3*Z*)-1,2-bis(methoxymethoxy)-3-hexenyl]-3-methyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (92).



91 **92**

To a cooled (0 °C) sttired solution of **91** (25.0 mg, 41.1 μmol) in pyridine (2 mL) was added thionyl chloride (6.0 μL, 82.1 μmol). After being stirred at 0 °C for 10 min, the solution was quenched with saturated aqueous $NaHCO_3$ (1 mL), diluted with EtOAc (30 mL), and washed with saturated aqueous $NaHCO_3$ (15 mL) and saturated brine (15 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 22.0 mg (91%) of **92** as a colorless oil: TLC R_f 0.51 (EtOAc/hexane, 1:3); $[\alpha]_D^{18}$ +25.1 (*c* 1.05, $CHCl_3$); IR (neat) 1790, 1715, 1645 cm^{-1}; ^1H NMR (300 MHz) δ 0.05, 0.12 (2 s, each 3 H, *tert*-BuSi(C$\underline{H}_3$)$_2$), 0.90 (s, 9 H, $Me_2SiC(C\underline{H}_3)_3$), 1.01 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.79 (s, 3 H, C$\underline{H}_3$ at C-3), 2.10−2.26 (m, 2 H, C$\underline{H}_2CH_3$), 3.14 (dd, 1 H, *J* = 2.4, 15.4 Hz, C$\underline{H}$HPh), 3.32, 3.39 (2 s, each 3 H, OC$\underline{H}_3$ × 2), 3.70 (dd, 1 H, *J* = 11.2, 15.4 Hz, CH$\underline{H}$Ph), 4.58−4.68 (m, 5 H, H-9, OC$\underline{H}_2$O × 2), 4.75 (dd, 1 H, *J* = 7.3, 9.8 Hz, H-2 of the side chain at C-2), 4.83 (ddd, 1 H, *J* = 2.4, 7.3, 11.2 Hz, H-8), 4.98 (d, 1 H, *J* = 7.3 Hz, H-1 of the side chain at C-2), 5.35 (dd, 1 H, *J* = 9.8, 10.7 Hz, H-3 of the side chain at C-2), 5.78 (dt, 1 H, *J* = 10.7, 7.6 Hz, H-4 of the side chain at C-2), 7.21−7.35 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ −5.2, −4.7, 5.6, 14.0, 17.9, 21.3, 25.5 × 3, 36.4, 55.8, 56.1, 71.2, 72.7, 74.1, 82.6, 89.0, 94.6, 95.2, 114.9, 125.6, 126.6, 128.6 × 2, 129.3 × 2, 137.6, 138.5, 166.3, 183.3, 195.4; HRMS calcd for $C_{30}H_{43}O_8Si$ ($M^+ - OCH_3$) *m/z* 559.2727, found 559.2723.

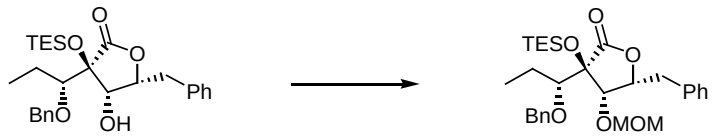
(2*R*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(benzyloxy)propyl]-3-hydroxy-2-triethylsilyloxy-4-butanolide (93) and (2*R*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(benzyloxy)propyl]-2,3-bis(triethylsilyloxy)-4-butanolide (67).



66 **93** **67**

The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **66** (55.1 mg, 154.6 μmol) in pyridine (3 mL) was added dropwise triethylsilyl trifluoromethanesulfonate (30.0 μL, 123.7 μmol). The solution was stirred for 1 h, and additional triethylsilyl trifluoromethanesulfonate (17.5 μL × 2, 77.3 μmol × 2) was added every 1 h. The solution was sttired for total 3 h, and quenched with saturated aqueous $NaHCO_3$ (3 mL) at 0 °C, diluted with EtOAc (50 mL), and washed with saturated aqueous $NaHCO_3$ (12 mL) and saturated brine (12 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:30 to 1:10) to provide 53.3 mg (73%) of **93** and 12.4 mg (22%) of **67**. Compound **93** was obtained as a colorless oil: TLC R_f 0.34 (EtOAc/hexane, 1:6); $[\alpha]_D^{21}$ +106 (*c* 1.99, $CHCl_3$); IR (neat) 3460, 1780 cm^{-1}; ^1H NMR (300 MHz) δ 0.66−0.76 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 1.03 (t, 9 H, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.09 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.55−1.89 (m, 2 H, $C\underline{H}_2CH_3$), 2.83 (dd, 1 H, *J* = 2.7, 14.6 Hz, C<u>H</u>HPh at C-4), 3.01 (dd, 1 H, *J* = 10.5, 14.6 Hz, CH<u>H</u>Ph at C-4), 3.32 (br s, 1 H, O<u>H</u>), 3.76 (dd, 1 H, *J* = 3.2, 9.5 Hz, H-1 of the side chain at C-2), 4.33 (d, 1 H, *J* = 4.2 Hz, H-3), 4.65, 5.08 (AB q, each 1 H, *J* = 10.3 Hz, $OC\underline{H}_2Ph$), 4.87 (ddd, 1 H, *J* = 2.7, 4.2, 10.5 Hz, H-4), 7.17−7.43 (m, 10 H, $C_6\underline{H}_5$ × 2); ^{13}C NMR (75 MHz) δ 5.2 × 3, 6.9 × 3, 10.5, 23.3, 35.8, 74.9, 77.2, 78.9, 79.4, 82.6, 126.6, 127.8, 128.3 × 4, 128.5 × 2, 129.1 × 2, 137.5, 138.1, 175.2; HRMS calcd for $C_{27}H_{38}O_5Si$ (M^+) *m/z* 470.2489, found 470.2489. Spectroscopic data for **67**; see pp 61−62 in this thesis.

(2*R*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(benzyloxy)propyl]-3-methoxymethoxy-2-triethylsilyloxy-4-butanolide (94).

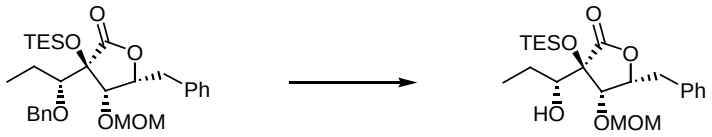


93 **94**

To a cooled (0 °C) stirred solution of **93** (53.3 mg, 113.2 μmol) in CH_2Cl_2 (2 mL) was added $CH_2(OMe)_2$ (3 mL) and P_2O_5 (160.7 mg, 1.13 mmol). After being stirred at 0 °C for 3 h, the mixture was quenched with saturated aqueous Na_2CO_3 (3 mL), diluted with EtOAc (30 mL), and washed with saturated aqueous Na_2CO_3 (8 mL) and saturated brine (8 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide 54.1 mg (93%) of **94** as a colorless oil: TLC R_f 0.35 (EtOAc/hexane, 1:6); $[\alpha]_D^{21}$ +70.6 (*c* 1.63, $CHCl_3$); IR (neat) 1790 cm^{-1}; ^1H NMR (300 MHz) δ 0.66−0.78 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 1.02 (t, 9 H, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.07 (t, 3 H, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.71−1.97 (m, 2 H, $C\underline{H}_2CH_3$), 2.79 (dd, 1 H, *J* = 2.5, 14.8 Hz, C<u>H</u>HPh at

C-4), 2.98 (dd, 1 H, *J* = 10.6, 14.8 Hz, CH<u>H</u>Ph at C-4), 3.32 (s, 3 H, OC<u>H</u>$_3$), 3.80 (dd, 1 H, *J* = 3.7, 8.5 Hz, H-1 of the side chain at C-2), 4.57 (d, 1 H, *J* = 5.0 Hz, H-3), 4.59, 4.93 (AB q, each 1 H, *J* = 11.0 Hz, OC<u>H</u>$_2$Ph), 4.75, 5.04 (AB q, each 1 H, *J* = 6.6 Hz, OC<u>H</u>$_2$O), 4.86 (ddd, 1 H, *J* = 2.5, 5.0, 10.6 Hz, H-4), 7.09−7.44 (m, 10 H, C$_6$<u>H</u>$_5$ × 2); ^{13}C NMR (75 MHz) δ 5.1 × 3, 6.9 × 3, 11.3, 23.7, 35.7, 56.6, 74.4, 77.1, 80.4, 82.5, 83.6, 94.3, 126.5, 127.4, 127.9 × 2, 128.2 × 2, 128.4 × 2, 129.0 × 2, 137.8, 138.5, 172.5; HRMS calcd for $C_{29}H_{43}O_6Si$ (M^+ + H) *m/z* 515.2829, found 515.2824.

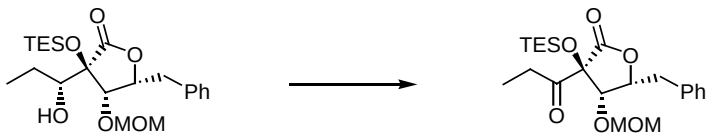
(2*R*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(hydroxy)propyl]-3-methoxymethoxy-2-triethylsilyloxy-4-butanolide (95).



94 **95**

A solution of **94** (32.0 mg, 62.2 μmol) in EtOAc (2 mL) was stirred under atmospheric H_2 gas in the presence of 10% Pd on charcoal (45.5 mg) for 3 days, and the catalyst was removed by filtration through a Celite-pad and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 20.0 mg (76%) of **95** as a colorless oil: TLC R_f 0.26 (EtOAc/hexane, 1:6); $[\alpha]_D^{21}$ +61.5 (*c* 0.990, $CHCl_3$); IR (neat) 3520, 1770 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.65−0.77 (m, 6 H, Si(C<u>H</u>$_2$CH$_3$)$_3$), 1.02 (t, 9 H, *J* = 8.1 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 1.09 (t, 3 H, *J* = 7.6 Hz, CH$_2$C<u>H</u>$_3$), 1.46−1.62, 1.67−1.86 (2 m, each 1 H, C<u>H</u>$_2$CH$_3$), 2.82 (dd, 1 H, *J* = 2.4, 14.8 Hz, C<u>H</u>HPh), 3.04 (dd, 1 H, *J* = 10.5, 14.8 Hz, CH<u>H</u>Ph), 3.32 (s, 3 H, OC<u>H</u>$_3$), 4.02 (dd, 1 H, *J* = 2.0, 10.5 Hz, H-1 of the side chain at C-2), 4.40 (d, 1 H, *J* = 3.8 Hz, H-3), 4.80, 5.12 (AB q, each 1 H, *J* = 6.6 Hz, OC<u>H</u>$_2$O), 4.94 (ddd, 1 H, *J* = 2.4, 3.8, 10.5 Hz, H-4), 7.20−7.37 (m, 5 H, C$_6$<u>H</u>$_5$); ^{13}C NMR (75 MHz) δ 5.1 × 3, 6.9 × 3, 10.4, 23.1, 35.9, 56.6, 73.1, 76.6, 81.9, 83.2, 94.9, 126.8, 128.6 × 2, 129.0 × 2, 137.3, 174.7; HRMS calcd for $C_{22}H_{36}O_6Si$ (M^+) *m/z* 424.2281, found 424.2281.

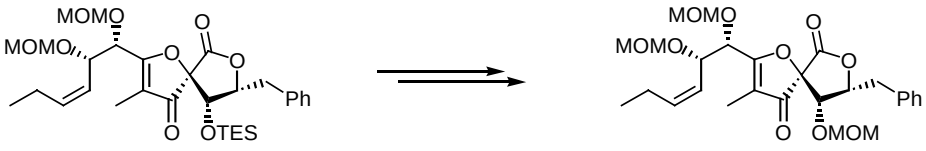
(2*S*,3*S*,4*R*)-4-Benzyl-3-methoxymethoxy-2-(1-propanoyl)-2-triethylsilyloxy-4-butanolide (96).



95 **96**

To a cooled (0 °C) stirred solution of **95** (22.7 mg, 53.5 μmol) in CH_2Cl_2 (2 mL) was added Dess–Martin periodinane (34.0 mg, 80.2 μmol). The mixture was stirred for 3 h, diluted with EtOAc (30 mL), and washed with saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 21.1 mg (93%) of **96** as a colorless oil: TLC R_f 0.34 (EtOAc/hexane, 1:6); $[\alpha]_D^{20}$ +13.4 (*c* 2.04, $CHCl_3$); IR (neat) 1780, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.60–0.72 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 1.00 (t, 9 H, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.09 (t, 3 H, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 2.66 (dq, 1 H, *J* = 7.1, 14.2 Hz, $C\underline{H}HCH_3$), 2.82 (dd, 1 H, *J* = 2.4, 14.9 Hz, $C\underline{H}HPh$), 2.98 (dq, 1 H, *J* = 7.1, 14.2 Hz, $CH\underline{H}CH_3$), 3.08 (dd, 1 H, *J* = 10.7, 14.9 Hz, $CH\underline{H}Ph$), 3.36 (s, 3 H, $OC\underline{H}_3$), 4.70, 4.88 (AB q, each 1 H, *J* = 6.8 Hz, $OC\underline{H}_2O$), 4.72 (d, 1 H, *J* = 8.1 Hz, H-3), 4.79 (ddd, 1 H, *J* = 2.4, 8.1, 10.7 Hz, H-4), 7.23–7.35 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.7 × 3, 6.7 × 3, 7.0, 35.0, 35.4, 56.8, 77.2, 82.9, 86.4, 94.3, 126.7, 128.6 × 2, 129.2 × 2, 137.3, 170.6, 206.3; HRMS calcd for $C_{22}H_{34}O_6Si$ (M^+) *m/z* 422.2125, found 422.2125.

(5*S*,8*R*,9*S*)-8-Benzyl-2-[(1*S*,2*S*,3*Z*)-1,2-bis(methoxymethoxy)-3-hexenyl]-9-methoxymethoxy-3-methyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (98).

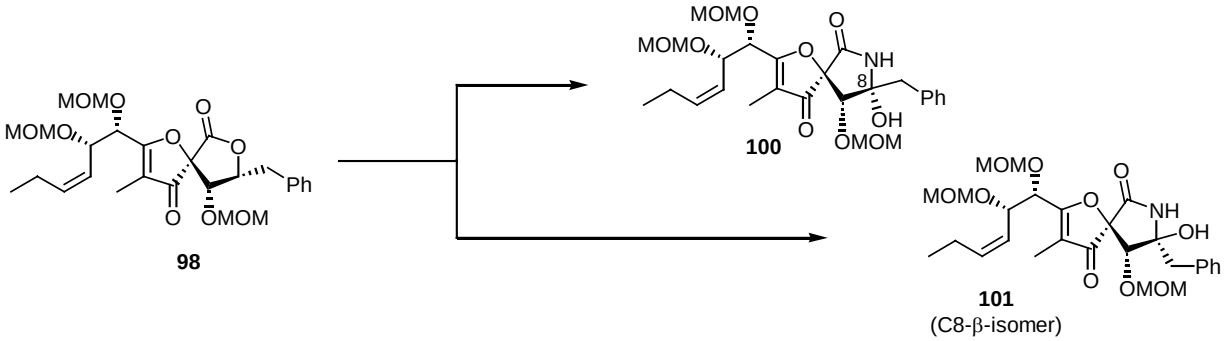


To a cooled (0 °C) stirred solution of **77** (153 mg, 259 μmol) in pyridine (10 mL) was added dropwise HF·pyridine complex (1 mL). After being stirred at rt for 3 h, the solution was quenched with saturated aqueous $NaHCO_3$ (10 mL), diluted with EtOAc (80 mL), and washed with saturated aqueous $NaHCO_3$ (30 mL) and saturated brine (30 mL). The organic layer was dried and concentrated in vacuo to give crude alcohol (139 mg), which was used directry in the next step.

To a cooled (0 °C) stirred suspension of P_2O_5 (185 mg, 1.30 mmol) in $CH_2(OMe)_2$ (5 mL) was added a solution of crude alcohol (139 mg) in CH_2Cl_2 (1 mL). After being stirred at 0 °C for 1.5 h, the mixture was quenched with saturated aqueous Na_2CO_3 (5 mL), diluted with EtOAc (50 mL), and washed with saturated aqueous Na_2CO_3 (20 mL) and saturated brine (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 131 mg (98% from **77**) of **98** as a colorless oil: TLC R_f 0.66 (EtOAc/hexane, 1:1); $[\alpha]_D^{21}$ +38.5 (*c* 0.600, $CHCl_3$); IR (neat) 1790, 1710, 1640 cm^{-1}; ^1H NMR (300 MHz) δ 1.01 (t, 3 H, *J* = 7.6 Hz,

$CH_2C\underline{H}_3$), 1.83 (s, 3 H, $C\underline{H}_3$ at C-3), 2.08−2.26 (m, 2 H, $C\underline{H}_2CH_3$), 3.30, 3.31, 3.37 (3 s, each 3 H, $OC\underline{H}_3$ × 3), 3.31 (dd, 1H, *J* = 3.4, 15.1 Hz, C<u>H</u>HPh), 3.64 (dd, 1 H, *J* = 10.0, 15.1 Hz, CH<u>H</u>Ph), 4.53−4.63 (m, 5 H, H-9, $OC\underline{H}_2O$ × 2), 4.67 (d, 1 H, *J* = 6.6 Hz, OC<u>H</u>HO), 4.69 (d, 1 H, *J* = 7.1 Hz, OCH<u>H</u>O), 4.71−4.78 (m, 1 H, H-2 of the side chain at C-2), 4.91 (d, 1 H, *J* = 7.8 Hz, H-1 of the side chain at C-2), 4.98 (ddd, 1 H, *J* = 3.4, 7.8, 10.0 Hz, H-8), 5.33 (dd, 1 H, *J* = 9.5, 11.0 Hz, H-3 of the side chain at C-2), 5.79 (dt, 1 H, *J* = 11.0, 7.6 Hz, H-4 of the side chain at C-2), 7.21−7.35 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 5.7, 14.1, 21.3, 36.5, 55.7, 56.0, 56.5, 71.2, 73.5, 78.1, 81.2, 88.3, 94.1, 95.3, 97.2, 114.5, 125.2, 126.7, 128.5 × 2, 129.4 × 2, 137.2, 138.9, 165.9, 184.3, 195.6; HRMS calcd for $C_{26}H_{33}O_9$ ($M^+ - OCH_3$) *m/z* 489.2124, found 489.2118.

(5*S*,8*R*,9*R*)-8-Benzyl-2-[(1*S*,2*S*,3*Z*)-1,2-bis(methoxymethoxy)-3-hexenyl]-8-hydroxy-9-methoxymethoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (100) and 8*S*-Isomer (101).

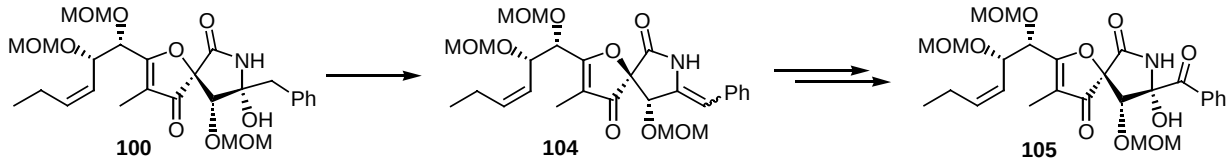


To a stirred solution of **98** (131 mg, 252 μmol) in *i*-PrOH (10 mL) was added a saturated NH_3 solution in *i*-PrOH (6 mL). After being stirred at rt for 3 h, the solution was concentrated in vacuo to provide crude amide derivative (140 mg), which was used directry in the next step.

To a cooled (0 °C) stirred solution of crude amide derivative (140 mg) in CH_2Cl_2 (10 mL) was added Dess−Martin periodinane (132 mg, 311 μmol). The mixture was stirred for 6 h at rt, diluted with EtOAc (100 mL), and washed with saturated aqueous $Na_2S_2O_3$ (40 mL) and saturated aqueous Na_2CO_3 (40 mL × 2). A saturated aqueous Na_2CO_3 (50 mL) was added to the resulting organic layer, and the mixture was strong stirred for 10 h. The layers were separated and the organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 110 mg (81% from **98**) of **100** and 21.1 mg (16% from **98**) of **101**. Compound **100** was obtained as a colorless oil: TLC R_f 0.26 (EtOAc/hexane, 1:2); $[\alpha]_D^{23}$ −79.2 (*c* 1.02, $CHCl_3$); IR (neat) 3280, 1730, 1680, 1620 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.00 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.81 (s, 3 H, $C\underline{H}_3$ at C-3), 2.07−2.25 (m, 2 H, $C\underline{H}_2CH_3$), 2.97 (d, 1 H, *J* = 13.7 Hz, C<u>H</u>HPh), 3.30, 3.36, 3.41 (3 s, each 3 H, $OC\underline{H}_3$ × 3), 3.36 (d, 1 H, *J* = 13.7 Hz,

CHHPh), 4.50 (s, 1 H, H-9), 4.54–4.61, 4.64–4.75 (2 m, 3 H + 4 H, H-1 of the side chain at C-2, OCH_2O × 3), 4.76 (dd, 1 H, *J* = 7.6, 9.5 Hz, H-2 of the side chain at C-2), 5.33 (dd, 1 H, *J* = 9.5, 11.0 Hz, H-3 of the side chain at C-3), 5.79 (dt, 1 H, *J* = 11.0, 7.6 Hz, H-4 of the side chain at C-2), 5.97 (br s, 1 H, OH), 6.30 (br s, 1 H, NH), 7.28–7.38 (m, 5 H, C_6H_5); ^{13}C NMR (75 MHz) δ 5.6, 14.0, 21.3, 43.6, 55.6, 56.0, 56.2, 71.3, 74.0, 79.0, 84.7, 92.9, 94.2, 95.3, 96.6, 114.2, 125.2, 127.6, 128.7 × 2, 130.5 × 2, 134.5, 138.9, 163.2, 187.5, 199.9; HRMS calcd for $C_{27}H_{35}NO_9$ ($M^+ - H_2O$) *m/z* 517.2311, found 517.2305. NOE experiment; 10.1% enhancement of the H-9 (δ 4.50) was observed when CHHPh (δ 2.97) was irradiated, and 5.8% enhancement of the CHHPh (δ 2.97) was observed when H-9 (δ 4.50) was irradiated. Compound **101** was obtained as a colorless oil: TLC R_f 0.11 (EtOAc/hexane, 1:2); $[\alpha]_D^{20}$ +32.3 (*c* 0.500, $CHCl_3$); IR (neat) 3400, 3260, 1730, 1690, 1635 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.01 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 1.81 (s, 3 H, CH_3 at C-3), 2.09–2.27 (m, 2 H, CH_2CH_3), 3.14 (dd, 1 H, *J* = 13.9 Hz, CHHPh), 3.31, 3.37, 3.39 (3 s, each 3 H, OCH_3 × 3), 3.90 (dd, 1 H, *J* = 13.9 Hz, CHHPh), 4.57–4.75 (m, 8 H, H-9, H-1 of the side chain at C-2, OCH_2O × 3), 4.78 (dd, 1 H, *J* = 7.8, 9.5 Hz, H-2 of the side chain at C-2), 5.35 (dd, 1 H, *J* = 9.5, 11.0 Hz, H-3 of the side chain at C-2), 5.78 (dt, 1 H, *J* = 11.0, 7.3 Hz, H-4 of the side chain at C-2), 5.97 (br s, 1 H, OH), 7.27–7.38 (m, 5 H, C_6H_5); ^{13}C NMR (75 MHz) δ 5.6, 14.1, 21.3, 42.2, 55.6, 55.9, 56.3, 71.2, 73.8, 85.5, 86.5, 91.3, 94.2, 95.1, 97.1, 114.2, 125.4, 127.4, 128.8 × 2, 130.8 × 2, 134.5, 138.7, 163.2, 184.7, 197.6; HRMS calcd for $C_{27}H_{35}NO_9$ ($M^+ - H_2O$) *m/z* 517.2311, found 517.2319.

(5*S*,8*S*,9*R*)-8-Benzoyl-2-[(1*S*,2*S*,3*Z*)-1,2-bis(methoxymethoxy)-3-hexenyl]-8-hydroxy-9-methoxymethoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (105).



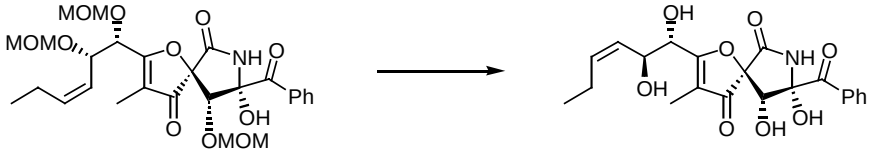
A solution of **100** (24.5 mg, 45.7 μmol) in 5% AcOH in *i*-PrOH (5 mL) was stirred at 70 °C for 66 h, and concentrated in vacuo to provide crude enamide **104** (27.7 mg) as a 5:4 geometric mixture (^{1}H NMR analysis), which was used directry in the next step. In a small-scale experiment, a pure inseparable geometric mixture of **104** was obtained by column chromatography on silica gel (EtOAc/hexane, 2:5) as a colorless oil: TLC R_f 0.27 (EtOAc/hexane, 1:2); IR (neat) 3260, 1750, 1695, 1635 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.99 (t, 3 H × 4/9, *J* = 7.3 Hz, CH_2CH_3), 1.02 (t, 3 H × 5/9, *J* = 7.3 Hz, CH_2CH_3), 1.81 (s, 3 H × 5/9, CH_3 at C-3), 1.82 (s, 3 H × 4/9, CH_3 at C-3), 2.12–2.26 (m, 2 H, CH_2CH_3), 3.32, 3.33, 3.38, 3.40, 3.43 (5 s, 3 H × 4/9 + 3 H ×

5/9 + 3 H × 4/9 + 3 H + 3 H × 5/9, OC$\underline{H}_3$ × 3), 4.53−4.83 (m, 8 H, H-1, 2 of the side chain at C-2, OC$\underline{H}_2$O × 3), 4.91 (s, 1 H × 4/9, H-9), 5.28 (d, 1 H × 5/9, *J* = 1.7 Hz, H-9), 5.32−5.42 (m, 1 H, H-3 of the side chain at C-2), 5.80 (dt, 1 H, *J* = 10.7, 7.3 Hz, H-4 of the side chain at C-2), 5.93 (s, 1 H × 4/9, C$\underline{H}$Ph), 5.96 (d, 1 H × 5/9, *J* = 1.7 Hz, C$\underline{H}$Ph), 7.24−7.31, 7.35−7.41 (2 m, 3 H + 2 H, $C_6\underline{H}_5$), 7.79 (br s, 1 H × 4/9, N$\underline{H}$), 7.81 (br s, 1 H × 5/9, N$\underline{H}$); HRMS calcd for $C_{27}H_{35}NO_9$ (M^+) *m/z* 517.2311, found 517.2307.

The following reaction was carried out under Ar. To a stirred solution of crude enamide **104** (27.7 mg) in CH_2Cl_2 (2 mL) was added 50 mM (1 M = 1 mol·dm^{-1}) mCPBA solution in CH_2Cl_2 (3.66 mL, 183 μmol). After being stirred at rt for 5 h, the solution was diluted with EtOAc (15 mL), and washed with saturated aqueous Na_2SO_3 (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and saturated brine (5 mL). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column on silica gel with excess EtOAc/hexane (1:1), and the combined eluates were concentrated in vacuo to give crude product (10.5 mg), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude benzyl alcohol (10.5 mg) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (16.1 mg, 38.0 μmol). The mixture was stirred at rt for 11 h, diluted with EtOAc (10 mL), and washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous Na_2CO_3 (5 mL × 2). The organic layer was dried and concentrated in vasuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:5) to provide 9.3 mg (37% from **100**) of **105** as a colorless oil: TLC R_f 0.49 (EtOAc/hexane, 1:1); $[\alpha]_D^{25}$ −68.7 (*c* 0.225, $CHCl_3$); IR (neat) 3260, 1750, 1695, 1680, 1620 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.01 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.86 (s, 3 H, C$\underline{H}_3$ at C-3), 2.07−2.27 (m, 2 H, C$\underline{H}_2$CH$_3$), 3.17, 3.32, 3.38 (3 s, each 3 H, OC$\underline{H}_3$ × 3), 4.56−4.69 (m, 6 H, OC$\underline{H}_2$O × 3), 4.74 (d, 1 H, *J* = 6.8 Hz, H-1 of the side chain at C-2), 4.80 (dd, 1 H, *J* = 6.8, 9.5 Hz, H-2 of the side chain at C-2), 5.13 (s, 1 H, H-9), 5.36 (dd, 1 H, *J* = 9.5, 11.0 Hz, H-3 of the side chain at C-2), 5.80 (dt, 1 H, *J* = 11.0, 7.6 Hz, H-4 of the side chain at C-2), 6.61 (s, 1 H, O$\underline{H}$), 6.83 (br s, 1 H, N$\underline{H}$), 7.49 (t, 2 H, *J* = 7.3 Hz, H-3, 5 of Ph), 7.62 (t, 1 H, *J* = 7.3 Hz, H-4 of Ph), 8.34 (d, 2 H, *J* = 7.3 Hz, H-2, 6 of Ph); ^{13}C NMR (75 MHz) δ 5.7, 14.0, 21.3, 55.7, 56.0, 56.4, 71.5, 74.1, 75.8, 87.9, 92.6, 94.2, 95.3, 96.5, 114.3, 125.2, 128.6 × 2, 130.9 × 2, 133.1, 134.1, 138.9, 163.0, 188.3, 192.2, 199.8; HRMS calcd for $C_{27}H_{34}NO_{10}$ (M^+ − OH) *m/z* 532.2183, found 532.2183. NOE experiment; 1.7% enhancement of the H-2, 6 of Ph (δ 8.34) was observed when H-9 (δ 5.13) was irradiated, and 1.4% enhancement of the H-9 (δ 5.13) was observed when H-2, 6 of Ph (δ 8.34) was irradiated.

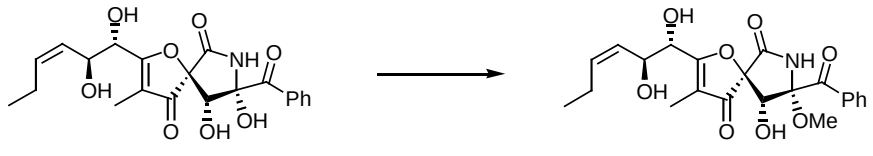
(5*S*,8*S*,9*R*)-8-Benzoyl-2-[(1*S*,2*S*,3*Z*)-1,2-dihydroxy-3-hexenyl]-8,9-dihydroxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (Pseurotin F_2) (6).



105 pseurotin F_2 (**6**)

Compound **105** (9.3 mg, 17 μmol) was dissolved in 6 M (1 M = 1 mol·dm^{-1}) aqueous HCl/MeOH (1:1, v/v, 1 mL). After being stirred at rt for 8 h, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to provide 6.3 mg (89%) of **6** (pseurotin F_2) as colorless crystals: mp 94.4–95.0 °C; TLC R_f 0.29 (acetone/toluene, 1:2); $[\alpha]_D^{25}$ +78.0 (*c* 0.165, $CHCl_3$); $[\alpha]_D^{20}$ −31.4 (*c* 0.100, MeOH); IR (neat) 3380, 3300, 1730, 1695, 1630 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.01 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.69 (s, 3 H, $C\underline{H}_3$ at C-3), 2.03−2.24 (m, 2 H, $C\underline{H}_2CH_3$), 4.64 (d, 1 H, *J* = 4.2 Hz, H-1 of the side chain at C-2), 4.78 (dd, 1 H, *J* = 4.2, 8.9 Hz, H-2 of the side chain at C-2), 4.87 (s, 1 H, H-9), 5.16 (dd, 1 H, *J* = 8.9, 11.0 Hz, H-3 of the side chain at C-2), 5.57 (dt, 1 H, *J* = 11.0, 7.3 Hz, H-4 of the side chain at C-2), 6.83 (s, 1 H, O<u>H</u>), 7.49 (t, 2 H, *J* = 7.3 Hz, H-3, 5 of Ph), 7.64 (t, 1 H, *J* = 7.3 Hz, H-4 of Ph), 8.40 (d, 2 H, *J* = 7.3 Hz, H-2, 6 of Ph), 8.55 (br s, 1 H, N<u>H</u>); ^{13}C NMR (75 MHz) δ 6.3, 14.1, 21.4, 70.8, 71.6, 71.7, 89.1, 94.8, 113.0, 126.2, 128.6 × 2, 131.4 × 2, 133.0, 134.6, 136.5, 164.8, 188.9, 193.8, 198.8; HRMS calcd for $C_{21}H_{21}NO_7$ ($M^+ - H_2O$) *m/z* 399.1318, found 399.1318. NOE experiment; 2.1% enhancement of the H-2, 6 of Ph (δ 8.40) was observed when H-9 (δ 4.87) was irradiated, and 2.6% enhancement of the H-9 (δ 4.87) was observed when H-2, 6 of Ph (δ 8.40) was irradiated.

(5*S*,8*S*,9*R*)-8-Benzoyl-2-[(1*S*,2*S*,3*Z*)-1,2-dihydroxy-3-hexenyl]-9-hydroxy-8-methoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (Pseurotin A) (1).



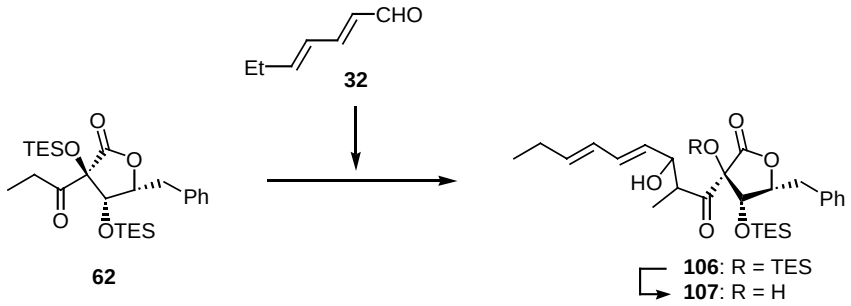
pseurotin F_2 (**6**) pseurotin A (**1**)

To a stirred solution of **6** (pseurotin F_2) (5.2 mg, 13 μmol) in MeOH (1 mL) was added CSA (4.3 mg, 19 μmol). After being stirred for 8 h at 40 °C, the solution was neutralized with saturated aqueous $NaHCO_3$ at 0 °C, diluted with saturated brine (5 mL), and extracted with EtOAc (5 mL × 5). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel

(EtOAc/hexane, 1:1) to provide 2.2 mg (41%) of **1** (pseurotin A) as colorless crystals: mp 126.0−126.9 °C; TLC R_f 0.50 (acetone/toluene, 1:1); $[\alpha]_D^{25}$ +70.8 (*c* 0.110, $CHCl_3$); $[\alpha]_D^{24}$ −8.1 (*c* 0.110, MeOH); IR (neat) 3400, 3280, 1730, 1680, 1635 cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.68 (s, 3 H, $C\underline{H}_3$ at C-3), 2.05−2.24 (m, 2 H, $C\underline{H}_2CH_3$), 3.44 (s, 3 H, $OC\underline{H}_3$), 4.59 (d, 1 H, *J* = 4.4 Hz, H-1 of the side chain at C-2), 4.70 (s, 1 H, H-9), 4.75 (dd, 1 H, *J* = 4.4, 9.0 Hz, H-2 of the side chain at C-2), 5.28 (dd, 1 H, *J* = 9.0, 11.0 Hz, H-3 of the side chain at C-2), 5.60 (dt, 1 H, *J* = 11.0, 7.6 Hz, H-4 of the side chain at C-2), 7.49 (t, 2 H, *J* = 7.3 Hz, H-3, 5 of Ph), 7.65 (t, 1 H, *J* = 7.3 Hz, H-4 of Ph), 8.27 (br s, 1 H, N<u>H</u>), 8.32 (d, 2 H, *J* = 7.3 Hz, H-2, 6 of Ph); ^{13}C NMR (75 MHz) δ 6.1, 14.1, 21.4, 51.7, 70.6, 70.9, 73.0, 90.3, 92.8, 113.4, 126.4, 128.7 × 2, 130.7 × 2, 132.3, 134.8, 136.8, 166.6, 185.8, 195.1, 196.3; HRMS calcd for $C_{21}H_{21}NO_7$ ($M^+ - CH_3OH$) *m/z* 399.1318, found 399.1318. NOE experiment; 4.5% enhancement of the H-2, 6 of Ph (δ 8.32) was observed when H-9 (δ 4.70) was irradiated, and 5.4% enhancement of the H-9 (δ 4.70) was observed when H-2, 6 of Ph (δ 8.32) was irradiated. No enhancement of the H-9 (δ 4.70) was observed when $OC\underline{H}_3$ (δ 3.44) was irradiated.

Experimental Procedures for Chapter 5

(2*S*,3*S*,4*R*)-4-Benzyl-2-hydroxy-2-[(4*E*,6*E*)-3-hydroxy-2-methylnona-4,6-dienoyl]-3-triethylsilyloxy-4-butanolide (107).

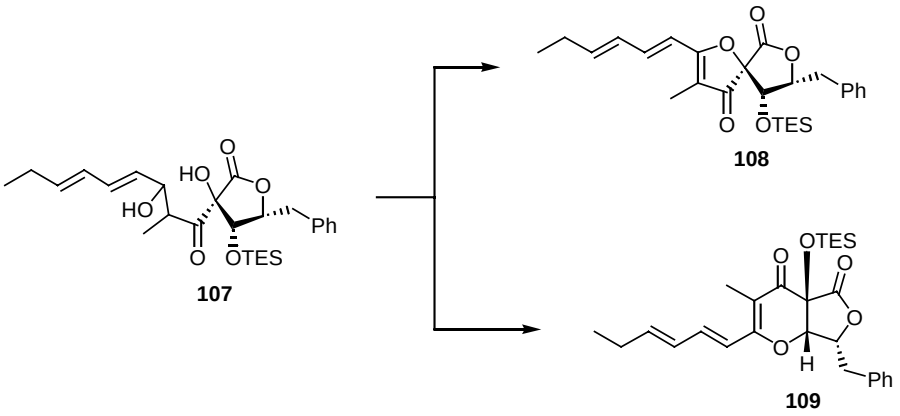


The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **62** (251 mg, 509 μmol) in THF (8 mL) was added dropwise potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution in toluene, 1.0 mL, 0.51 mmol). The solution was stirred at −78 °C for 1 h, and a solution of (2*E*,4*E*)-2,4-heptadienal (**32**) (353 μL, 2.54 mmol) with anhydrous LiBr (265 mg, 3.05 mmol) in THF (2 mL) were added. After being stirred at −78 °C for 1 h, the solution was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was diluted with EtOAc (50 mL), and washed with saturated aqueous NH_4Cl (30 mL) and saturated brine (30 mL). The organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:30), and the combined eluates were concentrated in vacuo to provide crude aldol product **106** (261 mg), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude aldol product **106** (261 mg) in pyridine (5 mL) was added a dilute solution of HF·pyridine complex in pyridine (1:125, v/v, 2 mL). The solution was stirred for 1 h, and additional solution of HF·pyridine complex in pyridine (1:125, v/v, 2 mL × 2) was added every 1 h.

The solution was stirred for total 3 h, and quenched with saturated aqueous $NaHCO_3$ (15 mL) at 0 °C. The resulting mixture was diluted with EtOAc (100 mL), and washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated brine (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20 to 1:6) to provide 146 mg (59% from **62**) of **107** as a colorless oil: TLC R_f 0.19 (EtOAc/hexane, 1:6); $[\alpha]_D^{26}$ +83.8 (*c* 1.99, $CHCl_3$); IR (neat) 3300, 1790, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.64−0.75 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 0.95−1.06 (m, 15 H, $Si(CH_2C\underline{H}_3)_3$), $CH_2C\underline{H}_3$, $C\underline{H}_3$-2 of the side chain at C-2), 2.06−2.19 (m, 2 H, $C\underline{H}_2CH_3$), 2.91 (dd, 1 H, *J* = 2.5, 14.7 Hz, C<u>H</u>HPh), 3.18 (dd, 1 H, *J* = 10.5, 14.7 Hz, CH<u>H</u>Ph), 3.88 (dq, 1 H, *J* = 5.0, 6.8 Hz, H-2 of the side chain at C-2), 4.27 (dd, 1 H, *J* = 5.0, 9.2 Hz,), 4.72 (ddd, 1 H, *J* = 2.5, 8.2, 10.5 Hz, H-3 of the side chain at C-2), 4.76 (d, 1 H, *J* = 8.2 Hz, H-3), 5.48 (dd, 1 H, *J* = 9.2, 14.9 Hz, H-4 of the side chain at C-2), 5.82 (dt, 1 H, *J* = 14.9, 6.6 Hz, H-7 of the side chain at C-2), 6.06 (dd, 1 H, *J* = 10.5, 14.9 Hz, H-6 of the side chain at C-2), 6.20 (dd, 1 H, *J* = 10.5, 14.9 Hz, H-5 of the side chain at C-2), 7.19−7.34 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.6 × 3, 6.6 × 3, 12.3, 13.2, 25.6, 34.7, 45.3, 76.8, 77.9, 82.2, 84.4, 126.3, 126.5, 128.0, 128.4 × 2, 129.3 × 2, 135.8, 137.9, 138.9, 174.1, 211.0; HRMS calcd for $C_{27}H_{40}O_6Si$ (M^+) *m/z* 488.2594, found 488.2599.

(5*S*,8*R*,9*S*)-8-Benzyl-2-[(1*E*,3*E*)-hexa-1,3-dienyl]-3-methyl-9-triethylsilyloxy-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (108) and (1*S*,6*R*,9*R*)-9-Benzyl-3-[(1*E*,3*E*)-hexa-1,3-dienyl]-4-methyl-6-triethylsilyloxy-2,8-dioxabicyclo[4.3.0]non-3-ene-5,7-dione (109).

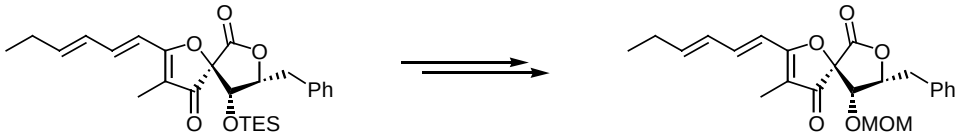


To a cooled (0 °C) stirred solution of **107** (160 mg, 326 μmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (277 mg, 653 μmol). The mixture was stirred for 3 h at rt, diluted with EtOAc (50 mL), and washed with saturated aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL × 2). The

organic layer was dried and concentrated in vacuo. The residue was eluted through a short column of silica gel with excess EtOAc/hexane (1:10), and the combined eluates were concentrated in vacuo to provide a crude mixture of 1,7-dioxaspiro[4.4]nonane derivative and 2,8-dioxabicyclo[4.3.0]nonane derivative (121 mg), which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of crude mixture of 1,7-dioxaspiro[4.4]nonane derivative and 2,8-dioxabicyclo[4.3.0]nonane derivative (121 mg) in pyridine (3 mL) was added thionyl chloride (48.0 μL, 658 μmol). After being stirred at 0 °C for 30 min, the solution was quenched with saturated aqueous $NaHCO_3$ (3 mL), diluted with EtOAc (50 mL), and washed with saturated aqueous $NaHCO_3$ (15 mL) and saturated brine (15 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 63.5 mg (42% from **107**) of **108** and 36.7 mg (24% from **107**) of **109**. Compound **108** was obtained as a colorless oil: TLC R_f 0.39 (EtOAc/ hexane, 1:6); $[\delta]_D^{24}$ +18.0 (*c* 1.58, $CHCl_3$); IR (neat) 1790, 1695, 1680, 1650, 1635, 1615 cm^{-1}; ^1H NMR (300 MHz) δ 0.48−0.57 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 0.88 (t, 9 H, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.08 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.78 (s, 3 H, $C\underline{H}_3$ at C-3), 2.20−2.36 (m, 2 H, $C\underline{H}_2CH_3$), 3.30 (dd, 1 H, *J* = 3.4, 15.4 Hz, C<u>H</u>HPh), 3.75 (dd, 1 H, *J* = 10.7, 15.4 Hz, CH<u>H</u>Ph), 4.84 (ddd, 1 H, *J* = 3.4, 8.1, 10.7 Hz, H-8), 5.03 (d, 1 H, *J* = 8.1 Hz, H-9), 6.17−6.37 (m, 3 H, H-1, 3, 4 of the side chain at C-2), 7.16 (dd, 1 H, *J* = 9.3, 15.1 Hz, H-2 of the side chain at C-2), 7.27− 7.34 (m, 5 H, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.4 × 3, 5.6, 6.4 × 3, 12.8, 26.2, 36.3, 74.1, 82.5, 89.1, 110.9, 114.8, 126.5, 128.4 × 3, 129.4 × 2, 137.9, 139.9, 146.8, 167.5, 179.2, 194.2; HRMS calcd for $C_{27}H_{36}O_5Si$ (M^+) *m/z* 468.2332, found 468.2332. Compound **109** was obtained as a colorless oil: TLC R_f 0.31 (EtOAc/hexane, 1:6); $[\alpha]_D^{28}$ +126 (*c* 0.620, $CHCl_3$); IR (neat) 1790, 1690, 1680, 1650, 1630, 1610 cm^{-1}; ^1H NMR (300 MHz) δ 0.56−0.68 (m, 6 H, $Si(C\underline{H}_2CH_3)_3$), 0.95 (t, 9 H, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.09 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.76 (s, 3 H, $C\underline{H}_3$ at C-4), 2.20−2.32 (m, 2 H, $C\underline{H}_2CH_3$), 2.93 (dd, 1 H, *J* = 4.1, 14.9 Hz, C<u>H</u>HPh), 3.22 (dd, 1 H, *J* = 9.3, 14.9 Hz, CH<u>H</u>Ph), 4.48 (d, 1 H, *J* = 3.3 Hz, H-1), 5.31 (ddd, 1 H, *J* = 3.3, 4.1, 9.3 Hz, H-9), 6.17−6.39 (m, 3 H, H-1, 3, 4 of the side chain at C-3), 7.22−7.35 (m, 6 H, H-2 of the side chain at C-3, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 4.7 × 3, 5.8, 6.7 × 3, 12.8, 26.3, 35.3, 74.3, 82.4, 89.6, 110.0, 114.6, 126.8, 128.4, 128.6 × 2, 129.2 × 2, 136.5, 140.9, 147.4, 168.0, 179.9, 195.7; HRMS calcd for $C_{27}H_{36}O_5Si$ (M^+) *m/z* 468.2332, found 468.2334.

(5*S*,8*R*,9*S*)-8-Benzyl-2-[(1*E*,3*E*)-hexa-1,3-dienyl]-9-mehtoxymethoxy-3-methyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (110).

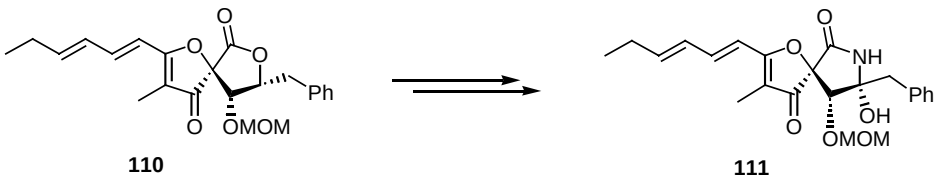


108 **110**

To a cooled (0 °C) stirred solution of **108** (50.0 mg, 107 μmol) in pyridine (5 mL) was added dropwise HF·pyridine complex (0.5 mL). After being stirred at rt for 6 h, the solution was quenched with saturated aqueous $NaHCO_3$ (10 mL), diluted with EtOAc (80 mL), and washed with saturated aqueous $NaHCO_3$ (30 mL) and saturated brine (30 mL). The organic layer was dried and concentrated in vacuo to provide crude alcohol (38.8 mg), which was used directly in the next step.

To a cooled (0 °C) stirred suspension of P_2O_5 (75.7 mg, 533 mmol) in $CH_2(OMe)_2$ (3 mL) was added a solution of crude alcohol (38.8 mg) in CH_2Cl_2 (1 mL). After being stirred at 0 °C for 2 h, the mixture was quenched with saturated aqueous Na_2CO_3 (5 mL), diluted with EtOAc (50 mL), and washed with saturated aqueous Na_2CO_3 (15 mL) and saturated brine (15 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 30.5 mg (72% from **108**) of **110** as a colorless oil: TLC R_f 0.51 (EtOAc/hexane, 1:2); $[\alpha]_D^{28}$ +81.3 (*c* 0.335, $CHCl_3$); IR (neat) 1790, 1695, 1615 cm^{-1}; ^1H NMR (300 MHz) δ 1.07 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.81 (s, 3 H, $C\underline{H}_3$ at C-3), 2.17−2.30 (m, 2 H, $C\underline{H}_2CH_3$), 3.25 (s, 3 H, $OC\underline{H}_3$), 3.34 (dd, 1 H, *J* = 4.4, 15.1 Hz, C<u>H</u>HPh), 3.72 (dd, 1 H, *J* = 9.5, 15.1 Hz, CH<u>H</u>Ph), 4.54 (s, 2 H, $OC\underline{H}_2O$), 4.90−5.03 (m, 2 H, H-8, 9), 6.20−6.37 (m, 3 H, H-1, 3, 4 of the side chain at C-2), 7.13−7.24, 7.28−7.34 (2 m, 2 H + 4 H, H-2 of the side chain at C-2, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 5.8, 12.9, 26.3, 36.5, 56.2, 77.8, 81.0, 88.1, 96.9, 110.8, 114.8, 126.6, 128.4, 128.5 × 2, 129.4 × 2, 137.4, 140.3, 147.2, 167.1, 179.5, 194.3; HRMS calcd for $C_{23}H_{26}O_6$ (M^+) *m/z* 398.1729, found 398.1729.

(5*S*,8*R*,9*R*)-8-Benzyl-2-[(1*E*,3*E*)-hexa-1,3-dienyl]-8-hydroxy-9-mehtoxymethoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (111).

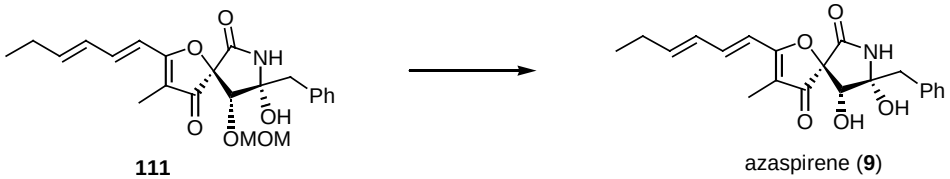


110 **111**

To a cooled (0 °C) stirred solution of **110** (29.1 mg, 73.0 μmol) in *i*-PrOH (2 mL) was added a saturated NH_3 solution in *i*-PrOH (4 mL). After being stirred at 0 °C for 1 h, the solution was concentrated in vacuo to provide crude amide derivative (31.8 mg), which was used directly in the next step.

To a cooled (0 °C) stirred solution of crude amide derivative (31.8 mg) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (62.0 mg, 146 μmol). The mixture was stirred for 4 h, diluted with EtOAc (50 mL), and washed with saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous Na_2CO_3 (10 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 25.8 mg (85% from **110**) of **111** as yellow crystals: mp 141.7−142.2 °C; TLC R_f 0.41 (EtOAc/hexane, 1:1); $[\alpha]_D^{21}$ −87.4 (*c* 0.450, $CHCl_3$); IR (neat) 3280, 1730, 1715, 1680, 1615 cm^{-1}; ^1H NMR (300M Hz) δ 1.06 (t, 3 H, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.78 (s, 3 H, $C\underline{H}_3$ at C-3), 2.18−2.29 (m, 2 H, $C\underline{H}_2CH_3$), 3.00, 3.35 (AB q, each 1 H, *J* = 13.7 Hz, $C\underline{H}_2Ph$), 3.33 (s, 3 H, $OC\underline{H}_3$), 4.46 (s, 1 H, H-9), 4.66 (s, 2 H, $OC\underline{H}_2O$), 6.22−6.36 (m, 3 H, H-1, 3, 4 of the side chain at C-2), 7.27−7.39 (m, 6 H, H-2 of the side chain at C-2, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 5.7, 12.8, 26.3, 43.6, 56.2, 79.4, 84.8, 92.3, 96.9, 110.7, 114.6, 127.5, 128.4, 128.7 × 2, 130.5 × 2, 134.6, 141.4, 148.0, 164.8, 182.1, 198.0; HRMS calcd for $C_{23}H_{27}NO_6$ (M^+) *m/z* 413.1838, found 413.1847. NOE experiment; 7.5% enhancement of the H-9 (δ 4.46) was observed when C<u>H</u>HPh (δ 3.00) was irradiated, and 5.1% enhancement of the C<u>H</u>HPh (δ 3.00) was observed when H-9 (δ 4.46) was irradiated.

(5*S*,8*R*,9*R*)-8-Benzyl-2-[(1*E*,3*E*)-hexa-1,3-dienyl]-8,9-dihydroxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (Azaspirene) (9).



111 azaspirene (**9**)

Compound **111** (4.4 mg, 11 μmol) was dissolved in 6 M (1 M = 1 mol·dm^{-1}) aqueous HCl/MeOH (1:1, v/v, 1 mL). After being stirred for 10 h at rt, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2, then MeOH/$CHCl_3$, 1:25) to provide 2.0 mg (51%) of **9** (azaspirene) as yellow crystals: mp 165.5−166.0 °C; TLC R_f 0.38 (EtOAc/hexane, 1:1); $[\alpha]_D^{23}$ −204 (*c* 0.100, MeOH); IR (KBr) 3250, 1735, 1715, 1675, 1610 cm^{-1}; ^1H NMR (300 MHz) δ 1.07 (t, 3 H, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 1.76 (s, 3 H, $C\underline{H}_3$ at C-3), 2.24 (dq, 2 H, *J* = 4.6, 7.3 Hz, $C\underline{H}_2CH_3$), 2.96, 3.27 (2 d, each 1 H, *J* = 13.9 Hz, $C\underline{H}_2Ph$), 2.98 (d, 1 H, *J* = 10.0 Hz, O<u>H</u>), 4.50 (d, 1 H, *J* = 10.0 Hz, H-9), 6.02 (br s,

1 H, O<u>H</u>), 6.23−6.36 (m, 3 H, H-1, 3, 4 of the side chain at C-2), 6.56 (br s, 1 H, N<u>H</u>), 7.25−7.38 (m, 6 H, H-2 of the side chain at C-2, $C_6\underline{H}_5$); ^{13}C NMR (75 MHz) δ 5.6, 12.8, 26.3, 42.8, 74.7, 84.5, 93.2, 110.6, 114.6, 127.6, 128.4, 128.8 × 2, 130.4 × 2, 134.2, 142.1, 148.3, 165.0, 183.3, 198.4; HRMS calcd for $C_{21}H_{23}NO_5$ (M^+) *m/z* 369.1576, found 369.1572.

References

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