 

# Total Syntheses of Natural Pseurotins A, $F_2$, and Azaspirene

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We describe the total syntheses of natural pseurotins A and $F_2$, inhibitors of chitin synthase, both of which possess an unusual 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione ring system. The total syntheses of these spiro-hetereocyclic natural products feature: 1) a stereoselective preparation of two segments, i.e., a 2,3-dihydroxylated heptenal derivative and a highly functionalized $\gamma$-lactone, each from D-glucose, 2) the connection of the 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 $\gamma$-lactone into a $\gamma$-lactam hemiaminal derivative, and 5) conversion of the benzyl substituent in the $\gamma$-lactam ring into a benzoyl group via a cyclic enamide followed by *m*-CPBA oxidation in the final stage of the total synthesis. In the initial stage, the quaternary spiro-carbon center in the target molecules was efficiently constructed by a stereochemically exclusive vinyl Grignard addition to the D-glucose-derived 3-ulose. Furthermore, the preparation of the $\gamma$-lactone included a stereo- and regioselective Cu(I)-mediated benzyl Grignard addition to aldehyde. We have also completed the total synthesis of a structurally related novel angiogenesis inhibitor, azaspirene, using the analogous reaction sequence.

Over the past three decades, structurally as well as biologically intriguing hetero-spirocyclic $\gamma$-lactam-type antibiotics have been found in nature. Pseurotin A (**1**) (Fig. 1), isolated from the culture filtrate of *Pseudeurotium ovalis* (Ascomycetes) by Tamm et al. in 1976,[1a] is a representative example of this class of secondary microbial metabolites. The structure of pseurotin A (**1**), including its relative and absolute stereochemistries, was determined by a combination of spectroscopic analysis and chemical modification,[1a] and finally by a single-crystal X-ray analysis of its 12,13-dibromo derivative.[1b] Pseurotin $F_2$ (8-*O*-demethylpseurotin A) (**2**) was first isolated from *Aspergillus fumigatus* DSM 6598 as an antagonist of apomorphine.[2] Compound **2** 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 $\gamma$-lactams related to pseurotins were reported. Synerazol (**3**) was isolated from a cultured broth of *A. fumigatus* SANK 10588 as an antifungal antibiotic.[5] FD-838 (**4**) was isolated from *A. fumigatus fresenius* F-838, which induces the differentiation of leukemia in culture and inhibits the growth of certain Gram-positive bacteria and fungi.[6] All of these natural products, **1**–**4**, 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**–**3**) or a furan ring (for **4**) at C2 and a benzoyl group at C8 (for **1**–**4**). Recently, azaspirene (**5**) 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 **5** is similar to those of **1**–**4**, the structure of **5** is characterized by an *E*,*E*-conjugate hexadiene side chain at C2 and a benzyl group instead of the benzoyl group at C8. In regard to synthetic studies on these natural products, some approaches toward the pseurotins family have been reported so far by the Tamm group[8] and by us.[9] In 2002, Hayashi and co-workers reported the first total synthesis of natural (−)-azaspirene (**5**).[10] We describe here the details of our total syntheses of natural **1**, **2**, and **5**.[11] Quite recently, Hayashi's group reported the asymmetric total syntheses of **1** and **2**.[12]

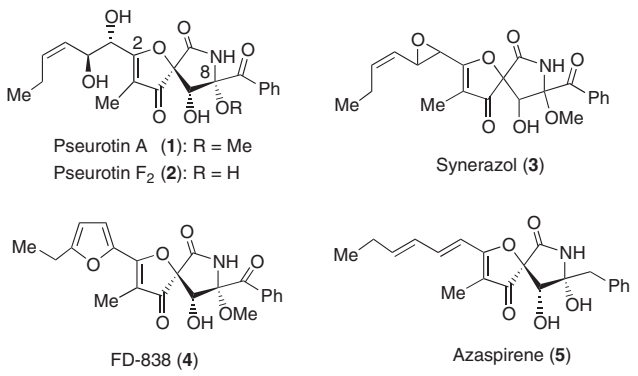


Fig. 1. Structures of the spiro-heterocyclic $\gamma$-lactam natural products **1**–**5**.

## Results and Discussion

Our initial synthetic approach to **1** and **2** is outlined in Scheme 1. We envisioned that the pseurotins **1** and **2** would be obtained from $\gamma$-benzoylated $\gamma$-lactone **6**, which contains all of the requisite carbon skeleton with correct stereogenic centers, via construction of the spiro-3(2*H*)-furanone substructure, transformation of the $\gamma$-lactone to a $\gamma$-lactam, and final adjustment of the oxidation level at C8. This advanced inter-

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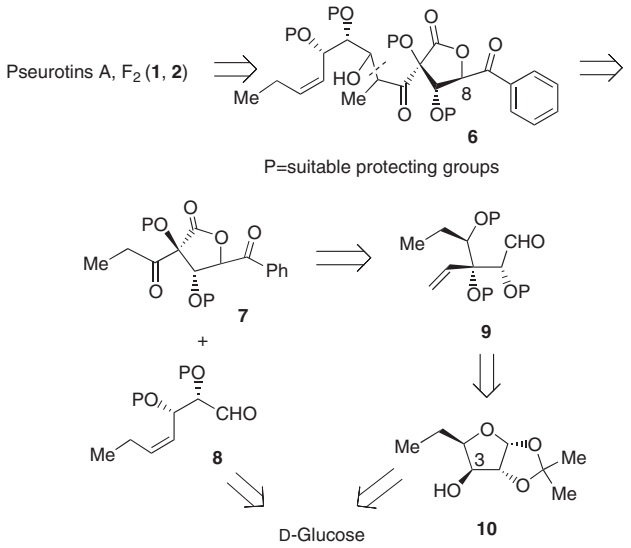


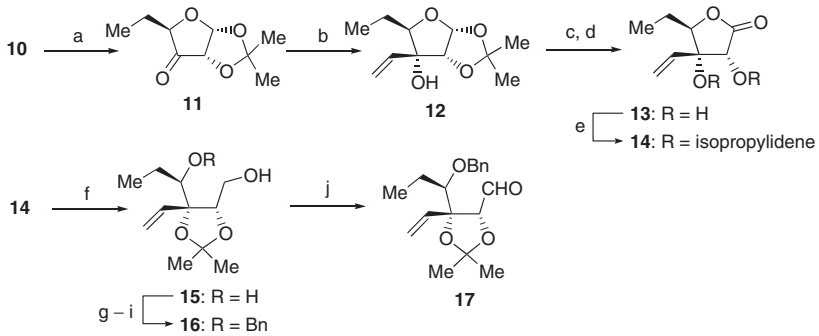

Scheme 1.

mediate **6** would be prepared by the aldol-type connection of a $\gamma$-lactone **7** equipped with an ethyl ketone moiety to a seven-carbon olefinic aldehyde **8** corresponding to the left-side chain. The preparation of the side-chain equivalent **8** was originally reported by the Tamm group.[8a] The aldol partner **7** could be obtained from an acyclic hexose derivative **9** via the installation of a benzoyl group, followed by the formation of the $\gamma$-lactone via an oxidative cleavage of the vinyl group. This functionalized branched deoxy hexose **9** 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-$\alpha$-D-*xylo*-hexofuranose (**10**), in turn prepared from D-glucose in six convenient steps.[13]

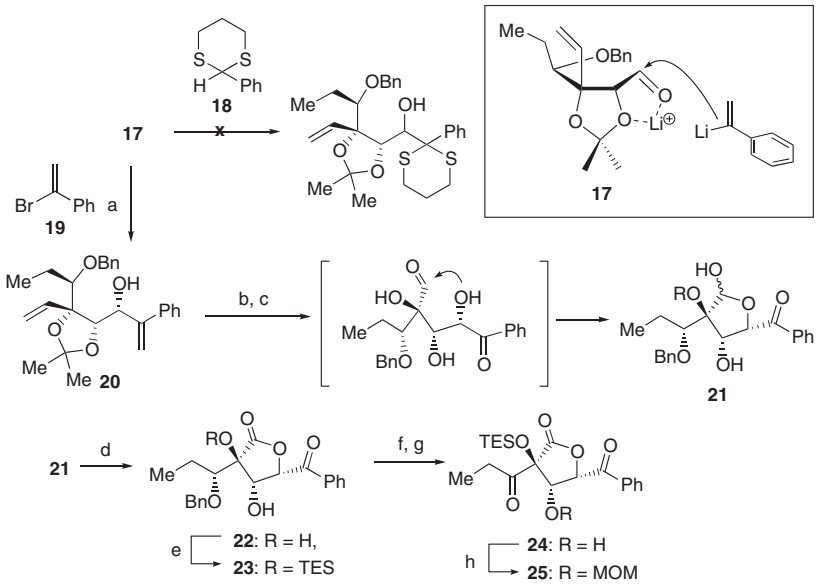
The synthesis of **17**, a suitably protected form of acyclic 5,6-dideoxy-aldohexose **9**, from **10** is summarized in Scheme 2. The oxidation of **10** with pyridinium chlorochromate (PCC), followed by the usual vinyl Grignard addition to the resultant 3-ulose **11**, provided the adduct **12** as a single diastereoisomer. The vinyl nucleophile attacked exclusively from the convex face of the trioxabicyclo[3.3.0]octane structure of **11**. The acidic hydrolysis of the acetal moiety in **12**, and subsequent chemoselective oxidation of the hemiacetal carbon with *N*-iodosuccinimide (NIS) in the presence of *n*-$Bu_4NI$,[14] provided $\gamma$-lactone-$\alpha,\beta$-diol **13**. The *cis*-diol in **13** was protected as an isopropylidene acetal **14**, which was treated with $LiAlH_4$ to provide a ring-opened diol **15**. A three-step protection/deprotection process from **15** via a trityl ether provided an acyclic suitably protected intermediate **16**. Dess–Martin oxidation[15] of **16** produced the aldehyde **17**.

The introduction of a benzoyl equivalent into **17** was next investigated. First, we chose 2-phenyl-1,3-dithiane (**18**) as a benzoyl equivalent (Scheme 3). However, the addition of the 2-lithio-1,3-dithiane generated from **18** to **17** did not proceed cleanly. On the other hand, the reaction of **17** with 1-lithiated 1-phenylethene, prepared from 1-bromo-1-phenylethene (**19**) and *t*-BuLi (2 molar amt.) in $Et_2O$ at $-78$ °C, proceeded smoothly to produce the 2-phenylallyl alcohol **20** as a single stereoisomer. The introduced (*R*)-stereogenic center in **20** was determined by NOE experiments of **22**. As shown in Scheme 3, this diastereoselective nucleophilic addition of the 1-lithiated 1-phenylethene to **17** can be explained on the basis that the lithium-ion-associated five-membered chelate formation occurs between the aldehyde oxygen and one of the acetal oxygens in **17**, to which the nucleophile attacks from the less-hindered $\beta$-side, leading to **20**. The simultaneous ozonolytic cleavage of the two carbon–carbon double bonds in **20**, followed by acidic hydrolysis of the acetal moiety, spontaneously formed a five-membered hemiacetal **21**, which was oxidized with NIS to $\gamma$-benzoyl-$\gamma$-lactone-$\alpha,\beta$-diol **22**. The tertiary hydroxy group in **22** could be selectively protected as a triethylsilyl (TES) ether to provide **23**. We suppose that this selective protection of the tertiary hydroxy group may be attributable to the electric effect of both the $\gamma$-lactone carbonyl and the benzoyl carbonyl, although a steric reason can not be excluded. Hydrogenolysis of the benzyl group in **23**, 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 **24**. Then, the secondary hydroxy group in **24** was protected as a methoxymethyl (MOM) ether to give **25** (P = TES and MOM in **7**), the substrate for the aldol reaction.

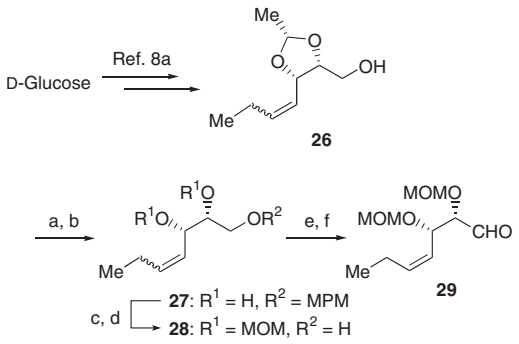
The coupling partner for the aldol reaction of **25**, the aldehyde **29** (P = MOM in **8**), was synthesized from D-glucose according to the reported procedure[8a] with an improvement of the *Z*-olefin introduction. For preparing the known compound **26**, we used potassium bis(trimethylsilyl)amide (KHMDS) as a




Scheme 2. Reagents and conditions: (a) PCC, MS4A, $CH_2Cl_2$; (b) $CH_2$=CHMgBr, THF, $-18$ °C (83% for 2 steps); (c) 80% aqueous AcOH, 80 °C; (d) NIS, *n*-$Bu_4NI$, $CH_2Cl_2$ (95% for 2 steps); (e) $Me_2C(OMe)_2$, $Me_2CO$, CSA, reduced pressure (ca. 300 hPa), 40 °C (79%); (f) $LiAlH_4$, THF, 0 °C (91%); (g) TrCl, DMAP, pyr, reflux; (h) BnBr, NaH, DMF; (i) CSA, MeOH, EtOAc (84% for 3 steps); (j) Dess–Martin periodinane, $CH_2Cl_2$ (96%).

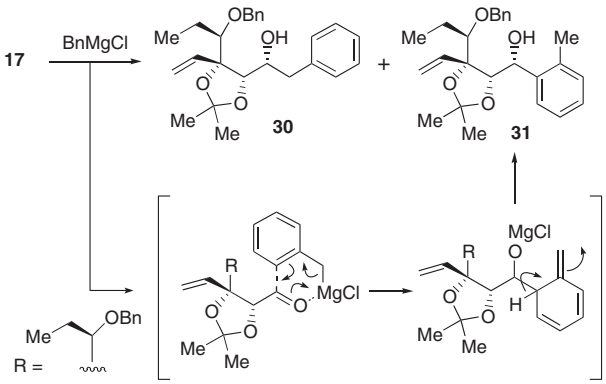


Scheme 3. Reagents and conditions: (a) **19** (2.0 equiv), *t*-BuLi (4.0 mol. amt.), $Et_2O$, −78 °C; then **17** (94%); (b) $O_3$, $CH_2Cl_2$, −78 °C; $Ph_3P$; (c) 60% aqueous TFA; (d) NIS, *n*-$Bu_4NI$, $CH_2Cl_2$ (57% from **20**); (e) TESOTf, pyr (91%); (f) $H_2$, 10% Pd on C, EtOAc; (g) IBX, DMSO (87% for 2 steps); (h) $CH_2(OMe)_2$, $P_2O_5$, $CH_2Cl_2$ (98%).



Scheme 4. Reagents and conditions: (a) MPMCl, NaH, DMF; (b) Amberlyst 15 ($H^+$), MeOH (91% for 2 steps); (c) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$; (d) DDQ, $CH_2Cl_2/H_2O$ (15:1, v/v); (e) separation of the geometrical isomers on silica gel (*Z*-isomer: 88% from **27**, *E*-isomer: 7% from **27**); (f) $(COCl)_2$, DMSO, $CH_2Cl_2$; $Et_3N$, −78 °C to rt (89%).

base for the Wittig olefination of the intermediary aldehyde to introduce a carbon–carbon double bond. Under our conditions, the selectivity was significantly improved (*Z*:*E* = 14:1) (Scheme 4). Swern oxidation[17] of **26** provided the aldehyde (not shown), which was unstable on silica gel to purify. Thus, we planned to prepare a more stable aldol partner by changing the acetal protecting group in **26** to vicinal *O*-MOM groups. The transformation of **26** to di-*O*-MOM ether **28** via *O*-*p*-methoxyphenylmethyl (MPM) ether **27** was conducted straightforwardly. At this stage, the *E*-geometrical isomer was cleanly removed. The Swern oxidation of the *Z*-isomer **28** provided **29**. We attempted the aldol connection of **25** with **29** under a variety of reaction conditions. Unfortunately, all of the cases examined resulted in the formation of a complex mixture of products, or the decomposition of **25**. Although lacking firm evidence, we considered that the presence of the



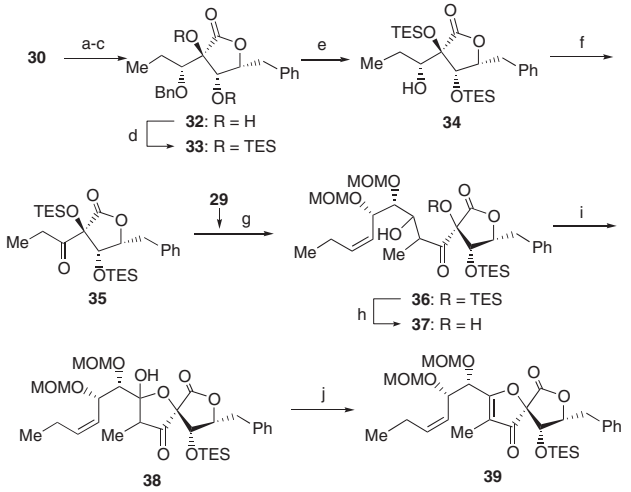
Scheme 5.

benzoyl moiety caused the instability of the substrate **25** under the basic conditions. We concluded that a more reliable synthetic approach would be to replace the benzoyl group with a benzyl group.

For the introduction of a benzyl group as a synthetic precursor of a benzoyl group, we investigated the benzyl Grignard addition to the aldehyde **17**. Using excess benzylmagnesium chloride in THF at room temperature, we obtained a mixture of the desired benzyl adduct **30** (14%) and the undesired and abnormal 2-methylphenyl (*ortho*-tolyl) adduct **31** (51%) along with a 9% recovery of **17** (Scheme 5). As shown, the 2-methylphenyl adduct **31** 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 **30** was slightly improved by the addition of an equal amount of $CeCl_3$[19] in the reaction mixture (26% of **30**, 36% of **31**, and 22% recovery of **17**). We were 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 **30**. As a result, the benzyl adduct

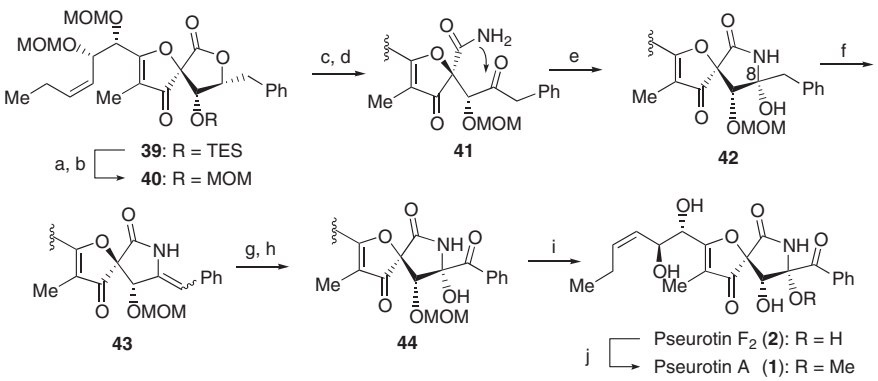
**30** was isolated in 89% yield along with a small amount (2%) of **31**. It was considered that the addition of the Cu(I) salt suppressed the formation of the six-membered transition state; thus, the expected normal addition occurred preferentially. Similar to the case involving the formation of **20**, the configuration of a newly introduced secondary alcohol carbon in **30** was determined as shown, after converting to the $\gamma$-lactone **32**.

The ozonolysis of **30** and successive hydrolytic removal of the acetal, followed by the chemoselective oxidation of the resultant $\gamma$-lactol with NIS, eventually provided $\gamma$-lactone **32** (Scheme 6). We examined the selective protection of the tertiary hydroxy group in **32**, as we had done in the case of **22**. Unfortunately, all attempts to protect the tertiary hydroxy group selectively, as *O*-TBS, *O*-TES, *O*-TMS, *O*-MOM or *O*-THP, failed. In the case of the *O*-TES protection, we obtained the desired mono-*O*-TES ether in a less-practical yield of 66% along with the di-*O*-TES derivative **33** in 24% yield (4.5 mol. amts. of TESOTf, lutidine, $CH_2Cl_2$, $-40$ to $-20$ °C). From this mono-*O*-TES derivative, we prepared the aldol substrate corresponding to **25** (not shown, a benzyl group in place of the benzoyl). Contrary to our expectation, the aldol reaction of this substrate with **29** did not provide any aldol adduct. Consequently, we selected di-*O*-TES derivative **33** as a synthetic precursor of the aldol substrate **35**. Thus, two hydroxy groups in **32** were protected as vicinal di-*O*-TES ether to provide **33** using slightly excess of TESOTf at 50 °C. Deprotection of the benzyl group in **33** by hydrogenolysis, followed by Dess–Martin oxidation of the resultant **34**, provided ethyl ketone **35**. The aldol reaction of **35** and aldehyde **29** was best achieved using 1.0 molar amount of KHMDS as a base in THF at $-78$ °C to produce the aldol product **36** with a high level of diastereoselectivity.[21] We did not determine the stereochemistry of the aldol adduct. Exposure of **36** to a dilute solution of hydrogen fluoride–pyridine complex in pyridine[22] selectively cleaved the TES group attached to the tertiary alcohol, giving **37**. Dess–Martin oxidation of **37**, followed by dehydration of the resultant spirocyclic five-membered hemiketal $\gamma$-lactone **38** with thionyl chloride, provided the desired spirocyclic 3(2*H*)-furanone **39**.




Scheme 6. Reagents and conditions: (a) $O_3$, $CH_2Cl_2$, $-78$ °C; $Ph_3P$; (b) 60% aqueous TFA; (c) NIS, $n$-$Bu_4NI$, $CH_2Cl_2$ (84% from **30**); (d) TESOTf, pyr, 50 °C (95%); (e) $H_2$, 10% Pd on C, EtOH (94%); (f) Dess–Martin periodinane, $CH_2Cl_2$ (98%); (g) KHMDS (1.0 mol. amt.), THF, $-78$ °C; then **29** (3.0 mol. amt.); (h) HF·pyr, pyr, THF; (i) Dess–Martin periodinane, $CH_2Cl_2$ (46% from **35**); (j) $SOCl_2$, pyr, 0 °C (97%).

In Scheme 7, the final steps for the total syntheses of **1** and **2** are illustrated. We examined the installation of a $\gamma$-lactam nitrogen atom to **39** by a variety of reagents, such as aqueous ammonia, ammonium acetate with catalytic sodium cyanide,[23] or 1,1,1,3,3,3-hexamethyldisilazane.[24] None of these conditions gave useful results. Finally, we found that a treatment of **39** with saturated $NH_3$ in *i*-PrOH resulted in a $\gamma$-lactone ring-opened amidation accompanied by cleavage of the TES group. Therefore, the TES group in **39** was replaced by an MOM group prior to ammonolysis.[25] After de-*O*-silylation of **39**, followed by etherification under acidic conditions provided the MOM ether **40** in good yield. The ammonolysis of **40** with saturated $NH_3$ in *i*-PrOH, followed by Dess–Martin oxidation, provided the ring-opened amide ketone **41**. By exposing **41** to saturated aqueous $Na_2CO_3$, an intramolecular attack of the amide-nitrogen to the carbonyl occurred to form the hemiaminal **42** (a $\gamma$-hydroxy-$\gamma$-lactam) as the predominant $\alpha$-anomer,




Scheme 7. Reagents and conditions: (a) HF·pyr, pyr, THF; (b) $CH_2(OMe)_2$, $P_2O_5$, $CH_2Cl_2$, 0 °C (98% for 2 steps); (c) saturated $NH_3$ in *i*-PrOH; (d) Dess–Martin periodinane, $CH_2Cl_2$; (e) saturated aqueous $Na_2CO_3$ (**42**: 81% for 3 steps, C8-$\beta$-isomer: 16% for 3 steps); (f) 5% AcOH in *i*-PrOH, 70 °C; (g) *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$; (h) Dess–Martin periodinane, $CH_2Cl_2$ (37% for 3 steps); (i) 6 M HCl/MeOH (1:1, v/v) (89%); (j) CSA, MeOH, 40 °C (41%).

along with the $\beta$-anomer (not shown) in a ratio of approximately 5:1. The anomers were separable by column chromatography on silica gel. The stereochemistry of the $\alpha$-anomeric carbon (C8) in **42** was determined by NOE experiments. After some experimentation, we found that the dehydrated enamide **43** was formed as an inseparable *E*,*Z*-mixture by heating **42** in 5% acetic acid in *i*-PrOH.[26,27] The $\beta$-isomer of **42** also provided a mixture of the *E*,*Z*-enamides **43** under similar acidic conditions. To our delight, the formation of the desired $\gamma$-hydroxy-$\gamma$-lactam, carrying a benzoyl side-chain, was successfully achieved by the regioselective epoxidation of the enamide double bond in **43** with *m*-CPBA,[28] 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. We could not isolate the intermediary epoxide. On the other hand, the treatment of **43** with dimethyldioxirane[29] gave undesired overoxidation products. In this case, epoxidation of the left-hand side-chain double bond was observed. Osmium tetraoxide in alcoholic solvents[30] provided a mixture of degradation products. Singlet oxygen[31] provided **42** via the hydration of the enamide moiety. Potassium permanganate in the presence of $CuSO_4 \cdot 5H_2O$[32] did not work. Removal of all the *O*-MOM groups in **44** by acidic hydrolysis completed the total sysnthesis of natural pseurotin $F_2$ (**2**). The spectroscopic data of synthetic **2** matched well with those reported for natural **2**.[3] Furthermore, methyl acetalization of **2** 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).

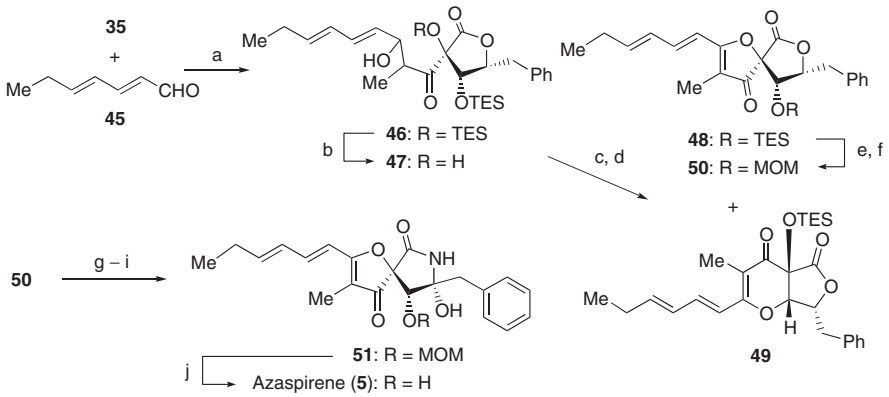
Our next concern focused on the total synthesis of azaspirene (**5**). The total synthesis was accomplished starting from the union of the intermediate **35** and commercially available (2*E*,4*E*)-2,4-heptadienal (**45**) (Scheme 8). Deprotonation of **35** with KHMDS in THF at $-78$ °C, followed by the addition of **45** in the presence of 5.0 molar amounts of LiBr,[33] provided the aldol adduct **46** as a sole product. The stereochemistry of **46** was not determined. When the reaction was conducted in the absence of LiBr, **46** was not formed.[34] Exposure of **46** to a dilute solution of HF·pyridine complex in pyridine selectively cleaved the *O*-TES group on the tertiary alcohol to provide **47**. The Dess–Martin oxidation of **47**, followed by dehydration of the resultant $\gamma$-lactone hemiketal with thionyl chloride, provided the desired 1,7-dioxaspiro[4.4]non-2-ene-4,6-dione **48**, along with a 2,8-dioxabicyclo[4.3.0]non-3-ene-5,7-dione **49**.[35] The spirocyclic $\gamma$-lactone **48** was converted into the hemiaminal **51** (a $\gamma$-oxgenated-$\gamma$-lactam) via the *O*-MOM ether **50** by the same reaction sequence used for the conversion of **39** into **42**. Hydrolysis of the *O*-MOM group in **51** completed the total synthesis of azaspirene (**5**). Synthetic **5** was identical to an authentic sample of natural **5** in all respects (mp, $[\alpha]_D$, IR, $^1$H and $^{13}$C NMR, HRMS, TLC).[7]

In conclusion, we completed the total syntheses of natural pseurotins A (**1**) and $F_2$ (**2**) using D-glucose as an enantiomeric pure starting material. The spiro-carbon in **1** and **2** was constructed by the stereoselective vinyl Grignard addition at C3 of the D-glucose-derived ulose **11**. The synthesis of an advanced intermediate **39**, a highly functionalized 1,7-dioxaspiro[4.4]non-2-ene-4,6-dione, featured 1) the Cu(I)-mediated benzyl Grignard addition to a functionalized hexanal derivative **17** and 2) the aldol reaction of a keto $\gamma$-lactone **35** with a seven-carbon aldehyde **29**. Transformation of the $\gamma$-lactone **40** derived from **35** to the $\gamma$-oxygenated-$\gamma$-lactam **42**, followed by benzylic oxidation, eventually provided pseurotins $F_2$ (**2**), and then A (**1**). By a similar synthetic venture including the aldol reaction of the common intermediate **35** with LiBr-coordinated dienal **45**, the total synthesis of natural azaspirene (**5**) was also completed.

## Experimental

**General Methods.** 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 a $CDCl_3$ solution with tetramethylsilane as an internal standard. $^{13}$C NMR spectra were recorded at 75 MHz in a $CDCl_3$ solution. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 $F_{254}$ plates. The crude reaction mixtures and extractive materials were purified by chromatography on Daisogel IR-60 (Daiso) or Wakogel C-300 (Wako). Combined organic extracts were concentrated under reduced pressure using an evaporator with a water bath at 35–45 °C.

**(2*R*,3*R*,4*R*,5*R*)-5-Ethyl-4-hydroxy-2,3-isopropylidenedioxy-4-vinyltetrahydrofuran (12).** To a cooled (0 °C) stirred solution




Scheme 8. Reagents and conditions: (a) KHMDS (1.0 mol. amt.), THF, $-78$ °C; then **45** (5.0 mol. amt.), LiBr (5.0 mol. amt.); (b) HF·pyr, pyr, THF (59% from **35**); (c) Dess–Martin periodinane, $CH_2Cl_2$; (d) $SOCl_2$, pyr, 0 °C (42% for **48** and 24% for **49** from **47**); (e) HF·pyr, pyr, THF; (f) $CH_2(OMe)_2$, $P_2O_5$, $CH_2Cl_2$, 0 °C (72% for 2 steps); (g) saturated $NH_3$ in *i*-PrOH; (h) Dess–Martin periodinane, $CH_2Cl_2$; (i) saturated aqueous $Na_2CO_3$ (85% for 3 steps); (j) 6 M HCl/MeOH (1:1, v/v) (51%).

of **10** (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 room temperature 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 **11** (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 **11** (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 **10**) of **12** 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) $\delta$ 0.98 (t, 3H, $J = 7.3$ Hz), 1.36, 1.60 (2 s, each 3H), 1.49 (quint, 2H, $J = 7.3$ Hz), 2.68 (s, 1H, OH), 3.70 (t, 1H, $J = 7.3$ Hz), 4.20 (d, 1H, $J = 3.9$ Hz), 5.28 (dd, 1H, $J = 1.7$, 11.0 Hz), 5.49 (dd, 1H, $J = 1.7$, 17.3 Hz), 5.75 (dd, 1H, $J = 11.0$, 17.3 Hz), 5.80 (d, 1H, $J = 3.9$ Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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*R*,4*R*)-4-Ethyl-2,3-dihydroxy-3-vinyl-4-butanolide (13).** Compound **12** (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 a crude $\gamma$-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 $\gamma$-lactol derivative (6.99 g) in $CH_2Cl_2$ (100 mL) were added *n*-$Bu_4NI$ (18.9 g, 51.2 mmol) and NIS (19.2 g, 85.4 mmol). The mixture was stirred at room temperature 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 **12**) of **13** 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) $\delta$ 1.03 (t, 3H, $J = 7.3$ Hz), 1.42–1.57, 1.64–1.77 (2 m, each 1H), 3.60 (br s, 2H, OH × 2), 4.30 (dd, 1H, $J = 3.7$, 10.7 Hz), 4.56 (s, 1H), 5.42 (dd, 1H, $J = 0.7$, 10.7 Hz), 5.60 (dd, 1H, $J = 0.7$, 17.1 Hz), 5.93 (dd, 1H, $J = 10.7$, 17.1 Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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*R*,4*R*)-4-Ethyl-2,3-isopropylidenedioxy-3-vinyl-4-butanolide (14).** To a stirred solution of **13** (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 **14** 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) $\delta$ 1.02 (t, 3H, $J = 7.3$ Hz), 1.31–1.48, 1.65–1.81 (2 m, each 1H), 1.42, 1.44 (2 s, each 3H), 4.44 (dd, 1H, $J = 3.7$, 9.8 Hz), 4.66 (s, 1H), 5.42 (dd, 1H, $J = 1.1$, 10.7 Hz), 5.58 (dd, 1H, $J = 1.1$, 17.1 Hz), 5.98 (dd, 1H, $J = 10.7$, 17.1 Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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 (15).** To a cooled (0 °C) stirred solution of **14** (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 **15** 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) $\delta$ 0.99 (t, 3H, $J = 7.3$ Hz), 1.18–1.30, 1.74–1.88 (2 m, each 1H), 1.39, 1.44 (2 s, each 3H), 2.54 (br s, 1H, OH), 3.67 (dd, 1H, $J = 2.2$, 10.3 Hz), 3.92–4.06 (m, 3H), 5.26 (dd, 1H, $J = 2.0$, 11.0 Hz), 5.49 (dd, 1H, $J = 2.0$, 17.2 Hz), 6.14 (dd, 1H, $J = 11.0$, 17.2 Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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 (16).** To a stirred solution of **15** (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 trityl ether (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 room temperature, 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 at room temperature 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 **15**) of **16** 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) $\delta$ 1.03 (t, 3H, $J = 7.7$ Hz), 1.41, 1.47 (2 s, each 3H), 1.60–1.74, 1.84–1.99 (2 m, each 1H), 2.37 (br s, 1H, OH), 3.57 (dd, 1H, $J = 3.7$, 5.1 Hz), 3.79 (d, 2H, $J = 6.6$ Hz), 3.98 (t, 1H, $J = 6.6$ Hz), 4.37, 4.69 (AB q, each 1H, $J = 10.7$ Hz), 5.19 (dd, 1H, $J = 2.0$, 10.7 Hz), 5.53 (dd, 1H, $J = 2.0$, 17.1 Hz), 6.17 (dd, 1H, $J = 10.7$, 17.1 Hz), 7.25–7.38 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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-vinylhexanal (17).** To a cooled (0 °C) stirred solution of **16** (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 room temperature, 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 **17** 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) $\delta$ 1.01 (t, 3H, $J = 7.7$ Hz), 1.42, 1.59 (2 s, each 3H), 1.53–1.67, 1.71–1.85 (2 m, each 1H), 3.40 (t, 1H, $J = 5.1$ Hz), 4.19, 4.50 (AB q, each 1H, $J = 11.0$ Hz), 4.35 (s, 1H), 5.31 (dd, 1H, $J = 1.7$, 11.0 Hz), 5.61 (dd, 1H, $J = 1.7$, 17.3 Hz), 6.27 (dd, 1H, $J = 11.0$, 17.3 Hz), 7.24–7.37 (m, 5H), 9.51 (s, 1H); $^{13}C$ NMR (75 MHz) $\delta$ 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 (20).** The following reaction was carried out under Ar. To a cooled (−78 °C) solution of 1-bromo-1-phenylethene (**19**) (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 **17** (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 **20** 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) $\delta$ 1.01 (t, 3H, $J = 7.6$ Hz), 1.29, 1.52 (2 s, each 3H), 1.56–1.70, 1.75–1.90 (2 m, each 1H), 3.16 (br s, 1H, OH), 3.93 (t, 1H, $J = 5.0$ Hz), 3.84 (d, 1H, $J = 1.5$ Hz), 4.66 (s, 2H), 5.07 (dd, 1H, $J = 1.7$, 11.0 Hz), 5.24 (br s, 1H), 5.33 (dd, 1H, $J = 1.7$, 17.3 Hz), 5.35–5.37 (m, 1H), 5.44 (d, 1H, $J = 1.2$ Hz), 6.13 (dd, 1H, $J = 11.0$, 17.3 Hz), 7.18–7.43 (m, 10H); $^{13}C$ NMR (75 MHz) $\delta$ 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 (22).** To a cooled (−78 °C) stirred solution of **20** (686 mg, 1.68 mmol) in $CH_2Cl_2$ (10 mL) was bubbled ozone ($O_2$ containing ca. 3% $O_3$) for 15 min until a light blue color persisted. 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 warming to rt for an additional 1 h. The solvent was removed by evaporation in vacuo to provide a crude aldehyde derivative (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 room temperature, the solution was neutralized with 5 M (1 M = 1 mol $dm^{-3}$) 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 EtOAc/hexane (1:2), and the combined eluates were concentrated in vacuo to provide crude $\gamma$-lactol **21** (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 $\gamma$-lactol **21** (890 mg) in $CH_2Cl_2$ (10 mL) were added *n*-$Bu_4NI$ (620 mg, 1.68 mmol) and NIS (633 mg, 2.81 mmol). The solution was stirred at room temperature for 24 h, and additional NIS (633 mg × 2, 2.81 mmol × 2) was added every 12 h. The solution was stirred for a total of 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 **20**) of **22** 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) $\delta$ 1.07 (t, 3H, $J = 7.3$ Hz), 1.67–1.95 (m, 2H), 3.87 (dd, 1H, $J = 3.9$, 8.5 Hz), 4.58 (d, 1H, $J = 2.8$ Hz), 4.70, 5.15 (AB q, each 1H, $J = 10.0$ Hz), 5.76 (d, 1H, $J = 2.8$ Hz), 7.26–7.40, 7.42–7.47 (2 m, 3H + 2H), 7.52 (t, 2H, $J = 7.1$ Hz), 7.67 (t, 1H, $J = 7.1$ Hz), 8.07 (d, 2H, $J = 7.1$ Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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 ($\delta$ 5.76) was observed when H-3 ($\delta$ 4.58) was irradiated, and 8.0% enhancement of H-3 was observed when H-4 was irradiated.

**(2*S*,3*S*,4*S*)-4-Benzoyl-2-[(1*R*)-1-(benzyloxy)propyl]-3-hydroxy-2-triethylsiloxy-4-butanolide (23).** The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **22** (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 room temperature, 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 **23** 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) $\delta$ 0.33–0.43 (m, 6H), 0.79 (t, 9H, $J = 7.9$ Hz), 1.06 (t, 3H, $J = 7.3$ Hz), 1.49–1.61, 1.69–1.82 (2 m, each 1H), 3.79 (dd, 1H, $J = 2.4$, 9.7 Hz), 4.66, 5.17 (AB q, each 1H, $J = 10.0$ Hz), 4.70 (d, 1H, $J = 3.4$ Hz), 5.85 (d, 1H, $J = 3.4$ Hz), 7.28–7.39, 7.44–7.49 (2 m, 3H + 2H), 7.51 (t, 2H, $J = 7.3$ Hz), 7.63 (t, 1H, $J = 7.3$ Hz), 8.04 (d, 2H, $J = 7.3$ Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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, 128.7 × 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 ($\delta$ 5.85) was observed when H-3 ($\delta$ 4.70) was irradiated, and 9.7% enhancement of the H-3 was

observed when H-4 was irradiated.

**(2*S*,3*S*,4*S*)-4-Benzoyl-3-hydroxy-2-(1-propanoyl)-2-triethylsiloxy-4-butanolide (24).** A solution of **23** (231 mg, 476 mmol) in EtOAc (5 mL) was stirred under atmospheric $H_2$ in the presence of 10% Pd on charcoal (41.0 mg) for 1 day, and an additional 10% Pd on charcoal (41.0 mg × 2) was added every 1 day. The mixture was stirred for a total of 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 room temperature, 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 **24** 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.09–0.31 (m, 6H), 0.69 (t, 9H, $J = 7.8$ Hz), 1.13 (t, 3H, $J = 7.1$ Hz), 2.79, 2.84 (2 dq, each 1H, $J = 15.4$, 7.1 Hz), 4.84 (br s, 1H, OH), 5.03 (d, 1H, $J = 7.6$ Hz), 6.14 (d, 1H, $J = 7.6$ Hz), 7.53 (t, 2H, $J = 7.8$ Hz), 7.66 (t, 1H, $J = 7.8$ Hz), 7.96 (d, 2H, $J = 7.8$ Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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 ($\delta$ 6.14) was observed when H-3 ($\delta$ 5.03) was irradiated, and 13.4% enhancement of the H-3 was observed when H-4 was irradiated.

**(2*S*,3*S*,4*S*)-4-Benzoyl-3-methoxymethoxy-2-(1-propanoyl)-2-triethylsiloxy-4-butanolide (25).** 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 **24** (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 **25** 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) $\delta$ 0.15–0.36 (m, 6H), 0.73 (t, 9H, $J = 8.1$ Hz), 1.09 (t, 3H, $J = 7.1$ Hz), 2.56, 3.21 (2 dq, each 1H, $J = 20.0$, 7.1 Hz), 3.36 (s, 3H), 4.70, 4.94 (AB q, each 1H, $J = 6.8$ Hz), 4.98 (d, 1H, $J = 3.7$ Hz), 5.81 (d, 1H, $J = 3.7$ Hz), 7.52 (t, 2H, $J = 7.3$ Hz), 7.65 (t, 1H, $J = 7.3$ Hz), 8.02 (d, 2H, $J = 7.3$ Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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 ($\delta$ 5.81) was observed when H-3 ($\delta$ 4.98) was irradiated, and 15.8% enhancement of the H-3 was observed when H-4 was irradiated.

**(2*R*,3*S*,4*Z*)-2,3-(Ethylidenedioxy)hept-4-en-1-ol (26) and 4*E*-Isomer.** The following reaction was carried out under Ar. To a stirred suspension of propyltriphenylphosphonium bromide (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 room temperature for 1.5 h, and 2,3-ethylidenedioxy-D-erythrofuranose[8a] (5.01 g, 34.3 mmol) was added. After being stirred at room temperature 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 **26** (*Z*/*E* = ca. 14:1, determined by $^1H$ NMR analysis) as a colorless oil. Spectroscopic data for **26**; see Ref. 8a.

**(2*R*,3*S*,4*Z*)-1-(4-Methoxybenzyloxy)hept-4-ene-2,3-diol (27) and 4*E*-Isomer.** To a cooled (0 °C) stirred solution of **26** (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 at room temperature for 5 h, 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 to 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% from **26**) of **27** (*Z*/*E* = ca. 14:1, determined by $^1H$ 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.98 (t, 3H, $J = 7.6$ Hz), 1.96–2.23 (m, 2H), 2.59 (br s, 2H, OH × 2), 3.56 (dd, 1H, $J = 4.2$, 9.8 Hz), 3.60 (dd, 1H, $J = 5.9$, 9.8 Hz), 3.74 (dt, 1H, $J = 5.9$, 4.2 Hz), 3.80 (s, 3H), 4.47 (s, 2H), 4.53 (dd, 1H, $J = 4.2$, 9.3 Hz), 5.36 (dd, 1H, $J = 9.3$, 11.0 Hz), 5.60 (dt, 1H, $J = 11.0$, 7.6 Hz), 6.85–6.91, 7.22–7.28 (2 m, 2H + 2H); $^{13}C$ NMR (75 MHz) $\delta$ 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 (28) and 4*E*-Isomer.** To a cooled (0 °C) stirred solution of **27** (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 at room temperature for 8 h, 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 2,3-bis(methoxymethyl ether) (5.78 g), which was used directly in the next step. To a cooled (0 °C) stirred suspension of crude 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 at room temperature for 12 h, 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 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 **27**) of **28** and 260 mg (7%) of **4*E*-isomer**. The *Z*-isomer **28** 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) $\delta$ 0.99 (t, 3H, $J = 7.6$ Hz), 2.04–2.22 (m, 2H), 3.38, 3.43 (2 s, each 3H),

3.64 (dt, 1H, $J = 9.5$, 4.9 Hz), 3.63–3.74 (m, 2H), 4.50–4.57 (m, 1H), 4.53, 4.67 (AB q, each 1H, $J = 6.6$ Hz), 4.73, 4.75 (AB q, each 1H, $J = 6.8$ Hz), 5.25–5.34 (m, 1H), 5.73 (dt, 1H, $J = 10.7$, 7.6 Hz); $^{13}$C NMR (75 MHz) $\delta$ 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. The **4*E*-isomer** 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$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.01 (t, 3H, $J = 7.6$ Hz), 2.04–2.15 (m, 2H), 3.38, 3.43 (2 s, each 3H), 3.61–3.66, 3.69–3.72 (2 m, 1H + 2H), 4.11 (dd, 1H, $J = 4.4$, 8.3 Hz), 4.54, 4.71 (AB q, each 1H, $J = 6.6$ Hz), 4.73, 4.76 (AB q, each 1H, $J = 6.8$ Hz), 5.32–5.41 (m, 1H), 5.79 (dt, 1H, $J = 15.6$, 6.3 Hz); $^{13}$C NMR (75 MHz) $\delta$ 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-enal (29).** 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 **28** (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 room temperature. 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 **29** 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$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 0.98 (t, 3H, $J = 7.6$ Hz), 1.98–2.22 (m, 2H), 3.36, 3.42 (2 s, each 3H), 4.04 (dd, 1H, $J = 2.0$, 4.6 Hz), 4.53, 4.67 (AB q, each 1H, $J = 6.8$ Hz), 4.74, 4.78 (AB q, each 1H, $J = 6.6$ Hz), 4.73–4.77 (m, 1H), 5.34–5.43 (m, 1H), 5.76 (dt, 1H, $J = 11.0$, 7.3 Hz), 9.67 (d, 1H, $J = 2.0$ Hz); $^{13}$C NMR (75 MHz) $\delta$ 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*R*,3*S*,4*R*,5*R*)-5-Benzyloxy-3,4-isopropylidenedioxy-1-phenyl-4-vinylheptan-2-ol (30) and (1*R*,2*S*,3*R*,4*R*)-4-Benzyloxy-2,3-isopropylidenedioxy-1-(2-methylphenyl)-3-vinylhexan-1-ol (31).** The following reaction was carried out under Ar. To a cooled (0 °C) solution of **17** (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 **30** and 125 mg (2%) of **31**. Compound **30** 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$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.00 (t, 3H, $J = 7.6$ Hz), 1.41, 1.54 (2 s, each 3H), 1.56–1.72, 1.77–1.91 (2 m, each 1H), 2.78 (dd, 1H, $J = 8.3$, 13.7 Hz), 2.90 (dd, 1H, $J = 5.4$, 13.7 Hz), 3.74 (d, 1H, $J = 3.9$ Hz), 3.78 (t, 1H, $J = 4.9$ Hz), 4.26 (ddd, 1H, $J = 3.9$, 5.4, 8.3 Hz), 4.56, 4.66 (AB q, each 1H, $J = 11.2$ Hz), 5.17 (dd, 1H, $J = 2.0$, 11.0 Hz), 5.45 (dd, 1H, $J = 2.0$, 17.2 Hz), 6.19 (dd, 1H, $J = 11.0$, 17.2 Hz), 7.16–7.31, (m, 10H); $^{13}$C NMR (75 MHz) $\delta$ 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 **31** 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) $\delta$ 1.05 (t, 3H, $J = 7.6$ Hz), 1.37, 1.59 (2 s, each 3H), 1.60–1.75, 1.80–1.96 (2 m, each 1H), 2.12 (s, 3H), 3.28 (br s, 1H, OH), 3.96 (s, 1H), 3.98 (t, 1H, $J = 4.9$ Hz), 4.71 (s, 2H), 5.20 (dd, 1H, $J = 2.0$, 11.0 Hz), 5.49 (dd, 1H, $J = 2.0$, 17.2 Hz), 5.53 (s, 1H), 6.31 (dd, 1H, $J = 11.0$, 17.2 Hz), 7.05–7.37, 7.45–7.48 (2 m, 8H + 1H); $^{13}$C NMR (75 MHz) $\delta$ 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 ($\delta$ 5.53) and 6.7% enhancement of the H-2 ($\delta$ 3.96) were observed when $CH_3$ of the tolyl group ($\delta$ 2.12) was irradiated.

**(2*S*,3*S*,4*R*)-4-Benzyl-2-[(1*R*)-1-(benzyloxy)propyl]-2,3-dihydroxy-4-butanolide (32).** To a cooled (−78 °C) stirred solution of **30** (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 until a light-blue color persisted. To this solution was added $Ph_3P$ (971 mg, 3.70 mmol), and the solution was stirred at −78 °C for 30 min and for an additional 1 h warming to room temperature. The solvent was removed by evaporation in vacuo to provide a crude aldehyde derivative (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 at room temperature for 9 h, the solution was neutralized with 5 M 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 EtOAc/hexane (1:2), and the combined eluates were concentrated in vacuo to provide the crude $\gamma$-lactol derivative (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 $\gamma$-lactol derivative (1.21 g) in $CH_2Cl_2$ (20 mL) were added $n$-$Bu_4NI$ (2.05 g, 5.55 mmol) and NIS (2.08 g, 9.24 mmol). The solution was stirred at room temperature 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 **30**) of **32** 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$^{-1}$; $^1$H NMR (300 MHz) $\delta$ 1.03 (t, 3H, $J = 7.3$Hz), 1.64–1.75 (m, 2H), 2.61, 3.63 (2 br s, each 1H, OH × 2), 2.99 (dd, 1H, $J = 7.3$, 13.9 Hz), 3.17 (dd, 1H, $J = 7.3$, 13.9 Hz), 3.78 (t, 1H, $J = 6.3$ Hz), 3.97 (br d, 1H, $J = 2.9$ Hz), 4.64, 5.08 (AB q, each 1H, $J = 10.3$ Hz), 4.92 (dt, 1H, $J = 2.9$, 7.3 Hz), 7.20–7.42 (m, 10H); $^{13}$C NMR (75 MHz) $\delta$ 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 ($\delta$ 4.92) was observed when H-3 ($\delta$ 3.97) was irradiated, and 7.5% enhancement of the H-3 was observed when H-4 was irradiated.

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

**(triethylsiloxy)-4-butanolide (33).** The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **32** (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 **33** 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) $\delta$ 0.60–0.77 (m, 12H), 0.91 (t, 9H, $J = 7.9$ Hz), 1.03 (t, 9H, $J = 7.8$ Hz), 1.06 (t, 3H, $J = 7.3$ Hz), 1.78–1.89, 1.90–2.06 (2 m, each 1H), 2.80 (dd, 1H, $J = 3.2$, 15.1 Hz), 2.90 (dd, 1H, $J = 10.3$, 15.1 Hz), 3.72 (dd, 1H, $J = 4.2$, 7.6 Hz), 4.56 (d, 1H, $J = 7.1$ Hz), 4.65, 4.82 (AB q, each 1H, $J = 11.2$ Hz), 4.75 (ddd, 1H, $J = 3.2$, 7.1, 10.3 Hz), 6.97–7.01, 7.1–7.45 (2 m, 2H + 8H); $^{13}C$ NMR (75 MHz) $\delta$ 4.9 × 3, 5.8 × 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-hydroxypropyl]-2,3-bis(triethylsiloxy)-4-butanolide (34).** A solution of **33** (2.20 g, 3.76 mmol) in EtOH (100 mL) was stirred under atmospheric $H_2$ 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 **34** 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.57–0.74 (m, 12H), 0.90 (t, 9H, $J = 7.6$ Hz), 1.02 (t, 9H, $J = 7.8$ Hz), 1.05 (t, 3H, $J = 7.3$ Hz), 1.46–1.77 (m, 2H), 2.85 (dd, 1H, $J = 2.4$, 14.9 Hz), 3.03 (dd, 1H, $J = 10.5$, 14.9 Hz), 3.35 (br s, 1H, OH), 3.88 (dd, 1H, $J = 1.5$, 10.7 Hz), 4.27 (d, 1H, $J = 4.6$ Hz), 4.87 (ddd, 1H, $J = 2.4$, 4.6, 10.5 Hz), 7.21–7.35 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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-propanoyl-2,3-bis(triethylsiloxy)-4-butanolide (35).** To a cooled (0 °C) solution of **34** (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 at room temperature for 9 h, 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 **35** 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) $\delta$ 0.57–0.78 (m, 12H), 0.94 (t, 9H, $J = 7.8$ Hz), 1.00 (t, 9H, $J = 8.3$ Hz), 1.09 (t, 3H, $J = 7.1$ Hz), 2.71, 2.82 (2 dq, each 1H, $J = 19.3$, 7.1 Hz), 2.85 (dd, 1H, $J = 2.5$, 14.9 Hz), 3.08 (dd, 1H, $J = 11.0$, 14.9 Hz), 4.52 (d, 1H, $J = 6.8$ Hz), 4.74 (ddd, 1H, $J = 2.5$, 6.8, 11.0 Hz), 7.20–7.35 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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.

**(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-triethylsiloxy-1,7-dioxaspiro-[4.4]nonane-4,6-dione (38).** The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **35** (43.5 mg, 88.3 mmol) in THF (2 mL) was added dropwise potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution in toluene, 0.19 mL, 95 mmol). The solution was stirred at −78 °C for 1 h, and a solution of **29** (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 EtOAc/hexane (1:8), and the combined eluates were concentrated in vacuo to provide crude **36** (65.7 mg), which was used in the next step without further purification. To a coold (0 °C) stirred solution of crude **36** (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 at room temperature for 30 min, 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 **37** (32.4 mg), which was used in the next step without further purification. To a cooled (0 °C) stirred solution of crude **37** (32.4 mg) in $CH_2Cl_2$ (2 mL) was added Dess–Martin periodinane (33.7 mg, 79.5 mmol). The mixture was stirred at room temperature for 6 h, 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 chronatography on silica gel (EtOAc/hexane, 1:6) to provide 23.6 mg (46% form **35**) of **38** 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) $\delta$ 0.64–0.73 (m, 6H), 0.96–1.02 (m, 12H), 1.18 (d, 3H, $J = 6.8$ Hz), 2.08–2.28 (m, 2H), 3.03–3.10 (m, 1H), 3.19 (dq, 1H, $J = 1.5$, 6.8 Hz), 3.36, 3.40 (2 s, each 3H), 3.41–3.51 (m, 1H), 3.74 (d, 1H, $J = 8.3$ Hz), 4.51, 4.53 (2 d, each 1H, $J = 6.8$ Hz), 4.69–4.80 (m, 4H), 5.07–5.14 (m, 1H), 5.24–5.33 (m, 1H), 5.62 (d, 1H, $J = 1.5$ Hz, OH), 5.83 (dt, 1H, $J = 11.0$, 7.3 Hz), 7.20–7.34 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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 ($\delta$ 3.74) was observed when $CH_3$ at C-3 ($\delta$ 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-triethylsiloxy-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (39).** To a cooled (0 °C) sttired solution of **38** (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 (97%) of **39** 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) $\delta$ 0.51–0.69 (m, 6H), 0.94, (t, 9H, $J = 8.1$ Hz), 1.01 (t, 3H, $J = 7.6$ Hz), 1.79 (s, 3H), 2.09–2.27 (m, 2H), 3.19 (dd, 1H, $J = 2.7$, 15.4 Hz), 3.31, 3.39 (2 s, each 3H), 3.65 (dd, 1H, $J = 11.0$, 15.4 Hz), 4.57–4.68 (m, 5H), 4.71–4.78 (m, 1H), 4.83 (ddd, 1H, $J = 2.7$, 7.3, 11.0 Hz), 5.00 (d, 1H, $J = 7.3$ Hz), 5.35 (dd, 1H, $J = 9.5$, 11.0 Hz), 5.78 (dt, 1H, $J = 11.0$, 7.3 Hz), 7.21–7.35 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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.

**(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 (40).** To a cooled (0 °C) stirred solution of **39** (153 mg, 259 mmol) in pyridine (10 mL) was added dropwise HF·pyridine complex (1 mL). After being stirred at room temperature 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 a crude alcohol derivative (139 mg), which was used directly 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 derivative (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 **39**) of **40** as a colorless oil: TLC $R_f$ 0.66 (EtOAc/hexane, 1:1); $[\alpha]_D^{21}$ +38.5 (*c* 0.60, $CHCl_3$); IR (neat) 1790, 1710, 1640 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 1.01 (t, 3H, $J = 7.6$ Hz), 1.83 (s, 3H), 2.08–2.26 (m, 2H), 3.30, 3.31, 3.37 (3 s, each 3H), 3.31 (dd, 1H, $J = 3.4$, 15.1 Hz), 3.64 (dd, 1H, $J = 10.0$, 15.1 Hz), 4.53–4.63 (m, 5H), 4.67 (d, 1H, $J = 6.6$ Hz), 4.69 (d, 1H, $J = 7.1$ Hz), 4.71–4.78 (m, 1H), 4.91 (d, 1H, $J = 7.8$ Hz), 4.98 (ddd, 1H, $J = 3.4$, 7.8, 10.0 Hz), 5.33 (dd, 1H, $J = 9.5$, 11.0 Hz), 5.79 (dt, 1H, $J = 11.0$, 7.6 Hz), 7.21–7.35 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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 (42) and 8*S*-Isomer.** To a stirred solution of **40** (131 mg, 252 mmol) in *i*-PrOH (10 mL) was added saturated $NH_3$ in *i*-PrOH (6 mL). After being stirred at room temperature for 3 h, the solution was concentrated in vacuo to provide a crude amide derivative (140 mg), which was used directly in the next step. To a cooled (0 °C) stirred solution of a crude amide derivative (140 mg) in $CH_2Cl_2$ (10 mL) was added Dess–Martin periodinane (132 mg, 311 mmol). The mixture was stirred for 6 h at room temperature, 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). Saturated aqueous $Na_2CO_3$ (50 mL) was added to the resulting organic layer, and the mixture was vigorously 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 **40**) of **42** and 21.1 mg (16%) of **8*S*-isomer**. Compound **42** 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 1.00 (t, 3H, $J = 7.3$ Hz), 1.81 (s, 3H), 2.07–2.25 (m, 2H), 2.97 (d, 1H, $J = 13.7$ Hz), 3.30, 3.36, 3.41 (3 s, each 3H), 3.36 (d, 1H, $J = 13.7$ Hz), 4.50 (s, 1H), 4.54–4.61, 4.64–4.75 (2 m, 3H + 4H), 4.76 (dd, 1H, $J = 7.6$, 9.5 Hz), 5.33 (dd, 1H, $J = 9.5$, 11.0 Hz), 5.79 (dt, 1H, $J = 11.0$, 7.6 Hz), 5.97 (br s, 1H, OH), 6.30 (br s, 1H, NH), 7.28–7.38 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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 ($\delta$ 4.50) was observed when CH*H*Ph ($\delta$ 2.97) was irradiated, and 5.8% enhancement of the CH*H*Ph was observed when H-9 was irradiated. **8*S*-Isomer** 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 1.01 (t, 3H, $J =$ 7.6 Hz), 1.81 (s, 3H), 2.09–2.27 (m, 2H), 3.14 (dd, 1H, $J =$ 13.9 Hz), 3.31, 3.37, 3.39 (3 s, each 3H), 3.90 (dd, 1H, $J =$ 13.9 Hz), 4.57–4.75 (m, 8H), 4.78 (dd, 1H, $J = 7.8$, 9.5 Hz), 5.35 (dd, 1H, $J = 9.5$, 11.0 Hz), 5.78 (dt, 1H, $J = 11.0$, 7.3 Hz), 5.97 (br s, 1H, OH), 7.27–7.38 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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 (44).** A solution of **42** (24.5 mg, 45.7 mmol) in 5% AcOH in *i*-PrOH (5 mL) was stirred at 70 °C for 66 h, and concentrated in vacuo to provide crude enamide **43** (27.7 mg) as a 5:4 geometric mixture ($^1H$ NMR analysis), which was used directly in the next step. In a small-scale experiment, a pure inseparable geometric mixture of **43** 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.99 (t, 3H × 4/9, $J = 7.3$ Hz), 1.02 (t, 3H × 5/9, $J = 7.3$ Hz), 1.81 (s, 3H × 5/9), 1.82 (s, 3H × 4/9), 2.12–2.26 (m, 2H), 3.32, 3.33, 3.38, 3.40, 3.43 (5 s, 3H × 4/9 + 3H × 5/9 + 3H × 4/9 + 3H + 3H × 5/9), 4.53–4.83 (m, 8H), 4.91 (s, 1H × 4/9), 5.28 (d, 1H × 5/9, $J = 1.7$ Hz), 5.32–5.42 (m, 1H), 5.80 (dt, 1H, $J = 10.7$, 7.3 Hz), 5.93 (s, 1H × 4/9), 5.96 (d, 1H × 5/9, $J = 1.7$ Hz), 7.24–7.31, 7.35–7.41 (2 m, 3H + 2H), 7.79 (br s, 1H × 4/9, NH), 7.81 (br s, 1H × 5/9, NH); 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 **43** (27.7 mg) in $CH_2Cl_2$ (2 mL) was added a 50 mM *m*-CPBA solution in $CH_2Cl_2$ (3.66 mL, 183 mmol). After being stirred at room temperature 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 EtOAc/hexane (1:1), and the combined eluates were concentrated in vacuo to give a 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 mmol). The mixture was stirred for at room temperature 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 vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:5) to provide 9.3 mg (37% from **42**) of **44** 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 1.01 (t, 3H, $J = 7.6$ Hz), 1.86 (s, 3H), 2.07–2.27 (m, 2H), 3.17, 3.32, 3.38 (3 s, each 3H), 4.56–4.69 (m, 6H), 4.74 (d, 1H, $J =$ 6.8 Hz), 4.80 (dd, 1H, $J = 6.8$, 9.5 Hz), 5.13 (s, 1H), 5.36 (dd, 1H, $J = 9.5$, 11.0 Hz), 5.80 (dt, 1H, $J = 11.0$, 7.6 Hz), 6.61 (s, 1H, OH), 6.83 (br s, 1H, NH), 7.49 (t, 2H, $J = 7.3$ Hz), 7.62 (t, 1H, $J = 7.3$ Hz), 8.34 (d, 2H, $J = 7.3$ Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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 the benzoyl group ($\delta$ 8.34) was observed when H-9 ($\delta$ 5.13) was irradiated, and 1.4% enhancement of the H-9 was observed when H-2,6 of the benzoyl group 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 $F_2$) (2).** Compound **44** (9.3 mg, 17 mmol) was dissolved in 6 M HCl/MeOH (1:1 v/v, 1 mL). After being stirred at room temperature 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 **2** as colorless crystals: mp 94.4–95.0 °C; TLC $R_f$ 0.29 (acetone/PhMe, 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 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 1.01 (t, 3H, $J = 7.6$ Hz), 1.69 (s, 3H), 2.03–2.24 (m, 2H), 4.64 (d, 1H, $J = 4.2$ Hz), 4.78 (dd, 1H, $J = 4.2$, 8.9 Hz), 4.87 (s, 1H), 5.16 (dd, 1H, $J = 8.9$, 11.0 Hz), 5.57 (dt, 1H, $J = 11.0$, 7.3 Hz), 6.83 (s, 1H, OH), 7.49 (t, 2H, $J = 7.3$ Hz), 7.64 (t, 1H, $J = 7.3$ Hz), 8.40 (d, 2H, $J = 7.3$ Hz), 8.55 (br s, 1H, NH); $^{13}C$ NMR (75 MHz) $\delta$ 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 the benzoyl group ($\delta$ 8.40) was observed when H-9 ($\delta$ 4.87) was irradiated, and 2.6% enhancement of the H-9 was observed when H-2,6 of the benzoyl group 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).** To a stirred solution of **2** (5.2 mg, 13 mmol) in MeOH (1 mL) was added CSA (4.3 mg, 19 mmol). After being stirred at 40 °C for 8 h, the solution was neutralized with saturated aqueous $NaHCO_3$, 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** as colorless crystals: mp 126.0–126.9 °C; TLC $R_f$ 0.50 (acetone/PhMe, 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) $\delta$ 0.99 (t, 3H, $J = 7.6$ Hz), 1.68 (s, 3H), 2.05–2.24 (m, 2H), 3.44 (s, 3H), 4.59 (d, 1H, $J = 4.4$ Hz), 4.70 (s, 1H), 4.75 (dd, 1H, $J = 4.4$, 9.0 Hz), 5.28 (dd, 1H, $J = 9.0$, 11.0 Hz), 5.60 (dt, 1H, $J = 11.0$, 7.6 Hz), 7.49 (t, 2H, $J = 7.3$ Hz), 7.65 (t, 1H, $J = 7.3$ Hz), 8.27 (br s, 1H, NH), 8.32 (d, 2H, $J = 7.3$ Hz); $^{13}C$ NMR (75 MHz) $\delta$ 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 the benzoyl group ($\delta$ 8.32) was observed when H-9 ($\delta$ 4.70) was irradiated, and 5.4% enhancement of the H-9 was observed when H-2,6 of the benzoyl group was irradiated. No enhancement of the H-9 ($\delta$ 4.70) was observed when $OCH_3$ ($\delta$ 3.44) was irradiated.

**(2*S*,3*S*,4*R*)-4-Benzyl-2-hydroxy-2-[(4*E*,6*E*)-3-hydroxy-2-methylnona-4,6-dienoyl]-3-triethylsiloxy-4-butanolide (47).** The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **35** (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 (**45**) (355 μL, 2.54 mmol) and 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 a crude aldol product **46** (261 mg), which was used in the next step without further purification. To a cooled (0 °C) stirred solution of crude aldol product **46** (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 at room temperature for 1 h, and an 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 a total of 3 h, and quenched with saturated aqueous $NaHCO_3$ (15 mL). The resulting mixture was diluted with EtOAc (100 mL), and washed with saturated aqueous $NaHCO_3$. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20 to 1:6) to provide 146 mg (59% from **35**) of **47** 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) $\delta$ 0.64–0.75 (m, 6H), 0.95–1.06 (m, 15H), 2.06–2.19 (m, 2H), 2.91 (dd, 1H, $J = 2.5$, 14.7 Hz), 3.18 (dd, 1H, $J = 10.5$, 14.7 Hz), 3.88 (dq, 1H, $J = 5.0$, 6.8 Hz), 4.27 (dd, 1H, $J = 5.0$, 9.2 Hz), 4.72 (ddd, 1H, $J = 2.5$, 8.2, 10.5 Hz), 4.76 (d, 1H, $J = 8.2$ Hz), 5.48 (dd, 1H, $J = 9.2$, 14.9 Hz), 5.82 (dt, 1H, $J = 14.9$, 6.6 Hz), 6.06 (dd, 1H, $J = 10.5$, 14.9 Hz), 6.20 (dd, 1H, $J = 10.5$, 14.9 Hz), 7.19–7.34 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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-triethylsiloxy-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (48) and (1*S*,6*R*,9*R*)-9-Benzyl-3-[(1*E*,3*E*)-hexa-1,3-dienyl]-4-methyl-6-triethylsiloxy-2,8-dioxabicyclo[4.3.0]non-3-ene-5,7-dione (49).** To a cooled (0 °C) stirred solution of **47** (160 mg, 326 μmol) in $CH_2Cl_2$ (5 mL) was added Dess–Martin periodinane (277 mg, 653 μmol). The mixture was stirred at room temperature for 3 h, 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

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 a 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 **47**) of **48** and 36.7 mg (24%) of **49**. Compound **48** was obtained as a colorless oil: TLC $R_f$ 0.39 (EtOAc/hexane, 1:6); $[\alpha]_D^{24}$ +18.0 (*c* 1.58, $CHCl_3$); IR (neat) 1790, 1695, 1680, 1650, 1635, 1615 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 0.48–0.57 (m, 6H), 0.88 (t, 9H, $J = 7.8$ Hz), 1.08 (t, 3H, $J = 7.3$ Hz), 1.78 (s, 3H), 2.20–2.36 (m, 2H), 3.30 (dd, 1H, $J = 3.4$, 15.4 Hz), 3.75 (dd, 1H, $J = 10.7$, 15.4 Hz), 4.84 (ddd, 1H, $J = 3.4$, 8.1, 10.7 Hz), 5.03 (d, 1H, $J = 8.1$ Hz), 6.17–6.37 (m, 3H), 7.16 (dd, 1H, $J = 9.3$, 15.1 Hz), 7.27–7.34 (m, 5H); $^{13}C$ NMR (75 MHz) $\delta$ 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 **49** 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) $\delta$ 0.56–0.68 (m, 6H), 0.95 (t, 9H, $J = 7.9$ Hz), 1.09 (t, 3H, $J = 7.6$ Hz), 1.76 (s, 3H), 2.20–2.32 (m, 2H), 2.93 (dd, 1H, $J = 4.1$, 14.9 Hz), 3.22 (dd, 1H, $J = 9.3$, 14.9 Hz), 4.48 (d, 1H, $J = 3.3$ Hz), 5.31 (ddd, 1H, $J = 3.3$, 4.1, 9.3 Hz), 6.17–6.39 (m, 3H), 7.22–7.35 (m, 6H); $^{13}C$ NMR (75 MHz) $\delta$ 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-methoxymethoxy-3-methyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (50).** To a cooled (0 °C) stirred solution of **48** (50.0 mg, 107 μmol) in pyridine (5 mL) was added dropwise HF·pyridine complex (0.5 mL). After being stirred at room temperature 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 a crude alcohol derivative (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 μmol) in $CH_2(OMe)_2$ (3 mL) was added a solution of crude alcohol derivative (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 **48**) of **50** 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) $\delta$ 1.07 (t, 3H, $J = 7.3$ Hz), 1.81 (s, 3H), 2.17–2.30 (m, 2H), 3.25 (s, 3H), 3.34 (dd, 1H, $J = 4.4$, 15.1 Hz), 3.72 (dd, 1H, $J = 9.5$, 15.1 Hz), 4.54 (s, 2H), 4.90–5.03 (m, 2H), 6.20–6.37 (m, 3H), 7.13–7.24, 7.28–7.34 (2 m, 2H + 4H); $^{13}C$ NMR (75 MHz) $\delta$ 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-methoxymethoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (51).** To a cooled (0 °C) stirred solution of **50** (29.1 mg, 73.0 μmol) in *i*-PrOH (2 mL) was added saturated $NH_3$ in *i*-PrOH (4 mL). After being stirred at 0 °C for 1 h, the solution was concentrated in vacuo to provide a crude amide derivative (31.8 mg), which was used directly in the next step. To a cooled (0 °C) stirred solution of a 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). A saturated aqueous $Na_2CO_3$ (20 mL) was added to the resulting organic layer, and the mixture was vigorously stirred for 3 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, 1:3) to provide 25.8 mg (85% from **50**) of **51** 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 (300 MHz) $\delta$ 1.06 (t, 3H, $J = 7.6$ Hz), 1.78 (s, 3H), 2.18–2.29 (m, 2H), 3.00, 3.35 (AB q, each 1H, $J = 13.7$ Hz), 3.33 (s, 3H), 4.46 (s, 1H), 4.66 (s, 2H), 6.22–6.36 (m, 3H), 7.27–7.39 (m, 6H); $^{13}C$ NMR (75 MHz) $\delta$ 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.

**(5*S*,7*R*,8*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) (5).** Compound **51** (4.4 mg, 11 μmol) was dissolved in 6 M HCl/MeOH (1:1 v/v, 1 mL). After being stirred at room temperature for 10 h, 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 **5** 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) $\delta$ 1.07 (t, 3H, $J = 7.3$ Hz), 1.76 (s, 3H), 2.24 (dq, 2H, $J = 4.6$, 7.3 Hz), 2.96, 3.27 (2 d, each 1H, $J = 13.9$ Hz), 2.98 (d, 1H, $J = 10.0$ Hz, OH), 4.50 (d, 1H, $J = 10.0$ Hz), 6.02 (br s, 1H, OH), 6.23–6.36 (m, 3H), 6.56 (br s, 1H, NH), 7.25–7.38 (m, 6H); $^{13}C$ NMR (75 MHz) $\delta$ 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.

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26 The geometrical ratio of this mixture **43** was ca. 5:4 (determined by $^1$H NMR at 300 MHz).

27 In the previous paper,[11b] we used the following conditions for the conversion of hemiaminal **42** into enamide **43**: heating in MeOH at 60 °C for 158 h, then heating in pyridine at 80 °C for 8 h. Under these conditions, the three-step overall yield of **44** from **42** was 31%. Therefore, we could achieved the improvement of the overall yield (37% yield of **44** from **42**) by the present modification, and also could shorten the reaction time significantly.

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35 We suppose that the *O*-TES group in **47** migrated to the tertiary hydroxy group in the oxidation step. Then the liberated secondary hydroxy group attacked to the formed carbonyl, producing **49** after dehydration. To suppress the formation of **49**, we examined a variety of oxidation conditions. However, the ratio of **48** to **49** was approximately 2:1 in all cases.