Total Synthesis of Bafilomycin A_1

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The highly stereoselective total synthesis of the macrolide antibiotic, bafilomycin A_1 (**1**), the first specific potent inhibitor of vacuolar H^+-ATPase, has been achieved by a convergent route involving the synthesis and coupling of its 16-membered tetraenic lactone and β-hydroxyl hemiacetal side-chain subunits. The C1−C17 16-membered lactone aldehyde **2** was synthesized through the coupling of the C5−C11 vinyl iodide **4** and the C12−C17 vinylstannane **5**, followed by construction of the C1−C4 diene and macrolactonization. The aldol coupling of **2** and the C18−C25 ethyl ketone **3** followed by desilylation provided **1**, which was identical with natural bafilomycin A_1. The key synthetic segments **3**−**5** were effectively synthesized from the readily available chiral materials, D-glucose, ethyl (*S*)-lactate, and methyl (*S*)-3-hydroxy-2-methylpropionate, respectively.

Introduction

Bafilomycin A_1 (**1**) was first isolated in 1983 by Werner and Hagenmaier[1a] from a culture of *Streptomyces griseus* sp. *sulphuru* as a new type of antibiotic that exhibited activity against Gram-positive bacterial and fungi.[1] Furthermore, bafilomycin A_1 (**1**) was later found to show immunosuppressive activity[2] and proved to be the first specific potent inhibitor of vacuolar H^+-ATPase attracting particular interest.[3] The absolute configuration of **1** was originally proposed by Corey[4] on the basis of NMR data and computer molecular modeling and then established by X-ray crystallographic analysis.[5] Structurally, bafilomycin A_1 (**1**) is constructed from a 16-membered tetraenic lactone ring and a β-hydroxyl hemiacetal side chain. The intramolecular hemiacetal ring and the macrolactone ring are linked by a C_3 spacer and a hydrogen-bonding system. Bafilomycin A_1 (**1**) belongs to a family of polyketide macrolide antibiotics, and the other macrolide antibiotics such as elaiophylin,[6] the concanamycins,[7] and the hygrolidins[8] are closely related to the bafilomycins (Figure 1). Among them, however, the bafilomycins and concanamycins have a novel diene system containing a methyl enol ether. Because of the unique structural and the impressive biological features of **1**, great effort has been devoted to the chemical synthesis of **1**. In this context, an efficient aldol method for the assembly of **1** was recently reported by Evans and Calter,[9] and elegant syntheses of the C13−C25 segments of **1** have been independently disclosed by Roush's[10] and Paterson's[11] groups. Hanessian et al. also reported the chemical transformation of bafilomycin A_1 to isobafilomycin A_1 possessing an 18-membered lactone.[12] In this paper, we describe the full account of our recent total synthesis of the architecturally and biologically attractive natural product, bafilomycin A_1 (**1**).[13]

Synthetic Plan

The retrosynthetic analysis of bafilomycin A_1 (**1**) is shown in Figure 2 along with our synthetic plan. The target molecule **1** would be obtained by deprotection of an aldol **A** followed by spontaneous intramolecular hemiacetalization. The aldol coupling[14] of a 16-membered lactone aldehyde **B** and a ethyl ketone **C** would give a key intermediate **A**. The lactone skeleton was further partitioned into three fragments, **D**, **E**, and **F**, through disconnection of the C4−C5, C11−C12, and acyl oxygen bonds. In the synthetic direction, each of these analog's bond constructions is based on powerful synthetic reactions. For example, the synthesis of dienes through the Pd(0)-catalyzed coupling of vinyl iodides and vinylstannanes (Stille cross coupling)[15] is reported to work well

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

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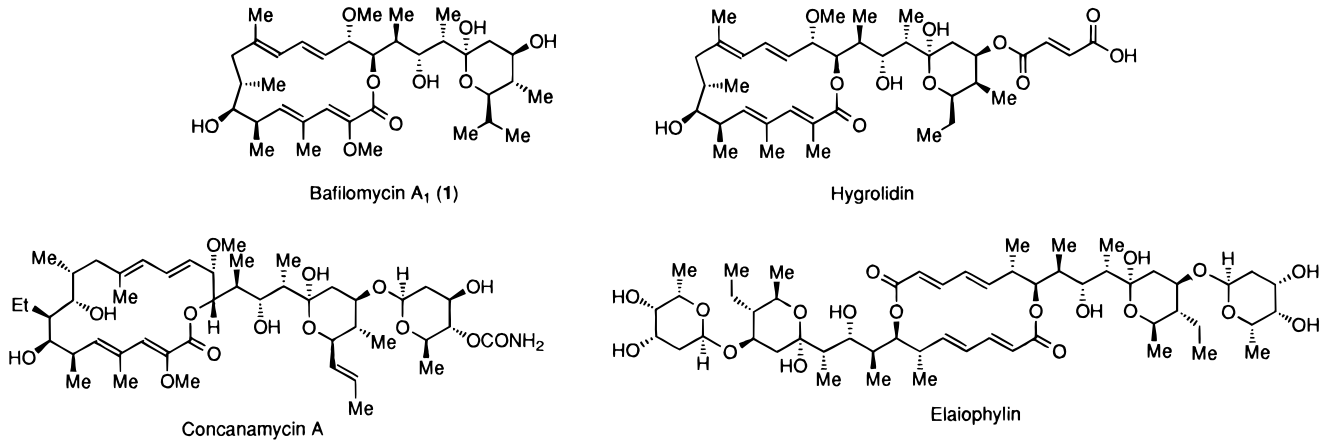

Figure 1. Molecular structures of bafilomycin A_1 (**1**) and structurally related macrolide antibiotics.

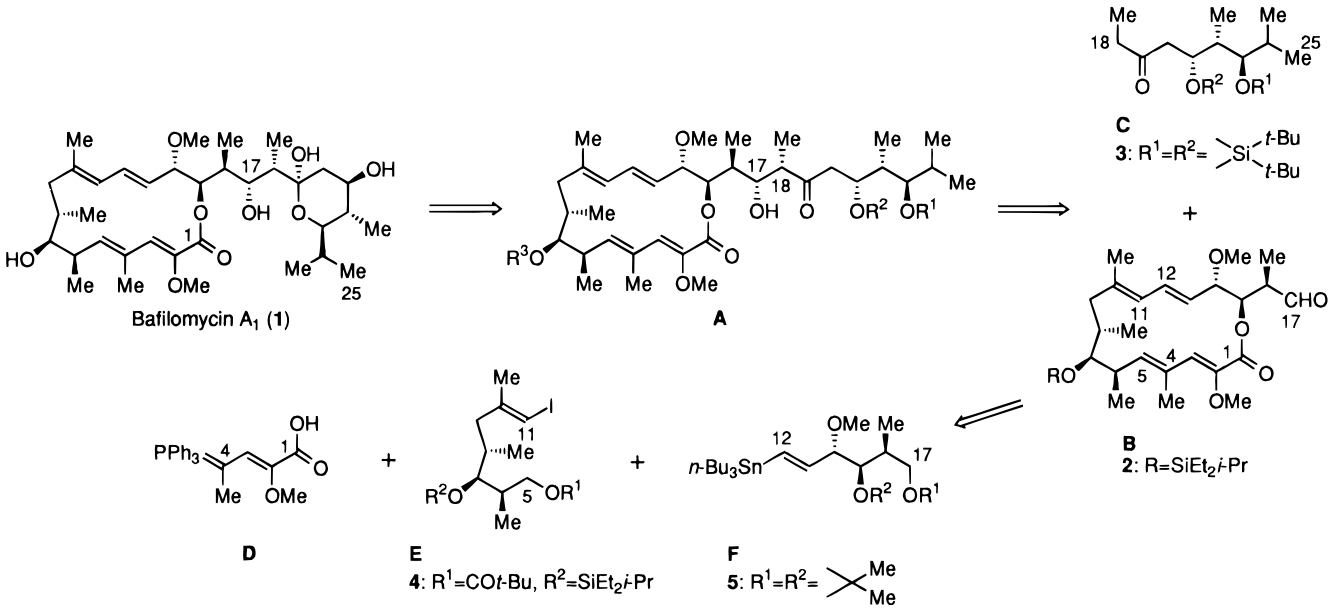

Figure 2. Retrosynthetic analysis of bafilomycin A_1 (**2**).

with highly functionalized coupling partners. The synthesis of dienes by the Wittig reaction also has a high potential. Furthermore, the highly evolved methods for macrolactonization are currently available.[16] The highly stereoselective syntheses of an appropriately protected 16-membered lactone aldehyde **2**, which makes use of the fragments **4**, **5**, and **D**, and a suitably protected ethyl ketone **3**[9] and aldol coupling of **2** and **3** leading to the total synthesis of **1** are described in the following discussion.

Results and Discussion

Synthesis of the C5−C11 Segment 4. The synthesis of the vinyl iodide **4** corresponding to the C5−C11 segment of bafilomycin A_1 (**1**) is summarized in Scheme 1. The starting material **6**,[17] readily prepared from ethyl (*S*)-lactate, was first converted into the diacetate **7** using acetic anhydride and 4-(dimethylamino)pyridine (4-DMAP) in quantitative yield. This temporary protection of the hydroxyl groups was necessary for clear ozonolysis of the olefin. Ozonolysis of **7** in MeOH−CH_2Cl_2 at −78 °C, followed by *in situ* reduction of the resultant aldehyde **8** using sodium borohydride and deacetylation of **9** employing sodium methoxide, afforded the triol **10** in 94% overall yield from **7**. Regioselective *p*-methoxybenzylidenation of the 1,3-diol in **10** using *p*-methoxybenzaldehyde dimethyl acetal and DL-10-camphorsulfonic acid (CSA) in *N*,*N*-dimethylformamide (DMF) at 25 °C proceeded smoothly to give the alcohol **11** in 94% yield. Oxidation of **11** employing pyridinium chlorochromate (PCC) and powdered molecular sieves 3A (MS 3A) in CH_2Cl_2 and the subsequent Wittig reaction of the resultant ketone **12** with methylenetriphenylphosphorane in benzene afforded **13** in 95% overall yield. At this stage, we found that the hydroboration of **13** using dicyclohexylborane in THF at 25 °C for 1 h proceeded with complete stereoselectivity to give only the desired alcohol **14** in 88% yield after the subsequent oxidative workup. The remarkable high stereoselectivity of this reaction might be explained as follows. ^{1}H-NMR studies of **13** including NOE experiments indicated that it existed in a chair conformation,

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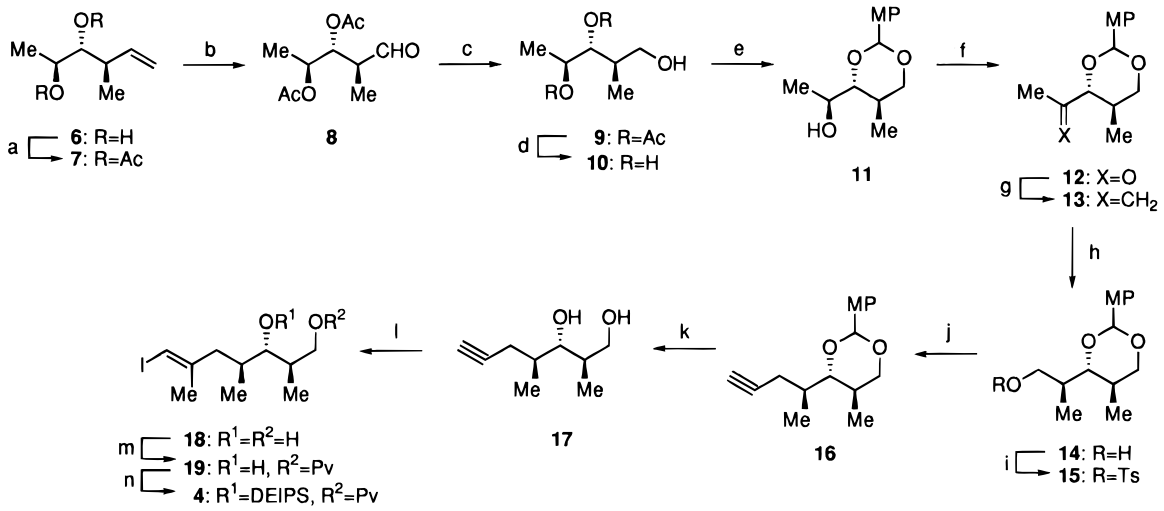
Scheme 1[a]



[a] Reagents and conditions: (a) Ac_2O, 4-DMAP, EtOAc, rt, 1 h, 100%; (b) O_3, MeOH−CH_2Cl_2, −78 °C, 2 h then Me_2S; (c) $NaBH_4$, MeOH−CH_2Cl_2, rt, 0.5 h; (d) NaOMe, MeOH, rt, 3 h, 94% from **7**; (e) $(MeO)_2CHC_6H_4OMe$, CSA, DMF, rt, 1.5 h, 94%; (f) PCC, MS 3A, CH_2Cl_2, rt, 1.5 h, 100%; (g) $Ph_3P{=}CH_2$, C_6H_6, rt, 1 h, 95%; (h) $BH_3{\cdot}Me_2S$, C_6H_{10}, THF, rt, 1 h then NaOH−H_2O, H_2O_2, 88%; (i) TsCl, Py, rt, 1.5 h, 100%; (j) HC≡CLi, DMSO, rt, 1.5 h, 66%; (k) 80% AcOH−H_2O, 40 °C, 13 h, 84%; (l) Cp_2ZrCl_2, Me_3Al, I_2, $(ClCH_2)_2$, rt, 13 h, 82%; (m) PvCl, Et_3N, CH_2Cl_2, rt, 14 h, 97%; (n) DEIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 4 h, 100%.

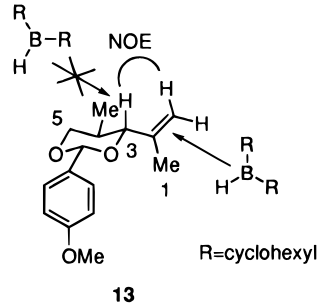


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Figure 3.

and the olefin and C3 hydrogen were located in the same orientation as depicted in Figure 3. Approach of dicyclohexylborane to the olefin of **13** might be strongly interrupted by the C4 methyl substituent. As a consequence, dicyclohexylborane reacts from the less hindered side leading to the desired *S* configuration at the C2 position in **14**. Tosylation of **14** using *p*-toluenesulfonyl chloride in pyridine yielded the tosylate **15**, which was subjected to the reaction with 5 equiv of lithium acetylide ethylenediamine complex in dimethyl sulfoxide (DMSO) to give the acetylene **16** in 66% overall yield. After deprotection of the *p*-methoxybenzylidene group in **16** under mild acidic conditions, the resultant diol **17** was treated with Cp_2ZrCl_2, Me_3Al, and I_2 in 1,2-dichloroethane[18] to cleanly afford only the trisubstituted *trans* vinyl iodide **18** in 63% overall yield from **16**. In contrast, it was found that the vinyl iodination of the protected **16** gave only a poor yield of the corresponding vinyl iodide. Selective protection of the primary alcohol in **18** with a pivaloyl group, followed by silylation of the resultant **19** with the diethylisopropylsilyl (DEIPS) group[19] using diethylisopropylsilyl trifluoromethanesulfonate (DEIPSOTf) and 2,6-lutidine in CH_2Cl_2 furnished the suitably protected vinyl iodide **4** in 97% overall yield. The DEIPS group in **4** was a key protecting group for the total synthesis of **1** because it was found that, in contrast to the corresponding triethylsilyl, *tert*-butyldimethylsilyl, and *p*-methoxylbenzyl ethers, this silyl ether had sufficient stability in subsequent reactions, while still offering reasonable liability in the final deprotection step using tetrabutylammonium fluoride (TBAF) and acetic acid in THF.[20] The *trans* configuration of the trisubstituted olefin of **4** was clearly confirmed by NOE experiments. Thus, NOE between the vinyl hydrogen and the methylene hydrogens was observed while no NOE between the vinyl hydrogen and the methyl group at the vinyl position was detected.

Synthesis of the C12−C17 Segment 5. Scheme 2 illustrates the synthesis of the vinylstannane **5** corresponding to the C12−C17 segment of bafilomycin A_1 (**1**). In this synthesis, the aldehyde **20**,[21] which could be easily prepared from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate, was chosen as the starting material. Treatment of **20** with *in situ* generated γ-methoxyallylchromium reagent,[10,22] which was prepared from $CrCl_2$ and $CH_2{=}CHCH(OMe)_2$ in the presence of trimethylsilyl iodide (TMS-I) in THF at −42 °C for 16 h, afforded the C2,C3-*syn*−C3,C4-*anti* homoallylic alcohol

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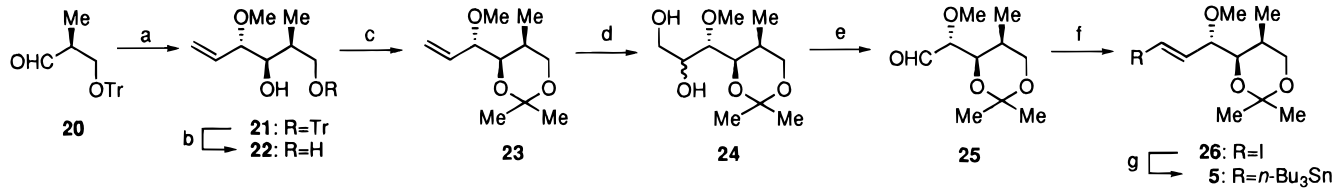
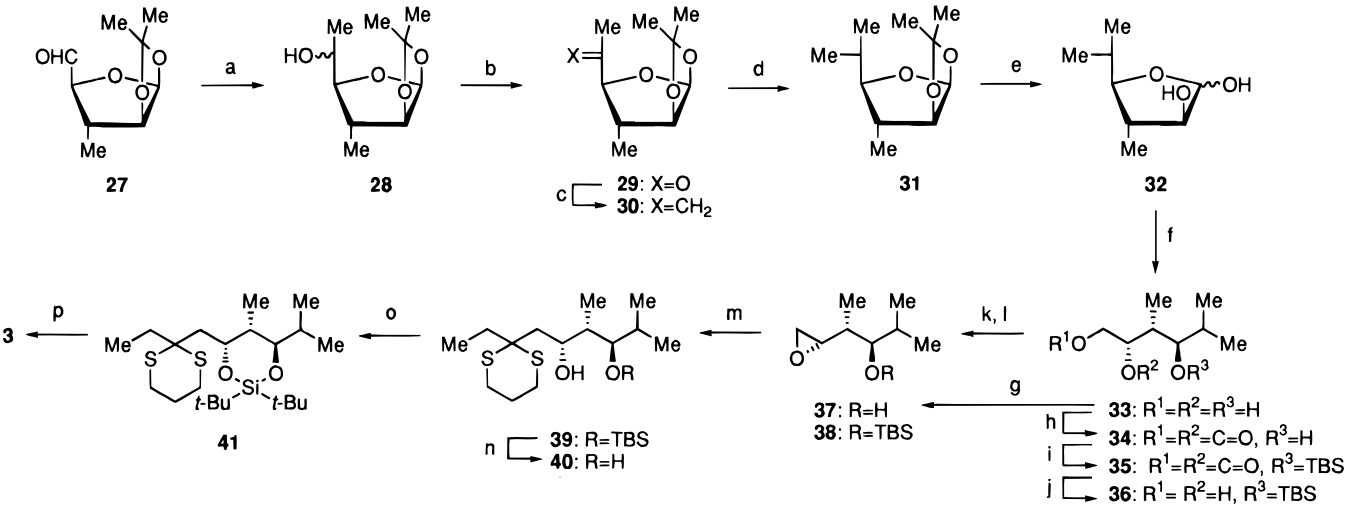
Scheme 2[a]



[a] Reagents and conditions: (a) $CrCl_2$, CH_2=CHCH$(OMe)_2$, TMS-I, THF, −42 °C, 16 h, 62%; (b) 1% HCl−MeOH, rt, 0.5 h, 100%; (c) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 16 h, 76%; (d) OsO_4, NMO, acetone−H_2O, rt, 16 h; (e) $NaIO_4$, THF−H_2O, rt, 0.5 h; (f) $CrCl_2$, CHI_3, THF, rt, 14 h, 50% from **23**; (g) *n*-Bu_3SnCl, *n*-BuLi, THF, −78 °C, 1 h, 69%.

Scheme 3[a]



[a] Reagents and conditions: (a) MeMgI, Et_2O, rt, 0.5 h, 94%; (b) PCC, MS 3A, CH_2Cl_2, rt, 0.5 h, 94%; (c) Ph_3P=CH_2, C_6H_6, rt, 0.5 h, 81%; (d) H_2, Raney-Ni(W4), dioxane, rt, 24 h, 92%; (e) 50% AcOH−H_2O, 80 °C, 2 h, 93%; (f) LAH, THF, 60 °C, 16 h, 77%; (g) Ph_3P, DEAD, MS 3A, C_6H_6, reflux, 7 h, 12%; (h) *N*,*N*-carbonyldiimidazole, CH_2Cl_2, rt, 2.5 h, 85%; (i) TBS-Cl, imidazole, DMF, 40 °C, 16 h, 87%; (j) 1 N NaOH, MeOH, rt, 16 h, 87%; (k) TsCl, Py, rt, 4 h; (l) NaOMe, MeOH−$CHCl_3$, rt, 16 h, 71% from **36**; (m) 2-ethyl-1,3-dithiane, *n*-BuLi, THF, −20 °C, 1 h; (n) TBAF, THF, rt, 2.5 h, 97% from **38**; (o) *t*-$Bu_2Si(OTf)_2$, DMF, rt, 2 h, 95%; (p) MeI, $CaCO_3$, MeCN−H_2O, rt, 6 h, 72%.

21 as a major diastereomer with 10:1.1:0.5 selectivity in 62% yield. The complete isolation of **21** from the other isomers was impractical at this stage. Therefore, the trityl group in the crude **21** was removed under acidic conditions using 1% HCl−MeOH, and the resultant crude diol **22** was then protected with an isopropylidene group employing 2,2-dimethoxypropane and CSA in CH_2Cl_2; a 76% yield of the pure acetonide **23** was obtained after chromatography. Dihydroxylation of **23** using a catalytic amount of OsO_4 and 4-methylmorpholine *N*-oxide (NMO) in acetone−H_2O followed by the sequential periodate-oxidation of **24** and Takai's reaction[23] of the resultant aldehyde **25** using $CrCl_2$ and CHI_3 in THF gave only the *trans* vinyl iodide **26** in 50% overall yield from **23**. Finally, treatment of **26** with *n*-Bu_3SnCl and *n*-BuLi in THF at −78 °C for 1 h afforded the vinylstannane **5** in 69% yield.

Synthesis of the C18−C25 Segment 3. The synthesis of the ethyl ketone **3** corresponding to the C18−C25 segment of bafilomycin A_1 (**1**) is depicted in Scheme 3. This synthesis began with the conversion of the sugar derivative **27**,[19d] which was obtained from D-glucose, into **31**, which possessed an isopropyl group by a standard manner. Thus, the Grignard reaction of **27** with MeMgI in ether, followed by PCC oxidation of **28**, the Wittig reaction of **29** using methylenetriphenylphosphorane, and hydrogenolysis of the olefin in **30** in the presence of Raney-Ni (W4) in dioxane gave **31** in high (66%) overall yield from **27**. Hydrolysis of the 1,2-isopropylidene group in **31** with 50% aqueous acetic acid gave the free sugar **32** in 93% yield, which was then treated with lithium aluminum hydride (LAH) in THF to afford the triol **33** in 77% yield. The triol **33** was first subjected to the one-pot epoxidation of the vicinal diol using triphenylphosphine and diethyl azodicarboxylate (DEAD) in refluxing benzene.[24] However, unfortunately, this reaction gave the epoxide **37** in only miserable yield while the furan ring was significantly produced. Therefore, stepwise synthesis of the protected epoxide **38** from **33** was next carried out. Selective protection of the 1,2-diol of **33** with a carbonate using *N*,*N*′-carbonyldiimidazole in CH_2Cl_2 followed by silylation of the resultant alcohol **34** with the *tert*-butyldimethylsilyl (TBS) group provided **35** in 74% overall yield. After removal of the carbonate group in **35** by hydrolysis under alkaline conditions, selective tosylation of the primary alcohol **36** and the sequential epoxidation of the resultant crude tosylate using sodium methoxide gave the epoxide **38** in 62% overall yield from **35**. The reaction of **38** with 5 equiv of 2-ethyl-2-lithio-1,3-dithiane in THF at −20 °C for 1 h afforded the dithioacetal **39**, whose silyl group was removed by TBAF in THF to give the diol **40** in 97% overall yield. Finally, the diol **40** was protected with a di-*tert*-butylsilyl group, and the dithioacetal group of **41** was then cleaved using

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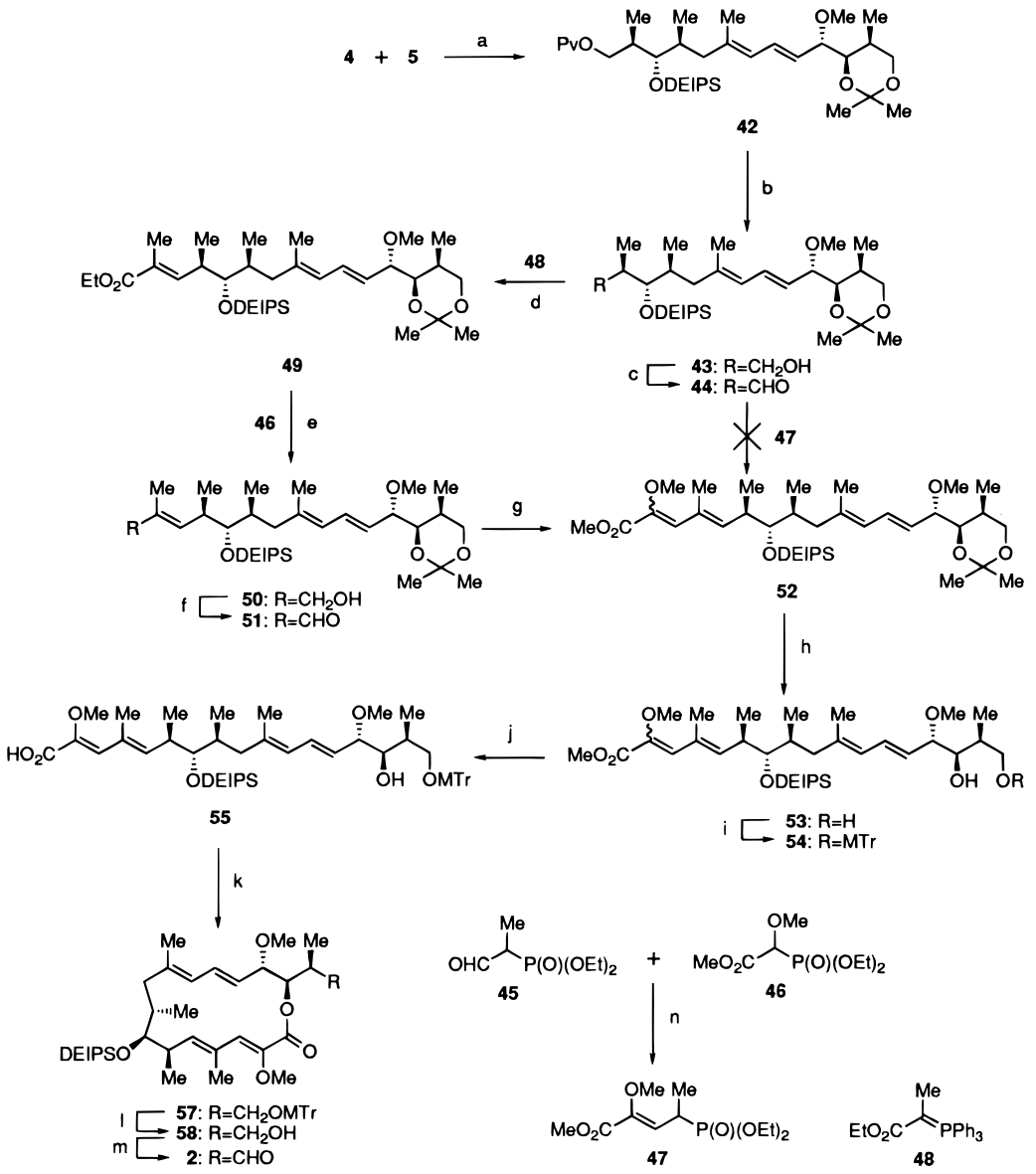
Scheme 4[a]



[a] Reagents and conditions: (a) $PdCl_2$(dppf), DMF, 50 °C, 15 h, 60%; (b) MeLi, Et_2O, rt, 0.5 h, 79%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 20 min; (d) PhMe, 100 °C, 14 h, 98% from **43**; (e) DIBAL, PhMe, −78 °C, 5 min, 97%; (f) MnO_2, CH_2Cl_2, rt, 2 h, 100%; (g) NaHMDS, THF, rt, 0.5 h, 89%; (h) PPTS, MeOH, rt, 0.5 h, 98%; (i) MTrCl, Et_3N, 4-DMAP, CH_2Cl_2, rt, 5 h, 91%; (j) 1 N KOH, dioxane, 80 °C, 2 h, 64% for **55**, 32% for **56**; (k) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 4-DMAP, PhMe (0.002 M for **55**), 110 °C, 16 h, 42%; (l) PPTS, MeOH, rt, 14 h, 80%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 20 min, 74%; (n) NaHMDS, THF, rt, 12 h, 39%.

MeI in the presence of $CaCO_3$ to furnish the ethyl ketone **3**[9] in 68% overall yield. The cyclic protection at the C5 and C7 positions in **3** was required for a high level of aldol stereoselectivity as suggested by Evans[9] and confirmed by Paterson.[10]

Synthesis of the Macrocyclic Aldehyde 2. With the C5−C11, C12−C17, and C18−C25 segments of bafilomycin A_1 (**1**) in hand, our attention next turned to the construction of the macrocyclic lactone moiety of **1**. The synthesis of the 16-membered lactonic aldehyde **2** for the aldol condensation with the ethyl ketone **3** is summarized in Scheme 4. We first examined the cross-coupling reactions between the vinyl iodide **4** corresponding to the C5−C11 segment and the vinylstannane **5** corresponding to the C12−C17 segment by the Stille method[15] using several Pd-catalysts, such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(MeCN)_2$, and $PdCl_2$(dppf). From the results shown in Table 1, the catalyst $PdCl_2$(dppf) developed by Hayashi[25] was clearly found to be superior in this coupling reaction. Thus, the reaction of 1 equiv of **4** and 1 equiv of **5** using a catalytic amount of $PdCl_2$(dppf) in DMF at 50 °C for 15 h afforded the desired *E*,*E*-diene **42** in 60% yield. The ^{1}H NMR spectrum of **42**, interestingly, showed that it consisted of a ca. 3:1 inseparable mixture. The ^{1}H NMR spectra of **43**−**56** also showed similar phenomenon. On the other hand, it was found that the ^{1}H NMR spectra

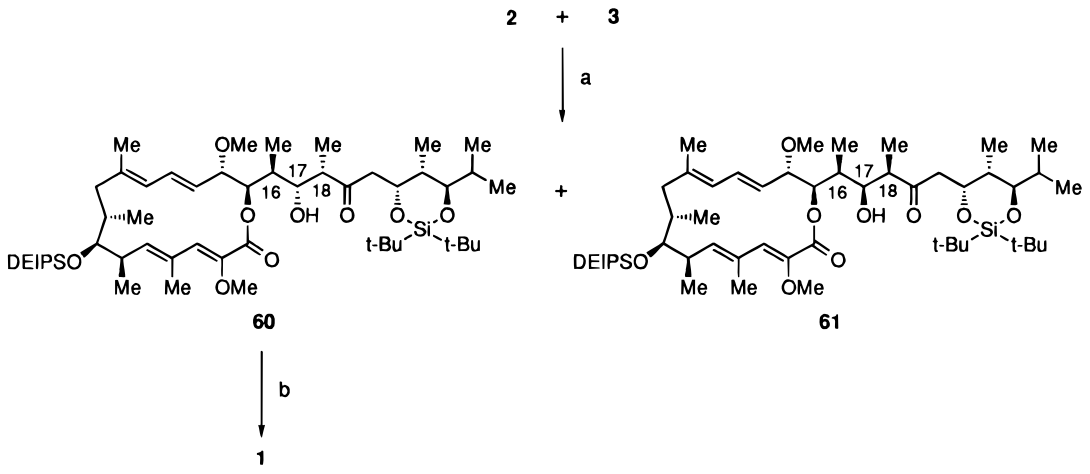
Table 1. The Cross Couplings of 4 and 5 by Pd-Catalysts

$$\mathbf{4} + \mathbf{5} \xrightarrow[\substack{\text{DMF}\\ 50\ ^\circ\text{C, 15 h}}]{} \mathbf{42}$$

entry	Pd-catalyst (0.2 equiv)	yield (%)
1	$Pd(PPh_3)_4$	trace
2	$PdCl_2(PPh_3)_2$	33
3	$PdCl_2(MeCN)_2$	36
4	$PdCl_2$(dppf)	60

(25) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

Scheme 5[a]



[a] Reagents and conditions: (a) $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 2.5 h, 58%; (b) TBAF, AcOH, THF, 60 °C, 12 h, 45%.

of the desilylation product of **42** and the conformationally rigid lactone **57** indicated that they are single compounds. Therefore, it is reasonable to assume that this inseparable mixture should be due to the conformational isomers. Deprotection of the pivaloyl group in **42** using methyllithium followed by Swern oxidation of the resultant alcohol **43** gave the aldehyde **44**. At this stage, we first tried the Horner−Wadsworth−Emmons reaction of **44** and **47**, the latter of which was obtained by the coupling of the phosphonic aldehyde **45**[26] and the phosphonic ester **46**,[27] to construct the C1−C4 diene in one step. However, this reaction in the presence of several bases such as lithium bis(trimethylsilyl)amide (LiHMDS), sodium bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide (KHMDS), and NaH caused only β-elimination of **44** even at low temperature (−78 °C), and the desired tetraene **52** was not obtained at all. Therefore, stepwise construction of the diene, which included the use of the base-free Wittig reagent **48** in the first step, was next carried out. The Wittig reaction of **44** with **48** in toluene at 100 °C for 14 h proceeded smoothly to afford only the *trans* isomer **49** in 98% overall yield from **43**. In order to determine the configuration of the newly formed olefin in **49**, an NOE experiment was conducted. Thus, irradiation of the C3 vinyl hydrogen caused no NOE enhancement of the C2 methyl group. This implied that the configuration of the olefin was *trans*. Reduction of the ethyl ester in **49** using diisobutylaluminum hydride (DIBAL) in toluene at −78 °C followed by oxidation of the resultant allyl alcohol **50** using MnO_2 provided the α,β-unsaturated aldehyde **51** in 97% overall yield. In the allyl alcohol **50**, the geometry of the C2−C3 olefin was clearly confirmed by the presence of NOE enhancement of the methylene hydrogens of the hydroxymethylene moiety by the irradiation of the C3 vinyl hydrogen. The Horner−Wadsworth−Emmons reaction of **51** with 5 equiv of the phosphonic ester **46** using NaHMDS in THF gave **52** in 89% yield as a mixture of the *cis*- and *trans*-isomers. It was found that NaHMDS was superior to the other previously mentioned bases with respect to both the yield and the stereoselectivity, and the desired *cis*-isomer of **52** was predominately obtained (Z/E = 2/1). Although these isomers could not be separated at this stage, each isomer was isolated in a pure form before the macrolactonization mentioned below. The isopropylidene group in **52** was removed under mild acidic conditions using pyridinium *p*-toluenesulfonate (PPTS) in MeOH, and the resultant diol **53** was then selectively protected with a monomethoxytrityl (MTr) group to afford the secondary alcohol **54** in 89% overall yield. Hydrolysis of the methyl ester of **54** under basic conditions yielded the hydroxyl carboxylic acid **55** and the isomer **56** in 64 and 32% yields, respectively. In the ^1H NMR spectra of **55** and **56**, the chemical shifts of the C3 vinyl hydrogens of **55** and **56** were quite different and at 6.74 and 5.80 ppm, respectively, and the former was very similar to that (6.67 ppm) of bafilomycin A_1. The cyclization of the *seco*-acid **55** in order to construct the 16-membered lactone ring was best effected by the Yamaguchi method[28] using 2,4,6-trichlorobenzoyl chloride, triethylamine, and 4-DMAP at 110 °C under high dilution conditions to give the macrocyclic lactone **57** in 42% yield. From the results shown in Table 2, it was unfortunately found that other macrolactonizations by Mukaiyama's,[29] Keck's,[30] and Palomo-Coll's[31] methods gave **57** in only poor yields in this case. Furthermore, we found that the macrolactonization of a mixture of **55** and **56** by the Yamaguchi method also gave **57** as the sole lactone product in a similar yield. Finally, treatment of **57** with PPTS in MeOH gave the alcohol **58** in 80% yield, which was subjected to Swern oxidation to furnish the 16-membered lactonic aldehyde **2** in 74% yield.

Total Synthesis of 1. We then had in our hands both the 16-membered lactonic aldehyde **2** and the ethyl ketone **3** leading to the total synthesis. The stereoselective connection of these segments by several aldol reactions was next tested as shown in Table 3. A similar type of aldol reaction using an α-substituted lactonic aldehyde and an α-unsubstituted β-siloxy ethyl ketone was previously studied and performed in our total synthesis of elaiophylin[19a,b] and in Seebach's elaiophylin aglycon synthesis.[32] The coupling of **2** and **59**,[33] which is an acyclic analog of **3**, by the method using *n*-Bu_2BOTf and

(26) Gallagher, G.; Welb, R. C. *Synthesis* **1974**, 122.
(27) Grell, W.; Machleidt, H. *Liebigs Ann. Chem.* **1966**, *699*, 53.
(28) Inagawa, J.; Hirata, K.; Katsuki, H.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(29) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(30) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.
(31) Diago-Meseguer, J.; Palomo-Coll, A. L. *Synthesis* **1980**, 547.
(32) (a) Seebach, D.; Chow, H.-F.; Lackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmenmann, J. *J. Am. Chem. Soc.* **1985**, *107*, 5292. (b) Seebach, D.; Chow, H.-F.; Lackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmenmann, J. *Liebigs Ann. Chem.* **1986**, 1281.

Table 2. Macrolactonizations of the *seco*-Acid 55

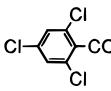
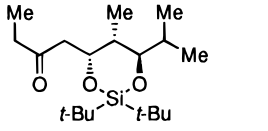
entry	reagents (equiv.)	solvent	temp. (°C)	time (h)	yield (%)
1	 (2), Et_3N (2.2), 4-DMAP (10)	PhMe	110	16	42
2	 (4), Et_3N (8)	MeCN	80	16	3
3	DCC (2), 4-DMAP (3), 4-DMAP•HCl (2)	$CHCl_3$	60	13	7
4	BOP-Cl (1), Et_3N (2)	CH_2Cl_2	25	13	trace

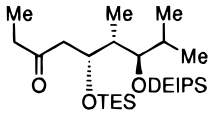
Table 3. Aldol Couplings of 2 and 3 or 59

2 + **3** or **59** → C16,C17-*anti*−C17,C18-*syn* aldol **G** + C16,C17-*syn*−C17,C18-*syn* aldol **H**

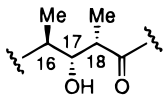
						yield (%)	
entry	ethyl ketone (2 equiv)	reagents (2 equiv)	solvent	*T* (°C)	time (h)	**G**	**H**
1	**59**	*n*-Bu_2BOTf, *i*-Pr_2NEt	CH_2Cl_2	25	4	19	38
2	**3**	*n*-Bu_2BOTf, *i*-Pr_2NEt	CH_2Cl_2	25	4	44	15
3	**3**	$PhBCl_2$, *i*-Pr_2NEt	CH_2Cl_2	−78	2.5	57	1
4	**3**	(−)-Ipc_2BOTf, *i*-Pr_2NEt	Et_2O	25	1	2	



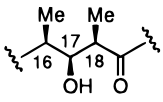
3



59



aldol **G**



aldol **H**

i-Pr_2NEt,[34] which were employed during the elaiophylin syntheses, afforded the corresponding aldol product **G** (C16,C17-*anti*−C17,C18-*syn*) and its diastereomer **H** (C16,C17-*syn*−C17,C18-*syn*)[35] in 19 and 38% yields, respectively. On the other hand, the stereoselectivity was dramatically changed in the aldol reaction of **2** and **3**, which possessed a cyclic protecting group, under similar conditions, and the aldols **60** (**G**-type) and **61** (**H**-type) were obtained in 44 and 15% yields, respectively (Scheme 5). Furthermore, the aldol reaction between **2** (1 equiv) and **3** (2 equiv) was found to be best achieved by Evans' recently disclosed procedure[9] using $PhBCl_2$[36] and *i*-Pr_2-NEt in CH_2Cl_2 at −78 °C for 2.5 h to produce **60** in 58% yield with >95:5 diastereoselectivity as the major aldol product,[37] while the chiral (−)-diisopinocamphenylboron enolate[38] of **3** was shown to be less effective in this case. Finally, desilylation of **60** using TBAF and acetic acid in THF at 60 °C for 12 h gave the synthetic **1** in 45% yield. Thus, the obtained synthetic **1** was identical to the authentic sample of natural bafilomycin A_1 on the basis of ^{1}H-NMR, IR, $[\alpha]_D$, mp, mmp, and TLC behaviors in several solvent systems.

Conclusions

The total synthesis of bafilomycin A_1, the first specific inhibitor of vacuolar H^+-ATPase, has been completed using three principle subunits, followed by macrolactonization and aldol reaction. The described total synthesis is characterized by high convergency and stereocontrol at several stages. This synthetic strategy should find wide application in the synthesis of the other structurally related and biologically important macrolide antibiotics such as the hygrolidins[39] and the concanamycins[19d,20g] and for the synthesis of designed bafilomycin A_1 analogs with potential applications in biology and medicine.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H-NMR spectra were measured in $CDCl_3$ using TMS as internal standard unless otherwise noted. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 (0.25 mm) and Merck Kieselgel 60 or Fuji-Davison BW-820MH,

(33) The ethyl ketone **57** was also prepared by a way similar to that of **3**.

(34) (a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(35) The stereochemistry of the minor isomer was assigned by analogy.

(36) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729.

(37) These findings are in agreement with those of Evans; see ref 9.

(38) (a) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945. (b) Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *103*, 4278. (c) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787. (d) Paterson, I. McClure, *Tetrahedron Lett.* **1987**, *28*, 1229.

(39) (a) Makino, K.; Kimura, K.; Nakajima, N.; Hashimoto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9073. (b) Makino, K.; Nakajima, N.; Hashimoto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9077.

respectively. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, organic solvents were purified and dried by the appropriate procedure, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

Diacetate 7. To a stirred solution of **6**[17] (11.1 g, 85.3 mmol) in dry ethyl acetate (111 mL) at 0 °C were added 4-(dimethylamino)pyridine (22.9 g, 188 mmol) and acetic anhydride (20.1 mL, 213 mmol). After the reaction mixture was stirred at 25 °C for 1 h, ethanol (5 mL) and water (130 mL) were added slowly to the reaction mixture under ice-cooling and the resultant mixture was then extracted with ethyl acetate (70 mL × 3). The extracts were washed with saturated aqueous NaCl (130 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (920 g of silica gel, 6:1 *n*-hexane−ethyl acetate) gave **7** (18.2 g, 100%) as a pale yellow oil: R_f 0.50 (8:1 *n*-hexane−ethyl acetate); $[\alpha]^{32}_D$ −44.3° (*c* 0.87, $CHCl_3$); ^{1}H-NMR δ 1.05 (3H, d, J = 6.8 Hz), 1.20 (3H, d, J = 6.4 Hz), 2.01 (3H, s), 2.07 (3H, s), 2.42 (1H, dq, J = 6.8, 6.8 Hz), 4.95−5.10 (3H, m), 5.68 (1H, ddd, J = 17.8, 9.8, 8.2 Hz); HRMS (EI) *m/z* 214.1219 (214.1205 calcd for $C_{11}H_{18}O_4$, M^+). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.76; H, 8.58.

Triol 10. Ozone was bubbled into a solution of **7** (10.0 g, 46.6 mmol) in MeOH−CH_2Cl_2 (1:1, 100 mL) at −78 °C for 2 h. Excess ozone was then removed by purging with argon, and dimethyl sulfide (34.1 mL, 46.6 mmol) was added dropwise. The reaction was warmed to 0 °C for 0.5 h, and $NaBH_4$ (2.65 g, 70.0 mmol) was then added to the reaction mixture. After the resultant mixture was stirred at 25 °C for 0.5 h, the mixture was neutralized with solid CO_2. Water (100 mL) was then added to the mixture, and then the resultant mixture was extracted with chloroform (40 mL × 3). The extracts were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. To an ice-cold solution of the residue in dry MeOH (102 mL) was added 5 M NaOMe/MeOH (23.7 mL, 117 mmol). After the reaction was stirred at 25 °C for 3 h, the reaction was quenched with ion-exchange resin IR-120B. The resultant mixture was filtered, and the resin was washed with MeOH. The combined filtrate and washings were concentrated in *vacuo*. Purification of the residue by flash column chromatography (320 g of silica gel, 6:1 chloroform−methanol) gave **10** (5.20 g, 94% from **7**) as a colorless oil: R_f 0.31 (5:1 chloroform−methanol); $[\alpha]^{27}_D$ −7.86° (*c* 1.73, $CHCl_3$); ^{1}H-NMR δ 0.89 (3H, d, J = 6.8 Hz), 1.19 (3H, d, J = 6.4 Hz), 1.84 (1H, m), 2.94 (1H, br s), 3.30 (1H, br d, J = 2.1 Hz), 3.45 (1H, br s), 3.58 (1H, br ddd, J = 6.6, 3.9, 2.1 Hz), 3.65 (2H, br d, J = 6.1 Hz), 3.91 (1H, br dq, J = 6.4, 3.9 Hz); HRMS (EI) *m/z* 134.0964 (134.0943 calcd for $C_6H_{14}O_3$, M^+). Anal. Calcd for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.53; H, 10.82.

Alcohol 11. To an ice-cold solution of **10** (5.20 g, 38.8 mmol) in dry DMF (52.0 mL) were added *p*-methoxybenzaldehyde dimethyl acetal (7.74 mL, 46.3 mmol) and DL-10-camphoresulfonic acid (0.899 g, 3.88 mmol) with stirring. After the reaction mixture was stirred at 25 °C for 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) under ice-cooling, and the resultant mixture was then extracted with ether (20 mL × 3). The extracts were washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (500 g of silica gel, 10:1 toluene−ethyl acetate) gave **11** (9.23 g, 94%) as a pale yellow oil: R_f 0.27 (10:1 chloroform−ethyl acetate); $[\alpha]^{30}_D$ −17.9° (*c* 1.38, $CHCl_3$); ^{1}H-NMR δ 0.81 (3H, d, J = 6.8 Hz), 1.27 (3H, d, J = 6.4 Hz), 1.92 (1H, m), 2.25 (1H, d, J = 9.6 Hz), 3.50 (1H, dd, J = 11.0, 11.0 Hz), 3.63 (1H, dd, J = 10.1, 2.6 Hz), 3.81 (3H, s), 3.97 (1H, m), 4.09 (1H, dd, J = 11.0, 4.6 Hz), 5.47 (1H, s), 6.90 (2H, d, J = 8.8 Hz), 7.42 (2H, d, J = 8.8 Hz); HRMS (EI) *m/z* 253.1431 (253.1440 calcd for $C_{14}H_{21}O_4$, $M + H^+$). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.38; H, 8.32.

Ketone 12. To an ice-cold solution of **11** (9.23 g, 36.6 mmol) in dry CH_2Cl_2 (92.3 mL) were slowly added powdered molecular sieves 3A (73.2 g) and pyridinium chlorochromate (15.3 g, 73.2 mmol) with stirring. After the reaction mixture was stirred at 25 °C for 1.5 h, ether (95.0 mL) was added, and the resultant mixture was then stirred. Purification of the mixture by flash column chromatography (700 g of silica gel, ether) gave **12** (9.15 g, 100%) as a pale yellow oil: R_f 0.17 (6:1 *n*-hexane−ethyl acetate); $[\alpha]^{31}_D$ +11.4° (*c* 0.27, $CHCl_3$); ^{1}H-NMR δ 0.86 (3H, d, J = 6.4 Hz), 2.08 (1H, dddq, J = 11.1, 10.6, 6.4, 4.8 Hz), 2.28 (3H, s), 3.55 (1H, dd, J = 11.1, 11.1 Hz), 3.82 (3H, s), 3.88 (1H, d, J = 10.6 Hz), 4.18 (1H, dd, J = 11.1, 4.8 Hz), 5.49 (1H, s), 6.92 (2H, d, J = 8.5 Hz), 7.44 (2H, d, J = 8.5 Hz); HRMS (EI) *m/z* 250.1191 (250.1205 calcd for $C_{14}H_{18}O_4$, M^+). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.18; H, 7.27.

Olefin 13. To a stirred solution of **12** (7.05 g, 28.2 mmol) in dry benzene (106 mL) was added methylenetriphenylphosphorane (23.4 g, 84.4 mmol) under argon. After the reaction mixture was stirred at 25 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (100 mL), and the resultant mixture was then extracted with ether (30 mL × 3). The extracts were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (350 g of silica gel, 10:1 *n*-hexane−ethyl acetate) gave **13** (6.65 g, 95%) as a white solid: R_f 0.30 (10:1 *n*-hexane−ethyl acetate); $[\alpha]^{30}_D$ −4.66° (*c* 0.30, $CHCl_3$); mp 43.5−44.5 °C (*n*-hexane, flakes); ^{1}H-NMR δ 0.73 (3H, d, J = 6.6 Hz), 1.82 (1H, dd, J = 1.2, 1.2 Hz), 2.05 (1H, dddq, J = 11.1, 10.0, 6.6, 4.6 Hz), 3.54 (1H, dd, J = 11.1, 11.1 Hz), 3.79 (3H, s), 3.86 (1H, d, J = 10.0 Hz), 4.17 (1H, dd, J = 11.1, 4.6 Hz), 4.95−5.05 (2H, m), 5.51 (1H, s), 6.87 (2H, d, J = 8.4 Hz), 7.43 (2H, d, J = 8.4 Hz). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.37; H, 8.31.

Alcohol 14. To a stirred solution of cyclohexene (23.8 mL, 233 mmol) in dry THF (88.0 mL) at 0 °C was added dropwise 10 M BH_3·SMe_2 (11.7 mL, 117 mmol). After 0.5 h, dry THF (29.0 mL) was further added to the reaction mixture, the resultant mixture was then stirred at 0 °C for 3 h, and a solution of **13** (5.83 g, 23.5 mmol) in dry THF (17.5 mL) was added at 0° C. After the mixture was stirred at 25 °C for 1 h, water (135 mL), 3 M aqueous NaOH (39.0 mL), and 30% aqueous H_2O_2 (39.8 mL) were carefully added to the ice-cooled reaction mixture. After 2 h at 50 °C, the mixture was cooled to ambient temperature and extracted with ether (100 mL × 3). The extracts were washed with saturated aqueous NaCl (300 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (625 g of silica gel, 5:2 *n*-hexane−acetone) gave **14** (5.50 g, 88%) as a white solid: R_f 0.13 (5:1 *n*-hexane−acetone); $[\alpha]^{30}_D$ −4.27° (*c* 0.15, $CHCl_3$); mp 78.5−79.5 °C (*n*-hexane, needles); ^{1}H-NMR δ 0.80 (3H, d, J = 6.6 Hz), 1.20 (3H, d, J = 7.2 Hz), 1.99 (1H, m), 2.17 (1H, m), 2.39 (1H, dd, J = 9.0, 2.4 Hz), 3.48 (1H, dd, J = 11.1, 11.1 Hz), 3.51 (1H, dd, J = 11.2, 2.0 Hz), 3.62 (1H, ddd, J = 11.2, 9.0, 4.3 Hz), 3.81 (3H, s), 3.95 (1H, ddd, J = 11.2, 2.0, 2.0 Hz), 4.13 (1H, dd, J = 11.1, 4.8 Hz), 5.38 (1H, s), 6.88 (2H, d, J = 8.4 Hz), 7.37 (2H, d, J = 8.4 Hz); HRMS (EI) *m/z* 267.1620 (267.1596 calcd for $C_{15}H_{22}O_4$, M^+). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.79; H, 8.63.

Tosylate 15. To a stirred solution of **14** (0.507 g, 1.90 mmol) in dry pyridine (10.1 mL) at 0 °C was added *p*-toluenesulfonyl chloride (1.09 g, 5.71 mmol). After the reaction mixture was stirred at 25 °C for 1.5 h, the reaction was quenched with water (10 mL) and the resultant mixture was then extacted with ethyl acetate (5 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (50 g of silica gel, 4:1 *n*-hexane−acetone) gave **15** (0.800 g, 100%) as a white solid: R_f 0.26 (3:1 *n*-hexane−ethyl acetate); $[\alpha]^{26}_D$ −3.28° (*c* 1.06, $CHCl_3$); mp 67.0−67.5 °C (*n*-hexane, cubes); ^{1}H-NMR δ 0.77 (3H, d, J = 6.8 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.97 (1H, m), 2.28 (1H, m), 2.43 (3H, s), 3.37 (1H, dd, J = 10.1, 2.0 Hz), 3.40 (1H, dd, J = 11.2, 11.2 Hz), 3.80 (3H, s), 3.92 (1H, dd, J = 10.0, 7.6 Hz), 4.05 (1H, dd, J = 11.2, 4.6 Hz), 4.28 (1H, dd, J = 10.0, 5.8 Hz), 5.34 (1H, s), 6.85 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.0 Hz); HRMS (EI) *m/z* 421.1660 (421.1685 calcd for $C_{22}H_{29}O_6S$,

M + H^+). Anal. Calcd for $C_{22}H_{28}O_6S$: C, 62.84; H, 6.71. Found: C, 62.58; H, 7.01.

Acetylene 16. To a stirred solution of **15** (1.06 g, 2.52 mmol) in dry dimethyl sulfoxide (10.6 mL) was added lithium acetylide ethylenediamine complex (90%, 1.29 g, 12.6 mmol). After the reaction mixture was stirred at 25 °C for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) under ice-cooling, and the resultant mixture was then extracted with ether (5 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (70 g of silica gel, 8:1 *n*-hexane−acetone) gave **16** (0.409 g, 66%) as a white solid: R_f 0.76 (5:1 chloroform−methanol); $[\alpha]^{30}_D$ −11.6° (*c* 0.38, $CHCl_3$); mp 79.5−80.5 °C (*n*-hexane, needles); ^{1}H-NMR δ 0.88 (3H, d, *J* = 6.8 Hz), 1.19 (3H, d, *J* = 6.6 Hz), 1.97 (1H, t, *J* = 2.1 Hz), 1.98−2.25 (3H, m), 2.46 (1H, m), 3.38 (1H, dd, *J* = 10.0, 2.0 Hz), 3.47 (1H, dd, *J* = 11.1, 11.1 Hz), 3.81 (3H, s), 4.09 (1H, dd, *J* = 11.1, 4.6 Hz), 5.42 (1H, s), 6.88 (2H, d, *J* = 8.4 Hz), 7.39 (2H, d, *J* = 8.4 Hz); HRMS (EI) *m*/*z* 275.1648 (275.1647 calcd for $C_{17}H_{23}O_3$, M + H^+). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.12; H, 8.38.

Diol 17. 16 (0.380 g, 1.39 mmol) was dissolved in 80% aqueous acetic acid (11.5 mL), and the resultant solution was stirred at 40 °C for 13 h. The reaction mixture was then concentrated *in vacuo*. Purification of the residue by flash column chromatography (20 g of silica gel, 1:1 *n*-hexane−ethyl acetate) gave **17** (0.182 g, 84%) as a white solid: R_f 0.16 (1:1 *n*-hexane−ethyl acetate); $[\alpha]^{30}_D$ −14.6° (*c* 1.39, $CHCl_3$); mp 38.0−39.0 °C (*n*-hexane, needles); ^{1}H-NMR δ 0.99 (3H, d, *J* = 6.8 Hz), 1.09 (3H, d, *J* = 6.8 Hz), 1.80−2.05 (2H, m), 2.00 (1H, t, *J* = 2.3 Hz), 2.27 (1H, ddd, *J* = 16.6, 8.0, 2.3 Hz), 2.40 (1H, ddd, *J* = 16.6, 4.3, 2.3 Hz), 2.55 (1H, br t, *J* = 4.2 Hz), 2.81 (1H, br d, *J* = 5.6 Hz), 3.45 (1H, br ddd, *J* = 6.4, 6.4, 5.6 Hz), 3.65 (1H, br ddd, *J* = 10.3, 6.0, 4.2 Hz), 3.85 (1H, br ddd, *J* = 10.3, 4.2, 1.8 Hz); HRMS (EI) *m*/*z* 157.1239 (157.1229 calcd for $C_9H_{17}O_2$, M + H^+). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.07; H, 10.58.

Vinyl Iodide 18. To a stirred solution of Cp_2ZrCl_2 (0.587 g, 2.01 mmol) in dry 1,2-dichloroethane (17.6 mL) was added dropwise 2 M Me_3Al/*n*-hexane (3.01 mL, 6.02 mmol). After 0.5 h at 25 °C, a solution of **17** (0.157 g, 1.00 mmol) in dry 1,2-dichloroethane (1.57 mL) was added to the reaction mixture. After 13 h, to the reaction mixture at −30 °C was added slowly a solution of I_2 (2.55 g, 10.0 mmol) in dry THF (17.8 mL), and the resultant mixture was stirred at −30 °C for 1.5 h. The reaction mixture was warmed to 0 °C, and ice-cooled saturated aqueous K_2CO_3 (40 mL) was added. The resultant mixture was extracted with ether (30 mL × 3). The extracts were washed with saturated aqueous $Na_2S_2O_3$ (30 mL × 2) and saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (30 g of silica gel, 3:1 *n*-hexane−acetone) gave **18** (0.244 g, 82%) as a colorless oil: R_f 0.43 (10:1 chloroform−methanol); $[\alpha]^{31}_D$ −26.1° (*c* 1.42, $CHCl_3$); ^{1}H-NMR δ 0.87 (3H, d, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 7.0 Hz), 1.73−1.95 (2H, m), 1.83 (3H, s), 2.09 (1H, dd, *J* = 13.6, 11.0 Hz), 2.45 (1H, br dd, *J* = 13.6, 2.6 Hz), 2.64 (1H, br s), 2.84 (1H, br s), 3.42 (1H, br dd, *J* = 6.8, 4.4 Hz), 3.65 (1H, br dd, *J* = 10.4, 7.1 Hz), 3.82 (1H, br dd, *J* = 10.4, 2.0 Hz), 5.90 (1H, br s); HRMS (EI) *m*/*z* 298.0460 (298.0430 calcd for $C_{10}H_{19}O_2I$, M^+).

Pivalate 19. To an ice-cold solution of **18** (1.13 g, 3.79 mmol) in dry CH_2Cl_2 (11.2 mL) were added dropwise triethylamine (0.950 mL, 6.82 mmol) and pivaloyl chloride (0.560 mL, 4.54 mmol) with stirring. After the reaction mixture was stirred at 25 °C for 14 h, the mixture was poured into ice-cooled water (13 mL), and the resultant mixture was then extracted with ether (10 mL × 3). The extracts were washed with saturated aqueous NaCl (13 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (75 g of silica gel, 5:1 *n*-hexane−acetone) gave **19** (1.41 g, 97%) as a colorless oil: R_f 0.24 (8:1 *n*-hexane−acetone); $[\alpha]^{32}_D$ −17.5° (*c* 0.79, $CHCl_3$); ^{1}H-NMR δ 0.88 (3H, d, *J* = 6.8 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 1.22 (9H, s), 1.82 (3H, s), 1.84 (1H, m), 2.00 (1H, m), 2.07 (1H, dd, *J* = 13.2, 10.6 Hz), 2.20 (1H, d, *J* = 5.7 Hz), 2.43 (1H, br dd, *J* = 13.2, 2.9 Hz), 3.23 (1H, ddd, *J* = 7.7, 5.7, 5.7 Hz), 4.10 (1H, dd, *J* = 11.0, 4.3 Hz), 4.27 (1H, dd, *J* = 11.0, 5.0 Hz), 5.90 (1H, br s); HRMS (EI) *m*/*z* 382.0992 (382.1005 calcd for $C_{15}H_{37}O_3I$, M^+).

C5−C11 Segment 4. To a stirred solution of **19** (0.443 g, 1.16 mmol) in dry CH_2Cl_2 (8.9 mL) at 0 °C were added dropwise 2,6-lutidine (0.351 mL, 3.02 mmol) and diethylisopropylsilyl trifluoromethansulfonate (0.482 mL, 2.32 mmol). After the reaction mixture was stirred at 25 °C for 4 h, the mixture was poured into ice-cooled water (9 mL), and the resultant mixture was then extracted with ether (7 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (30 g of silica gel, 15:1 *n*-hexane−acetone) gave **4** (0.591 g, 100%) as a colorless oil: R_f 0.23 (25:1 *n*-hexane−ethyl acetate); $[\alpha]^{32}_D$ −0.06°, $[\alpha]^{32}_{435}$ −1.73° (*c* 1.20, $CHCl_3$); ^{1}H-NMR δ 0.64 (4H, q, *J* = 7.7 Hz), 0.86 (3H, d, *J* = 7.0 Hz), 0.95−1.03 (16H, m), 1.21 (9H, s), 1.80 (3H, s), 1.8−1.93 (1H, m), 1.95−2.07 (1H, m), 2.02 (1H, dd, *J* = 13.0, 10.8 Hz), 2.42 (1H, br dd, *J* = 13.0, 3.0 Hz), 3.51 (1H, dd, *J* = 4.5, 4.5 Hz), 3.87 (1H, dd, *J* = 11.0, 7.3 Hz), 4.25 (1H, dd, *J* = 11.0, 4.9 Hz), 5.85 (1H, br s); HRMS (EI) *m*/*z* 510.2001 (510.2026 calcd for $C_{22}H_{43}O_3SiI$, M^+).

Alcohol 21. To a stirred suspension of $CrCl_3$ (5.60 g, 35.4 mmol) in dry THF (56.0 mL) at 0 °C was added slowly $LiAlH_4$ (0.671 g, 17.7 mmol). After 20 min at 0 °C, CH_2=$CHCH(OMe)_2$ (1.40 mL, 11.8 mmol), 1 M TMS-I/*n*-hexane (10.1 mL, 11.8 mmol), and a solution of aldehyde **20**[21] (0.975 g, 2.95 mmol) in dry THF (3.0 mL) were added to the reaction mixture at −42 °C. After 16 h at −42 °C, the reaction was quenched with 1 M aqueous HCl (43.4 mL) under ice-cooling, and the resultant mixture was then extracted with ether (30 mL × 3). The extracts were washed with saturated aqueous NaCl (40 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (120 g of silica gel, 2:1 *n*-hexane−ethyl acetate) gave **21** and its unseparable diastereomers (0.736 g, 62%, 10:1.1:0.5) as a colorless oil: R_f 0.50 (3:1 *n*-hexane−ethyl acetate); ^{1}H-NMR δ 1.14 (3H, d, *J* = 7.0 Hz), 1.99 (1H, m), 2.55 (1H, d, *J* = 2.3 Hz), 3.05 (1H, dd, *J* = 9.0, 4.2 Hz), 3.22 (3H, s), 3.23 (1H, m), 3.33 (1H, dd, *J* = 8.1, 6.2 Hz), 3.73 (1H, m), 5.08 (1H, dd, *J* = 17.1, 1.9 Hz), 5.28 (1H, dd, *J* = 10.2, 1.9 Hz), 5.72 (1H, ddd, *J* = 17.1, 10.2, 8.1 Hz), 7.20−7.35 (9H, m), 7.40−7.48 (6H, m). Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51. Found: C, 80.48; H, 7.75.

Diol 22. To an ice-cold solution of a mixture of **21** and its diastereomers (1.10 g, 2.73 mmol) in dry MeOH (10.0 mL) was added dropwise 10% HCl−MeOH (1.0 mL). After the reaction mixture was stirred at 25 °C for 0.5 h, the reaction was neutralized with Et_3N under ice-cooling, and the resultant mixture was then concentrated in *vacuo*. Purification of the residue by flash column chromatography (200 g of silica gel, 1:2 *n*-hexane−ethyl acetate) gave **22** (0.438 g, 100%) as a mixture of its diastereomers: R_f 0.22 (1:2 *n*-hexane−ethyl acetate); ^{1}H-NMR δ 1.01 (3H, d, *J* = 7.0 Hz), 1.98 (1H, m), 2.46 (1H, br s), 2.50 (1H, br d, *J* = 3.9 Hz), 3.30 (3H, s), 3.56 (1H, dd, *J* = 7.9, 7.8 Hz), 3.60−3.78 (3H, m), 5.37 (1H, dd, *J* = 17.0, 1.9 Hz), 5.42 (1H, dd, *J* = 10.2, 1.9 Hz), 5.76 (1H, ddd, *J* = 17.0, 10.2, 7.9 Hz); HRMS (EI) *m*/*z* 161.1176 (161.1178 calcd for $C_8H_{17}O_3$, M + H^+).

Acetonide 23. To a stirred solution of a mixture of **22** and its diastereomers (0.398 g, 2.48 mmol) in dry CH_2Cl_2 (8.0 mL) at 0 °C were added 2,2-dimethoxypropane (1.20 mL, 9.94 mmol) and DL-10-camphoresulfonic acid (0.231 g, 0.990 mmol). After the reaction mixture was stirred at 25 °C for 16 h, the reaction was neutralized with Et_3N under ice-cooling, and the resultant mixture was then concentrated in *vacuo*. Purification of the residue by flash column chromatography (50 g of silica gel, 20:1 *n*-hexane−ethyl acetate) gave the pure **23** (0.378 g, 76%) as a colorless oil: R_f 0.20 (15:1 *n*-hexane−ethyl acetate); $[\alpha]^{26}_D$ +14.5° (*c* 1.70, $CHCl_3$); ^{1}H-NMR δ 1.11 (3H, d, *J* = 7.0 Hz), 1.36 and 1.39 (each 3H, each s), 1.78 (1H, m), 3.29 (3H, s), 3.43 (1H, dd, *J* = 8.4, 6.8 Hz), 3.61 (1H, dd, *J* = 11.9, 1.8 Hz), 3.81 (1H, dd, *J* = 8.4, 2.2 Hz), 4.09 (1H, dd, *J* = 11.9, 2.8 Hz), 5.27 (1H, dd, *J* = 17.0, 1.9 Hz), 5.29 (1H, dd, *J*

= 9.8, 1.9 Hz), 5.68 (1H, ddd, J = 17.0, 9.8, 6.8 Hz); HRMS (EI) m/z 200.1393 (200.1412 calcd for $C_{11}H_{20}O_3$, M^+). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.83; H, 10.32.

Vinyl Iodide 26. To a stirred solution of **23** (0.497 g, 2.48 mmol) in acetone−water (8:3, 27.5 mL) were added OsO_4 (63.1 mg, 0.250 mmol) and 4-methylmorphorine *N*-oxide (1.46 g, 12.4 mmol). After 16 h at 25 °C, the reaction mixture was poured into saturated aqueous Na_2SO_3 (30 mL), and the resultant mixture was then extracted with ethyl acetate (15 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue (0.500 g) was dissolved in THF−water (3:1, 20 mL), and $NaIO_4$ (0.913 g, 4.26 mmol) was added to the solution. The reaction mixture was stirred at 25 °C for 0.5 h and then poured into ice-cooled water. The resultant mixture was extracted with ether (10 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. A solution of the residue (0.359 g) in dry THF (3.6 mL) was added to a suspension of $CrCl_2$ (1.20 g, 10.6 mmol) in dry THF (12.0 mL) under ice-cooling. The reaction mixture was stirred at 0 °C for 20 min, and CHI_3 (1.4 g, 3.55 mmol) was then added. After 14 h at 25 °C, the reaction mixture was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (1:1, 20 mL), and the resultant mixture was extracted with ether (15 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (60 g of silica gel, 15:1 *n*-hexane−ethyl acetate) gave **26** (0.406 g, 50% from **23**) as a colorless oil: R_f 0.35 (10:1 *n*-hexane−ethyl acetate); $[\alpha]^{32}_D$ +13.6° (*c* 0.85, $CHCl_3$); ^{1}H-NMR δ 1.08 (3H, d, J = 7.0 Hz), 1.36 and 1.39 (each 3H, each s), 1.75 (1H, m), 3.30 (3H, s), 3.43 (1H, dd, J = 8.6, 6.1 Hz), 3.60 (1H, dd, J = 11.9, 1.9 Hz), 3.81 (1H, dd, J = 8.6, 3.0 Hz), 4.08 (1H, dd, J = 11.9, 2.6 Hz), 6.32 (1H, d, J = 14.4 Hz), 6.43 (1H, dd, J = 14.4, 6.1 Hz); HRMS (EI) m/z 327.0435 (327.0453 calcd for $C_{11}H_{20}O_3I$, M + H^+).

C12−C17 Segment 5. To a stirred solution of **26** (0.487 g, 1.49 mmol) in dry THF (15.0 mL) at −78 °C were added dropwise 1.6 M *n*-BuLi/*n*-hexane (1.83 mL, 2.98 mmol) and *n*-Bu_3SnCl (0.970 mL, 3.58 mmol). After the reaction mixture was stirred at −78 °C for 1 h, water (20 mL) was added, and the resultant mixture was warmed to 25 °C and then extracted with ether (10 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (37 g of silica gel, 20:1 *n*-hexane−ethyl acetate) gave **5** (0.504 g, 69%) as a colorless oil: R_f 0.45 (10:1 *n*-hexane−ethyl acetate); $[\alpha]^{32}_D$ +16.4° (*c* 1.01, $CHCl_3$); ^{1}H-NMR δ 0.85−0.93 (15H, m), 1.10 (3H, d, J = 7.0 Hz), 1.24−1.38 (6H, m), 1.35 (3H, s), 1.37 (3H, s), 1.44−1.57 (6H, m), 1.77 (1H, m), 3.28 (3H, s), 3.40 (1H, ddd, J = 9.0, 6.3, 1.2 Hz), 3.60 (1H, dd, J = 11.6, 1.8 Hz), 3.82 (1H, dd, J = 9.0, 2.2 Hz), 4.08 (1H, dd, J = 11.6, 2.8 Hz), 5.79 (1H, dd, J = 19.0, 6.3 Hz), 6.21 (1H, dd, J = 19.0, 1.2 Hz); HRMS (EI) m/z 490.2427 (490.2469 calcd for $C_{23}H_{46}O_3Sn$, M^+).

Alcohol 28. To a stirred solution of **27**[19d] (1.90 g, 10.2 mmol) in dry ether (19.0 mL) was added dropwise 4 M MeMgI/ether (25.0 mL, 100 mmol) under ice-cooling. The reaction mixture was stirred at 25 °C for 0.5 h, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) under ice-cooling, and the resultant mixture was then extracted with ethyl acetate (20 mL × 3). The extracts were washed with saturated aqueous NaCl (30 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (100 g of silica gel, 1:1 toluene−ethyl acetate) gave **28** (1.92 g, 94%) as a colorless oil and a mixture of C5 epimers: R_f 0.30 (2:1 *n*-hexane−ethyl acetate); ^{1}H-NMR δ 1.11 (1/3 × 3H, d, J = 7.0 Hz), 1.13 (2/3 × 3H, d, J = 7.0 Hz), 1.16 (1/3 × 3H, d, J = 6.4 Hz), 1.21 (2/3 × 3H, d, J = 6.4 Hz), 1.30 and 1.54 (each 1/3 × 3H, each s), 1.32 and 1.55 (each 2/3 × 3H, each s), 2.24 (1/3H, m), 2.36 (2/3H, d, J = 3.9 Hz), 2.53 (2/3H, m), 2.77 (1/3H, d, J = 1.7 Hz), 3.48 (1/3H, dd, J = 8.2, 4.2 Hz), 3.58 (2/3H, dd, J = 5.9, 4.1 Hz), 3.90−4.10 (1H, m), 4.33 (2/3H, dd, J = 4.0, 1.9 Hz), 4.35 (1/3H, dd, J = 4.0, 1.0 Hz), 5.79 (2/3H, d, J = 4.0 Hz), 5.86 (1/3H, d, J = 4.0 Hz). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.10; H, 9.21.

Ketone 29. To a stirred solution of **28** (2.75 g, 13.7 mmol) in dry CH_2Cl_2 (27.5 mL) at 0 °C were added powdered molecular sieves 3A (14.1 g) and pyridinium chlorochromate (11.8 g, 54.8 mmol). After the reaction mixture was stirred at 25 °C for 0.5 h, ether (42 mL) was added. The resultant mixture was stirred and then purified by flash column chromatography (134 g of silica gel, ether) to give **29** (2.55 g, 94%) as a colorless oil: R_f 0.41 (2:1 *n*-hexane−ethyl acetate); $[\alpha]^{33}_D$ −21.1° (*c* 0.94, $CHCl_3$); ^{1}H-NMR δ 1.13 (3H, d, J = 7.1 Hz), 1.27 and 1.42 (each 3H, each s), 2.34 (3H, s), 2.93 (1H, dq, J = 7.1, 1.6 Hz), 4.00 (1H, d, J = 1.6 Hz), 4.32 (1H, d, J = 4.0 Hz), 5.92 (1H, d, J = 4.0 Hz). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.15. Found: C, 59.87; H, 8.26.

Olefin 30. To a stirred solution of **29** (2.50 g, 12.5 mmol) in dry benzene (37.5 mL) was added methylenetriphenylphosphorane (13.9 g, 50.0 mmol). The reaction mixture was stirred at 25 °C for 0.5 h and then concentrated in *vacuo*. Purification of the residue by flash column chromatography (900 g of silica gel, 10:1 *n*-hexane−ethyl acetate) gave **30** (2.02 g, 81%) as a colorless oil: R_f 0.22 (10:1 *n*-hexane−ethyl acetate); $[\alpha]^{26}_D$ −1.60°, $[\alpha]^{26}_{435}$ −2.29° (*c* 0.43, $CHCl_3$); ^{1}H-NMR δ 1.09 (3H, d, J = 7.2 Hz), 1.35 and 1.55 (each 3H, each s), 1.80 (3H, br s), 2.26 (1H, ddq, J = 7.2, 7.2, 2.8 Hz), 3.95 (1H, br d, J = 7.2 Hz), 4.35 (1H, dd, J = 4.1, 2.8 Hz), 4.88 (1H, br s), 5.03 (1H, br s), 5.74 (1H, d, J = 4.1 Hz). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.75. Found: C, 66.45; H, 9.89.

Acetonide 31. To a solution of **30** (0.500 g, 2.52 mmol) in dioxane (10.0 mL) was added a catalytic amount of Raney-Ni (W4). After the reaction mixture was vigorously stirred at 25 °C for 24 h under H_2, the mixture was filtered, and the catalyst was washed with dioxane. The combined filtrate and washings were concentrated in *vacuo*. Purification of the residue by flash column chromatography (25 g of silica gel, 3:1 *n*-hexane−acetone) gave **31** (0.468 g, 92%) as a colorless oil: R_f 0.20 (10:1 *n*-hexane−ethyl acetate); $[\alpha]^{30}_D$ +25.5° (*c* 1.86, $CHCl_3$); ^{1}H-NMR δ 0.91 (3H, d, J = 6.4 Hz), 1.00 (3H, d, J = 6.4 Hz), 1.06 (3H, d, J = 7.1 Hz), 1.31 and 1.53 (each 3H, each s), 1.99 (1H, dseptet, J = 8.6, 6.4 Hz), 2.27 (1H, ddq, J = 7.1, 3.6, 0.9 Hz), 3.27 (1H, dd, J = 8.6, 3.6 Hz), 4.29 (1H, dd, J = 4.0, 0.9 Hz), 5.77 (1H, d, J = 4.0 Hz). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.06. Found: C, 66.23; H, 9.69.

Free Sugar 32. A solution of **31** (4.68 g, 23.3 mmol) in 50% aqueous acetic acid (47.0 mL) was stirred at 80 °C for 2 h and then concentrated in *vacuo*. Purification of the residue by flash column chromatography (230 g of silica gel, 3:2 *n*-hexane−acetone) gave **32** (3.05 g, 93%) as a white solid: R_f 0.20 (3:2 *n*-hexane−acetone); mp 75.0−75.5 °C (*n*-hexane, needles); ^{1}H-NMR δ 0.94 (3H, d, J = 7.0 Hz), 0.95 (3H, d, J = 6.4 Hz), 1.12 (4/5 × 3H, d, J = 6.4 Hz), 1.14 (1/5 × 3H, d, J = 6.4 Hz), 1.65−1.95 (2H, m), 2.70 (4/5H, br d, J = 9.2 Hz), 2.83 (1/5H, br d, J = 5.2 Hz), 3.30 (4/5H, dd, J = 8.4, 6.0 Hz), 3.62 (1/5H, dd, J = 8.0, 5.9 Hz), 3.65 (4/5H, ddd, J = 9.2, 9.2, 4.2 Hz), 3.78 (1/5H, ddd, J = 5.2, 5.2, 2.0 Hz), 4.09 (4/5H, br d, J = 3.6 Hz), 4.14 (1/5H, br s), 5.10−5.25 (1H, m). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.01; H, 10.49.

Triol 33. To a stirred solution of **32** (3.05 g, 19.0 mmol) in dry THF (47.0 mL) at 0 °C was added slowly $LiAlH_4$ (1.44 g, 38.0 mmol). After the reaction mixture was stirred at 25 °C for 16 h, water (2.3 mL), 10% aqueous NaOH (2.5 mL), and water (6.8 mL) were carefully added under ice-cooling. The resultant mixture was filtered, and the filter cake was washed with $CHCl_3$. The filtrate and washing were combined and then concentrated in *vacuo*. Purification of the residue by flash column chromatography (500 g of silica gel, 10:1 chloroform−methanol) gave **33** (2.38 g, 77%) as a white solid: R_f 0.40 (10:1 chloroform−methanol); $[\alpha]^{30}_D$ −38.3° (*c* 0.70, $CHCl_3$); mp 65.5−66.0 °C (*n*-hexane, flakes); ^{1}H-NMR δ 0.92−0.97 (9H, m), 1.75−1.95 (2H, m), 1.95−2.15 (3H, br s), 3.36 (1H, dd, J = 6.0, 6.0 Hz), 3.60 (1H, dd, J = 11.0, 4.0 Hz), 3.71 (1H, dd, J = 11.0, 8.0 Hz), 4.00 (1H, ddd, J = 8.0, 4.0, 2.4 Hz). Anal. Calcd for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.18; H, 11.20.

Carbonate 34. To a stirred solution of **33** (2.08 g, 12.8 mmol) in dry CH_2Cl_2 (62.4 mL) was added *N*,*N*′-carbonyldi-

imidazole (2.70 g, 16.6 mmol). After the reaction mixture was stirred at 25 °C for 2.5 h, saturated aqueous NaCl (60 mL) was added, and the resultant mixture was then extracted with ethyl acetate (30 mL × 3). The extracts were concentrated *in vacuo*. Purification of the residue by flash column chromatography (150 g of silica gel, 1:1 *n*-hexane−ethyl acetate) gave **34** (2.45 g, 85%) as a white solid: R_f 0.66 (1:4 toluene−ethyl acetate); $[\alpha]^{27}_D$ −40.0° (*c* 0.33, $CHCl_3$); mp 46.0−46.5 °C (*n*-hexane, flakes); ^{1}H-NMR δ 0.84 (3H, d, J = 6.4 Hz), 0.99 (3H, d, J = 6.4 Hz), 1.00 (3H, d, J = 7.0 Hz), 1.74 (1H, d, J = 4.6 Hz), 1.75−1.95 (2H, m), 3.34 (1H, ddd, J = 9.9, 4.6, 2.4 Hz), 4.27 (1H, dd, J = 10.4, 8.0 Hz), 4.61 (1H, dd, J = 10.4, 8.0 Hz), 4.93 (1H, ddd, J = 8.0, 8.0, 5.9 Hz). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.17; H, 8.74.

Silyl Ether 35. To a stirred solution of **34** (6.54 g, 34.7 mmol) in dry DMF (130 mL) at 0 °C were added imidazole (8.51 g, 125 mol) and *tert*-butyldimethylsilyl chloride (15.7 g, 104 mmol). After the reaction mixture was stirred at 40 °C for 16 h, ice-cold water (150 mL) was added, and the resultant mixture was then extracted with ether (50 mL × 3). The extracts were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (500 g of silica gel, 4:1 *n*-hexane−ethyl acetate) gave **35** (9.32 g, 87%) as a colorless oil: R_f 0.73 (1:1 *n*-hexane−ethyl acetate); $[\alpha]^{27}_D$ −53.3° (*c* 1.19, $CHCl_3$); ^{1}H-NMR δ 0.08 (6H, s), 0.89 (9H, s), 0.98 (3H, d, J = 6.4 Hz), 1.03 (3H, d, J = 6.4 Hz), 1.04 (3H, d, J = 7.0 Hz), 1.93 (1H, dseptet, J = 6.4, 4.4 Hz), 2.30 (1H, m), 3.86 (2H, d, J = 4.4 Hz), 4.30−4.36 (2H, m). Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.27; H, 10.19.

Diol 36. To a stirred solution of **35** (1.74 g, 5.64 mmol) in MeOH (35.0 mL) at 0 °C was added dropwise 1 M aqueous NaOH (11.9 mL, 11.9 mmol). After the reaction mixture was stirred at 25 °C for 16 h, the reaction was neutralized with ion-exchange resin CG-50 under ice-cooling. The resultant mixture was filtered, and the resin was washed with MeOH. The filtrate and washing were combined and then concentrated in *vacuo*. Purification of the residue by flash column chromatography (80 g of silica gel, 3:2 *n*-hexane−ethyl acetate) gave **36** (1.39 g, 87%) as a colorless oil: R_f 0.20 (1:1 *n*-hexane−ethyl acetate); $[\alpha]^{27}_D$ −5.71° (*c* 1.05, $CHCl_3$); ^{1}H-NMR δ 0.10 (3H, s), 0.12 (3H, s), 0.92 (3H, d, J = 6.6 Hz), 0.93 (9H, s), 0.94 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 7.1 Hz), 1.77 (1H, ddq, J = 7.1, 2.1, 2.0 Hz), 1.93 (1H, dseptet, J = 6.6, 6.6 Hz), 2.55 (2H, br s), 3.43 (1H, dd, J = 6.6, 2.1 Hz), 3.45 (1H, dd, J = 10.4, 4.1 Hz), 3.64 (1H, dd, J = 10.4, 8.0 Hz), 4.17 (1H, ddd, J = 8.0, 4.1, 2.0 Hz). Anal. Calcd for $C_{14}H_{32}O_3Si$: C, 60.82; H, 11.67. Found: C, 60.59; H, 11.83.

Epoxide 38. To a stirred solution of **36** (2.54 g, 9.20 mmol) in dry pyridine (50.9 mL) at 0 °C was added *p*-toluenesulfonyl chloride (5.26 g, 27.6 mmol). The reaction mixture was stirred at 25 °C for 4 h and then poured into ice-cold water (60 mL). The resultant mixture was extracted with ethyl acetate (30 mL × 3). The extracts were washed with saturated aqueous NaCl (100 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. To a stirred solution of the residue (3.56 g) in dry $CHCl_3$ (35.6 mL) at 0 °C was added dropwise 5 M NaOMe/MeOH (2.48 mL, 12.4 mmol). After the reaction mixture was stirred at 25 °C for 16 h, the reaction was neutralized with solid CO_2, and the resultant mixture was poured into ice-cold water (40 mL). The resultant mixture was extracted with $CHCl_3$ (20 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (120 g of silica gel, 6:1 *n*-hexane−ethyl acetate) gave **38** (1.69 g, 71% from **36**) as a colorless oil: R_f 0.56 (4:1 *n*-hexane−ethyl acetate); $[\alpha]^{30}_D$ −8.97° (*c* 1.36, $CHCl_3$); ^{1}H-NMR δ 0.05 (6H, s), 0.87 (3H, d, J = 6.4 Hz), 0.91 (9H, s), 0.92 (3H, d, J = 6.4 Hz), 1.04 (3H, d, J = 6.8 Hz), 1.42 (1H, m), 1.83 (1H, m), 2.58 (1H, dd, J = 4.6, 2.4 Hz), 2.79 (1H, dd, J = 4.6, 4.0 Hz), 2.87 (1H, dd, J = 6.9, 4.0, 2.4 Hz), 3.41 (1H, dd, J = 5.2, 5.0 Hz). Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.05; H, 11.70. Found: C, 64.81; H, 11.94.

Dithioacetal 40. A solution of 2−ethyl-1,3-dithiane (0.437 g, 2.96 mmol) in dry THF (4.78 mL) was cooled to −40 °C under argon. A solution of 1.69 M *n*-BuLi/hexane (1.75 mL, 2.96 mmol) was added to the solution under stirring. After the reaction mixture was stirred at −20 °C for 2 h, the mixture was cooled to −50 °C. To this solution was added dropwise a solution of **38** (0.153 g, 0.930 mmol) in dry THF (0.46 mL). The resultant solution was further stirred at −50 → −20 °C for 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl (10 mL) under ice-cooling, and the resultant mixture was then extracted with ethyl acetate (5 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (30 g of silica gel, 15:1 *n*-hexane−ethyl acetate) gave essentially pure **39** (0.241 g) as a pale yellow oil. To a stirred solution of **39** (0.241 g) in dry THF (2.41 mL) at 0 °C was added dropwise 1 M TBAF/THF (0.889 mL, 0.889 mmol). After the reaction mixture was stirred at 25 °C for 2.5 h, the reaction was quenched with ice-cold water (3 mL), and the resultant mixture was then extracted with ethyl acetate (3 mL × 3). The extracts were washed with saturated aqueous NaCl (4 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (10 g of silica gel, 6:1 *n*-hexane−ethyl acetate) gave **40** (0.168 g, 97% from **38**) as a colorless oil: R_f 0.19 (4:1 *n*-hexane−ethyl acetate); $[\alpha]^{27}_D$ +42.0° (*c* 0.70, $CHCl_3$); ^{1}H-NMR δ 0.96 (6H, d, J = 6.4 Hz), 0.97 (3H, d, J = 7.0 Hz), 1.04 (3H, t, J = 7.4 Hz), 1.72−2.20 (7H, m), 2.50 (1H, dd, J = 15.0, 9.2 Hz), 2.72−2.86 (2H, m), 2.88−3.08 (2H, m), 3.34 (1H, dd, J = 12.0, 5.4 Hz), 3.41 (1H, d, J = 5.2 Hz), 3.88 (1H, d, J = 1.9 Hz), 4.27 (1H, br d, J = 9.6 Hz). Anal. Calcd for $C_{14}H_{28}O_2S_2$: C, 57.49; H, 9.65. Found: C, 57.31; H, 9.88.

Cyclic Silyl Ether 41. To a stirred solution of **40** (0.175 g, 0.575 mmol) in dry DMF (0.383 mL) at 0 °C was added dropwise *t*-$Bu_2Si(OTf)_2$ (97%, 0.259 mL, 0.690 mmol). After the reaction mixture was stirred at 25 °C for 2 h, the reaction was quenched with ice-cold water (1 mL), and the resultant mixture was then extracted with ethyl acetate (0.5 mL × 3). The extracts were washed with saturated aqueous NaCl (1 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (12 g of silica gel, 15:1 *n*-hexane−ethyl acetate) gave **41** (0.245 g, 95%) as a white solid: R_f 0.75 (4:1 *n*-hexane−ethyl acetate); $[\alpha]^{28}_D$ +59.0° (*c* 0.41, $CHCl_3$); mp 74.0−75.0 °C (hexane, flakes); ^{1}H-NMR δ 0.88 (6H, d, J = 6.4 Hz), 0.98 (3H, d, J = 6.8 Hz), 1.03 (18H, s), 1.07 (3H, t, J = 7.2 Hz), 1.75 (1H, m), 1.88−2.20 (7H, m), 2.65−2.86 (4H, m), 3.61 (1H, dd, J = 8.0, 3.0 Hz), 4.39 (1H, ddd, J = 8.0, 5.2, 1.7 Hz). Anal. Calcd for $C_{22}H_{44}O_2SiS_2$: C, 61.05; H, 10.25. Found: C, 61.22; H, 10.13.

C18−C25 Segment 3. To a stirred solution of **41** (0.165 g, 0.381 mmol) in 80% aqueous MeCN (4.95 mL) were added $CaCO_3$ (0.382 g, 3.81 mmol) and MeI (0.712 mL, 11.4 mmol). After the reaction mixture was stirred at 25 °C for 6 h, water (10 mL) was added, and the resultant mixture was extracted with ethyl acetate (7 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (13 g of silica gel, 40:1 *n*-hexane−ethyl acetate) gave **3** (0.0940 g, 72%) as a white solid: R_f 0.63 (10:1 *n*-hexane−ethyl acetate); $[\alpha]^{30}_D$ +85.2° (*c* 0.89, $CHCl_3$); mp 40.0−40.5 °C (hexane); IR ($CHCl_3$) 1719 cm^{-1} (C═O); ^{1}H-NMR δ 0.73 (3H, d, J = 7.0 Hz), 0.86 (3H, d, J = 6.9 Hz), 0.97 (9H, s), 0.99 (9H, s), 1.01 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.1 Hz), 1.73 (1H, dseptet, J = 7.0, 2.1 Hz), 2.23 (1H, m), 2.38 (1H, dd, J = 14.2, 3.4 Hz), 2.53 (1H, dq, J = 10.8, 7.0 Hz), 2.56 (1H, dq, J = 10.8, 7.0 Hz), 2.71 (1H, dd, J = 14.2, 10.1 Hz), 3.68 (1H, dd, J = 9.6, 2.1 Hz), 4.62 (1H, ddd, J = 10.1, 5.9, 3.4 Hz). Anal. Calcd for $C_{19}H_{38}O_3Si$: C, 66.37; H, 11.53. Found: C, 66.61; H, 11.18.

Coupling 4 and 5. To a solution of **4** (1.01 g, 1.98 mmol) and **5** (0.969 g, 1.98 mmol) in dry DMF (24.2 mL) was added [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) chloride ($PdCl_2$(dppf)) (0.290 g, 0.396 mmol). After the reaction mixture was stirred at 50 °C for 15 h under argon, ice-cold water (25 mL) was added, and the resultant mixture was then extracted with ether (15 mL × 3). The extracts were washed with saturated aqueous NaCl (15 mL), dried over anhydrous Na_2-

SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (230 g of silica gel, 50:1 benzene−acetone) gave **42** (0.694 g, 60%) as a colorless oil: R_f 0.25 (80:1 chloroform−methanol); $[\alpha]^{30}_D$ +18.1° (*c* 1.32, $CHCl_3$); ^{1}H-NMR δ 0.64 (4H, q, J = 7.8 Hz), 0.88 (3H, d, J = 6.4 Hz), 0.95−1.05 (16H, m), 1.11 (3H, d, J = 6.8 Hz), 1.21 (9H, s), 1.365 and 1.37 (3H, each s), 1.385 and 1.39 (3H, each s), 1.72−1.93 (3H, m), 1.74 (3H, s), 2.03 (1H, m), 2.30 (1H, br d, J = 11.6 Hz), 3.28 (3H, s), 3.45−3.55 (2H, m), 3.60 (1H, dd, J = 11.9, 1.8 Hz), 3.83 (1H, dd, J = 8.5, 2.3 Hz), 3.87 (1H, dd, J = 10.6, 7.7 Hz), 4.09 (1H, dd, J = 11.9, 2.6 Hz), 4.28 (1H, dd, J = 10.6, 4.6 Hz), 5.37 and 5.39 (1H, each dd, J = 15.6, 7.6 Hz), 5.86 (1H, d, J = 11.0 Hz), 6.45 (1H, dd, J = 15.6, 11.0 Hz); HRMS (EI) *m*/*z* 582.4320 (582.4316 calcd for $C_{33}H_{62}O_6Si$, M^+). Anal. Calcd for $C_{33}H_{62}O_6Si$: C, 67.99; H, 10.72. Found: C, 67.60; H, 11.02.

Alcohol 43. To a stirred solution of **42** (0.602 g, 1.03 mmol) in dry ether (18.1 mL) at 0 °C was added dropwise 1.06 M MeLi/ether (2.46 mL, 2.58 mmol). After the reaction mixture was stirred at 25 °C for 0.5 h, the reaction was quenched with ice-cold water (20 mL), and the resultant mixture was then extracted with ether (8 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (50 g of silica gel, 50:1 *n*-hexane−acetone) gave **43** (0.407 g, 79%) as a pale yellow oil: R_f 0.24 (5:1 *n*-hexane−acetone); $[\alpha]^{27}_D$ +14.7° (*c* 2.46, $CHCl_3$); ^{1}H-NMR δ 0.63−0.75 (4H, m), 0.89 (3H, d, J = 6.6 Hz), 0.97−1.07 (16H, m), 1.12 (3H, d, J = 6.8 Hz), 1.365 and 1.37 (3H, each s), 1.385 and 1.39 (3H, each s), 1.73−2.00 (4H, m), 1.76 (3H, s), 2.27 (1H, br dd, J = 12.4, 3.0 Hz), 2.70 (1H, t, J = 5.9 Hz), 3.29 (3H, s), 3.45−3.78 (5H, m), 3.83 (1H, dd, J = 8.9, 2.3 Hz), 4.09 (1H, dd, J = 11.8, 2.4 Hz), 5.38 and 5.41 (1H, each dd, J = 15.2, 7.2 Hz), 5.87 (1H, d, J = 10.8 Hz), 6.45 (1H, dd, J = 15.2, 10.8 Hz); HRMS (EI) *m*/*z* 498.3744 (498.3741 calcd for $C_{28}H_{54}O_5Si$, M^+).

Phosphonic Ester 47. To a stirred solution of **46** (0.200 g, 0.833 mmol) in dry THF (1.0 mL) at −78 °C was added 1 M $NaN(TMS)_2$/THF (1.25 mL, 1.25 mmol). After the reaction mixture was stirred at −78 °C for 0.5 h, a solution of **45** (0.243 g, 1.25 mmol) in dry THF (1.62 mL) was added to the reaction mixture. The resultant mixture was further stirred at 25 °C for 12 h, and the reaction was quenched with saturated aqueous NH_4Cl (5 mL) under ice-cooling. The resultant mixture was extracted with ether (5 mL × 3). The extracts were washed with saturated aqueous NaCl (7 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (25 g of silica gel, 10:1 chloroform−methanol then 25 g of silica gel, 3:2 *n*-hexane−acetone) gave **47** (0.0910 g, 39%) and the *trans* isomer (0.0769 g, 33%) as colorless oils. **47**: R_f 0.51 (3:1 *n*-hexane−acetone); ^{1}H-NMR δ 1.25−1.38 (9H, m), 3.27 (1H, m), 3.72 (3H, s), 3.80 (3H, s), 4.05−4.20 (4H, m), 6.14 (1H, dd, J = 11.0, 6.2 Hz). Anal. Calcd for $C_{11}H_{21}O_6P$: C, 47.14; H, 7.55. Found: C, 46.89; H, 7.29. *Trans* isomer of **47**: R_f 0.49 (3:1 *n*-hexane−acetone); ^{1}H-NMR δ 1.25−1.38 (9H, m), 3.64 (3H, s), 3.83 (3H, s), 3.94 (1H, m), 4.03−4.18 (4H, m), 5.10 (1H, dd, J = 11.0, 8.0 Hz). Anal. Calcd for $C_{11}H_{21}O_6P$: C, 47.14; H, 7.55. Found: C, 46.90; H, 7.27.

Ethyl Ester 49. To a stirred solution of oxalyl chloride (0.136 mL, 1.56 mmol) in dry CH_2Cl_2 (3.68 mL) at −78 °C was added dropwise a solution of dimethyl sulfoxide (0.207 mL, 3.12 mmol) in dry CH_2Cl_2 (0.519 mL). After the reaction mixture was stirred at −78 °C for 3 min, a solution of **43** (0.389 g, 0.780 mmol) in dry CH_2Cl_2 (2.34 mL) was added to the reaction mixture. After the resultant mixture was stirred at −78 °C for 20 min, triethylamine (0.654 mL, 4.68 mmol) was added, and the resultant mixture was allowed to warm to 0 °C over 40 min with stirring. The reaction was quenched with water (15 mL) and the resultant mixture was then extracted with a mixture of benzene−ether (4:1, 10 mL × 3). The extracts were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. To a stirred solution of the crude oil (0.388 g) in dry toluene (11.6 mL) was added ethyl 2-(triphenylphosphoranylidene)propionate **48** (2.32 g, 7.02 mmol). After the reaction mixture was stirred at 100 °C for 14 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 25 °C and the resultant mixture was extracted with ether (5 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (45 g of silica gel, 8:1 *n*-hexane−ethyl acetate) gave **49** (0.444 g, 98%) as a colorless oil: R_f 0.35 (8:1 *n*-hexane−ethyl acetate); $[\alpha]^{24}_D$ +27.3° (*c* 0.80, $CHCl_3$); ^{1}H-NMR δ 0.64 (4H, q, J = 7.8 Hz), 0.78 (3H, d, J = 6.4 Hz), 0.95−1.05 (16H, m), 1.10 (3H, d, J = 6.8 Hz), 1.28 (3H, t, J = 7.2 Hz), 1.365 and 1.37 (3H, each s), 1.385 and 1.39 (3H, each s), 1.70−1.90 (3H, m), 1.74 (3H, s), 1.85 (3H, d, J = 1.6 Hz), 2.24 (1H, m), 2.70 (1H, m), 3.28 (3H, s), 3.45−3.58 (2H, m), 3.59 (1H, dd, J = 11.9, 1.6 Hz), 3.82 (1H, dd, J = 8.6, 2.4 Hz), 4.08 (1H, dd, J = 11.9, 2.6 Hz), 4.10−4.24 (2H, m), 5.37 and 5.39 (1H, each dd, J = 15.2, 7.2 Hz), 5.85 (1H, d, J = 10.9 Hz), 6.44 (1H, dd, J = 15.2, 10.9 Hz), 6.96 (1H, dd, J = 10.0, 1.6 Hz); HRMS (EI) *m*/*z* 580.4153 (580.4160 calcd for $C_{33}H_{60}O_6Si$, M^+). Anal. Calcd for $C_{33}H_{60}O_6Si$: C, 68.23; H, 10.41. Found: C, 68.11; H, 10.79.

Allyl Alcohol 50. To a stirred solution of **49** (0.343 g, 0.578 mmol) in dry toluene (10.3 mL) at −78 °C was added dropwise 1.02 M diisobutylalminum hydride/toluene (1.26 mL, 1.27 mmol). After the reaction mixture was stirred at −78 °C for 5 min, the reaction was carefully quenched with methanol, and the resultant mixture was then allowed to warm to 25 °C. A solution of potassium sodium tartrate tetrahydrate (1.63 g, 5.78 mmol) in water (8.16 mL) was added to the mixture, and the resultant mixture was then extracted with ether (5 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (31 g of silica gel, 4:1 *n*-hexane−ethyl acetate) gave **50** (0.301 g, 97%) as a colorless oil: R_f 0.23 (5:1 *n*-hexane−ethyl acetate); $[\alpha]^{28}_D$ +17.9° (*c* 1.03, $CHCl_3$); ^{1}H-NMR δ 0.64 (4H, q, J = 7.9 Hz), 0.78 (3H, d, J = 6.4 Hz), 0.94−1.05 (16H, m), 1.11 (3H, d, J = 6.8 Hz), 1.365 and 1.37 (3H, each s), 1.385 and 1.39 (3H, each s), 1.69 (3H, d, J = 1.4 Hz), 1.72−1.85 (3H, m), 1.74 (3H, s), 2.30 (1H, m), 2.61 (1H, m), 3.28 (3H, s), 3.45−3.55 (2H, m), 3.60 (1H, dd, J = 11.8, 1.8 Hz), 3.83 (1H, dd, J = 8.4, 2.4 Hz), 4.00 (2H, br d, J = 5.5 Hz), 4.09 (1H, dd, J = 11.8, 2.6 Hz), 5.87 and 5.89 (1H, each dd, J = 15.6, 7.6 Hz), 5.57 (1H, dd, J = 9.6, 1.4 Hz), 5.85 (1H, d, J = 11.0 Hz), 6.44 (1H, dd, J = 15.6, 11.0 Hz); HRMS (EI) *m*/*z* 538.4040 (538.4054 calcd for $C_{31}H_{58}O_5Si$, M^+).

Aldehyde 51. To a solution of **50** (0.980 g, 1.82 mmol) in dry CH_2Cl_2 (29.4 mL) was added MnO_2 (4.74 g, 54.5 mmol). After the reaction mixture was stirred at 25 °C for 2 h, the mixture was filtered through Celite, and the filter cake was washed with CH_2Cl_2. The filtrate and washings were combined and concentrated *in vacuo*. Purification of the residue by flash column chromatography (100 g of silica gel, 8:1 *n*-hexane−ethyl acetate) gave **51** (0.976 g, 100%) as a colorless oil: R_f 0.47 (4:1 *n*-hexane−ethyl acetate); $[\alpha]^{27}_D$ +21.7° (*c* 0.90, $CHCl_3$); ^{1}H-NMR δ 0.67 (4H, q, J = 7.8 Hz), 0.75 (3H, d, J = 6.4 Hz), 0.95−1.15 (19H, m), 1.365 and 1.37 (3H, each s), 1.38 and 1.39 (3H, each s), 1.68−1.90 (3H, m), 1.74 (3H, s), 1.78 (3H, d, J = 1.6 Hz), 2.22 (1H, m), 2.91 (1H, m), 3.28 (3H, s), 3.50 (1H, m), 3.57−3.65 (2H, m), 3.82 and 3.83 (1H, each dd, J = 8.4, 2.4 Hz), 4.09 (1H, dd, J = 11.8, 2.6 Hz), 5.39 and 5.41 (1H, dd, J = 15.4, 7.0 Hz), 5.85 (1H, d, J = 10.8 Hz), 6.44 (1H, dd, J = 15.4, 10.8 Hz), 6.78 (1H, dd, J = 10.0, 1.6 Hz), 9.42 (1H, s); HRMS (EI) *m*/*z* 537.3975 (537.3975 calcd for $C_{31}H_{57}O_5Si$, $M + H^+$).

Methyl Ester 52. To a solution of **46** (0.570 g, 2.37 mmol) in dry THF (5.70 mL) at −78 °C was added dropwise 1.0 M $NaN(TMS)_2$/THF (2.28 mL, 2.28 mmol) with stirring. After the reaction mixture was stirred at −78 °C for 0.5 h, a solution of **51** (0.255 g, 0.475 mmol) in dry THF (2.50 mL) was added to the reaction mixture at −78 °C. After the resultant mixture was stirred at 25 °C for 0.5 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) under ice-cooling, and the resultant mixture was then extracted with ether (5 mL × 3). The extracts were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography

(30 g of silica gel, 6:1 *n*-hexane−ethyl acetate) gave **52** (0.589 g, 89%) as a colorless oil and a mixture of *cis*- and *trans*-isomers (*Z*/*E* = 2/1): R_f 0.45 (6:1 *n*-hexane−acetone); ^{1}H-NMR δ 0.57−0.70 (4H, m), 0.76 and 0.78 (3H, each d, J = 6.4 Hz), 0.93−1.05 (16H, m), 1.11 (3H, d, J = 6.8 Hz), 1.355 and 1.36 (3H, each s), 1.38 and 1.39 (3H, each s), 1.70−1.85 (3H, m), 1.73 (3H, s), 1.99 (3H, d, J = 1.4 Hz), 2.20−2.37 (1H, m), 2.55−2.78 (1H, m), 3.28 (3H, s), 3.43−3.55 (2H, m), 3.56 (1H, dd, J = 11.9, 1.5 Hz), 3.63 (1/3 × 3H, s), 3.65 (2/3 × 3H, s), 3.76 (1/3 × 3H, s), 3.80 (2/3 × 3H, s), 3.82 (1H, dd, J = 8.6, 2.3 Hz), 4.09 (1H, dd, J = 11.9, 2.4 Hz), 5.37 and 5.39 (1H, each dd, J = 15.4, 7.2 Hz), 5.48 (1/3H, d, J = 9.9 Hz), 5.60 (1/3H, s), 5.85 (1H, d, J = 10.8 Hz), 6.03 (2/3H, d, J = 9.9 Hz), 6.44 (1H, dd, J = 15.4, 10.8 Hz), 6.61 (2/3H, s). Anal. Calcd for $C_{31}H_{62}O_7Si$: C, 67.48; H, 10.03. Found: C, 67.48; H, 10.28.

Diol 53. To a stirred solution of **52** (0.104 g, 0.166 mmol) in dry MeOH (3.10 mL) at −20 °C was added pyridinium *p*-toluenesulfonate (41.7 mg, 0.166 mmol). After the reaction mixture was stirred at 25 °C for 0.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) under ice-cooling, and the resultant mixture was then extracted with ether (3 mL × 3). The extracts were washed with saturated aqueous NaCl (4 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (10 g of silica gel, 1:1 *n*-hexane−ethyl acetate) gave **53** (0.0954 g, 98%) as a colorless oil: R_f 0.26 (1:1 *n*-hexane−ethyl acetate); ^{1}H-NMR δ 0.58−0.70 (4H, m), 0.74 and 0.76 (3H, each d, J = 6.4 Hz), 0.92−1.06 (19H, m), 1.65−1.85 (3H, m), 1.73 (3H, s), 1.98 (3H, s), 2.15−2.23 (2H, m), 2.23−2.38 (1H, m), 2.55−2.78 (1H, m), 3.27 (3H, s), 3.42−3.82 (5H, m), 3.63 (1/3 × 3H, s), 3.65 (2/3 × 3H, s), 3.76 (1/3 × 3H, s), 3.80 (2/3 × 3H, s), 5.43 (1H, dd, J = 15.2, 8.6 Hz), 5.46 (1/3H, d, J = 9.8 Hz), 5.58 and 5.60 (1/3H, each s), 5.86 (1H, d, J = 10.8 Hz), 6.00 (2/3H, d, J = 9.8 Hz), 6.52 (1H, dd, J = 15.2, 10.8 Hz), 6.59 and 6.61 (2/3H, each s). Anal. Calcd for $C_{32}H_{58}O_7Si$: C, 65.94; H, 10.03. Found: C, 65.70; H, 10.27.

Trityl Ether 54. To an ice-cold solution of **53** (0.236 g, 0.404 mmol) in dry CH_2Cl_2 (7.10 mL) were added triethylamine (0.169 mL, 1.21 mmol), 4-(dimethylamino)pyridine (2.47 mg, 0.0202 mmol) and (*p*-methoxyphenyl)diphenylmethyl chloride (0.274 g, 0.889 mmol) with stirring. After the reaction mixture was stirred at 25 °C for 5 h, the reaction was quenched with water (10 mL), and the resultant mixture was extracted with ether (3 mL × 3). The extracts were washed with saturated aqueous NaCl (5 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (35 g of silica gel, 5:1 *n*-hexane−ethyl acetate) gave **54** (0.313 g, 91%) as a colorless oil: R_f 0.69 (2:1 *n*-hexane−acetone); ^{1}H-NMR δ 0.57−0.69 (4H, m), 0.73 and 0.74 (3H, each d, J = 6.4 Hz), 0.93−1.06 (16H, m), 1.15 (3H, d, J = 6.8 Hz), 1.67−1.80 (3H, m), 1.68 (3H, s), 1.98 (3H, s), 2.20−2.35 (1H, m), 2.50 (1/3H, d, J = 2.4 Hz), 2.53 (2/3H, d, J = 2.4 Hz), 2.55−2.78 (1H, m), 3.04 (1H, m), 3.17−3.53 (4H, m), 3.20 (3H, s), 3.63 (1/3 × 3H, s), 3.65 (2/3 × 3H, s), 3.78 and 3.79 (6H, each s), 5.44 (1H, dd, J = 15.4, 8.4 Hz), 5.46 (1/3H, d, J = 9.8 Hz), 5.59 (1/3H, s), 5.82 (1H, d, J = 11.0 Hz), 6.01 (2/3H, d, J = 9.8 Hz), 6.22 (1/3H, dd, J = 15.4, 11.0 Hz), 6.25 (2/3H, dd, J = 15.4, 11.0 Hz), 6.60 and 6.61 (2/3H, each s), 6.83 (2H, d, J = 8.8 Hz), 7.15−7.37 (8H, m), 7.44 (4H, d, J = 7.4 Hz); MS (ESI) *m*/*z* 872 (872 calcd for $C_{52}H_{78}NO_8Si$, $M + NH_4^+$).

***seco*-Acid 55.** To an ice-cold solution of **54** (0.275 g, 0.321 mmol) in dioxane (8.25 mL) was added dropwise 1 M aqueous KOH (3.21 mL, 3.21 mmol). After the reaction mixture was stirred at 80 °C for 2 h, the reaction was neutralized with ion-exchange resin CG-50, the resultant mixture was filtered, and the resin was washed with dioxane. The combined filtrate and washings were concentrated *in vacuo*. Purification of the residue by flash column chromatography (50 g of silica gel, 1:2 *n*-hexane−ethyl acetate) gave **55** (0.167 g, 64%) and **56** (0.0832 g, 32%) as colorless oils. **55**: R_f 0.35 (2:1 *n*-hexane−acetone); $[\alpha]^{28}_D$ +20.5° (*c* 2.19, $CHCl_3$); ^{1}H-NMR δ 0.64 (4H, q, J = 7.9 Hz), 0.73 and 0.74 (3H, each d, J = 6.4 Hz), 0.93−1.07 (16H, m), 1.15 (3H, d, J = 6.8 Hz), 1.67−1.83 (3H, m), 1.69 (3H, s), 1.92−2.05 (1H, m), 2.00 (3H, s), 2.20−2.35 (1H, m), 2.65−2.80 (1H, m), 3.03 (1H, dd, J = 8.6, 4.2 Hz), 3.15−3.27 (1H, m), 3.20 (3H, s), 3.38 (1H, dd, J = 8.6, 6.4 Hz), 3.45−3.53 (1H, m), 3.69 (3H, s), 3.75−3.83 (1H, m), 3.78 (3H, s), 5.44 (1H, dd, J = 15.4, 8.6 Hz), 5.82 (1H, d, J = 10.8 Hz), 6.07 (1H, d, J = 10.0 Hz), 6.22 and 6.24 (1H, each dd, J = 15.4, 10.8 Hz), 6.74 (1H, s), 6.83 (2H, d, J = 8.4 Hz), 7.15−7.35 (8H, m), 7.43 (4H, d, J = 7.2 Hz); MS (ESI) *m*/*z* 858 (858 calcd for $C_{51}H_{76}NO_8Si$, $M + NH_4^+$). **56**: R_f 0.27 (2:1 *n*-hexane−acetone); $[\alpha]^{28}_D$ +5.8° (*c* 1.19, $CHCl_3$); ^{1}H-NMR δ 0.63 (4H, q, J = 7.9 Hz), 0.75 and 0.755 (3H, each d, J = 6.4 Hz), 0.92−1.05 (16H, m), 1.16 (3H, d, J = 6.8 Hz), 1.65−1.88 (3H, m), 1.69 (3H, s), 1.80 (3H, s), 1.90−2.05 (1H, m), 2.25−2.43 (1H, m), 2.55−2.70 (1H, m), 3.03 (1H, dd, J = 8.6, 4.2 Hz), 3.18−3.28 (1H, m), 3.20 (3H, s), 3.38 (1H, dd, J = 8.5, 6.4 Hz), 3.42−3.48 (1H, m), 3.67 (3H, s), 3.76−3.82 (1H, m), 3.78 (3H, s), 5.44 (1H, dd, J = 15.4, 8.6 Hz), 5.56 (1H, d, J = 9.9 Hz), 5.80 (1H, s), 5.83 (1H, d, J = 10.8 Hz), 6.22 and 6.24 (1H, each dd, J = 15.4, 10.8 Hz), 6.83 (2H, d, J = 8.4 Hz), 7.15−7.35 (8H, m), 7.43 (4H, d, J = 7.2 Hz); MS (ESI) *m*/*z* 858 (858 calcd for $C_{51}H_{76}NO_8Si$, $M + NH_4^+$).

Lactone 57. A solution of **55** (0.145 g, 0.172 mmol) in dry THF (1.72 mL) were added triethylamine (0.0528 mL, 0.378 mmol) and 2,4,6-trichlorobenzoyl chloride (0.0537 mL, 0.344 mmol). After the reaction mixture was stirred at 25 °C for 2 h, the resultant triethylamine hydrochloride was then filtered off, and the filtrate was diluted with dry toluene (86.0 mL) under argon. This solution was then added slowly at 110 °C to a solution of 4-(dimethylamino)pyridine (0.210 g, 1.72 mmol) in dry toluene (2.87 mL). After the addition was complete, the resultant mixture was further stirred at 110 °C for 15 h and then diluted with water (100 mL) at 25 °C. The resultant mixture was extracted with ether (30 mL × 3). The extracts were washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (15 g of silica gel, 10:1 *n*-hexane−ethyl acetate) gave **57** (0.0596 g, 42%) as a colorless oil: R_f 0.53 (3:1 *n*-hexane−ethyl acetate); $[\alpha]^{22}_D$ −178° (*c* 0.33, $CHCl_3$); ^{1}H-NMR δ 0.65−0.80 (4H, m), 0.95−1.15 (22H, m), 1.53 (3H, s), 1.62−1.80 (2H, m), 1.92 (3H, d, J = 1.4 Hz), 1.95−2.10 (1H, m), 2.33−2.48 (1H, m), 2.61 (1H, dd, J = 14.6, 9.6 Hz), 3.07 (1H, dd, J = 9.9, 4.9 Hz), 3.17 (1H, dd, J = 9.9, 5.6 Hz), 3.22 (3H, s), 3.63 (1H, br s), 3.65 (3H, s), 3.79 (3H, s), 3.85 (1H, br d, J = 3.9 Hz), 5.15 (1H, dd, J = 8.3, 1.6 Hz), 5.40 (1H, dd, J = 15.4, 4.0 Hz), 5.90 (1H, d, J = 11.0 Hz), 5.94 (1H, d, J = 10.0 Hz), 6.43 (1H, ddd, J = 15.4, 11.0, 1.4 Hz), 6.69 (1H, s), 6.83 (2H, d, J = 8.4 Hz), 7.17−7.38 (8H, m), 7.47 (4H, d, J = 8.2 Hz). Anal. Calcd for $C_{51}H_{70}O_7Si$: C, 74.41; H, 8.57. Found: C, 74.16; H, 8.78.

Alcohol 58. To a stirred solution of **57** (83.4 mg, 0.101 mmol) in dry MeOH (2.50 mL) at 0 °C was added pyridinium *p*-toluenesulfonate (22.5 mg, 0.101 mmol). After the reaction mixture was stirred at 25 °C for 14 h and then poured into ice-cold saturated aqueous $NaHCO_3$ (3 mL), the resultant mixture was extracted with ethyl acetate (1 mL × 3). The extracts were washed with saturated aqueous NaCl (3 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (6 g of silica gel, 2:1 *n*-hexane−ethyl acetate) gave **58** (44.6 mg, 80%) as a colorless oil: R_f 0.23 (2:1 *n*-hexane−ethyl acetate); $[\alpha]^{26}_D$ −192° (*c* 0.24, $CHCl_3$); ^{1}H-NMR δ 0.64−0.83 (4H, m), 0.90 (3H, d, J = 6.8 Hz), 0.98−1.13 (19H, m), 1.68 (3H, s), 1.70−1.85 (2H, m), 1.94 (3H, s), 2.05−2.25 (1H, m), 2.40−2.55 (2H, m), 3.00 (1H, dd, J = 8.6, 5.4 Hz), 3.29 (3H, s), 3.30−3.43 (1H, m), 3.47−3.60 (1H, m), 3.62 (1H, t, J = 2.8 Hz), 3.67 (3H, s), 3.94 (1H, dd, J = 5.7, 5.7 Hz), 5.12 (1H, dd, J = 4.4, 3.8 Hz), 5.39 (1H, dd, J = 15.4, 6.2 Hz), 5.88 (1H, d, J = 9.2 Hz), 5.92 (1H, d, J = 10.8 Hz), 6.47 (1H, dd, J = 15.4, 10.8 Hz), 6.67 (1H, s); HRMS (EI) *m*/*z* 550.3698 (550.3690 calcd for $C_{31}H_{54}O_6Si$, M^+).

Aldehyde 2. To a stirred solution of oxalyl chloride (0.0127 mL, 0.146 mmol) in dry CH_2Cl_2 (0.342 mL) at −78 °C was added dropwise a solution of dimethyl sulfoxide (0.0194 mL, 0.0729 mmol) in dry CH_2Cl_2 (0.0486 mL). After the reaction mixture was stirred at −78 °C for 3 min, a solution of **58** (40.2 mg, 0.0729 mmol) in dry CH_2Cl_2 (0.241 mL) was added to the reaction mixture. After the resultant mixture was stirred at −78 °C for 20 min, triethylamine (0.0612 mL, 0.438 mmol) was added, and the resultant mixture was allowed to warm to 0 °C over 40 min with stirring. The reaction was quenched

with water (3 mL), and the resultant mixture was then extracted with a mixture of benzene−ether (4:1, 2 mL × 3). The extracts were washed with saturated aqueous NaCl (3 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (5 g of silica gel, 5:1 *n*-hexane−acetone) gave **2** (29.8 mg, 74%) as a colorless oil: R_f 0.22 (8:1 *n*-hexane−acetone); $[\alpha]^{30}_D$ −180° (*c* 1.20, $CHCl_3$); ^{1}H-NMR δ 0.67−0.80 (4H, m), 0.98−1.13 (13H, m), 1.01 (3H, d, *J* = 7.0 Hz), 1.05 (3H, d, *J* = 7.0 Hz), 1.17 (3H, d, *J* = 7.0 Hz), 1.68 (3H, s), 1.7−1.8 (2H, m), 1.93 (3H, d, *J* = 1.3 Hz), 2.40−2.55 (2H, m), 2.78 (1H, ddq, *J* = 9.2, 7.0, 1.9 Hz), 3.31 (3H, s), 3.62 (1H, dd, *J* = 2.4, 1.9 Hz), 3.65 (3H, s), 3.87 (1H, dd, *J* = 6.0, 5.6 Hz), 5.31 (1H, dd, *J* = 5.6, 5.4 Hz), 5.36 (1H, dd, *J* = 15.2, 6.0 Hz), 5.87 (1H, d, *J* = 9.2 Hz), 5.92 (1H, d, *J* = 11.0 Hz), 6.50 (1H, dd, *J* = 15.2, 11.0 Hz), 6.62 (1H, s), 9.77 (1H, d, *J* = 1.8 Hz); HRMS (EI) *m*/*z* 548.3510 (548.3533 calcd for $C_{31}H_{52}O_6Si$, M^+).

Aldol 60. To a stirred solution of **3** (29.8 mg, 0.0872 mmol) in dry CH_2Cl_2 (0.348 mL) at −78 °C were added dropwise $PhBCl_2$ (0.0113 mL, 0.0872 mmol) and *i*-Pr_2NEt (0.0152 mL, 0.0872 mmol). After the reaction mixture was stirred at −78 °C for 0.5 h and at 0 °C for 0.5 h, a solution of **2** (24.0 mg, 0.0436 mmol) in dry CH_2Cl_2 (0.218 mL) was added to the reaction mixture at −78 °C. The resultant mixture was further stirred at −78 °C for 2.5 h, and the reaction was quenched with pH 7 phosphate buffer (2 mL). The resultant mixture was then extracted with ether (1 mL × 3). The extracts were washed with saturated aqueous NaCl (2 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (4 g of silica gel, 5:1 *n*-hexane−ethyl acetate and then 4 g of silica gel, 10:1 chloroform−ethyl acetate) gave **60** (22.2 mg, 57%) and **61** (0.4 mg, 1%) as colorless oils. **60**: R_f 0.16 (10:1 chloroform−ethyl acetate); $[\alpha]^{28}_D$ −42.7° (*c* 0.44, $CHCl_3$); ^{1}H-NMR δ 0.68−0.80 (4H, m), 0.73 (3H, d, *J* = 7.2 Hz), 0.85 (3H, d, *J* = 6.9 Hz), 0.91 (3H, d, *J* = 7.0 Hz), 0.95−1.12 (22H, m), 0.95 (9H, s), 0.97 (9H, s), 1.16 (3H, d, *J* = 7.2 Hz), 1.65−1.85 (3H, m), 1.66 (3H, s), 1.94 (3H, s), 1.98 (1H, m), 2.20 (1H, m), 2.4−2.55 (2H, m), 2.45 (1H, dd, *J* = 15.4, 3.6 Hz), 2.80 (1H, dd, *J* = 15.4, 10.0 Hz), 2.83 (1H, ddq, *J* = 9.2, 7.0, 2.2 Hz), 3.28 (3H, s), 3.60−3.70 (3H, m), 3.66 (3H, s), 3.81 (1H, ddd, *J* = 9.8, 4.0, 2.4 Hz), 3.96 (1H, dd, *J* = 6.0, 4.0 Hz), 4.66 (1H, ddd, *J* = 10.0, 5.9, 3.6 Hz), 5.29 (1H, dd, *J* = 4.0, 2.6 Hz), 5.43 (1H, dd, *J* = 15.6, 6.0 Hz), 5.90 (1H, d, *J* = 9.2 Hz), 5.93 (1H, d, *J* = 11.2 Hz), 6.47 (1H, dd, *J* = 15.6, 11.2 Hz), 6.68 (1H, s); MS (ESI) *m*/*z* 908 (908 calcd for $C_{50}H_{94}NO_9Si_2$, M + NH_4^+). **61**: R_f 0.22 (10:1 chloroform−ethyl acetate); ^{1}H-NMR δ 0.66−0.82 (4H, m), 0.78 (3H, d, *J* = 7.2 Hz), 0.87 (3H, d, *J* = 6.6 Hz), 0.95−1.10 (25H, m), 0.98 (9H, s), 1.00 (9H, s), 1.19 (3H, d, *J* = 6.9 Hz), 1.65−1.85 (3H, m), 1.66 (3H, s), 1.93 (3H, s), 1.95−2.08 (1H, m), 2.15−2.30 (1H, m), 2.35−2.58 (2H, m), 2.58 (1H, dd, *J* = 14.4, 3.8 Hz), 2.74 (1H, dd, *J* = 14.4, 10.2 Hz), 2.88 (1H, d, *J* = 3.6 Hz), 3.29 (3H, s), 3.35−3.47 (1H, m), 3.58−3.70 (2H, m), 3.64 (3H, s), 3.78 (1H, ddd, *J* = 7.6, 3.9, 3.2 Hz), 3.88 (1H, dd, *J* = 6.2, 5.2 Hz), 4.78 (1H, ddd, *J* = 9.8, 6.0, 3.8 Hz), 4.98 (1H, dd, *J* = 5.0, 3.9 Hz), 5.34 (1H, dd, *J* = 15.6, 7.0 Hz), 5.83 (1H, d, *J* = 9.6 Hz), 5.90 (1H, d, *J* = 11.0 Hz), 6.45 (1H, dd, *J* = 15.6, 11.0 Hz), 6.62 (1H, s); MS (ESI) *m*/*z* 908 (908 calcd for $C_{50}H_{94}NO_9Si_2$, M + NH_4^+).

Bafilomycin A_1 (1). To an ice-cold solution of **60** (22.4 mg, 0.0250 mmol) in dry THF (0.67 mL) were added acetic acid (0.0072 mL, 0.125 mmol) and 1 M TBAF/THF (0.125 mL, 0.125 mmol) with stirring. After the reaction mixture was stirred at 60 °C for 12 h, the mixture was poured into ice-cold saturated aqueous $NaHCO_3$ (2 mL), and the resultant mixture was then extracted with ethyl acetate (1 mL × 3). The extracts were washed with saturated aqueous NaCl (2 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the residue by flash column chromatography (2 g of silica gel, 3:2 *n*-hexane−ethyl acetate) gave **1** (7.0 mg, 45%) as a white solid: R_f 0.37 (1:1 *n*-hexane−ethyl acetate); $[\alpha]^{30}_D$ −3.34° (*c* 0.26, CH_2Cl_2) [$[\alpha]^{30}_D$ of natural bafilomycin A_1: −3.07° (*c* 0.26, CH_2Cl_2)]; mp 97.0−98.0 °C [mp of natural bafilomycin A_1: 98.0−99.0 °C]; mixed mp 97.5−99.0 °C; IR (KBr) 3440, 2966, 2933, 2875, 2372, 2345, 1688, 1625, 1467, 1365, 1247, 1110, 966, 915, 758, 591 cm^{-1}; ^{1}H-NMR δ 0.77 (3H, d, *J* = 6.7 Hz), 0.83 (3H, d, *J* = 6.7 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 0.93 (3H, d, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 6.4 Hz), 1.04 (3H, d, *J* = 7.2 Hz), 1.06 (3H, d, *J* = 7.0 Hz), 1.16 (1H, ddd, *J* = 11.9, 11.0, 2.0 Hz), 1.33 (1H, m), 1.45−1.70 (2H, br), 1.76 (1H, br q, *J* = 7.2 Hz), 1.89 (1H, m), 1.94 (3H, s), 1.95 (1H, m), 1.98 (3H, d, *J* = 1.0 Hz), 2.07−2.20 (2H, m), 2.30 (1H, dd, *J* = 11.9, 4.6 Hz), 2.54 (1H, ddq, *J* = 9.2, 7.0, 1.9 Hz), 3.25 (3H, s), 3.29 (1H, br), 3.49 (1H, dd, *J* = 10.2, 2.2 Hz), 3.64 (3H, s), 3.68 (1H, ddd, *J* = 11.0, 9.9, 4.6 Hz), 3.89 (1H, dd, *J* = 9.2, 8.9 Hz), 4.14 (1H, ddd, *J* = 11.0, 4.0, 2.0 Hz), 4.63 (1H, d, *J* = 4.0 Hz), 4.96 (1H, dd, *J* = 8.9, 1.2 Hz), 5.17 (1H, dd, *J* = 15.2, 9.2 Hz), 5.51 (1H, d, *J* = 2.0 Hz), 5.78 (1H, br d, *J* = 9.2 Hz), 5.81 (1H, d, *J* = 10.6 Hz), 6.51 (1H, dd, *J* = 15.2, 10.6 Hz), 6.67 (1H, s); HRMS (EI) *m*/*z* 623.4161 (623.4159 calcd for $C_{35}H_{59}O_9$, M + H^+). The ^{1}H-NMR and IR spectra were identical with those of the authentic sample of bafilomycin A_1.

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