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Total Synthesis of a Nonclassical Bioactive Acetogenin, (+)-Muconin

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Abstract—A convergent total synthesis of the tetrahydropyran-bearing acetogenin (+)-muconin **1** is described. All five chiral building blocks **7**, **9**, **17**, **21**, and **29** were prepared from d-glutamic acid, respectively. Four out of them were used to furnish the alkyne **16** and the iodoalkyne **33**, respectively, and palladium(0)-mediated cross-coupling of alkynes **16** and **33**, followed by hydrogenation, afforded **36**. Simultaneous deprotection of the MOM and TBS groups in **36** with $BF_3{\cdot}Et_2O$ in the presence of Me_2S provided (+)-muconin **1**.

Introduction

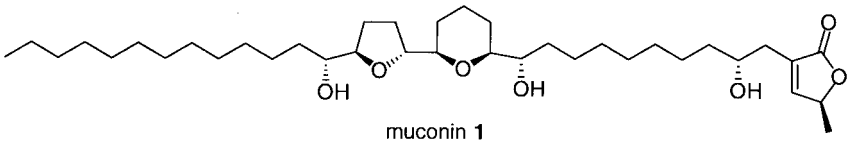
The annonaceous acetogenins are a class of natural products that have excellent anticancer, antiinfective pesticidal, antimalarial, immunosuppressive, and antifeedant properties.[1] Approximately 300 acetogenins have been isolated from various annonaceae plants, and most of the reported acetogenins belong to several classic types with unsubstituted tetrahydrofuran (THF) rings.[1] Recently, several nonclassical annonaceous acetogenin have been discovered and they bear a hydroxylated or an unsubstituted tetrahydropyran (THP) ring.[2] Muconin **1**,[2b] isolated from leaves of *Rollinia mucosa* (Jacq.) Baill. (Annonaceae), is the second THP-bearing acetogenin bearing an unsubstituted THP ring along with an adjacent THF ring. Compared to adriamycin, muconin showed to be more potent and selective in vitro cytotoxicity against PACA-2 (pancreatic cancer) and MCF-7 (breast cancer) in a panel of six human solid tumor cell lines. The remarkable antitumor activity and the unique structure of **1** have consequently stimulated synthetic efforts toward **1**.[3] We show here an approach to **1** via an efficient and convergent route[4] using only d-glutamic acid as the origin of all absolute stereochemistry (Fig. 1).

As illustrated in our retrosynthetic analysis (Scheme 1), muconin **1** may be constructed from two key building blocks, **I** and **II**. The aldehyde **III** and the bromide **IV**, both of which would be synthesized from d-glutamic acid, respectively, would furnish the segment **I** bearing both THP and THF rings. Using the same amino acid, the iodides **V** and **VI** might be derived and used for alkylation of the lactone **VII**, which is obtainable via the known procedure from d-glutamic acid. The corresponding alkylated products should be convertible to the moiety **II** in a few steps. Finally, palladium(0)-mediated coupling of the two blocks **I** and **II** followed by hydrogenation and deprotection would complete our total synthesis of muconin.

Results and Discussion

Synthesis of the building block I

We modified Koert's procedure to provide the aldehyde **4** in 12% overall yield through eight steps from d-glutamic acid.[5] In our procedure, it is noteworthy that the thermodynamically controlled conversion of the undesired



muconin **1**

Figure 1.

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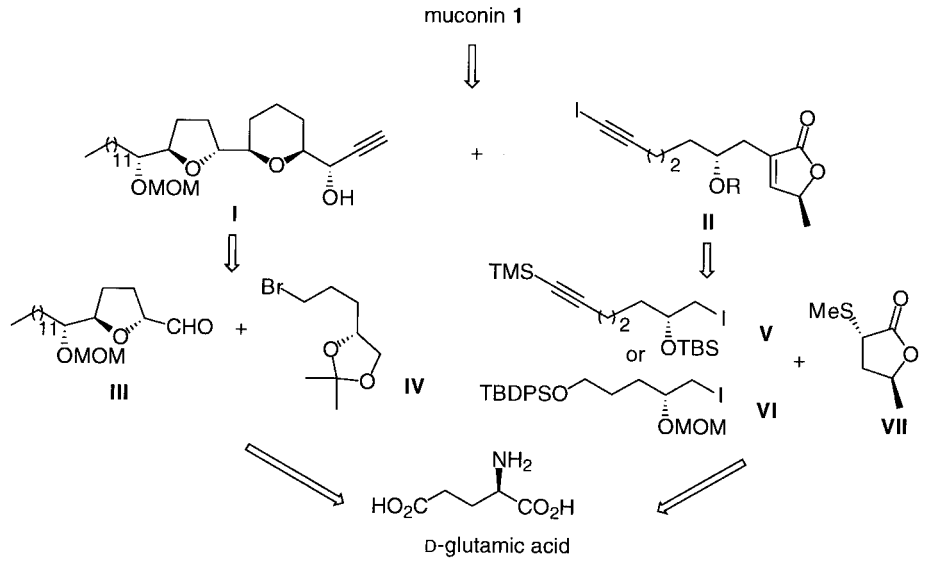


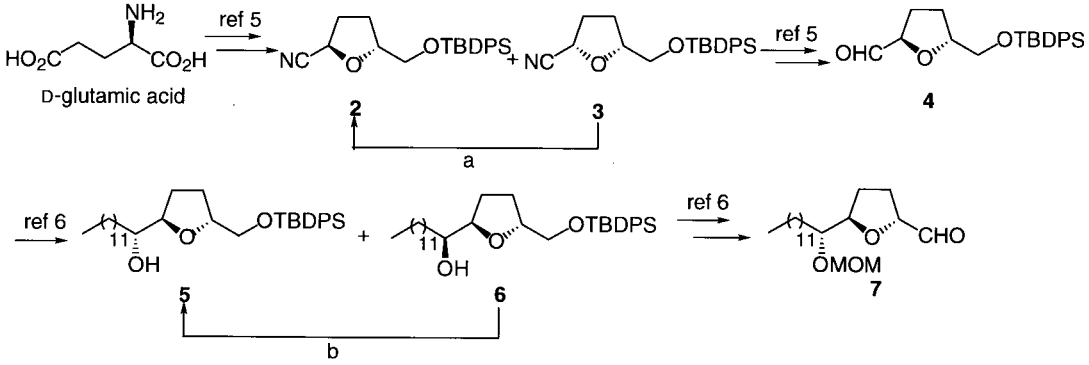
Scheme 1.

cis-nitrile **3** into the useful *trans*-nitrile **2** was developed: the *cis*-nitrile **3** was treated with KO*t*-Bu in THF-*t*-BuOH at room temperature to give isomers **2** and **3** in 83% yield in a ratio of 5:1. Subsequent four-step transformation from **4** developed by our group in the synthesis of solamin[6] was adopted to elongate the side chain furnishing the aldehyde **7** in overall 62% yield. In order to improve the yield, again the undesired *erythro* isomer **6** was inverted to *threo* isomer **5** by means of a Dess–Martin oxidation[7]/l-Selectride reduction sequence. Consequently, the overall yield of the aldehyde **7** from the starting d-glutamic acid was much more improved (Scheme 2).

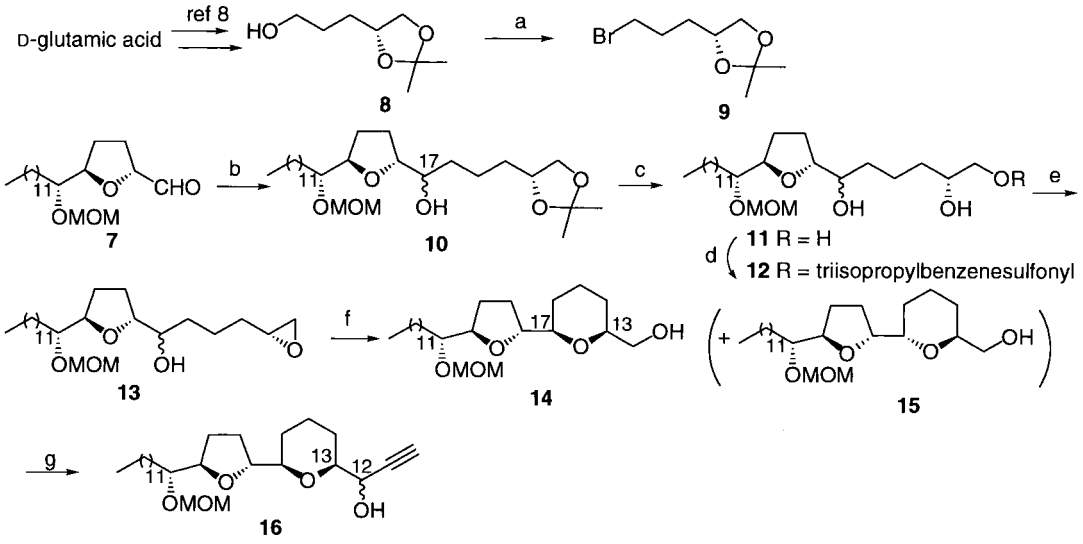
Treatment of the alcohol **8**, which was also synthesized from d-glutamic acid according to the known procedure in 29% yield,[8] with $Ph_3P/CBr_4/Et_3N$ in methylene chloride gave the bromide **9** in 78% yield. With the bromide **9** and the aldehyde **7**, we investigated the chelation-controlled addition reaction. The coupled product **10** was obtained as an inseparable mixture with a 3:1 diastereoselection at C-17 favoring the desired α-epimer in 80% yield when 14 equiv. amount of the bromide **9** was used. To our surprise, addition of $CuBr{\cdot}SMe_2$ to the solution of the Grignard reagent prior to addition of **7** did not give any isolable product nor the starting aldehyde. The stereochemistry of **10** was assigned by the analysis of the ^1H NMR spectra: the chemical shift of the proton at C-17 of the major isomer was 3.37 ppm, indicating that the ring was flanked by the hydroxyl group in *threo* fashion according to Born's rule.[9]

Deprotection of the acetonide group of **10** with AcOH in $THF–H_2O$ gave the triol **11** in 70% yield. Selective sulfonylation of the primary hydroxyl group in **11** with triisopropylbenzenesulfonyl chloride in the presence of excess pyridine afforded the sulfonate **12** in 79% yield. It is noteworthy that using toluenesulfonyl chloride or mesitylsulfonyl chloride as the sulfonating agent led to poor yield (<40%) with recovery of the triol (>30%). The sulfonate **12** was treated with NaOMe in $MeOH–CH_2Cl_2$ to provide the epoxide **13**, which was cyclized smoothly with CSA in CH_2Cl_2 at 0°C to give a separable mixture of **14** (60%) and **15** (20%). The *cis*-THP ring of **14** was confirmed by the positive NOESY correlation at H-13(δ 3.44)/H-17(δ 3.28).

Dess–Martin oxidation of **14** under basic conditions furnished an aldehyde, which was allowed to react with



Scheme 2. *Reagents and conditions:* (a) KO*t*-Bu, *t*-BuOH, THF, rt, 83%, **2:3** = 5:1; (b) (i) Dess–Martin periodinane, DCM, rt; (ii) l-Selectride, THF, −78°C, 74%, **5:6**=10:1.

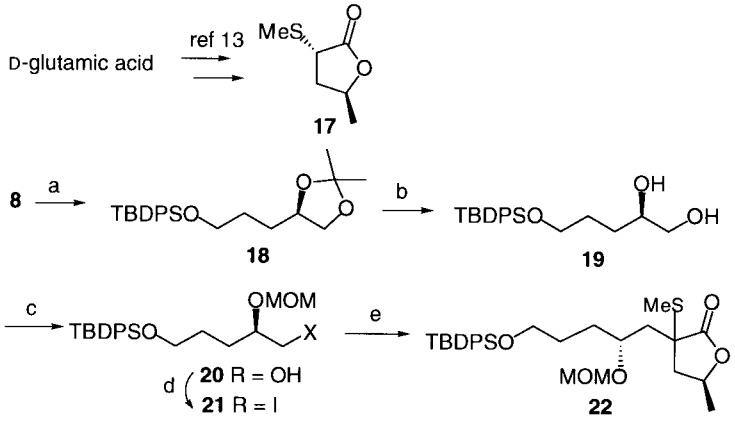


Scheme 3. *Reagents and conditions:* (a) Ph_3P, CBr_4, Et_3N, DCM, rt, 78%; (b) **9**, Mg, Et_2O, −78°C∼rt, 80%, *threo*:*erythro*=3:1; (c) AcOH, H_2O, THF, rt, 70%; (d) triisopropylbenzenesulfonyl chloride, Py, DCM, 0°C∼rt, 79%; (e) NaOMe, MeOH, DCM, rt, 90%; (f) CSA, DCM, 0°C, 80%, **14:15**=3:1; (g) (i) Dess–Martin periodinane, $NaHCO_3$, DCM, rt; (ii) HC≡CMgBr, Tol, THF, ∼78°C∼rt, 80%, α-isomer:β-isomer=1:1.4.

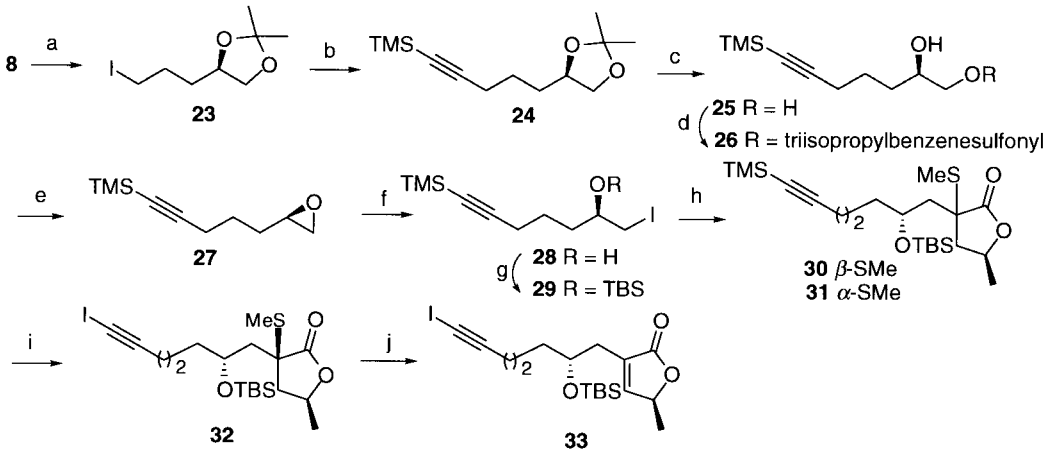
ethynylmagnesium bromide in toluene–THF[10] to give **16** as a 1:1.4 inseparable mixture of the desired α-isomer and its epimer in 80% overall yield. The stereochemical assignment of the two isomers in **16** was based on McLaughlin's analysis, extrapolating Born's rule from the THF to a THP system.[2] In our case, if Born's rule should also hold true for a propargylated-hydroxyl flanked THP ring system, we may predict the relatively smaller δ value of H-12 at 4.22 ppm indicated a *threo* relationship at C-12/13. This assignment was confirmed by converting **16** to the corresponding reduced compounds **36** and **37** and both of them would be transferred into muconin (vide infra). In order to increase the stereoselectivity of the addition, we selected to use a solution of TMSC≡CMgBr in Et_2O as the Grignard agent since it was known that its addition to sugar aldehydes occurred stereoselectively.[11] To our disappointment, the addition just led to a little higher stereoselectivity (*threo*:*erythro*=1.4:1) but in a lower yield (43%) (Scheme 3).

Synthesis of the building block II

Initially, we selected iodide **21** as the alkylating agent since it was protected by the same MOM group as that of **16**. Preparation of **21** is shown in Scheme 4. Protection of the hydroxyl group in **8** with TBDPSCl/Et_3N/DMAP, followed by deprotection of the acetonide group of **18** with AcOH in THF–H_2O provided the diol **19** in good yield. Selective protection of the secondary hydroxyl group was effected by the method of Yamamoto using trimethyl orthoformate and DIBAL.[12] The resulting primary alcohol **20** was transformed to the iodide **21** by treatment with Ph_3P/I_2/imidazole. Unfortunately, alkylation of the lactone **17**, derived from d-glutamic acid in five steps[13] with **21** using NaHMDS as the base, gave the alkylated lactone **22** in poor yield (23%). We considered that this result might be due to the presence of the MOM group adjacent to the iodo substituent. Since it was known that using TBS as a protective group in a similar alkylation reaction worked very



Scheme 4. *Reagents and conditions:* (a) TBDPSCI, Et_3N, DMAP, DCM, 0°C∼rt, 90%; (b) AcOH, THF, H_2O, rt, 74%; (c) (i) $(MeO)_3CH$, CSA, DCM, rt; (ii) DIBAL, −78°C, 70% (d) Ph_3P, I_2, imidazole, CH_3CN, Et_2O, −10°C∼rt, 78%; (e) **17**, NaHMDS, THF, HMPA, −10°C∼rt, 23%.



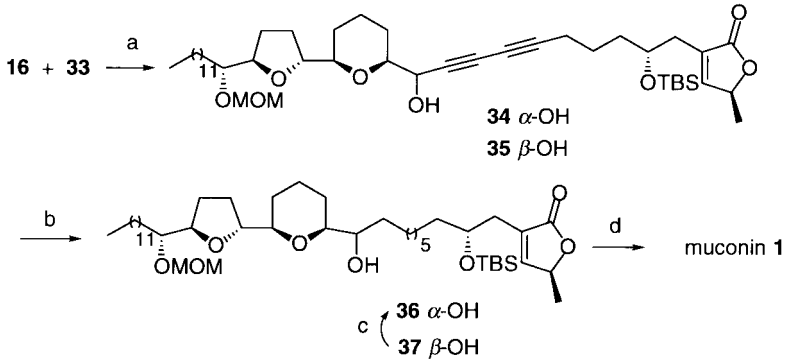
Scheme 5. *Reagents and conditions:* (a) Ph_3P, I_2, imidazole, CH_3CN, Et_2O, −10°C, 63%; (b) TMSC≡CH, *n*-BuLi, THF, HMPA, −78~0°C, 95%; (c) AcOH, H_2O, 60°C, 88%; (d) triisopropylbenzenesulfonyl chloride, Py, DCM, 0°C~rt, 77%; (e) NaH, THF, 0°C, 95%; (f) LiI, AcOH, H_2O, THF, 0°C, 82%; (g) TBSCl, DMF, imidazole, rt, 90%; (h) **17**, NaHMDS, THF, HMPA, −10°C~rt, 76%, **30**:**31**=6.6:1; (i) (i) K_2CO_3, MeOH, 0°C~rt; (ii) I_2, morpholine, C_6H_6, 45°C, 75%; (j) (i) *m*-CPBA, DCM, ~78°C, (ii) Tol, reflux, 50%, 40% yield of **33** from **31**.

well,[3] we attempted our second route employing the iodide with the TBS group.

Iodination of the alcohol **8** with Ph_3P/I_2/imidazole in CH_3CN–Et_2O at −10°C gave the iodide **23**, which was then alkylated with TMSC≡CH in the presence of *n*-BuLi to afford compound **24**. Deprotection of the acetonide group in **24** with AcOH in water at 60°C provided diol **25** in 88% yield, but on using other condition (HCl/THF, AcOH/THF/H_2O, CSA/TsOH/MeOH, TFA/THF/H_2O) at room temperature, all the reactions resulted in poor to modest yields (25–60%) with recovery of **24**. Sulfonylation of the primary hydroxyl group with triisopropylbenzenesulfonyl chloride in the presence of excess pyridine gave the sulfonate **26**, which was treated with NaH in THF at 0°C to afford the epoxide **27**. Treatment of **27** with LiI/AcOH/THF at 0°C, followed by protection of the newly generated hydroxyl group as TBS ether afforded the iodide **29**. As expected, alkylation of the enolate derived from **17** with iodoether **29** furnished a mixture of sulfides **30** and **31** in good yield, which were separable on silical gel. Stereochemical assignment of **30** and **31** was conclusively done by the following ^1H NMR data: chemical shifts of thiomethyl protons in **30** whose methylthio group locates *cis*-position to the methyl substituent were 1.50 ppm, at lower field compared with that of **31** at 1.40 ppm. Selective removal of the TMS group in **30** with K_2CO_3/MeOH liberated the terminal alkyne, which was then iodinated with I_2/morpholine[14] to give **32** in overall 75% yield. Trial of one-pot transformation of **30** into **32** with NBS catalyzed by silver salts ($AgNO_3$, $AgOCOCF_3$)[15] led to the decomposition of the compound **30**, probably due to the presence of the methylthio group. Oxidation of the methyl sulfide with *m*-CPBA followed by thermal elimination provided the butenolide **33**. Similarly, the lactone **33** was also obtained from **31** via four steps in overall 40% yield (Scheme 5).

Coupling and completion of the total synthesis

Palladium(0)-mediated coupling of the alkyne **16** with the iodoalkyne **33** using Schreiber's protocol [$Pd_2(dba)_3$, CuI, *i*-Pr_2NH, (2-furyl)$_3$P][16] afforded a separable mixture of diynes **34** (23%) and **35** (32%). Hydrogenation of **34** and **35** using Wilkinson's catalyst gave the corresponding reduced products **36** and **37**, respectively (Scheme 6). At this stage, we first tried to invert the β-alcohol under Mitsunobu's conditions ($ClCH_2COOH$, Ph_3P, DEAD)[17] since we intended to completely convert the β-alcohol to



Scheme 6. *Reagents and conditions:* (a) $Pd_2(dba)_3$, CuI, *i*-Pr_2NH, (2-furyl)$_3$P, C_6H_6, rt, 55% **34**:**35**=1:1.4; (b) $(Ph_3P)_3RhCl$, H_2, C_6H_6, MeOH, rt, 77% yield of **36**, 75% yield of **37**; (c) (i) Dess–Martin periodinane, DCM, rt; (ii) $LiAl(O\text{-}t\text{-}Bu)_3H$, THF, −60°C, 80%, **36**:**37**=3:1; (d) $BF_3{\cdot}Et_2O$, Me_2S, −10°C, 82%.

the corresponding α-alcohol. It is surprising that the diyne **35** was converted to **34** in very poor yield with recovery of a large amount of **35**. There was no reaction observed by the treatment of the compound **37** under the same conditions. These results suggested to us to employ another possible method: an oxidation–reduction sequence. By oxidation of the diyne **35** with Dess–Martin reagent or MnO_2, no obvious reaction could be observed. Fortunately, oxidation of the β-alcohol **37** with Dess–Martin periodinane, followed by selective reduction of ketone with LiAl(O*t*-Bu)$_3$H proceeded smoothly to give the α-alcohol **36** with 3:1 diastereoselectivity in 80% yield. Deprotection of the MOM and TBS groups in **36** with AcCl/MeOH or TMSBr caused the decomposition of the substrate, but treatment with $BF_3{\cdot}Et_2O$ in the presence of Me_2S at −10°C provided (+)-muconin **1** with spectral properties identical to those of the natural product.

In conclusion, we have succeeded in total synthesis of muconin via a convergent route. Further studies on the syntheses and biological activities of the related analogs are in progress and will be reported in due course.

Experimental

All melting points (mp's) were uncorrected. Infrared spectra (IR) were measured on a Jasco FT/IR-230 spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were recorded on a JEOL JNM EX-90, a BRUKER AC300 or a JEOL JNM α-500 spectrometer. Chemical shifts are reported in parts per million (δ) relative to internal chloroform (δ 7.26). FABMS spectra were recorded on a JEOL JMS-HX110 mass spectrometer. Optical rotations were measured on a Jasco DIP 1000 polarimeter. Analytical thin-layer chromatography (TLC) was carried out using 0.25-mm Merck silica gel 60 F_{254} precoated glass-backed plates. Compounds were visualized by ultraviolet light (254 nm), iodine vapor or phosphomolybdic acid spray reagent. Preparative TLC was carried out using 0.5-mm Merck silica gel 60 F_{254} precoated glass-backed plates. Column chromatography was performed on Merck silica gel 60. All solvents were of reagent grade. Tetrahydrofuran and diethyl ether were freshly distilled from sodium–benzophenone under argon. Dichloromethane, benzene and hexamethylphosphoric triamide were distilled from calcium hydride and stored over 4 Å-molecular seives. Absolute methanol was distilled from $Mg(OMe)_2$ and stored over 3 Å-molecular sieves.

Conversion of the *cis*-nitrile 3 to the *trans*-nitrile 2

To a solution of **3** (7.31 g, 20.0 mmol) in tetrahydrofuran (130 mL) and *tert*-butyl alcohol (10 mL) was added potassium *tert*-butoxide (11.20 g, 100.0 mmol). After being stirred at room temperature for 24 h, the resulting mixture was acidified to pH 5 with 2 M hydrochloric acid and extracted with diethyl ether. The organic phase was washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=6:1) to give **2** (5.04 g, 69%, less polar) and **3** (1.01 g, 14%). *trans*-Nitrile **2**; colorless oil; $[\alpha]_d^{24}=+6.4°$ (*c* 0.50, $CHCl_3$); lit.[5] $[\alpha]_d^{20}=+6.5°$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.69 and 7.46–7.42 (m, 10H), 4.78 (m, 1H), 4.33 (m, 1H), 3.78 (dd, *J*=11.0, 4.0 Hz, 1H), 3.68 (dd, *J*=11.0, 4.0 Hz, 1H), 2.40–2.03 (m, 4H), 1.11 (s, 9H). *cis*-Nitrile **3**; white solid; mp 78–79°C; lit.[5] mp 79°C; $[\alpha]_d^{24}=+20.0°$ (*c* 0.72, $CHCl_3$); lit.[5] $[\alpha]_d^{20}=+20.6°$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.69 and 7.46–7.42 (m, 10H), 4.67 (m, 1H), 4.16 (m, 1H), 3.73 (d, *J*=2.8 Hz, 2H), 2.32–2.04 (m, 4H), 1.07 (s, 9H).

Conversion of the β-alcohol 6 to the α-alcohol 5

To a solution of **6** (1.24 g, 2.30 mmol) in dichloromethane (18 mL) was added Dess–Martin periodinane (1.17 g, 2.76 mmol). After being stirred at room temperature for 1.5 h, saturated aqueous sodium bicarbonate (15 mL) and sodium thiosulfate (4.5 g) were added. The resulting mixture was stirred for 20 min and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in tetrahydrofuran (18 mL) at −78°C. A solution of l-Selectride (2.76 mL, 1.0 M, 2.76 mmol) in tetrahydrofuran was added dropwise and the resulting mixture was stirred for 1 h at the same temperature. After quenching the reaction by the dropwise addition of methanol, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=10:1–6:1) to give **5** (831 mg, 67%, less polar) and **6** (83 mg, 7%) as colorless oil. *threo*-Isomer **5**; $[\alpha]_d^{24}=+3.5°$ (*c* 0.50, $CHCl_3$); lit.[6] $[\alpha]_d^{22}=+3.4°$(*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.61 and 7.45–7.33 (m, 10H), 4.11 (m, 1H), 3.81 (m, 1H), 3.66 (d, *J*=4.7 Hz, 2H), 3.37 (m, 1H) 2.17–1.61 (m, 4H), 1.48–1.16 (m, 22H), 1.05 (s, 9H), 0.88 (t, *J*=6.7 Hz, 3H). *erythro*-Isomer **6**; $[\alpha]_d^{24}=+0.40°$ (*c* 1.10, $CHCl_3$); lit.[6] $[\alpha]_d^{25}=+0.36°$(*c* 1.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.66 and 7.42–7.35 (m, 10H), 4.14 (m, 1H), 3.87 (m, 1H), 3.77 (m, 1H), 3.65 (d, *J*=4.7 Hz, 2H), 2.07–1.71 (m, 4H), 1.43–1.14 (m, 22H), 1.05 (s, 9H), 0.88 (t, *J*=6.7 Hz, 3H).

(*R*)-5-Bromo-1,2-*O*-isopropylidenepentane-1,2-diol (9)

To a solution of **8** (1.60 g, 10.0 mmol), carbon tetrabromide (4.65 g, 14.0 mmol) and triethylamine (1.53 mL, 11.0 mmol) in dichloromethane (10 mL) was added dropwise a solution of triphenylphosphine (3.14 g, 12.0 mmol) in dichloromethane (8 mL) over 2 h. After an additional 1 h of stirring at room temperature, the mixture was diluted with *n*-pentane (70 mL) and then poured into ice-cold half-saturated sodium bicarbonate (10 mL). The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=5:1) to give **9** (1.74 g, 78%) as a colorless oil. $[\alpha]_d^{24}=-7.2°$ (*c* 0.88, $CHCl_3$); IR (film) ν 2990, 2940, 2880, 1460, 1370, 1220, 1160, 1060, 860; ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.20–4.00 (m, 2H), 3.70–3.38 (m, 3H), 2.10–1.60 (m, 4H) 1.42 (s, 3H), 1.35 (s, 3H); Anal. Calcd for $C_8H_{15}BrO_2$: C 43.07, H 6.78; Found: C 43.55, H 6.73.

(1″*R*, 2′*R*, 5′*R*, 2*R*, 6*RS*)-1,2-*O*-Isopropylidene-6-(5′-(1″-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl)hexane-1,2,6-triol (10)

A solution of **9** (23.4 g, 105 mmol) in diethyl ether (80 mL) was added dropwise to magnesium turnings (5.0 g, 210 mmol) covered with diethyl ether (20 mL) after dibromoethane-initiation. The mixture was stirred at room temperature for 2 h to complete the formation of the Grignard reagent. The ethereal solution of the Grignard reagent thus prepared was transferred with a syringe to a stirred solution of **7** (2.57 g, 7.5 mmol) in diethyl ether (15 mL) at −78°C, and the mixture was allowed to warm to room temperature overnight. The reaction mixture was treated with saturated aqueous ammonium chloride at 0°C and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane: diethyl ether=1:2) to give **10** (2.93 g, 80%) as an inseparable mixture of two isomers, which was employed in the next step without further purification. Colorless oil; IR (film) ν 3480, 2920, 2860, 1460, 1370, 1220, 1040, 920; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (d, J=7.0 Hz, 0.25H), 4.79 (d, J=7.0 Hz, 0.75H), 4.69 (d, J=7.0 Hz, 0.75H), 4.69 (d, J=7.0 Hz, 0.25H), 4.07 (m, 1H), 4.02 (m, 1H), 3.95 (m, 1H), 3.86 (m, 0.25H), 3.79 (m, 1H), 3.53–3.42 (m, 2H), 3.39 (s, 3H), 3.38 (m, 0.75H), 2.02–1.87 (m, 2H), 1.72–1.22 (m, 31H), 1.40 (s, 3H), 1.34 (s, 3H), 0.87 (t, J=7.0 Hz, 3H); Anal. Calcd for $C_{28}H_{54}O_6$: C 69.09, H 11.18; Found: C 68.67, H 11.08.

(1″*R*, 2′*R*, 5′*R*, 2*R*,6*RS*)-6-(5′-(1″-(Methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl)hexane-1,2,6-triol (11)

To a solution of **10** (3.21 g, 6.6 mmol) in tetrahydrofuran (15 mL) and water (7.5 mL) was added acetic acid (18.8 mL). After being stirred at room temperature for 24 h, the solvent was removed by co-evaporation with toluene and the residue was chromatographed on silica gel (diethyl ether:methanol=40:1) to give **11** (2.07 g, 70%) as an inseparable mixture of two isomers, which was employed in the next step without further purification. Colorless oil; IR (film) ν 3400, 2920, 2860, 1460, 1100, 1040, 920; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (d, J=7.0 Hz, 0.25H), 4.75 (d, J=7.0 Hz, 0.75H), 4.65 (d, J=7.0 Hz, 1H), 3.97 (m, 0.25H), 3.91 (m, 0.75H) 3.82 (m, 0.25H), 3.77 (m, 1H), 3.67 (m, 1H), 3.59 (m, 1H), 3.45-3.33 (m, 2.75H), 3.36 (s, 3H), 2.69 (br 1H, OH), 2.26 (br, 1H, OH), 1.98–1.20 (m, 33H), 0.83 (t, J=7.0 Hz, 3H); Anal. Calcd for $C_{25}H_{50}O_6$: C 67.22, H 11.28; Found: C 67.27, H 11.18.

(1″*R*,2′*R*,5′*R*,2*R*,6*RS*)-2,6-Dihydroxy-6-(5′-(1″-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl)hexyl 2,4,6-triisopropylbenzenesulfonate (12)

To a solution of **11** (2.10 g, 4.70 mmol) in dichloromethane (25 mL) was added pyridine (15 mL) and triisopropylbenzenesulfonyl chloride (4.27 g, 14.1 mmol) successively at 0°C. After being stirred at the same temperature for 15 min, the mixture was stirred at room temperature overnight. The excess acid chloride was destroyed with ice-water by stirring for 1 h and the resulting mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=1:2) to give **12** (2.65 g, 79%) as an inseparable mixture of two isomers, which was employed in the next step without further purification. Colorless oil; IR (film) ν 3440, 2920, 2860, 2830, 1600, 1460, 1350, 1180, 1040, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J=0.5 Hz, 2H), 4.87 (d, J=6.5 Hz, 0.25H), 4.86 (d, J=7.0 Hz, 0.75H), 4.76 (d, J=6.5 Hz, 1H), 4.20 (sept., J=6.5 Hz, 2H), 4.12 (m, 1H), 4.04–3.82 (m, 4.25H), 3.56–3.42 (m, 1.75H), 3.47 (s, 3H), 2.98 (sept., J=7.0 Hz, 1H), 2.12–1.22 (m, 52H), 0.95 (t, J=7.0 Hz, 3H); Anal. Calcd for $C_{40}H_{72}O_8S$: C 67.38, H 10.18; Found: C 66.94, H 9.84.

(1″*R*,2′*R*,5′*R*,1*RS*,5*R*)-5,6-Epoxy-1-(5′-(1″-(methoxymethoxy)tridecyl)tetrahydrofuran-2′-yl)hexan-1-ol (13)

To a solution of **12** (2.64 g, 3.70 mmol) in dichloromethane (80 mL) and methanol (100 mL) was added dropwise a solution of sodium methoxide (7.4 mL, 1.0 M, 7.4 mmol) at 0°C. After being stirred at the same temperature for 1 h, the mixture was stirred at room temperature for 2 h. The reaction mixture was then treated with saturated aqueous ammonium chloride and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=1:2) to give **13** (1.43 g, 90%) as an inseparable mixture of two isomers, which was employed in the next step without further purification. Colorless oil; IR (film) ν 3470, 3040, 2920, 2860, 1460, 1150, 1100, 1040, 920; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (d, J=6.5 Hz, 0.25H), 4.80 (d, J=7.0 Hz, 0.75H), 4.70 (d, J=7.0 Hz, 0.75H), 4.69 (d, J=7.0 Hz, 0.25H), 4.02 (m, 0.25H), 3.96 (m, 0.75H), 3.87 (m, 0.25H), 3.80 (m, 1H), 3.47 (m, 1H), 3.41 (m, 0.75H), 3.40 (s, 3H), 2.91 (m, 1H), 2.75 (t, J=4.0 Hz, 1H), 2.47 (m, 1H), 2.02–1.22 (m, 33H), 0.88 (t, J=7.0 Hz, 3H); Anal. Calcd for $C_{25}H_{48}O_5$: C 70.05, H 11.29; Found: C 69.71, H 11.23.

(1″*R*,2′*R*,5′*R*,2*S*,6*R*)-6-(5′-(1″-(Methoxymethoxy)-tridecyl)tetrahydrofuran-2′-yl)tetrahydropyran-2-methanol (14) and (1″*R*,2′*R*,5′*R*,2*S*,6*S*)-6-(5′-(1″-(Methoxymethoxy)tetrahydrofuran-2′-yl)tetrahydropyran-2-methanol (15)

To a solution of **13** (1.59 g, 3.70 mmol) in dichloromethane (100 mL) was added camphorsulfonic acid (72 mg, 0.31 mmol) at 0°C. After being stirred at the same temperature for 3 h, the mixture was treated with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=1:2) to give **14** (952 mg, 60%, more polar) and **15** (317 mg, 20%) as colorless oils. Compound **14**; $[\alpha]_d^{19}$=+28.2° (*c* 0.48, $CHCl_3$); IR (film) ν 3440, 2920, 2860, 1460, 1100, 1040, 920; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (d, J=6.5 Hz, 1H), 4.63 (d, J=7.0 Hz, 1H), 3.97 (m, 1H), 3.84 (m, 1H), 3.53 (m, 1H), 3.48–3.40 (m, 3H), 3.35 (s, 3H), 3.28 (m, 1H), 1.92–1.17

(m, 33H), 0.83 (t, *J*=7.0 Hz, 3H); Anal. Calcd for $C_{25}H_{48}O_5$: C 70.05, H 11.29; Found: C 69.63, H 10.92. Compound **15**; $[\alpha]_d^{19}=+28.4°$ (*c* 1.65, $CHCl_3$); IR (film) ν 3440, 2920, 2860, 1460, 1220, 1100, 1040, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (d, *J*=6.5 Hz, 1H), 4.63 (d, *J*=7.0 Hz, 1H), 4.06 (m, 1H), 3.91 (m, 1H), 3.75 (m, 1H), 3.66 (m, 1H), 3.49 (m, 1H), 3.44–3.36 (m, 2H), 3.35 (s, 3H), 2.07–1.12 (m, 33H), 0.83 (t, *J*=7.0 Hz, 3H); Anal. Calcd for $C_{25}H_{48}O_5$: C 70.05, H 11.29; Found: C 69.93, H 11.24.

(1‴*R*,2″*R*,5″*R*,2′*S*,6′*R*,1*RS*)-1-(6′-(5″-(1‴-(Methoxymethoxy)tridecyl)tetrahydrofuran-2″-yl)tetrahydropyran-2′-yl)prop-2-yn-1-ol (16)

To a solution of **14** (472 mg, 1.10 mmol) and sodium bicarbonate (153 mg, 1.82 mmol) in dichloromethane (15 mL) was added Dess–Martin periodinane (700 mg, 1.65 mmol). After being stirred at room temperature for 3 h, saturated aqueous sodium bicarbonate (14 mL) and sodium thiosulfate (1.2 g) were added. The resulting mixture was stirred for 20 min and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in toluene (50 mL) at −78°C. A solution of ethynylmagnesium bromide (15.4 mL, 0.50 M, 7.70 mmol) in tetrahydrofuran was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction mixture was treated with saturated aqueous ammonium chloride at 0°C and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:ethyl acetate=3:1) to give **16** (399 mg, 80%) as an inseparable mixture of two isomers, which was employed in the next step without further purification. Colorless oil; IR (film) ν 3400, 3310, 3020, 2930, 2860, 1220, 1040, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (d, *J*=6.5 Hz, 0.42H), 4.82 (d, *J*=7.0 Hz, 0.58H), 4.68 (d, *J*=6.5 Hz, 0.58H), 4.67 (d, *J*=7.0 Hz, 0.42H), 4.41 (dd, *J*=3.5, 2.5 Hz, 0.58H), 4.22 (dd, *J*=7.5, 2.5 Hz, 0.42H), 4.01 (m, 1H), 3.91 (m, 1H), 3.54–3.45 (m, 2H), 3.40 (s, 1.74H), 3.39 (s, 1.26H), 3.35 (m, 1H), 2.43 (d, *J*=2.5 Hz, 0.42H), 2.41 (d, *J*=2.0 Hz, 0.58H), 1.98–1.20 (m, 33H), 0.88 (t, *J*=7.0 Hz, 3H); Anal. Calcd for $C_{27}H_{48}O_5$: C 71.64, H 10.69; Found: C 71.38, H 10.67.

(*R*)-5-*tert*-Butyldiphenylsilyoxy-1,2-*O*-isopropylidenepentane-1,2-diol (18)

To a solution of **8** (4.80 g, 30.0 mmol) and triethyl amine (7.0 mL, 50.4 mmol) in dichloromethane (30 mL) was added to *tert*-butyldiphenylsilyl chloride (9.0 mL, 34.6 mmol) and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) at 0°C. After being stirred at the same temperature for 5 min, the mixture was stirred at room temperature for 6 h. The reaction mixture was then treated with water and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane: diethyl ether=15:1–10:1) to give **18** (10.86 g, 90%) as a colorless oil, which was employed in the next step without further purification. $[\alpha]_d^{19}=-8.6°$ (*c* 1.07, $CHCl_3$); IR (film) ν 3080, 3040, 2940, 2860, 1590, 1430, 1380, 1110, 1060, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.65 and 7.44–7.36 (m, 10H), 4.08 (m, 1H), 4.01 (t, *J*=6.5 Hz, 1H), 3.68 (t, *J*=5.5 Hz, 2H), 3.50 (t, *J*=7.5 Hz, 1H), 1.76–1.53 (m, 4H), 1.40 (s, 3H), 1.35 (s, 3H), 1.05 (s, 9H).

(*R*)-5-*tert*-Butyldiphenylsilyoxypentane-1,2-diol (19)

To a solution of **18** (3.99 g, 10.0 mmol) in tetrahydrofuran (20 mL) and water (10 mL) was added acetic acid (25 mL). After being stirred at room temperature for 24 h, the solvent was removed by co-evaporation with toluene and the residue was chromatographed on silica gel (*n*-hexane:ethyl acetate=1:1) to give **19** (2.65 g, 74%) as a colorless oil, which was employed in the next step without further purification. $[\alpha]_d^{19}=+1.0°$ (*c* 0.39, $CHCl_3$); IR (film) ν 3380, 3070, 3050, 2960, 2860, 1590, 1470, 1120, 1000, 820, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.65 and 7.45–7.36 (m, 10H), 3.78–3.62 (m, 4H), 3.47 (m, 1H), 2.96 (br, 1H, OH), 2.02 (br, 1H, OH), 1.76–1.51 (m, 4H), 1.07 (s, 9H).

(*R*)-5-*tert*-Butyldiphenylsilyoxy-2-methoxymethoxypentan-1-ol (20)

To a solution of **19** (1.706 g, 3.0 mmol) in dichloromethane (6.0 mL) was added triethyl orthoformate (0.66 mL, 6.0 mmol) and camphorsulfonic acid (7.0 mg, 0.030 mmol). After being stirred at room temperature for 2 h, the mixture was cooled to −78°C. A solution of diisobutylaluminum hydride (32.0 mL, 0.94 M, 30 mmol) in hexane was added dropwise and the resulting mixture was stirred at −78°C for 30 min and at 0°C for 10 min. The reaction mixture was then treated with methanol and saturated aqueous sodium bicarbonate. After extraction with diethyl ether, the organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:ethyl acetate=4:1) to give **20** (824 mg, 70%) as a colorless oil, which was employed in the next step without further purification. IR (film) ν 3400, 3070, 3050, 2960, 2860, 1590, 1470, 1430, 1110, 1040, 820, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.65 and 7.44–7.36 (m, 10H), 4.70 (dd, *J*=7.0, 1.0 Hz, 1H), 4.64 (dd, *J*=7.0, 1.0 Hz, 1H), 3.68 (t, *J*=6.0 Hz, 2H), 3.62–3.46 (m, 3H), 3.42 (s, 3H), 1.70–1.54 (m, 4H), 1.05 (s, 9H).

(*R*)-5-*tert*-Butyldiphenylsilyoxy-1-iodo-2-methoxymethoxypentane (21)

To a solution of **20** (785 mg, 2.0 mmol) in acetonitrile (8 mL) and diethyl ether (12 mL) was added imidazole (299 mg, 4.4 mmol), triphenylphosphine (1.05 g, 4.0 mmol) and iodine (1.22 g, 4.8 mmol) successively at −10°C. After being stirred at the same temperature for 1 h, the mixture was stirred at room temperature for 5 h. The reaction was quenched with 10% aqueous sodium thiosulfate and saturated aqueous ammonium chloride, and the resulting mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under

reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=10:1–6:1) to give **21** (784 mg, 78%) as a colorless oil, which was employed in the next step without further purification. IR (film) ν 3070, 3050, 2920, 2860, 1590, 1430, 1110, 1040, 820, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.65 and 7.44–7.36 (m, 10H), 4.63 (d, *J*=7.0 Hz, 1H), 4.60 (d, *J*=7.0 Hz, 1H), 3.63 (t, *J*=6.5 Hz, 2H), 3.37 (m, 1H), 3.35 (s, 3H), 3.27 (m, 1H), 3.21 (m, 1H), 1.80–1.56 (m, 4H), 1.05 (s, 9H).

(2′*R*, 3*RS*, 5*S*)-3-(5′-*tert*-Butyldiphenylsilyoxy-2′-(methoxymethyoxy)pentyl)-5-methyl-3-(methylsulfenyl)-tetrahydrofuran-2-one (22)

To a solution of **17** (73 mg, 0.50 mmol) in tetrahydrofuran (1.5 mL) was added dropwise a solution of sodium bis(trimethylsilyl)amide (0.84 mL, 0.60 M, 0.50 mmol) in toluene at −10°C. After being stirred at the same temperature for 30 min, a solution of **21** (252 mg, 0.50 mmol) in hexamethylphosphoric triamide (1.5 mL) was added dropwise. The resulting mixture was then stirred at room temperature for 2 h. After quenching with 0.5 M hydrochloric acid at 0°C, the mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:ethyl acetate=10:1–7:1) to give **22** (61 mg, 23%) as a colorless oil. $[\alpha]_d^{30}=-39.3°$ (*c* 0.25, $CHCl_3$); IR (film) ν 3070, 3050, 2930, 2860, 1760, 1430, 1180, 1110, 1040, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.64 and 7.44–7.36 (m, 10H), 4.69 (d, *J*=6.5 Hz, 1H), 4.64 (d, *J*=6.5 Hz, 1H), 4.61 (m, 1H), 4.00 (m, 1H), 3.66 (t, *J*=6.0 Hz, 2H), 3.36 (s, 3H), 2.90 (dd, *J*=14.5, 8.5 Hz, 1H), 2.12 (s, 3H), 2.05 (m, 1H), 1.87 (m, 1H), 1.82 (m, 1H), 1.74–1.66 (m, 2H), 1.65–1.47 (m, 2H), 1.51 (d, *J*=6.5 Hz, 3H), 1.04 (s, 9H). Anal. Calcd for $C_{29}H_{42}O_5SSi$: C 65.62, H 7.98; Found: C 65.28, H 7.91.

(*R*)-5-Iodo-1,2-*O*-isopropylidenepentane-1,2-diol (23)

To a solution of **8** (4.80 g, 30 mmol) in acetonitrile (120 mL) and diethyl ether (180 mL) was added imidazole (4.49 g, 66 mmol), triphenylphosphine (15.72 g, 60 mmol) and iodine (18.29 g, 72 mmol) successively at −10°C. After being stirred at the same temperature for 1 h, the mixture was then stirred at room temperature for 6 h. The reaction was quenched with 10% aqueous sodium thiosulfate and saturated aqueous ammonium chloride and the resulting mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=15:1–10:1) to give **23** (5.10 g, 63%) as a colorless oil. $[\alpha]_d^{29}=-4.8°$ (*c* 0.84, $CHCl_3$); IR (film) ν 2980, 2940, 2880, 1460, 1370, 1220, 1060, 860; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (m, 1H), 4.04 (dd, *J*=6.0, 8.0 Hz, 1H), 3.53 (dd, *J*=6.5, 8.0 Hz, 1H), 3.24–3.18 (m, 2H), 1.99 (m, 1H), 1.88 (m, 1H), 1.70–1.62 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H); Anal. Calcd for $C_8H_{15}IO_2$: C 35.57, H 5.60; Found: C 35.84, H 5.64.

(*R*)-1,2-*O*-Isopropylidene-7-trimethylsilyl-6-heptyne-1,2-diol (24)

To a solution of trimethylsilylacetylene (5.22 mL, 37.0 mmol) in tetrahydrofuran (70 mL) was added dropwise a solution of butyllithium (24.2 mL, 1.53 M, 37.0 mmol) in hexane at −78°C. After being stirred at the same temperature for 40 min, a solution of **23** (5.00 g, 18.5 mmol) in hexamethylphosphoric triamide (7.0 mL) and tetrahydrofuran (6.0 mL) was added dropwise and the resulting mixture was then allowed to warm to room temperature overnight. After quenching with half-saturated aqueous ammonium chloride, the mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=15:1) to give **24** (4.22 g, 95%) as a colorless oil $[\alpha]_d^{30}=-9.9°$ (*c* 1.60, $CHCl_3$); IR (film) ν 2980, 2920, 2880, 2170, 1370, 1250, 840, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (m, 1H), 4.04 (dd, *J*=6.0, 8.0 Hz, 1H), 3.53 (dd, *J*=7.0, 7.5 Hz, 1H), 2.27 (t, *J*=6.5 Hz, 2H), 1.82–1.50 (m, 4H), 1.41 (s, 3H), 1.35 (s, 3H), 0.15 (2, 9H); Anal. Calcd for $C_{13}H_{24}O_2Si$: C 64.95, H 10.06; Found: C 64.95, H 9.95.

(*R*)-7-Trimethylsilyl-6-heptyne-1,2-diol (25)

A solution of **24** (3.55 g, 14.8 mmol) in water (9 mL) and acetic acid (36 mL) was stirred at 60°C for 5 h. The solvent was then removed by co-evaporation with toluene and the residue was chromatographed on silica gel (*n*-hexane:ethyl acetate=2:1) to give **25** (2.60 g, 88%) as a colorless oil. $[\alpha]_d^{31}=+2.8°$ (*c* 1.69, $CHCl_3$); IR (film) ν 3360, 2960, 2870, 2170, 1250, 1040, 840; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (m, 1H), 3.64 (dd, *J*=11.0, 3.0 Hz, 1H), 3.43 (dd, *J*=11.0, 7.0 Hz, 1H), 2.37 (br, 2H, OH), 2.25 (d, *J*=7.0, 1.0 Hz, 2H), 1.73–1.47 (m, 4H), 0.15 (s, 9H); Anal. Calcd for $C_{10}H_{20}O_2Si$: C 59.95, H 10.06; Found: C 59.57, H 9.96.

(*R*)-2-Hydroxy-7-trimethylsilyl-6-heptynyl 2,4,6-triisopropylbenzenesulfonate (26)

To a solution of **25** (2.80 g, 14.0 mmol) in dichloromethane (82 mL) was added pyridine (46 mL) and triisopropylbenzenesulfonyl chloride (12.73 g, 42.0 mmol) successively at 0°C. After being stirred at the same temperature for 15 min, the mixture was stirred at room temperature overnight. The excess acid chloride was destroyed with ice-water by stirring for 1 h and the resulting mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=10:1–5:1) to give **26** (5.03 g, 77%) as a white solid. mp 68–69°C; $[\alpha]_d^{29}=-1.7°$ (*c* 0.30, $CHCl_3$); IR (nujol) ν 3420, 2920, 2170, 1710, 1600, 1460, 1380, 840, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J*=1.0 Hz, 2H) 4.18 (sept., *J*=6.5 Hz, 2H), 4.13 (m, 1H), 4.03–3.97 (m, 2H), 2.98 (sept., *J*=7.0 Hz, 1H), 2.35–2.28 (m, 2H), 1.80–1.60 (m, 4H), 1.33 (d, *J*=7.0 Hz, 12H), 1.32 (d, *J*=6.5 Hz, 6H), 0.19 (s, 9H); Anal. Calcd for $C_{25}H_{42}O_4SSi$: C 64.33, H 9.07; Found: C 64.10, H 9.00.

(*R*)-7-Trimethylsilyl-6-heptyn-1,2-epoxide (27)

To a suspension of sodium hydride (1.76 g of 60% dispersion in mineral oil was washed repeatedly with *n*-hexane, 44.0 mmol) in tetrahydrofuran (200 mL) was added dropwise a solution of **26** (5.14 g, 11.0 mmol) in tetrahydrofuran (60 mL) at 0°C. After being stirred at the same temperature for 1 h, the mixture was stirred at room temperature overnight. The resulting mixture was then treated with saturated aqueous ammonium chloride and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-pentane:diethyl ether=10:1) to give **27** (1.90 g, 95%) as a colorless oil. $[\alpha]_d^{29}=+34.0°$ (*c* 0.38, $CHCl_3$); IR (film) ν 3040, 2960, 2860, 2170, 1730, 1250, 840, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (m, 1H), 2.76 (dd, *J*=5.0, 4.0 Hz, 1H), 2.49 (dd, *J*=5.0, 3.5 Hz, 1H), 2.34–2.27 (m, 2H), 1.74–1.58 (m, 4H), 0.14 (s, 9H); Anal. Calcd for $C_{10}H_{18}OSi$: C 65.87, H 9.95; Found: C 65.61, H 9.86.

(*R*)-1-Iodo-7-timethylsilyl-6-heptyn-2-ol (28)

To a solution of **27** (546 mg, 3.0 mmol) in tetrahydrofuran (9.0 mL) and water (1.8 mL) was added lithium iodide (1.61 g, 12.0 mmol) and acetic acid (9.0 mL) at 0°C. After being stirred at the same temperature for 5 h the mixture was treated with saturated aqueous sodium bicarbonate and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=10:1–4:1) to give **28** (763 mg, 82%) as a colorless oil. $[\alpha]_d^{30}=+1.2°$ (*c* 1.05, $CHCl_3$); IR (film) ν 3400, 2960, 2170, 1250, 840, 760; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57 (m, 1H), 3.38 (dd, *J*=10.0, 4.0 Hz, 1H), 3.24 (dd, *J*=10.5, 7.0 Hz, 1H), 2.24 (t, *J*=6.0 Hz, 2H), 2.04 (br, 1H, OH), 1.75–1.55 (m, 4H), 0.14 (s, 9H); Anal. Calcd for $C_{10}H_{19}IOSi$: C 38.71, H 6.17; Found: C 38.96, H 6.16.

(*R*)-6-*tert*-Butyldimethylsilyloxy-7-iodo-1-trimethylsilylheptyne (29)

To a solution of **28** (2.70 g, 8.7 mmol) in dimethylformamide (20 mL) was added imidazole (2.37 g, 34.8 mmol) and *tert*-butyldimethylsilyl chloride (2.63 g, 17.4 mmol). After being stirred at room temperature overnight, the mixture was treated with water and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=40:1) to give **29** (3.32 g, 90%) as a colorless oil. $[\alpha]_d^{30}=+6.4°$ (*c* 0.65, $CHCl_3$); IR (film) ν 2960, 2860, 2170, 1470, 1250, 1080, 840, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (m, 1H), 3.19 (d, *J*=5.0, 2 Hz), 2.24 (t, *J*=7.0 Hz, 2H), 1.75 (m, 1H), 1.67 (m, 1H), 1.59–1.49 (m, 2H), 0.90 (s, 9H), 0.15 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); Anal. Calcd for $C_{10}H_{33}IOSi_2$: C 45.27, H 7.84; Found: C 45.67, H 7.87.

(2′*R*, 3*R*, 5*S*)-3-(2′-*tert*-Butyldimethylsilyoxy-7′-trimethylsilyl-6′-heptynyl)-5-methyl-3-(methylsulfenyl)-tetrahydrofuran-2-one (30) and (2′*R*,3*S*,5*S*)-3-(2′-*tert*-butyldimethylsilyoxy-7′-trimethylsilyl-6′-heptynyl)-5-methyl-3-(methylsulfenyl)-tetrahydrofuran-2-one (31)

To a solution of **17** (438 mg, 3.0 mmol) in tetrahydrofuran (9 mL) was added dropwise a solution of sodium bis(trimethylsilyl)amide (5.0 mL, 0.60 M, 3.0 mmol) in toluene at −10°C. After being stirred at the same temperature for 40 min, a solution of **29** (1.27 g, 3.0 mmol) in hexamethylphosphoric triamide (9 mL) was added dropwise and the resulting mixture was then stirred at room temperature for 2 h. After quenching with 0.5 M hydrochloric acid at 0°C, the mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=40:1–20:1) to give **30** (876 mg, 66%, more polar) and **31** (133 mg, 10%). Compound **30**; white solid; mp 44–46°C; $[\alpha]_d^{30}=-45.9°$ (*c* 0.45, $CHCl_3$); IR (nujol) ν 2960, 2930, 2860, 2170, 1760, 1250, 1180, 1020, 840; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (m, 1H), 4.20 (m, 1H), 2.93 (dd, *J*=14.5, 8.5 Hz, 1H), 2.30–2.20 (m, 2H), 2.12 (s, 3H), 2.06 (dd, *J*=15.0, 2.5 Hz, 1H), 1.82–1.75 (m, 2H), 1.70–1.40 (m, 4H), 1.50 (d, *J*=6.5 Hz, 3H), 0.89 (s, 9H), 0.14 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); Anal. Calcd for $C_{22}H_{42}O_3SSi_2$: C 59.67, H 9.56; Found: C 59.19, H 9.49. Compound **31**; colorless oil; $[\alpha]_d^{30}=+14.6°$ (*c* 0.50, $CHCl_3$); IR (film) ν 2960, 2930, 2860, 2170, 1760, 1250, 1190 840; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (m, 1H), 3.96 (m, 1H), 2.29–2.12 (m, 5H), 2.12 (s, 3H), 1.90 (dd, *J*=15.0, 6.0 Hz, 1H), 1.70–1.50 (m, 4H), 1.40 (d, *J*=6.5 Hz, 3H), 0.89 (s, 9H), 0.14 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H); Anal. Calcd for $C_{22}H_{42}O_3SSi_2$: C 59.67, H 9.56; Found: C 59.33, H 9.58.

(2′*R*, 3*R*,5*S*)-3-(2′-*tert*-Butyldimethylsilyoxy-7′-iodo-6′-heptynyl)-5-methyl-3-(methylsylfenyl)tetrahydrofuran-2-one (32)

To a solution of **30** (2.66 g, 6.0 mmol) in methanol (100 mL) was added potassium carbonate (1.08 g, 7.8 mmol) at 0°C. After being stirred at the same temperature for 10 min, the mixture was stirred at room temperature for 4 h. After being diluted with diethyl ether, the resulting mixture was filtered through a Celite pad. The filtrate was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in benzene (96 mL). Morpholine (8.1 mL, 93 mmol) and iodine (7.62 mL, 30.0 mmol) were added and the mixture was stirred at 45°C for 2 h. The reaction mixture was then cooled to room temperature and diluted with diethyl ether. After being filtered through a Celite pad, the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane:diethyl ether=10:1) to give **32** (2.23 g, 75%) as a colorless oil. $[\alpha]_d^{29}=-26.2°$ (*c* 0.54, $CHCl_3$); IR (film) ν 2960, 2930, 2860, 1760, 1250, 1180, 1020, 840, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (m, 1H), 4.21 (m, 1H), 2.92 (dd, *J*=14.0, 8.5 Hz, 1H), 2.43–2.37 (m, 2H), 2.12 (s, 3H), 2.04 (dd, *J*=15.0, 2.5 Hz, 1H), 1.82–1.77 (m, 2H, 1.70–1.40 (m, 4H), 1.50 (d, *J*=6.5 Hz, 3H), 0.89 (s, 9H),

0.13 (s, 3H), 0.11 (s, 3H); Anal. Calcd for $C_{19}H_{33}IO_3SSi$: 45.96, H 6.70; Found: C 46.23, H 6.64.

(2′*R*,5*S*)-3-(2′-*tert*-Butyldimethylsilyoxy-7′-iodo-6′-heptynyl)-5-methyl-2,5-dihydrofuran-2-one (33)

To a solution of **32** (2.43 g, 4.9 mmol) in dichloromethane (90 mL) was added dropwise a solution of *m*-chloroperoxybenzoic acid (1.06 g, 4.9 mmol) in dichloromethane (45 mL) at −78°C. After being stirred at the same temperature for 1 h, the reaction was quenched with 10% aqueous sodium thiosulfate. The resulting mixture was extracted with diethyl ether and the organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was dissolved in toluene (45 mL) and refluxed at 120°C for 5 h. After being cooled to room temperature, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:diethyl ether=5:1) to give **33** (1.10 g, 50%) as a colorless oil. $[\alpha]_d^{29}$=+15.6° (*c* 0.56, $CHCl_3$); IR (film) ν 2960, 2920, 2860, 1750, 1260, 1190, 840, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J*=1.0 Hz, 1H), 5.02 (m, 1H), 3.99 (m, 1H), 2.47–2.36 (m, 3H), 1.60–1.53 (m, 5H), 1.42 (d, *J*=7.0 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); Anal. Calcd for $C_{18}H_{29}IO_3Si$: C 48.21, H 6.52; Found: C 48.21, H 6.47.

Compound **33** was also obtained from **31** via four steps as described above in overall 40% yield.

(+)-4-*tert*-Butyldimethylsilyloxy-22-methoxymethoxy-8,8,9,9,10,10,11,11-octadehydromuconin (34) and (+)-4-*tert*-Butyldimethylsilyloxy-22-methoxymethoxy-8,8,9,9,10,10,11,11-octadehydro-12-epi-muconin (35)

To a degassed solution of tris(dibenzylideneacetone)dipalladium (27.5 mg, 0.030 mmol), copper(I) iodine (11.4 mg, 0.060 mmol) and tri(2-furyl)phosphine (17.4 mg, 0.075 mmol) in benzene (3.0 mL) was added a solution of **16** (295 mg, 0.65 mmol) in benzene (6.8 mL) and a solution of **33** (305 mg, 0.68 mmol) in benzene (6.8 mL) successively. The mixture was then degassed with argon in the dark at room temperature for 20 min. Diisopropyl amine (0.28 mL, 2.0 mmol) was added to this and the resulting mixture was stirred in the dark for 18 h. After being diluted with diethyl ether, the mixture was washed with saturated aqueous ammonium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:ethyl acetate=4:1–2:1) to give **34** (116 mg, 23%, less polar) and **35** (161 mg, 32%) as colorless oils. Compound **34**; $[\alpha]_d^{30}$=+22.0° (*c* 0.40, $CHCl_3$); IR (film) ν 3440, 2920, 2850, 1760, 1460, 1100, 1040, 840, 790; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J*=1.5 Hz, 1H), 5.03 (m, 1H), 4.82 (d, *J*=6.5 Hz, 1H), 4.66 (d, *J*=6.5 Hz, 1H), 4.25 (d, *J*=7.5 Hz, 1H), 4.01–3.95 (m, 2H), 3.88 (m, 1H), 3.46 (m, 1H), 3.40–3.31 (m, 2H), 3.39 (s, 3H), 2.48–2.38 (m, 2H), 2.30–2.26 (m, 2H), 1.96–1.18 (m, 37H), 1.42 (d, *J*=7.0 Hz, 3H), 0.87 (t, *J*=6.5 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); Anal. Calcd for $C_{45}H_{76}O_8Si$: C 69.91, H 9.91; Found: C 69.87, H 9.75. Compound **35**; $[\alpha]_d^{30}$=+11.0° (*c* 0.48, $CHCl_3$); IR (film) ν 3440, 2920, 2860, 1760, 1460, 1260, 1080, 1040, 840, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J*=1.5 Hz, 1H), 5.02 (m, 1H), 4.81 (d, *J*=7.0 Hz, 1H), 4.67 (d, *J*=7.0 Hz, 1H), 4.45 (d, *J*=3.0 Hz, 1H), 4.05–3.95 (m, 2H), 3.92 (m, 1H), 3.52–3.45 (m, 2H), 3.40 (s, 3H), 3.34 (m, 1H), 2.48–2.38 (m, 2H), 2.30–2.26 (m, 2H), 1.95–1.20 (m, 37H), 1.42 (d, *J*=6.5 Hz, 3H), 0.88 (t, *J*=7.0 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); FABMS *m/z*: 756 $[MH-H_2O]^+$, 742 $[MH-CH_3OH]^+$, 712 $[MH-CH_3OCH_2OH]^+$.

(+)-4-*tert*-Butyldimethylsilyloxy-22-methoxymethoxy-muconin (36)

To a degassed solution of **34** (62 mg, 0.080 mmol) in benzene (9 mL) and methanol (9 mL) was added tris(triphenylphosphine)rhodium(I) chloride (74 mg, 0.080 mmol) under hydrogen atmosphere. After being stirred at room temperature for 24 h, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane:ethyl acetate=4:1) to give **36** (48 mg, 77%) as a colorless oil. $[\alpha]_d$=+15.2° (*c* 0.30, $CHCl_3$); IR (film) ν 3460, 2920, 2860, 1760, 1460, 1260, 1070, 1040, 840, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 1H), 5.00 (m, 1H), 4.84 (d, *J*=6.5 Hz, 1H), 4.66 (d, *J*=7.0 Hz, 1H), 4.01–3.80 (m, 3H), 3.47 (m, 1H), 3.40 (m, 1H), 3.39 (s, 3H), 3.30 (m, 1H), 3.14 (m, 1H), 2.41 (d, *J*=5.5 Hz, 2H), 1.91–1.20 (m, 47H), 1.41 (d, *J*=6.5 Hz, 3H), 0.88 (t, *J*=6.5 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); Anal. Calcd for $C_{45}H_{84}O_8Si$: C 69.18, H 10.84; Found: C 69.21, H 10.73.

(+)-4-*tert*-Butyldimethylsilyloxy-22-methoxymethoxy-12-epi-muconin (37)

Hydrogenation of **35** (39.0 mg, 0.050 mmol) and workup were performed as described above to give **37** (29.3 mg, 75%) as a colorless oil. $[\alpha]_d^{28}$=+22.0° (*c* 0.47, $CHCl_3$); IR (film) ν 3460, 2920, 2860, 1760, 1460, 1260, 1090, 1040, 840, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J*=1.5 Hz, 1H), 5.02 (m, 1H), 4.83 (d, *J*=7.0 Hz, 1H), 4.67 (d, *J*=7.0 Hz, 1H), 4.02 (m, 1H), 3.93 (m, 1H), 3.87 (m, 1H), 3.67 (m, 1H), 3.48 (m, 1H), 3.40 (s, 3H), 3.36–3.28 (m, 2H), 2.42 (d, *J*=5.5 Hz, 2H), 1.96–1.20 (m, 47H), 1.41 (d, *J*=7.0 Hz, 3H), 0.88 (t, *J*=6.5 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); Anal. Calcd for $C_{45}H_{84}O_8Si$: C 69.18, H 10.84; Found: C 68.76, H 10.71.

Conversion of the β-alcohol 37 to the α-alcohol 36

To a solution of **37** (15.6 mg, 0.020 mmol) in dichloromethane (1.0 mL) was added Dess–Martin periodinane (12.7 mg, 0.030 mmol). After being stirred at room temperature for 3 h, saturated aqueous sodium bicarbonate (0.8 mL) and sodium thiosulfate (60 mg) were added. The resulting mixture was stirred for 20 min and extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in tetrahydrofuran (0.6 mL) at −60°C. A solution of lithium tri-*tert*-butoxyaluminohydride (60 μL, 1.0 M, 0.060 mmol) in tetrahydrofuran was added dropwise and the resulting mixture was stirred for 1 h at the same temperature. After quenching the reaction by dropwise

addition of 1 M hydrochloric acid, the mixture was extracted with diethyl ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (*n*-hexane:ethyl acetate=2:1 to give **36** (9.4 mg, 60%, less polar) and **37** (3.1 mg, 20%). Their ^{1}H NMR spectra were identical with those reported above.

(+)-Muconin (1)

To a solution of **36** (11.7 mg, 0.015 mmol) in dimethyl sulfide (1.2 mL) was added boron trifluoride diethyl etherate (76 μL, 0.60 mmol) at −10°C. After being stirred at the same temperature for 30 min, the mixture was treated with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (ethyl acetate) to give **1** (7.7 mg, 82%) as white wax. Mp 75–77°C; $[\alpha]_d^{27}=+13.5°$ (*c* 0.28, $CHCl_3$); IR (film) ν 3440, 2920, 2850, 1760, 1460, 1320, 1210, 1080; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J*=0.5 Hz, 1H), 5.06 (m, 1H), 3.90–3.77 (m, 3H), 3.43 (m, 1H), 3.38 (m, 1H), 3.31 (m, 1H), 3.16 (m, 1H), 2.52 (m, 1H), 2.37 (m, 1H), 2.20–1.20 (m, 49H), 1.43 (d, *J*=6.5 Hz, 3H), 0.87 (t, *J*=7.0 Hz, 3H); HRFABMS: Calcd for $C_{37}H_{67}O_7$ 623.4887, Found 623.4851.

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