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Total synthesis of TT-1 (rasfonin), an α-pyrone-containing natural product from a fungus *Trichurus terrophilus*

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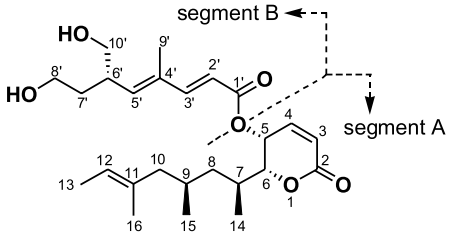
Abstract—Total synthesis of TT-1 (**1**=rasfonin), an α-pyrone-containing natural product from a Fungi Imperfecti *Trichurus terrophilus* culture was achieved by a stereoselective method in optically active form, which further provided evidence for the whole structure of TT-1 (**1**) including the absolute stereochemistry.

1. Introduction

In 2000, an α-pyrone-containing natural product, TT-1, was isolated from the ethyl acetate extract of a Fungi Imperfecti *Trichurus terrophilus* culture by Fujimoto and co-workers in our laboratory.[1] Almost at the same time, Hayakawa and co-workers reported isolation of rasfonin, which had the same planar structure as TT-1, from the fermented mycelia of an Ascomycete *Talaromyces* sp. 3656-A1.[2] Rasfonin was reported as a new apoptosis inducer in *ras*-dependent cells, while TT-1 significantly suppressed proliferation (blastogenesis) of mouse splenic lymphocytes stimulated with mitogens, concanavalin A (Con A) and lipopolysaccharide (LPS), with IC_{50} values of 0.7 and 0.5 μg/mL, respectively.[1] We investigated the absolute stereochemistry of five chiral centers of **1** on the basis of synthesis of partial structural units (segments **A** and **B**) of **1** in optically active forms and comparison of their spectral and optical data with those of natural specimens, and reported in 2003 that **1** had 5*R*, 6*R*, 7*S*, 9*R*, and 6′*S*-configurations.[3] In the synthesis of segment A of **1**, we previously obtained 5-membered lactone (**2**) instead of 6-membered lactone (**3**),[3] and we here describe the stereoselective synthesis of the 6-membered lactone (**3**) by a modified procedure and the total synthesis of TT-1 (**1**) to provide further unequivocal evidence for the whole structure of TT-1 (**1**) including the absolute stereochemistry.



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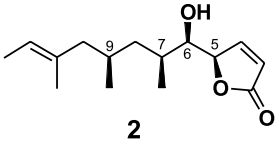

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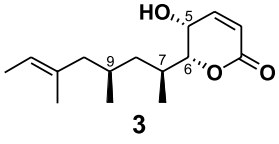

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2. Results and discussion

2.1. Synthesis of segment A

Our modified synthesis of segment A (**3**) (Scheme 1) began with the known monoacetate (**4**),[4–7] which was converted into *E*-unsaturated ester (**5**, $J_{4,5}$=15.6 Hz)[8] by a four-step reaction [(i) protection with *t*-butyldimethylsilyl (TBS) ether; (ii) alkaline hydrolysis of the acetate; (iii) Swern oxidation; (iv) Horner–Emmons reaction]. The asymmetric dihydroxylation of ester (**5**) with AD-mix β[9] led to the α,β-dihydroxy ester (**6**), which was protected with a benzyl acetal, and the $LiAlH_4$ reduction of the ester moiety afforded the alcohol (**7**). Treatment of **7** with borane-methyl sulfide in the presence of boron trifluoride diethyl etherate[10] led to reductive deprotection of the benzyl acetal to give a 1,2-diol

Keywords: TT-1 (rasfonin); *Trichurus terrophilus*; α-Pyrone; Total synthesis.
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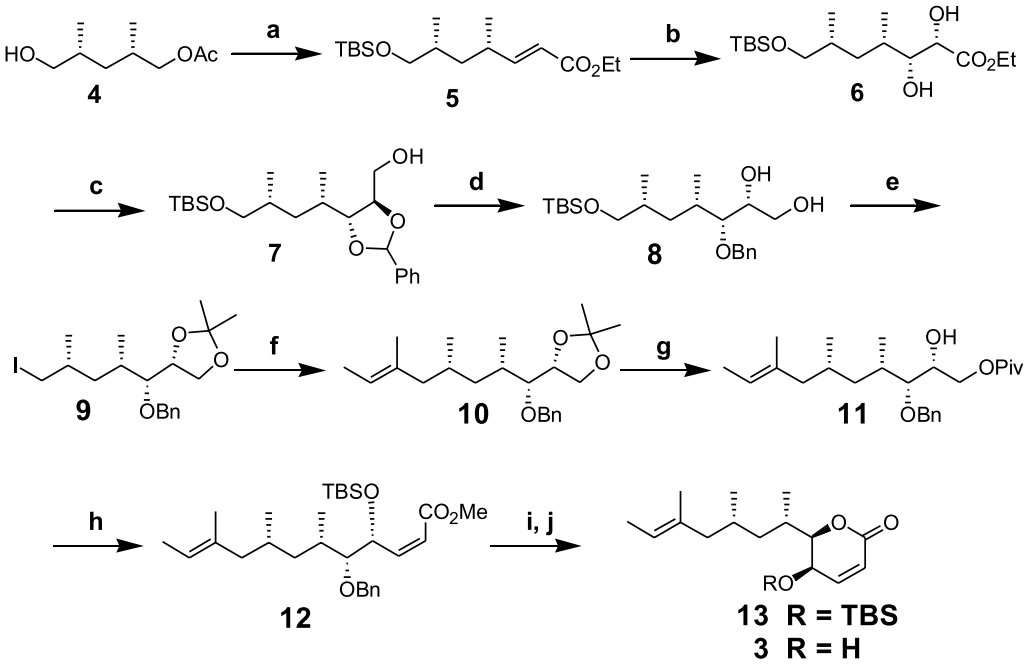
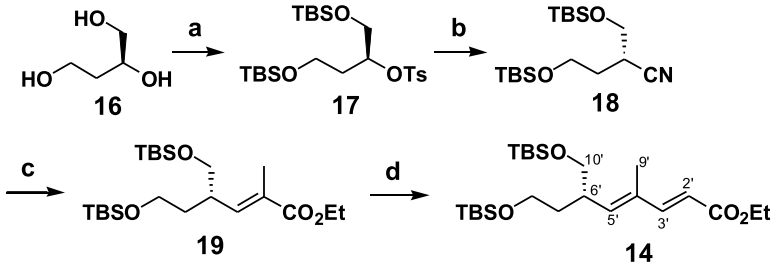


Scheme 1. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, rt, 1 h (82%); (ii) NaOH aq, MeOH, rt, 2 h (97%); (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 0 °C 2 h (84% for 2 steps); (b) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C-rt, 45 h (80%); (c) (i) $PhCH(OCH_3)_2$, TsOH, CH_2Cl_2, rt, 1 h (90%); (ii) $LiAlH_4$, THF, 0 °C, 0.5 h (81%); (d) BH_3 SMe_2, BF_3 OEt_2, CH_2Cl_2, 0 °C, 1 h (70%); (e) (i) $(CH_3)_2C(OCH_3)_2$, TsOH, acetone, rt, 1 h (91%); (ii) TBAF, THF, rt, 1 h (91%); (iii) I_2, Ph_3P, imidazole, benzene, rt, 2 h (95%); (f) 2-bromo-*cis*-2-butene, Li, THF, 0 °C-rt, 2 h (62%); (g) (i) TsOH, MeOH, rt, 2 h (84%); (ii) PivCl, pyridine, 0 °C-rt, 14 h (93%); (h) (i) TBSCl, imidazole, DMF, rt, 14 h (95%); (ii) DIBAL, CH_2Cl_2, −78 °C, 1 h (86%); (iii) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; (iv) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −78 °C, 2 h (80% for 2 steps); (i) (i) DDQ, H_2O, CH_2Cl_2, rt, 2 h (78%); (ii) DIBAL, CH_2Cl_2, −78 °C, 1 h; (iii) MnO_2, CH_2Cl_2, rt (68% for 2 steps); (j) TBAF, THF, rt, 2 h (89%).

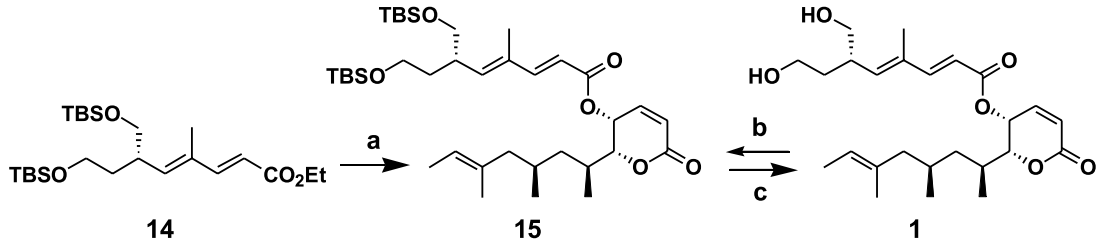
(**8**) selectively (formation of 1,3-diol was not detectable). The 1,2-diol (**8**) was protected with an acetonide, and deprotection of the TBS ether and treatment with iodine and triphenylphosphine gave the iodide (**9**). The iodide (**9**) was treated with the alkenyllithium reagent[11] derived from 2-bromo-*cis*-2-butene to give the alkene (**10**). Deprotection of the acetonide group of **10** and selective protection of the primary hydroxy group with pivaloyl ester afforded **11**. The remaining secondary hydroxy group of **11** was protected by the TBS ether, which was converted into *Z*-unsaturated ester (**12**, $J_{3,4}=11.7$ Hz) through three steps [(i) removal of the pivaloyl group with DIBAL; (ii) Swern oxidation; (iii) Still's variant of the Horner–Emmons reaction[12]]. Deprotection of the benzyl ether with DDQ, and reduction with DIBAL followed by allylic oxidation with MnO_2[13] afforded the 6-membered lactone (**13**), whose TBS ether was removed by treatment with tetrabutylammonium fluoride to afford segment A (**3**).

2.2. Coupling of segments A and B

Preparation of the ethyl ester of the di-TBS ether of segment B (**14**) was described previously,[3] and summarized in Scheme 2 and Section 3. Coupling of segment A (**3**) with the acid obtained by alkaline hydrolysis of the ethyl ester (**14**) was carried out, as shown in Scheme 3, by treatment with 1,3-dicyclohyxylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) to give the TT-1 di-TBS ether (**15**). The TT-1 di-TBS ether (**15**) was also prepared from natural product the TT-1 (**1**) by treatment with TBSOTf in the presence of 2,6-lutidine in dichloromethane. The ^1H and ^{13}C NMR and FABMS spectra of synthetic **15** and natural-product-derived **15** proved to be completely identical and the sign of their optical rotation data were both levorotatory. The di-TBS ether of **15** was removed by treatment with *p*-toluenesulfonic acid to give TT-1 (**1**) to complete the total synthesis of TT-1 (**1**).



Scheme 2. (a) (i)TBSCl, imidazole, DMF, 0 °C, 2 h (85%); (ii) TsCl, pyridine, rt, 72 h (80%). (b) NaCN, DMSO, 90 °C, 3.5 h (54%). (c) (i) DIBAL, CH_2Cl_2, −78 °C, 1 h; (ii) $Ph_3P=C(CH_3)CO_2Et$, CH_2Cl_2, rt, 73 h (47% for 2 steps). (d) (i) DIBAL, CH_2Cl_2, −78 °C, 1 h; (ii) MnO_2, CH_2Cl_2, rt, 14 h; (iii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 0 °C, 1 h (81% for 3 steps).



Scheme 3. (a) (i) 2 N NaOH aq, MeOH, rt, 19 h (80%); (ii) segment A (**3**), DCC, DMAP, CH_2Cl_2, rt, 17 h (86%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 4 h (43%); (c) *p*-TsOH, MeOH, rt, 1 h (21%).

From these results, the total synthesis of TT-1 (**1**) was accomplished and the whole structure of **1** has been unambiguously established by the present study.

3. Experimental

3.1. General procedures

Optical rotations were recorded on a JASCO J-20. IR spectra were measured on NaCl disks in a Hitachi 260-10 infrared spectrophotometer. NMR spectra were recorded on JEOL JNM GSX-A400, A500 and ecp600 spectrometers. High-resolution fast atom bombardment (HRFAB) mass spectra were acquired on a JMS HX-110 and JMS AX-500 mass spectrometer.

3.1.1. (2*E*,4*S*,6*R*)-Ethyl 7-(*t*-Butyldimethysilyloxy)-4,6-dimethyl-2-heptenoate (5). The known monoacetate[4–7] (**4**, 12.94 g) was dissolved in DMF (100 mL) and treated with TBSCl (13.66 g) in the presence of imidazole (11.85 g) at room temperature for 1 h. After addition of water, the reaction mixture was extracted with ether (100 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to afford a TBS ether (17.42 g, 82%), which was subjected to hydrolysis by treatment with 2 M NaOH aqueous solution (100 mL) and MeOH (150 mL) at room temperature for 2 h. The reaction mixture was extracted with chloroform (150 mL×6), and dried over $MgSO_4$, and evaporation of the organic phase under reduced pressure afforded an alcohol (14.49 g, 97%). This alcohol (6.98 g) was added to the solution of DMSO (8.1 mL) and oxalyl chloride (7.5 mL) in CH_2Cl_2 (150 mL) at −78 °C, and stirred at room temperature for 1 h under argon atmosphere. After addition of triethylamine (24.4 mL), the reaction mixture was gradually warmed to room temperature and stirred for 1 h. After addition of water, the mixture was extracted with $CHCl_3$ (100 mL×5), washed with water, dried over $MgSO_4$ to give an aldehyde, which was without purification subjected to the following Horner–Emmons reaction. To a solution of sodium hydride (60% in oil, 1.27 g) in DME (50 mL), triethyl phosphonoacetate (6.3 mL) was added at 0 °C under argon atmosphere and the mixture was stirred for 1 h. The aldehyde obtained above was added to this solution and the mixture was stirred for 1 h additionally. After addition of ammonium chloride aqueous solution, extraction with ethyl acetate (100 mL×5) and purification of the organic phase with silica gel column chromatography (EtOAc/hexane, 1:19) afforded the unsaturated ester (**5**, 7.53 g, 84% for 2 steps): $[\alpha]_D^{26}$ −0.7 (*c* 2.00, $CHCl_3$); IR ν (neat) 2957, 1703, 1652, 1462, 1369, 1259, 1181, 1094, and 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, $SiCH_3$), 0.85 (3H, d, J=6.6 Hz, H-9), 0.88 (9H, s, $SiC(CH_3)_3$), 1.05 (3H, d, J=6.6 Hz, H-8), 1.09 (1H, m, H-5), 1.28 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.50 (1H, ddd, J=4.6, 9.1, 13.9 Hz, H-5), 1.60 (1H, m, H-6), 2.43 (1H, m, H-4), 3.38 (2H, dd, J=4.6, 6.1 Hz, H-7), 4.18 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.78 (1H, dd, J=1.0, 15.6 Hz, H-2), and 6.80 (1H, dd, J=8.3, 15.6 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.4(2C), 14.3, 16.6, 18.3, 20.5, 25.9(3C), 33.4, 34.2, 39.9, 60.1, 68.4, 119.8, 154.4, and 116.9; FABMS *m/z* 315 $[M+H]^+$; HRFABMS found *m/z* 315.2382 (calcd for 315.2355, $C_{17}H_{35}O_3Si$).

3.1.2. (2*R*,3*R*,4*S*,6*R*)-Ethyl 7-(*t*-Butyldimethysilyloxy)-2,3-dihydroxy-4,6-dimethylheptanoate (6). AD-mix-β (40.43 g) was dissolved in 60 mL of *t*-BuOH/H_2O (1:1), and the solution was stirred at room temperature for 1 h. To this solution, methanesulfonamide (2.79 g) was added and the mixture was cooled to 0 °C. The ester (**5**, 8.97 g) was added to this solution and stirred for 45 h at room temperature. After addition of sodium sulfite (40 g), extraction with ethyl acetate (100 mL×6) followed by purification with silica gel column chromatography (EtOAc/hexane, 1:1) afforded the diol (**6**, 7.79 g, 80%): $[\alpha]_D^{26}$ −7.1 (*c* 2.08, $CHCl_3$); IR ν (neat) 3377, 2957, 2929, 2857, 1723, 1465, 1387, 1255, 1222, 1136, and 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.90 (1H, m, H-5), 0.91 (3H, d, J=6.6 Hz, H-9), 1.02 (3H, d, J=6.6 Hz, H-8), 1.31 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.53 (1H, ddd, J=5.2, 7.3, 13.8 Hz, H-5), 1.71 (1H, m, H-6), 1.78 (1H, m, H-4), 3.03 (1H, brd, J=4.4 Hz, H-3), 3.37 (1H, dd, J=6.1, 9.7 Hz, H-7), 3.45 (1H, dd, J=5.4, 9.7 Hz, H-7), 3.56 (1H, brd, J=5.9 Hz, H-2), and 4.26 (2H, q, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.4(2C), 14.2, 16.1, 18.1, 25.9(3C), 33.3, 34.0, 37.2, 43.4, 62.1, 67.6, 71.4, 76.2, and 174.1; FABMS *m/z* 349 $[M+H]^+$; HRFABMS found *m/z* 349.2402 (calcd for 349.2411, $C_{17}H_{37}O_5Si$).

3.1.3. (2*R*,3*R*,4*S*,6*R*)-7-(*t*-Butyldimethysilyloxy)-2,3-benzylidendioxy-4,6-dimethylheptanol (7). A solution of the diol (6, 7.79 g) in dichloromethane (40 mL) was treated with benzaldehyde dimethylacetal (6.8 mL) in the presence of *p*-toluenesulfonic acid monohydrate (230 mg) at room temperature for 1 h. After addition of sodium hydrogen carbonate aqueous solution, the mixture was extracted with ethyl acetate (50 mL×6), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) afforded an ester (8.12 g, 83%). A part of this ester (7.07 g) in THF solution (10 mL) was added to the solution of $LiAlH_4$ (952 mg) in THF (40 mL), and the mixture was

stirred at 0 °C for 30 min. After addition of water and neutralization with 2 M HCl, the mixture was extracted with ethyl acetate (30 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:9) to afford the alcohol (**7**, 5.17 g, 83%): $[\alpha]_D^{26}+2.5$ (*c* 2.00, $CHCl_3$); IR (neat) ν 3414, 2954, 2928, 2884, 2856, 1459, 1406, 1387, 1219, 1093, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, SiCH_3), 0.89 (9H, s, SiCCH_3), 0.92 (3H, d, J=6.6 Hz, H-9), 1.06 (3H, d, J=6.8 Hz, H-8), 1.07 (1H, m, H-5), 1.51 (1H, m, H-5), 1.76 (1H, m, H-6), 1.87 (1H, m, H-4), 3.37 (1H, dd, J=6.1, 9.8 Hz, H-7), 3.48 (1H, dd, J=4.9, 9.8 Hz, H-7), 3.76 (2H, t, J=4.8 Hz, H-1), 3.81 (1H, dd, J=5.1, 6.8 Hz, H-3), 4.09 (1H, dt, J=6.8, 4.8 Hz, H-2), 5.97 (1H, s, OC*H*Ph), 7.38–7.49 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.4(2C), 15.4, 18.2, 25.9(3C), 32.8, 33.1, 37.2, 63.4, 65.4, 67.4, 79.8, 82.2, 103.1, 127.0, 128.4(2C), 129.5(2C), 137.3; FABMS *m/z* 395 $[M+H]^+$; HRFABMS found *m/z* 395.2618 (calcd for 395.2618, $C_{22}H_{39}O_4Si$).

3.1.4. (2*R*,3*R*,4*S*,6*R*)-3-Benzyloxy-7-(*t*-butyldimethysilyloxy)-4,6-dimethyl-1,2-heptanediol (8). To a solution of the alcohol (**7**, 6.68 g) in dichloromethane (80 mL), dimethylsulfide borane (1.8 mL) was slowly added at 0 °C under argon atmosphere, and the mixture was stirred and gradually warmed to room temperature over 1 h. This reaction mixture was cooled again to 0 °C and boron trifluoride ethyl ether complex (2.15 mL) was added. The mixture was further stirred for 10 min. After addition of water, extraction with EtOAc (50 mL×5) followed by purification with silica gel column chromatography (EtOAc/hexane, 1:1) afforded a 1,2-diol (**8**, 4.68 g, 70%): $[\alpha]_D^{27}-22.9$ (*c* 2.00, $CHCl_3$); IR ν (neat) 3448, 2956, 2928, 2857, 1462, 1421, 1388, 1265, 1091, and 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, SiCH_3), 0.89 (9H, s, SiCCH_3), 0.90 (3H, d, J=6.6 Hz, H-9), 0.98 (3H, d, J=6.9 Hz, H-8), 1.04 (1H, m, H-5), 1.65 (1H, m, H-5), 1.75 (1H, m, H-6), 1.86 (1H, m, H-4), 3.35 (1H, dd, J=4.8, 5.7 Hz, H-3), 3.41 (2H, dd, J=5.3, 7.8 Hz, H-7), 3.54 (1H, m, H-1), 3.63 (1H, m, H-1), 3.74 (1H, m, H-2), 4.55 (1H, d, J=11.2 Hz, OCH_2Ph), 4.74 (1H, s, OCH_2Ph), and 7.30–7.37 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.4(2C), 15.5, 17.8, 18.3, 25.9(3C), 32.7, 33.2, 37.7, 64.5, 68.0, 72.0, 74.6, 82.2, 127.8(2C), 127.9, 128.5(2C), and 138.2; FABMS *m/z* 397 $[M+H]^+$; HRFABMS found *m/z* 397.2747 (calcd for 397.2774, $C_{22}H_{41}O_4Si$).

3.1.5. (2*R*,3*R*,4*S*,6*R*)-3-Benzyloxy-7-iodo-1,2-isopropylidendioxy-4,6-dimethylheptane (9). A solution of the diol (**8**, 5.35 g) in dichloromethane (40 mL) was treated with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid monohydrate (120 mg) at room temperature for 1 h. After addition of sodium hydrogen carbonate aqueous solution, the mixture was extracted with ethyl acetate (50 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford an acetonide (5.38 g, 91%), which was dissolved in THF (30 mL) and treated with tetrabutylammonium fluoride, 1.0 M solution in THF (16 mL) at room temperature for 1 h. After addition of water, the mixture was extracted with ethyl acetate (50 mL×4), washed with brine, dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:4) to give an alcohol (3.63 g, 91%). A part of this alcohol (1.50 g) was dissolved in benzene (40 mL), and treated with imidazole (809 mg), triphenylphosphine (3.13 g), and iodine (2.38 g) at room temperature for 2 h. After addition of sodium sulfite aqueous solution, extraction with EtOAc (3 mL×4) followed by purification with silica gel column chromatography (EtOAc/hexane, 1:9) afforded an iodide (**9**, 1.92 g, 95%): $[\alpha]_D^{27}+32.8$ (*c* 2.00, $CHCl_3$); IR ν (neat) 2956, 2928, 2857, 1462, 1421, 1388, 1265, 1091, and 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.91 (3H, d, J=6.6 Hz, H-9), 0.93 (3H, d, J=6.9 Hz, H-8), 1.09 (1H, m, H-5), 1.30 (1H, m, H-5), 1.42 (3H, s, OCCH_3), 1.43 (2H, m, H-4,6), 1.46 (3H, s, OCCH_3), 3.00 (1H, dd, J=5.9, 9.6 Hz, H-7), 3.08 (1H, dd, J=4.1, 9.6 Hz, H-7), 3.29 (1H, dd, J=1.0, 7.8 Hz, H-3), 3.52 (1H, dt, J=1.0, 7.8 Hz, H-1), 4.00 (1H, dt, J=1.0, 7.8, H-1), 4.33 (1H, q, J=7.8 Hz, H-2), 4.64 (1H, d, J=11.2 Hz, OCH_2Ph), 4.86 (1H, s, OCH_2Ph), and 7.33–7.39 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.4, 17.9, 20.8, 25.8, 26.8, 31.3, 32.6, 40.9, 66.5, 73.7, 79.1, 81.8, 109.3, 127.5(2C), 128.0, 128.2(2C), and 139.1; FABMS *m/z* 433 $[M+H]^+$; HRFABMS found *m/z* 433.1224 (calcd for 433.1240, $C_{19}H_{30}IO_3$).

3.1.6. (2*R*,3*R*,4*S*,6*R*,8*E*)-3-Benzyloxy-1,2-isopropylidendioxy-4,6,8-trimethyl-8-heptene (10). To the mixture of lithium metal (87.1 mg) and anhydrous ether (4 mL) under argon atmosphere, 2-bromo-*cis*-2-butene (851 mg) was added over 30 min, and the mixture was stirred for 2 h at room temperature. Then, the mixture was cooled to 0 °C and a solution of the iodide (**9**, 901 mg) in THF (6 mL) was added to this mixture, which was gradually warmed to room temperature and stirred for 2 h. After addition of ammonium chloride aqueous solution, the mixture was extracted with ethyl acetate (30 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to give the alkene (**10**, 461 mg, 62%): $[\alpha]_D^{27}+20.8$ (*c* 2.00, $CHCl_3$); IR ν (neat) 2958, 2930, 1654, 1455, 1378, 1250, 1214, 1159, and 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.77 (3H, d, J=6.3 Hz, H-12), 0.93 (3H, d, J=6.6 Hz, H-11), 0.95 (1H, m, H-5), 1.38 (3H, s, OCCH_3), 1.39 (1H, m, H-5), 1.45 (2H, m, H-4,6), 1.54 (3H, d, J=6.4 Hz, H-10), 1.55 (3H, s, H-13), 1.57 (1H, m, H-7), 1.61 (1H, m, H-6), 1.70 (1H, m, H-4), 1.90 (1H, brdd, J=5.5, 13.0 Hz, H-7), 3.32 (1H, dd, J=1.8, 8.1 Hz, H-3), 3.50 (1H, t, J=8.1 Hz, H-1), 4.00 (1H, dd, J=6.2, 8.1 Hz, H-1), 4.29 (1H, m, H-2), 4.55 (1H, d, J=11.7 Hz, OCH_2Ph), 5.15 (1H, d, J=11.7 Hz, OCH_2Ph), 5.14 (1H, q, J=6.4 Hz, H-9), and 7.30–7.38 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.3, 14.9, 15.7, 25.8, 26.9, 27.9, 32.7, 41.8, 47.9, 66.5, 73.9, 77.2, 79.4, 120.1, 127.2, 127.6(2C), 128.1(2C), 134.4, and 139.4; FABMS *m/z* 361 $[M+H]^+$; HRFABMS found *m/z* 361.2736 (calcd for 361.2743, $C_{23}H_{37}O_3$).

3.1.7. (2*R*,3*R*,4*S*,6*R*,8*E*)-3-Benzyloxy-2-hydroxy-4,6,8-trimethyl-8-decenyl pivaloate (11). A solution of the alkene (**10**, 891 mg) in methanol (20 mL) was treated with *p*-toluenesulfonic acid monohydrate (86 mg) at room temperature for 2 h. After addition of water, the mixture was extracted with ethyl acetate (30 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:4) to give a diol (662 mg, 84%), a part of which (507 mg) was dissolved in pyridine (1 mL) at 0 °C and treated with pivaloyl chloride (0.32 mL) at room

temperature for 14 h. After addition of water and neutralization with 2 M HCl, the mixture was extracted with ethyl acetate (20 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to give the pivaloyl ester (**11**, 668 mg, 93%): $[\alpha]_D^{27}-16.0$ (*c* 2.00, $CHCl_3$); IR ν (neat) 3448, 2962, 2929, 1730, 1654, 1480, 1457, 1397, 1375, 1283, 1160, 1095, and 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.83 (3H, d, $J=6.3$ Hz, H-12), 0.98 (3H, d, $J=6.8$ Hz, H-11), 1.06 (1H, m, H-5), 1.24 (9H, s, OCCH_3), 1.49 (1H, m, H-5), 1.54 (3H, d, $J=6.6$ Hz, H-10), 1.55 (3H, s, H-13), 1.66 (1H, m, H-7), 1.73 (1H, m, H-6), 1.84 (1H, m, H-4), 2.04 (1H, m, H-7), 3.32 (1H, t, $J=4.4$ Hz, H-3), 3.88 (1H, dt, $J=5.8$, 4.4 Hz, H-2), 4.09 (2H, d, $J=5.8$ Hz, H-1), 4.59 (1H, d, $J=11.0$ Hz, CH_2Ph), 4.67 (1H, d, $J=11.0$ Hz, CH_2Ph), 5.17 (1H, q, $J=6.6$ Hz, H-9), and 7.30–7.36 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.3, 15.6, 20.4, 27.2(3C), 28.4, 32.6, 38.8, 42.3, 47.3, 65.6, 70.3, 74.7, 81.8, 120.1, 127.3(2C), 127.8, 128.5(2C), 134.3, 138.1, and 178.3; FABMS *m/z* 405 $[M+H]^+$; HRFABMS found *m/z* 405.2979 (calcd for 405.3005, $C_{25}H_{41}O_4$).

3.1.8. (2*Z*,4*R*,5*R*,6*S*,8*R*,10*E*)-Methyl 5-benzyloxy-4-(*t*-butyldimethylsilyloxy)-6,8,10-trimethyl-dodecadienate (12). The pivaloyl ester (**11**, 668 mg) was dissolved in DMF (6 mL) and treated with TBSCl (752 mg) in the presence of imidazole (1.16 g) at room temperature for 14 h. After addition of water, the reaction mixture was extracted with ether (30 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford a TBS ether (806 mg, 95%), a part of which (771 mg) was dissolved in dichloromethane (14 mL). To this solution, 0.93 M diisobutylaluminium hydride in hexane solution (3.6 mL) was added, and the mixture was stirred at −78 °C under argon atmosphere. After addition of potassium sodium (+)-tartarate aqueous solution, the mixture was extracted with ethyl acetate (20 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford an alcohol (553 mg, 86%). A part of this alcohol (259 mg) was dissolved in dichloromethane (4 mL) and treated with Dess-Martin periodinane (389 mg) at room temperature for 1 h. After addition of water, the mixture was extracted with ether (10 mL×3), washed with aqueous solution of sodium hydrogen carbonate and sodium thiosulfate (1:1), dried over $MgSO_4$, and evaporated under reduced pressure to afford an aldehyde, which was used without purification in the following reaction. A solution of 18-crown-6 (802 mg) in THF (6 mL) at −78 °C under argon atmosphere, 0.5 M toluene solution of potassium bis(trimethylsilyl)-amide (1.4 mL) and bis-(2,2,2-trifluoroethyl)-(methoxycarbonyl methyl)phosphonate (0.14 mL) were added and the mixture was stirred at −78 °C for 1 h. To this solution, the aldehyde obtained above dissolved in THF (3 mL) was added, and the mixture was further stirred for 2 h. After addition of ammonium chloride aqueous solution, the mixture was extracted with ethyl acetate (10 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:9) to afford the unsaturated ester (**12**, 233 mg, 80% for 2 steps): $[\alpha]_D^{26}+19.4$ (*c* 2.20, $CHCl_3$); IR ν (neat) 2954, 2928, 2857, 1726, 1653, 1459, 1437, 1254, 1197, 1179, and 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 0.75 (3H, d, $J=6.1$ Hz, H-14), 0.88 (9H, s, SiCCH_3), 0.95 (3H, d, $J=6.6$ Hz, H-13), 0.96 (1H, m, H-7), 1.40 (1H, m, H-7), 1.51 (3H, s, H-15), 1.52 (3H, d, $J=6.6$ Hz, H-12), 1.57 (1H, m, H-9), 1.62 (1H, m, H-8), 1.77 (1H, m, H-6), 1.89 (1H, m, H-9), 3.27 (1H, dd, $J=3.0$, 6.3 Hz, H-5), 3.69 (3H, s, OCH_3), 4.52 (1H, d, $J=11.7$, CH_2Ph), 4.58 (1H, d, $J=11.7$, CH_2Ph), 5.14 (1H, q, $J=6.6$ Hz, H-11), 5.58 (1H, dd, $J=6.3$, 9.5 Hz, H-4), 5.80 (1H, d, $J=11.8$ Hz, H-2), 6.15 (1H, dd, $J=9.5$, 11.8 Hz, H-3), and 7.29–7.35 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −4.5(2C), 13.3, 15.5, 15.6, 19.9, 25.9(3C), 28.1, 31.4, 42.2, 47.6, 51.3, 69.9, 74.4, 84.9, 119.4, 119.8, 127.3(2C), 128.0(2C), 134.5, 139.4, 149.6, and 166.2; FABMS *m/z* 489 $[M+H]^+$; HRFABMS found *m/z* 489.3423 (calcd for 489.3400, $C_{29}H_{49}O_4Si$).

3.1.9. (5*R*,6*R*,1′*S*,3′*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-6-(1′,3′,5′-trimethyl-hept-5-enyl)-5,6-dihydro-pyran-2-one (13). The unsaturated ester (**12**, 5.0 mg) was dissolved in dichloromethane (0.2 mL), and this solution was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (23.1 mg) and water (0.013 mL) at room temperature for 2 h. After addition of water, extraction with chloroform (50 mL×4) and purification with silica gel column chromatography (EtOAc/hexane, 1:9) afforded an alcohol (3.0 mg, 78%), which was dissolved in dichloromethane (0.2 mL) at −78 °C under argon atmosphere. To this solution, 0.93 M dichloromethane solution of DIBAL (0.2 mL) was added, and this mixture was stirred for 1 h. After warming to room temperature, potassium sodium (+)-tartarate aqueous solution was added, and the mixture was extracted with ethyl acetate (10 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was dissolved in dichloromethane (0.3 mL). To this solution, manganese dioxide (4.2 mg) was added, and this mixture was stirred at room temperature for 23 h. Filtration through celite to remove MnO_2 followed by purification with silica gel preparative TLC gave the 6-membered lactone (**13**, 2.0 mg, 68% for 2 steps): $[\alpha]_D^{21}-160$ (*c* 1.50, $CHCl_3$); IR ν (neat) 3053, 2986, 2958, 2929, 2857, 1723, 1654, 1458, 1421, 1380.8, 1159, 1126, and 1053 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.03 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 0.76 (3H, d, $J=6.6$ Hz, H-15), 0.88 (9H, s, SiCCH_3), 0.98 (1H, m, H-8), 1.11 (3H, d, $J=6.6$ Hz, H-14), 1.37 (1H, m, H-8), 1.53 (1H, m, H-10), 1.55 (3H, s, H-16), 1.56 (3H, d, $J=6.6$ Hz, H-13), 1.75 (1H, m, H-9), 2.10 (1H, m, H-10), 2.14 (1H, m, H-7), 3.87 (1H, ddd, $J=2.4$, 8.5, 16.1 Hz, H-6), 4.26 (1H, dt, $J=5.6$, 2.4 Hz, H-5), 5.17 (1H, q, $J=6.6$ Hz, H-12), 6.08 (1H, dd, $J=1.0$, 9.7 Hz, H-3), and 6.87 (1H, dd, $J=5.6$, 9.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −4.3 (2C), 13.3, 14.8, 15.2, 15.4, 20.6, 25.7 (3C), 27.6, 30.8, 40.2, 46.1, 61.7, 85.3, 120.0, 122.8, 134.3, 144.6, and 163.9; FABMS *m/z* 367 $[M+H]^+$; HRFABMS found *m/z* 367.2644 (calcd for 367.2668, $C_{21}H_{39}O_3Si$).

3.1.10. (5*R*,6*R*,1′*S*,3′*R*)-5-Hydroxy-6-(1′,3′,5′-trimethyl-hept-5-enyl)-5,6-dihydro-pyran-2-one (3). The 6-membered lactone (**13**, 8.1 mg) was dissolved in THF (0.15 mL) and treated with 1.0 M solution of tetrabutylammonium fluoride in THF (0.03 mL) at room temperature for 2 h. After addition of water, the mixture was extracted with ethyl acetate (10 mL×3), dried over $MgSO_4$, and purified with silica gel prepatative TLC (EtOAc/hexane, 1:1) to give an

alcohol (segment A, **3**, 5.0 mg, 89%): $[\alpha]_D^{24}-72.5$ (*c* 2.00, $CHCl_3$); IR ν (neat) 3385, 2927, 1712, 1381, 1265, and 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.84 (3H, d, $J=6.8$ Hz, H-15), 1.15 (3H, d, $J=6.4$ Hz, H-14), 1.65 (6H, br.s; H-13 and H-16), 3.92 (1H, dd, $J=9.1$, 1.9 Hz, H-6), 4.23 (1H, br.s, H-5), 5.20 (1H, q, $J=6.4$ Hz, H-12), 6.13 (1H, dd, $J=9.4$ Hz, H-3), and 7.01 (1H, dd, $J=9.4$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 13.4, 15.6, 15.7, 21.0, 27.9, 31.3, 39.8, 46.4, 60.7, 85.2, 120.1, 123.2, 134.5, 144.2, and 163.9; FABMS *m/z* 253 $[M+H]^+$; HRFABMS found *m/z* 253.1807 (calcd for 253.1804, $C_{15}H_{25}O_3$).

3.1.11. Preparation of segment B di-TBS ether (14) (Scheme 2). The known triol[14] (**16**, 2.968 g) was dissolved in DMF (30 mL) and treated with TBSCl (9.697 g) in the presence of imidazole (9.532 g) at room temperature for 2 h under argon atmosphere. After addition of water, the reaction mixture was extracted with $CHCl_3$ (100 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:1) to afford a TBS ether (7.954 g, 85%), part of which (2.011 g) was treated with TsCl (1.711 g) in pyridine (12 mL) at room temperature for 72 h. After addition of water, the reaction mixture was neutralized with potassium hydrogensulfate, and extracted with $CHCl_3$ (100 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to afford a tosylate (**17**, 2.337 g, 80%): $[\alpha]_D^{22}-16.8$ (*c* 0.20, $CHCl_3$); IR ν (neat) 2955, 2929, 2885, 2857, 1598, 1471, 1462, 1362, 1256, 1177, and 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H −0.01(3H, s, SiCH_3), 0.00 (3H, s, SiCH_3), 0.01 (6H, s, SiCH_3), 0.85 (18H, s, SiC(CH_3)$_3$), 1.80 (1H, m, H-3), 1.90 (1H, m, H-3), 2.44 (3H, s, ArCH_3), 3.48 (1H, ddd, $J=6.0$, 7.1, 10.5 Hz, H-4), 3.56 (1H, dt, $J=10.5$, 6.0 Hz, H-4), 3.72 (2H, d, $J=8.0$ Hz, H-1), 7.31 (2H, d, $J=8.0$ Hz, Ar), and 7.80 (2H, d, $J=8.0$ Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$)δ_C −5.5, −5.4, 21.6, 25.7(2C), 25.9(2C), 25.9, 34.3, 58.7, 64.3, 81.0, 127.8(2C), 129.7(2C), and 144.8; FABMS *m/z* 489 $[M+H]^+$; HRFABMS found *m/z* 489.2490 (calcd for 489.2526, $C_{23}H_{45}O_5SSi_2$).

To a solution of sodium cyanide (517.8 mg) in DMSO (52 mL), the tosylate (**17**, 2.337 g) was added, and the mixture was stirred at 90 °C for 3.5 h. After cooling to room temperature and addition of water, the mixture was extracted with extracted with $CHCl_3$ (50 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:4) to afford a nitrile (**18**, 887 mg, 54%): $[\alpha]_D^{22}+15.6$ (*c* 0.50, $CHCl_3$); IR ν (neat) 2955, 2930, 2885, 2858, 1472, 1256, and 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H −0.08 (6H, s, SiCH_3), 0.10 (6H, s, SiCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.91 (9H, s, SiC(CH_3)$_3$), 1.83 (2H, m, H-3), 2.95 (1H, dq, $J=8.5$, 5.8 Hz, H-2), and 3.78 (4H, m, H-1, 4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_H −5.4(4C), 18.3, 26.0(6C), 31.8, 59.9, 63.1, and 120.9; FABMS *m/z* 344 $[M+H]^+$; HRFABMS found *m/z* 344.2416 (calcd for 344.2441, $C_{17}H_{38}O_2Si_2N$).

To the solution of the nitrile (**18**, 171.8 mg) in CH_2Cl_2 under argon atmosphere at −78 °C, 0.93 M dichloromethane solution of DIBAL was added, and this mixture was stirred for 1 h. After warming to room temperature, potassium sodium (+)-tartarate aqueous solution was added, and the mixture was extracted with $CHCl_3$ (30 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was dissolved in dichloromethane (0.5 mL). This solution was treated with (1-carbethoxyethylidene)-triphenylphosphorane (364.5 mg) under argon atmosphere at room temperature for 73 h. After evaporation under reduced pressure, the residue was purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford an ester (**19**, 100.6 mg, 47% for 2 steps): $[\alpha]_D^{22}+21.0$ (*c* 0.11, $CHCl_3$); IR ν (neat) 2954, 2929, 2895, 2858, 1713, 1653, 1472, 1388, 1362, and 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.08 (6H, s, SiCH_3), 0.10 (6H, s, SiCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.91 (9H, s, SiC(CH_3)$_3$), 1.28 (1H, t, $J=$ 7.2 Hz, –OCH$_2$CH_3), 1.45 (1H, m, H-5), 1.81 (1H, m, H-4), 1.86 (3H, d, $J=1.4$ Hz, H-7), 2.78 (1H, m, H-4), 3.52 (1H, m, H-8), 3.54 (2H, dd, $J=4.1$, 6.1 Hz, H-6), 3.60 (1H, m, H-8), 4.18 (2H, q, $J=7.2$ Hz, –OCH_2CH$_3$), and 6.57 (1H, dd, $J=1.4$, 10.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.4(4C), 12.9, 14.3, 18.3, 25.8(6C), 34.3, 38.4, 60.4, 60.9, 65.9, 129.0, 143.5, and 168.2; FABMS *m/z* 431 $[M+H]^+$; HRFABMS found *m/z* 431.2990 (calcd for 431.3013, $C_{22}H_{47}O_4Si_2$).

To the solution of the ester (**19**, 85.7 mg) in CH_2Cl_2 under argon atmosphere at −78 °C, 0.93 M dichloromethane solution of DIBAL (0.44 mL) was added, and this mixture was stirred for 1 h. After warming to room temperature, potassium sodium (+)-tartarate aqueous solution was added, and the mixture was extracted with $CHCl_3$ (30 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was dissolved in dichloromethane (10 mL). This solution was treated with MnO_2 (161.2 mg) at room temperature for 13 h. After evaporation under reduced pressure, the residue (aldehyde) was used to the next reaction. A mixture of triethyl phosphonoacetate and sodium hydride (50% in oil, 21 mg) in dimethoxyethane (2.5 mL) was stirred at 0 °C under argon atmosphere for 1 h. To this mixture, the aldehyde obtained as above was added and stirred for 1 h. After addition of water, the mixture was extracted with ether (20 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:49) to afford the segment B di-TBS ether (**14**, 74.3 mg, 81% for 3 steps): $[\alpha]_D^{22}+20.2$ (*c* 0.60, $CHCl_3$); IR ν (neat) 2954, 2928, 2857, 1718, 1624, 1471, 1388, 1364, 1300, 1256, and 1169 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.01 (12H, s, SiCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 1.30 (1H, t, $J=$ 7.2 Hz, –OCH$_2$CH_3), 1.41 (1H, ddt, $J=8.5$, 13.5, 5.3 Hz, H-7), 1.80 (3H, d, s, H-9), 1.86 (ddt, $J=8.5$, 13.5, 5.3 Hz, H-7), 2.82 (1H, ddt, $J=4.2$, 10.4, 6.2 Hz, H-6), 3.50 (1H, ddt, $J=5.1$, 6.4, 10.1 Hz, H-8), 3.52 (2H, t, $J=6.2$ Hz, H-10), 3.60 (1H, ddt, $J=5.1$, 6.4, 10.1 Hz, H-8), 4.52 (2H, q, $J=7.2$ Hz, –OCH_2CH$_3$), 5.74 (1H, d, $J=10.1$ Hz, H-5), 5.80 (1H, d, $J=15.6$ Hz, H-2), and 7.31 (1H, d, $J=15.6$ Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.3(4C), 12.7, 14.3, 18.2, 25.8(6C), 34.3, 38.3, 60.2, 60.8, 66.1, 115.9, 134.0, 143.5, 149.6, and 167.6; FABMS *m/z* 457 $[M+H]^+$; HRFABMS found *m/z* 457.3132 (calcd for 457.3169, $C_{24}H_{49}O_4Si_2$).

3.1.12. Coupling of segments A and B. Segment B di-TBS ether (**14**, 8.0 mg) in methanol (0.5 mL) was treated with

2 M sodium hydroxide aqueous solution (0.5 mL) at room temperature for 19 h. After addition of water, the mixture was extracted with ethyl acetate (10 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give an acid (segment B, 6.0 mg, 80%). The alcohol (segment A, **3**, 2.0 mg) and the acid (segment B, 4.0 mg) were dissolved in dichloromethane (0.2 mL), and this mixture was treated with 1,3-dicyclohyxylcarbodiimide (DCC, 2.0 mg) in the presence of 4-dimethylaminopyridine (DMAP, 1.2 mg) at room temperature for 17 h. After addition of water, the mixture was extracted with ether (10 mL×4), dried over $MgSO_4$, and silica gel prepatative TLC (EtOAc/hexane, 1:4) to give TT-1 di-TBS ether (**15**, 4.5 mg, 86%): $[\alpha]_D^{23}-125$ (*c* 2.0, $CHCl_3$); IR ν (neat) 1718, 1617, 1256, 1157, and 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.00 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 0.78 (3H, d, J=7.0 Hz, H-15), 0.87 (9H, s, SiCCH_3), 0.88 (9H, s, SiCCH_3), 1.15 (3H, d, J=6.5 Hz, H-14), 1.52 (3H, br.s, H-16), 1.53 (3H, d, J=6.2 Hz, H-13), 1.79 (3H, s, H-9′), 2.83 (1H, br.s, H-6′), 3.48–3.62 (4H, m, H-8′ and H-10′), 4.13 (1H, dd, J=8.8, 1.8 Hz, H-6), 5.12 (1H, q, J=6.2 Hz, H-12), 5.36 (1H, dd, J=6.0, 1.8 Hz, H-5), 5.73–5.85 (2H, m, H-2′ and H-5′), 6.21 (d, J=9.5 Hz, H-3), 7.05 (1H, dd, J=9.5, 6 Hz, H-4), and 7.34 (1H, d, J=15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.43, −5.40, −5.38, −5.30, 12.7, 13.3, 15.5, 15.9, 18.2, 18.2, 20.6, 25.84, 25.88, 27.9, 31.4, 34.6, 38.4, 40.0, 46.3, 60.7, 61.6, 66.0, 83.3, 114.1, 120.0, 124.9, 134.0, 134.1, 140.7, 145.3, 151.6, 163.3, and 166.4; FABMS *m/z* 663 $[M+H]^+$; HRFABMS found *m/z* 663.4480 (calcd for 663.4476, $C_{37}H_{67}O_6Si_2$).

3.2. Preparation of TT-1 di-TBS ether (15) from TT-1 (1)

To the solution of TT-1 (**1**, 5.0 mg) in dichloromethane (0.1 mL), 2,6-lutidine (5.4 mL) was added at 0 °C under argon atmosphere. To this solution, TBSOTf (7.9 μL) was added dropwise over 5 min and the mixture was stirred for 4 h at 0 °C. After addition of water (0.5 mL), the reaction mixture was extracted with $CHCl_3$ (10 mL×4), dried over $MgSO_4$, and purified with preparative TLC (silica gel, EtOAc/hexane, 1:4) to afford a TT-1 TBS ether (**15**, 3.3 mg, 43%), which was completely identical with synthetic **15** on the basis of comparison of ^1H and ^{13}C NMR and FABMS spectral data, and the sign of the optical rotation was also the same ($[\alpha]_D^{24}-70$ (*c* 2.0, $CHCl_3$)).

3.3. Conversion of TT-1 di-TBS ether (15) into TT-1 (1)

TT-1 TBS ether (**15**, 2.2 mg) was dissolved in MeOH (0.55 mL) and treated with *p*-toluenesulfonic acid mono hydrate (28 mg) at room temperature for 1 h. After addition of water, the mixture was extracted with $CHCl_3$ (10 mL×4), dried over $MgSO_4$, and purified with HPLC (Develosil ODS-HG; 10×250 mm; flow rate: 2.0 mL; UV detection at 251 nm; eluent: CH_3CN/H_2O, 1:1) to afford TT-1 (**1**, 0.3 mg, 21%).

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