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Synthesis and configurations of YF-0200R A and B

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ABSTRACT

Two natural unsaturated fatty acids with aspargyl protease inhibition activity were synthesized for the first time. The stereogenic centers were installed by using Brown asymmetric allylation or chiral building blocks derived from D-glucose, respectively. The conjugate diene unit was introduced via an HWE reaction. The geometry of the C–C double bonds was clearly shown to be (*E*) by ^{1}H NMR in C_6D_6. The spectroscopic data for the synthetic samples were in excellent consistency with those reported for the corresponding natural ones. The optical rotations were also compatible with those for the natural ones. The absolute configurations for natural YF-0200R A and B thus could be reliably assigned as (8*S*) and (8*S*,10*S*), respectively.

1. Introduction

Unsaturated fatty acids YF-0200R A and B were isolated from the culture broth of *Streptomyces* sp. YF-0200R, a fungus found in a soil sample from South Sumatra, Indonesia, by Sato[1] and coworkers. In preliminary tests on aspartyl protease inhibition activity both **1** and **2** showed an IC_{50} of ca. 6×10^{-4} M activity against *Candida albicans*, with, demonstrating the first examples of unsaturated fatty acids possessing this activity.

On the basis of extensive spectroscopic analyses, the gross structures for YF-0200R A and B were assigned as shown in Fig. 1 (**1** and **2**, respectively). However, the previous investigators did not seem to have made any attempts to determine the absolute configurations for both compounds. And the critical stereochemical information remains missing to date, clearly calling for an enantioselective synthesis to complete the long-pending full characterization of these potentially useful natural products. As an extension of our studies on enantioselective synthesis and absolute configuration of naturally occurring diols,[2] we synthesized both **1** and **2** in optically active forms; the configurations of their natural counterparts were also hence elucidated. Details are given below.

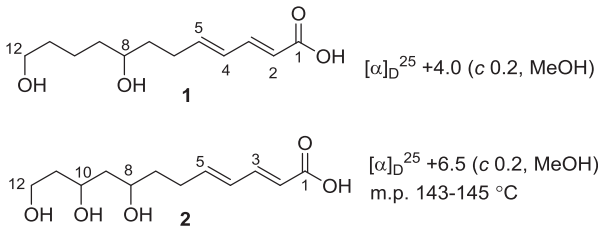

Fig. 1. The gross structures of YF-0200R A (**1**) and B (**2**).

2. Results and discussion

Our study began with a synthesis of (*R*)-**1** as shown in Scheme 1. The known[3] aldehyde **3** was subjected to Brown[4] asymmetric allylation to afford alcohol **4**[5] as reported by Menche. The hydroxyl group in **4** was then protected[6] with TBSCl to give **5**, which on treatment with $BH_3\cdot SMe_2$ followed by H_2O_2/NaOH gave alcohol **6** in 70% overall yield (from **3**). The terminal alcohol was then oxidized under the standard Swern conditions to result in the corresponding aldehyde **7**. It is noteworthy that the Ipc_2BOMe related species in the asymmetric allylation were very difficult to remove from **4**, **5** and **6**; complete elimination of such species was possible only after conversion of **6** into **7**.

A Horner–Wadsworth–Emmons reaction with **8**[7] then delivered the desired ester **9** in 71% yield; the (*E*,*E*) C–C double bond configuration was confirmed by ^{1}H NMR in C_6D_6.[8] The final

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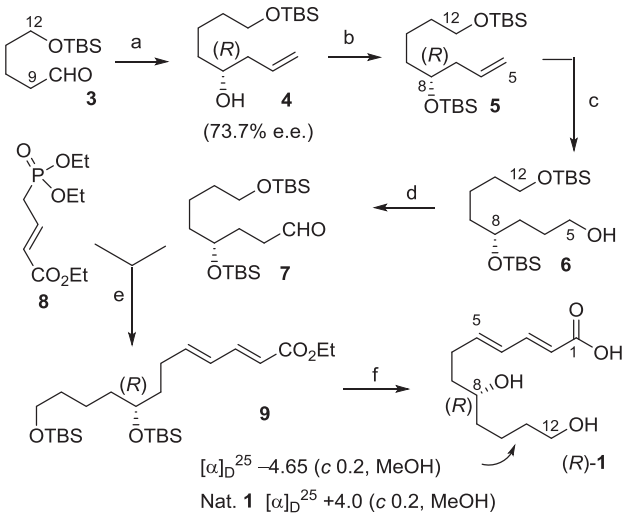
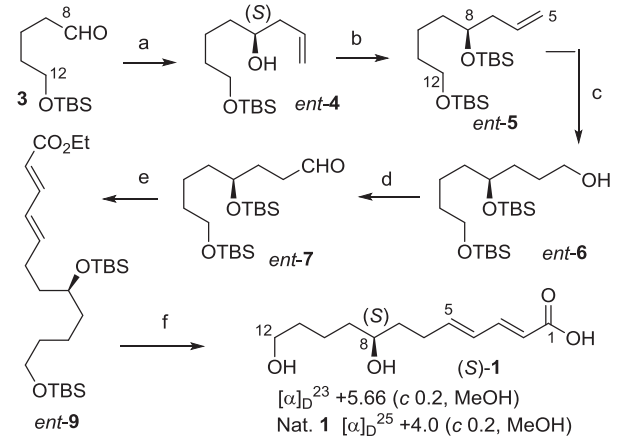


Scheme 1. a) (i) (−)-Ipc$_2$BOMe, CH_2=$CHCH_2$MgBr, Et_2O, (ii) H_2O_2, 3 N NaOH, −78 °C, 5 h; b) TBSCl, imidazole, DMAP, DMF, 16 h; c) (i) BH_3·SMe_2,THF, (ii) H_2O_2, 3 N NaOH, 5 h, 70% overall from **3**; d) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 1 h, 81%; e) LiHMDS, THF, −78 °C, 3 h, 71% from **7**; f) LiOH, EtOH–H_2O (5:1, v/v), 1 N HCl, 16 h, 60%. (−)-Ipc$_2$BOMe=(−)-*B*-Methoxydiisopino-campheylborane. TBS=*tert*-Butyldimethylsilyl. LiHMDS=Lithium hexamethyldisilazide. DMAP=4-*N*,*N*′-Dimethylaminopyridine. DMSO=Dimethylsulfoxide.

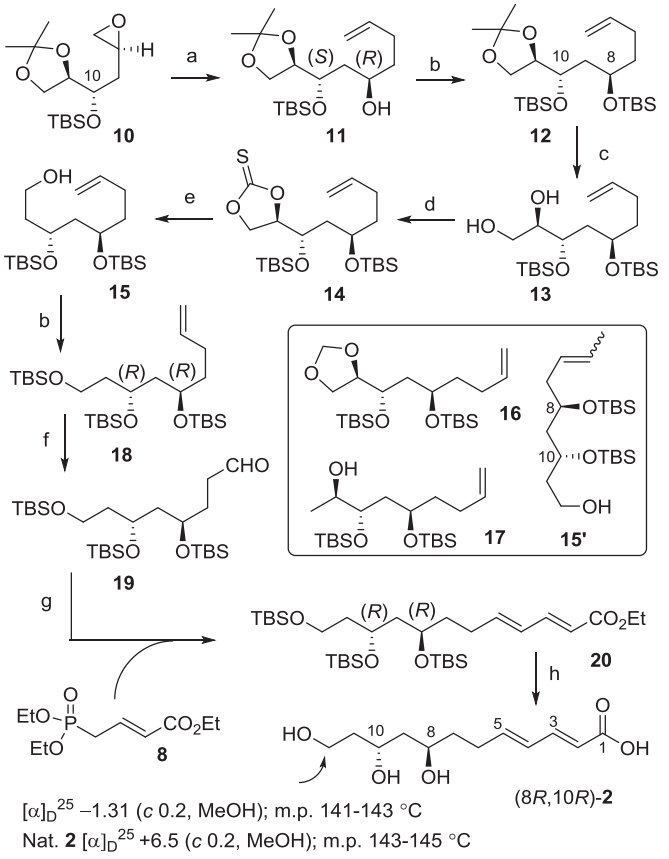
deprotection was effected using LiOH in aqueous EtOH[9a] and 1 N HCl,[10] respectively. The end product (*R*)-**1** showed ^{1}H and ^{13}C NMR in full consistency with those reported for natural **1**.[11] However, the optical rotation for (*R*)-**1** was determined to be −4.65, indicating that what we obtained must be the mirror image of natural YF-0200R A.

A synthesis of (*S*)-**1** was then performed. Using the same route but with (+)-Ipc$_2$BOMe to replace (−)-Ipc$_2$BOMe (Scheme 2), the desired (*S*) isomer was attained without any complications. The optical rotation for (*S*)-**1** was measured to be +5.66, confirming that natural YF-0200R A indeed possesses the same configuration as (*S*)-**1**.



Scheme 2. a) (i) CH_2=$CHCH_2$MgBr, (+)-Ipc$_2$BOMe, Et_2O, (ii) H_2O_2, 3 N NaOH, −78 °C, 5 h; b) TBSCl, imidazole, DMAP, DMF, 16 h; c) (i) BH_3·SMe_2,THF, (ii) H_2O_2, 3 N NaOH, 5 h, 70% overall from **3**; d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, 72%; e) LiHMDS, THF, −78 °C, 3 h, 60% from *ent*-**7**; f) (i) LiOH, aq EtOH, (ii) 1 N HCl, 16 h, 64%.

YF-0200R B has two stereogenic centers. In principle its relative configuration might be either *syn* or *anti*. We arbitrarily chose to begin with the *anti*-isomer. As shown in Scheme 3, treatment of the known[2e] epoxide **10** with CH_2=$CHCH_2$MgBr in the presence of CuI led to **11** in 82% yield. Protection of the newly formed OH with TBS followed by hydrolysis of the acetonide in 50% CF_3CO_2H/CH_2Cl_2[12] gave diol **13**, which was then converted into **14** by reaction with 1,1-thiocarbonyldiimidazole[13] to set the stage for the subsequent deoxygenation.



Scheme 3. a) CH_2=$CHCH_2$MgBr, CuI, THF, −20 °C, 3 h, 82%; b) TBSCl, imidazole, DMAP, DMF, 16 h, 89% for **12**, 98% for **18**; c) 50% CF_3CO_2H, CH_2Cl_2, 1 h, 82%; d) 1,1-thiocarbonyldi-imidazole, toluene, 110 °C, 1 h, 93%; e) AIBN, nBu$_3$SnH, toluene, 100 °C, 5 h, 47%; f) (i) O_3, CH_2Cl_2, −78 °C, 20 min, (ii) PPh_3, 95% from **18**; g) LiHMDS, THF, −78 °C, 3 h, 73%; h) (i) LiOH, aq EtOH, 16 h, (ii) 1 N HCl, 16 h, 85%. AIBN=azodiisobutyronitrile.

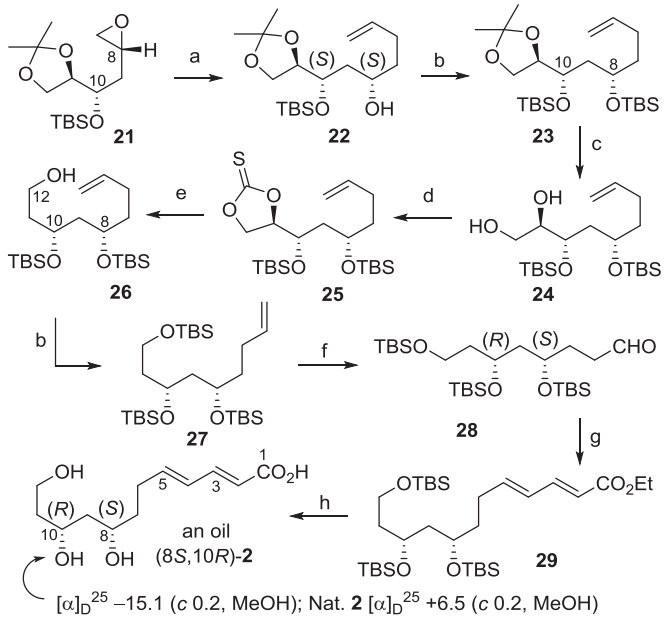
A radical mediated deoxygenation of **14** was then carried out under the AIBN/nBu$_3$SnH/toluene/100 °C[14] conditions. As expected, the reaction was complicated by concurrent side reactions, which led to formation of **16**, **17** and **15'**. Although chromatographic separation of **16** and **17** from **15** was feasible, Removal of **15'** could be realized only by chromatography on $AgNO_3$-treated[15] silica gel.

The hydroxyl group in the purified **15** was then protected with TBS. The resulting **18** was converted into aldehyde **19** by ozonolysis[16] followed by Ph_3P reduction. The conjugate diene motif was installed through a Horner–Wadsworth–Emmons reaction with **8** as in the synthesis of **1**. The ethyl ester was then hydrolyzed with LiOH. The crude intermediate carboxylic acid was directly desilylated with aq HCl to afford end product (8*R*,10*R*)-**2**.

The synthetic (8*R*,10*R*)-**2** showed ^{1}H and ^{13}C NMR (in CD_3OD) in excellent consistency with those reported for natural **2** (cf. Supplementary data). Like **1**, **2** is also insoluble in $CDCl_3$, strongly suggesting that the previous NMR data were actually recorded in CD_3OD (at least a mixture of CD_3OD and $CDCl_3$) rather than $CDCl_3$ as reported in the literature. Normally, such excellent agreements of the NMR data would allow for concluding that natural **2** and synthetic (8*R*,10*R*)-**2** shared the same relative configuration. However, in a previous[2a] study we observed that *syn* and *anti* isomers of a linear 1,3-diol showed identical ^{13}C NMR. To exclude this rare yet not always excludable possibility in the present case,

we decided to synthesize (8*S*,10*R*)-**2** (a *syn* isomer) for comparison.

The synthetic route leading to (8*S*,10*R*)-**2** is shown in Scheme 4. Using another known epoxy building block **21**[2c] we have in hand as the source of the stereogenic centers, the desired (8*S*,10*R*)-**2** was obtained in comparable yields. It is noteworthy that at the radical-mediated deoxygenation step, the C–C double migration appeared to occur to a negligible extent compared with the same reaction of **14**; in this case a second chromatography on $AgNO_3$-silica gel was thus no longer necessary.



Scheme 4. a) CH_2=$CHCH_2MgBr$, CuI, THF, −20 °C, 3 h, 85%; b) TBSCl, imidazole, DMAP, DMF, 16 h, 97% for **23**, 91% for **27**; c) 50% CF_3CO_2H, CH_2Cl_2, 30 min, 83%; d) 1,1-thiocarbonyldiimidazole, toluene, 110 °C, 1 h, 93%; e) AIBN, $n$$Bu_3SnH$, toluene, 110 °C, 5 h, 50%; f) (i) O_3, CH_2Cl_2, −78 °C, 20 min, (ii) PPh_3, 91% from **27**; g) **8**, LiHMDS, THF, −78 °C, 3 h, 64%; h) (i) LiOH, aq EtOH, 18 h, (ii) 1 N HCl, 16 h, 78%.

The ^{1}H NMR for (8*S*,10*R*)-**2** was essentially the same as that for (8*R*,10*R*)-**2**. However, significant differences were indeed found between the two diastereomers in the signals for the C-8 and C-10 (Table 1), which definitely excluded the possibility for natural **2** to be a *syn* isomer. Therefore, natural **2** must have the *anti* relative configuration. As for the absolute configuration, because the signs for the optical rotations for natural **2** and (8*R*,10*R*)-**2** are opposite to each other (vide infra), an (8*S*,10*S*) configuration can be reliably assigned to natural **2**.

Table 1
Comparison of the ^{13}C NMR for the natural **2**, (8*R*,10*R*)-**2** (*anti* **2**) and (8*S*,10*R*)-**2** (*syn* **2**)

Natural 2[a]	(8*R*,10*R*)-2[b]	(8*S*,10*R*)-2[b]
170.9 (C-1)	170.9 (C-1)	171.6 (C-1)
146.9 (C-3)	146.7 (C-3)	147.2 (C-3)
145.5 (C-5)	145.3 (C-5)	145.8 (C-5)
129.9 (C-4)	129.9 (C-4)	130.5 (C-4)
120.6 (C-2)	120.7 (C-2)	121.5 (C-2)
68.6(C-8)	68.5 (C-8)	71.2 (C-8)
67.0 (C-10)	66.9 (C-10)	69.6 (C-10)
60.2 (C-12)	60.2 (C-12)	60.7 (C-12)
45.9 (C-9)	45.9 (C-9)	45.9 (C-9)
41.5 (C-11)	41.5 (C-11)	41.5 (C-11)
38.1 (C-7)	38.1 (C-7)	38.1 (C-7)
30.2 (C-6)	30.2 (C-6)	30.6 (C-6)

[a] Taken with assignments from Ref. 1; reported to be measured at 125 MHz 'in $CDCl_3$'. However, we observed that neither (8*R*,10*R*)-**2** nor (8*S*,10*R*)-**2** was soluble in $CDCl_3$.

[b] This work, measured at 125 MHz in CD_3OD; the assignments were made with the aid of 2D NMR.

The optical rotation for the (8*R*,10*R*)-**2** was measured to be between −2.28 and −0.67 in MeOH at different time points[17] (or between −3.69 and −0.74 in CD_3OD, cf. Supplementary data), which is apparently closer in magnitude to that for natural **2** (+6.5) than (8*S*,10*R*)-**2** (−15.1). This, together with the appearance of the two diastereomers (one was a solid like the natural **2**, while the other was an oil), provided additional support for the *anti* relative configuration assigned to natural **2** on the basis of ^{13}C NMR.

In efforts to understand the discrepancy between the magnitudes of the optical rotations for natural **2** and (8*R*,10*R*)-**2** we also explored potential causes, such as sample purity and sample concentration[18] employed in the determination of optical rotations. The (8*R*,10*R*)-**2** was homogenous on ^{1}H and ^{13}C NMR. Besides, the chiral building block **10** employed was definitely free from any isomers.[19] Therefore, the sample purity could be reasonably excluded as the cause for the small magnitude of the optical rotation for (8*R*,10*R*)-**2**. Next, we measured the $[\alpha]_D$ at a higher concentration (c=0.5, MeOH). The results appeared to be time-dependent. At 26 min after preparation of the sample, the $[\alpha]_D$ was −1.71. But over the next few minutes, the magnitude of $[\alpha]_D$ decreased by ca. half. (cf. Table S-6, Supplementary data). It thus appears that (8*R*,10*R*)-**2** may indeed have a rather small magnitude for optical rotation (when the reading fluctuation finally reduced, ca. 25 min after preparation of the sample solution),[20] which was not mentioned by previous investigators[1] but definitely deserves particular attention in data comparisons of similar compounds if one wishes to avoid unnecessary confusions. Finally, it is interesting to note that the two closely related natural unsaturated fatty acids have different C-8 configurations, although both are (8*S*) as a result of changes in the substituents sequence.

3. Conclusion

YF-0200R A and B, two natural unsaturated fatty acids with aspargyl protease inhibition activity, were synthesized for the first time. The optically active synthetic samples (synthesized via chiral pool based routes) showed spectroscopic data fully consistent with those reported for their natural counterparts. The so far missing ^{1}H–^{1}H coupling constants for YF-0200R A and B are thus made known. The absolute configurations of the natural products were signed on the basis of comparison of the ^{1}H and ^{13}C NMR as well as optical rotations. The tricky optical rotation of the *anti* triol is also revealed.

4. Experimental

4.1. General methods

The NMR spectra were recorded on an Agilent 500/54 (operating at 500 MHz for ^{1}H) or a Bruker Avance (operating at 400 MHz for ^{1}H) NMR spectrometer with TMS as the internal standard. IR spectra were measured on a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer. HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. Melting points were uncorrected (measured on a hot stage melting point apparatus equipped with a microscope). CH_2Cl_2 was dried with activated 4 Å MS (molecular sieves). Deaerated toluene was obtained by bubbling N_2 into 4 Å MS dried toluene for 20 min. All chemicals were reagent grade and used as purchased. Column chromatography was performed on silica gel (230–400 mesh) under slightly positive pressure. Petroleum ether refers to the fraction boiling between 60 and 90 °C. $AgNO_3$-treated silica gel for column chromatography was prepared

by stirring 40 g of silica gel (230–400 mesh) with aq $AgNO_3$ (12 g of $AgNO_3$ in 120 mL of distilled water) for 10 min, evacuating the flask under membrane pump vacuum, and heated in a 120 °C oven (covered with aluminum foil to exclude light) for 4 h before use. The $AgNO_3$-treated TLC plates were prepared by dipping commercially available TLC plates into a solution of $AgNO_3$ (2.5 g) in MeCN (50 mL) for 5 min and dried in a 120 °C oven for 1 h.

4.2. Synthesis of aldehyde 7

A solution of CH_2=$CHCH_2MgBr$ (1.0 M, in Et_2O, 0.65 mL, 0.65 mmol) was added to a solution of (−)-*B*-methoxy-diisopinocampheylborane (2.0 M, in Et_2O, 0.35 mL, 0.694 mmol) in dry Et_2O (3.3 mL) stirred at −78 °C under argon (balloon). The resulting dark mixture was then stirred at ambient temperature for 1 h to give a white suspension. The bath was recooled to −78 °C and a solution of aldehyde **3** (100 mg, 0.434 mmol) in dry Et_2O (1 mL) was introduced. Stirring was continued at the same temperature for 5 h (TLC showed completion of the reaction). Aq NaOH (3 N, 0.8 mL) was added, followed by H_2O_2 (30%, 0.8 mL). The mixture was stirred at ambient temperature for 12 h before being extracted with Et_2O (10 mL×4). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5:1 petroleum ether/EtOAc) on silica gel gave the known allyl alcohol **4** as a colorless oil (120.3 mg, 0.465 mmol), which was dissolved in dry DMF (0.5 mL). To this solution were added imidazole (317 mg, 4.65 mmol), DMAP (37 mg, 0.465 mmol) and TBSCl (280.6 mg, 1.86 mmol). The mixture was stirred at ambient temperature for 12 h (TLC showed completion of the reaction). Water was added. The mixture was extracted with EtOAc (10 mL×3). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10:1 petroleum ether/EtOAc) on silica gel gave **5** as a colorless oil (160 mg, 0.429 mmol), which was dissolved in dry THF (2.8 mL) and stirred in an ice-water bath under argn (balloon). A solution of $BH_3{\cdot}SMe_2$ (2.0 M, in THF, 1.1 mL, 2.2 mmol) was added. Stirring was continued firt at 0 °C for 30 min and then at ambient temperature for 3 h (TLC showed completion of the reaction). Aq NaOH (3 N, 1 mL) was added, followed by followed by H_2O_2 (30%, 0.8 mL). The mixture was stirred at ambient temperature for 12 h before being extracted with Et_2O (10 mL×4). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (8:1 petroleum ether/EtOAc) on silica gel afforded the known alcohol **6** as a colorless oil (124 mg, 0.316 mmol).

Dry DMSO (55 μL, 1.04 mmol) was added to a solution of $(COCl)_2$ (0.44 mL, 0.521 mmol) in dry CH_2Cl_2 (0.5 mL) stirred at −78 °C under argon (balloon). The mixture was stirred at he same temperature for 35 min. A solution of the above obtained alcohol **6** (102 mg, 0.26 mmol) in dry CH_2Cl_2 (0.2 mL) was then introduced slowly. Stirring was continued at −78 °C for 1 h (TLC showed completion of the reaction). Dry Et_3N (0.22 mL, 1.56 mmol) was added slowly. The mixture was stirred for another 45 min while the bath was allowed to warm to ambient temperature. Water was then added. The mixture was stirred for 15 min and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5:1 petroleum ether/EtOAc) afforded the known aldehyde **7** as a colorless oil (free from the boron-containing impurities, 86 mg, 0.221 mmol, 57% overall from aldehyde **3**). $[\alpha]_D^{27}$ −4.0 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.78 (t, *J*=1.7 Hz, 1 H), 3.74–3.70 (m, 1 H), 3.60 (t, *J*=6.4 Hz, 2 H), 2.48 (td, *J*=7.5, 1.6 Hz, 2 H), 1.87–1.80 (m, 1 H), 1.74–1.69 (m, 1 H), 1.53–1.30 (m, 6 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.045 (s, 9 H), 0.039 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=202.6, 71.1, 63.0, 39.7, 36.8, 33.0, 28.9, 26.0, 25.9, 21.6, 18.4, 18.1, −4.4, −4.5, −5.28–5.29; FTIR (film): 2954, 2930, 2895, 2858, 2711, 1729, 1472, 1463, 1361, 1255, 1101, 1005, 939, 836, 774 cm^{-1}. (For other data, cf. those for *ent*-**7** below).

4.3. Condensation of 7 with 8 to afford 9

LiHMDS (1.0 M, in THF, 343 μL, 0.343 mmol) was added dropwise to a solution of phosphate **8** (96 mg, 0.429 mmol) in dry THF (0.5 mL) stirred at −78 °C under argon (balloon). The stirring was continued for 1 h before a solution of aldehyde **7** (111.2 mg, 0.286 mmol) in dry THF (0.2 mL) was added. The mixture was stirred at the same temperature for 15 min, then at 0 °C for 30 min, and finally at ambient temperature for 2 h (TLC showed completion of the reaction). Aq NH_4Cl was added. The mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (25:1 petroleum ether/EtOAc) on silica gel furnished **9** as a colorless oil (98 mg, 0.202 mmol, 71%). $[\alpha]_D^{27}$ −3.4 (*c* 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26 (dd, *J*=15.4, 10.0 Hz, 1 H), 6.20–6.09 (m, 2 H), 5.78 (d, *J*=15.4 Hz, 1 H), 4.20 (q, *J*=7.1 Hz, 2 H), 3.67 (quint, *J*=5.6 Hz, 1 H), 3.60 (t, *J*=6.5 Hz, 2 H), 2.27–2.14 (m, 2 H), 1.57–1.47 (m, 4 H), 1.46–1.42 (m, 2 H), 1.41–1.32 (m, 2 H), 1.29 (t, *J*=7.1 Hz, 3 H), 0.893 (s, 9 H), 0.886 (s, 9 H), 0.05–0.04 (several unresolved singlets, 12 H altogether). ^{13}C NMR (125 Hz, $CDCl_3$): δ=167.4, 145.1, 144.6, 128.5, 119.4, 71.7, 63.3, 60.3, 37.0, 36.0, 33.2, 28.9, 26.13, 26.06, 21.7, 18.5, 18.3, 14.5, −4.2, −4.3, −5.1. ^{1}H NMR (500 MHz, C_6D_6): δ=7.49 (dd, *J*=15.3, 11.0 Hz, 1 H), 5.97 (dd, *J*=15.0, 11.2 Hz, 1 H), 5.90 (d, *J*=15.4 Hz, 1 H), 5.75 (dt, *J*=15.2, 7.0 Hz, 1 H), 4.08 (q, *J*=7.1 Hz, 2 H), 3.58 (t, *J*=6.1 Hz, 2 H), 3.59–3.54 (m, 1 H), 2.09–1.95 (m, 2 H), 1.55–1.49 (m, 2 H), 1.48–1.35 (m, 6 H), 1.01 (t, *J*=7.2 Hz, 3 H), 1.00 (s, 18 H), 0.084 (s, 6 H), 0.078 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ=166.8, 145.0, 144.0, 128.8, 120.2, 72.0, 63.2, 60.1, 37.2, 36.3, 33.5, 29.0, 26.21, 26.18, 22.1, 18.6, 18.4, 14.4, -4.1, −4.2, −5.1. FTIR (film): 2953, 2930, 2857, 1717, 1644, 1472, 1388, 1367, 1255, 1099, 1000, 835, 774 cm^{-1}. (For other data, cf. those for *ent*-**9** below).

4.4. Conversion of 9 into (*R*)-1

A solution of **9** (40 mg, 0.0825 mmol) and LiOH (monohydrate, 22.5 mg, 0.536 mmol) in EtOH–H_2O (5:1 v/v, 4.1 mL) was stirred at ambient temperature for 12 h (TLC showed completion of the reaction). Aq HCl (1 N) was added to bring the mixture to *p*H 1. The mixture was stirred for another 2 h and then was extracted with EtOAc (10 mL×5). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5:1 CH_2Cl_2/MeOH) on silica gel afforded (*R*)-**1** as a white solid (11.1 mg, 0.0486 mmol, 60%). Mp 87–90 °C. $[\alpha]_D^{26}$ −4.7 (*c* 0.2, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ=7.25 (dd, *J*=15.3, 10.5 Hz, 1 H), 6.28 (dd, *J*=15.3, 10.6 Hz, 1 H), 6.20 (dt, *J*=15.2, 6.6 Hz, 1 H), 5.78 (d, *J*=15.3 Hz, 1 H), 3.56 (t, *J*=6.4 Hz, 2H), 3.54 (quint, *J*=4.2 Hz, 1H), 2.38–2.31 (m, 1 H), 2.29–2.21 (m, 1 H), 1.63–1.37 (m, 8 H). ^{13}C NMR (125 MHz, CD_3OD): δ=170.1, 146.2, 144.9, 129.1, 119.8, 71.0, 62.2, 37.5, 36.7, 33.0, 29.6, 22.4. (For other data, cf. those for (*R*)-**1** below).

4.5. Synthesis of ent-7

The same procedure given above for synthesis of aldehyde **7** was employed, except (−)-*B*-methoxydiisopinocampheylborane was replaced by (+)-*B*-methoxydiisopinocampheylborane. *ent*-**7** was obtained as a colorless oil (439 mg, 1.13 mmol, 50% overall from **3**). $[\alpha]_D^{27}$ +3.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.78 (t,

J=1.7 Hz, 1 H), 3.74–3.70 (m, 1 H), 3.60 (t, *J*=6.4 Hz, 2 H), 2.48 (dt, *J*=1.6, 7.5 Hz, 2 H), 1.87–1.80 (m, 1 H), 1.74–1.67 (m, 1 H), 1.53–1.30 (m, 6 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.05–0.04 (several unresolved singlets, 12 H altogether). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 71.1, 63.1, 39.7, 36.8, 33.0, 28.9, 26.0, 25.9, 21.6, 18.4, 18.1, −4.4, −4.5, −5.27, −5.28. FTIR (film): 2954, 2930, 2895, 2858, 2711, 1729, 1472, 1463, 1361, 1255, 1101, 1005, 939, 836, 774 cm^{-1}. ESI-MS *m/z* 389.4 $[M+H]^+$. ESI-HRMS: calcd for $C_{20}H_{45}O_3Si_2$ $[M+H]^+$ 389.2902; found 389.2910, $C_{20}H_{44}NaO_3Si_2$ $[M+Na]^+$: 411.2721; found: 411.2728.

4.6. Condensation of ent-7 with 8 to afford *ent*-9

The same procedure given above for synthesis of **9** was employed. *ent*-**9** was obtained as a colorless oil (328.2 mg, 0.677 mmol, 60%). $[\alpha]_D^{27}$ +1.5 (*c* 2.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26 (dd, *J*=15.4, 10.0 Hz, 1 H), 6.20–6.09 (m, 2 H), 5.78 (d, *J*=15.4 Hz, 1 H), 4.20 (q, *J*=7.1 Hz, 2 H), 3.67 (quint, *J*=5.5 Hz, 1 H), 3.60 (t, *J*=6.4 Hz, 2 H), 2.27–2.14 (m, 2 H), 1.57–1.47 (m, 4 H), 1.46–1.42 (m, 2 H), 1.41–1.32 (m, 2 H), 1.29 (t, *J*=7.1 Hz, 3 H), 0.89 (m, 9 H), 0.89 (m, 9 H), 0.05–0.04 (several unresolved singlets, 12 H altogether). ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.3, 145.0, 144.5, 128.3, 119.3, 71.6, 63.1, 60.2, 36.9, 35.9, 33.1, 28.8, 26.0, 25.9, 21.6, 18.4, 18.1, 14.3, −4.3, −4.4, −5.3. ^{1}H NMR (500 MHz, C_6D_6): δ=7.50 (dd, *J*=15.3, 11.0 Hz, 1 H), 5.97 (dd, *J*=14.8, 11.2 Hz, 1 H), 5.91 (d, *J*=15.4 Hz, 1 H), 5.74 (dt, *J*=15.2, 7.0 Hz, 1 H), 4.08 (q, *J*=7.1 Hz, 2 H), 3.58 (t, *J*=6.1 Hz, 2 H), 3.59–3.54 (m, 1 H), 2.09–1.95 (m, 2 H), 1.55–1.49 (m, 2 H), 1.48–1.35 (m, 6 H), 1.01 (t, *J*=7.1 Hz, 3 H), 1.00 (s, 18 H), 0.09 (s, 6 H), 0.08 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ=166.8, 145.0, 144.0, 128.8, 120.2, 72.0, 63.2, 60.1, 37.2, 36.3, 33.5, 29.0, 26.21, 26.18, 22.1, 18.6, 18.4, 14.4, −4.1, −4.2, −5.1. FTIR (film): 2954, 2930, 2857, 1717, 1644, 1472, 1388, 1367, 1255, 1099, 1000, 835, 774 cm^{-1}. ESI-MS *m/z* 485.6 $[M+H]^+$, *m/z* 507.6 $[M+Na]^+$. ESI-HRMS: calcd for $C_{26}H_{53}O_4Si_2$ $[M+H]^+$ 485.3477; found 485.3476.

4.7. Conversion of ent-9 into (*S*)-1

The same procedure given above for synthesis of **(*R*)-1** was employed. (*S*)-**1** was obtained as a white solid (9 mg, 0.0394 mmol, 64%). Mp 88–91 °C (mp data for natural **1** was reported in Ref. 1). $[\alpha]_D^{23}$ +5.7 (*c* 0.2, MeOH) (lit.[1] $[\alpha]_D^{25}$=+4.0 (*c*=0.2, MeOH)). ^{1}H NMR (500 MHz, CD_3OD): δ=7.24 (dd, *J*=15.3, 10.5 Hz, 1 H, H-3), 6.28 (dd, *J*=15.2, 10.8 Hz, 1 H, H-4), 6.20 (dt, *J*=15.2, 6.6 Hz, 1 H, H-5), 5.78 (d, *J*=15.3 Hz, 1 H, H-2), 3.56 (t, *J*=6.4 Hz, 2H, H-12), 3.54 (quint, *J*=4.2 Hz, 1H, H-8), 2.38–2.31 (m, 1 H, H-6), 2.29–2.21 (m, 1 H, H-6), 1.63–1.37 (m, 8 H, H-7, H-9, H-10 and H-11). ^{13}C NMR (125 MHz, CD_3OD): δ=170.2, 146.1, 144.8, 129.1, 120.0, 71.0, 62.2, 37.5, 36.7, 33.0, 29.6, 22.4. FTIR (KBr): 3334, 2935, 2860, 2628, 1688, 1640, 1412, 1259, 1001, 669 cm^{-1}. ESI-MS *m/z* 229.1 $[M+H]^+$, *m/z* 251.1 $[M+Na]^+$. ESI-HRMS: calcd for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1434; found 229.1433.

4.8. Reaction of epoxide 10 with CH_2=$CHCH_2MgBr$ to afford alcohol 11

CH_2=$CHCH_2MgBr$ (1.0 M, in Et_2O, 6.5 mL, 6.5 mmol) was added to a white suspension of CuI (123 mg, 0.65 mmol) in dry THF (20 mL) stirred in an −20 °C bath under argon (balloon). The resulting dark-gray mixture was stirred for another 15 min before a solution of epoxide **10** (1.30 g, 4.3 mmol) in dry THF (30 mL) was introduced. The mixture was stirred at −20 °C for 1 h and then at ambient temperature for 2 h. Aq saturated NH_4Cl was added. The mixture was extracted with EtOAc (50 mL×3). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (8:1 petroleum ether/EtOAc) gave alcohol **11** as a colorless oil (1.215 g, 3.53 mmol, 82%). $[\alpha]_D^{22}$ +7.6 (*c* 1.26, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.88–5.80 (m, 1 H), 5.04 (dq, *J*=17.1, 1.6 Hz, 1 H), 4.97–4.95 (m, 1 H), 4.10–4.05 (m, 2 H), 3.93–3.86 (m, 2 H), 3.83–3.77 (m, 1 H), 3.24 (s, 1 H), 2.25–2.09 (m, 2 H), 1.76 (dq, *J*=14.6, 2.2 Hz, 1 H), 1.68 (dq, *J*=14.6, 5.0 Hz, 1 H), 1.62–1.55 (m, 1 H), 1.53–1.47 (m, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.5, 114.6, 109.3, 78.1, 72.8, 68.0, 67.5, 41.6, 37.2, 29.9, 26.7, 25.8, 25.4, 17.9, −4.1, −4.6. FTIR (film): 3488, 2984, 2953, 2930, 2857, 1640, 1472, 1462, 1379, 1370, 1255, 1072, 837, 776, 668 cm^{-1}. ESI-MS *m/z* 367.3 $[M+Na]^+$. ESI-HRMS: calcd for $C_{18}H_{36}NaO_4Si$ $[M+Na]^+$ 367.2275; found 367.2271.

4.9. TBS protection of 11 to afford 12

A solution of alcohol **11** (1.20 g, 3.48 mmol), imidazole (2.34 g, 34.83 mmol), DMAP (425 mg, 3.48 mmol) and TBSCl (2.10 g, 13.93 mmol) in dry DMF (3.5 mL) was stirred at ambient temperature for 12 h (TLC showed completion of the reaction). Water was added. The mixture was extracted with EtOAc (10 mL×4). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (50:1 petroleum ether/EtOAc) on silica gel gave **12** as a colorless oil (1.422 g, 3.10 mmol, 89%). $[\alpha]_D^{21}$ +11.2 (*c* 1.13, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.85–5.77 (m, 1 H), 5.03–4.94 (m, 2 H), 4.04–3.96 (m, 2 H), 3.89 (quint, *J*=5.8 Hz, 1 H), 3.84–3.80 (m, 2 H), 2.12–2.06 (m, 2 H), 1.68–1.50 (m, 4 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.08 (s, 6 H), 0.074 (s, 3 H), 0.067 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.6, 114.4, 109.0, 79.4, 70.4, 69.1, 66.0, 43.4, 37.1, 29.3, 26.5, 25.93, 25.89, 25.4, 18.10, 18.09, −3.96, −4.03, −4.1. FTIR (film): 2955, 2929, 2887, 2858, 1641, 1472, 1369, 1255, 1074, 1004, 836, 774 cm^{-1}. ESI-MS *m/z* 481.5 $[M+Na]^+$. ESI-HRMS: calcd for $C_{24}H_{51}O_4Si_2$ $[M+H]^+$ 459.3320; found 459.3313. ESI-HRMS: calcd for $C_{24}H_{50}NaO_4Si_2$ $[M+Na]^+$ 481.3140; found 481.3139.

4.10. Hydrolysis of the acetonide in 12 to afford 13

A solution of **12** (385.6 mg, 0.839 mmol) in CH_2Cl_2 (17 mL) containing aq CF_3CO_2H (50% v/v, 1.25 mL) was stirred in an ice-water bath for 1 h (TLC showed completion of the reaction). Aq saturated $NaHCO_3$ was added to neutralize the acid (*p*H=7). The mixture was extracted with EtOAc (10 mL×4). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (3:1 petroleum ether/EtOAc) on silica gel afforded diol **13** as a colorless oil (287.5 mg, 0.686 mmol, 82%). $[\alpha]_D^{21}$ −3.1 (*c* 1.32, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.83–5.75 (m, 1 H), 5.04–4.95 (m, 2 H), 3.89 (dd, *J*=10.0, 5.7 Hz, 1 H), 3.81 (quint, *J*=5.7 Hz, 1 H), 3.76 (dd, *J*=11.4, 5.3 Hz, 1 H), 3.67 (dd, *J*=11.4, 3.5 Hz, 1 H), 3.62–3.59 (m, 1 H), 2.14–2.02 (m, 2 H), 1.72–1.69 (m, 2 H), 1.62–1.57 (m, 2 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.089 (s, 3 H), 0.085 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.2, 114.8, 74.2, 73.0, 70.2, 63.2, 41.8, 37.0, 29.2, 25.9, 25.8, 18.04, 17.96, −3.9, -4.1, −4.3, −4.5. FTIR (film): 3404, 3078, 2954, 2929, 2886, 2857, 1641, 1472, 1360, 1255, 1086, 938, 910, 835, 774 cm^{-1}. ESI-MS *m/z* 419.5 $[M+H]^+$, *m/z*=441.4 $[M+Na]^+$. HRMS (EI): calcd for $C_{21}H_{46}NaO_4Si_2$ $[M+Na]^+$ 441.2827; found 441.2821.

4.11. Conversion of 13 into 14

A solution of diol **13** (1.18 g, 2.81 mmol) and 1,1-thiocarbonyldiimidazole (600 mg, 3.37 mmol) in dry toluene (29 mL) was stirred in an 110 °C oil bath under argon (balloon) for 1 h

(TLC showed completion of the reaction). The mixture was concentrated on a rotary evaporator. The residue was purified by column chromatography (8:1 petroleum ether/EtOAc) on silica gel to give **14** as a colorless oil (1.20 g, 2.60 mmol, 93%). $[\alpha]_D^{22}$ −3.0 (*c* 2.21, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=5.81–5.72 (m, 1 H), 5.08–4.97 (m, 3 H), 4.72 (dd, *J*=8.1, 7.2 Hz, 1 H), 4.57 (t, *J*=8.5 Hz, 1 H), 4.14–4.11 (m, 1 H), 3.84–3.79 (m, 1H), 2.12–1. 96 (m, 2 H), 1.66–1.57 (m, 2 H), 1.56–1.49 (m, 1 H), 1.41 (dt, *J*=14.5, 8.3 Hz, 1 H), 0.891 (s, 9 H), 0.899 (s, 9 H), 0.15 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.8, 137.7, 115.2, 84.3, 69.7, 69.2, 68.3, 40.8, 37.2, 29.1, 25.9, 25.7, 18.0, 17.8, −3.9, −4.2, −4.4, −4.6. FTIR (film): 2954, 2929, 2886, 2857, 1641, 1472, 1360, 1292, 1255, 1124, 988, 836, 776 cm^{-1}. ESI-MS *m/z* 461.4 $[M+H]^+$, *m/z* 483.4 $[M+Na]^+$. ESI-HRMS: calcd for $C_{22}H_{45}O_4SSi_2$ $[M+H]^+$ 461.2572; found 461.2564.

4.12. Deoxygenation of 14 to afford alcohol 15

A solution of **14** (500 mg, 1.09 mmol), *n*-Bu_3SnH (1.75 mL, 6.51 mmol) and AIBN (178 mg, 1.09 mmol) in deaired toluene (37 mL) was stirred in a 100 °C oil bath under argon (balloon) for 5 h (TLC showed completion of the reaction). The mixture was concentrated on a rotary evaporator. The residue was purified by column chromatography (8:1 petroleum ether/EtOAc) on silica gel to remove **16** and **17** (126 mg and 122 mg, respectively, both were polluted by small amounts of other side products, both were less polar than **15**). The fractions contain **15** (and the inseparable **15′**) were combined, concentrated and further purified by column chromatography (eluting with 15:1, 12:1, 10:1, and 8:1 petroleum ether/EtOAc) on $AgNO_3$-treated silica gel to give pure **15** as a colorless oil (206 mg, 0.512 mmol, 47%). $[\alpha]_D^{25}$ +15.4 (*c* 1.89, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=5.85–5.77 (m, 1 H), 5.04–4.94 (m, 2 H), 3.98–3.94 (m, 1 H), 3.84 (dq, *J*=10.9, 4.6 Hz, 1 H), 3.74–3.69 (m, 2 H), 2.16–2.04 (m, 2 H), 1.90–1.84 (m, 1 H), 1.72 (t, *J*=6.5 Hz, 2 H), 1.67–1.61 (m, 1 H), 1.58–1.47 (m, 2 H), 0.892 (s, 9 H), 0.887 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.6, 114.5, 69.8, 69.6, 60.1, 44.9, 38.6, 36.7, 29.3, 25.9, 25.8, 18.1, 17.9, −4.10, −4.13, −4.3, −4.5. FTIR (film): 3355, 3078, 2954, 2929, 2886, 2857, 1641, 1472, 1462, 1407, 1361, 1255, 1058, 1005, 938, 910, 836, 774 cm^{-1}. EESI-MS *m/z* 403.4 $[M+H]^+$, *m/z*=425.4 $[M+Na]^+$. ESI-HRMS: calcd for $C_{21}H_{47}O_3Si_2$ $[M+H]^+$ 403.3058; found 403.3051, $C_{21}H_{46}NaO_3Si_2$ $[M+Na]^+$ 425.2878; found 425.2876.

4.13. TBS protection of 15 to afford 18

A solution of alcohol **15** (206 mg, 0.512 mmol), imidazole (348 mg, 5.11 mmol), DMAP (62 mg, 0.51 mmol) and TBSCl (309 mg, 2.05 mmol) in dry DMF (0.5 mL) was stirred at ambient temperature for 12 h (TLC showed completion of the reaction). Water was added. The mixture was extracted with EtOAc (10 mL×3). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (50:1 petroleum ether/EtOAc) on silica gel gave **18** as a colorless oil (260 mg, 0.503 mmol, 98%). $[\alpha]_D^{25}$ +13.8 (*c* 1.23, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=5.85–5.77 (m, 1 H), 5.03–4.92 (m, 2 H), 3.89–3.84 (m, 1 H), 3.76–3.72 (m, 1 H), 3.67 (t, *J*=6.6 Hz, 2 H), 2.16–2.02 (m, 2 H), 1.71–1.45 (m, 1 H), 0.889 (s, 9 H), 0.885 (s, 9 H), 0.880 (s, 9 H), 0.06–0.04 (several unresolved singlets, 18 H altogether). ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.8, 114.3, 69.6, 67.2, 59.7, 46.0, 40.9, 36.8, 29.4, 25.96, 25.94, 25.92, 18.3, 18.1, 18.0, −4.09, −4.12, −4.14, −4.3, −5.29, −5.30. FTIR (film): 3078, 2955, 2929, 2895, 2857, 1642, 1472, 1388, 1361, 1255, 1095, 1005, 939, 835, 774 cm^{-1}. ESI-MS *m/z* 517.5 $[M+H]^+$, *m/z* 539.6 $[M+Na]^+$. EESI-HRMS: calcd for $C_{27}H_{61}NaO_3Si_3$ $[M+Na]^+$ 517.3923; found 517.3912.

4.14. Ozonolysis of alkene 18 to afford aldehyde 19

Ozone-containing oxygen was bubbled into a solution of **18** (100 mg, 0.193 mmol) in CH_2Cl_2 (3.8 mL) cooled in an acetone-dry ice bath (−78 °C) until a blue color developed. N_2 gas was bubbled into the solution to expel the excess ozone. The resulting colorless solution was then stirred with Ph_3P (76 mg, 0.29 mmol) first at −78 °C for 30 min and then at ambient temperature for 4 h. The mixture was concentrated on a rotary evaporator. The residue was purified by column chromatography (25:1 petroleum ether/EtOAc) on silica gel to give aldehyde **19** as a colorless oil (95 mg, 0.183 mmol, 95%). $[\alpha]_D^{27}$ +14.9 (*c* 1.11, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=9.78 (t, *J*=1.6 Hz, 1 H), 3.88–3.83 (m, 1 H), 3.82–3.77 (m, 1 H), 3.66 (t, *J*=6.5 Hz, 2 H), 2.48 (dt, *J*=1.4, 7.5 Hz, 2 H), 1.92–1.85 (m, 1 H), 1.73–1.56 (m, 5 H), 0.89 (s, 9 H), 0.88 (s, 18 H), 0.07 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 3 H), 0.04 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=202.3, 69.1, 67.2, 59.6, 45.6, 40.8, 39.5, 29.5, 25.94, 25.89, 25.87, 18.3, 18.0, 18.0, −4.1, −4.2, −4.3, −5.3. FTIR (film): 2955, 2929, 2886, 2857, 2711, 1730, 1472, 1388, 1361, 1256, 1098, 1005, 836, 774 cm^{-1}. ESI-MS *m/z* 519.6 $[M+H]^+$, *m/z* 541.6 $[M+Na]^+$. ESI-HRMS: calcd for $C_{26}H_{59}O_4Si_3$ $[M+H]^+$ 519.3716; found 519.3708.

4.15. Condensation of 19 with 8 to afford 20

LiHMDS (1.0 M, in THF, 161 μL, 0.161 mmol) was added dropwise to a solution of phosphate **8** (49 mg, 0.20 mmol) in dry THF (0.1 mL) stirred at −78 °C under argon (balloon). The stirring was continued for 1 h before a solution of aldehyde **19** (69.5 mg, 0.134 mmol) in dry THF (0.2 mL) was added. The mixture was stirred at −78 °C for 15 min, then 0 °C for 30 min, and finally ambient temperature for 2 h (TLC showed completion of the reaction). Aq NH_4Cl was added. The mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (25:1 petroleum ether/EtOAc) on silica gel furnished **20** as a colorless oil (60 mg, 0.0976 mmol, 73%), which was 98.5% pure as shown by HPLC analysis using a Agilent 1260 Infinity LC equipped with an ACE 5 C_{18} column (4.6×150 mm, particle size 5 μM) eluting with MeCN/H_2O (initially 90:10 and then from 15 min to the end 10:90 v/v) at a flow rate of 1.0 mL (column temperature: 25 °C) with the UV detector set 210 nm). $[\alpha]_D^{27}$ +10.3 (*c* 1.01, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (dd, *J*=15.4, 10.2 Hz, 1 H), 6.19–6.08 (m, 2 H), 5.78 (d, *J*=15.4 Hz, 1 H), 4.20 (q, *J*=7.1 Hz, 2 H), 3.89–3.84 (m, 1 H), 3.77–3.72 (m, 1 H), 3.66 (t, *J*=6.5 Hz, 2 H), 2.29–2.15 (m, 2 H), 1.69–1.57 (m, 5 H), 1.56–1.48 (m, 1 H), 1.29 (t, *J*=7.1 Hz, 3 H), 0.89 (s, 18 H), 0.88 (s, 9 H), 0.062 (s, 3 H), 0.059 (s, 6 H), 0.050 (s, 3 H), 0.04 (s, 6H). ^{13}C NMR (125 Hz, $CDCl_3$): δ 167.3, 144.9, 144.2, 128.4, 119.3, 69.5, 67.2, 60.2, 59.6, 45.9, 40.9, 36.5, 28.6, 25.94, 25.91, 25.90, 18.3, 18.08, 18.06, 14.3, −4.07, −4.15, −4.2, −5.30, −5.31. ^1H NMR (500 MHz, C_6D_6): δ=7.49 (dd, *J*=15.3, 11.0 Hz, 1 H), 6.02 (dd, *J*=15.1, 11.1 Hz, 1 H), 5.91 (d, *J*=15.4 Hz, 1 H), 5.80 (dt, *J*=15.2, 7.0 Hz, 1 H), 4.07 (q, *J*=7.1 Hz, 3 H), 3.85 (quint, *J*=5.9 Hz, 1 H), 3.79–3.74 (m, 1 H), 3.70–3.66 (m, 1 H), 2.19–2.06 (m, 2 H), 1.81–1.70 (m, 4 H), 1.61–1.49 (m, 2 H), 1.01 (t, *J*=7.2 Hz, 3 H), 1.00 (s, 9 H), 0.995 (s, 9 H), 0.988 (s, 9 H), 0.151 (s, 3 H), 0.146 (s, 3 H), 0.13 (s, 3 H), 0.09 (s, 3 H), 0.084 (s, 3 H), 0.081 (s, 3 H). ^{13}C NMR (125 MHz, C_6D_6): δ=166.7, 144.9, 143.7, 129.0, 120.3, 70.0, 67.6, 60.1, 59.7, 46.3, 41.6, 37.1, 28.9, 26.21, 26.20, 26.19, 18.5, 18.4, 14.4, −3.80, −3.82, −3.85, −3.88, −5.1. FTIR (film): 2955, 2929, 2886, 2857, 1718, 1644, 1472, 1388, 1367, 1256, 1097, 1002, 836, 774 cm^{-1}. ESI-MS *m/z*=615.6 $[M+H]^+$, *m/z* 637.6 $[M+Na]^+$. ESI-HRMS: calcd for $C_{32}H_{67}O_5Si_3$ $[M+H]^+$ 615.4291; found 615.4287.

4.16. Conversion of 20 into (8*R*,10*R*)-2

A solution of **20** (50 mg, 0.0813 mmol) and LiOH (monohydrate, 25 mg, 0.59 mmol) in EtOH–H_2O (5:1 v/v, 3.1 mL) was stirred at ambient temperature for 12 h (TLC showed completion of the reaction). Aq HCl (1 N) was added to bring the mixture to *p*H 1. The mixture was stirred for another 2 h. The mixture was concentrated on a rotary evaporator. The residue was purified by reverse-phase chromatography (eluting first H_2O, then 9:1 H_2O/MeOH and finally 2:1 H_2O/MeOH) on C-18 alkyl modified silica gel to give (8*R*,10*R*)-**2** as a white solid (16.8 mg, 0.0688 mmol, 85%). Mp 141–143 °C (lit.[1] mp 143–145 °C for natural **2**). $[\alpha]_D^{25}$ −1.3 (*c* 0.2, MeOH), $[\alpha]_D^{25}$=−3.7 (*c*=0.2, CD_3OD) (for more data, cf. Supplementary data) (lit.[1] $[\alpha]_D^{25}$=+6.5 (*c*=0.2, MeOH) for natural **2**). ^{1}H NMR (500 MHz, CD_3OD): *δ*=7.25 (dd, *J*=15.3, 10.5 Hz, 1 H, H-3), 6.28 (dd, *J*=15.2, 10.6 Hz, 1 H, H-4), 6.20 (dt, *J*=15.2, 6.7 Hz, 1 H, H-5), 5.78 (d, *J*=15.3 Hz, 1 H, H-2), 4.01–3.96 (m, 1 H, H-10), 3.86–3.81 (m, 1 H, H-8), 3.70 (t, *J*=6.6 Hz, 2 H, H-12), 2.38–2.31 (m, 1 H, H-6), 2.31–2.23 (m, 1 H, H-6), 1.67 (dd, *J*=13.0, 6.5 Hz, 2 H, H-11), 1.60–1.56 (m, 2 H, H-7 or H-9), 1.54–1.51 (m, 2 H, H-9 or H-7). ^{13}C NMR cf. Table 1. FTIR (KBr): 3353, 2940, 2611, 1698, 1641, 1408, 1258, 1060, 1003, 669 cm^{-1}. ESI-MS *m/z* 243.2 $[M-H]^-$. ESI-HRMS: calcd for $C_{12}H_{19}O_5$ $[M-H]^-$ 243.1238; found 243.1237.

4.17. Reaction of epoxide 21 with CH_2=$CHCH_2MgBr$ to afford alcohol 22

CH_2=$CHCH_2MgBr$ (1.0 M, in Et_2O, 0.5 mL, 0.5 mmol) was added to a white suspension of CuI (9.44 mg, 0.049 mmol) in dry THF (1 mL) stirred in an −20 °C bath under argon (balloon). The resulting dark-gray mixture was stirred for another 15 min before a solution of epoxide **21** (100 mg, 0.33 mmol) in dry THF (3.0 mL) was introduced. The mixture was stirred at −20 °C for 1 h and then at ambient temperature for 2 h. Aq saturated NH_4Cl was added. The mixture was extracted with EtOAc (10 mL×3). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (8:1 petroleum ether/EtOAc) gave alcohol **22** as a colorless oil (96.7 mg, 0.281 mmol, 85%). $[\alpha]_D^{23}$ +19.0 (*c* 2.01, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *δ*=5.88–5.80 (m, 1 H), 5.04 (dq, *J*=17.1, 1.7 Hz, 1 H), 4.98–4.95 (m, 1 H), 4.11–4.04 (m, 2 H), 3.92–3.87 (m, 2 H), 3.79 (dd, *J*=7.8, 6.6 Hz, 1 H), 2.60 (s, 1 H), 2.25–2.09 (m, 2 H), 1.76 (dq, *J*=14.4, 5.1 Hz, 1 H), 1.66 (dq, *J*=14.4, 2.9 Hz, 1 H), 1.61–1.47 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 0.88 (s, 9 H), 0.094 (s, 3 H), 0.092 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ*=138.5, 114.6, 109.4, 78.7, 71.4, 67.6, 67.3, 42.7, 37.0, 29.9, 26.6, 25.8, 25.4, 17.9, −4.1, −4.5. FTIR (film): 3483, 3077, 2984, 2930, 2887, 2857, 1641, 1472, 1462, 1380, 1371, 1255, 1074, 837, 776 cm^{-1}. ESI-MS *m/z* 367.3 $[M+Na]^+$. ESI-HRMS: calcd for $C_{18}H_{36}NaO_4Si$ $[M+Na]^+$ 367.2275; found 367.2278.

4.18. TBS protection of 22 to afford 23

The same procedure given above for the conversion of **11** into **12** was employed. After chromatography (50:1 petroleum ether/EtOAc) **23** was obtained as a colorless oil (125 mg, 0.273 mmol, 97%). $[\alpha]_D^{24}$ +15.9 (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=5.87–5.76 (m, 1 H), 5.04–4.93 (m, 2 H), 4.06–4.01 (m, 1 H), 3.95 (dd, *J*=7.5, 6.3 Hz, 1 H), 3.91–3.86 (m, 2 H), 3.79 (t, *J*=7.6 Hz, 1 H), 2.17–2.02 (m, 2 H), 1.71–1.63 (m, 1 H), 1.63–1.56 (m, 2 H), 1.54–1.45 (m, 1 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 0.893 (s, 9 H), 0.886 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=138.8, 114.4, 108.9, 78.9, 69.4, 68.5, 65.9, 42.7, 36.5, 29.3, 26.6, 25.9, 25.4, 18.0, −4.2, −4.27, −4.30, −4.5. FTIR (film): 3078, 2955, 2930, 2887, 2858, 1641, 1472, 1369, 1255, 1073, 1005, 837, 774 cm^{-1}. ESI-MS *m/z* 481.5 $[M+Na]^+$. ESI-HRMS: calcd for $C_{24}H_{51}O_4Si_2$ $[M+H]^+$ 459.3320; found 459.3314.

4.19. Hydrolysis of the acetonide in 23 to afford 24

The same procedure given above for the conversion of **12** into **13** was employed. After chromatography (3:1 petroleum ether/EtOAc) diol **24** was obtained as a colorless oil (940 mg, 2.24 mmol, 83%). $[\alpha]_D^{24}$ +48.9 (*c* 0.83, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *δ*=5.84–5.76 (m, 1 H), 5.05–4.96 (m, 2 H), 3.93–3.88 (m, 2 H), 3.74–3.68 (m, 2 H), 3.60 (dd, *J*=9.5, 5.2 Hz, 1 H), 2.08 (dd, *J*=14.6, 7.7 Hz, 2 H), 1.84 (dq, *J*=14.6, 4.6 Hz, 1 H), 1.67 (dq, *J*=14.6, 4.0 Hz, 1 H), 1.64–1.59 (m, 2 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.10 (s, 6 H), 0.091 (s, 3 H), 0.085 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 138.1, 114.8, 73.6, 71.5, 69.1, 63.6, 41.4, 36.1, 29.5, 25.85, 25.81, 18.0, 17.9, −4.36, −4.39, −4.41, −4.7. FTIR (film): 3414, 3078, 2954, 2929, 2887, 2857, 1642, 1472, 1361, 1255, 1084, 1004, 938, 910, 837, 775 cm^{-1}. ESI-MS *m/z* 441.4 $[M+Na]^+$. ESI-HRMS: calcd for $C_{21}H_{46}NaO_4Si_2$ $[M+Na]^+$ 441.2827; found 441.2828.

4.20. Conversion of 25 into 26

The same procedure given above for the conversion of **14** into **15** was employed, except the second chromatography on $AgNO_3$-silica gel was skipped. After chromatography (8:1 petroleum ether/EtOAc) alcohol **26** was obtained as a white solid (175 mg, 0.435 mmol, 50%). $[\alpha]_D^{22}$ +18.5 (*c* 0.67, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *δ*=5.84–5.76 (m, 1 H), 5.03–4.94 (m, 2 H), 4.11–4.06 (m, 1 H), 3.86–3.82 (m, 1 H), 3.74–3.68 (m, 2 H), 2.08 (dd, *J*=14.4, 7.6 Hz, 2H), 1.93–1.86 (m, 1 H), 1.76–1.70 (m, 1 H), 1.69–1.60 (m, 2 H), 1.58–1.52 (m, 2 H), 0.90 (s, 9 H), 0.89 (s, 9H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ*=138.6, 114.5, 69.4, 69.0, 60.2, 43.8, 37.4, 36.9, 29.2, 25.9, 25.8, 18.0, 17.9, −4.2, −4.4, −4.5, −4.7. FTIR (film): 3415, 3078, 2955, 2929, 2857, 1641, 1472, 1463, 1361, 1255, 1055, 1005, 938, 910, 836, 774 cm^{-1}. ESI-MS *m/z* 403.5 $[M+H]^+$, *m/z* 425.5 $[M+Na]^+$. ESI-HRMS: calcd for $C_{21}H_{47}O_3Si_2$ $[M+H]^+$ 403.3058; found 403.3052.

4.21. TBS protection of 26 to afford 27

The same procedure given above for the conversion of **15** into **18** was employed. After chromatography (50:1 petroleum ether/EtOAc) **27** was obtained as a colorless oil (29 mg, 0.056 mmol, 91%). $[\alpha]_D^{22}$ +1.8 (*c* 1.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 5.85–5.77 (m, 1 H), 5.02–4.92 (m, 2 H), 3.89 (quint, *J*=6.2 Hz, 1 H), 3.78 (quint, *J*=5.9 Hz, 1 H), 3.71–3.63 (m, 2 H), 2.15–2.02 (m, 2 H), 1.74–1.54 (m, 5 H), 1.51–1.43 (m, 1 H), 0.89 (s, 27 H), 0.05–0.04 (several unresolved singlets, 18 H altogether). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 139.0, 114.4, 69.2, 67.0, 60.1, 45.3, 40.7, 36.7, 29.5, 26.2, 26.08, 26.07, 18.5, 18.20, 18.19, −4.1, −4.17, −4.24, −4.3, −5.1, −5.2. FTIR (film): *ν*=3078, 2955, 2929, 2895, 2857, 1642, 1472, 1388, 1361, 1255, 1095, 1005, 939, 836, 774 cm^{-1}. ESI-MS *m/z* 517.6 $[M+H]^+$, *m/z* 539.6 $[M+Na]^+$. ESI-HRMS: calcd for $C_{27}H_{61}O_3Si_3$ $[M+H]^+$ 517.3929; found 517.3914.

4.22. Ozonolysis of alkene 27 to afford aldehyde 28

The same procedure given above for the conversion of **18** into **19** was employed. After chromatography (25:1 petroleum ether/EtOAc) aldehyde **28** was obtained as a colorless oil (291 mg, 0.193 mmol, 91%). $[\alpha]_D^{21}$ −5.5 (*c* 1.38, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *δ*=9.78 (s, 1 H), 3.89–3.85 (m, 2 H), 3.70–3.63 (m, 2 H), 2.48 (t, *J*=7.3 Hz, 2 H), 1.93–1.87 (m, 1 H), 1.72–1.64 (m, 4 H), 1.58–1.53 (m, 1 H), 0.89 (s, 9 H), 0.88 (s, 18 H), 0.06–0.04 (several unresolved singlets, 18 H altogether). ^{13}C NMR (125 MHz, $CDCl_3$): *δ*=202.4, 68.2, 66.8, 59.7, 44.7, 40.6, 39.4, 28.9, 26.0, 25.9, 18.3, 18.0, −4.35, −4.38, −4.40, −4.5, −5.31, −5.33. FTIR (film): 2955, 2929, 2886, 2857, 2711,

1730, 1472, 1388, 1361, 1256, 1098, 1005, 836, 774 cm^{-1}. ESI-MS *m/z* 519.6 $[M+H]^+$, *m/z* 541.6 $[M+Na]^+$. ESI-HRMS: calcd for $C_{26}H_{59}O_4Si_3$ $[M+H]^+$ 519.3716; found 519.3706.

4.23. Condensation of 28 with 8 to afford 29

The same procedure given above for the condensation of **19** with **8** to afford **20** was employed. After chromatography (25:1 petroleum ether/EtOAc) **29** was obtained as a colorless oil (22.8 mg, 0.0371 mmol, 64%). $[\alpha]_D^{22}$ −2.7 (*c* 0.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=7.25 (dd, *J*=15.4, 9.8 Hz, 1 H), 6.20–6.08 (m, 2 H), 5.78 (d, *J*=15.4 Hz, 1 H), 4.20 (q, *J*=7.1 Hz, 2 H), 3.87 (quint, *J*=6.1 Hz, 1 H), 3.80 (quint, *J*=6.2 Hz, 1 H), 3.69–3.63 (m, 2H), 2.30–2.13 (m, 2 H), 1.71–1.45 (m, 6 H), 1.29 (t, *J*=7.1 Hz, 3 H), 0.89 (s, 18 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.045 (s, 3 H), 0.040 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.3, 145.0, 144.4, 128.4, 119.3, 68.9, 66.8, 60.2, 59.8, 45.0, 40.5, 36.1, 28.6, 26.0, 25.90, 25.88, 18.3, 18.03, 18.01, 14.3, −4.3, −4.4, −4.38, −5.30, −5.32. ^1H NMR (500 MHz, C_6D_6): δ=7.46 (dd, *J*=15.3, 11.0 Hz, 1 H), 5.97 (dd, *J*=15.2, 11.0 Hz, 1 H), 5.87 (d, *J*=15.3 Hz, 1 H), 5.76 (dt, *J*=15.1, 7.0 Hz, 1 H), 4.03 (q, *J*=7.1 Hz, 2 H), 4.00–3.96 (m, 1 H), 3.81 (quint, *J*=6.1 Hz, 1 H), 3.73–3.66 (m, 2 H), 2.14–2.01 (m, 2 H), 1.82–1.77 (m, 1 H), 1.73 (dd, *J*=12.5, 6.3 Hz, 2 H), 1.65–1.60 (m, 1 H), 1.57–1.50 (m, 1 H), 1.47–1.40 (m, 1 H), 0.98 (s, 9 H), 0.97 (s, 9 H), 0.949 (s, 9 H), 0.947 (t, *J*=7.3 Hz, 3 H), 0.11 (s, 3 H), 0.10 (s, 6 H), 0.053 (s, 3 H), 0.046 (s, 6 H). ^{13}C NMR (125 MHz, C_6D_6): δ=166.7, 145.0, 143.8, 128.9, 120.3, 69.3, 67.2, 60.1, 60.0, 45.6, 41.1, 36.6, 28.8, 26.22, 26.18, 26.17, 18.6, 18.30, 18.29, 14.4, −4.0, −4.08, −4.13, −5.09, −5.14. FTIR (film): 2954, 2929, 2886, 2857, 1718, 1644, 1472, 1388, 1366, 1256, 1096, 1001, 836, 774 cm^{-1}. ESI-MS *m/z* 615.6 $[M+H]^+$, *m/z* 637.6 $[M+Na]^+$. ESI-HRMS: calcd for $C_{32}H_{67}O_5Si_3$ $[M+H]^+$ 615.4291; found 615.4278.

4.24. Conversion of 29 into (8*S*,10*R*)-2

The same procedure given above for the conversion of **20** into (8*R*,10*R*)-**2** was employed. After reverse phase chromatography (eluting with first H_2O, then 9:1 H_2O/MeOH and finally 2:1 H_2O/MeOH) on C-18 alkyl modified silica gel to (8*S*,10*R*)-**2** was obtained as a colorless oil (5.1 mg, 0.021 mmol, 72%). $[\alpha]_D^{25}$ −15.1 (*c* 0.2, MeOH). ^1H NMR (500 MHz, CD_3OD): δ=7.24 (dd, *J*=15.3, 10.6 Hz, 1 H), 6.28 (dd, *J*=15.2, 10.7 Hz, 1 H), 6.20 (dt, *J*=15.2, 6.7 Hz, 1 H), 5.79 (d, *J*=15.3 Hz, 1 H), 3.95–3.90 (m, 1 H), 3.81–3.76 (m, 1 H), 3.70 (t, *J*=6.6 Hz, 2 H), 2.38–2.31 (m, 1 H), 2.30–2.22 (m, 1 H), 1.75–1.69 (m, 1 H), 1.68–1.58 (m, 4 H), 1.57–1.51 (m, 1 H). ^{13}C NMR (125 MHz, CD_3OD): δ=171.6, 147.2, 145.8, 130.5, 121.5, 71.2, 69.6, 60.7, 45.9, 41.5, 38.1, 30.6. FTIR (film of a solution in MeOH): 3358, 2939, 2362, 1699, 1641, 1381, 1257, 1054, 881, 669 cm^{-1}. ESI-MS *m/z* 245.2 $[M+H]^+$, *m/z* 267.2 $[M+Na]^+$. ESI-HRMS: calcd for $C_{12}H_{21}O_5$ $[M+H]^+$ 245.1384; found 245.1382.

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Supplementary data

Supplementary data (Copies of the ^1H and ^{13}C NMR spectra, FTIR spectra for all new compounds. Time-dependent optical rotations data for (8*R*,10*R*)-**2**) related to this article can be found, in the online version at http://dx.doi.org/10.1016/j.tet.2016.04.033.

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