Stereoselective synthesis of the enantiomer of the fatty acid component of the potent immunosuppressant, stevastelin†

Sadagopan Raghavan*,1 S Ramakrishna Reddy1 & B Rajitha2
1Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India
2Department of Chemistry, National Institute of Technology, Warangal 506 004, India
E mail: purush101@yahoo.com
Received 11 August 2004; accepted (revised) 9 May 2005

A stereoselective synthesis of the enantiomer of the fatty acid chain of stevastelin is disclosed. The C4 methyl group is introduced regio- and stereoselectively via dimethylcuprate opening of epoxy alcohol while the C5 stereogenic center was introduced in a highly stereoselective fashion by Grignard reaction.

Keywords: Stereoselective synthesis, enantiomer, fatty acid, immunosuppressant, stevastelin, dimethylcuprate, epoxy alcohol, Grignard reaction

IPC: Int.Cl.7 C 07 C, C 07 D // A 61 P 37/06

The stevastelins 1-5, are novel cyclic depsipeptides (Figure 1) isolated from the culture broths of Penicillium sp. NK 3741861, that possess potent immunosuppressive activity2. The mechanism of action, via inhibition of T-cell proliferation is different from other well-known immunosuppressants like cyclosporin A3, FK-5064 in that it does not inhibit the phosphatase activity of calcineuern4. The structure, assigned to stevastelins by spectral and degradation studies, consists of a dihydroxydimethylstearic acid moiety with four contiguous chiral centers, L-serine, L-threonine and L-valine in a 13/15-membered ring. Their novel structure and mechanism of action make them attractive targets for synthesis5,6. Herein, we describe a stereoselective synthesis of (2S,3S,4R,5S)-3,5-dihydroxy-2,4-dimethylstearic acid subunit 6.

Results and Discussion

By a retrosynthetic analysis (Scheme I), we envisaged the stearic acid moiety 6 to be derived from the β-hydroxyaldehyde derivative 7, hoping to introduce the C5 stereogenic center of 6 (stevastelin numbering) selectively using the substituent at C3 in 7. The aldehyde 7 can be obtained from the sulfoxide 8 which in turn can be secured from the allyl ether 9.

Figure 1

†IICT Communication No. 040322
The synthesis began with the olefin 9 (ref. 7) which was transformed in three high yielding steps into the epoxy alcohol 10 (ref. 8). The C4 methyl group of stevastelin was introduced by the regioselective opening of 10 with Me2CuLi to yield 11 (ref. 9). The anti-syn stereo triad was thus synthesized stereoselectively. The elaboration of 11 to 6 called for the concurrent introduction of the C5 stereocenter and the alkyl chain. There were two broad options available for the preparation of 6, one, wherein the C5 stereocenter is introduced prior to revealing the carboxy group (or its equivalent) and the second, introduction of the carboxy group (or its equivalent) prior to the C5 stereogenic center. Exploring the first option selective protection of the primary hydroxy group in 11 with tert-butyldimethylchlorosilane yielded 12 (Scheme II). Coupling of 12 with benzoic acid using DCC afforded the ester 13 as an epimeric mixture of sulfoxides that could be separated readily by column chromatography. Exploring the first option, deprotection of the silyl group in one of the diastereomerically pure sulfoxide 13, followed by oxidation of the resulting alcohol 14 with Dess-Martin periodinane cleanly afforded the aldehyde 15, which on treatment with tridecylmagnesium bromide (prepared from 1-bromotridecane and Mg turnings in THF) afforded the secondary carbinols 16 and 17 in a 2:1 ratio, respectively as an inseparable mixture. The benzoate ester was hydrolyzed and the resulting mixture of diols 18/19 were converted to the acetonides 20/21 which also were inseparable. With the hope of being able to improve the diastereoselectivity during the Grignard reaction by an appropriate choice of reaction conditions, the acetonide 20/21 was subjected to the Pummerer reaction conditions to reveal the hydroxy group, which could be oxidized to an acid group. Disappointingly, a complex mixture of products resulted from the Pummerer reaction (Scheme II).

We therefore explored the second option. Thus silyl ether 13 was subjected to Pummerer reaction conditions and the resulting intermediate, without isolation was treated with sodium borohydride and saturated aqueous sodium bicarbonate to yield the alcohol 22 cleanly. Protection as the t-butyldiphenylsilyl ether 23 followed by selective removal of the t-butyldimethylsilyl group gave 24. Oxidation of 24 with Dess-Martin periodinane followed by reaction with tridecylmagnesium bromide in a mixture of THF and toluene at −78°C afforded cleanly the carbinol 26 as the major product (9:1 (Scheme III). The stereochemical outcome of the reaction can be rationalized using the Felkin-Ahn model.

The structure of 26 was confirmed by 1H NMR and NOE measurements on the acetonide 28 obtained by a straightforward sequence of reactions (Scheme IV). The 13C NMR spectrum of 28 revealed signals at δ 19.75, 29.68 for the methyl groups and at 98.69 for the quaternary ketal carbon supporting the assigned structure. The hydroxy groups are differentially protected in 26 and it can be elaborated to the enantiomer of stevastalin following the chemistry described by Chida and co-workers.

Conclusion
In conclusion, we have disclosed a highly stereoselective route to the enantiomer of the stearic acid moiety of stevastelin. The key steps of the route include regio- and stereoselective preparation of the bromohydrin from an olefin, regioselective opening of the epoxide with dimethylcuprate and stereoselective introduction of the C5 stereocenter with the required configuration.

Experimental Section
General. All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents...
were distilled freshly, THF over Na/benzophenone ketyl, DCM over P₂O₅ followed by CaH₂ and toluene over P₂O₅. Thin layer chromatography was performed with precoated silica gel plates. Column chromatography was carried out using silica gel (60-120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ¹H NMR and ¹³C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

**Scheme II**

Reaction conditions: (a) see ref. 8; (b) Me₂CuLi, THF, 0°C, 70%; (c) TBDMS-Cl, imidazole, CH₂Cl₂, rt, 95%; (d) PhCO₂H, DCC, CH₂Cl₂, rt, 90%; (e) CSA, MeOH, rt, 90%; (f) DMP, CH₂Cl₂, rt, 85%; (g) C₁₃H₂₇MgBr, THF, toluene, -42°C, 80%; (h) K₂CO₃, MeOH, rt, 90%; (i) 2,2-dimethoxypropane, CSA, rt, 90%

**Scheme III**

Reaction conditions: (a) TFAA, Et₃N, acetonitrile, aq. NaHCO₃, NaBH₄, rt, 75%; (b) TBDPS-Cl, imidazole, CH₂Cl₂, rt, 95%; (c) PPTS, EtOH, 55°C, 90%; (d) DMP, CH₂Cl₂, rt, 90%; (e) C₁₃H₂₇MgBr, THF, toluene, -78°C, 85%.
dried over Na₂SO₄. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 80% EtOAc-petroleum ether (v/v) as the eluent to give the diol 11 (466 mg, 1.82 mmoles) in 70% yield as viscous oil; ¹H NMR (200 MHz, CDCl₃): δ 7.70-7.40 (m, 10H), 3.75-3.40 (m, 6H), 3.30-3.0 (m, 2H), 2.80 (dd, J=9.5, 3.6 Hz, 1H), 2.50 (dd, J=12.4, 8.0 Hz, 1H), 2.17-2.01 (m, 2H), 1.85-1.75 (m, 2H), 1.10 (d, J=7.3 Hz, 3H), 1.04 (d, J=7.3 Hz, 3H), 0.95-0.87 (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 143.61, 131.90, 129.26, 124.08, 124.04, 75.93, 75.69, 66.79, 66.51, 63.35, 61.92, 33.16, 33.16, 33.03, 17.31, 16.61, 8.88, 8.66; MS (FAB): 257, 241, 186, 167, 149, 95, 57; [α]D²⁵ +52.5 (c 2.0, CHCl₃). Anal. Calcd for C₁₃H₂₀O₃S: C, 60.91; H, 7.86; S, 12.51.  Found: C, 60.82; H, 7.95; S, 12.80%.

To the solution of diol 11 (435 mg, 1.7 mmoles) in dry DCM (3.4 mL) was added imidazole (176 mg, 2.6 mmoles) followed by the addition of TBDMS-Cl (307 mg, 2.0 mmoles). The reaction mixture was stirred at room temperature for 30 min under an atmosphere of nitrogen. The reaction mixture was diluted with DCM and washed successively with water, brine and dried over Na₂SO₄. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using 40% EtOAc-petroleum ether (v/v) as the eluent to give 12 (555 mg, 1.5 mmoles) in dry DCM (6 mL) was added DCC (340 mg, 1.65 mmoles) and DMAP (18 mg, 0.15 mmoles) followed by benzoic acid (202 mg, 1.65 mmoles) and the reaction mixture stirred at r.t. for 12 hr. The reaction mixture was diluted with DCM (6 mL) and filtered through a small pad of celite. The filtrate was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 20% EtOAc-petroleum ether (v/v) as the eluent to furnish compound 13 (640 mg, 1.35 mmoles) in 90% yield as viscous oil. A small sample of the epimeric mixture of sulfoxide was separated into the individual isomers 13a and 13b.

13a: Liquid; ¹H NMR (300 MHz, CDCl₃): δ 8.10 (d, J=7.5 Hz, 2H), 7.65-7.34 (m, 8H), 5.25 (dd, J=7.5, 4.5 Hz, 1H), 3.50-3.40 (m, 2H), 2.90 (dd, J=12.0, 3.0 Hz, 1H), 2.50 (dd, J=12.0, 6.0 Hz, 1H), 2.10-2.0 (m, 1H), 1.30 (d, J=6.0 Hz, 3H), 1.28-1.20 (m, 1H), 0.96 (d, J=7.5 Hz, 1H), 0.87 (s, 9H), 0.01 (s, 6H); ¹³C NMR (50 MHz, CDCl₃): δ 166.90, 144.20, 133.31, 130.93, 130.1, 129.64, 129.26, 128.37, 123.98, 77.27, 65.06, 61.70, 37.46, 30.94, 25.84, 18.20, 16.57, 11.38, -5.55; MS (FAB): 475, 353, 295,
25.85, 18.33, 11.18, -5.55; MS

124.03, 78.10, 65.15, 62.64, 37.69, 31.12, 29.65, 133.42, 131.08, 130.15, 129.75, 129.27, 128.40, J= 4.4 Hz, 1H), 3.24 (dd, 2, 4-dimethyl-5-phenylsulfinylpentanal 15 solution of compound

221, 179, 105, 73; [α]D 221, 179, 105, 73; [α]D = 58.6 (c 1.0, CHCl3). Anal.

Caled for C20H24O4S: C, 66.64; H, 6.71; S, 8.89. Found: C, 65.90; H, 8.07; S, 6.75. Found: C, 65.90; H, 8.25; S, 6.80%.

13b: Liquid; 1H NMR (300 MHz, CDCl3): δ 8.10 (d, J=7.5 Hz, 2H), 7.62-7.42 (m, 8H), 5.35 (dd, J=7.5, 3.0 Hz, 1H), 3.46-3.38 (m, 2H), 3.05 (dd, J=13.6, 7.5 Hz, 1H), 2.80 (dd, J=13.6, 4.5 Hz, 1H), 2.70-2.58 (m, 1H), 1.35-1.23 (m, 1H), 1.17 (d, J=7.5 Hz, 3H), 1.07 (d, J=7.5 Hz, 3H), 0.9 (s, 9H), -0.02 (s, 6H); 13C NMR (75 MHz, CDCl3): δ 166.42, 144.59, 133.42, 131.08, 130.15, 129.75, 129.27, 128.40, 124.03, 78.10, 65.15, 62.64, 37.69, 31.12, 29.65, 25.85, 18.33, 11.18, -5.55; MS (FAB): 475, 353, 295, 183, 179, 137, 99. 0.03 mmole). The reaction mixture was stirred at r.t. for 30 min and quenched by the addition of aq. saturated NaHSO3 solution. The aq. layer was extracted with ether and dried over Na2SO4. The organic layer was evaporated under reduced pressure to afford the product which was purified by column chromatography using 25% EtOAc-petroleum ether (v/v) afforded products 16 and 17 as an inseparable mixture (65 mg, 0.12 mmole) in 80% yield as viscous oil; 1H NMR (300 MHz, CDCl3): δ 8.0 (d, J=7.2 Hz, 2H), 7.89 (d, J=7.2 Hz, 2H), 7.57-7.31 (m, 16H), 5.24-5.12 (m, 2H), 3.67-3.58 (m, 2H), 2.97-2.86 (m, 2H), 2.47-2.39 (m, 2H), 2.26-2.11 (m, 2H), 1.88-1.80 (m, 2H), 1.40-1.34 (m, 4H), 1.27-1.13 (m, 5OH), 0.94-0.79 (m, 12H); Anal. Caled for C23H30O5S: C, 73.02; H, 9.28; S, 5.91. Found: C, 73.28; H, 9.42; S, 5.78%.

(S5,SR,3S,4R)-3-Benzoyloxy-2,4-dimethyl-1-phenylsulfinyloctadecane-3,5-diol and (SR, 2S, 3S, 4R, 5R)-3-benzoyloxy-2,4-dimethyl-1-phenylsulfinyloctadecane-3,5-diol 18; (SR, 2S, 3S, 4R, 5R)-3-benzoyloxy-2,4-dimethyl-5-phenylsulfinyloctadecane-3,5-diol 19. To the solution of compound 16 and 17 (54 mg, 0.1 mmole) in DCM (0.5 mL) was added K2CO3 (5 mg). The reaction mixture was stirred at r.t. for 6 hr and diluted with diethyl ether (5 mL). The reaction mixture was filtered through a small pad of celite and the filtrate was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 25% EtOAc-petroleum ether (v/v) as the eluent to afford the diols 18 and 19 as an inseparable mixture (38 mg, 0.09 mmole) in 90% yield as viscous oil; 1H NMR (300 MHz, CDCl3): δ 7.65-7.61 (m, 4H), 7.53-7.46 (m, 6H), 3.80-3.68 (m, 2H), 3.63-3.50 (m, 2H), 3.27-3.14 (m, 2H), 2.58-2.49 (m, 2H), 2.35-2.23 (m, 2H), 1.67-1.44 (m, 6H), 1.25 (m, 4H), 1.10-1.06 (m, 6H), 0.99 (d, J=6.8 Hz, 3H),
0.91-0.86 (m, 6H); Anal. Calcd for C_{26}H_{46}O_{3}S: C, 71.18; H, 10.57; S, 7.31. Found: C, 71.26; H, 10.32; S, 7.20%.

(\text{S}_5, 4 \text{S}, 5 \text{R}, 6 \text{S})\text{-2, 2, 5-Trimethyl-4-\{1-methyl-2-phenylsulfinyl-1(S)-ethyl\}\text{-6-tridecyl-1,3-dioxane and (\text{S}_8, 4 \text{S}, 5 \text{R}, 6 \text{S})\text{-2, 2, 5-Trimethyl-4-\{1-methyl-2-phenylsulfinyl-1(S)-ethyl\}\text{-6-tridecyl-1,3-dioxane 20 (S, 4 \text{S}, 5 \text{R}, 6 \text{R})\text{-2, 2, 5-Trimethyl-4-\{1-methyl-2-phenylsulfinyl-1(S)-ethyl\}\text{-6-tridecyl-1,3-dioxane 21. To the solution of diols 18 and 19 (35 mg, 0.08 mmole) in 2,2-dimethoxypropane (0.5 mL) was added CSA (5 mg) and stirred at r.t. for 1 hr. Two drops of Et\text{3}N were added to the reaction mixture to neutralize CSA. The solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography using 10% EtOAc-petroleum ether (v/v) as the eluent to yield acetonides 20 and 21 (33 mg, 0.07 mmole) in 90% yield as semi-solid; ^{1}H NMR (300 MHz, CDCl\text{3}): \delta 7.64-7.60 (m, 4H), 7.52-7.45 (m, 6H), 3.78-3.73 (m, 1H), 3.65 (dd, J=10.2, 2.2 Hz, 1H), 3.53 (dd, J=10.5, 4.2 Hz, 1H), 3.19-3.10 (m, 2H), 3.04 (dd, J=13.2, 4.1 Hz, 1H), 2.50 (dd, J=13.2, 7.9 Hz, 1H), 2.25 (dd, J=13.2, 8.3 Hz, 1H), 2.15-2.01 (m, 2H), 1.60-1.56 (m, 2H), 1.50-1.25 (m, 60H), 1.10-1.04 (m, 6H), 0.90-0.80 (m, 6H), 0.83 (J=6.8 Hz, 3H), 0.70 (d, J=6.8 Hz, 3H); Anal. Calcd for C_{29}H_{50}O_{3}S: C, 72.75; H, 10.53; S, 6.70. Found: C, 72.58; H, 10.20; S, 6.58%.

(2R, 3R, 4R)-3-Benzoyloxy-5-\text{tert}-butyldimethylsilyloxy-2,4-dimethylpentane-1-ol 22. To the solution of compound 13 (355 mg, 0.75 mmole) in dry acetonitrile (3.8 mL) was added Et\text{3}N (1.0 mL, 7.5 mmoles) at r.t. under nitrogen atmosphere. TFAA (1.0 mL, 7.5 mmoles) was added to the reaction mixture and stirred at r.t. for 10 min. Then a solution of NaHCO\text{3} (1.25 g, 15 mmole) in water (3 mL) was added to the reaction mixture at 0°C followed by solid NaBH\text{4} (570 mg, 15 mmoles) in portions. The reaction mixture was allowed to attain r.t. gradually over a period of 30 min. The reaction mixture was diluted with ether (10 mL) and the layers separated. The aq. layer was extracted with ether and the combined organic layers were washed with water and brine. Drying and evaporation under reduced pressure afforded the crude product which was purified by chromatography using 10% EtOAc-petroleum ether (v/v) as the eluent to give alcohol 22 (206 mg, 0.56 mmole) in 75% yield. Liquid; ^{1}H NMR (300 MHz, CDC\text{1}): \delta 8.02 (d, J=6.6 Hz, 2H), 7.60-7.40 (m, 3H), 5.21 (dd, J=10.2, 2.9 Hz, 1H), 3.60-3.35 (m, 4H), 2.10-2.05 (m, 1H), 1.95-1.80 (m, 1H), 1.10 (d, J=7.3 Hz, 3H), 1.02 (d, J=7.3 Hz, 3H), 0.85 (d, J=7.3 Hz, 3H), 0.85 (s, J=7.3 Hz) -0.08 (s, 3H); ^{13}C NMR (75 MHz, CD\text{Cl}3): \delta 167.35, 133.90, 130.19, 129.71, 128.44, 75.16, 65.51, 64.05, 37.20, 37.0, 25.84, 18.19, 14.0, 10.18, -5.58; MS (FAB): 367, 309, 298, 179, 113, 89, 73; [\alpha]_{D}^{25} +23.0 (c 1.0, CHCl3). Anal. Calcd for C_{26}H_{46}O_{3}Si: C, 65.53; H, 9.35. Found: C, 65.68; H, 9.20%.

(2R, 3R, 4R)-3-Benzoyloxy-5-\text{tert}-butyldiphenylsilyloxy-2,4-dimethylpentane 23. To the solution of alcohol 22 (165 mg, 0.45 mmole) in dry DCM (1 mL) was added imidazole (46 mg, 0.68 mmole) followed by TBDDS-Cl (0.14 mL, 0.5 mmole). The reaction mixture was stirred at room temperature for 30 min under an atmosphere of nitrogen and then diluted with DCM and washed successively with water, brine and dried over Na_{2}SO\text{4}. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using 5% EtOAc-petroleum ether (v/v) as the eluent to afford 23 (254 mg, 0.42 mmole) in 95% yield. Liquid; ^{1}H NMR (200 MHz, CDCl\text{3}): \delta 7.94 (d, J=6.6 Hz, 2H), 7.75-7.72 (m, 5H), 7.44-7.16 (m, 8H), 5.30 (dd, J=8.0, 3.7 Hz, 1H), 3.67-3.50 (m, 3H), 3.40-3.36 (dd, J=10.3, 6.6 Hz, 1H), 2.17-1.96 (m, 2H), 1.10-1.02 (m, 12H), 0.97 (d, J=6.6 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl3): \delta 165.81, 135.58, 133.66, 132.51, 130.52, 129.57, 129.45, 128.23, 127.49, 75.79, 65.80, 65.25, 37.81, 37.57, 26.78, 25.88, 19.18, 18.22, 14.47, 11.09, -5.47, -5.53; MS (FAB): 605, 303, 283, 197, 179, 135, 105, 73; [\alpha]_{D}^{25} +4.7 (c 1.0, CHCl3). Anal. Calcd for C_{38}H_{52}O_{4}Si_{2}: C, 71.47; H, 8.66. Found: C, 71.60; H, 8.42%.

(2R, 3S, 4R)-3-Benzoyloxy-5-\text{tert}-butyldiphenylsilyloxy-2,4-dimethylpentane-1-ol 24. To the solution of compound 23 (212 mg, 0.35 mmole) in EtOH (1.8 mL) was added PPTS (26 mg, 0.1 mmole). The reaction mixture was stirred at 55°C for 12 hr and quenched by the addition of Et\text{3}N (5 \muL). The solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography using 10% EtOAc-petroleum ether (v/v) as the eluent to afford compound 24 (157 mg, 0.32 mmole) in 90% yield as viscous oil; ^{1}H NMR (200 MHz, CDCl\text{3}): \delta 7.95 (d, J=7.3 Hz, 2H), 7.60-7.50 (m, 3H), 7.45-7.16 (m, 8H), 7.06-6.99 (m, 2H), 5.40 (dd, J=10.2, 2.2 Hz, 1H), 3.63 (dd, J=10.3, 5.1 Hz, 1H), 3.53 (dd, J=10.3, 2.2 Hz, 1H), 3.45-3.35 (m, 2H), 2.22-2.02 (m, 2H),
1.13 (d, J=6.6 Hz, 3H), 1.0 (s, 9H), 0.83 (d, J=6.6 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 167.59, 135.58, 135.45, 133.19, 129.76, 129.50, 129.37, 128.44, 127.54, 127.40, 74.07, 65.21, 64.12, 36.93, 36.71, 26.71, 19.18, 14.19, 9.24; MS (FAB): 491, 433, 311, 303, 243, 199, 113, 105; [α]D25 + 13.7 (c 1.0, CHCl3).

Anal. Calcd for C30H38O4Si: C, 73.43; H, 7.81. Found: C, 73.60; H, 7.60%.

(2R, 3R, 4R)-3-Benzoyloxy-5-tert-butyldiphenylsilyloxy-2,4-dimethylpentanal 25. To the solution of compound 24 (132 mg, 0.27 mmole) in DCM (1 mL) was added DMP (127 mg, 0.3 mmole) and the reaction mixture stirred at r.t. for 30 min. The reaction was quenched by the addition of sat. NaHCO3 solution. The aq. layer was extracted with ether and the combined organic layers washed with aq. saturated NaHCO3 solution, water, brine and dried over Na2SO4. The organic layer was evaporated under reduced pressure to afford the crude product 25 (117 mg, 0.24 mmole) in 90% yield which was taken ahead to the next step without further purification. Viscous oil; 1H NMR (200 MHz, CDCl3): δ 7.70-7.56 (m, 4H), 7.45-7.30 (m, 6H), 3.83-3.79 (m, 1H), 3.65-3.54 (m, 1H), 1.95-1.84 (m, 1H), 1.60-1.35 (m, 5H), 1.25 (s, 20H), 1.05 (s, 9H), 0.93-0.82 (m, 6H), 0.65 (d, J=6.5 Hz, 3H); [α]D25 +39.0 (c 0.25, CHCl3).

Anal. Calcd for C36H56O4Si: C, 76.0; H, 10.63. Found: C, 76.32; H, 10.42%.

(4R, 5R, 6S)-4-[tert-Butyldiphenylsilyloxy-1-methyl-(1R)-ethyl]-2,2,5-trimethyl-6-tridecyl-1,3-dioxane 28. To the solution of diol 27 (56 mg, 0.09 mmole) in 2,2-dimethoxypropane (0.5 mL) was added CSA (5 mg) and the reaction mixture stirred at r.t. for 1 hr. Two drops of Et3N were added to the reaction mixture to neutralize CSA. The solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography using 5% EtOAc-petroleum ether as the eluent to give the diol 28 (54 mg, 0.09 mmole) in 90% yield; 1H NMR (200 MHz, CDCl3): δ 7.71-7.60 (m, 4H), 7.45-7.30 (m, 6H), 3.90-3.70 (m, 3H), 3.55 (dd, J=7.8, 2.6 Hz, 1H), 1.75-1.60 (m, 1H), 1.50-1.44 (m, 1H), 1.40-1.12 (m, 30H), 1.05 (s, 9H), 0.94 (d, J=6.5 Hz, 3H), 0.88 (t, J=6.5 Hz, 3H), 0.78 (d, J=6.5 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 135.63, 133.50, 129.45, 127.49, 98.69, 73.69, 73.14, 64.72, 36.82, 32.98, 32.33, 31.93, 30.07, 29.68, 29.36, 26.88, 25.47, 22.69, 19.75, 19.37, 14.12, 12.52, 4.49; [α]D25 −6.2 (c 1.0, CHCl3).

Anal. Calcd for C38H64O4Si: C, 76.92; H, 10.69. Found: C, 76.78; H, 10.32%.

Acknowledgement
One of the authors (S R) is thankful to Dr J S Yadav for constant support and encouragement, to Dr A C Kunwar for NMR spectra and Dr M Vairamani.
for the mass spectra. S R K is thankful to the CSIR, New Delhi for the grant of SRF.

References

5 For the total synthesis refer (a) Kohyama N & Yamamoto Y, *Synlett*, 2001, 694.
9 The structure assigned to 11 was confirmed by acetonide formation after oxidation to the sulfone.
11 Based on the results of the Grignard addition to 25, the major isomer was assigned the structure 16.