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

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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.

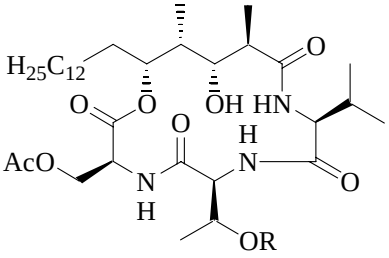
Keywords: Stereoselective synthesis, enantiomer, fatty acid, immunosuppressant, stevastelin, dimethylcuprate, epoxy alcohol, Grignard reaction

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

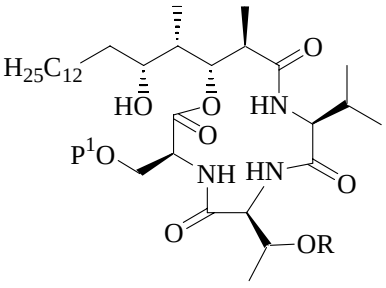
The stevastelins **1-5**, are novel cyclic depsipeptides (**Figure 1**) isolated from the culture broths of *Penicillium* sp. NK 374186[1], that possess potent immunosuppressive activity[2]. The mechanism of action, via inhibition of T-cell proliferation is different from other well-known immunosuppressants like cyclosporin A[3], FK-506[4] in that it does not inhibit the phophatase activity of calcineuerin[4]. 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 synthesis[5,6]. Herein, we describe a stereoselective synthesis of (2*S*,3*S*,4*R*,5*S*)-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**.



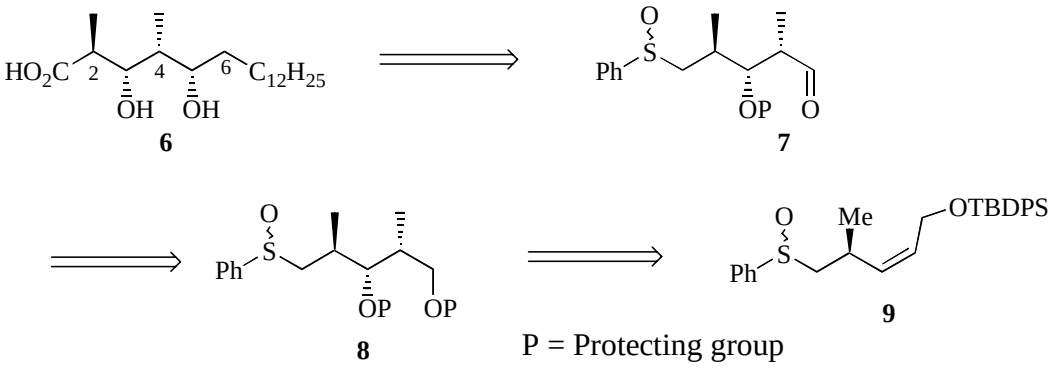
Stevastalins A **1**, R = SO_3H
B **2**, R = H



Stevastalins A3 **3**, P^1 = Ac, R = SO_3H
B3 **4**, P^1 = Ac, R = H
C3 **5**, P1 = R = H

Figure 1

†IICT Communication No. 040322



Scheme I

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 Me_2CuLi 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 *t*-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[10] 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[11] 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[12] 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.

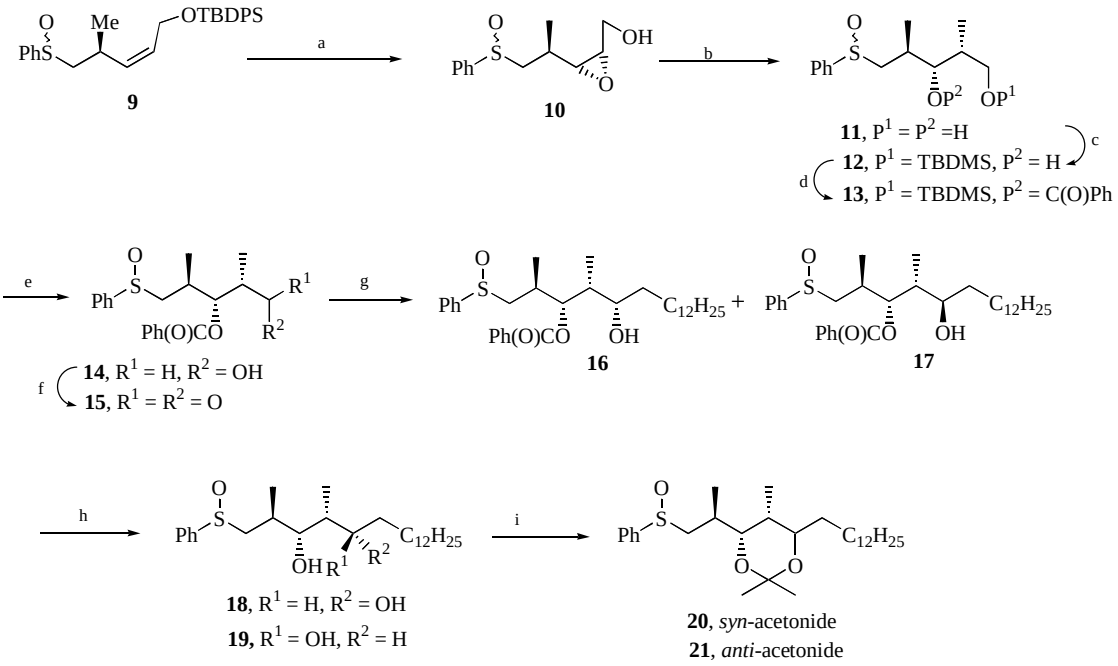
The structure of **26** was confirmed by ^{1}H NMR and NOE measurements on the acetonide **28** obtained by a straightforward sequence of reactions (**Scheme IV**). The ^{13}C NMR spectrum of **28** revealed signals at δ 19.75, 29.68 for the methyl groups and at 98.69 for the quaternary ketal carbon supporting the assigned structure[13]. 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[5].

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.

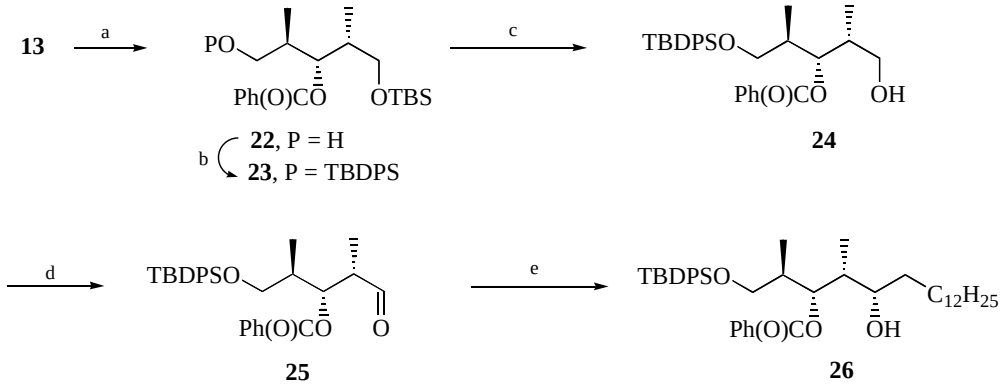
Experimental Section

General. All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents



Reaction conditions: (a) see ref. 8; (b) Me_2CuLi, THF, 0°C, 70%; (c) TBDMS-Cl, imidazole, CH_2Cl_2, rt, 95%; (d) $PhCO_2H$, DCC, CH_2Cl_2, rt, 90%; (e) CSA, MeOH, rt, 90%; (f) DMP, CH_2Cl_2, rt, 85%; (g) $C_{13}H_{27}MgBr$, THF, toluene, -42°C, 80%; (h) K_2CO_3, MeOH, rt, 90%; (i) 2,2-dimethoxypropane, CSA, rt, 90%

Scheme II

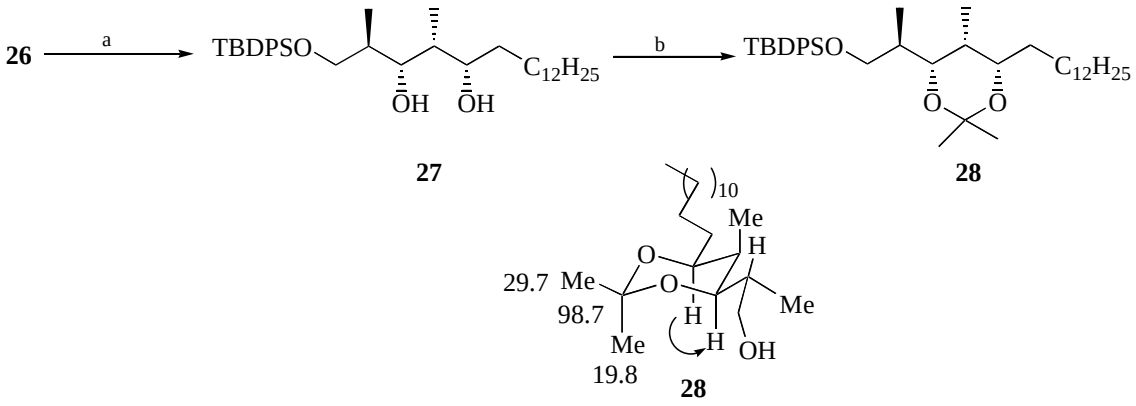


Reaction conditions: (a) TFAA, Et_3N, acetonitrile, aq. $NaHCO_3$, $NaBH_4$, rt, 75%; (b) TBDPS-Cl, imidazole, CH_2Cl_2, rt, 95%; (c) PPTS, EtOH, 55°C, 90%; (d) DMP, CH_2Cl_2, rt, 90%; (e) $C_{13}H_{27}MgBr$, THF, toluene, -78°C, 85%.

Scheme III

were distilled freshly, THF over Na/benzophenone ketyl, DCM over P_2O_5 followed by CaH_2 and toluene over P_2O_5. 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 ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

(S_S, 2*R*, 3*S*, 4*S*)- and (S_R, 2*R*, 3*S*, 4*S*)-2, 4-Dimethyl-5-phenylsulfinylpentane-1, 3-diol 11. To the suspension of CuI (2.48 g, 13 mmoles) in THF (65 mL) cooled at 0°C was added MeLi (1.5 M in ether, 17.4 mL, 26 mmoles) and the reaction mixture stirred at the same temperature for 30 min. The epoxy alcohol **10** (624 mg, 2.6 mmoles) dissolved in THF (11 mL) was added to the resulting dimethylcuprate and stirred at 0°C for 30 min. The reaction was quenched by the addition of a saturated aq. NH_4Cl solution. The layers were separated and the aq. layer was extracted with diethyl ether. The combined organic layers were washed with water, brine and



Reaction conditions: (a) DIBAL-H, toluene, -78°C, 85%; (b) 2,2-dimethoxypropane, CSA, rt, 90%.

Scheme IV

dried over Na_2SO_4. 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; ^{1}H NMR (200 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.61, 131.90, 129.26, 124.08, 124.04, 75.93, 75.69, 66.79, 66.51, 63.35, 61.92, 36.34, 36.15, 33.16, 33.03, 17.31, 16.61, 8.88, 8.66; MS (FAB): 257, 241, 186, 167, 149, 95, 57; $[\alpha]_D^{25}$+52.5 (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_3S$: C, 60.91; H, 7.86; S, 12.51. Found: C, 60.82; H, 7.95; S, 12.80%.

(*S*$_S$, 2*R*, 3*S*, 4*S*)- and (*S*$_R$, 2*R*, 3*S*, 4*S*)-1-*tert*-Butyldimethylsilyloxy-2, 4-dimethyl-5-phenylsulfinylpentan-3-ol 12. 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 Na_2SO_4. 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** (592 mg, 1.6 mmoles) in 95% yield as liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68-7.60 (m, 4H), 7.54-7.43 (m, 6H), 3.76-3.52 (m, 6H), 3.22 (dd, *J*=12.6, 3.7 Hz, 1H), 2.91-2.70 (m, 2H), 2.51 (dd, *J*=13.4, 8.9 Hz, 1H), 2.30-2.12 (m, 2H), 1.86-1.71 (m, 2H), 1.14 (d, *J*=6.7 Hz, 3H), 1.08 (d, *J*=7.4 Hz, 3H), 0.94-0.78 (bs, 24H), 0.06 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.66, 144.39, 131.06, 130.82, 129.14, 129.10, 124.0, 77.41, 76.47, 68.66, 68.07, 63.12, 62.44, 36.33, 35.95, 33.81, 32.71, 25.77, 18.19, 18.12, 17.14, 16.24, -5.32, -5.57, -5.62, -5.65; MS (FAB): 371, 313, 239, 221, 145, 95, 73, 57; $[\alpha]_D^{25}$ + 37.8 (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{34}O_3SSi$: C, 61.57; H, 9.25; S, 8.65. Found: C, 61.68; H, 9.32; S, 8.38%.

(*S*$_S$,2*S*,3*S*,4*R*)- and (*S*$_R$,2*S*, 3*S*, 4*R*)-3-Benzoyloxy-1-*tert*-butyldimethylsilyloxy-2,4-dimethylpentyl phenyl sulfoxide 13. To the solution of alcohol **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 mmole) 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; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (50 MHz, $CDCl_3$): 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,

221, 179, 105, 73; $[\alpha]_D^{25}$ + 58.6 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{26}H_{38}O_4SSi$: C, 65.78; H, 8.07; S, 6.75. Found: C, 65.90; H, 8.25; S, 6.80%.

13b: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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, 221, 179, 105, 73; $[\alpha]_D^{25}$ – 52.2 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{26}H_{38}O_4SSi$: C, 65.78; H, 8.07; S, 6.75. Found: C, 65.90; H, 8.25; S, 6.80%.

(*S*$_S$,2*R*,3*S*,4*S*)-and (*S*$_R$, 2*R*, 3*S*, 4*S*)-3-Benzoyloxy-2, 4-dimethyl-phenysulfinylpentane-1-ol 14. To the solution of compound **13a** (118 mg, 0.25 mmole) in 1:1 MeOH/DCM (1.3 mL) was added CSA (6 mg, 0.03 mmole). The reaction mixture was stirred at r.t. for 12 hr and quenched by the addition of Et_3N (5 μL). The solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography. Elution with 40% EtOAc-petroleum ether (v/v) afforded compound **14** (79 mg, 0.22 mmole) in 90% yield as viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.0 (d, *J*=6.6 Hz, 2H), 7.60-7.38 (m, 8H), 5.16 (dd, *J*=8.7, 3.6 Hz, 1H), 3.47 (dd, *J*=11.7, 4.4 Hz, 1H), 3.24 (dd, *J*=11.7, 9.5 Hz, 1H), 2.95 (dd, *J*=12.4, 2.2 Hz, 1H), 2.80-2.60 (m, 1H), 2.44 (dd, *J*=12.4, 10.9 Hz, 1H), 2.20-2.11 (m, 1H), 1.32 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=7.3 Hz, 3H); Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71; S, 8.89. Found: C, 66.46; H, 6.82; S, 9.02%.

(*S*$_S$,2*S*,3*S*,4*S*)-and (*S*$_R$, 2*R*, 3*S*, 4*S*)-3-Benzoyloxy-2, 4-dimethyl-5-phenylsulfinylpentanal 15. To the solution of compound **14** (72 mg, 0.2 mmole) in DCM (0.8 mL) was added DMP (95 mg, 0.22 mmole). The reaction mixture was stirred at r.t. for 30 min and quenched by the addition of an aq. saturated $NaHSO_3$ solution. The aq. layer was extracted with DCM and the combined organic layers washed with aq. saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the product **15** (60 mg, 0.17 mmole) in 85% yield which was taken ahead to the next step without further purification. Viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.90 (dd, *J*=7.2 Hz, 2H), 7.60-7.35 (m, 8H), 5.50 (dd, *J*=6.6, 4.4 Hz, 1H), 2.90 (dd, *J*=12.4, 2.3 Hz, 1H), 2.82-2.75 (m, 1H), 2.66-2.59 (m, 1H), 2.54 (dd, *J*=12.4, 9.8 Hz, 1H), 1.35 (d, *J*=6.4 Hz, 3H), 1.18 (d, *J*=7.8 Hz, 3H).

(*S*$_S$, 2*S*, 3*S*, 4*R*,5*S*)-3-Benzoyloxy-2,4-dimethyl-1-phenylsulfinyloctadecane-5-ol and (*S*$_R$, 2*S*, 3*S*, 4*R*, 5S)-3-benzoyloxy-2,4-dimethyl-5-phenylsulfinyloctadecane-5-ol 16; (*S*$_S$,2*S*,3*S*,4*R*,5*R*)-3-benzoyloxy-2,4-dimethyl-1-phenylsulfinyloctadecane-5-ol and (*S*$_R$, 2*S*,3*S*,4*R*,5*R*)-3-benzoyloxy-2,4-dimethyl-5-phenylsulfinyloctadecane-5-ol 17. To the solution of compound **15** (53 mg, 0.15 mmole) in toluene (0.75 mL) cooled at – 42 °C was added tridecylmagnesium bromide (1*M* in THF, 0.22 mL, 0.22 mmole). The reaction mixture was stirred at – 42 °C for 10 min and quenched by the addition of aq. saturated NH_4Cl solution. The aq. layer was extracted with ether and the combined organic layers washed with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography. Elution with 15% 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; ^{1}H NMR (300 MHz, $CDCl_3$): 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, 50H), 0.94-0.79 (m, 12H); Anal. Calcd for $C_{33}H_{50}O_4S$: C, 73.02; H, 9.28; S, 5.91. Found: C, 73.28; H, 9.42; S, 5.78%.

(*S*$_S$,2*S*,3*S*,4*R*,5*S*)-2,4-Dimethyl-1-phenylsulfinyloctadecane-3, 5-diol and (*S*$_R$, 2*S*, 3*S*, 4*R*, 5*S*)-2, 4-dimethyl-5-phenylsulfinyloctadecane-3,5-diol 18; (*S*$_S$,2*S*,3*S*,4*R*,5*R*)-2,4-dimethyl-1-phenylsulfinyloctadecane-3,5-diol and (*S*$_R$,2*S*,3*S*,4*R*,5*R*)-2,4-dimethyl-5-phenylsulfinyloctadecane-3,5-diol 19. To the solution of compound **16** and **17** (54 mg, 0.1 mmole) in MeOH (0.5 mL) was added K_2CO_3 (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; ^{1}H NMR (300 MHz, $CDCl_3$): 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, 44 H), 1.10-1.06 (m, 6H), 0.99 (d, *J*=6.8 Hz, 3H),

0.91-0.86 (m, 6H); Anal. Calcd for $C_{26}H_{46}O_3S$: C, 71.18; H, 10.57; S, 7.31. Found: C, 71.26; H, 10.32; S, 7.20%.

(*S*$_S$, 4*S*, 5*R*, 6*S*)-2, 2, 5-Trimethyl-4-[1-methyl-2-phenylsulfinyl-(1*S*)-ethyl]-6-tridecyl-1,3-dioxane and (*S*$_R$,4*S*,5*R*,6*S*)-2,2,5-trimethyl-4-[1-methyl-2-phenylsulfinyl-(1*S*)-ethyl]-6-tridecyl-1,3-dioxane 20; (*S*$_S$, 4*S*,5*R*,6*R*)-2,2,5-trimethyl-4-[1-methyl-2-phenylsulfinyl-(1*S*)-ethyl]-6-tridecyl-1,3-dioxane and (*S*$_R$, 4*S*, 5R,6R)-2,2,5-trimethyl-4-[1-methyl-2-phenylsulfinyl-(1*S*)-ethyl]-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_3N 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, $CDCl_3$): δ 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), 2.35 (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 (d, *J*=6.8 Hz, 3H), 0.70 (d, *J*=6.8 Hz, 3H); Anal. Calcd for $C_{29}H_{50}O_3S$: C, 72.75; H, 10.53; S, 6.70. Found: C, 72.58; H, 10.20; S, 6.58%.

(2*R*, 3*R*, 4*R*)-3-Benzoyloxy-5-*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_3N (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 $NaHCO_3$ (1.25 g, 15 mmoles) in water (3 mL) was added to the reaction mixture at 0^o C followed by solid $NaBH_4$ (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, $CDCl_3$): δ 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 (s, 9H), –0.04 (s, 3H) , –0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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, $CHCl_3$). Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.68; H, 9.20%.

(2*R*, 3*R*, 4*R*)-3-Benzoyloxy-5-*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 TBDPS-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_2SO_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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CHCl_3$). Anal. Calcd for $C_{36}H_{52}O_4Si_2$: C, 71.47; H, 8.66. Found: C, 71.60; H, 8.42%.

(2*R*, 3*S*, 4*R*)-3-Benzoyloxy-5-*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^{o}C for 12 hr and quenched by the addition of Et_3N (5 μL). 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, $CDCl_3$): δ 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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; $[\alpha]_D^{25}$ + 13.7 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{30}H_{38}O_4Si$: C, 73.43; H, 7.81. Found: C, 73.60; H, 7.60%.

(2*R*, 3*R*, 4*R*)-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. $NaHSO_3$ solution. The aq. layer was extracted with DCM and the combined organic layers washed with aq. saturated $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the product **25** (117 mg, 0.24 mmole) in 90% yield which was taken ahead to the next step without further purification. Viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.89 (d, *J*=7.4 Hz, 2H), 7.65-7.12 (m, 13H), 5.65 (dd, *J*=8.2, 3.7 Hz, 1H), 3.63-3.55 (m, 2H), 2.86-2.74 (m, 1H), 2.20-2.08 (m, 1H), 1.10 (d, *J*=6.7 Hz, 3H), 1.08-0.94 (m, 12H); MS (FAB): 303, 199, 135, 105, 69, 55.

(2*R*,3*R*,4*R*,5*S*)-3-Benzoyloxy-1-*tert*-butyldiphenylsilyloxy-2,4-dimethyloctadecane-5-ol 26. To the solution of compound **25** (117 mg, 0.24 mmole) in toluene (1.2 mL) cooled at –78°C was added tridecylmagnesium bromide (1 M in THF, 0.36 mL, 0.36 mmole). The reaction mixture was stirred at –78°C for 10 min and quenched by the addition of aq. saturated NH_4Cl solution. The aq. layer was extracted with ether and the combined organic layers washed with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 15% EtOAc-petroleum ether (v/v) as the eluent to afford product **26** (134 mg, 0.2 mmole) in 85% yield as viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (d, *J*=7.3 Hz, 2H), 7.70-7.53 (m, 5H), 7.50-7.18 (m, 8H), 5.30 (dd, *J*=7.3, 3.7 Hz, 1H), 3.70-3.50 (m, 3H), 2.25-2.12 (m, 1H), 2.0-1.86 (m, 1H), 1.43-1.42 (m, 4H), 1.28 (bs, 20H), 1.10-1.05 (m, 12H), 0.98-0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.63, 135.57, 133.52, 133.34, 132.84, 130.32, 129.63, 129.55, 129.50, 128.32, 127.57, 127.53, 77.69, 73.94, 65.03, 39.56, 38.29, 34.93, 31.92, 29.66, 29.35, 26.80, 26.13, 22.68, 19.17, 14.47, 14.11, 8.26; MS (FAB): 673, 656, 493, 473, 303, 199, 135, 105, 55; $[\alpha]_D^{25}$ –1.6 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{43}H_{64}O_4Si$: C, 76.74; H, 9.58. Found: C, 76.92; H, 9.65%.

(2*R*, 3*R*, 4*R*, 5*S*)-1-*tert*-Butyldiphenylsilyloxy-2, 4-dimethyloctadecane-3,5-diol 27. To the solution of compound **26** (100 mg, 0.15 mmole) in toluene (0.2 mL) at –78°C was added DIBAL-H (1.8 M in toluene, 0.18 mL, 0.32 mmole). The reaction mixture was stirred at –78°C for 30 min and quenched by the addition of MeOH (0.1 mL). The reaction mixture was diluted with ether (5 mL) and allowed to attain r.t. and stirred until white precipitate was observed. The reaction mixture was filtered through a small pad of celite and the filtrate evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 10% EtOAc-petroleum ether (v/v) as the eluent to give the diol **27** (73 mg, 0.13 mmole) in 85% yield as viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70-7.56 (m, 4H), 7.45-7.30 (m, 6H), 3.83-3.79 (m, 1H), 3.76 (dd, *J*=9.1, 1.2 Hz, 1H), 3.70 (dd, *J*=9.1, 3.9 Hz, 1H), 3.65-3.52 (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); $[\alpha]_D^{25}$ +39.0 (*c* 0.25, $CHCl_3$). Anal. Calcd for $C_{36}H_{60}O_4Si$: C, 76.0; H, 10.63. Found: C, 76.32; H, 10.42%.

(4*R*, 5*R*, 6*S*)-4-[2-*tert*-Butyldiphenylsilyloxy-1-methyl-(1*R*)-ethyl]-2,2,5-trimethyl-6-tridecyl-1,3-dioxane 28. To the solution of diol **27** (56 mg, 0.1 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 Et_3N 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 acetonide **28** (54 mg, 0.09 mmole) in 90% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71-7.60 (m, 4H), 7.45-7.30 (m, 6H), 3.90-3.70 (m, 3 H), 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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; $[\alpha]_D^{25}$ – 6.2 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{39}H_{64}O_3Si$: C, 76.92; H, 10.59.Found: C, 76.78; H, 10.32%.

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