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Asymmetric synthesis of (−)-tetrahydrolipstatin

Sadagopan Raghavan *, Kailash Rathore

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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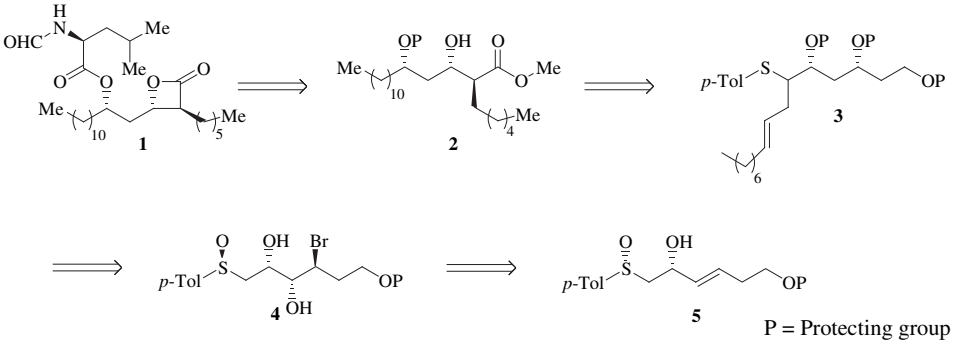
ABSTRACT

Attempts toward the asymmetric synthesis of (−)-tetrahydrolipstatin are described. A palladium catalyzed Wacker-type reaction to convert an alkene to a ketone, highly diastereoselective reduction of a β-hydroxy ketone, selective oxidation of a diol, and modular synthesis are the key features of the successful approach.

1. Introduction

Tetrahydrolipstatin (THL) **1**, a β-lactone antibiotic of microbial origin,[1] functions as a potent and irreversible inhibitor of pancreatic lipase. It is currently marketed as an anti-obesity drug under the trade name of Xenical.® The biological activity is due to the *trans* substituted β-lactone, which reacts with serine hydroxy group to form an ester bond in the active site of pancreatic lipase, thereby slowing down the hydrolysis of triglycerides and absorption of dietary fat by the small intestine.[2] THL possesses a β-lactone moiety derived from 5-substituted-3,5-dihydroxy-2-hexylpentanoic acid having *S*,*S*,*S* absolute configuration. In view of the interesting structure and important biological activity in vivo, a number of groups have reported the total synthesis of THL by a variety of synthetic strategies.[3]

We report herein in full,[4] our efforts toward the total synthesis of **1**. The disconnective analysis shown in Scheme 1 is based on utilizing the sulfinyl group in **5** as an intramolecular nucleophile to prepare bromohydrin **4**. Epoxide formation, hydroxyl directed opening of epoxide followed by Pummerer and ene reactions would yield triol derivative **3**. The primary hydroxyl group in **3** can be oxidized to the carboxylic acid and subsequent transformations following previously established protocol would afford THL.[3] Our strategy differs from earlier approaches in that the sulfoxide



Scheme 1.

* Corresponding author.
E-mail address: sraghavan@iict.res.in (S. Raghavan).

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chirality was to be utilized to introduce the allylic stereogenic center and this in turn another stereocenter by asymmetric induction.

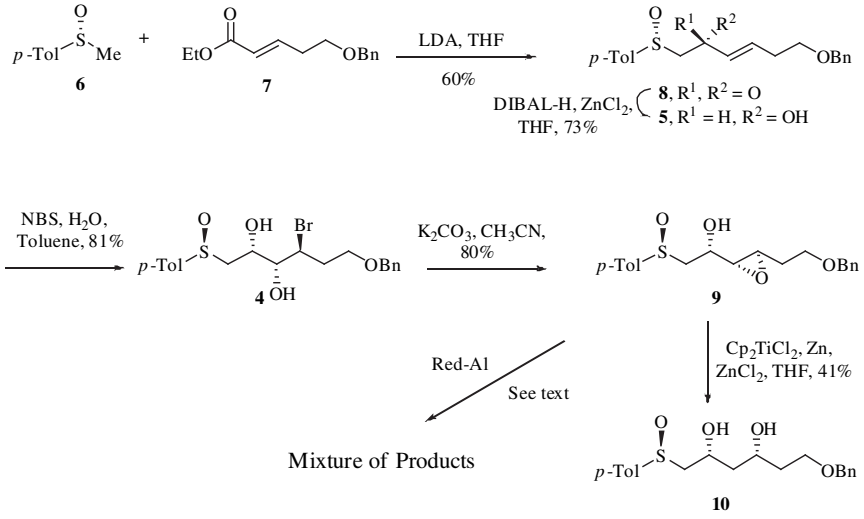
2. Results and discussion

The synthesis began with the reaction of the organolithium reagent derived from (*R*)-methyl *p*-tolyl sulfoxide[5] **6** with unsaturated ester[6] **7** to furnish β-keto sulfoxide **8**.[7] Diastereoselective reduction of **8** following Solladie's protocol[8] using DIBAL-H in the presence of anhydrous zinc chloride yielded the allylic alcohol **5** (P=OBn, dr >95:<5). Treatment of **5** with freshly recrystallized *N*-bromosuccinimide[9] (NBS) afforded bromohydrin **4** (P=OBn) as a single isomer regio- and stereoselectively. We envisioned the transformation of the 1,2-diol **4** to the 1,3-diol derivative **10**, by epoxide formation followed by hydroxyl directed reduction of the epoxide using Red-Al.[10] Thus treatment of **4** with anhydrous potassium carbonate in dry acetonitrile yielded epoxide **9**. The reduction of **9** using Red-Al in anhydrous THF was complicated due to the competitive reduction of the sulfinyl moiety. The reduction was non-chemoselective when attempted in a variety of solvents and at different temperatures. While exploring other reducing agents, it was observed that titanocene(III) chloride[11] afforded the 1,3-diol **10** cleanly though the isolated yield was poor, Scheme 2.[12,13]

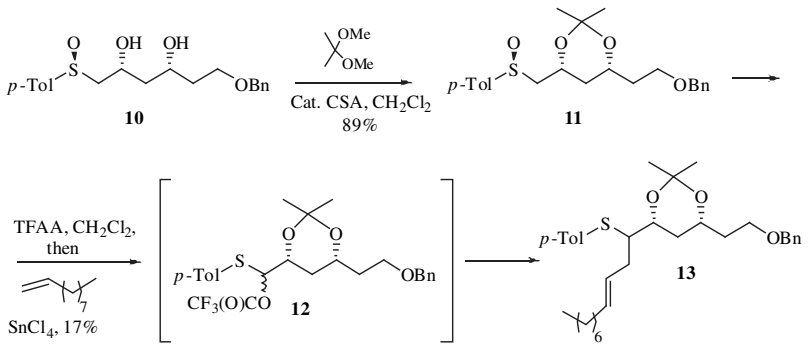
treatment of **10** with excess of 2,2-dimethoxypropane in the presence of catalytic amounts of CSA afforded acetonide **11**.[14] Subjecting acetonide **11** to Pummerer reaction in the presence of trifluoroacetic anhydride cleanly afforded the Pummerer intermediate **12**, which without isolation was allowed to react with an excess of 1-decene in the presence of stoichiometric amount of anhydrous $SnCl_4$.[15] A complex mixture of products resulted from which the desired product **13** could be isolated in poor yields only, Scheme 3.

Since we had encountered difficulties in the reduction of epoxy alcohol **9** and Pummerer followed by ene reaction on **11**, we chose to explore an alternate strategy wherein the decyl side chain would be introduced at the initial stages of the synthesis. According to the retrosynthetic plan depicted in Scheme 4, we decided to introduce the decyl chain by alkylation of the dianion derived from **16** and subject the resulting product **15** to further transformations.

Methyl phenyl sulfoxide[5] was chosen instead of methyl *p*-tolyl sulfoxide to avoid the potential deprotonation of the aromatic methyl group by the second equivalent of the base, instead of the methylene protons directly bonded to sulfur,[16] after the first equivalent of the base has abstracted the hydroxyl proton. In addition, 4-methoxy benzyl was chosen in lieu of the benzyl group (compare with **5**) to differentiate the secondary hydroxy groups in



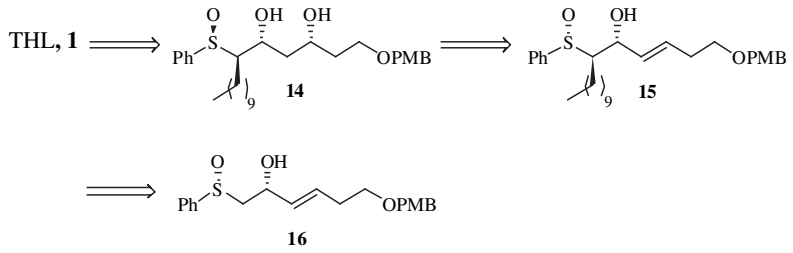
Scheme 2.



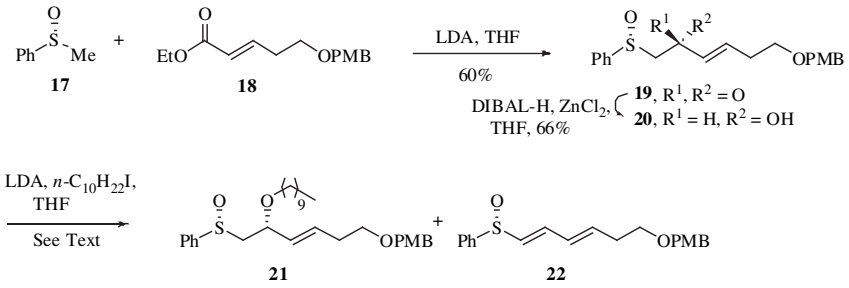
Scheme 3.

Proceeding ahead, setting aside the issue of improving the yield in the titanocene mediated reduction to be addressed later, the diol **10** was protected as its acetonide to attempt the one-pot Pummerer followed by ene reaction to introduce the *n*-decyl side chain. Thus

14 by intramolecular acetal formation. The β-hydroxy sulfoxide **20**, prepared in a fashion analogous to **5**, was subjected to treatment with excess of LDA (3.5 equiv) and subsequently with 1-decyl iodide. A mixture of products was isolated in addition to recovered



Scheme 4.



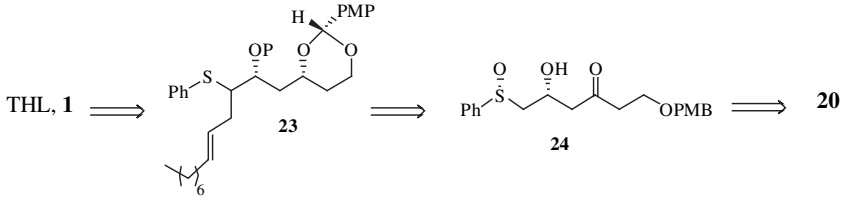
Scheme 5.

unreacted starting material. The crude ^{1}H NMR spectrum indicated the presence of *O*-allylated product **21** and the diene sulfoxide **22** along with unreacted starting material, Scheme 5. The result was not better using methyl lithium,[17] other bases (LiHMDS), varying the temperature, and in the presence of additives (HMPA, TMEDA).

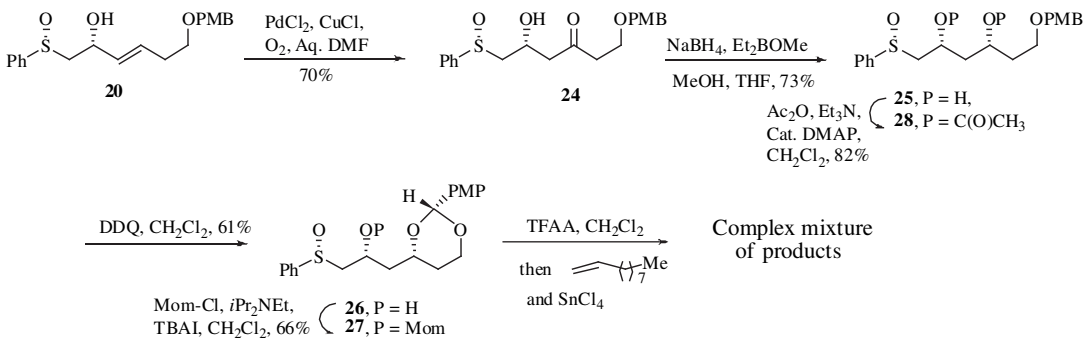
Having been unsuccessful in introducing the side chain, we were forced to explore an alternate route to tetrahydrolipstatin. At this juncture, we chose to exploit the Wacker-type reaction[18] to prepare β-hydroxy ketones from allylic alcohols in a key step of THL synthesis. As illustrated in the retrosynthetic design, Scheme 6, we planned hydroxyl directed reduction of the keto group and introduction of the decyl side chain by Pummerer ene reaction.

The β-hydroxy sulfoxide **20** was subjected to palladium catalyzed oxidative functionalization using a protocol recently reported by us[19] to furnish β-hydroxy ketone **24**. Stereoselective reduction[20] of **24** using sodium borohydride in the presence of diethylmethoxyborane afforded 1,3-diol **25** (>95:<5 dr). Treatment of **25** with DDQ[21] in anhydrous dichloromethane yielded the 4-methoxy benzylidene acetal **26**. The hydroxy group in **26** was protected as its Mom-ether **27** by treatment with Mom-Cl in the presence of Hunig's base. Attempted one-pot Pummerer ene reaction afforded once again a complex mixture of products, Scheme 7.

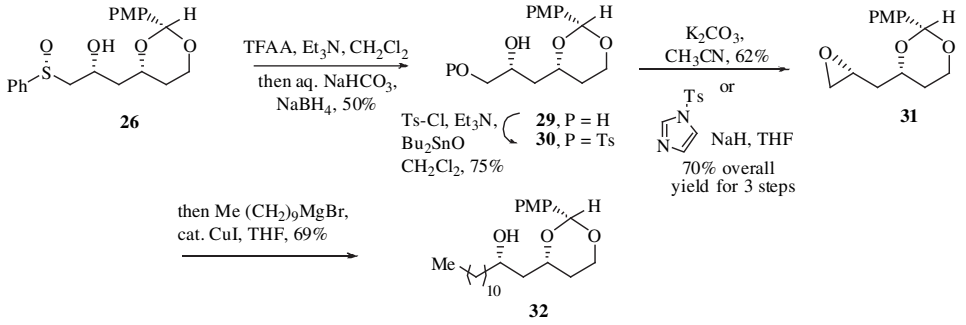
The diol **25** was converted to diacetate **28** and subjected to the Pummerer ene reaction to yield a complex mixture of products. We have earlier successfully executed[15a,22] the Pummerer ene reaction on 1,2-acetonides to prepare key intermediates en route to the synthesis of target molecules. We believe the reason for our failure is due to the competitive activation of the oxygens in 1,3-acetonide **11**, the acetal **27**, and the 4-methoxy benzyl group in **28** leading to many side reactions. Thus again we were unable to introduce the decyl



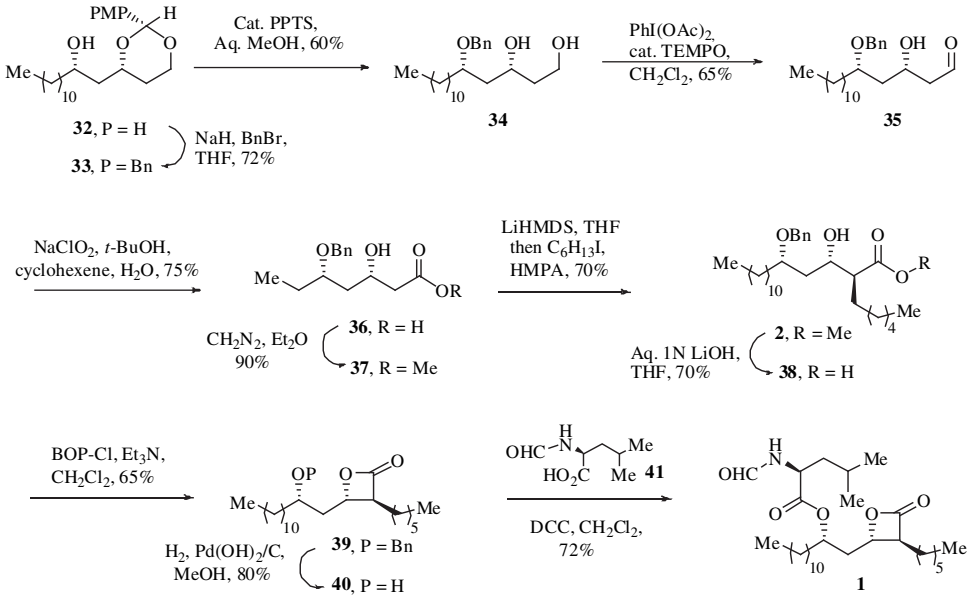
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

side chain using the sulfinyl moiety as the handle. The decyl chain was introduced by a different strategy. β-Hydroxy sulfoxide **26** was subjected to Pummerer reaction to afford an intermediate, which without isolation was transformed to alcohol **29** in an one-pot operation by treatment with saturated aq $NaHCO_3$ followed by sodium borohydride. The diol **29** was selectively monotosylated using *p*-toluenesulfonyl chloride in the presence of Et_3N and dibutyltin oxide[23] to furnish tosylate **30**, which on treatment with anhydrous potassium carbonate in acetonitrile yielded the epoxide **31**. This on treatment with an excess of decylmagnesium bromide in the presence of catalytic quantities of CuI yielded the alcohol **32**. The alcohol **32** was more conveniently prepared in an one-pot operation following the Forsyth protocol.[24] Thus diol **29** on treatment with tosyl imidazole using sodium hydride as the base furnished epoxide **31**, which without isolation was reacted with an excess of decylmagnesium bromide as before to furnish **32**, Scheme 8.

The alcohol **32** was protected as its benzyl ether **33** by treatment with sodium hydride and benzyl bromide. Deprotection of the acetal group using PPTS in methanol yielded the diol **34**. Selective oxidation of the primary hydroxy group using iodobenzene diacetate and catalytic TEMPO[25] yielded aldehyde **35**. Oxidation of **35** using the Pinnick protocol[26] cleanly afforded the acid **36**, which was converted to the methyl ester **37** using ethereal diazomethane. Frater–Seebach alkylation[27] of **37** with hexyl iodide using LiHMDS as the base proceeded cleanly to afford the mono alkylated product **2** (P=Bn). Hydrolysis of the ester using aq LiOH yielded the acid **38**, which was converted to the β-lactone **39** using BOP-Cl[28] in the presence of Et_3N, Scheme 9. Hydrogenolysis of the benzyl ether afforded the alcohol **40**, which was coupled[29] to *N*-formyl leucine **41** using reported conditions to furnish tetrahydrolipstatin **1**. The physical data of **1** were in full agreement to those reported in the literature.[3b]

3. Conclusion

In summary, we have shown a chemoselective reduction of an epoxide in the presence of a sulfinyl group using the titanocene reagent. We were unable to introduce the decyl side chain by a Pummerer ene reaction on a 1,3-acetonide and 4-methoxy benzyl group containing substrates. The synthesis of tetrahydrolipstatin was successfully accomplished taking advantage of the Wacker-type oxidative functionalization reaction. The sulfur chirality has been used initially to introduce the hydroxy stereogenic center and the other centers have been introduced sequentially by substrate control.

4. Experimental

4.1. General remarks

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were distilled over Na/benzophenone ketyl for THF, over P_2O_5 followed by CaH_2 for DCM, and over P_2O_5 for toluene. Commercially available reagents were used without purification except NBS, which was freshly recrystallized from hot water

before use. Thin layer chromatography was performed on 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. ^{1}H and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

*4.1.1. (E)-6-(Benzyloxy)-1-(Rs)-(p-tolylsulfinyl)hex-3-en-2-one [**8**].* To a solution of LDA (0.08 M in solvents, 52.5 mmol) prepared from diisopropylamine (7.7 mL, 55 mmol) and *n*-BuLi (1.6 M in hexane, 32.8 mL, 52.5 mmol) cooled at −40 °C was added a solution of (*R*)-methyl *p*-tolyl sulfoxide **6** (3.85 g, 25 mmol) in anhydrous THF (330 mL) and stirred at the same temperature for 30 min. The reaction mixture was gradually allowed to warm to 0 °C and a solution of the unsaturated ester **7** (5.85 g, 25 mmol) in THF (70 mL) was added dropwise and stirred further for a period of 1 h. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (150 mL) and the pH adjusted to 2 by the addition of 5% aqueous H_2SO_4 solution. The two layers were separated and the aqueous phase extracted with Et_2O (3×70 mL). The combined organic layers were washed with water (120 mL), saturated brine (120 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude product, which was purified by column chromatography using 8% EtOAc/$CHCl_3$ (v/v) as the eluent to afford the β-keto sulfoxide **8** (5.01 g, 15 mmol) in 60% yield as a viscous yellow oil; TLC, R_f (60% EtOAc/hexane) 0.42; $[\alpha]_D$ +81.5 (*c* 1.65, $CHCl_3$); ν_{max} (KBr) 2922, 2859, 1723, 1662, 1625, 1492, 1452, 1363, 1284, 1177, 1088, 1044, 810, 742, 699, 504 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.50 (d, *J*=7.9 Hz, 2H), 7.36–7.20 (m, 7H), 6.83 (td, *J*=6.4, 15.9 Hz, 1H), 6.15 (dd, *J*=1.5, 15.9 Hz, 1H), 4.49 (s, 2H), 4.00 (d, *J*=13.2 Hz, 1H), 3.81 (d, *J*=13.2 Hz, 1H), 3.55 (t, *J*=6.4 Hz, 2H), 2.50 (q, *J*=6.4 Hz, 2H), 2.41 (s, 3H); δ_C (75 MHz, $CDCl_3$) δ 190.5, 147.9, 141.9, 137.8, 131.4, 129.9, 128.3, 127.5, 124.1, 123.4, 72.9, 67.8, 66.3, 32.9, 21.2; *m*/*z* (ESI) 343 $[M+H]^+$; HRMS (ESI): $[M+H]^+$ found 343.1354. $C_{20}H_{23}O_3S$ requires 343.1367.

*4.1.2. (2R,E)-6-(Benzyloxy)-1-(Rs)-(p-tolylsulfinyl)hex-3-en-2-ol [**5**].* To a solution of anhydrous zinc chloride (2.45 g, 18 mmol) in THF (100 mL) maintained at ambient temperature was added a solution of the β-keto sulfoxide **8** (5.01 g, 15 mmol) in anhydrous THF (50 mL) and the mixture stirred for 15 min. The reaction mixture was cooled to −78 °C and a solution of DIBAL-H (1.4 M in toluene, 16 mL, 22.4 mmol) was added dropwise over a period of 10 min. After 2 h of stirring at the same temperature, methanol (15 mL) was added and the reaction mixture allowed to warm to rt. The solvent was evaporated under reduced pressure and the residue was treated with 5% aqueous HCl solution (50 mL). The aqueous layer was extracted into CH_2Cl_2 (3×70 mL), the organic layer washed once with 5% aqueous NaOH solution (25 mL), saturated brine (25 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the crude product, which was purified by column chromatography using 45% EtOAc/hexane (v/v) as the eluent to afford the allyl alcohol **5** (3.68 g, 11 mmol) as a single diastereomer in 73% yield as white crystals. Mp 74–75 °C; TLC, R_f (60% EtOAc/hexane) 0.35; $[\alpha]_D$ +70.3 (*c* 2.6, $CHCl_3$); ν_{max} (KBr) 3338, 3032, 2899, 2856, 1596, 1492, 1447, 1406, 1364, 1305, 1115, 1009, 811, 735, 699, 623, 499, 455 cm^{-1}; δ_H (400 MHz, $CDCl_3$) δ 7.51 (d, *J*=8.7 Hz, 2H), 7.32–7.18 (m, 7H), 5.77 (td, *J*=7.1, 15.8 Hz, 1H), 5.53 (dd, *J*=6.3, 15.8 Hz, 1H), 4.65–4.56 (m, 1H), 4.45 (s, 2H), 3.46 (t, *J*=7.1 Hz, 2H), 3.01 (dd, *J*=8.7, 13.4 Hz, 1H), 2.73 (dd, *J*=3.9, 13.4 Hz, 1H), 2.42 (s, 3H), 2.32 (q, *J*=7.1 Hz, 2H); δ_C (75 MHz, $CDCl_3$) δ 141.6, 140.3, 138.1, 131.9, 129.9, 129.3, 128.1, 127.4, 127.3, 123.9, 72.6, 69.2, 68.6, 63.2, 32.3, 21.2; *m*/*z* (ESI) 345 $[M+H]^+$; HRMS (ESI): $[M+H]^+$ found 345.1531. $C_{20}H_{25}O_3S$ requires 345.1524.

*4.1.3. (2R,3R,4S)-6-(Benzyloxy)-4-bromo-1-(Ss)-(p-tolylsulfinyl)hexane-2,3-diol [**4**].* To a solution of the allylic alcohol **5** (3.68 g, 11 mmol) in dry toluene (55 mL) was added water (295 μL, 16.4 mmol) followed by *N*-bromosuccinimide (2.34 g, 13.1 mmol) and the reaction mixture was stirred at room temperature for 15 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were successively washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using 45% EtOAc/hexane (v/v) as the eluent to afford bromohydrin **4** (3.93 g, 8.9 mmol) as the sole product in 81% yield as crystalline solid. Mp 112–113 °C; TLC, R_f (60% EtOAc/hexane) 0.35; $[\alpha]_D$ −104 (*c* 2.2, $CHCl_3$); ν_{max} (KBr) 3320, 2923, 2875, 1772, 1706, 1363, 1178, 1081, 1028, 1004, 805, 738, 694, 632, 504 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.53 (d, *J*=8.2 Hz, 2H), 7.35–7.23 (m, 7H), 4.66–4.58 (m, 1H), 4.51 (s, 2H), 4.37 (d, *J*=5.2 Hz, 1H), 4.35–4.29 (m, 1H), 3.75–3.67 (m, 1H), 3.67–3.59 (m, 1H), 3.23 (dd, *J*=9.6, 13.4 Hz, 1H), 2.68 (dd, *J*=2.9, 13.4 Hz, 1H), 2.44 (s, 3H); δ_C (75 MHz, $CDCl_3$) δ 141.7, 139.6, 137.7, 130.1, 128.4, 127.7, 124.0, 76.4, 73.3, 67.3, 66.1, 60.8, 52.7, 34.3, 21.4; *m*/*z* (FAB) 441 $[M+H]^+$; HRMS (FAB): $[M+H]^+$ found 441.0721. $C_{20}H_{26}BrO_4S$ requires 441.0735.

*4.1.4. (R)-1-{(2R,3R)-3-[2-(Benzyloxy)ethyl]oxiran-2-yl}-2-(Ss)-(p-tolylsulfinyl)ethanol [**9**].* Anhydrous K_2CO_3 (1.35 g, 9.8 mmol) was added to a solution of bromohydrin **4** (3.93 g, 8.9 mmol) in dry acetonitrile (90 mL) cooled at 0 °C. The reaction mixture was then allowed to warm to rt over a period of 15 min and stirred further for 8 h, when TLC examination revealed complete conversion of starting material. Ether (60 mL) was then added to the reaction mixture and after 10 min the precipitated solids were filtered through a plug of Celite. The filtrate was evaporated to afford the crude product, which was purified by column chromatography using 50% EtOAc/hexane (v/v) as the eluent to afford epoxy alcohol **9** (2.57 g, 7.1 mmol) in 80% yield as a white crystalline solid. Mp 86–88 °C; TLC, R_f (60% EtOAc/hexane) 0.32; $[\alpha]_D$ −18.8 (*c* 2.5, $CHCl_3$); ν_{max} (KBr) 3292, 3030, 2924, 2864, 1710, 1367, 1243, 1110, 1031, 811, 737, 698 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.49 (d, *J*=8.4 Hz, 2H), 7.35–7.21 (m, 7H), 4.46 (s, 2H), 4.16–4.09 (m, 1H), 3.54 (t, *J*=5.3 Hz, 2H), 3.47–3.42 (m, 1H), 3.05–3.01 (m, 1H), 3.00 (dd, *J*=9.1, 12.9 Hz, 1H), 2.79–2.75 (m, 1H), 2.69 (dd, *J*=2.3, 12.9 Hz, 1H), 2.44 (s, 3H), 1.87–1.75 (m, 2H); δ_C (75 MHz, $CDCl_3$) δ 141.6, 139.9, 138.1, 130.0, 128.3, 127.7, 127.5, 123.9, 73.0, 66.7, 65.8, 60.6, 60.3, 53.8, 31.8, 21.3; *m*/*z* (FAB) 361 $[M+H]^+$; HRMS (FAB): $[M+H]^+$ found 361.1464. $C_{20}H_{25}O_4S$ requires 361.1473.

*4.1.5. (2R,4R)-6-(Benzyloxy)-1-(Ss)-(p-tolylsulfinyl)hexane-2,4-diol [**10**].* To a mixture of Cp_2TiCl_2 (2.65 g, 10.6 mmol) and activated Zn-powder (1.39 g, 21.3 mmol) in dry THF (100 mL) at ambient temperature was added freshly fused anhydrous $ZnCl_2$ (1.47 g, 10.6 mmol) in one portion and stirred for 1 h. While stirring color of the reaction mixture gradually changed from red to dark green. It was then cooled to −23 °C and a solution of epoxy alcohol **9** (2.57 g, 7.1 mmol) in dry THF (100 mL) was added slowly. The reaction mixture was warmed to 0 °C and the stirring continued for an additional 6 h. The reaction mixture was then quenched by the slow addition of saturated aqueous NH_4Cl solution (50 mL). The layers were separated and the aqueous layer extracted with ether (3×30 mL). The combined organic layer was washed with 1 N aqueous HCl solution (20 mL), water (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), saturated brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude product, which was purified by column chromatography using 55% EtOAc/hexane (v/v) as the eluent to furnish the desired 1,3-diol **10** (1.06 g, 2.9 mmol) in 41% yield as a crystalline solid. Mp 70–73 °C; TLC, R_f (60% EtOAc/hexane) 0.22; $[\alpha]_D$ −118 (*c* 0.8, $CHCl_3$); ν_{max} (KBr) 3308, 3029, 2917, 2865, 2358, 1597, 1447, 1327, 1108, 1035, 848, 734, 697, 459 cm^{-1}; δ_H (200 MHz, $CDCl_3$): δ 7.51 (d, *J*=8.1 Hz, 2H), 7.36–7.25 (m, 7H), 4.73–4.65 (br s, 1H), 4.50 (s, 2H),

4.45 (t, J=9.5 Hz, 1H), 4.09 (t, J=9.5 Hz, 1H), 3.94–3.79 (br s, 1H), 3.71–3.58 (m, 2H), 2.97 (dd, J=9.5, 13.2 Hz, 1H), 2.66 (dd, J=2.2, 13.2 Hz, 1H), 2.44 (s, 3H), 1.83–1.61 (m, 4H); δ_C (75 MHz, $CDCl_3$) δ 141.5, 140.2, 137.8, 130.1, 128.5, 127.8, 127.7, 124.0, 73.4, 71.1, 68.5, 66.9, 63.4, 42.9, 36.9, 21.4; m/z (FAB) 363 $[M+H]^+$; HRMS (FAB): $[M+H]^+$ found 363.1620. $C_{20}H_{27}O_4S$ requires 363.1630.

*4.1.6. (4R,6R)-4-(2-(Benzyloxy)ethyl)-2,2-dimethyl-6-(Ss)-(p-tolylsulfinylmethyl)-1,3-dioxane [**11**].* To a stirred solution of diol **10** (1.06 g, 2.9 mmol) in dichloromethane (15 mL), were added 2,2-dimethoxypropane (1.8 mL, 14.6 mmol) and CSA (34 mg, 0.15 mmol) successively and the reaction mixture was stirred at rt for 6 h. Et_3N (0.03 mL, 0.21 mmol) was then added and the reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to furnish the acetonide **11** (1.05 g, 2.6 mmol) in 89% yield, as a crystalline solid. Mp 72–73 °C; TLC, R_f (40% EtOAc/hexane) 0.32; $[\alpha]_D$ −108 (c 1.43, $CHCl_3$); ν_{max} (KBr) 2926, 2860, 1451, 1383, 1264, 1094, 1022, 935, 809, 747, 698, 460 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.52 (d, J=7.4 Hz, 2H), 7.36–7.27 (m, 7H), 4.53–4.43 (m, 3H), 4.15–4.06 (m, 1H), 3.61–3.45 (m, 2H), 2.79–2.67 (m, 2H), 2.42 (s, 3H), 1.80–1.68 (m, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.35–1.23 (m, 2H); δ_C (75 MHz, $CDCl_3$) δ 141.6, 141.4, 138.5, 130.0, 128.4, 127.6, 124.0, 123.8, 99.3, 73.0, 66.0, 65.0, 63.6, 36.6, 36.5, 30.0, 21.0, 19.9; m/z (FAB) 403 $[M+H]^+$; HRMS (FAB): $[M+H]^+$ found 403.1936. $C_{23}H_{31}O_4S$ requires 403.1943.

*4.1.7. (4R,6R,E)-4-[2-(Benzyloxy)ethyl]-2,2-dimethyl-6-[1-(p-tolylthio)undec-2-enyl]-1,3-dioxane [**13**].* TFAA (91 μL, 0.65 mmol) was added to the solution of acetonide **11** (52 mg, 0.13 mmol) and 1-decene (49 μL, 0.26 mmol) in dichloromethane (65 μL) cooled at 0 °C and the mixture stirred for 30 min. To the above reaction mixture was added anhydrous $SnCl_4$ (26 μL, 0.15 mmol) dropwise and the mixture stirred for a further 15 min. The reaction mixture was quenched by the addition of saturated aqueous Na_2CO_3 solution (1 mL). The two layers were separated and the aqueous phase was extracted with dichloromethane (3×2 mL). The combined organic layers were washed successively with water (2 mL), saturated brine (2 mL) and dried over anhydrous Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was purified by column chromatography using 3% EtOAc/hexane (v/v) as the eluent to furnish the pure sulfide **13** (11 mg, 0.02 mmol) in 17% yield as a colorless oil; TLC, R_f (20% EtOAc/hexane) 0.82; δ_H (200 MHz, $CDCl_3$) δ 7.33–7.18 (m, 7H), 7.03 (d, J=8.1 Hz, 2H), 5.48–5.32 (m, 2H), 4.47 (s, 2H), 4.32–4.03 (m, 1H), 3.85–3.69 (m, 1H), 3.62–3.49 (m, 1H), 3.57–3.49 (m, 1H), 3.05–2.95 (m, 1H), 2.50–2.37 (m, 2H), 2.31 (s, 3H), 2.02–1.90 (m, 2H), 1.78–1.44 (m, 2H), 1.40 (s, 3H), 1.36–1.21 (br s, 11H), 0.93–0.85 (distorted t, 3H).

*4.1.8. (E)-6-(4-Methoxybenzyloxy)-1-(Rs)-(phenylsulfinyl)hex-3-en-2-one [**19**].* To a solution of LDA (0.08 M in solvents, 35 mmol) prepared from diisopropylamine (5.14 mL, 36.7 mmol) and n-BuLi (1.6 M in hexane, 21.9 mL, 35 mmol) cooled at −40 °C was added a solution of (*R*)-phenyl methyl sulfoxide **17** (2.33 g, 16.7 mmol) in anhydrous THF (220 mL) and stirred at the same temperature for 30 min. The reaction mixture was allowed gradually to warm to 0 °C and a solution of the unsaturated ester **18** (4.4 g, 16.7 mmol) in THF (45 mL) was added dropwise and stirred further for a period of 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and the pH adjusted to 2 by the addition of 5% aqueous H_2SO_4 solution. The two layers were separated and the aqueous phase extracted with Et_2O (3×50 mL). The combined organic layers were washed with water (80 mL), saturated brine (80 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude product, which was purified by column chromatography using 8% EtOAc/$CHCl_3$ (v/v) as the eluent to afford the β-keto sulfoxide **19** (3.58 g, 10 mmol) in 60% yield as a viscous yellow oil; TLC, R_f (10% EtOAc/$CHCl_3$) 0.25; $[\alpha]_D$ +51 (c 0.7, $CHCl_3$); ν_{max} (KBr) 2925, 2856, 2362, 1723, 1660, 1615, 1512, 1446, 1247, 1174, 1087, 1035, 820, 748, 692, 495 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.63–7.56 (m, 2H), 7.48–7.40 (m, 3H), 7.17 (d, J=8.1 Hz, 2H), 6.88–6.70 (m, 3H), 6.09 (td, J=1.5, 16.1 Hz, 1H), 4.37 (s, 2H), 4.04 (d, J=13.2 Hz, 1H), 3.81 (d, J=13.2 Hz, 1H), 3.73 (s, 3H), 3.46 (t, J=6.6 Hz, 2H), 2.42 (q, J=6.6 Hz, 2H); δ_C (75 MHz, $CDCl_3$) δ 190.6, 159.3, 148.3, 131.5, 130.0, 129.4, 124.2, 113.9, 72.8, 67.6, 66.5, 55.3, 33.1; m/z (ESI) 381 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 381.1132. $C_{20}H_{22}O_4NaS$ requires 381.1136.

*4.1.9. (2R,E)-6-(4-Methoxybenzyloxy)-1-(Rs)-(phenylsulfinyl)hex-3-en-2-ol [**20**].* To a solution of anhydrous zinc chloride (4.9 g, 36 mmol) in THF (200 mL) maintained at ambient temperature was added a solution of the β-keto sulfoxide **19** (10.74 g, 30 mmol) in anhydrous THF (100 mL) and the mixture stirred for 15 min. The reaction mixture was cooled to −78 °C and a solution of DIBAL-H (1.4 M in toluene, 32.2 mL, 45 mmol) was added dropwise over a period of 10 min. After 2 h of stirring at the same temperature, methanol (30 mL) was added and the reaction mixture allowed to warm to rt. The solvent was evaporated under reduced pressure and the residue was treated with 5% aqueous HCl solution (100 mL). The aqueous layer was extracted into CH_2Cl_2 (3×150 mL), the combined organic layers were washed once with aqueous 5% aqueous NaOH solution (50 mL), saturated brine (50 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the crude product, which was purified by column chromatography using 60% EtOAc/hexane (v/v) as the eluent to afford the allyl alcohol **20** (7.13 g, 19.8 mmol) as a single diastereomer in 66% yield as a viscous pale yellow oil; TLC, R_f (70% EtOAc/hexane) 0.32; $[\alpha]_D$ +62.6 (c 2.3, $CHCl_3$); ν_{max} (KBr) 3379, 2927, 2856, 1720, 1611, 1512, 1443, 1246, 1175, 1089, 1031, 820, 752, 692, 468 cm^{-1}; δ_H (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 2H), 7.55–7.46 (m, 3H), 7.18 (d, J=8.5 Hz, 2H), 6.79 (d, J=8.5 Hz, 2H), 5.79 (td, J=7.1, 15.6 Hz, 1H), 5.52 (dd, J=6.4, 15.6 Hz, 1H), 4.75–4.68 (m, 1H), 4.38 (s, 2H), 4.04 (d, J=13.2 Hz, 1H), 3.78 (s, 3H), 3.46 (t, J=6.4 Hz, 2H), 2.98 (dd, J=9.2, 12.8 Hz, 1H), 2.77 (dd, J=2.8, 12.8 Hz, 1H), 2.31 (q, J=6.4 Hz, 2H); δ_C (75 MHz, $CDCl_3$) δ 159.1, 143.8, 131.7, 131.3, 130.3, 129.8, 129.3, 129.2, 123.9, 113.7, 72.4, 69.2, 69.0, 62.8, 55.2, 32.5; m/z (ESI) 383 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 383.1287. $C_{20}H_{24}O_4NaS$ requires 383.1293.

*4.1.10. (5R)-5-Hydroxy-1-(4-methoxybenzyloxy)-6-(Rs)-(phenylsulfinyl)hexan-3-one [**24**].* A suspension of palladium(II)chloride (352 mg, 1.98 mmol) and copper(I)chloride (1.96 g, 19.8 mmol) in a mixture of *N*,*N*-dimethylformamide (DMF) and water (1:1, 20 mL) was stirred under an oxygen atmosphere for 1 h. A solution of allyl alcohol **20** (7.13 g, 19.8 mmol) in DMF and water (1:1, 10 mL) was added to the above reaction mixture and was stirred at 50 °C for 4 h. The reaction mixture was extracted with Et_2O (3×75 mL), washed successively with water (2×20 mL), saturated brine (20 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude product, which was purified by column chromatography using 60% EtOAc/hexane (v/v) as the eluent to furnish β-hydroxy ketone **24** (5.21 g, 13.9 mmol) in 70% yield as a viscous pale yellow oil; TLC, R_f (70% EtOAc/hexane) 0.15; $[\alpha]_D$ +84.9 (c 0.35, $CHCl_3$); ν_{max} (KBr) 3138, 2925, 2657, 1630, 1384, 1245, 1088, 1029, 754 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.67–7.59 (m, 2H), 7.56–7.48 (m, 3H), 7.16 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.8 Hz, 2H), 4.52 (quintet, J=5.9 Hz, 1H), 4.39 (s, 2H), 3.78 (s, 3H), 3.66 (t, J=5.9 Hz, 2H), 2.98–2.73 (m, 4H), 2.66 (t, J=5.9 Hz, 2H); δ_C (50 MHz, $CDCl_3$) δ 208.6, 159.3, 143.6, 131.3, 129.9, 129.4, 129.4, 124.0, 113.9, 77.0, 72.9, 64.7, 62.0, 55.3, 49.0, 43.7; m/z (ESI) 399 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 399.1240. $C_{20}H_{24}O_5NaS$ requires 399.1242.

*4.1.11. (2R,4R)-6-(4-Methoxybenzyloxy)-1-(Rs)-(phenylsulfinyl)-hexane-2,4-diol [**25**].* To a solution of β-hydroxy ketone **24** (5.21 g,

13.9 mmol) in THF (110 mL) cooled at −78 °C was added diethylmethoxyborane (1 M in THF, 15.4 mL, 15.4 mmol) followed by methanol (28 mL) and stirred for 30 min. Then solid sodium borohydride (577 mg, 15.3 mmol) was added in three portions and the mixture stirred for 2 h at the same temperature. The reaction was quenched using a mixture of pH 7 phosphate buffer (20 mL), methanol (30 mL), and 30% (w/v) hydrogen peroxide solution (10 mL). This mixture was allowed to warm to rt and stirred further at rt for 18 h. The organic solvent was evaporated in vacuo and the aqueous layer was extracted with Et_2O (3×75 mL). The combined organic layers were washed with saturated brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo yielded the crude product, which was purified by column chromatography using 65% EtOAc/hexane (v/v) as the eluent to afford the *syn* 1,3-diol **25** (3.82 g, 10.1 mmol) in 73% yield as a viscous colorless oil; TLC, R_f (70% EtOAc/hexane) 0.22; $[\alpha]_D$ +56 (*c* 2.25, $CHCl_3$); ν_{max} (KBr) 3386, 2923, 2856, 2362, 1611, 1512, 1441, 1303, 1246, 1175, 1088, 1030, 820, 753, 691, 503 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2H), 7.55–7.46 (m, 3H), 7.18 (d, *J*=8.3 Hz, 2H), 6.82 (d, *J*=8.3 Hz, 2H), 4.41 (s, 2H), 4.36–4.24 (m, 1H), 3.78 (s, 3H), 3.69–3.53 (m, 3H), 3.03 (dd, *J*=7.6, 12.8 Hz, 1H), 2.80 (dd, *J*=4.5, 12.8 Hz, 1H), 1.86–1.62 (m, 4H); δ_C (75 MHz, $CDCl_3$) δ 159.4, 143.9, 131.2, 129.8, 129.4, 124.1, 113.9, 77.0, 73.1, 71.5, 68.4, 63.4, 55.3, 42.7, 29.7; *m*/*z* (ESI) 401 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 401.1405. $C_{20}H_{26}O_5NaS$ requires 401.1398.

*4.1.12. (R)-1-[(2R,4R)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]-3-(Rs)-(phenylsulfinyl)propan-2-ol [**26**].* DDQ (2.53 g, 11.1 mmol) was added portionwise over a period of 10 min to a solution of diol **25** (3.82 g, 10.1 mmol) in anhydrous CH_2Cl_2 (55 mL) cooled at 0 °C under nitrogen atmosphere and stirred at the same temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and the precipitated solid was filtered off. The filtrate was washed successively with aqueous saturated $NaHCO_3$ solution (2×30 mL), water (30 mL), saturated brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude product, which was purified by column chromatography using 60% EtOAc/hexane (v/v) as the eluent to yield acetal **26** (2.32 g, 6.2 mmol) in 61% yield as a viscous colorless oil; TLC, R_f (70% EtOAc/hexane) 0.32; $[\alpha]_D$ +34.4 (*c* 1.4, $CHCl_3$); ν_{max} (KBr) 3386, 2924, 2857, 1614, 1515, 1444, 1389, 1254, 1091, 1025, 802, 757, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.53–7.47 (m, 3H), 7.24 (d, *J*=9.1 Hz, 2H), 6.77 (d, *J*=9.1 Hz, 2H), 5.42 (s, 1H), 4.47–4.37 (m, 1H), 4.24 (dd, *J*=4.5, 11.3 Hz, 1H), 4.2–4.11 (m, 1H), 3.93 (dt, *J*=2.3, 11.3 Hz, 1H), 3.78 (s, 3H), 3.06 (dd, *J*=7.6, 12.8 Hz, 1H), 2.89 (dd, *J*=3.8, 12.8 Hz, 1H), 2.04–1.78 (m, 4H); δ_C (75 MHz, $CDCl_3$) δ 160.0, 143.9, 131.2, 130.9, 129.4, 127.2, 124.0, 113.6, 101.0, 75.5, 66.9, 66.8, 63.3, 55.3, 42.1, 31.2; *m*/*z* (ESI) 399 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 399.1247. $C_{20}H_{24}O_5NaS$ requires 399.1242.

*4.1.13. (2R,4R)-4-[(R)-2-(Methoxymethoxy)-3-(Rs)-(phenylsulfinyl)-propyl]-2-(4-methoxyphenyl)-1,3-dioxane [**27**].* To a solution of the acetal **26** (121 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C were added diisopropylethyl amine (167 μL, 0.96 mmol), TBAI (2 mg), and Mom-Cl (48 μL, 0.64 mmol) successively and the mixture stirred for 6 h at ambient temperature. The reaction mixture was then quenched with water (2 mL) and the aqueous phase was extracted into CH_2Cl_2 (2×5 mL). The combined organic extracts were washed with saturated brine (3 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by column chromatography using 10% EtOAc/$CHCl_3$ (v/v) as the eluent to afford the Mom-ether **27** (88 mg, 0.21 mmol) in 66% yield as a viscous colorless oil; TLC, R_f (50% EtOAc/$CHCl_3$) 0.51; $[\alpha]_D$ +26 (*c* 0.53, $CHCl_3$); ν_{max} (KBr) 3413, 2925, 2853, 1727, 1443, 1253, 1028, 753 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.67–7.59 (m, 2H), 7.55–7.46 (m, 3H), 7.19 (d, *J*=9.1 Hz, 2H), 6.79 (d, *J*=9.1 Hz, 2H), 5.36 (s, 1H), 4.56 (s, 2H), 4.05–3.85 (m, 1H), 3.79 (s, 3H), 3.75–3.64 (m, 2H), 3.64–3.54 (m, 1H), 3.32 (s, 3H), 3.24 (dd, *J*=6.0, 12.8 Hz, 1H), 2.89 (dd, *J*=6.0, 12.8 Hz, 1H), 1.91–1.74 (m, 2H), 1.70–1.50 (m, 2H); *m*/*z* (ESI) 443 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 443.1500. $C_{22}H_{28}O_6NaS$ requires 443.1504.

*4.1.14. (2R,4R)-6-(4-Methoxybenzyloxy)-1-(Rs)-(phenylsulfinyl)-hexane-2,4-diyl diacetate [**28**].* To a solution of the diol **25** (137 mg, 0.39 mmol) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C were added Et_3N (164 μL, 1.18 mmol), DMAP (2 mg), and acetic anhydride (111 μL, 1.18 mmol) successively and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 10% aqueous citric acid solution (2×3 mL), water (3 mL), saturated brine (3 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by column chromatography using 45% EtOAc/hexane (v/v) as the eluent to afford the diacetate **28** (148 mg, 0.32 mmol) in 82% yield as a viscous colorless oil; TLC, R_f (70% EtOAc/hexane) 0.42; $[\alpha]_D$ +54 (*c* 1.05, $CHCl_3$); ν_{max} (KBr) 3457, 2927, 1736, 1513, 1371, 1244, 1032, 752 cm^{-1}; δ_H (400 MHz, $CDCl_3$) δ 7.64 (d, *J*=6.6 Hz, 2H), 7.57–7.48 (m, 3H), 7.20 (d, *J*=8.8 Hz, 2H), 6.83 (d, *J*=8.8 Hz, 2H), 5.17 (quintet, *J*=6.6 Hz, 1H), 5.06 (quintet, *J*=6.6 Hz, 1H), 4.38 (d, *J*=11.7 Hz, 1H), 4.35 (d, *J*=11.7 Hz, 1H), 3.80 (s, 3H), 3.48–3.36 (m, 2H), 3.14–3.07 (m, 2H), 1.99 (s, 3H), 1.95 (s, 3H), 1.79 (q, *J*=5.9 Hz, 2H); *m*/*z* (ESI) 485 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 485.1595. $C_{24}H_{30}O_7NaS$ requires 485.1609.

*4.1.15. (R)-3-[(2R,4R)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]propane-1,2-diol [**29**].* To a solution of acetal **26** (2.32 g, 6.17 mmol) in anhydrous CH_2Cl_2 (35 mL) cooled at 0 °C was added Et_3N (2.6 mL, 18.5 mmol) followed by TFAA (3.6 mL, 18.5 mmol) under an atmosphere of nitrogen and stirred for 15 min. Then a solution of $NaBH_4$ (933 mg, 24.7 mmol) dissolved in 5% aqueous $NaHCO_3$ solution (50 mL) was added to the above reaction mixture at 0 °C and stirred for a further 20 min at the same temperature. The reaction mixture was then extracted into CH_2Cl_2 (3×75 mL). The combined organic layers were washed successively with water (2×40 mL), saturated brine (40 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by column chromatography using 70% EtOAc/hexane (v/v) as the eluent to afford diol **29** (0.8 g, 3.1 mmol) in 50% yield as a viscous pale yellow oil; TLC, R_f (70% EtOAc/hexane) 0.15; $[\alpha]_D$ −21.8 (*c* 1.3, $CHCl_3$); ν_{max} (KBr) 3414, 2925, 1674, 1605, 1515, 1431, 1307, 1250, 1103, 1027, 830, 767, 599 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.32 (d, *J*=9.1 Hz, 2H), 6.83 (d, *J*=9.1 Hz, 2H), 5.43 (s, 1H), 4.22 (dd, *J*=4.5, 11.3 Hz, 1H), 4.13–3.99 (m, 1H), 3.98–3.85 (m, 2H), 3.78 (s, 3H), 3.54 (d, *J*=10.6 Hz, 1H), 3.43 (dd, *J*=5.3, 10.6 Hz, 1H), 1.90–1.72 (m, 2H), 1.69–1.55 (m, 1H), 1.54–1.43 (m, 1H); δ_C (100 MHz, $CDCl_3$) δ 160.0, 130.7, 127.2, 113.7, 101.1, 76.7, 70.9, 66.9, 66.4, 55.3, 38.9, 31.3.

*4.1.16. (R)-2-Hydroxy-3-[(2R,4R)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]propyl 4-methylbenzenesulfonate [**30**].* To a solution of diol **29** (267 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (5 mL) cooled at 0 °C were added Et_3N (153 μL, 1.1 mmol) followed by *p*-toluenesulfonyl chloride (262 mg, 1.1 mmol) and Bu_2SnO (12 mg, 0.05 mmol). The reaction mixture was then gradually allowed to warm to rt and stirred for a period of 3 h. The reaction mixture was then quenched with 10% aqueous citric acid solution (5 mL) and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic extracts were successively washed with water (5 mL), saturated brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using 10% EtOAc/hexanes (v/v) as the eluent to afford tosylate **30** (312 mg, 0.75 mmol) in 75% yield as a viscous yellow oil; TLC, R_f (70% EtOAc/hexane) 0.83; δ_H (200 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.1, 2H), 7.35–7.23 (m, 4H), 6.82 (d, *J*=8.8 Hz, 2H),

5.41 (s, 1H), 4.21 (dd, J=4.4, 11.7 Hz, 1H), 4.15–4.01 (m, 2H), 3.99–3.83 (m, 3H), 3.79 (s, 3H), 2.45 (s, 3H), 1.89–1.63 (m, 2H), 1.49 (d, J=11.7 Hz, 1H), 1.35–1.20 (m, 1H).

*4.1.17. (2R,4R)-2-(4-Methoxyphenyl)-4-[(R)-oxiran-2-ylmethyl]-1,3-dioxane [**31**].* To the solution of tosylate **30** (312 mg, 0.75 mmol) in acetonitrile/methanol (19:1, 7 mL) was added potassium carbonate (113 mg, 0.83 mmol) at rt and stirred for a period of 3 h. The reaction mixture was then diluted with Et_2O (20 mL) and the precipitated solids filtered through a plug of Celite. Evaporation of the solvent under reduced pressure furnished the crude product, which was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to afford epoxide **31** (113 mg, 0.47 mmol) in 62% yield as a viscous colorless oil; TLC, R_f (30% EtOAc/hexane) 0.35; $[\alpha]_D$ −5.7 (c 3.5, $CHCl_3$); ν_{max} (KBr) 2924, 2853, 1614, 1516, 1461, 1364, 1247, 1103, 1030, 826, 777 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.35 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 5.43 (s, 1H), 4.26 (dd, J=5.1, 11.8 Hz, 1H), 4.07–3.85 (m, 2H), 3.79 (s, 3H), 3.16–3.01 (m, 1H), 2.74 (t, J=4.4, 1H), 2.54–2.46 (m, 1H), 2.07–1.76 (m, 4H); δ_C (50 MHz, $CDCl_3$) δ 159.9, 131.1, 127.3, 113.6, 101.1, 74.4, 66.9, 55.3, 48.9, 46.8, 38.4, 30.8; m/z (ESI) 250 $[M]^+$; HRMS (ESI): $[M+Na]^+$ found 273.1108. $C_{24}H_{40}O_4Na$ requires 273.1102.

*4.1.18. (S)-1-[(2R,4R)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl]tridecan-2-ol [**32**].* The mixture of epoxide **31** (113 mg, 0.46 mmol) and CuCN (2 mg, 0.02 mmol) in anhydrous THF (2.5 mL) was stirred at rt for 10 min. The reaction mixture was then cooled to −10 °C and treated with a freshly prepared solution of *n*-decylmagnesium bromide (0.83 M in ether, 1.68 mL, 1.4 mmol). The reaction mixture was then gradually warmed to 0 °C and stirred for 2 h. It was quenched with saturated aqueous NH_4Cl solution (2 mL) and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with saturated brine (4 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography using 10% EtOAc/hexane (v/v) as the eluent afforded triol derivative **32** (125 mg, 0.32 mmol) in 69% yield as a viscous colorless oil.

One-pot operation. To a suspension of sodium hydride (60% in Nujol, 310 mg, 7.7 mmol) in anhydrous THF (10 mL) cooled at 0 °C was added a solution of diol **29** (810 mg, 3.1 mmol) in THF (20 mL) dropwise. The mixture was gradually allowed to warm to rt and further stirred for 1 h at the same temperature. It was then recooled at 0 °C and *N*-Ts-imidazole (686 mg, 3.1 mmol) was added in three equal portions over a period of 20 min. The mixture was warmed to rt and stirred for 40 min, then CuCN (55 mg, 0.61 mmol) was added in one portion. After stirring for an additional 5 min, the mixture was cooled to −10 °C and a freshly prepared solution of *n*-decylmagnesium bromide (0.7 M in Et_2O, 13.3 mL, 9.31 mmol) was added via syringe. The reaction mixture was kept at the same temperature for 2 h and then allowed to warm gradually to 0 °C over a period of 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) and diluted with Et_2O (65 mL). The aqueous phase was re-extracted with Et_2O (2×25 mL) and the combined organic layers were washed with water (2×25 mL), saturated brine (25 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo furnished the crude residue, which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford triol **32** (846 mg, 2.1 mmol) in 70% yield as a viscous colorless oil; TLC, R_f (20% EtOAc/hexane) 0.52; $[\alpha]_D$ −14.9 (c 1.1, $CHCl_3$); ν_{max} (KBr) 3447, 2922, 2853, 1634, 1459, 558 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.31 (d, J=9.1 Hz, 2H), 6.82 (d, J=9.1 Hz, 2H), 5.45 (s, 1H), 4.22 (dd, J=4.5, 12.1 Hz, 1H), 4.13–4.02 (m, 1H), 3.92 (dt, J=2.3, 12.1 Hz, 1H), 3.86–3.80 (m, 1H), 3.78 (s, 3H), 1.92–1.23 (m, 24H), 0.88 (distorted t, J=6.8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) δ 159.8, 130.7, 127.2, 113.6, 101.1, 78.1, 71.4, 67.0, 55.3, 42.8, 37.7, 31.6, 29.8, 29.7, 29.4, 25.5, 22.8, 14.2; m/z (ESI) 393 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 415.2804. $C_{24}H_{40}O_4Na$ requires 415.2824.

*4.1.19. (2R,4R)-4-[(S)-2-(Benzyloxy)butyl]-2-(4-methoxyphenyl)-1,3-dioxane [**33**].* To a suspension of sodium hydride (60% in Nujol, 129 mg, 3.24 mmol) in anhydrous THF (2.5 mL) cooled at 0 °C was added *n*-tetrabutylammonium iodide (43 mg, 10 mol %, 0.21 mmol) followed by the dropwise addition of carbinol **32** (846 mg, 2.16 mmol) in THF (2.5 mL) and stirred at the same temperature for 30 min. Neat benzyl bromide (0.38 mL, 3.24 mmol) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was allowed to gradually warm to rt and stirred further for 12 h under an atmosphere of nitrogen. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (3 mL). Two phases were separated and the aqueous layer was extracted with EtOAc (4×10 mL). The combined organic layers were washed successively with water (2×5 mL), saturated brine (5 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 5% EtOAc/hexane (v/v) as the eluent to yield benzyl ether **33** (749 mg, 1.6 mmol) in 72% yield as a colorless oil; TLC, R_f (10% EtOAc/hexane) 0.35; $[\alpha]_D$ −14 (c 0.3, $CHCl_3$); ν_{max} (KBr) 3028, 2925, 2853, 2771, 1728, 1615, 1517, 1459, 1369, 1248, 1107, 1035, 825, 747, 698 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.36–7.24 (m, 7H), 6.81 (d, J=8.1 Hz, 2H), 5.39 (s, 1H), 4.51 (d, J=11.7 Hz, 1H), 4.44 (d, J=11.7 Hz, 1H), 4.18 (dd, J=4.4, 9.5 Hz, 1H), 4.01–3.83 (m, 2H), 3.79 (s, 3H), 3.54 (quintet, J=5.9 Hz, 1H), 1.99 (quintet, J=6.9 Hz, 1H), 1.87–1.50 (m, 4H), 1.46–1.20 (m, 19H), 0.89 (distorted t, J=6.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) δ 159.9, 139.0, 131.5, 128.3, 127.9, 127.5, 127.4, 113.5, 101.1, 75.1, 74.4, 70.5, 67.0, 55.1, 45.1, 40.3, 34.1, 32.1, 31.6, 30.0, 29.8, 29.7, 29.5, 25.3, 22.8, 14.3; m/z (ESI) 483 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 505.3318. $C_{31}H_{46}O_4Na$ requires 505.3293.

*4.1.20. (3R,5S)-5-(Benzyloxy)hexadecane-1,3-diol [**34**].* To a stirred solution of benzyl ether **33** (749 mg, 1.55 mmol) in methanol/water (4:1) was added PPTS (39 mg, 0.16 mmol) and the mixture heated at reflux for 4 h. The solvent was evaporated in vacuo and the crude product was purified by column chromatography using 30% EtOAc/hexane (v/v) as the eluent to afford the diol **34** (339 mg, 0.93 mmol) in 60% yield as a colorless oil; TLC, R_f (30% EtOAc/hexane) 0.23; $[\alpha]_D$ +25.3 (c 2.65, $CHCl_3$); ν_{max} (KBr) 3440, 2924, 2853, 1640, 1456, 1217, 1057, 760, 696 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 4.67 (d, J=11.1 Hz, 1H), 4.42 (d, J=11.1 Hz, 1H), 4.14–3.99 (m, 1H), 3.81 (t, J=5.9 Hz, 2H), 3.76–3.64 (m, 1H), 1.83–1.53 (m, 6H), 1.28–1.26 (br s, 18H), 0.89 (distorted t, J=6.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) δ 137.8, 128.6, 127.9, 80.3, 72.3, 70.6, 61.4, 41.0, 38.8, 33.3, 31.9, 29.8, 29.6, 29.3, 24.5, 22.7, 14.1; m/z (ESI) 365 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 387.2891. $C_{23}H_{40}O_3Na$ requires 387.2875.

*4.1.21. (3S,5S)-5-(Benzyloxy)-3-hydroxyhexadecanal [**35**].* To a stirred solution of the diol **34** (339 mg, 0.93 mmol) in CH_2Cl_2 (18 mL) was added TEMPO (44 mg, 0.28 mmol) followed by iodobenzene diacetate (901 mg, 2.8 mmol). After stirring for 2 h at rt, the reaction mixture was treated with 5% aqueous $Na_2S_2O_3$ solution (7 mL) and saturated aqueous $NaHCO_3$ solution (7 mL). After 15 min, the organic phase was separated and the aqueous phase was extracted with Et_2O (3×25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude residue, which was purified by column chromatography using 20% EtOAc/hexane (v/v) as the eluent to afford the corresponding aldehyde **35** (219 mg, 0.61 mmol) in 65% yield as a viscous pale yellow oil; TLC, R_f (50% EtOAc/hexane) 0.72; $[\alpha]_D$ +2.6 (c 1.05, $CHCl_3$); ν_{max} (KBr) 3447, 2925, 2854, 1730, 1458, 1352, 1246, 1097, 743, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) δ 9.81 (t, J=1.5 Hz, 1H), 7.38–7.28 (m, 5H), 4.65 (d, J=11.0 Hz, 1H), 4.43 (d,

J=11.0 Hz, 1H), 4.36–4.28 (m, 1H), 3.76–3.68 (m, 1H), 2.58 (ddd, J=2.2, 7.3, 16.8 Hz, 1H), 2.50 (ddd, J=1.5, 4.3, 16.8 Hz, 1H), 1.81–1.48 (m, 4H), 1.41–1.15 (br s, 18H), 0.88 (distorted t, J=6.6 Hz, 3H); δ_C (100 MHz, $CDCl_3$) δ 202.1, 137.8, 128.6, 127.9, 79.5, 70.5, 67.1, 51.0, 40.5, 33.2, 31.9, 29.8, 29.6, 29.6, 29.3, 24.5, 22.7, 14.1.

*4.1.22. (3S,5S)-5-(Benzyloxy)-3-hydroxyhexadecanoic acid [**36**].* To a stirred solution of the aldehyde **35** (219 mg, 0.61 mmol) in cyclohexene (0.6 mL) and *t*-BuOH (1.8 mL) cooled at 0 °C was added dropwise a solution of sodium chlorite (83 mg, 0.91 mmol) and $NaH_2PO_4 \cdot H_2O$ (126 mg, 0.91 mmol) in water (0.6 mL). The mixture was stirred for 30 min at the same temperature and then 3 h at rt. The reaction mixture was then partitioned between Et_2O (50 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (3×15 mL) and the combined organic layers were washed successively with water (5 mL), saturated brine (5 mL) and then dried over anhydrous Na_2SO_4. Removal of solvent in vacuo furnished the crude product, which was purified by base–acid treatment to afford acid **36** (172 mg, 0.45 mmol) in 75% yield as a colorless oil. TLC, R_f (50% EtOAc/hexane) 0.21; $[\alpha]_D$ +29.4 (*c* 1.45, $CHCl_3$); ν_{max} (KBr) 3407, 2925, 2854, 1711, 1580, 1455, 1065, 910, 737, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.62 (d, J=11.3 Hz, 1H), 4.42 (d, J=11.3 Hz, 1H), 4.26–4.12 (m, 1H), 3.77–3.65 (m, 1H), 2.54–2.40 (m, 2H), 1.86–1.45 (m, 4H), 1.27 (br s, 18H), 0.88 (distorted t, J=6.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) δ 137.7, 128.6, 127.9, 79.2, 70.6, 68.0, 40.0, 33.2, 31.9, 29.8, 29.6, 29.3, 24.5, 22.7, 14.1; m/z (ESI) 378 $[M]^+$; HRMS (ESI): $[M+Na]^+$ found 401.2675. $C_{23}H_{38}O_4Na$ requires 401.2667. Note: signal for the carbonyl carbon not observed in ^{13}C NMR.

*4.1.23. (3S,5S)-Methyl 5-(benzyloxy)-3-hydroxyhexadecanoate [**37**].* A solution of acid **36** (172 mg, 0.45 mmol) in Et_2O (5 mL) was esterified by reaction with an ethereal solution of diazomethane. The excess of diazomethane was quenched by adding few drops of glacial acetic acid. Removal of the solvent in vacuo, followed with purification by column chromatography using 10% EtOAc/hexane (v/v) as the eluent afforded methyl ester **37** (161 mg, 0.41 mmol) in 90% yield as a colorless oil; TLC, R_f (20% EtOAc/hexane) 0.32; $[\alpha]_D$ +27.5 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3466, 2925, 2854, 1734, 1443, 1271, 1169, 1067, 743 cm^{-1}; δ_H (200 MHz, $CDCl_3$) δ 7.39–7.19 (m, 5H), 4.59 (d, J=11.4 Hz, 1H), 4.44 (d, J=11.4 Hz, 1H), 4.22–4.05 (m, 1H), 3.68 (s, 3H), 3.62–3.56 (m, 1H), 2.47 (dd, J=6.8, 15.9 Hz, 1H), 2.36 (dd, J=5.3, 15.9 Hz, 1H), 1.85–1.50 (m, 4H), 1.45–1.19 (br s, 18H), 0.89 (distorted t, J=6.6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) δ 172.2, 138.2, 128.5, 127.8, 127.7, 78.5, 70.6, 67.3, 51.4, 41.7, 40.5, 33.6, 32.0, 30.0, 29.8, 29.5, 24.8, 22.8, 14.3; m/z (ESI) 393 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 415.2820. $C_{24}H_{40}O_4Na$ requires 415.2824.

*4.1.24. (2S,3S,5S)-Methyl 5-(benzyloxy)-2-hexyl-3-hydroxyhexadecanoate [**2**].* To a stirred solution of LHMDS (1 M in THF, 0.94 mL, 0.94 mmol) in THF (1 mL) cooled at −55 °C was added a solution of methyl ester **37** (161 mg, 0.41 mmol) in THF (1.4 mL). The reaction mixture was stirred at −55 °C for 1 h and then hexyl iodide (90 μL, 0.61 mmol) in HMPA (0.36 mL, 2.05 mmol) was added dropwise at the same temperature. The resulting mixture was stirred at −55 °C for 1 h, allowed to warm to −30 °C, stirred at the same temperature for another 1 h. It was then allowed to warm to −15 °C and stirred further at −15 °C for 1 h. The yellow reaction mixture was diluted with Et_2O (20 mL) and poured into saturated aqueous NH_4Cl solution (10 mL). Two phases were portioned and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed successively with water (4 mL), saturated brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. Purification by column chromatography using 4% EtOAc/hexane (v/v) as the eluent afforded compound **2** (136 mg, 0.29 mmol) in 70% yield as a colorless oil; TLC, R_f (20% EtOAc/hexane) 0.63; $[\alpha]_D$ +19.2 (*c* 1.25, $CHCl_3$); ν_{max} (KBr) 3459, 2926, 2855, 1734, 1638, 1459, 1369, 1210, 1165, 1066, 760, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.6 (d, J=11.3 Hz, 1H), 4.43 (d, J=11.3 Hz, 1H), 3.95–3.85 (m, 1H), 3.73–3.63 (m, 4H), 2.48–2.37 (m, 1H), 1.74–1.44 (m, 6H), 1.33–1.22 (br s, 26H), 0.92–83 (m, 6H); δ_C (75 MHz, $CDCl_3$) δ 175.5, 138.0, 128.4, 127.8, 127.7, 79.3, 72.2, 70.5, 51.9, 38.5, 33.3, 31.6, 29.8, 29.6, 29.3, 29.2, 28.7, 27.5, 24.6, 22.7, 22.5, 14.1, 14.0; m/z (ESI) 477 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 499.3742. $C_{30}H_{52}O_4Na$ requires 499.3763.

*4.1.25. (2S,3S,5S)-5-(Benzyloxy)-2-hexyl-3-hydroxyhexadecanoic acid [**38**].* To a solution of compound **2** (136 mg, 0.29 mmol) in THF (3 mL) cooled at 0 °C, 1 M LiOH (1.4 mL, 1.4 mmol) was added in one portion and the mixture gradually warmed to ambient temperature and then heated at 65 °C for 2 h. The reaction mixture was cooled to 0 °C and acidified using 1 N aqueous HCl solution to adjust pH to 2. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with water (3 mL), saturated brine (2 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the crude product, which was purified by base–acid treatment to furnish acid **38** (92 mg, 0.2 mmol) in 70% yield as a viscous colorless oil; TLC, R_f (20% EtOAc/hexane) 0.15; $[\alpha]_D$ +14 (*c* 0.53, $CHCl_3$) [lit.[3c] +12.6 (*c* 0.92, $CHCl_3$)]; ν_{max} (KBr) 3445, 2925, 2855, 1708, 14.58, 1215, 1064, 763, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 4.66 (d, J=11.3 Hz, 1H), 4.41 (d, J=11.3 Hz, 1H), 3.97–3.85 (m, 1H), 3.77–3.66 (m, 1H), 2.41–2.29 (m, 1H), 1.84–1.48 (m, 4H), 1.39–1.15 (br s, 28H), 0.95–0.82 (m, 6H); δ_C (100 MHz, $CDCl_3$) δ 137.4, 128.6, 128.0, 127.9, 80.1, 72.2, 70.6, 51.7, 38.6, 33.1, 31.9, 31.6, 29.8, 29.6, 29.6, 29.3, 29.1, 27.3, 24.4, 22.7, 22.6, 14.1, 14.0; m/z (ESI) 463 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 485.3595. $C_{29}H_{50}O_4Na$ requires 485.3606.

Note: signal for the carbonyl carbon not observed in ^{13}C NMR.

*4.1.26. (3S,4S)-4-[(S)-2-(Benzyloxy)tridecyl]-3-hexyloxetan-2-one [**39**].* To a solution of β-hydroxy acid **38** (92 mg, 0.2 mmol) in CH_2Cl_2 (6 mL) was added Et_3N (83 μL, 0.6 mmol) followed by BOP-Cl (77 mg, 0.3 mmol) at rt. After 1 h, the resulting reaction mixture was diluted with water (2 mL) and extracted with EtOAc (3×8 mL). The combined organic phase was washed with water (4 mL), saturated brine (4 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography using 3% EtOAc/hexane (v/v) as the eluent to afford β-lactone **39** (58 mg, 0.13 mmol) in 65% yield as a colorless oil; TLC, R_f (20% EtOAc/hexane) 0.73; $[\alpha]_D$ −4 (*c* 0.97, $CHCl_3$) [lit.[3d] −3.44 (*c* 0.93, $CHCl_3$)]; ν_{max} (KBr) 2926, 2855, 1823, 1741, 1460, 1378, 1119, 884, 736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.55 (d, J=11.7 Hz, 1H), 4.45–4.36 (m, 2H), 3.55–3.48 (m, 1H), 3.23 (dt, J=4.4, 8.1 Hz, 1H), 2.15 (td, J=6.6, 14.7 Hz, 1H), 1.97–1.86 (m, 1H), 1.80–1.45 (m, 4H), 1.42–1.21 (br s, 26H), 0.93–0.84 (m, 6H); δ_C (300 MHz, $CDCl_3$) δ 171.6, 138.2, 128.4, 127.7, 75.6, 75.2, 70.7, 56.5, 38.1, 33.3, 31.9, 31.4, 29.5, 29.5, 29.3, 28.9, 27.7, 26.6, 25.1, 22.6, 22.5, 14.1, 14.0; m/z (ESI) 445 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 467.3490. $C_{29}H_{48}O_3Na$ requires 467.3501.

*4.1.27. (3S,4S)-3-Hexyl-4-((S)-2-hydroxytridecyl)oxetan-2-one [**40**].* Palladium hydroxide on carbon (5.8 mg, 10 wt %) was added to the solution of β-lactone **39** (58 mg, 0.13 mmol) in methanol (1 mL) at ambient temperature and the mixture was stirred under an atmosphere of hydrogen at atmospheric pressure for 4 h. The solid catalyst was filtered and washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure to afford the crude residue, which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to furnish alcohol **40** (37 mg, 0.1 mmol) in 80% yield as white crystals. Mp 62–63 °C [lit.[3d] 63–64 °C]; TLC, R_f (10% EtOAc/hexane) 0.11; $[\alpha]_D$ −16 (*c* 1.75, $CHCl_3$) [lit.[3c] −16.3 (*c* 1.05, $CHCl_3$)]; ν_{max} (KBr) 3546, 2921, 2852, 1812, 1464, 1382, 1125, 1088, 838, 759, 723, 574 cm^{-1}; δ_H (300 MHz, $CDCl_3$)

δ 4.44 (dt, J=4.0, 6.4 Hz, 1H), 3.80–3.73 (m, 1H), 3.29 (ddd, J=4.0, 6.8, 8.5 Hz, 1H), 1.93–1.66 (m, 4H), 1.55–1.38 (m, 4H), 1.38–1.21 (m, 24H), 0.95–0.83 (m, 6H); δ_C (100 MHz, $CDCl_3$) δ 171.1, 76.2, 69.3, 56.7, 41.2, 37.7, 31.9, 31.5, 29.7, 29.6, 29.4, 29.0, 27.9, 26.9, 25.5, 22.7, 22.6, 14.2, 14.1; m/z (ESI) 355 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 377.3016. $C_{22}H_{42}O_3Na$ requires 377.3031.

*4.1.28. (1S)-1-[(2S,3S)-3-Hexyl-4-oxooxetan-2-yl]tridecan-2-yl (2S)-2-formylamino-4-methylpentanoate [**1**].* A mixture of (*S*)-*N*-formyl-L-leucine (25 mg, 0.16 mmol), DCC (32 mg, 0.16 mmol), and DMAP (3 mg, 0.02 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was stirred at ambient temperature for 10 min before a solution of the alcohol **40** (37 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (0.5 mL) being introduced dropwise. The mixture was then stirred at ambient temperature for 24 h before being diluted with Et_2O (10 mL). The precipitate solid was filtered through a pad of Celite and the filtrate was washed successively with water (2×1 mL), saturated brine (1 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure the residue was purified through column chromatography using 15% EtOAc/hexane (v/v) as the eluent to afford (−) THL **1** (37 mg, 0.08 mmol) in 72% yield as white crystals. Mp 41–42 °C [lit.[3b] 40–42 °C]; TLC, R_f (30% EtOAc/hexane) 0.42; $[\alpha]_D$ −31 (c 0.1, $CHCl_3$) [lit.[3b] −33 (c 0.36, $CHCl_3$)]; ν_{max} (KBr) 2925, 2855, 1822, 1738, 1675, 1549, 1459, 1255, 1124 cm^{-1}; δ_H (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 5.95–5.83 (m, 1H), 5.06–4.98 (m, 1H), 4.72–4.60 (m, 1H), 4.30–4.22 (m, 1H), 3.24–3.16 (m, 1H), 2.21–2.11 (m, 1H), 2.07–1.94 (m, 1H), 1.87–1.40 (m, 7H), 1.38–1.20 (m, 23H), 1.01–0.96 (m, 6H), 0.92–0.86 (m, 6H); δ_C (100 MHz, $CDCl_3$) δ 160.7, 74.8, 72.7, 57.0, 49.6, 41.5, 38.7, 34.0, 31.9, 31.4, 29.6, 29.5, 29.4, 29.3, 28.9, 27.6, 26.7, 25.5, 25.0, 24.9, 22.9, 22.7, 22.5, 21.7, 14.1, 14.0; m/z (ESI) 496 $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ found 518.3821. $C_{29}H_{53}NO_5Na$ requires 518.3821.

Note: signals for the two carbonyl carbon not observed in ^{13}C NMR.

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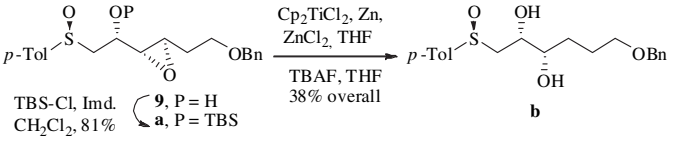

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