Oxazoline-*N*-Oxide mediated [2+3] Cycloadditions. Application to a Synthesis of (-)-Tetrahydrolipstatin.

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Supporting Information

Experimental section.

Generalities. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200 or 250 MHz and 50 or 62.5 MHz respectively, using residual chloroform signal (7.24 ppm and 77 ppm) as the internal reference. Coupling constants are given in Hz. Optical rotations were recorded at 20 °C. Chromatographic purifications were performed on 230-400 mesh silica gel (Merck 9385) using the indicated solvent system. Ether refers to diethyl ether. Dichloromethane, acetonitrile, dimethylformamide and trimethyl orthoacetate were distilled from calcium hydride. Toluene, diethyl ether and tetrahydrofuran were distilled from sodium metal/benzophenone ketyl. Chloroform used for optical measurements was filtered through basic alumina before use. All other reagents were obtained from commercial sources and were used as received. All non- aqueous reactions were performed under an argon atmosphere using oven-dried glassware.

(*R*)-1-Pentadecen-4-ol (3)

A solution of (-)-*B*-chlorodiidopinocampheynyl borane ((-)-DIPCl, derived from (+)-pinene, 9.6g, 30 mmol) in dry ether (30 mL) was cooled to -40 °C and an allylmagnesium bromide solution (1M in ether, 25 mL, 25 mmol) was added dropwise. The solution was stirred 1h at room temperature, then cooled to -78 °C. A solution of freshly distilled dodecanal (4.41 mL, 20 mmol) in dry ether (10 mL) was added very slowly. The mixture was stirred 6h at -78 °C then warmed to 0 °C; acetaldehyde (10 mL, 180 mmol) was then added. After stirring 18h at room temperature, the reaction was quenched by successive addition of a 3M aqueous sodium acetate solution (20 mL) and 35% hydrogen peroxide solution (10 mL). After 30 min, the solution was diluted with water (50 mL) and extracted with ether (3 x 100 mL). The combined organic layer was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification

by chromatography (20% ether/heptane; Rf: 0.26) gave the known[4] homoallylic alcohol **2** as a colourless oil (2.68 g; yield: 60%). The enantiomeric excess was determined to be 90% by NMR analysis of the (+)-*O*-acetylmandelate ester.

Data for **3**: IR (film): ν (cm^{-1}): 3360, 2920, 2840, 1700, 1455, 1115, 1075, 1018, 985, 900; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 5.82 (1H, m, C_2-H), 5.11 (2H, m, C_1-H x 2), 3.62 (1H, m, C_4-H), 2.19 (2H, m, C_3-H x 2), 1.47 (2H, m, C_5-H x 2), 1.25 (18H, broad s, C_6-C_{14}-H), 0.87 (3H, t, J= 7 Hz, C_{15}-H x 3; ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 134.9 (C_2), 117.9 (C_1), 70.6 (C_4), 41.9 (C_3), 36.8 (C_5), 31.9, 29.61, 29.59, 29.53, 29.47, 29.42, 29.32, 25.6, 22.6 (C_6-C_{14}), 14.1 (C_{15}); $[\alpha]_D^{20}$: + 5.4 (c= 1.06, $CHCl_3$); lit.[4]: $[\alpha]_D^{20}$: + 5.8 (c= 2.89, $CHCl_3$).

(*R*)-4-Phenylmethoxy-1-pentadecen.

A suspension of oil-free sodium hydride (1.76g, 44 mmol) in anhydrous tetrahydrofuran (25 mL) was cooled to 0 °C with stirring, and a solution of the alcohol **3** (6.6g, 29.2 mmol) in tetrahydrofuran (100 mL) was added dropwise (gas evolution). The mixture was stirred 15 min at 0 °C, then 10 min at room temperature before being recooled to 0 °C. Dimethylformamide (16 mL) was added dropwise, followed by benzyl bromide (4.16 mL, 35 mmol). The white suspension was stirred 30 min at 0 °C, then 1h at room temperature, then quenched at 0 °C by careful addition of an ether/water mixture (90 mL/10 mL). The mixture was partioned between water (50 mL) and ether (200 mL) and the aqueous layer was extracted with ether (2 x 200 mL). The combined organic layer was washed with brine (100 mL), dried (Na_2SO_4), filtered an concentrated *in vacuo*. The residue was purified by chromatography (pentane followed by 5% ether/pentane) to give the benzyl ether **3** as a colourless oil (8.95 g; yield: 97%).

^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.43-7.27 (5H, broad s, Ar-H), 5.90 (1H, m, C_2-H), 5.12 (2H, m, C_1-H x 2), 4.60 (1H, d, J= 11.7, one of Ar-C*H*$_2$), 4.52 (1H, d, J= 11.7, one of Ar-C*H*$_2$), 3.48 (1H, m, C_4-H), 2.37 (2H, m, C_3-H x 2), 1.55 (2H, m, C_5-H x 2), 1.22 (18H, broad s, C_6-C_{14}-H), 0.92 (3H, t, J= 6.8, C_{15}-H x 3); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 138.9 (C_2), 135.0, 128.2, 127.6, 127.3 (Ar), 116.7 (C_1), 78.5 (C_4), 70.8 (Ar-*C*), 38.3 (C_3), 33.7, 31.9, 29.61, 29.59, 29.53, 29.47, 29.42, 29.32, 25.3, 22.7 (C_5-C_{14}), 14.1 (C_{15}).

(*R*)-3-Phenylmethyloxy-tetradecanal (4).

To a solution of the alkene **3** (1g, 3.17 mmol) in acetone (17 mL) and water (5.5 mL) were successively added *N*-methylmorpholine *N*-oxide (0.52g, 4.4 mmol) and osmium tetroxide solution (2.5 wt in *tert*-butanol, 0.94 mL). After stirring 90 min at room temperature, TLC analysis indicated complete disappearance of the starting material. A solution of sodium periodate (1.6 g, 6.66 mmol) in water was then added. After stirring for 1h at room temperature, water (20 mL) was added and the

mixture was extracted with ether (3 x 50 mL). The combined organic layer was washed with 10% aqueous sodium thiosulfate solution (50 mL), then with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by chromatography (10% ether/pentane followed by 50% ether/pentane) gave the aldehyde **4** as a colourless oil (0.815g; yield: 81%).

Rf: 0.19 (10% ether/pentane); IR (film): ν (cm^{-1}): 3400, 2910, 2840, 1712, 1450, 1440, 1335, 1085, 1060, 735, 690; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm): 9.81 (1H, dd, J= 2.6, 2.0, C_1-H), 7.43-7.27 (5H, broad s, Ar-H), 4.55 (2H, AB system, J= 11.5, Ar-C*H*$_2$), 3.95 (1H, m, C_3-H), 2.66 (2H, m, C_2-H x 2), 1.66 (2H, m, C_4-H x 2), 1.27 (18H, broad s, C_5-C_{13}-H), 0.89 (3H, t, J= 6.8, C_{14}-H x 3); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 201.6 (C_1), 138.2, 128.3, 127.7, 127.6 (Ar), 74.3 (C_3), 71.1 (Ar-*C*H$_2$), 48.2 (C_2), 34.2, 31.8, 29.61, 29.59, 29.53, 29.47, 29.42, 29.32, 25.0, 22.6 (C_4-C_{13}), 14.0 (C_{14}); $[\alpha]_D^{20}$: -14.0 (c= 2, $CHCl_3$); lit.[4]: -14.25 (c= 1.24, $CHCl_3$); High resolution mass spectrum, calculated for $C_{21}H_{34}NaO_2$ (M+ Na): 341.2456; found: 341.2454.

(2 *E*, 5*R*)-5-Phenylmethyloxy-2-hexadienoic acid ethyl ester (5).

Carbethoxyethylidene triphenylphosphorane (10 g, 27.4 mmol) was added to a solution of the aldehyde **4** (4.35 g; 13.7 mmol) in toluene (200 mL) and the solution was stirred at 80 °C for 1h. After cooling to room temperature, the solvent was removed *in vacuo*, the residue triturated with pentane (100 mL), filtered and concentrated. The residue was purified by chromatography (5% ether/pentane) to give, in order of elution, a small amount of the *Z*-α,β-unsaturated ester (Rf: 0.45; 0.21 g), followed by the *E*-ester **5** (4.94 g; yield: 93%), which was obtained as a yellow oil.

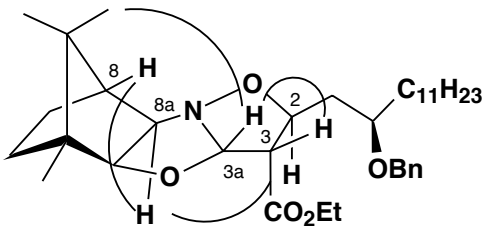
Rf: 0.32 (5% ether/pentane); IR (film): ν (cm^{-1}): 3380, 2910, 2840, 1710, 1640, 1455, 1440, 1353, 1308, 1257, 1168, 1088, 1035, 970, 738, 690; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 7.30 (5H, broad s, Ar-H), 6.98 (1H, dt, J= 15.3, 7.5, C_3-H), 5.86 (1H, dt, J= 15.6, 1.2, C_2-H), 4.51 (2H, AB system, J= 11.6, Ar-C*H*$_2$), 4.18 (2H, q, J= 7, O-C*H*$_2$-CH_3), 3.50 (1H, m, C_5-H), 2.43 (2H, m, C_4-H x 2), 1.50 (2H, m, C_6-H x 2), 1.22 (18H, broad s, C_7-C_{15}-H), 0.87 (6H, 2t, C_{16}-H x 3 and O-CH_2-C*H*$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 166.3 (C_1), 145.4 (C_3), 138.5, 128.3, 127.7, 127.5 (Ar), 123.3 (C_2), 77.7 (C_5), 71.0 (Ar-*C*H$_2$), 60.1 (O-*C*H$_2$-CH_3), 36.8 (C_4), 34.0, 31.8, 29.61, 29.59, 29.53, 29.47, 29.42, 29.32, 25.2, 22.6 (C_6-C_{15}), 14.2 (O-CH_2-*C*H$_3$), 14.0 (C_{16}); $[\alpha]_D^{20}$: + 6.1 (c= 1, $CHCl_3$); mass (CI NH_3): m/z: 406 (M+ 18), 389 (MH^+); (electrospray): m/z: 411 (M+ Na); high resolution mass spectrum, calculated for $C_{24}H_{40}NaO_2$ (M+ Na): 411.2875; found: 411.2873.

(2*S*,3*S*, 3a*S*, 4a*S*, 5*R*, 8*S*, 8a*R*, 2'*R*)-2-(2'-Phenylmethyloxy-tridecyl)-5,10,10-trimethyl-5,8-methano-octahydro-2*H*-isoxazolo-[3,2-*b*]-benzoxazole-3-carboxylic acid ethyl ester (8).

Calcium carbonate (2 g, 20 mmol) and powdered 4Ä molecular sieves (2g) were flame-dried and cooled under a stream of argon. (3-Hydroxyamino)isoborneol hydrochloride **6** (2g, 9 mmol) was added and the solids were suspended in toluene (100 mL). Trimethyl orthoformate (4 mL, 37 mmol) was added and the suspension stirred 4h at 40 °C. The α,β-unsaturated ester **5** (1.7 g, 4.4 mmol) was then added, the temperature raised to 80 °C, and the mixture stirred for 16h. After cooling to room temperature, the solids were removed by filtration through a short pad of celite, eluting with toluene, and the filtrate was concentrated *in vacuo*. ^{1}H NMR analysis of the crude product revealed the presence of three cycloadducts: the major compound **8**, and small amounts (both less than 5%) of two cycloadducts, one arising from and *exo* transition state, the other arising from cycloaddition with the minor enantiomer of **5**. The desired cycloadduct **8** was isolated by chromatography (9% ether/pentane followed by 20% ether/pentane), and was obtained as a colourless oil (1.56g; yield: 61% from **5**).

Rf: 0.44 (20% ether/pentane); IR (film): ν (cm^{-1}): 3012, 2955, 1728, 1440, 1360, 1260, 1170, 1080, 1020, 735; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.30 (5H, broad s, Ar-H), 5.39 (1H, d, J= 7.6, C_{3a}-H), 4.55 (1H, m, C_2-H), 4.48 (2H, AB system, J= 11.9, Ar-C*H*$_2$), 4.13 (1H, m, one of O-C*H*$_2$-CH_3), 3.94 (1H, m, one of O-C*H*$_2$-CH_3), 3.86 (1H, d, J= 4.6, C_{4a}-H), 3.50 (1H, m, $C_{2'}$-H), 3.18 (1H, d, J= 7.6, C_{8a}-H), 2.98 (1H, dd, J= 10.4, 7.6, C_3-H), 2.02 (1H, d, J= 4.06, C_8-H), 1.90-1.40 (6H, m, $C_{1'}$-H x 2, C_6-H x 2, C_7-H x 2), 1.20 (20H, broad s, $C_{3'}$-$C_{12'}$-H), 0.90-0.70 (15H, 3s and 2t, O-CH_2-C*H*$_3$, $C_{13'}$-H x 3 and CH_3 x 3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 168.7 (CO), 139.0, 128.2, 127.3, 127.2 (Ar), 98.7 (C_{3a}), 89.7 (C_{4a}), 76.1, 76.0, 75.8 (C_2, C_{8a}, $C_{2'}$), 70.4 (Ar-*C*H_2), 60.8 (O-*C*H_2-CH_3), 58.8 (C_3), 49.1 (C_8), 48.4 (C_{10}), 45.9 (C_5), 37.4 ($C_{1'}$), 31.3 (C_6), 25.4 (C_7), 34.0, 31.9, 29.7, 29.62, 29.60, 29.57, 29.56, 29.3, 24.9, 22.7 ($C_{3'}$-$C_{12'}$), 14.1 (O-CH_2-*C*H_3), 14.0 ($C_{13'}$), 22.1, 18.7, 10.7 (CH_3 x 3); $[\alpha]_D^{20}$: -85.6 (c= 1, $CHCl_3$); mass (CI NH_3): m/z: 584 (M+ 1), 180; (electrospray): m/z: 606.3 (M+ Na), 584.3 (M+ 1); high resolution mass spectrum, calculated for $C_{36}H_{57}NNaO_5$ (M+ Na): 606.4134; found: 606.4135.

principal nOe relationships (NOESY NMR, 250 MHz, $CDCl_3$):



8

(2*S*,3*S*, 3a*S*, 4a*S*, 5*R*, 8*S*, 8a*R*, 2'*R*)-2-(2'-Phenylmethyloxy-tridecyl)-5,10,10-trimethyl-5,8-methano-octahydro-2*H*-isoxazolo-[3,2-*b*]-benzoxazole-3-carboxaldehyde (9).

The cycloadduct **8** (1.56 g, 2.67 mmol) was dried by azeotropic evaporation of toluene, then redissolved in toluene (50 mL), and the solution cooled to -78 °C. A diisobutylaluminium hydride solution (1M in toluene, 4 mL, 4 mmol) was added dropwise. After 1h at -78 °C, the reaction was quenchend by careful addition of a saturated aqueous ammonium chloride solution (5 mL), and subsequent warming to room temperature. The mixture was partioned between water (50 mL) and ether (100 mL) and the aqueous layer was extracted with ether (2 x 100 mL). The combined organic layer was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. TLC analysis of the crude product (25% ether/pentane) revealed the presence of two products, the aldehyde **9** (Rf: 0.34) and a small amount of the overreduction alcohol (Rf: 0.15). Purification by chromatography (25% ether/pentane) gave the aldehyde **9** as a colourless oil (1.1 g, yield: 76%). The alcohol (0.26 g, 0.47 mmol) was immediately redissolved in dichloromethane (25 mL), 4Å molecular sieves (0.3 g) were added, followed by *N*-methylmorpholine *N*-oxide (77 mg, 0.66 mmol) and tetra *n*-propylammonium perruthenate (8.3 mg, 24 μmol). The black suspension was vigorously stirred at room temperature for 1h, then filtered through a pad of celite, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue purified by chromatography (25% ether/pentane) to give 170 mg of additional aldehyde **9**. The total yield is 88% (1.271 g).

IR (film): ν (cm^{-1}): 3020, 2910, 2838, 1705, 1410, 1260, 1120, 1080, 880, 738; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm): 9.51 (1H, d, J= 1.5, CHO), 7.30 (5H, broad s, Ar-H), 5.53 (1H, d, J= 7.6, C_{3a}-H), 4.57 (1H, dt, J= 12.5, 5.0, C_2-H), 4.42 (2H, AB system, J= 11.9, Ar-CH_2), 3.71 (1H, d, J= 4.6, C_{4a}-H), 3.49 (1H, m, $C_{2'}$-H), 3.15 (1H, d, J= 7.6, C_{8a}-H), 3.09 (1H, ddd, J= 12, 7.6, 1.5, C_3-H), 2.03 (1H, d, J= 4.06, C_8-H), 1.90-1.40 (6H, m, $C_{1'}$-H x 2, C_6-H x 2, C_7-H x 2), 1.20 (20H, broad s, $C_{3'}$-$C_{12'}$-H), 0.90-0.70 (12H, 3s and 1t, $C_{13'}$-H x 3 and CH_3 x 3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 197.2 (CO), 138.7, 128.2, 127.6, 127.4 (Ar), 98.0 (C_{3a}), 89.5 (C_{4a}), 76.0, 75.5, 73.9 (C_2, C_{8a}, $C_{2'}$), 70.4 (Ar-*C*H_2), 64.0 (C_3), 49.0 (C_8), 48.4 (C_{10}), 45.8 (C_5), 37.4 ($C_{1'}$), 31.3 (C_6), 25.4 (C_7), 33.7, 31.9, 29.7, 29.62, 29.60, 29.57, 29.56, 29.3, 24.7, 22.7 ($C_{3'}$-$C_{12'}$), 14.0 ($C_{13'}$), 22.1, 18.8, 10.7 (CH_3 x 3); $[\alpha]_D^{20}$: -69.7 (c= 1, $CHCl_3$); mass (CI NH_3): m/z: 540 (M+ 1), 180; (electrospray): m/z: 562.3 (M+ Na), 540.3 (M+ 1); high resolution mass spectrum, calculated for $C_{34}H_{53}NNaO_4$ (M+ Na): 562.3872; found: 562.3880.

(2*S*,3*S*, 3a*S*, 4a*S*, 5*R*, 8*S*, 8a*R*, 2'*R*, 1" *E*)-2-(2'-Phenylmethyloxy-tridecyl)-3-(1"-hexenyl)-5,10,10-trimethyl-5,8-methano-octahydro-2*H*-isoxazolo-[3,2-*b*]-benzoxazole (11).

To a solution of *n*-pentyltriphenylphosphonium bromide (12.6 g, 31 mmol) in tetrahydrofuran (70 mL) was added portionwise sodium amide (from a freshly opened bottle, 1.19 g, 31 mmol). The bright red solution was strirred at reflux for 4h, then cooled to room temperature and filtered under an argon atmosphere. The resulting ylide **10** solution was added dropwise to a stirred and cooled (-78

°C) solution of the aldehyde **9** (1.1 g, 2 mmol) in tetrahydrofuran (50 mL), until the red colour persists. The excess reagent was immediately destroyed by addition of acetone (5 mL), the solution warmed to room temperature and then concentrated *in vacuo*. The residual oil was triturated with pentane (100 mL), filtered and concentrated. This operation was repeated three times. The crude alkene **11** thus obtained was immediately carried into the next reaction. An analytical sample was prepared by chromatography (10% ether/pentane, 50% loss of product upon purification).

Rf: 0.64 (25% ether/pentane); IR (film): ν (cm^{-1}): 3020, 2910, 2830, 1440, 1260, 1125, 1080, 740; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.30 (5H, broad s, Ar-H), 5.63 (1H, dt, J= 11.0, 7.3, $C_{2"}$-H), 5.20 (1H, m, $C_{1"}$-H), 5.16 (1H, d, J= 6.4, C_{3a}-H), 4.53 (2H, AB system, J= 11.9, Ar-CH_2), 3.80 (1H, m, C_2-H), 3.74 (1H, d, J= 7.3, C_{4a}-H), 3.55 (1H, m, $C_{2'}$-H), 3.18 (1H, d, J= 7.3, C_{8a}-H), 2.82 (1H, m, C_3-H), 2.04 (1H, d, J= 4, C_8-H), 2.00 (2H, m, $C_{3"}$-H), 1.85-1.25 (8H, m, C_6-H x 2, C_7-H x 2, $C_{1'}$-H x 2, $C_{3'}$-H x 2), 1.22 (22H, broad s, $C_{4'}$-$C_{12'}$-H, $C_{4"}$-H x 2, $C_{5"}$-H x 2), 0.90-0.75 (15H, 3s and 2t, $C_{13'}$-H x 3, $C_{6"}$-H x 3, CH_3 x 3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 139.0, 128.2, 127.5, 127.4 (Ar), 134.5 ($C_{2"}$), 122.2 ($C_{1"}$), 99.8 (C_{3a}), 89.7 (C_{4a}), 77.3, 77.1, 76.2 (C_2, C_{8a}, $C_{2'}$), 71.2 (O-*C*H_2-Ar), 51.3 (C_3), 49.4 (C_8), 48.7 (C_{10}), 45.5 (C_5), 36.7 ($C_{1'}$), 34.4 ($C_{3'}$), 31.8 (C_6), 25.6 (C_7), 31.7, 31.5, 29.7, 29.58, 29.54, 29.52, 29.50, 29.26, 27.6, 24.8, 22.6, 22.2 ($C_{4'}$-$C_{12'}$, $C_{3"}$-$C_{5"}$), 14.0 ($C_{13'}$), 13.9 ($C_{6"}$), 22.1, 18.7, 10.9 (CH_3 x 3); $[\alpha]_D^{20}$: -92.2 (c= 1, $CHCl_3$); mass (CI NH_3): m/z: 594 (M+ 1), 593 (M^+), 180; (electrospray): m/z: 616.3 (M+ Na), 594.3 (M+ 1); high resolution mass spectrum, calculated for $C_{39}H_{64}NO_3$ (M+ 1): 594.4886; found: 594.4889.

(2*S*, 3*S*, 5*R*, 1' *E*)-2-(1'-hexenyl)-3-hydroxy-5-phenylmethyloxy-hexadecanal (12).

The crude product **11** was dissolved in ether (50 mL) and *meta*-chloroperoxybenzoic acid (1.4 g, 8 mmol) was added. The clear solution was stirred 1h at room temperature, then 10 mL of an aqueous 10% sodium thiosulfate/ 10% sodium bicarbonate solution was added. The biphasic mixture was vigorously stirred for 1h, then separated and the aqueous layer extracted with ether (2 x 50 mL). The combined organic layer was washed with aqueous 5% sodium bicarbonate solution (2 x 50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to a colourless oil. The crude nitrone was used immediately into the next reaction.

The crude product from the above reaction was dissolved in tetrahydrofuran (25 mL) and 2M hydrochloric acid solution (25 mL) was added. The solution was stirred 2h at room temperature, then diluted with water (25 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude product by chromatography (25% ether/pentane) gave, in order of elution, the recovered ketol **13** (Rf: 0.35, 0.3 g, 98% recovery), followed by the aldehyde **12** (Rf: 0.26, 0.46 g). The overall yield was 51% from the aldehyde **9**.

IR (film): ν (cm^{-1}): 3400, 3025, 2920, 2840, 1710, 1440, 1260, 1060, 740; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 9.56 (1H, d, J= 2.7, C_1-H), 7.30 (5H, broad s, Ar-H), 5.73 (1H, dt, J= 10.7, 7.4, $C_{2'}$-H), 5.16 (1H, m, $C_{1'}$-H), 4.53 (2H, AB system, J= 11.4, Ar-C*H*$_2$), 4.26 (1H, m, C_3-H), 3.69 (1H, m, C_5-H), 3.40-3.28 (2H, m, C_2-H and OH), 2.15-1.92 (4H, m, $C_{3'}$-H x 2 and C_4-H x 2), 1.78-1.18 (22H, m, C_6-C_{14}-H, $C_{4'}$-H x 2, $C_{5'}$-H x 2), 0.95-0.78 (6H, 2t, C_{16}-H x 3, $C_{6'}$-H x 3); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 200.9 (C_1), 138.1, 128.5, 127.9, 127.8 (Ar), 137.0 ($C_{2'}$), 120.4 ($C_{1'}$), 76.5 (C_5), 71.2 (O-*C*H$_2$), 68.6 (C_3), 58.1 (C_2), 37.2 (C_4), 31.9, 31.5, 29.7, 29.58, 29.54, 29.52, 29.50, 29.26, 27.9, 25.3, 22.6, 22.3 (C_6-C_{15}, $C_{3'}$-$C_{5'}$), 14.1 (C_{16}), 13.9 ($C_{6'}$); $[\alpha]_D^{20}$: -53.1 (c= 0.64, $CHCl_3$); mass (electrospray): m/z: 467.3 (M+ Na); high resolution mass spectrum, calculated for $C_{29}H_{48}NaO_3$ (M+ Na):467.3501; found: 467.3499.

(3*S*, 4*S*, 2'*R*, 1"*Z*)-3-(1"-hexenyl)-4-(2'-phenylmethyloxy-tridecyl)-2-oxetanone (14).

The aldehyde **12** was dissolved in a mixture of *tert*-butanol (18 mL) and 2-methyl-2-butene (7 mL) and a freshly prepared aqueous 10% sodium chlorite and 10% sodium dihydrogen phosphate solution (6 mL) was added. The solution was strrred 24h at room temperature, then diluted with water (20 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude secco-acid (Rf: 0.11, 50% ether/heptane), which was used without further purification.
The crude product was redissolved in pyridine (5 mL) and and the solution cooled to 0 °C. Benzenesulfonyl chloride (0.245 mL, 1.91 mmol) was added, and the solution left overnight in a refrigerator. Water (3 mL) was added, and the solution extracted with ether (3 x 25 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude product by chromatography (10% ether/pentane) gave the β-lactone **14** as a colourless oil (0.13 g, overall yield: 50% from **12**).

Rf: 0.69 (25% ether/pentane); IR (film): ν (cm^{-1}): 3035, 2910, 1805, 1445,3 1260, 740; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 7.30 (5H, broad, Ar-H), 5.67 (1H, ddt, J= 10.7, 7.3, 1.0, $C_{2"}$-H), 5.45 (1H, ddt, J= 10.7, 8.8, 1.0, $C_{1"}$-H), 4.52 (1H, m, C_4-H), 4.50 (2H, AB system, J= 11.4, Ar-C*H*$_2$), 4.11 (1H, ddd, 8.8, 3.9, 1.0, C_3-H), 3.59 (1H, m, $C_{2'}$-H), 1.99 (4H, m, $C_{1'}$-H x 2, $C_{3"}$-H x 2), 1.60 (2H, m, $C_{3'}$-H), 1.28 (20H, m, $C_{4'}$-$C_{12'}$-H, $C_{4"}$-H x 2, $C_{5"}$-H x 2), 0.87 (6H, 2t, $C_{13'}$-H x 3, $C_{6"}$-H x 3); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 169.9 (C_2), 138.3, 128.4, 127.9, 127.8 (Ar), 136.7 ($C_{2"}$), 129.5 ($C_{1"}$), 76.1 ($C_{2'}$), 75.4 (C_4), 71.5 (O-*C*H$_2$-Ar), 55.4 (C_3), 39.3 (C_1), 33.9 ($C_{3'}$), 31.9, 31.5, 29.7, 29.58, 29.54, 29.52, 29.50, 29.26, 27.9, 25.3, 22.6, 22.3 ($C_{4'}$-$C_{12'}$, $C_{3"}$-$C_{5"}$), 14.1 ($C_{13'}$), 13.9 ($C_{6"}$); $[\alpha]_D^{20}$: -63.1 (c= 1, $CHCl_3$); mass (electrospray): m/z: 465.3 (M+ Na); high resolution mass spectrum, calculated for $C_{29}H_{46}NaO_3$ (M+ Na): 465.3345; found: 465.3348.

(3*S*, 4*S*, 2'*R*)-3-Hexyl-4-(2'-hydroxytridecyl)-2-oxetanone (15).

10% Palladium on carbon (0.14 g) was added to a solution of the β-lactone **14** (0.122 g, 0.276 mmol) in ethyl acetate (5mL) and the resulting black suspension was stirred overnight under a hydrogen atmosphere. The mixture was then filtered through a short pad of celite, rinsing with ethyl acetate, and the filtrate was concentrated *in vacuo*. Purification of the crude product by chromatography (25% ether/pentane) gave the known[4,8] β-lactone **15** as a white solid (98 mg; yield: 99%). An analytical sample was prepared by recristallisation from hexanes. All analytical and spectral data were in complete agreement with those reported in the literature.

Rf: 0.17 (25% ether/pentane); mp: 62.5 °C; litt[4,8]: 62 °C; IR ($CHCl_3$): ν (cm^{-1}): 3450, 3030, 2910, 2838, 1800, 1450, 1260, 1115, 880, 740, 700; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 4.48 (1H, dt, J= 8.3, 4.0, C_4-H), 3.78 (1H, m, $C_{2'}$-H), 3.23 (1H, dt, J= 7.5, 3.9, C_3-H), 1.95-1.60 (6H, m, $C_{1'}$-H x 2, $C_{3'}$-H x 2), 1.55-1.10 (26H, m, $C_{4'}$-$C_{12'}$-H, $C_{2''}$-$C_{5''}$-H), 0.85 (6H, 2t, $C_{13'}$-H x 3, $C_{6''}$-H x 3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 171.6 (C_2), 75.6 ($C_{2'}$), 68.4 (C_4), 56.5 (C_3), 41.8 ($C_{1'}$), 38.1 ($C_{3'}$), 31.9, 31.5, 29.7, 29.58, 29.54, 29.52, 29.50, 29.47, 29.26, 27.9, 25.3, 25.0, 22.6, 22.3 ($C_{4'}$-$C_{12'}$, $C_{1''}$-$C_{5''}$), 14.1 ($C_{13'}$), 14.0 ($C_{6''}$); $[\alpha]_D^{20}$: -40.0 (c= 1, $CHCl_3$); lit.[4,8]: $[\alpha]_D^{20}$: -40.8 (c= 1, $CHCl_3$); mass (electrospray): m/z: 377.2 (M+ Na); high resolution mass spectrum, calculated for $C_{22}H_{42}NaO_3$ (M+ Na): 377.3032; found: 377.3030.

Tetrahydrolipstatin (1).

To a solution of the hydroxy-β-lactone **15** (30 mg, 87 μmol) in tetrahydrofuran were successively added *N*-formyl-L-leucine (47 mg, 297 μmol) and triphenylphosphine (66 mg, 250 μmol). The solution was cooled to 0 °C, and diisopropylazodicarboxylate (DIAD, 58 μL, 297 μmol) was added dropwise. The mixture was stirred 3h at room temperature then concentrated *in vacuo*. Purification of the crude product by chromatography (15% ethyl acetate/toluene) gave tetrahydrolipstatin **1** as a white solid (39 mg; yield: 93%). This solid was dissolved in the minimum amount of pentane, and the solution left in a freezer at -20 °C. The white crystals of **1** were collected by filtration.

Rf: 0.42 (25% ether/pentane); mp: 42 °C; lit.[1]: 40-42 °C; IR ($CHCl_3$): ν (cm^{-1}): 2970, 2940, 2870, 1835, 1745, 1705, 1500, 1470, 1200, 1120; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 8.20 (1H, s, CHO), 5.92 (1H, d, J= 8.4, NH), 5.01 (1H, m, $C_{2'}$-H), 4.67 (1H, ddd, J= 8.9, 8.9, 4.7, C*H*-N), 3.20 (1H, ddd, J= 7.6, 7.6, 4.1, C_3-H), 2.15 (1H, ddd, J= 15.3, 7.7, 7.7, one of $C_{1'}$-H), 1.95 (1H, ddd, J= 15.3, 4.5, 4.5, one of $C_{1'}$-H), 1.86-1.48 57H, m), 1.46-1.18 (23H, m), 0.86 (6H, 2t, $C_{13'}$-H x 3, $C_{6''}$-H x 3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 171.9 (C_2), 170.7 (CO), 160.6 (NH*C*HO), 74.7 ($C_{2'}$), 72.7 (C_4), 57.0 (C_3), 49.6 (*C*H-NH), 41.6 ($C_{1'}$), 38.7 ($C_{3'}$), 34.0, 31.9, 31.5, 29.6, 29.4, 29.3, 29.2, 29.1, 28.9, 27.6, 26.7, 25.1, 24.9, 22.9 (CH_3), 22.7, 22.6, 22.5, 21.7 (CH_3), 14.1 ($C_{13'}$), 14.0 ($C_{6''}$); $[\alpha]_D^{20}$: -32.0 (c= 0.74, $CHCl_3$); lit.[1]: $[\alpha]_D^{20}$: -33.0 (c= 0.79,

$CHCl_3$); mass (electrospray): m/z: 518.3 (M+ Na); high resolution mass spectrum, calculated for $C_{29}H_{53}NNaO_5$ (M+ Na): 518.382143; found: 518.382140.