# A Chiron Approach to (–)-Tetrahydrolipstatin

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**Abstract:** An efficient chiron approach to the total synthesis of (–)-tetrahydrolipstatin is described. The main features of the synthetic strategy, which starts from tri-*O*-acetyl-D-glucal, are copper-mediated C–C bond formation, Frater alkylation, and Barton–McCombie deoxygenation.

**Key words:** (–)-tetrahydrolipstatin, anti-obesity, tri-*O*-acetyl-D-glucal, Frater alkylation

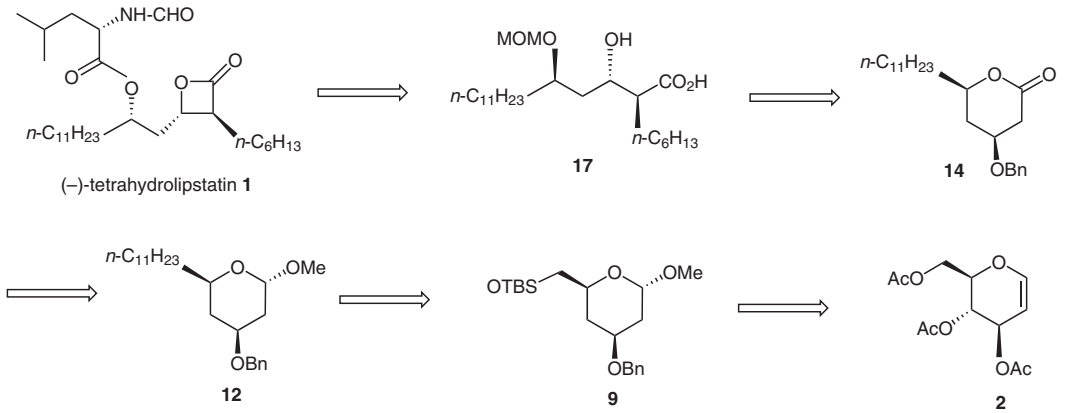
(–)-Tetrahydrolipstatin 1, a β-lactone, is a potent and irreversible inhibitor of pancreatic lipase; it is the saturated analogue of lipstatin and was first isolated from *Streptomyces toxytricini* in 1987.[1] Recently, it has been marketed in several countries as an anti-obesity agent under the name Xenical. The key to the biological activity of the lipstatins is the β-lactone moiety, which features *anti* stereochemistry about the ring. Due to its biological properties, tetrahydrolipstatin has been the target of many synthetic organic chemists since its isolation.[2]

Our retrosynthetic analysis is depicted in Scheme 1. Thus, (–)-tetrahydrolipstatin (**1**) could be obtained in a three-step sequence from β-hydroxy acid **17**. It is envisaged that the hydroxy acid **17** could be obtained from δ-lactone **14**. The δ-lactone **14** could be, in turn, obtained from tri-*O*-acetyl-D-glucal, with methanol addition and Barton–McCombie deoxygenation as the key transformations.

The synthesis begins by C-glycosidation of tri-*O*-acetyl-D-glucal (**2**) by addition of methanol and cerium(III) chloride heptahydrate/sodium iodide in acetonitrile, a method developed by our group,[3] to afford methyl acetal **3**. The methyl acetal **3** was subjected to methanolysis and subsequent selective protection of the 1,3-diol part to furnish **4** in 66% overall yield. Compound **4** was protected its benzyl ether **5** and then subjected to benzylidene acetal cleavage with 4-toluenesulfonic acid in methanol to afford 1,3-diol **6**, which was selectively protected with a *tert*-butyldimethylsilyl group at the primary hydroxy group to give **7** and the secondary hydroxy group was then protected as its xanthate ester to afford **8** in 40% yield over four steps. Now the stage is set for Barton–McCombie deoxygenation. Accordingly, compound **8** was treated with tributyltin hydride and a catalytic amount of 2,2′-azobis(isobutyronitrile) in dry toluene under reflux conditions to afford the deoxygenated compound **9**.[4]

The *tert*-butyldimethylsilyl group of compound **9** was removed and the resulting alcohol **10** was treated with 4-toluenesulfonyl chloride and triethylamine in dichloromethane to afford the corresponding tosylate **11**, which was treated with *n*-decylmagnesium bromide and catalytic copper(I) bromide to obtain the coupled product **12**.[5] Compound **12** could also be obtained from alcohol **10** via conversion to the corresponding triflate and copper-mediated Grignard displacement.[6]

The methyl acetal of **12** was converted into lactol **13** by treatment with 80% aqueous acetic acid, which in turn was subjected to oxidation with Dess–Martin periodinane[7] to yield lactone **14**. The β-lactone **14** was opened in the presence of triethylamine in methanol to




**Scheme 1**

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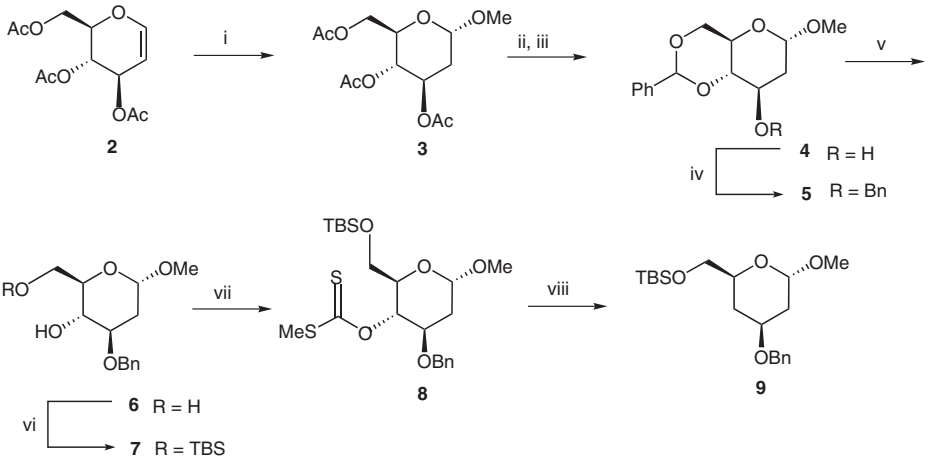
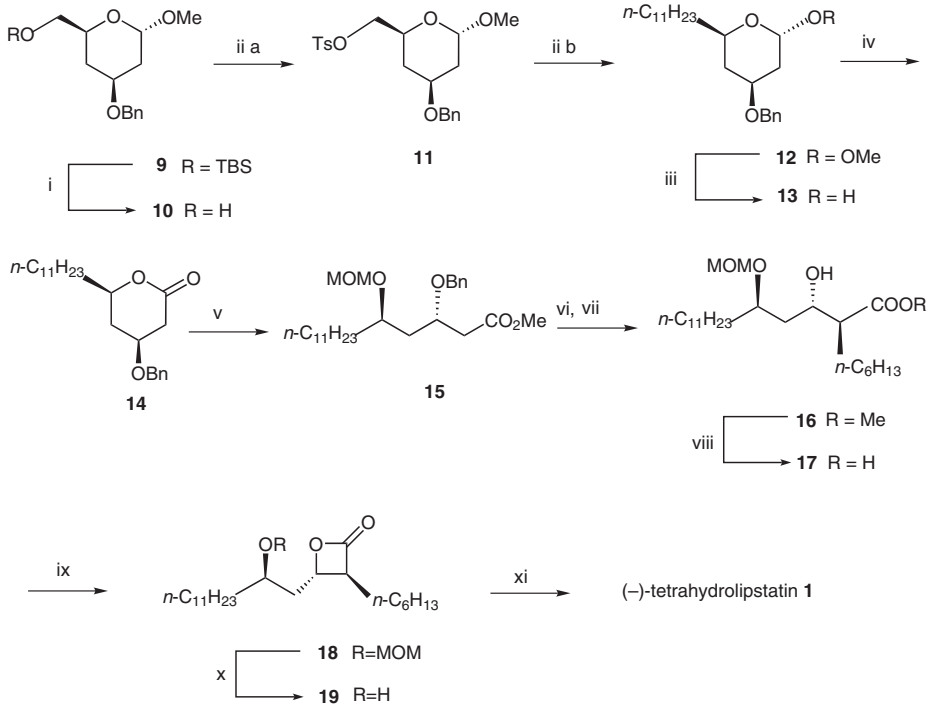



**Scheme 2** *Reagents and conditions:* (i) $CeCl_3$–NaI, MeCN, MeOH, reflux, 3 h, 87%; (ii) NaOMe, MeOH, r.t., 2 h; (iii) $PhCH(OMe)_2$, PTSA (cat.), toluene, reflux, 2 h, 66% for 2 steps; (iv) NaH, BnBr, TBAI (cat.), THF, reflux, 6 h, 78%; (v) PTSA (cat.), MeOH, overnight, 79%; (vi) TBSCl, imidazole, $CH_2Cl_2$, 0 °C to r.t., 4 h, 83%; (vii) NaH, $CS_2$, MeI, 0 °C to r.t., overnight, 78%; (viii) *n*-$Bu_3SnH$, AIBN (cat.), toluene, reflux, 6 h, 79%.

yield the corresponding δ-hydroxy ester, which without workup, on removal of methanol under reduced pressure was protected as its methoxymethyl ether **15** in the presence of *N*,*N*-diisopropylethylamine and methoxymethyl chloride in dichloromethane. Attempts made to isolate the methanol addition product, the δ-hydroxy ester, were unsuccessful as it cyclized back to lactone **14**. The methyl ester **15** was hydrogenated with palladium(II) hydroxide $Pd(OH)_2$ in ethyl acetate to afford a β-hydroxy ester. The key step, stereocontrolled alkylation, was effected by treating the β-hydroxy ester with lithium diisopropylamide in tetrahydrofuran, followed by addition of *n*-hexyl iodide to the dianion to give **16** as the major diastereomer in 75% yield after a flash column chromatography.[8] The crude product of the reaction revealed ~2% of the other diastereomer.

Hydroxy ester **16** was converted to β-lactone **18** by hydrolysis of ester group with lithium hydroxide followed by exposure of acid **17** to benzenesulfonyl chloride in pyridine. Deprotection of the methoxymethyl ether of β-lactone **18** with boron trifluoride–diethyl ether complex and




**Scheme 3** *Reagents and conditions:* (i) TBAF, THF, 0 °C to r.t., 2 h, 98%; (ii) (a) TsCl, $Et_3N$, DMAP (cat.), $CH_2Cl_2$, 0 °C to r.t., 2 h, 92%; (ii) (b) *n*-$C_{10}H_{21}MgBr$, CuBr (cat.), THF, 0 °C to r.t., 5 h, 76%; (iii) 80% aq AcOH, reflux, 6 h, 72%; (iv) Dess–Martin periodinane, $CH_2Cl_2$, 0 °C to r.t., 2 h, 84% (v) $Et_3N$, MeOH, 0 °C to r.t., 12 h, then MOMCl, DIPEA, $CH_2Cl_2$, 0 °C to r.t., 12 h, 71%; (vi) $Pd(OH)_2$/C, EtOAc, 12 h, 94%; (vii) LDA, *n*-$C_6H_{13}I$, HMPA, THF, –78 °C, 3 h, 75%; (viii) LiOH, THF–$H_2O$, (4:1), 0 °C to r.t., 12 h, 88%; (ix) $PhSO_2Cl$, pyridine, 12 h, 0 °C, 76%; (x) $BF_3{\cdot}OEt_2$, $(CH_2SH)_2$, 0 °C to r.t., 1 h, 88%; (xi) DIAD, TPP, *N*-formyl-L-leucine, 0 °C to r.t., 2 h, 90%.

ethane-1,2-dithiol[9] in dichloromethane produced alcohol **19** which on esterification with (*S*)-*N*-formyl-L-leucine under Mitsunobu conditions[10] furnished (–)-tetrahydrolipstatin (**1**). The spectroscopic and physical data of **1** were in good agreement with those in literature.

In conclusion, an efficient total synthesis of (–)-tetrahydrolipstatin using the chiron approach has been achieved. Simple manipulations of commercially available, inexpensive tri-*O*-acetyl-D-glucal led to the complex and demanding anti-obesity drug (–)-tetrahydrolipstatin (**1**).

Melting points were recorded on a Fisher John melting point apparatus. IR spectra were recorded on a Perkin Elmer Infrared-683 spectrophotometer with NaCl optics. $^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200 and AV-300 spectrometers. Optical rotations were measured on JASCO DIP-360 digital polarimeter. Analytical TLC was performed on precoated silica gel-60 $F_{254}$ (0.5 mm) glass plates. Column chromatography was performed using silica gel (60–120 mesh) and the column was generally eluted with EtOAc–petroleum ether.

**(2*R*,3*R*,4*R*,6*S*)-3,4-Diacetoxy-2-(acetoxymethyl)-6-methoxytetrahydro-2*H*-pyran (3)**

A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (**2**; 20.6 g, 75.6 mmol), MeOH (6.13 mL, 151.2 mmol), $CeCl_3 \cdot 7\,H_2O$ (42.32g, 113.6 mmol), and NaI (17.02 g, 113.6 mmol) in MeCN (150 mL) was stirred at reflux temperature for 6 h. The mixture was diluted with $H_2O$ (150 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (anhyd $Na_2SO_4$), concentrated in vacuo, and purified by column chromatography to give methyl glucoside **3** as a colorless oil; yield: 20.0 g (87%); 10:1 mixture of anomers.

Data for the major anomer:

$[\alpha]_D^{20}$ +130.76 (*c* 1.5, $CHCl_3$).

$R_f$ = 0.4 (silica gel, 30% EtOAc–hexane).

IR (neat): 2947, 2838, 1745 (C=O), 1231, 1049 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 5.25 (ddd, *J* = 11.7, 9.4, 5.3 Hz, 1 H), 4.93 (t, *J* = 9.8 Hz, 1 H), 4.81 (d, *J* = 3.4 Hz, 1 H), 4.28 (dd, *J* = 12.0, 4.53 Hz, 1 H), 4.01 (dd, *J* = 12.0, 2.2 Hz, 1 H), 3.88 (ddd, *J* = 10.2, 4.5, 2.2 Hz, 1 H), 3.35 (s, 3 H), 2.22 (ddd, *J* = 12.8, 5.7, 1.1 Hz, 1 H), 2.08 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.78 (ddd, *J* = 12.8, 11.7, 3.8 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 170.01, 169.46, 169.22, 97.43, 68.83, 68.48, 67.17, 61.88, 54.22, 34.33, 20.24, 20.04.

MS (ESI): *m*/*z* = 327 ($M^+$ + Na).

HRMS: *m*/*z* [$M^+$ + Na] calcd for $C_{13}H_{20}NaO_8$: 327.1055; found: 327.1058.

**(4a*R*,6*S*,8*R*,8a*S*)-6-Methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-ol (4)**

To a soln of methyl glucoside **3** (12.8 g, 42.1 mmol) in MeOH (100 mL) was added 1 M NaOMe in MeOH (6.6 mL, 0.660 mmol). The mixture was stirred at r.t. for 1 h and the reaction was quenched by addition of Amberlyst. The mixture was filtered and concentrated under reduced pressure to give the crude triol, which was used in the next step without further purification.

A mixture of the crude triol, toluene (50 mL), benzaldehyde dimethyl acetal (6.1 mL, 41.1 mmol), and PTSA (325 mg, 1.7 mmol) was heated at reflux in a Soxhlet containing freshly activated powdered 4 Å molecular sieves (10 g) under an $N_2$ flow for 5 h. After 5 h, another batch of 4 Å molecular sieves (10 g) was placed in the Soxhlet extractor and reflux was continued for 1 h. The solid was filtered off, and the soln was diluted with $CH_2Cl_2$ and $H_2O$. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were washed with $H_2O$, dried ($MgSO_4$) and filtered and the solvents were evaporated to give crude acetal. Column chromatography afforded the pure acetal **4** as colorless needles; yield: 7.4 g (66%); mp 153–154 °C.

$[\alpha]_D^{20}$ +93.74 (*c* 7.0, $CHCl_3$).

$R_f$ = 0.4 (silica gel, 40% EtOAc–hexane).

IR (KBr): 3358 (OH), 2930, 1457, 1380, 1114, 1022 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.32 (m, 5 H), 5.50 (s, 1 H), 4.74 (d, *J* = 3.7 Hz, 1 H), 4.20 (m, 1 H), 4.08 (m, 1 H), 3.70 (m, 2 H), 3.38 (m, 1 H), 3.32 (s, 3 H), 2.47 (d, 1 H, OH), 2.16 (dd, *J* = 12.8, 5.3 Hz, 1 H), 1.71 (ddd, *J* = 13.6, 11.3, 3.7 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 137.40, 129.17, 128.30, 126.35, 102.00, 99.03, 83.87, 68.98, 65.63, 62.55, 54.75, 37.33.

MS (ESI): *m*/*z* = 267 [$M^+$ + H].

**(4a*R*,6*S*,8*R*,8a*S*)-8-(Benzyloxy)-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin (5)**

A magnetically stirred suspension of dry, oil-free NaH (1.24 g, 51.8 mmol) in anhyd THF (5 mL) at 0 °C was treated with the alcohol **4** (6.9 g, 25.9 mmol) in THF (25 mL). After 15 min, BnBr (3.38 mL, 28.5 mmol) was added followed by catalytic TBAI (479 mg). The mixture was brought to r.t. and stirred at reflux for 4 h, cooled to 0 °C, and treated slowly with sat. aq $NH_4Cl$ (20 mL). The product was extracted into EtOAc (2 × 100 mL); the combined extracts were dried ($Na_2SO_4$) and concentrated and the residual oil was purified by chromatography (silica gel) to afford **5** as white solid; yield: 6.64 g (78%); mp 95–96 °C.

$[\alpha]_D^{25}$ +71.35 (*c* 1.5, $CHCl_3$).

$R_f$ = 0.6 (silica gel, 30% EtOAc–hexane).

IR (neat): 2973, 1219, 1054, 1013, 772 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.45–7.28 (m, 10 H), 5.56 (s, 1 H), 4.81–4.61 (m, 3 H), 4.20 (q, *J* = 8.3, 3.0 Hz, 1 H), 3.97–3.89 (m, 1 H), 3.74–3.70 (m, 2 H), 3.67–3.57 (m, 1 H), 3.30 (s, 3 H), 2.20 (dd, *J* = 12.9, 4.53 Hz, 1 H), 1.73 (ddd, *J* = 12.8, 10.5, 3.7 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 128.0, 127.6, 127.4, 126.9, 126.7, 125.4, 100.6, 98.3, 83.2, 72.1, 68.4, 62.2, 53.9, 35.8.

MS (ESI): *m*/*z* = 357 [$M^+$ + H].

HRMS (ESI): *m*/*z* [$M^+$ + H] calcd for $C_{21}H_{25}O_5$: 357.1701; found: 357.1700.

**(2*R*,3*S*,4*R*,6*S*)-4-(Benzyloxy)-2-(hydroxymethyl)-6-methoxytetrahydro-2*H*-pyran-3-ol (6)**

To **5** (6.7 g, 18.8 mmol) in MeOH (15 mL) was added catalytic PTSA (178 mg) and the mixture was stirred for 12 h. It was quenched by addition of sat. aq $NaHCO_3$ (5 mL), MeOH was evaporated under reduced pressure, and the aqueous phase was extracted with EtOAc (2 × 75 mL). The organic extracts were washed with brine (20 mL) and dried (anhyd $Na_2SO_4$). The solvent was evaporated and the residue was purified by column chromatography to afford pure diol **6** as a greasy solid; yield: 3.98 g (79%); mp 38–40 °C.

$[\alpha]_D^{25}$ +62.77 (*c* 5.0, $CHCl_3$).

$R_f$ = 0.2 (silica gel, 60% EtOAc–hexane).

IR (neat): 3417 (OH), 1618, 1352, 1063, 772 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 5 H), 4.77 (d, *J* = 3.1 Hz, 1 H), 4.58 (q, *J* = 28.1, 11.7 Hz, 2 H), 3.78–3.69 (m, 3 H), 3.55–3.52 (m, 2 H), 3.31 (s, 3 H), 3.0 (br s, 1 H, OH), 2.37 (br s, 1 H, OH), 2.22 (dd, *J* = 12.5, 4.6 Hz, 1 H), 1.57 (ddd, *J* = 14.8, 11.7, 3.1 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 127.8, 127.0, 97.9, 76.3, 70.7, 70.6, 70.4, 61.8, 54.0, 34.0.

MS (ESI): *m*/*z* = 291 [$M^+$ + Na].

HRMS (ESI): *m*/*z* [$M^+$ + Na] calcd for $C_{14}H_{20}NaO_5$: 291.1208; found: 291.1206.

**(2*R*,3*S*,4*R*,6*S*)-4-(Benzyloxy)-2-[(*tert*-butyldimethylsiloxy)methyl]-6-methoxytetrahydro-2*H*-pyran-3-ol (7)**

To a magnetically stirred soln of diol **6** (3.5 g, 13.0 mmol) in anhyd $CH_2Cl_2$ (5 mL) and imidazole (1.77 g, 26.0 mmol) at 0 °C under an $N_2$ atmosphere was added TBSCl (1.96 g, 13.0 mmol); the mixture was allowed to warm up to r.t. and it was stirred for 4 h. The mixture was diluted with $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (anhyd $Na_2SO_4$), and concentrated in vacuo to afford the crude product. Column chromatography of the crude product afforded **7** as a colorless liquid; yield: 4.14 g (83%).

$[\alpha]_D^{25}$ +45.38 (*c* 3.75, $CHCl_3$).

$R_f$ = 0.5 (silica gel, 20% EtOAc–hexane).

IR (neat): 3478 (OH), 2931, 2896, 2857, 1464, 1053, 836, 777 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 4.74 (d, *J* = 3.1 Hz, 1 H), 5.59 (q, *J* = 18.7, 11.7 Hz, 2 H), 3.80 (m, 3 H), 3.56 (m, 2 H), 3.29 (s, 3 H), 2.65 (br s, 1 H, OH), 2.17 (dd, *J* = 14.0, 4.6 Hz, 1 H), 1.55 (ddd, *J* = 13.2, 11.7, 3.9 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 138.6, 128.4, 127.7, 98.4, 76.9, 72.5, 71.5, 71.2, 64.1, 54.5, 34.6, 25.9, –5.3.

MS (ESI): *m*/*z* = 383 [$M^+$ + H].

HRMS (ESI): *m*/*z* [$M^+$ + H] calcd for $C_{20}H_{35}O_5Si$: 383.2253; found: 383.2260.

**(2*R*,3*S*,4*R*,6*S*)-4-(Benzyloxy)-2-[(*tert*-butyldimethylsiloxy)methyl]-6-methoxy-3-{[(methylsulfanyl)carbothioyl]oxy}tetrahydro-2*H*-pyran (8)**

To a magnetically stirred suspension of NaH (460 mg, 19.2 mmol) in $CS_2$ (150 mL) was added a soln of **7** (3.7 g, 9.6 mmol) in $CS_2$ (12 mL). After 4 h, neat MeI (3.02 mL, 48.4 mmol) was introduced via syringe. The mixture was stirred for 12 h and then diluted with $Et_2O$ (200 mL) and washed with $H_2O$ (100 mL) and aq $NH_4Cl$ soln (30 mL), dried ($Na_2SO_4$), and the solvent evaporated. The residue was purified by chromatography to give xanthate **8** as a viscous yellow liquid; yield: 3.56 g (78%).

$[\alpha]_D^{25}$ +28.25 (*c* 5.0, $CHCl_3$).

$R_f$ = 0.5 (silica gel, 10% EtOAc–hexane).

IR (neat): 2929, 2856, 1463, 1363, 1217, 1057, 837, 777 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 5 H), 5.85 (t, *J* = 9.5 Hz, 1 H), 4.83 (d, *J* = 3.47 Hz, 1 H), 4.55 (q, *J* = 12.1 Hz, 2 H), 4.10–3.98 (m, 1 H), 3.87–3.75 (m, 1 H), 3.69–3.61 (m, 2 H), 3.34 (s, 3 H), 2.56 (s, 3 H), 2.27 (dd, *J* = 13.0, 5.2, 1 H), 1.78 (dt, *J* = 11.2, 3.4 Hz, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 215.4, 138.2, 128.2, 127.5, 97.9, 80.3, 74.4, 71.7, 71.1, 62.8, 54.5, 35.5, 25.9, 19.2, 18.3, –5.27, –5.36.

MS (ESI): *m*/*z* = 495 [$M^+$ + Na].

**[(2*S*,4*S*,6*S*)-4-(Benzyloxy)-2-[(*tert*-butyldimethylsiloxy)methyl]-6-methoxytetrahydro-2*H*-pyran (9)**

To a magnetically stirred soln of xanthate **8** (3.1 g, 6.56 mmol) and AIBN (ca. 30 mg) in anhyd toluene (20 mL) was added $Bu_3SnH$ (8.7 mL, 32.8 mmol). The resulting soln was stirred at reflux temperature for 1.5 h. The reaction contents were cooled, concentrated in vacuo, and flushed rapidly through a short column of silica gel to afford **9** as a clear, colorless oil; yield: 1.89 g (79%).

$[\alpha]_D^{25}$ +71.68 (*c* 2.0, $CHCl_3$).

$R_f$ = 0.45 (silica gel, 10% EtOAc–hexane).

IR (neat): 2932, 2895, 1460, 1055, 831, 772 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.28 (m, 5 H), 4.81 (d, *J* = 3.00 Hz, 1 H), 4.52 (m, 2 H), 3.82 (m, 1 H), 3.65 (m, 2 H), 3.53 (m, 2 H), 3.27 (s, 3 H), 2.08 (ddd, *J* = 16.6, 12.0, 4.53 Hz, 2 H), 1.50 (ddd, *J* = 15.1, 11.3, 3.7 Hz, 1 H), 1.23 (q, *J* = 11.3 Hz, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 128.24, 127.42, 99.02, 96.11, 70.83, 69.80, 68.62, 66.31, 54.30, 36.55, 34.42, 25.93, –5.29.

MS (ESI): *m*/*z* = 389 [$M^+$ + Na].

HRMS: *m*/*z* [$M^+$ + Na] calcd for $C_{20}H_{34}NaO_4Si$: 389.2124; found: 389.2134.

**(2*S*,4*S*,6*S*)-4-(Benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-methanol (10)**

To a cold (0 °C), magnetically stirred soln of **9** (3.5 g, 9.56 mmol) in anhyd THF (10 mL) was added 1.0 M TBAF in THF (19 mL, 19.1 mmol). The mixture was warmed to 25 °C, stirred for 2 h, treated with aq $NH_4Cl$ soln (30 mL), and extracted with EtOAc. The combined organic layers were dried ($Na_2SO_4$) and concentrated. The crude product was purified by chromatography (silica gel) to give **10** as a clear, colorless oil; yield: 2.36 g (98%).

$[\alpha]_D^{25}$ +110.6 (*c* 4.5, $CHCl_3$).

$R_f$ = 0.4 (silica gel, 50% EtOAc–hexane).

IR (neat): 3447, 2930, 1363, 1119, 1048, 737 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 5 H), 4.86 (d, *J* = 2.5 Hz, 1 H), 4.52 (s, 2 H), 3.95–3.71 (m, 2 H), 3.58–3.53 (m, 2 H), 3.30 (s, 3 H), 2.32 (br s 1 H, OH), 2.17 (dd, *J* = 12.7, 4.2 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.53 (dt, *J* = 12.7, 3.4 Hz, 1 H), 1.36 (q, *J* = 11.8 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 138.4, 128.2, 127.3, 99.0, 70.4, 69.7, 68.4, 65.5, 54.4, 36.4, 33.5.

MS (ESI): *m*/*z* = 275 [$M^+$ + Na].

HRMS (ESI): *m*/*z* [$M^+$ + Na] calcd for $C_{14}H_{20}NaO_4$: 275.1259; found: 275.1252.

**(2*S*,4*S*,6*S*)-4-(Benzyloxy)-2-methoxy-6-(tosyloxymethyl)tetrahydro-2*H*-pyran (11)**

To soln of **10** (1.96 g, 7.77 mmol) in anhyd $CH_2Cl_2$ (15 mL) was added $Et_3N$ (2.16 mL, 15.5 mmol) at 0 °C and this was followed by addition of TsCl (1.63 g, 8.55 mmol). The mixture was allowed to warm to r.t. and stirred for 3 h. The reaction was treated with aq 1 M HCl (12 mL) and extracted with $CH_2Cl_2$ (3 × 25 mL). The organic layer was washed with sat. aq $NaHCO_3$ (20 mL) and $H_2O$. The combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure. Flash chromatography of the crude product afforded tosylate **11** as a colorless viscous liquid; yield: 2.9 g (92%).

$[\alpha]_D^{25}$ +77.04 (*c* 4.1, $CHCl_3$).

$R_f$ = 0.4 (silica gel, 30% EtOAc–hexane).

IR (neat): 2933, 1362, 1177, 772 $cm^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.4 Hz, 2 H), 7.34–7.27 (m, 7 H), 4.77 (d, *J* = 2.5 Hz, 1 H), 4.49 (s, 2 H), 4.00–3.91 (m, 2 H), 3.88–3.72 (m, 2 H), 3.23 (s, 3 H), 2.46 (s, 3 H), 2.15–1.94 (m, 2 H), 1.47 (ddd, *J* = 1.52, 12.7, 3.4 Hz, 1 H), 1.23 (q, *J* = 11.8 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 129.6, 128.2, 127.8, 127.3, 99.0, 71.9, 70.1, 69.7, 65.6, 54.5, 36.1, 33.5, 21.4.

MS (ESI): *m*/*z* = 429 [$M^+$ + Na].

HRMS (ESI): *m*/*z* [$M^+$ + Na] calcd for $C_{21}H_{26}NaO_6S$: 429.1347; found: 429.1344.

**(2*S*,4*S*,6*R*)-4-(Benzyloxy)-2-methoxy-6-undecyltetrahydro-2*H*-pyran (12)**

To a suspension of CuBr (170 mg, 1.2 mmol) in THF (10 mL) at 0 °C was added 0.67 M *n*-$C_{10}H_{21}MgBr$ in $Et_2O$ (13 mL, 8.71 mmol), followed by monotosylate **11** (2.5 g, 6.15 mmol) in THF (25 mL); the mixture was stirred at r.t. for 5 h. The reaction was quenched with sat. aq $NH_4Cl$ soln and the insoluble residue was removed by filtration through Celite. The filtrate was concentrated and the residue was poured into $Et_2O$. The organic layer was rinsed with $H_2O$ and sat. brine (20 mL). Following solvent removal, the crude product was purified by column chromatography to give **12** as a colorless oil; yield: 1.76 g (76%).

$[\alpha]_D^{25}$ +54.26 (*c* 2.2, $CHCl_3$).

$R_f$ = 0.7 (silica gel, 30% EtOAc–hexane).

IR (neat): 2933, 1659, 1391, 770 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 5 H), 4.82 (d, *J* = 3.0 Hz, 1 H), 4.55–4.54 (m, 2 H), 3.87–3.76 (m, 1 H), 3.63 (t, *J* = 9.8 Hz, 1 H), 3.30 (s, 3 H), 2.16 (dd, *J* = 12.0, 3.7 Hz, 1 H), 2.03–1.99 (m, 1 H), 1.56–1.24 (m, 22 H), 0.91 (t, *J* = 6.0 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 128.3, 127.5, 99.1, 77.1, 69.8, 67.6, 54.4, 38.1, 36.5, 35.9, 31.9, 29.6, 29.3, 25.6, 22.6, 14.0.

MS (ESI): *m*/*z* = 399 ($M^+$ + Na).

HRMS: *m*/*z* [$M^+$ + Na] calcd for $C_{24}H_{40}NaO_3$: 399.2875; found: 399.2865.

**(2*S*,4*S*,6*R*)-4-(Benzyloxy)-6-undecyltetrahydro-2*H*-pyran-2-ol (13)**

A soln of methyl acetal **12** (1.39 g, 3.69 mmol) in 80% aq AcOH (25 mL) was refluxed for 4 h. The mixture was cooled to 0 °C, neutralized by addition of solid $NaHCO_3$, and extracted with $CH_2Cl_2$ (2 × 20 mL). The organic extracts were washed with $H_2O$ (2 × 10 mL), brine (10 mL), and dried (anhyd $Na_2SO_4$). Filtration and evaporation of the solvent followed by purification (column chromatography) afforded pure lactol **13** as a syrupy liquid; yield: 0.96 g (72%).

$[\alpha]_D^{25}$ +6.24 (*c* 2.25, $CHCl_3$).

$R_f$ = 0.4 (silica gel, 30% EtOAc–hexane).

IR (neat): 3367, 2921, 2850, 1092, 741 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 5 H), 5.39 (br s, 1 H), 4.54 (s, 2 H), 3.93–3.83 (m, 1 H), 3.57– 3.46 (m, 1 H), 3.32–3.24 (m, 1 H), 2.34–2.15 (m, 2 H), 2.06–1.91 (m, 1 H), 1.52–1.15 (m, 21 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

MS (ESI): *m*/*z* = 385 ($M^+$ + Na).

**(4*S*,6*R*)-4-(Benzyloxy)-6-undecyltetrahydro-2*H*-pyran-2-one (14)**

To a soln of lactol **13** (1.8 g, 4.9 mmol) in $CH_2Cl_2$ (20 mL) was added Dess–Martin periodinane (3.16 g, 7.45 mmol) at 0 °C and the mixture was stirred for 1 h under argon. The mixture was poured into 10% $Na_2S_2O_3$ soln and extracted with $Et_2O$. The organic layer was washed with sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography of the residue (silica gel) afforded lactone **14** as a waxy solid; yield: 1.50 g (84%); mp 31–33 °C.

$[\alpha]_D^{25}$ +10.14 (*c* 3.0, $CHCl_3$).

$R_f$ = 0.45 (silica gel, 30% EtOAc–hexane).

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 5 H), 4.53 (q, *J* = 11.3 Hz, 2 H), 4.10 (m, 1 H), 2.82 (dd, *J* = 16.6, 10.5 Hz, 1 H), 2.51 (dd, *J* = 17.3, 9.8 Hz, 1 H), 2.23 (d, *J* = 16.6 Hz, 1 H), 1.71 (m, 1 H), 1.61–1.55 (m, 2 H), 1.34– 1.18 (m, 18 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 170.3, 137.6, 128.5, 127.8, 127.5, 77.0, 70.3, 36.7, 35.5, 31.8, 29.5, 29.3, 24.8, 22.6, 14.0.

MS (ESI): *m*/*z* = 361 ($M^+$ + H).

HRMS (ESI): *m*/*z* [$M^+$ + H] calcd for $C_{23}H_{37}O_3$: 361.2742; found: 361.2747.

**Methyl (3*S*,5*R*)-3-(Benzyloxy)-5-(methoxymethoxy)hexadecanoate (15)**

To the lactone **14** (1.2 g, 3.33 mmol) in anhyd MeOH (8 mL) was added $Et_3N$ (2.32 mL, 16.6 mmol) at r.t. and the mixture was stirred at this temperature for 10 h. The MeOH was removed under reduced pressure, anhyd $CH_2Cl_2$ was added, and the soln cooled to 0 °C. The DIPEA (1.73 mL, 10.0 mmol), DMAP (7 mg), and MOMCl (536 mg, 6.6 mmol) were added sequentially at 0 °C and the mixture was stirred at r.t. for 6 h. It was then diluted with $H_2O$ (15 mL) and extracted with $CH_2Cl_2$ (2 × 15 mL) and the combined extracts were washed with $H_2O$ (10 mL) and brine (10 mL). The solvent was evaporated in vacuo and the crude product was subjected to column chromatography to afford **15** as colorless oil; yield: 1.03 g (71%).

$[\alpha]_D^{25}$ –24.46 (*c* 3.3, $CHCl_3$).

$R_f$ = 0.9 (silica gel, 20% EtOAc–hexane).

IR (neat): 2926, 2854, 1740 (C=O), 1459, 1038, 740 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.31–7.28 (m, 5 H), 4.59–4.46 (m, 4 H), 4.05–3.97 (m, 1 H), 3.72–3.64 (m, 4 H), 3.34 (s, 3 H), 2.55 (m, 2 H), 1.75–1.43 (m, 2 H), 1.34–1.25 (m, 20 H), 0.88 (t, *J* = 6.0 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 171.8, 128.3, 127.8, 127.6, 97.9, 75.2, 73.4, 71.6, 55.6, 51.6, 40.7, 40.1, 35.2, 31.9, 29.8, 29.6, 29.3, 24.9, 22.6, 14.1.

MS (ESI): *m*/*z* = 459 ($M^+$ + Na).

HRMS: *m*/*z* [$M^+$ + Na] calcd for $C_{26}H_{44}NaO_5$: 459.3086; found: 459.3107.

**Methyl (3*S*,5*R*)-3-Hydroxy-5-(methoxymethoxy)hexadecanoate**

Compound **15** (0.9 g, 2.06 mmol) in EtOAc (40 mL) was added $Pd(OH)_2/C$ (250 mg) and the suspension was hydrogenated for 12 h. Removal of the catalyst by filtration and flash chromatography gave alcohol as a colorless liquid; yield: 0.67 g (94%).

$[\alpha]_D^{25}$ –42.89 (*c* 2.85, $CHCl_3$).

$R_f$ = 0.6 (silica gel, 20% EtOAc–hexane).

IR (neat): 3471, 2925, 2854, 1738 (C=O), 1461, 1153, 1038 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.63 (q, *J* = 9.0, 2.2 Hz, 2 H), 4.21 (m, 1 H), 3.77 (m, 1 H), 3.69 (s, 3 H), 3.39 (s, 3 H), 3.29 (br s, 1 H, OH), 2.42 (m, 2 H), 1.55 (m, 4 H), 1.25 (m, 18 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 172.6, 96.2, 75.5, 64.7, 55.7, 51.4, 41.7, 41.1, 34.9, 31.8, 29.5, 25.1, 22.5, 13.9.

MS (ESI): *m*/*z* = 347 ($M^+$ + H).

HRMS (ESI): *m*/*z* [$M^+$ + Na] calcd for $C_{19}H_{38}NaO_5$: 369.2616; found: 369.2610.

**Methyl (2*S*,3*S*,5*R*)-2-Hexyl-3-hydroxy-5-(methoxymethoxy)hexadecanoate (16)**

To a stirred soln (–50 °C) of LDA (2.5 mmol) [generated from 1.6 M *n*-BuLi in THF (2.7 mL) and *i*-$Pr_2NH$ (0.61 mL)] in THF (3 mL) was quickly added a soln of methyl (3*S*,5*R*)-3-hydroxy-5-(methoxymethoxy)hexadecanoate (600 mg, 1.73 mmol) in THF (6 mL). The mixture was stirred at –50 °C for 1 h and then hexyl iodide (1.47 g, 6.9 mmol) in HMPA (0.8 mL) was then added dropwise.

The resulting mixture was stirred at this temperature for 1 h, warmed to –20 °C, again stirred for 1 h, warmed to 0 °C and stirred for 1 h. The yellow mixture was diluted with $Et_2O$ (80 mL) and poured in to sat. aq $NH_4Cl$ (50 mL). The aqueous layer was extracted with $Et_2O$ (3 × 50 mL), the combined organic layers were washed with $H_2O$ (15 mL) and brine (20 mL) and dried ($Na_2SO_4$), and the solvent was removed in vacuo. Flash chromatography afforded the **16** as the major diastereomer; yield: 559.2 mg (75%).

$[\alpha]_D^{25}$ –3.91 (*c* 0.6, $CHCl_3$).

$R_f$ = 0.3 (silica gel, 10% EtOAc–hexane).

IR (neat): 3449, 2924, 2854, 1735 (C=O), 1460, 1159, 1037 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.67 (d, *J* = 8.4, Hz, 2 H), 3.96 (m, 1 H), 3.80 (m, 1 H), 3.70 (s, 3 H), 3.39 (s, 3 H), 2.47–2.36 (m, 1 H), 1.71–1.4 (m, 6 H), 1.25 (m, 26 H), 0.89–0.84 (m, 6 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 175.6, 96.3, 76.9, 68.9, 51.9, 39.5, 34.9, 31.5, 29.6, 29.1, 27.3, 25.2, 22.4, 13.9.

MS (ESI): *m*/*z* = 431 ($M^+$ + H).

**(3*S*,4*S*)-3-Hexyl-4-[(2*R*)-2-(methoxymethoxy)tridecyl]oxetan-2-one (18)**

To a soln of **16** (360 mg, 0.83 mmol) in THF–MeOH–$H_2O$ (3:1:1, 5 mL) at 0 °C was added LiOH·$H_2O$ (350 mg, 8.3 mmol) in one portion and the mixture stirred for 1 h and the temperature allowed to rise from 0 °C to r.t.. It was then acidified with 1 M HCl at 0 °C to pH 2 and diluted with EtOAc (10 mL) and washed with brine (5 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The crude acid **17** was used directly in the next reaction.

To a stirred soln of acid **17** in anhyd pyridine (10 mL) cooled at 0 °C was added, dropwise via a syringe, $PhSO_2Cl$ (0.18 mL, 1.43 mmol). The light yellow soln was stirred at 0 °C overnight and then diluted with $Et_2O$ (30 mL). $H_2O$ (20 mL) was added, and the aqueous layer was extracted with $Et_2O$ (3 × 25 mL). The combined organic layers were washed once with $H_2O$ (15 mL) and dried (anhyd $Na_2SO_4$). The residue was subjected to column chromatography to afford **18**; yield: 210 mg (66% over two steps).

$[\alpha]_D^{25}$ –9.34 (*c* 0.45, $CHCl_3$).

$R_f$ = 0.4 (silica gel, 10% EtOAc–hexane).

IR (neat): 2926, 1824 (C=O lactone), 1730, 1271, 1038 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.62 (q, *J* = 14.9, 8.31 Hz, 2 H), 4.38 (m, 1 H), 3.67 (m, 1 H), 3.35 (s, 3 H), 3.15 (m, 1 H), 1.80–1.67 (m, 2 H), 1.61–1.46 (m, 2 H), 1.26 (m, 28 H), 0.88 (m, 6 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 171.3, 95.9, 75.1, 74.5, 56.5, 55.6, 39.9, 34.7, 31.8, 29.6, 29.5, 29.2, 28.9, 27.6, 26.7, 24.8, 22.6, 22.4, 14.0.

MS (ESI): *m*/*z* = 399 ($M^+$ + H).

**(3*S*,4*S*)-3-Hexyl-4-[(2*R*)-2-hydroxytridecyl]oxetan-2-one (19)**

A stirred soln of compound **18** (130 mg, 0.320 mmol) in $CH_2Cl_2$ (4 mL) was cooled to 0 °C and treated with $BF_3$·$OEt_2$ (28.5 mg, 0.20 mmol) and ethane-1,2-dithiol (75.7 mg, 0.8 mmol). The resulting mixture was stirred at 0 °C for 1 h and then quenched with aq $NaHCO_3$ soln (2 mL), and the aqueous layer was extracted with $Et_2O$ (2 × 5 mL). The combined organic extracts were washed with brine (3 mL), dried ($Na_2SO_4$), and concentrated in vacuo. Column chromatography (silica gel) of the crude product afforded **19** as a white solid; yield: 101.7 mg (88%); mp 61–62 °C.

$[\alpha]_D^{25}$ –41.3 (*c* 0.9, $CHCl_3$).

$R_f$ = 0.6 (silica gel, 20% EtOAc–hexane).

IR (KBr): 2924, 2854, 1730, 1461, 1273, 1078, 967 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.46–4.40 (m, 1 H), 3.84–3.72 (m, 1 H), 3.24–3.17 (dt, *J* = 7.55, 3.8 Hz, 1 H), 1.93–1.67 (m, 4 H), 1.46–1.40 (m, 2 H), 1.26 (m, 26 H), 0.88 (t, *J* = 6.0 Hz, 6 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 171.3, 75.1, 68.4, 56.8, 41.5, 38.3, 31.4, 31.7, 29.3, 26.3, 25.8, 22.3, 13.9.

MS (ESI): *m*/*z* = 355 ($M^+$ + H).

**(1*S*)-1-{[(2*S*,3S)-3-Hexyl-4-oxooxetan-2-yl]methyl}dodecyl (2*S*)-2-(Formylamino)-4-methylpentanoate (1)**

To a stirred mixture of **19** (25 mg, 0.07 mmol), $Ph_3P$ (22.2 mg, 0.08 mmol) and (*S*)-*N*-formyl-L-leucine (13.4 mg, 0.08 mmol) in anhyd THF (2 mL) cooled at 0 °C was added DIAD (17.1 mg, 0.08 mmol) via a syringe. The mixture was then stirred at r.t. overnight. Removal of solvent under reduced pressure followed by flash chromatography afforded **1** as white crystals; yield: 31.5 mg (90%); mp 39–41 °C.

$[\alpha]_D^{20}$ –33.2 (*c* 0.85, $CHCl_3$).

$R_f$ = 0.2 (silica gel, 20% EtOAc–hexane).

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 6.05 (d, *J* = 8.5 Hz, 1 H, NH), 5.02 (m, 1 H), 4.68 (m, 1 H), 4.28 (m, 1 H), 3.22 (dt, *J* = 7.6, 3.9 Hz, 1 H), 2.25–2.11 (m, 1 H), 2.02 (m, 1 H), 1.80–1.15 (m, 33 H), 0.95 (d, *J* = 5.2 Hz, 6 H), 0.87 (distorted t, 6 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 171.9, 170.8, 160.7, 74.8, 72.6, 56.9, 49.7, 41.4, 38.7, 34.0, 31.9, 31.2, 29.6, 29.5, 29.4, 29.3, 29.2, 28.8, 27.7, 26.8, 25.2, 24.9, 22.8, 22.7, 22.5, 21.7, 14.1, 14.0.

MS (ESI): *m*/*z* = 496 (M + H).

HRMS (ESI): *m*/*z* [$M^+$ + H] calcd for $C_{29}H_{54}NO_5$: 496.4001; found: 496.3994.

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