129. Stereoselective Syntheses of Tetrahydrolipstatin and of an Analogue, Potent Pancreatic-Lipase Inhibitors Containing a β-Lactone Moiety

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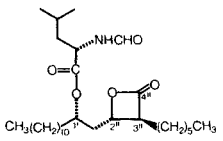
Tetrahydrolipstatin (**1**) and its analogue **2** are representatives of a new class of pancreatic-lipase inhibitors. Two stereoselective synthetic approaches are described.

Early syntheses of tetrahydrolipstatin (**1**), in connection with the determination of its absolute configuration, have already been described [1]. Our continued interest in pancreatic-lipase inhibitors has led us to prepare tetrahydrolipstatin (**1**) as well as several analogues, *e.g.* **2**, by stereoselective syntheses[1]).



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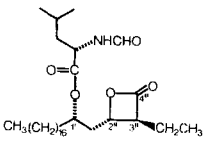

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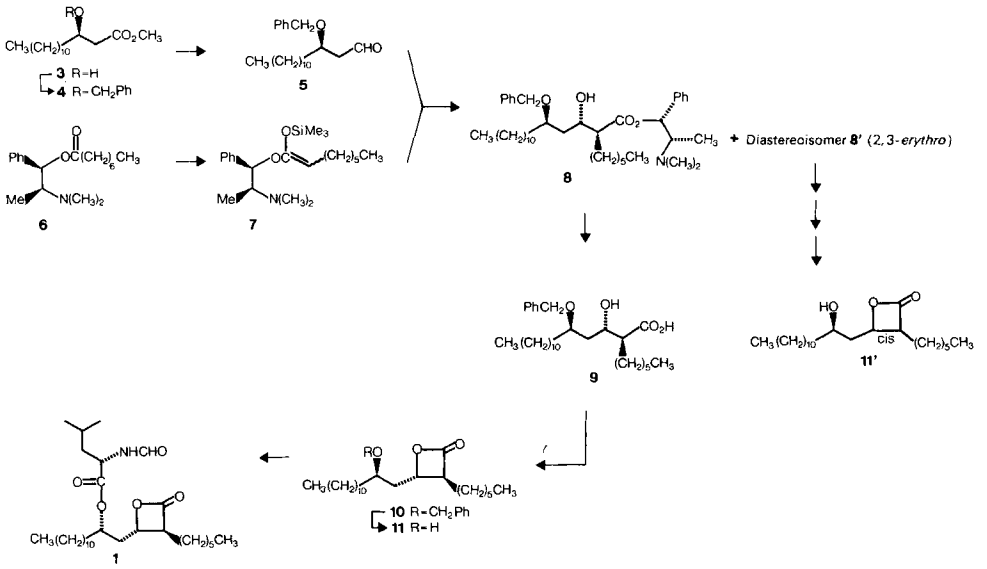
1. Tetrahydrolipstatin (1). – As a key step in this synthesis, the $TiCl_4$-mediated condensation of ketene silyl acetal derivative **7** of (–)-*N*-methylephedrine with aldehyde **5** was used, following a procedure of *Gennari et al.* [2].

Hydroxy ester **3** [3] (e.e. 98%, determined by GC of a probe esterified with (–)-*Mosher*'s reagent) was transformed into the benzyl derivative **4** according to a novel procedure [4], and reduction of **4** with diisobutylaluminium hydride (DIBAH) yielded aldehyde **5** *(Scheme 1)*. The other component in the condensation was ketene silyl acetal **7** which was obtained by silylation of ester **6**. Condensation of **7** with **5** in the presence of $TiCl_4$ yielded only two hydroxy esters in the proportion of 3:1. The major one, **8**, has the desired (2*S*,3*S*)-configuration, as shown by its transformation into tetrahydrolipstatin (**1**). The minor isomer **8'** has *erythro*-configuration at C(2),C(3), as indicated by its transformation into *cis*-β-lactone **11'** (the *cis*-conformation was established by NMR spectroscopy, see *Exper. Part*). Ester **8** was saponified to hydroxy acid **9** which, by ring closure with benzenesulfonyl chloride and pyridine, furnished β-lactone **10** in good yield. By hydrogenolysis, hydroxy-β-lactone **11** was obtained which was reacted with (*S*)-*N*-formylleucine under *Mitsunobu*'s conditions to yield tetrahydrolipstatin (**1**) without racemisation of the amino-acid moiety.

[1]) The synthesis of further derivatives, in connection with structure-activity relationships, will be described elsewhere.

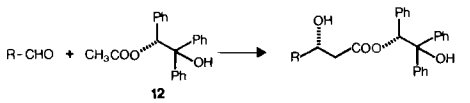
Scheme 1



The advantage of this synthesis is to form two new chiral centers, namely C(2″) and C(3″) in one reaction.

2. (1′*S*)-1′-[(2″*S*,3″*S*)-3″-Ethyl-4″-oxooxetan-2″-yl)methyl]octadecyl (*S*)-*N*-Formylleucinate (2). – The key step in this synthesis as shown in *Scheme 2* is the aldol-type condensation of an aldehyde with the anion of acetate **12**, esterified with an optically active alcohol derived from mandelic acid [5].

Scheme 2



Condensation of (*Z*)-9-octadecenal (**13**)[2]) with the dianion of acetate **12** gave, after transesterification of **14** with NaOMe, the hydroxyester **15** with an e.e. of approximately 75%. Protection of the OH group as its tetrahydropyranyl ether (→**16**) and reduction of the ester function with DIBAH yielded aldehyde **17**. Condensation of the latter with the dianion of acetate **12**, already used in the first aldol condensation, led to a mixture of diastereoisomeric hydroxy esters. By NMR analysis, two products could be identified in a ratio of 4:1[3]), desired **18** being the main product. This mixture was not further purified. Transesterification with NaOMe furnished diol **19** and hydroxy ester **20** with a yield of *ca.*

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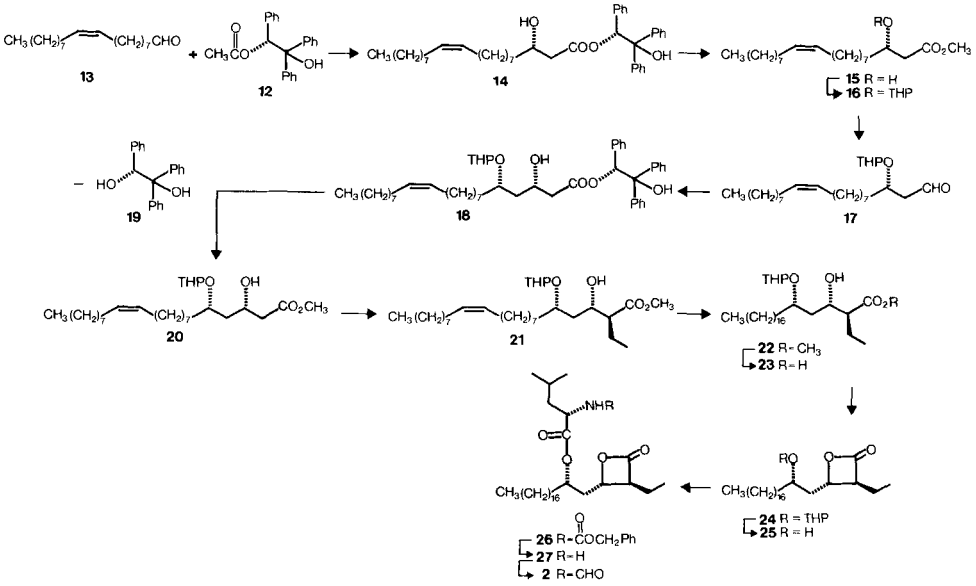
[2]) No reaction occurred, if octadecanal was used, presumably due to its low solubility in THF at −78°.

[3]) Cleavage of crude **18** with pyridinium *p*-toluenesulfonate in EtOH at 55–60° yielded the corresponding diol. Both H–C(3) and H–C(5) were found as 2 broad *m* in a ratio of 4:1. The same ratio was found for H–C(2) of the chiral auxiliary moiety. Since the first diastereoselective condensation step **13**→**14** gave **14** with a d.e. of *ca.* 80%, a similar value may be calculated for the second condensation **17**→**18**.

Scheme 3



75%. Stereoselective alkylation of **20** with EtI using the conditions given in [6] gave compound **21**, presumably with a high C(2),C(3) *erythro/threo* ratio.

By hydrogenation of the double bond (→**22**), followed by saponification to hydroxy acid **23** and ring closure with $PhSO_2Cl$ and pyridine, *β*-lactone **24** was obtained. Cleavage of the tetrahydropyranyl ether yielded, after chromatography, 2 *trans*-hydroxy-*β*-lactones in a ratio of *ca.* 4:1. As anticipated, isomer **25** was the main product which could be purified by recrystallization. Hydroxy-*β*-lactone **25** was esterified with the anhydride of (*S*)-*N*-(benzyloxycarbonyl)leucine to give ester **26**. Hydrogenolysis of the benzyloxycarbonyl protecting group (→**27**) and formylation yielded target compound **2**.

The advantage of this synthesis is the repeated use of the same chiral auxiliary reagent **12**. Moreover, after transesterification of the two condensation products with NaOMe, diol **19** is isolated in good yield and can be smoothly acetylated to give reagent **12** again.

Our thanks are due to Dr. *E. Broger* from *Hoffmann-La Roche & Co. AG*, Central Research, for making available to us hydroxy ester **3** in large amounts and to Mr. *C. Bardeanu*, *S. Burner*, and *R. Simon* for their excellent technical assistance. We thank our colleagues from *Hoffmann-La Roche & Co. AG*, Central Research, for spectral data and elemental analysis.

Experimental Part

General. Column chromatography: *Merck* silica gel *60* (70–230 mesh ASTM). M.p.: *Tottoli* capillary melting point apparatus; uncorrected. IR (cm^{-1}): *Nicolet 7199* FT-IR. ^{1}H-NMR (δ[ppm] relative to internal TMS; *J* in Hz): *Bruker WM 250*. MS: *MS9-ZAB*, data system *SS 200*.

Methyl (R)-3-(Benzyloxy)tetradecanoate (**4**). Methyl (*R*)-3-hydroxytetradecanoate (**3**; 370 g, 1.432 mol) and benzyl trichloroacetimidate (434 g, 1.718 mol) were dissolved in CH_2Cl_2 (2.3 l) and cyclohexane (4.6 l). The temp. fell to 10°. Trifluoromethansulfonic acid (37 ml) was added under stirring and Ar. The mixture was stirred for 3.5 h

at r.t. The crystalline material was filtered off, the filtrate was washed with aq. sat. $NaHCO_3$ (3 l) and H_2O (2 l). The aq. extracts were washed once with CH_2Cl_2 (500 ml) and the combined org. extracts dried (Na_2SO_4) and evaporated to give crude **4** (608 g). Crude **4** was treated with hexane (700 ml) and the insoluble material filtered off. The filtrate was chromatographed on silica gel (6 kg) with hexane/Et_2O 19:1, 9:1, 4:1, and 1:1 to give 387.6 g (78%) of **4** as an oil. IR (film): 1741, 1496. ^{1}H-NMR ($CDCl_3$): 7.31 (*m*, 5 arom. H); 4.53 (*s*, PhCH_2O); 3.88 (*m*, CHO); 3.67 (*s*, CH_3O); 2.62 (*dd*, *J* = 15.9, 7.9, H–C(2)); 2.48 (*dd*, *J* = 15.9, 5.9, H–C(2)); 1.25 (20 H); 0.88 (*t*-like, 3 H–C(14)). MS: 348 ($M^{+\cdot}$), 242, 91.

(R)-3-(Benzyloxy)tetradecanal (**5**). A soln. of **4** (455 g, 1.305 mol) in CH_2Cl_2 (4.5 l) was cooled under stirring and Ar to – 78°. A 1.2M DIBAH soln. in toluene (1.2 l) was added dropwise within 2 h. Then, the mixture was stirred for 30 min at – 78°, and an aq. sat. NH_4Cl soln. (330 ml), followed by 1N HCl (660 ml) were each added dropwise, each within 80 min. The mixture was warmed to r.t., the org. phase decanted from the solid which was washed with CH_2Cl_2 (1 l), and the combined org. phase dried (Na_2SO_4) and evaporated. The oily residue (439.4 g) was dissolved in hexane (500 ml) and chromatographed on silica gel (3 kg) with hexane and hexane/Et_2O 19:1, 9:1, and 4:1 to yield **5** (341 g, 82%) as a yellowish oil. $[\alpha]_{589}^{20} = -13.8°$ (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 9.87 (*t*, *J* = 3, CHO); 7.36 (*s*, 5 arom. H); 4.55 (*s*, PhCH_2O); 3.94 (*m*, H–C(3)); 2.60 (*m*, 2 H–C(2)); 1.77–1.12 (br. signal, 20 H); 0.88 (*m*, 3 H–C(14)).

(1R,2S)-2-(Dimethylamino)-1-phenylpropyl (2S,3S,5R)-5-(benzyloxy)-2-hexyl-3-hydroxyhexadecanoate (**8**). A soln. of **5** (200 g, 0.62 mol) in CH_2Cl_2 (3 l) was cooled to – 78°. $TiCl_4$ (75 ml) was added within 30 min, and the mixture was stirred for 10 min. A filtrated soln. of **7** (384 g; see below) in CH_2Cl_2 (2.4 l) was added within 2.5 h, and stirring was continued at – 78° for 1.5 h. At – 78°, 2N HCl (500 ml) was added dropwise, the mixture heated to r.t., and the aq. phase separated. The org. phase was washed with H_2O (3 l), dried (Na_2SO_4) and evaporated. The residue was partitioned between Et_2O (8 l) and H_2O (6 l). The org. phase was separated, washed twice with H_2O (3 l), dried (Na_2SO_4) and filtered. Et_3N (35 ml) was added to the org. phase which was washed twice with H_2O (1 l), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (1 kg) with hexane, hexane/AcOEt (1, 2, 3, 5, 10, 20 and 50%) to give **8** (155 g, 40%) as an oil. $[\alpha]_{589}^{20} = -23°$ (*c* = 0.3, $CHCl_3$). IR (film): 3478, 1733. ^{1}H-NMR ($CDCl_3$): 7.30 (*m*, 10 arom. H); 6.33 (*d*, *J* = 3.9, COOC*H*Ph); 4.63 (*d*, *J* = 11.9, 1 H, PhCH_2O); 4.54 (*d*, *J* = 11,9, 1 H, PhCH_2O); 4.06 (*m*, H–C(3)); 3.82 (*m*, H–C(5)); 2.46 (*m*, 2 H); 2.34 (*s*, $(CH_3)_2N$); 2.26 (*m*, 2 H); 1.85–1.19 (br. signal, 30 H); 0.90 (*m*, 9 H). CI-MS: 624 ($(M + H)^+$). Anal. calc. for $C_{40}H_{65}NO_4$ (623.96): C 77.00, H 10.50, N 2.24; found: C 77.26, H 10,64, N 2.26.

Starting from 0.9 g (2.83 mmol) of **5** and 1 g (2.65 mmol) of **7** using the same conditions, the product was separated to give the major **8** (513 mg) and the more polar, minor **8′** (170 mg). Total yield 40%, **8**/**8′** 3:1. **8′**: ^{1}H-NMR ($CDCl_3$, 270 MHz): 7.36–7.21 (*m*, 10 arom. H); 6.18 (*d*, *J* = 4,3, COOC*H*Ph); 4.6 (*AB*, *J* = 11, 1 H, PhCH_2O); 4.51 (*AB*, *J* = 11, 1 H, PhCH_2O); 4.21–4.10 (*m*, H–C(5)); 3.79–3.68 (*m*, H–C(3)); 2.72–2.57 (*m*, H–C(2), CHN); 2.31 (*s*, $(CH_3)_2N$); 1.78–1.13 (*m*, 33 H); 1.0 (*d*, *J* = 6, CH_3CHN); 0.93–0.79 (*m*, 2 CH_3CH_2).

Ester **8′** was, as described for **8**, saponified, cyclized, and debenzylated to give *cis-3-hexyl-4-[(R)-2′-hydroxytridecyl]oxetan-2-one* (**11′**; 63 mg). IR (film): 3413 (OH), 1829 (β-lactone). ^{1}H-NMR ($CDCl_3$, 250 MHz): 4.94–4.83 (*m*, H–C(4)); 3.91–3.75 (*m*, H–C(2′)); 3.72–3.59 (*m*, H–C(3)); 1.94–1.17 (*m*, 33 H); 0.87 (*t*, *J* = 6, 2 CH_3CH$_2$). MS: 337 ($M^{+\cdot} - H_2O$). Anal. calc. for $C_{22}H_{42}O_3$: C 74.52, H 11.94; found: C 74.22, H 11.98.

(2S,3S,5R)-5-(Benzyloxy)-3-hydroxy-2-hexylhexadecanoic Acid (**9**). A soln. of **8** (472 g, 0.75 mol) in 2N KOH/MeOH (5.7 l) was heated under reflux for 3 h. After cooling to r.t., the mixture was treated with 4N HCl (1.8 l, pH 7–8), keeping the temp. ≤ 30°. The solvent was evaporated and the residue partitioned between Et_2O (4 l) and H_2O (3 l). Addition of 1N HCl brought pH to 1. The org. phase was washed with 1N HCl (2 l) and H_2O (2 l), dried (Na_2SO_4), and evaporated to yield a yellow oil (352 g) which was chromatographed on silica gel with hexane/AcOEt (1, 2, 3, 5, 10, and 20%) giving **9** (222.6 g, 64%) as a yellowish oil. TLC (*Merck* silica gel *60 F* 254): $CHCl_3$/EtOH 94:6, R_f 0.5.

(3S,4S)-4-[(R)-2-(Benzyloxy)tridecyl]-3-hexyloxetan-2-one (**10**). A soln. of **9** (222.6 g, 0.48 mol) in pyridine (4.7 l) was cooled to 0° and under Ar and stirring, benzenesulfonyl chloride (128 ml, 0.962 mol) was added within 10 min. The mixture was stirred for 24 h at 0° and added to a 10% aq. NaCl soln. (18 l). Extraction with Et_2O (3 × 3 l), drying of the org. phase (Na_2SO_4), and evaporation yielded crude **10**, which was chromatographed on silica gel (3 kg) with hexane/Et_2O 19:1, 9:1, and 4:1 to give **10** (130.2 g, 61%) as an oil. IR (film): 1823. ^{1}H-NMR ($CDCl_3$): 7.33 (*s*, 5 arom. H); 4.67–4.37 (*m*, PhCH_2, H–C(4)); 3.59 (*m*, PhCH_2OC*H*); 3.25 (*m*, H–C(3)); 2.00–1.19 (br. signal, 32 H); 0.88 (*m*, 2 CH_3CH_2). Anal. calc. for $C_{29}H_{48}O_3$ (444.70): C 78.33, H 10.88; found: C 78.25, H 10.97.

(3S,4S)-3-Hexyl-4-[(R)-2′-hydroxytridecyl]oxetan-2-one (**11**). A soln. of **10** (130.2 g, 0.292 mol) in THF (4 l) was treated with 10% Pd/C (13 g) and hydrogenated at r.t. and normal pressure. After *ca.* 17 h, the catalyst was filtered and the filtrate evaporated. The residue was taken up in Et_2O, treated with charcoal, and filtered over *Celite*. The filtrate was evaporated to give crude **11** (106.1 g) which was chromatographed over silica gel (3 kg) with

hexane/AcOEt (1, 2, 4, 6, 8, 10, 15, 20, and 50%), and pure crystalline **11** was obtained (72.9 g, 70%). Recrystallization of a sample from hexane gave anal. pure **11**, m.p. 58.8–59°. $[\alpha]_{589}^{20} = -41.4°$ ($c = 0.5$, $CHCl_3$). IR (KBr): 3343, 3261, 1820, 1115. ^{1}H-NMR ($CDCl_3$): 4.50 (*m*, H–C(4)); 3.82 (*m*, OHC*H*); 3.27 (*m*, H–C(3)); 2.00–1.78 (*m*, 2 H–C(1')); 1.57 (*s*, OH); 1.54–1.12 (br. signal, 30 H); 0.88 (*t*-like, 2 CH_3). MS: 337 ($M^{+\cdot}$ – OH). Anal. calc. for $C_{22}H_{42}O_3$ (354.57): C 74.52, H 11.94; found: C 74.44, H 12.36.

(1'S)-1'-[((2"S,3"S)-3"-Hexyl-4"-oxooxetan-2"-yl)methyl]dodecyl (S)-N-Formylleucinate (= Tetrahydrolipstatin; **1**). A soln. of **11** (72.9 g, 0.205 mol), triphenylphosphine (64.6 g, 0.240 mol), and (*S*)-*N*-formylleucine (39.2 g, 0.246 mol) in THF (1 l) was cooled under stirring to 0°. Diethyl azodicarboxylate (43 ml, 0.246 mol) was added dropwise within 30 min, the mixture kept for 1 h at 0°, stirred for 2 h at r.t., and evaporated. The residue was taken up in hexane (500 ml) and Et_2O (500 ml), filtered, and evaporated. The residue was chromatographed on silica gel (3 kg) with toluene/AcOEt (1, 2, 4, 6, 8, 10, 12, 15, and 20%) to give **1** (84.5 g) which was recrystallized from pentane (78.9 g, 77%). M.p. 40–42°. $[\alpha]_{589}^{20} = -33°$ ($c = 0.36$, $CHCl_3$) identical in all respects (IR, NMR, MS, and $[\alpha]_D$) with tetrahydrolipstatin from natural origin [1] [7].

(1R,2S)-2-(Dimethylamino)-1-phenylpropyl Octanoate (**6**). A soln. of (–)-*N*-methylephedrine (50 g, 0.28 mol) in (*t*-Bu)OMe (1 l) was cooled to 0° and a soln. of octanoyl chloride (49.9 g, 0.3 mol) in (*t*-Bu)OMe (1.5 l) added dropwise. The mixture was stirred at r.t. for 72 h, and the crystals were filtered off and washed with (*t*-Bu)OMe (2 l). The crystals were shaken between (*t*-Bu)OMe (3 l) and H_2O (1 l); 1N NaOH was added (252 ml, 0.9 equiv.) and the org. phase washed with H_2O (1 l), dried (Na_2SO_4), and evaporated to yield pure **6** (76 g, 89.2%). IR (film): 1739, 1163. ^{1}H-NMR ($CDCl_3$): 7.28 (*m*, 5 arom. H); 5.94 (*d*, $J = 3.9$, PhC*H*); 2.90 (*m*, NCH); 2.35 (*t*, $J = 7.9$, CH_2(2)); 2.29 (*s*, $(CH_3)_2N$); 1.69 (*m*, CH_2); 1.26 (*m*, 4 CH_2); 1.05 (*d*, $J = 7.9$, CH_3CH); 0.87 (*t*, $J = 5.9$, CH_3CH_2). CI-MS: 306 ($M^{+\cdot}$ + H).

1-Octen-1-al [(1R,2S)-2-(Dimethylamino)-1-phenylpropyl] Trimethylsilyl Acetal (**7**). A soln. of (i-Pr)$_2$NH (210 ml, 1.47 mol) in THF (5 l) was cooled under Ar and stirring to –78°. The cooling bath was removed and 1.6M BuLi in hexane (1.1 l) added dropwise within 30 min. The mixture was stirred for 40 min and the temp. rose to –15°. The mixture was cooled to –78° and a soln. of **6** (450 g, 1.47 mol) in THF (2 l) was added dropwise within 3 h. Then, the mixture was stirred for 1 additional h at –78°. Me_3SiCl (225 ml) was added dropwise within 25 min and the mixture stirred for 1 h at –78°, then heated to r.t., and evaporated at 30°. The residue was used without purification. ^{1}H-NMR ($CDCl_3$): H–C(1) of **6** at 6.3 (*d*, $J = 3$) and of **7** at 5.3 (*d*, $J = 3$).

(R)-2-Hydroxy-1,2,2-triphenylethyl (S,Z)-3-Hydroxy-11-icosenoate (**14**). To a stirred soln. of (i-Pr)$_2$NH (30 ml, 0.21 mol) in THF (100 ml) at 0°, 1.6M BuLi in hexane (130 ml, 0.21 mol) was added under Ar. After 15 min at 0°, the reagent was added to a stirred suspension of (*R*)-2-hydroxy-1,2,2-triphenylethyl acetate (**12**; 27.7 g, 0.083 mol) [5] in THF (280 ml) at –75 to –68°. After completed addition, the mixture was warmed to 0°. An orange soln. formed which was cooled, after 10 min, to –118°. A soln. of (*Z*)-9-octadecenal (24.4 g, 0.092 mol) in Et_2O (50 ml) was added and stirring continued for 1 h at –112°. A sat. aq. NH_4Cl soln. (70 ml) was added and the mixture warmed to r.t. The org. layer was separated, washed twice with H_2O (100 ml), dried (Na_2SO_4), and evaporated. The yellowish residue was recrystallized from MeOH to give **14** (35.4 g, 71%). M.p. 111–113°. IR (KBr): 3497, 1717, 1158, 748, 697. ^{1}H-NMR ($CDCl_3$): 7.58 (*m*, 1 arom. H); 7.43–7.00 (*m*, 14 arom. H); 6.72 (*s*, COOCH); 5.35 (*m*, H–C(11), H–C(12)); 3.82 (*m*, H–C(3)); 2.38 (*s*, OH); 2.37 (*s*, OH)[4]; 2.49–2.24 (*m*, 3 H); 2.10–1.90 (*m*, 2 H–C(10), 2 H–C(13)); 1.45–1.14 (*m*, 24 H); 0.88 (*t*, $J = 6$, 3 H–C(20)). MS: 326 ($M^{+\cdot}$ – (triphenylethylen oxide)), 273, 183, 165, 105.

Methyl (Z,S)-3-Hydroxy-11-icosenoate (**15**). To a stirred suspension of **14** (21.5 g, 36 mmol) in MeOH (210 ml) was added 1M NaOMe/MeOH (36 ml, 36 mmol) and stirring continued for 1 h at r.t. The undissolved material was filtered off and the soln. poured upon a sat. aq. NH_4Cl soln. (1 l). The aq. phase was extracted 3 times with Et_2O, the combined org. extract washed with brine, dried (Na_2SO_4), and evaporated. The residue was stirred with hexane, the crystalline (*R*)-1,2,2-triphenyl-1,2-ethanediol (**19**) was filtered off, and the filtrate evaporated to give **15** as a yellow oil (11.6 g, 94.5%). This material has an e.e. of 76%, as determined by NMR in the presence of Eu(hfc)$_3$. IR (film): 3458, 1738, 1293, 1172. ^{1}H-NMR ($CDCl_3$): 5.35 (*m*, H–C(11), H–C(12)); 4.02 (*m*, H–C(3)); 3.72 (*s*, CH_3O); 2.89 (*d*, $J = 4.0$, OH); 2.54 (*dd*, $J = 16.0$, 3.2, H–C(2)); 2.41 (*dd*, $J = 16.0$, 9.0, H–C(2)); 2.00 (*m*, 2 H–C(10), 2 H–C(13)); 1.60–1.15 (*m*, 24 H); 0.88 (*t*, $J = 6$, 3 H–C(20)). MS: 340 ($M^{+\cdot}$), 290, 248, 103, 81, 67, 55.

Methyl (S,Z)-3-[(Tetrahydro-2H-pyran-2-yl)oxy]-11-icosenoate (**16**). To a soln. of **15** (11.6 g, 34 mmol) in CH_2Cl_2 (125 ml) dihydro-2*H*-pyran (6.2 ml, 68 mmol) was added. The mixture was cooled to 0°, TsOH (130 mg) added under stirring, and the mixture kept at 0° for 45 min. The cooling bath was then removed, and when the temp. reached 10°, the org. phase was washed with aq. sat. $NaHCO_3$ (90 ml) and brine (90 ml). The org. layer was dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel (hexane; hexane/Et_2O 9:1) to yield

[4]) The intensity of the 2 signals at 2.38 and 2.37 ppm is *ca.* 1:9, indicating a d.e. of *ca.* 80%.

10.8 g of **16** (74.5%) as a colourless oil. ^{1}H-NMR ($CDCl_3$): 5.37 (*m*, H–C(11), H–C(12)); 4.70 (*m*, OCHO); 3.68 (*s*, CH_3O); 4.2–3.2 (*m*, H–C(3), CH_2OCHO); 2.9–2.2 (*m*, 2 H–C(2)); 2.2–1.0 (*m*, 34 H); 0.85 (*m*, 3 H–C(20)).

(S,Z)-3-[(Tetrahydro-2H-pyran-2-yl)oxy]-11-icosenal (**17**). A soln. of **16** (10.8 g, 25.4 mmol) in CH_2Cl_2 (100 ml) under Ar was cooled to $-75°$ and treated dropwise with 1.2M DIBAH in toluene (23 ml, 28 mmol). The reaction was stirred subsequently for 35 min. Keeping the temp. below $-70°$, an aq. sat. soln. of NH_4Cl (6.5 ml) was added, followed by the addition of 1M HCl (13 ml). After warming to r.t., the org. phase was decanted from the crystals which were washed thoroughly with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated to give a yellow oil. Chromatography on silica gel with hexane/Et_2O 6:1 furnished **17** (9.1 g, 91%) as a yellowish oil. IR (film): 1726, 1118, 1077. ^{1}H-NMR ($CDCl_3$): 9.90 (*t*, *J* = 2.0, CHO); 5.40 (*m*, H–C(11), H–C(12)); 4.70 (*m*, OCHO); 4.3–3.35 (*m*, H–C(3), CH_2OCHO); 2.85–2.3 (*m*, 2 H–C(2)); 2.2–1.0 (*m*, 34 H); 0.9 (*t*, *J* = 6, 3 H–C(20)). MS: 292 ($M^{+\cdot} - C_5H_{10}O_2$), 85.

(R)-2-Hydroxy-1,2,2-triphenylethyl (3S,5S,Z)-3-Hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]-13-docosenoate (**18**). Li(i-Pr)$_2$N prepared from (i-Pr)$_2$NH (8.2 ml, 57.6 mmol) and 1.6M BuLi in hexane (36 ml, 57.6 mmol) was added to **12** (7.7 g, 23.1 mmol) in THF (75 ml) as indicated above for the synthesis of **14**. A soln. of **17** (9.1 g, 23 mmol) in Et_2O (230 ml) was added at $-118°$ and stirring continued for 1 h. A sat. aq. NH_4Cl soln. (20 ml) was added and the mixture warmed up to r.t. The org. layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated. The resulting yellow foam was dissolved in hot MeOH (100 ml), the cloudy soln. filtered, and by repeated crystallization, a total of 13 g of **18** were obtained (77%), the different crops having m.p. ranging from 83 to 92°. IR (KBr): 3534, 1718, 1494, 1258, 1156, 1133, 1115, 1060, 752, 733, 696. ^{1}H-NMR ($CDCl_3$): 7.65–7.0 (*m*, 15 arom. H); 6.71 (*s*, COOCH); 5.35 (*m*, H–C(13), H–C(14)); 4.62, 4.55 (2 *m*, OCHO); 4.46–2.81 (*m*, 6 H); 2.55–2.30 (*m*, 2 H–C(12), 2 H–C(15)); 2.10–1.89 (*m*, 2 H–C(2)); 1.85–1.0 (*m*, 32 H); 0.85 (*t*, *J* = 6.0, 3 H–C(22)). MS: 460 ($M^{+\cdot}$ – dihydropyran – benzophenone), 273, 183, 85.

Methyl (3S,5S,Z)-3-Hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]-13-docosenoate (**20**). To a suspension of **18** (12.76 g, 17.5 mmol) in dry MeOH (130 ml), 1M NaOMe/MeOH (17.5 ml, 17.5 mmol) was added. The mixture was stirred for 30 min at r.t. and poured onto a sat. aq. NH_4Cl soln. (650 ml). The soln. was extracted with Et_2O (3 × 300 ml), the combined extract dried (Na_2SO_4), and the solvent evaporated to yield a yellow oil (13.7 g) which was stirred with hexane (70 ml). The white crystals of *(R)-1,2,2-triphenyl-1,2-ethanediol* (**19**) were filtered off and the filtrate evaporated. Chromatography of the residue on silica gel (120 g) with hexane/Et_2O 2:1 and 1:1 afforded **20** as a yellow oil (7.35 g, 89.4%). IR (film): 3473, 1739, 1076. ^{1}H-NMR ($CDCl_3$): 5.41–5.27 (*m*, H–C(13), H–C(14)); 4.69, 4.58 (2 *m*, OCHO); 4.33–3.75 (*m*, 3 H); 3.71, 3.70 (2 *s*, CH_3O); 3.56–3.36 (*m*, 2 H); 2.59–2.39 (*m*, 2 H–C(2)); 2.11–1.87 (*m*, 2 H–C(12), 2 H–C(15)); 1.85–1.12 (*m*, 32 H); 0.88 (*t*, *J* = 6.0, 3 H–C(22)). MS: 384 ($M^{+\cdot}$ – dihydropyran), 147, 85.

Methyl (2S,3S,5S,Z)-2-Ethyl-3-hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]-13-dodecosenoate (**21**). Li(i-Pr)$_2$N was prepared from (i-Pr)$_2$NH (3.4 ml, 24.2 mmol) and 1.6M BuLi in hexane (15 ml, 24.2 mmol) in THF (10 ml) as described for the synthesis of **14**. The soln. was cooled to $-50°$ and a soln. of **20** (5.15 g, 11 mmol) in THF (5 ml) added, whereby the temp. rose to $-15°$. The mixture was stirred at $-10°$ for 10 min and cooled to $-50°$, followed by dropwise addition of a soln. of EtI (1.3 ml, 16.5 mmol) in dry hexamethylphosphoric triamide (HMPA; 2.6 ml). Stirring was continued for 15 min at this temp. and subsequently for 3 h at r.t. The mixture was poured onto ice-cold H_2O (150 ml), extracted 5 times with Et_2O, the combined org. extract dried (Na_2SO_4), filtered, and evaporated to give **21** as a yellow oil. Chromatography on silica gel (250 g) with hexane/AcOEt 4:1 afforded pure **21** (4.1 g, 75%). Yellowish oil. IR (film): 3477, 1738, 1167, 1076, 1024. ^{1}H-NMR ($CDCl_3$): 5.42–5.28 (*m*, H–C(13), H–C(14)); 4.69, 4.65 (2 *m*, OCHO); 4.04–3.72 (*m*, 3 H); 3.72, 3.70 (2 *s*, CH_3O); 3.56–3.40 (*m*, 2 H); 2.99–2.50 (*m*, H–C(2)); 2.20–1.90 (*m*, 2 H–C(12), 2 H–C(15)); 1.90–1.11 (*m*, 34 H); 0.97–0.78 (*m*, 3 H–C(22), 3 H–C(2′)). MS: 412 ($M^{+\cdot}$ – dihydropyran), 131, 85.

Methyl (2S,3S,5S)-2-Ethyl-3-hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]dodecosanoate (**22**). At r.t. and normal pressure, **21** (4.1 g, 8.25 mmol) in THF (90 ml) was hydrogenated in the presence of 10% Pd/C (0.5 g). After completed hydrogenation, the catalyst was filtered off and the filtrate evaporated to give **22** (4.0 g, 97.5%) as a yellowish oil. IR: 3463, 1738, 1199, 1167, 1132, 1115, 1076, 1023. ^{1}H-NMR ($CDCl_3$): 4.68, 4.55 (2 *m*, OCHO); 4.06–3.77 (*m*, 3 H); 3.72, 3.71 (2 *s*, CH_3O); 3.59–3.39 (*m*, 2 H); 2.59–2.38 (*m*, H–C(2)); 1.92–1.11 (*m*, 42 H); 0.98–0.79 (*m*, 3 H–C(2′), 3 H–C(22)). MS: 379 ($M^{+\cdot}$ – tetrahydropyranyloxy – H_2O), 295, 131, 102, 85.

(2S,3S,5S)-2-Ethyl-3-hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]docosanoic Acid (**23**). A soln. of **22** (4.0 g, 8.0 mmol) in 2M KOH/MeOH (80 ml) was kept for 19 h at r.t. The mixture was poured onto H_2O (300 ml), followed by addition of 2M HCl to pH 2. Extraction with Et_2O, drying of the combined org. extracts (Na_2SO_4), and evaporation yielded an oily residue which was chromatographed on silica gel (180 g) with CH_2Cl_2/Et_2O 9:1, then with CH_2Cl_2/MeOH 9:1, yielding **23** as a yellowish oil (3.72 g, 96%). IR (film): 3430, 1709, 1023. ^{1}H-NMR ($CDCl_3$): 5.29 (br. *s*, OH); 4.72–4.54 (2 *m*, OCHO); 4.16–3.73 (*m*, 3 H); 3.59–3.28 (*m*, 1 H); 2.40–2.26 (*m*, H–C(2));

1.92–1.12 (*m*, 43 H); 1.00 (*t*, *J* = 7, 3 H–C(2′)); 0.84 (*t*, *J* = 6.0, 3 H–C(22)). MS: 365 ($M^{+\cdot}$ – tetrahydropyranyloxy – H_2O), 295, 117, 85.

(3S,4S)-3-Ethyl-4-[(S)-2-[(tetrahydro-2H-pyran-2-yl)oxy]nonadecyl]oxetan-2-one (**24**). A soln. of **23** (3.72 g, 7.67 mmol) in dry pyridine (75 ml) was cooled to 0–5° and benzenesulfonyl chloride (2 ml, 15.34 mmol) added. Stirring was continued for 22 h, the soln. poured onto a 10% aq. NaCl soln. (500 ml), extracted with Et_2O (3 × 100 ml), and the combined org. extract dried (Na_2SO_4), and evaporated. The oily residue was chromatographed on silica gel (200 g) with hexane/Et_2O 4:1 to give **24** (2.55 g, 71%) as a yellowish oil. IR (film): 1826, 1119, 1077, 1024. ^{1}H-NMR ($CDCl_3$): 4.63–4.34 (*m*, 2 H); 3.96–3.63 (*m*, 2 H); 3.55–3.39 (*m*, 1 H); 3.34–3.11 (*m*, 1 H); 2.30–1.15 (*m*, 42 H); 1.05 (*m*, 3 H–C(2″)); 0.84 (*t*, *J* = 6.0, 3 H–C(19′)). MS: 365 ($M^{+\cdot}$ – tetrahydropyranyloxy), 295, 85.

(3S,4S)-3-Ethyl-4-[(S)-2-hydroxynonadecyl]oxetan-2-one (**25**). A soln. of **24** (2.55 g, 5.46 mmol) in abs. EtOH (25 ml) was treated with pyridinium *p*-toluenesulfonate (140 mg) and the mixture heated to 50–55° for 2 h. After cooling with an ice-bath, the white crystals were filtered off and dried to give **25** (1.16 g, 55%) with m.p. 81–83°. Recrystallization of a sample from EtOH gave m.p. 82–84° which was shown by HPLC (cyclohexane/i-PrOH 99:1) to contain 4% of another diastereoisomer. IR (KBr): 3553, 1815, 1119, 1076. ^{1}H-NMR ($CDCl_3$): 4.5 (*dt*, *J* = 4.1, 6.8, H–C(4)); 3.85–3.70 (*m*, H–C(2′)); 3.32–3.23 (*m*, H–C(3)); 2.1–1.5 (*m*, 7 H); 1.25 (*m*, 30 H); 1.06 (*t*, *J* = 7, 3 H–C(2″)); 0.87 (*t*, *J* = 6.0, 3 H–C(19′)). MS: 364 ($M^{+\cdot}$ – H_2O), 269, 143, 125, 97, 85, 70.

(S)-1′-[[(2″S,3″S)-3″-Ethyl-4″-oxooxetan-2″-yl]methyl]octadecyl (S)-N-[(Benzyloxy)carbonyl]leucinate (**26**). A soln. of (*S*)-*N*-[(benzyloxy)carbonyl]leucine (796 mg, 3.0 mmol) in CH_2Cl_2 (10 ml) was cooled to 2–3° and DCC (309 mg, 1.5 mmol) added. Stirring was continued for 15 min, and the white crystals were filtered off. The filtrate was evaporated at < 30° and the residue dissolved in DMF (7 ml). This soln. was added at r.t. to a stirred mixture of **25** (574 mg, 1.5 mmol) and *p*-(dimethylamino)pyridine (22 mg, 0.18 mmol) in DMF (6 ml). Stirring was continued for 30 min. The mixture was poured onto ice-cold H_2O (100 ml) and extracted with Et_2O. The combined org. extracts were dried (Na_2SO_4) and evaporated to yield a yellowish oil (1.2 g) which was chromatographed on silica gel (50 g) with hexane/AcOEt 4:1: **26** as white crystals (0.60 g, 63.5%). M.p. 44–47°. IR (KBr): 3345, 1839, 1712, 1525, 1231, 1112, 738, 695. ^{1}H-NMR ($CDCl_3$): 7.34 (*m*, 5 arom. H); 5.18–4.91 (*m*, 2 H); 5.11 (*s*, PhCH_2O); 4.43–4.24 (*m*, 2 H); 3.25–3.11 (*m*, H–C(3″)); 2.28–1.11 (*m*, 39 H); 1.03 (*t*, *J* = 7.2, CH_3CH$_2$); 0.93 (*m*, $(CH_3)_2$C); 0.87 (*t*, *J* = 6.5, 3 H–C(18′)). MS: 365 ($M^{+\cdot}$ – Z-leucyl), 320, 220, 176, 91.

(S)-1′-[[(2″S,3″S)-3″-Ethyl-4″-oxooxetan-2″-yl]methyl]octadecyl (S)-N-Formylleucinate (**2**). At r.t. and normal pressure, **26** (565 mg, 0.9 mmol) in THF (12 ml) was hydrogenated in the presence of 10% Pd/C (40 mg). Hydrogenation was complete after 4 h and the catalyst filtered off. The filtrate was evaporated to yield **27** (425 mg) which was treated dropwise with formic acetic anhydride (72 µl, 0.94 mmol). The mixture was diluted with Et_2O and washed with a 2% aq. $NaHCO_3$ soln. (5 ml) and then with H_2O (5 ml). The org. phase was dried (Na_2SO_4) and evaporated. The residue was recrystallized from pentane to yield **2** (245 mg, 55%) as white crystals. M.p. 60–61°. $[\alpha]_{589}^{20}$ = – 43.1° (*c* = 1.07, CCl_4). IR (KBr): 3298, 1825, 1732, 1667, 1202, 1131. ^{1}H-NMR ($CDCl_3$): 8.22 (br., CHO); 6.00 (br. *d*, *J* = 8, NH); 5.04 (*m*, H–C(2)); 4.81 (*dt*, *J* = 8.0, 4.5, H–C(2″)); 4.35–4.25 (*m*, H–C(1′)); 3.20 (*dt*, *J* = 8.0, 4.5, H–C(3″)); 2.26–1.40 (*m*, 8 H); 1.35–1.18 (*m*, 31 H); 1.04 (*t*, *J* = 7.5, CH_3CH$_2$); 0.96 (*d*, *J* = 6.0, $(CH_3)_2$C); 0.88 (*t*, *J* = 6.5, 3 H–C(18′)). MS: 523 ($M^{+\cdot}$), 467, 364, 320, 160, 142, 114. Anal. calc. for $C_{31}H_{57}NO_5$ (523.80): C 71.08, H 10.97, N 2.67; found: C 70.78, H 11.12, N 2.70.

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