dynamically less favored. These two effects can combine to make the Barbier reaction significantly slower, even if the cavitational pitting keeps its efficiency (Figure 10). As a result, the usual rate dependence on temperature is observed.

Conclusion

The remarkable accelerating effect of the ultrasonic waves has been evidenced by semiquantitative experiments, which served to determine optimal intensity and temperature conditions. These two factors have the important influence that was suspected at the origin of our study. However from the present work it cannot be stated that cavitation is the only important phenomenon. No information has been obtained on the effects of noncavitational shock waves, or the frequency.[21] This work then has to be considered as an approach for a better knowledge of the interaction of ultrasound with a heterogeneous system, but the problem in its generality cannot be considered as fully understood.

Experimental Section

Freshly distilled benzaldehyde (530 mg, 5 mmol), 895 mg (5 mmol) of 1-bromoheptane, and 1130 mg of hexadecane in 30 mL of dry THF (from benzophenone–Na) were placed in the reaction vessel with 139 mg of lithium (20 mmol, 3-mm wire, <0.01% Na, from Alfa). The cell was thermostated at the desired initial temperature under magnetic stirring (1000 rpm). Sonication was started with the desired intensity, and analytical samples were periodically withdrawn (0.3 mL), quenched (1 N aqueous HCl), and extracted with ether. After drying, the sample was analyzed by VPC on a Erba Science chromatograph, equipped with a 10% Carbowax 20 M, 2 m × 2 mm i.d. column, with temperature programmed from 70 to 200 °C (5 °C/min). Identification of the peaks was effected by comparison and coinjection with authentic specimens. For the determination of the polar pinacols, the analytical sample was silylated with bis(trimethylsilyl)trifluoroacetamide in dry pyridine at 80 °C for 15–30 min.[22]

VPC response factors (K), determined by standard procedures,[23] were as follows: benzaldehyde, 1.9; hexadecane, 1; 1-phenyloctanol, 1.4; n-heptyl bromide, 1.7; tetradecane, 1; benzyl alcohol, 2.2; 1-phenyloctanol trimethylsilyl ether, 0.9; 1,2-diphenyl-1,2-ethanediol bis(trimethylsilyl) ether, 0.8. Molar concentrations of the addition alcohol, C^i, were determined by the same procedure. From the stoichiometry of the reaction, the final maximum molar concentration of alcohol 1 was equal to the initial molar concentration of aldehyde C_0, thus the yields correspond to 100 C^i/C_0. These values were determined 4 times. For each measurement the difference between extreme values was taken as the initial error. The mean value of all the initial errors was taken as the final error (±4%). The error on the initial rates V_0 was determined graphically.

Micrographs were obtained with a scanning electron apparatus, JEOL JSM-840.

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Registry No. 1, 19396-73-7; PhCHO, 100-52-7; n-$C_7H_{15}Br$, 629-04-9; Li, 7439-93-2.

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Synthesis of Tetrahydrolipstatin and Tetrahydroesterastin, Compounds with a β-Lactone Moiety. Stereoselective Hydrogenation of a β-Keto δ-Lactone and Conversion of the δ-Lactone into a β-Lactone

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Stereoselective syntheses of tetrahydrolipstatin (1) and tetrahydroesterastin (2) are described. The key intermediate β-keto δ-lactone 7 is hydrogenated stereoselectively to yield hydroxy δ-lactone 9, which is transformed into hydroxy β-lactone 10. Esterification of 10 with (S)-N-formylleucine under Mitsunobu's conditions yields tetrahydrolipstatin (1). Esterification of 10 with (S)-N-acetylasparagine under the same conditions yields 17 (mixture of two diastereomers), which gives by saponification hydroxy β-lactone 18. Reaction of the latter with the mixed anhydride of (S)-N-Z-asparagine, hydrogenation, and acetylation give tetrahydroesterastin (2).

Our interest in tetrahydrolipstatin (1) (Figure 1), an inhibitor of pancreatic lipase,[1] has led us to undertake the synthesis of this class of compounds. We have recently published several synthetic approaches,[2,4] and we want to report herein a highly stereospecific synthesis based on the preparation of a suitably substituted β-keto-δ-lactone 7, its stereoselective conversion into β-hydroxy δ-lactone 9 by hydrogenation, and transformation of the latter into hydroxy β-lactone 10, which serves as an intermediate for the preparation of tetrahydrolipstatin (1) as well as of tetrahydroesterastin (2), a closely related compound.[3]

Starting aldehyde 3[4] is condensed with the anion of lithium octanoate to yield hydroxy acid 4 as a mixture of diastereomers, which by deprotection yields hydroxy acid 5. Cyclization gives β-hydroxy δ-lactone 6 as a mixture of

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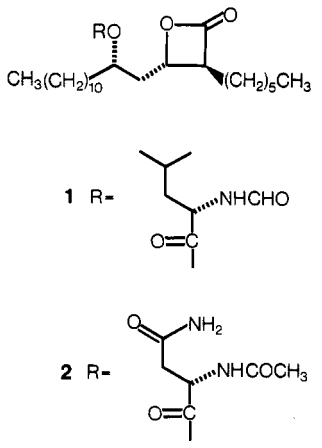
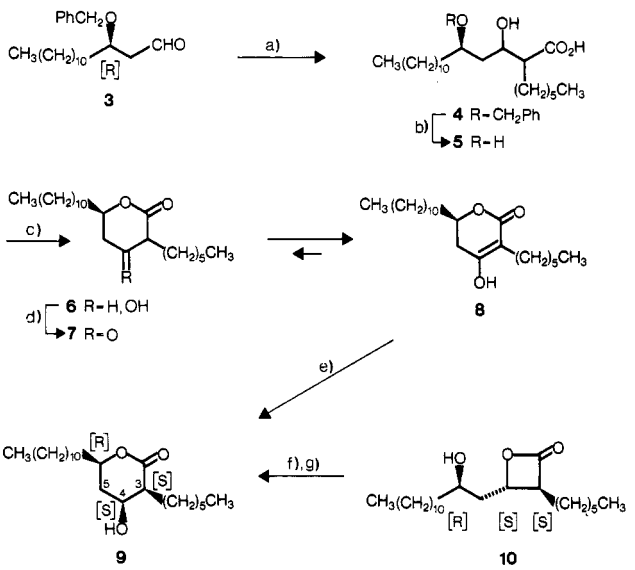


Figure 1.

Scheme I[a]



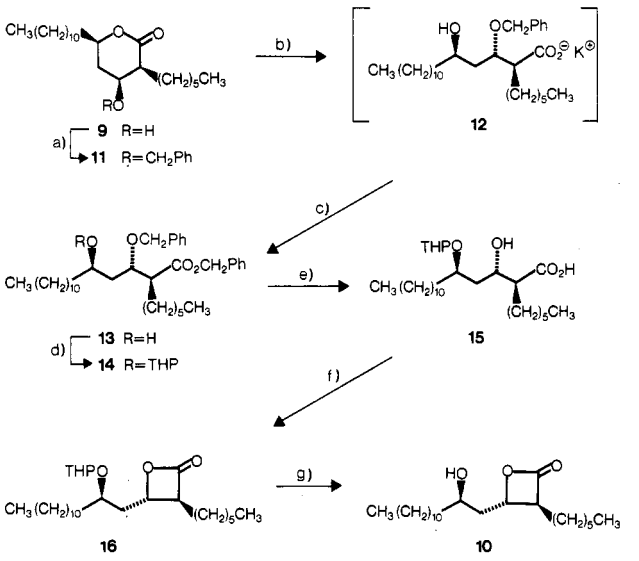
[a] (a) Octanoic acid, LDA; (b) H_2, Pd/C, 10%; (c) *p*-TsOH, $CHCl_3$; (d) Jones' oxidation; (e) H_2, Pt, 50 bars; (f) 1 N aqueous KOH; (g) *p*-TsOH, $CHCl_3$.

diastereomers, which is oxidized into β-keto δ-lactone **7**, present in chloroform solution under its enol form **8**. Hydrogenation yields the crucial β-hydroxy δ-lactone **9** isolated as one single crystalline isomer.

The absolute configuration at C-6 is *R*, this center originating from *R*-configurated aldehyde **3**, and the configuration at C-3 and C-4 are both *S*, as shown by the identity of **9** with the β-hydroxy δ-lactone obtained from hydroxy β-lactone **10**[4] by saponification and ring closure. The absolute configuration of **10** can be deduced from the absolute configuration of tetrahydrolipstatin.[2,4] That no change of configuration occurred during the transformation of **10** into **9** was established by the transformation of **9** into **10** described below (Scheme I).

In order to transform δ-lactone **9** into β-lactone **10**, the alcohol function at C-4 is protected as its benzyl ether. Ring opening of δ-lactone occurs on treatment with KOH to give the potassium salt of hydroxy acid **12**, which is immediately treated with benzyl bromide to yield benzyl ester **13**. After careful protection of the alcohol function as its tetrahydropyranyl ether **14**, the benzyl groups are removed by hydrogenolysis and hydroxy acid **15** is treated with benzenesulfonyl chloride and pyridine to give β-lactone **16**. The tetrahydropyranyl ether is removed, and the known hydroxy β-lactone **10** is obtained[4] (Scheme II).

Scheme II[a]



[a] (a) Benzyl trichloroacetimidate, CF_3SO_3H, CH_2Cl_2; (b) 1 N aqueous KOH; (c) benzyl bromide, THF, HMPA; (d) dihydropyran, *p*-TsOH, CH_2Cl_2; (e) H_2, Pd/C, 10%, THF; (f) benzenesulfonyl chloride, pyridine; (g) pyridinium *p*-toluenesulfonate, EtOH.

Esterification under Mitsunobu's conditions of hydroxy β-lactone **10** with (*S*)-*N*-formylleucine gives, as earlier described,[4] tetrahydrolipstatin (**1**). When hydroxy β-lactone **10** is esterified under identical conditions with (*S*)-*N*-acetylasparagine, epimerization occurs at the amino acid to give **17** as a mixture of two epimers (see NMR data). In order to prepare pure tetrahydroesterastin (**2**), compound **17** is saponified[3] with 1 equiv of NaOH in dioxane/H_2O to give hydroxy β-lactone **18**. We were unable to obtain **18** from tetrahydrolipstatin (**1**) under the same conditions, the β-lactone ring being cleaved under the reaction conditions. Esterification of **18** with the mixed anhydride prepared from pivaloyl chloride and (*S*)-*N*-Z-asparagine yields ester **19**, and cleavage of the Z protecting group by hydrogenolysis and acetylation of **20** with acetyl chloride give pure tetrahydroesterastin (**2**) (Scheme III).

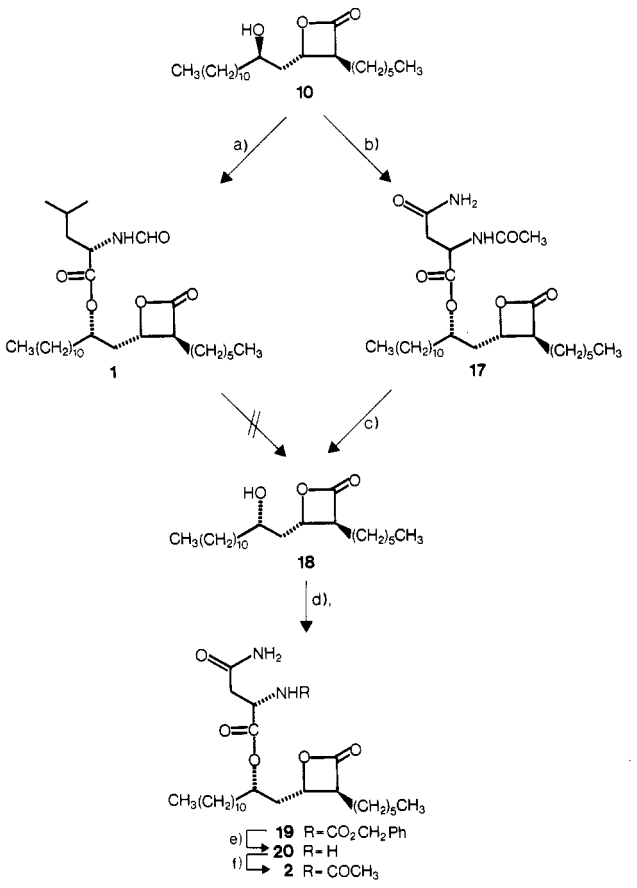
Experimental Section

General. Column chromatography: Merck silica gel 60 (70–230 mesh ASTM). Melting points: Tottoli capillary melting point apparatus; uncorrected. IR (cm^{-1}): Nicolet 7199 FT-IR instrument. ^1H NMR [(ppm) relative to internal TMS; *J* in hertz]: Bruker AC 250 and Bruker HX 270 instruments. MS: MS9-ZAB instrument, data system SS 200.

(5*R*)-5-(Benzyloxy)-3-hydroxy-2-hexylhexadecanoic Acid (4). A stirred solution of $(i\text{-}Pr)_2NH$ (7.24 g, 71.55 mmol) in THF (50 mL) was cooled to 0 °C, and 1.6 N BuLi in hexane (46.93 mL, 1.05 equiv) was added. After 10 min at 0 °C, the mixture was cooled to −50 °C and a solution of octanoic acid (5.16 g, 35.78 mmol) in THF (50 mL) was added. After being stirred for 15 min at −50 °C, the mixture was warmed to room temperature and stirred for 1 h at room temperature. The mixture was cooled to −78 °C, and a solution of **3** (9.5 g, 29.83 mmol) in THF (50 mL) was added dropwise. After being stirred for 3 h at −78 °C, the mixture was warmed to room temperature, and an aqueous 1 N HCl solution (100 mL) was added. The mixture was extracted five times with Et_2O and the combined organic extract washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and evaporated to yield crude **4** (15.5 g), as an oil, which was used without purification.

(6*R*)-3-Hexyl-3,4,5,6-tetrahydro-4-hydroxy-6-undecyl-2*H*-pyran-2-one (6). A solution of **4** (15.5 g) in THF (250 mL) was treated with 10% Pd/C (2 g) and hydrogenated at room temperature and normal pressure. After completed hydrogenation

Scheme III[a]



[a] (a) (*S*)-*N*-Formylleucine, PPh_3, diethyl azodicarboxylate, THF; (b) (*S*)-*N*-acetylasparagine, PPh_3, diethyl azodicarboxylate, THF; (c) 0.02 N aqueous NaOH, dioxane; (d) (*S*)-*N*-(benzyloxycarbonyl)asparagine, pivaloyl chloride, Et_3N, DMF; (e) H_2, Pd/C, 10%, THF; (f) CH_3COCl, Et_3N, THF.

(ca. 800 mL), the catalyst was filtered and the filtrate evaporated. The residue was dissolved in $CHCl_3$ (250 mL) and treated with *p*-TsOH (200 mg) overnight at room temperature with stirring. The solution was evaporated, and the residue was taken up in Et_2O (200 mL), washed with a saturated aqueous $NaHCO_3$ solution (100 mL) and H_2O (100 mL), dried over Na_2SO_4, and evaporated to yield crude **6** (11.25 g) as a wax, which was used without purification. Trituration of a sample in hexane gave analytically pure **6** as a wax: ^1H NMR ($CDCl_3$, 250 MHz) 4.6–4.50 and 4.24–4.11 (2 m, 1 H, COOCH), 4.05–3.87 (m, 1 H, HOC*H*), 2.51–2.37 (m, 1 H, CHCOO), 2.25–1.21 (m, 33 H), 0.87 (t, 6 H, 2 × CH_2CH_3, J = 6); IR (KBr) 3440 (OH), 1700 (ester), 1100 (OH); MS, 355 (M^+). Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.50; H, 12.19.

(6*R*)-3-Hexyl-5,6-dihydro-6-undecyl-2*H*-pyran-2,4(3*H*)-dione (7). A solution of crude **6** (10.25 g) in acetone (500 mL) was treated dropwise at 10 °C, with stirring, with 8 N Jones' reagent (6 mL, slight excess). After 1 h, the solution was poured into H_2O (2 L) and filtered. The residue was dissolved in ether, and the organic phase was dried over Na_2SO_4 and evaporated. The crude oil was dissolved in hexane, and after cooling to −78 °C, a wax (12 g) precipitated, which was used without further purification. Trituration of a sample in hexane gave analytically pure **7** as a wax: ^1H NMR ($CDCl_3$, 270 MHz) 6.65 (s, 0.7 H, OH enol form), 4.75–4.62 (m, 0.3 H, COOCH, keto form), 4.40–4.25 (m, 0.7 H, COOCH, enol form), 3.4 (t, 0.3 H, $C_6H_{13}CH$, J = 5), 2.78–2.16 (m, 4 H), 1.96–1.15 (m, 28 H), 0.88 (t, 6 H, 2 × CH_2CH_3, J = 6); IR (KBr) 2680 (OH), 1594 (conj ester), 1400; MS, 353 (M^+). Anal. Calcd for $C_{22}H_{40}O_3$: C, 74.95; H, 11.44. Found: C, 74.72; H, 11.49.

(3*S*,4*S*,6*R*)-3-Hexyl-3,4,5,6-tetrahydro-4-hydroxy-6-undecyl-2*H*-pyran-2-one (9). (a) From 7. A solution of **7** (3.26 g) in ethyl acetate (0.8 L) was treated with PtO_2 (1.3 g) and hydrogenated at room temperature under 50 bars. After completed hydrogenation (48 h), the catalyst was filtered and the filtrate evaporated. The residue was recrystallized from ether/hexane to yield 2.7 g of pure **9** (84%): mp 95–97 °C; ^1H NMR (270 MHz) 4.42–4.33 (dt, 1 H, $CH_{ax}OH$, $J_{ax/ax}$ = 8.5, $J_{ax/eq}$ = 3.5, 3.5), 4.26–4.13 (m, 1 H_{ax}, COOCH), 2.50–2.09 (m, 2 H), 2.02–1.86 (m, 1 H), 1.82–1.18 (m, 31 H), 0.88 (t, 6 H, 2 × CH_2CH_3, J = 7); IR (KBr) 3427 (OH), 1708 (CO), and 1216; MS, 355 (M^+); $[\alpha]^{22}_D$ +44° (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.51; H, 12.00.

(b) From 10. A solution of **10**[4] (100 mg, 0.28 mmol) in dioxane (5 mL) was treated overnight at room temperature with aqueous 1 N KOH (0.56 mL, 2 equiv). The solution was neutralized with aqueous 1 N HCl (0.56 mL) and evaporated. The residue was partitioned between ether and H_2O and the organic layer dried over Na_2SO_4. After evaporation of the ether, the residue was dissolved in $CHCl_3$ (30 mL), treated with a catalytic amount of *p*-TsOH for 2 h at room temperature, and then washed with saturated aqueous $NaHCO_3$ solution/saturated aqueous NaCl solution/H_2O, 1:1:2. The organic layer was dried over Na_2SO_4 and evaporated, and the residue was recrystallized from ether/hexane to yield 60 mg of pure **9** (60%) (melting point, ^1H NMR, IR, and $[\alpha]^{22}_D$ are identical with those of the material obtained from **7**).

(3*S*,4*S*,6*R*)-4-(Benzyloxy)-3-hexyl-3,4,5,6-tetrahydro-6-undecyl-2*H*-pyran-2-one (11). A solution of **9** (2.74 g, 7.72 mmol) and benzyl trichloroacetimidate (2.34 g, 9.27 mmol) in CH_2Cl_2 (80 mL) was treated at 0 °C with CF_3SO_3H (70 μL) with stirring. The temperature rose to 20 °C. After 2 h at this temperature, the solution was cooled to 0 °C and the crystalline trichloroacetamide was filtered off. The filtrate was then washed with aqueous saturated $NaHCO_3$ (50 mL) and twice with H_2O (50 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (250 g) with hexane/ether (9:1) to give 2.5 g of pure **11** (73%): mp 71–75 °C; ^1H NMR ($CDCl_3$, 270 MHz) 7.38–7.26 (m, 5 H, C_6H_5), 4.59 (d, 1 H, $C_6H_5C(H)HO$, J_{AB} = 12), 4.34 (d, 1 H, $C_6H_5C(H)HO$, J_{AB} = 12), 4.24–4.10 (m, 1 H, COOCH), 4.0–3.92 (dt, 1 H, CH_2OCH, J = 8, 4.4), 2.49–2.38 (m, 1 H, $C_6H_{13}CH$), 2.26–2.13 (m, 1 H, $C_5H_{11}CHHCH$), 1.93–1.04 (m, 31 H), 0.91–0.76 (m, 6 H, 2 × CH_2CH_3); IR (KBr) 1724 (lactone), 1495 (phenyl); MS, 465 (M^+); $[\alpha]^{22}_D$ +12.8° (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.22, H, 11.06.

Benzyl (2*S*,3*S*,5*R*)-3-(Benzyloxy)-2-hexyl-5-hydroxyhexadecanoate (13). A solution of **11** (2.4 g, 5.4 mmol) in dioxane (50 mL) was treated with aqueous 1 N KOH (6.3 mL) and kept at room temperature for 5 h. The reaction mixture was evaporated and the residue dissolved in toluene (150 mL) and evaporated. The potassium salt **12** was then dissolved in a mixture of THF (25 mL) and HMPA (20 mL) and treated with benzyl bromide (3 mL, 5 equiv). After 24 h, the reaction mixture was partitioned between H_2O and hexane. The organic layer was washed twice with H_2O, dried on Na_2SO_4, and evaporated to yield, after chromatography on silica gel (250 g) with hexane/ether (9:1), 1.75 g of pure **13** (60%): ^1H NMR ($CDCl_3$, 270 MHz) 7.34–7.26 (m, 10 H, 2 × C_6H_5), 5.17 (d, 1 H, $COOC(H)HC_6H_5$, J_{AB} = 12), 5.10 (d, 1 H, $COOC(H)HC_6H_5$, J_{AB} = 12), 4.59 (d, 1 H, $CHOC(H)HC_6H_5$, J_{AB} = 12), 4.51 (d, 1 H, $CHOC(H)HC_6H_5$, J_{AB} = 12), 4.06–3.96 (m, 1 H, $CHOCH_2C_6H_5$), 3.85–3.74 (m, 1 H, CHOH), 2.86 (ddd, 1 H, $C_6H_{11}CH$, J = 4, 8, 11), 2.38 (d, 1 H, OH, J = 4), 1.72–1.16 (m, 32 H), 0.94–0.82 (m, 6 H, 2 × CH_2CH_3); IR (film) 3500 (OH), 1734 (ester), 1496 (aromat); MS, 444 (M^+ − BnOH); $[\alpha]^{22}_D$ −4.7° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{36}H_{56}O_4$: C, 78.21; H, 10.21. Found: C, 77.84; H, 10.10.

Benzyl (2*S*,3*S*,5*R*)-3-(Benzyloxy)-2-hexyl-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]hexadecanoate (14). To a solution of **13** (0.8 g, 1.45 mmol) in CH_2Cl_2 (25 mL) was added dihydropyran (1 mL, 10 equiv). The solution was cooled to −10 °C, and one crystal of *p*-toluenesulfonic acid was added. The cooling bath was removed, and when the temperature reached room temperature (3 h), the reaction mixture was poured into aqueous saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated and the residue chromatographed on silica gel (100 g) with hexane/Et_2O (9:1) to yield 670 mg of pure **14** (73%): ^1H NMR ($CDCl_3$, 270 MHz) 7.41–7.10 (m, 10 H, 2 × C_6H_5), 5.16–5.03 (m, 2 H), 4.70–4.25 (m, 3 H), 4.16–3.61 (m, 3 H), 3.45–3.33 (m, 1 H), 2.83–2.66 (m, 1 H), 1.84–1.04

(m, 38 H), 0.91–0.77 (m, 6 H, 2 × CH_2CH_3); IR (film) 1736 (ester), 1604 and 1586 (aromat); MS, 535 [M^+ – (tetrahydropyranyl)oxy]. Anal. Calcd for $C_{41}H_{64}O_5$: C, 77.31; H, 10.21. Found: C, 77.55; H, 10.31.

(3*S*,4*S*)-3-Hexyl-4-[(*R*)-2-[(tetrahydro-2*H*-pyran-2-yl)-oxy]tridecyl]-2-oxetanone (16). A solution of **14** (0.622 g, 0.98 mmol) in THF (10 mL) was treated with 10% Pd/C (60 mg) and hydrogenated under normal pressure and at room temperature. After 4 h, the catalyst was removed by filtration and the filtrate evaporated to yield crude **15** (0.445 g), which was used without purification. This residue was dissolved in dry pyridine (13 mL) and, after cooling to 0 °C, treated with 2 equiv of benzenesulfonyl chloride (0.25 mL). The reaction mixture was stirred overnight at this temperature, then poured into precooled H_2O (100 mL), and extracted three times with Et_2O (100 mL). The organic layer was evaporated to dryness to eliminate pyridine, and the residue was dissolved in Et_2O, dried over Na_2SO_4, and after evaporation of the solvent, chromatographed on silica gel [100 g, with hexane/Et_2O (9:1)] to yield 235 mg of pure **16** (55% from **14**): ^1H NMR ($CDCl_3$, 250 MHz) 4.65–4.52 and 4.43–4.32 (2 m, 2 H), 3.98–3.68 (m, 2 H), 3.56–3.43 (m, 1 H), 3.29–3.17 (m, 1 H), 2.02–1.21 (m, 38 H), 0.95–0.83 (m, 6 H, 2 CH_2CH_3); IR (film) 1843 (β-lactone); MS, 292 ($M^+ - H_2O - CO$). Anal. Calcd for $C_{27}H_{50}O_4$: C, 73.92; H, 11.49. Found: C, 74.05; H, 11.84.

(3*S*,4*S*)-3-Hexyl-4-[(*R*)-2-hydroxytridecyl]-2-oxetanone (10). A solution of **16** (0.170 g, 0.39 mmol) in absolute ethanol (12 mL) was treated with pyridinium *p*-toluenesulfonate (9 mg), and the mixture was heated to 50–55 °C for 2 h. The solution was then evaporated and the residue directly chromatographed on silica gel (30 g) with hexane/Et_2O (3:1) to yield 0.120 g of pure **10** (88%): mp 57–58.5 °C; ^1H NMR ($CDCl_3$, 250 MHz) 4.25 [dt, 1 H, H-C(4), J = 4.25, 8.5], 3.90–3.75 (m, 1 H, C*H*OH), 3.26 [dt, 1 H, H-C(3), J = 8, 4.25], 2.0–1.68 (m, 5 H), 1.62–1.14 (m, 30 H), 0.88 (t-like, 6 H, CH_2CH_3); IR (KBr) 1810 (β-lactone); MS, 354 (M^+); $[\alpha]^{22}_D$ –38.8° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.44; H, 12.36.

10 was identical with the sample [mp 58.8–59 °C; $[\alpha]^{22}_D$ –41.4° (*c* 0.5, $CHCl_3$)] previously prepared in our laboratories.[4]

(*S*)-*N*-Formylleucine (*S*)-1-[[(2*S*,3*S*)-3-Hexyl-4-oxo-2-oxetanyl]methyl]dodecyl Ester (Tetrahydrolipstatin, 1). A solution of **10** (58 mg, 0.16 mmol), triphenylphosphine (52 mg, 0.19 mmol), and (*S*)-*N*-formylleucine (31 mg, 0.20 mmol) in THF (3 mL) was cooled with stirring to 0 °C. Diethyl azodicarboxylate (34.4 μL, 0.20 mmol) was added, and the mixture was then stirred for 2 h at room temperature and evaporated. The residue was chromatographed on silica gel (50 g) with toluene/ethyl acetate (4:1) to yield 68 mg of pure **1** (80%): mp 40–42 °C; $[\alpha]^{22}_D$ –33° (*c* 0.36, $CHCl_3$); identical with tetrahydrolipstatin of natural origin[5] [mp 43 °C; $[\alpha]^{22}_D$ –33° (*c* 1, $CHCl_3$)].

(*RS*)-*N*-Acetylasparagine (*S*)-1-[[(2*S*,3*S*)-3-Hexyl-4-oxo-2-oxetanyl]methyl]dodecyl Ester (17). The same procedure as above was used to esterify **10** (1 g, 28 mmol) with (*S*)-*N*-acetylasparagine (0.5 g, 2.9 mmol). Chromatography on silica gel (250 g) with $CHCl_3$/EtOH (19:1) afforded 0.5 g of pure **17** (38%): mp 85 °C; ^1H NMR ($CDCl_3$, 270 MHz) 6.77 (d, 1 H, N*H*Ac, J = 8), 5.75–5.60 (2 m, 1 H, CONH*H*), 5.38–5.25 (m, 1 H, CONH*H*), 5.09–4.94 (m, 1 H, $C_{11}H_{23}CH$), 4.84–4.70 (m, 1 H, C*H*NHAc), 4.45–4.29 [m, 1 H, H-C(4)], 3.28–3.16 (m, 1 H), $C_6H_{13}CH$), 3.04–2.72 (m, 2 × AB, 2 H, CH_2CHNHAc), 2.25–1.94 (m, 2 H), 2.01 (s, 3 H, NHCOCH_3), 1.86–1.14 (m, 30 H), 0.94–0.81 (m, 6 H, 2 × CH_2CH_3); IR (KBr) 3420, 3311, 3213 (NH, NH_2), 1834 (β-lactone), 1728 (ester), 1675, 1656 (amide); MS, 511 ($M + H)^+$.

(3*S*,4*S*)-3-Hexyl-4-[(*S*)-2-hydroxytridecyl]-2-oxetanone (18). A solution of **17** (0.5 g, 0.98 mmol) in a mixture of 0.02 N aqueous NaOH (50 mL) and dioxane (50 mL) was stirred overnight at room temperature. The reaction mixture was then extracted three times with hexane (50 mL). The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel (50 g) with hexane/Et_2O (3:1) afforded 220 mg of pure **18** (63%): mp 64–65 °C; ^1H NMR ($CDCl_3$, 250 MHz) 4.53–4.42 [m, 1 H, H-C(4)], 3.88–3.73 [m, 1 H, H-C(2′)], 3.38–3.27 (m, 1 H, $C_6H_{13}CH$), 2.21–1.08 (m, 33 H), 0.95–0.81 (t-like, 6 H, 2 × CH_2CH_3); IR (KBr) 3548, 3440 (OH), 1814 (β-lactone); MS, 372 ($M + NH_4)^+$; $[\alpha]^{22}_D$ 14.75° (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.71; H, 12.00.

(*S*)-*N*-(Benzyloxycarbonyl)asparagine (*S*)-1-[[(2*S*,3*S*)-3-Hexyl-4-oxo-2-oxetanyl]methyl]dodecyl Ester (19). A solution of *N*-(Benzyloxycarbonyl)-L-asparagine (113 mg, 0.56 mmol) in DMF (5 mL) was cooled to –5 °C and treated on stirring with Et_3N (116 μL) and pivaloyl chloride (52 μL, 0.56 mmol). After 5 min, a solution of **18** (100 mg, 0.28 mmol) in DMF (2 mL) was slowly added. The reaction mixture was stirred for 2 h at –5 °C, then poured into H_2O (50 mL), and extracted three times with ether. The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel (50 g) with $CHCl_3$/EtOH (19:1) afforded 55 mg of pure **19** (33%): ^1H NMR ($CDCl_3$, 250 MHz) 7.44–7.22 (m, 5 H, C_6H_5), 6.0 (d, 1 H, CHN*H*, J = 8), 5.60–5.48 (m, 1 H, CONH*H*), 5.37–5.23 (m, 1 H, CONH*H*), 5.13 (s, 2 H, $CH_2C_6H_5$), 5.08–4.96 (m, 1 H, $C_{11}H_{23}CH$), 4.60–4.50 (m, 1 H, C*H*NH), 4.38–4.27 [m, 1 H, H-C(4)], 3.19 (dt, 1 H, $C_6H_{13}CH$, J = 4, 8), 3.0 (part A of ABX, 1 H, C*H*HCHNH, J = 16, 4), 2.79 (part B of ABX 1 H, CH*H*CHNH, J = 16, 4), 2.91–1.94 (m, 2 H, $C_{11}H_{23}CHCH_2$), 1.86–1.17 (m, 30 H), 0.98–0.79 (m, 6 H, 2 × CH_2CH_3); IR (KBr) 3422, 3315, 3211 (NH, NH_2), 1834 (β-lactone), 1724 (ester), 1691 (carbamate), 1662 (amide); MS, 603 ($M + H)^+$; $[\alpha]^{22}_D$ –1° (*c* 0.25, $CHCl_3$).

(*S*)-*N*-Acetylasparagine (*S*)-1-[[(2*S*,3*S*)-3-Hexyl-4-oxo-2-oxetanyl]methyl]dodecyl Ester (Tetrahydroesterastin, 2). A solution of **19** (50 mg, 0.08 mmol) in THF (5 mL) was treated with 10% Pd/C (10 mg) and hydrogenated at room temperature under normal pressure. After $^1/_2$ h, the apparatus was purged with argon, 2 equiv of Et_3N (22.3 μL) added, and the crude **20** directly treated with 1 equiv of AcCl (4.6 μL). After 1 h, the solution was filtered, the filtrate evaporated, and the residue chromatographed on silica gel (50 g) with $CHCl_3$/EtOH (19:1) to afford 40 mg of pure **2** (98%): mp 99–101 °C; ^1H NMR ($CDCl_3$, 250 MHz) 6.81 (d, 1 H, N*H*Ac, J = 8), 5.79–5.66 (m, 1 H, N*H*H), 5.48–5.37 (m, 1 H, NH*H*), 5.10–4.98 (m, 1 H, $C_{11}H_{23}CH$), 4.40–4.29 [m, 1 H, H-C(4)], 3.29 (dt, 1 H, $C_6H_{13}CH$, J = 7.6, 4), 2.98 (part A of ABX, 1 H, C*H*HCHNH, J = 16, 4), 2.81 (part B of ABX, 1 H, CH*H*CHNH, J = 16, 4), 2.24–1.97 (m, 2 H), 2.04 (s, 3 H, NHAc), 1.86–1.17 (m, 30 H), 0.95–0.81 (m, 6 H, 2 × CH_2CH_3); IR (film) 3426, 3343, 3208 (NH, NH_2), 1840 (β-lactone), 1729 (ester), 1672, 1642 (amide); MS, 511 ($M + H)^+$; $[\alpha]^{22}_D$ 0° (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{28}H_{50}N_2O_6$: C, 65.85; H, 9.87; N, 5.49 Found: C, 65.91; H, 10.02; N, 5.35. (Literature:[3] mp 102.5–104 °C; similar IR; no ^1H NMR and $[\alpha]_D$ published.)

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