101. Stereoselective Syntheses of Tetrahydroesterastin-β-Lactam Analogues

by **Isabelle Huber**[1])* and **Fernand Schneider**

Pharmaceutical Research Department, *F. Hoffmann-La Roche Ltd.*, CH–4002 Basel

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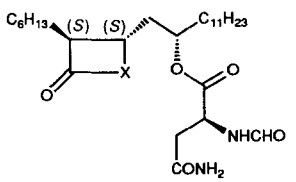
A total synthesis of the optically active tetrahydroesterastin β-lactam analogue **2** using *Miller*'s hydroxamate approach is described (*Scheme 2*). Significant modification of published procedures has resulted in a short and facile stereospecific preparation of the *N*-[(benzyloxycarbonyl)methyl]-β-lactam **17** starting from the readily available D-serine. This material served as intermediate for the preparation of a variety of *N*-[(benzyloxycarbonyl)methyl]tetrahydroesterastin β-lactam analogues (*Scheme 5*).

1. Introduction. – In the course of our research concerning the development of new antiinflammatory agents for various skin disorders, we became interested in potential diacylglycerol (DG) lipase inhibitors. DG Lipase [1] is an enzyme which is involved in one of the possible pathways responsible for the release of arachidonic acid (AA), an intracellular mediator of inflammatory and hypersensitivity responses [2]. Broad screening led us to the discovery of a very potent DG lipase inhibitor, a β-lactone with the (3*S*,4*S*) absolute configuration known as tetrahydroesterastin (**1**, THE) [3]. Tetrahydroesterastin



1 X = O, Tetrahydroesterastin
2 X = NH

(**1**) is the saturated derivative of esterastin, a β-lactone of microbial origin already well-known for its useful pharmacological activities [4]. THE inhibits DG lipase with an IC_{50} of 2.4 nM; however, THE as well as all the β-lactone analogues synthesized are inactive *in vivo*. A problem may well be poor cell penetration or instability. To overcome these difficulties, we decided to replace the β-lactone ring by the more stable β-lactam ring. In this paper, we describe the asymmetric total synthesis of β-lactam analogues of THE.

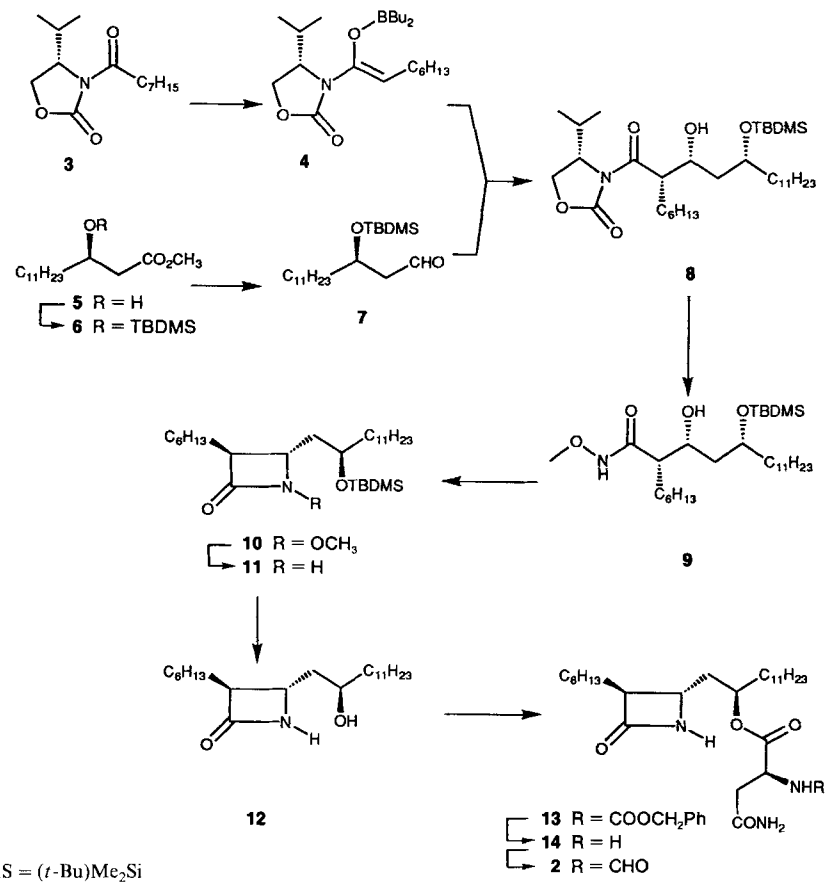
[1]) Present address: *Firmenich SA*, CH–1283 La Plaine.

2. Results and Discussion. – 2.1. *Synthesis of β-Lactam* **2**. For the synthesis of β-lactam **2**, we chose the strategy based on the cyclization of β-hydroxy-hydroxamate developed by *Miller* [5] (*Scheme 1*).

Scheme 1

The two stereocenters of the β-lactam ring were established *via* the asymmetric (highly stereoselective) *Evans* aldol [6] condensation between the chiral boron enolate **4** and the aldehyde **7** (*Scheme 2*). Thus, the known methyl (*R*)-3-hydroxytetradecanoate (**5**) [7] was protected as its (*tert*-butyl)dimethylsilyl ether **6** which was reduced with diisobutylaluminum hydrid (DIBAH) yielding the enantiomerically pure aldehyde **7**. The chiral oxa-

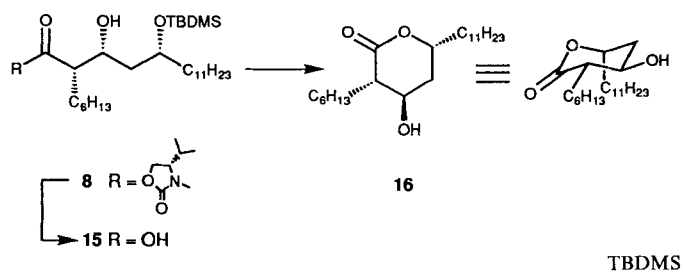
Scheme 2



TBDMS = (*t*-Bu)Me_2Si

zolone **3** was readily prepared by acylation of the (*S*)-4,5-dihydro-4-isopropyl-2*H*-oxazol-2-one with caproyl chloride in 88.2% yield. Aldol addition of the boron enolate **4**, generated from **3**, dibutylboron triflate, and $EtN(i\text{-}Pr)_2$, to the aldehyde **7**, the key step in this total synthesis, afforded after oxidative workup, the desired *syn*-aldol adduct **8** in 74% yield. Within high-field-NMR detection limits, a single diastereoisomer is formed. A small amount of the unpurified material was transformed into the tetrahydro-4-hydroxypyran-2-one **16** (*cf. Scheme 3*) to establish the absolute configuration [8]. Oxidative hydrolysis with lithium hydrogen peroxide [9] provided the corresponding acid **15** which was desilylated and cyclized in a one-step procedure by treatment with HF in MeCN. NMR Analysis of **16** showed the OH function and the alkyl chain at C(3) (C_6H_{13}) to be equatorial, the alkyl chain at C(6) ($C_{11}H_{23}$) being axial. Knowing that the absolute configuration at C(4) is (*R*), this center originating from (*R*)-configurated aldehyde **7**, the absolute configuration of the aldol adduct **8** is, thus, established, as expected, as (2*S*,3*R*,5*R*).

Scheme 3



TBDMS = (*t*-Bu)Me_2Si

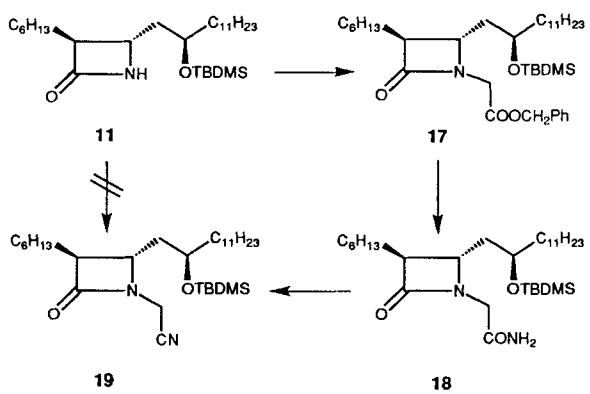
The total synthesis of the β-lactam has been continued as follows. Removal of the chiral auxiliary from **8** to give the hydroxamic acid **9** was achieved in 94% yield without detectable epimerization using the aluminum-amide reagent derived from methoxyamine hydrochloride and Me_3Al [10]. Formation of the azetidinone **10** was accomplished in 80% yield through mesylation of **9** and subsequent treatment with K_2CO_3 in refluxing acetone according to the procedure in [11]. The cyclization occurred under inversion of configuration at C(3) to give the *trans* β-lactam, as shown by NMR data, having the (3*S*,4*S*) absolute configuration. In the next step, the reduction in the presence of metallic Na in liquid ammonia successfully accomplished the N–O bond cleavage to give the desired azetidinone **11** in 83% yield. The (*t*-Bu)Me_2Si group was removed and the resulting hydroxy azetidinone **12** esterified with (*S*)-*N*-(benzyloxycarbonyl)asparagine using *Mitsunobu*'s condition [12] (inversion of configuration at the alcohol center) to yield the ester **13**. Cleavage of the benzyloxycarbonyl (Z) protecting group by hydrogenolysis and formylation with the mixed anhydride [13] gave pure **2**, the THE β-lactam analogue with the (*S*,*S*,*S*,*S*) absolute configuration.

2.2. *Synthesis of* N-*Substituted* β-*Lactam*. The inhibitory activity of THE towards DG lipase might well be partly due to irreversible acylation of the enzyme by OC=O bond cleavage of the β-lactone ring. Improving too much the stability of the ring would lead to a decrease or lack of reactivity and, therefore, activity. Activation of the β-lactam ring toward nucleophilic attack by the presence of an electron-withdrawing substituent on the

azetidinyl N-atom is an observation that has been already widely discussed in the literature [14]. In this paper, we focused on *N*-(benzyloxycarbonyl)methyl- and *N*-cyanomethyl-substituted azetidinones. A short and stereospecific synthetic pathway (extending the hydroxamide-mediated β-lactam-synthesis methodology) giving access to them is described.

Direct *N*-alkylation of β-lactam **11** was first explored (*Scheme 4*). For this purpose, several combinations of solvents (THF, MeCN, 1,2-dimethoxyethane) and bases (NaH [15], lithium hexamethyldisilazan, Cs_2CO_3 [16]), were used in the presence of benzyl bromoacetate; either no reaction occurred or azetidinone **17** was formed in very low yield (1–30%). Similar results were obtained using the phase-transfer-catalyzed methodology [17]. However, when β-lactam **11** was treated with the stronger electrophile benzyl iodoacetate in the presence of Cs_2CO_3 in boiling 1,2-dimethoxyethane, the *N*-alkylation progressed smoothly to give **17** in 65% yield. Unfortunately, after trying various conditions, we never succeeded in the direct formation of the azetidinone **19**. This one could be obtained in two easy steps from the ester **17**: aminolysis of **17** with methanolic ammonia in the presence of a catalytic amount of NaCN [18] afforded the carboxamide **18** which was subsequently dehydrated with phosphorous oxychloride and Et_3N in $CHCl_3$ solution [19] to give the nitrile **19** in 70.4% yield from **17**.

Scheme 4



TBDMS = (*t*-Bu)Me_2Si

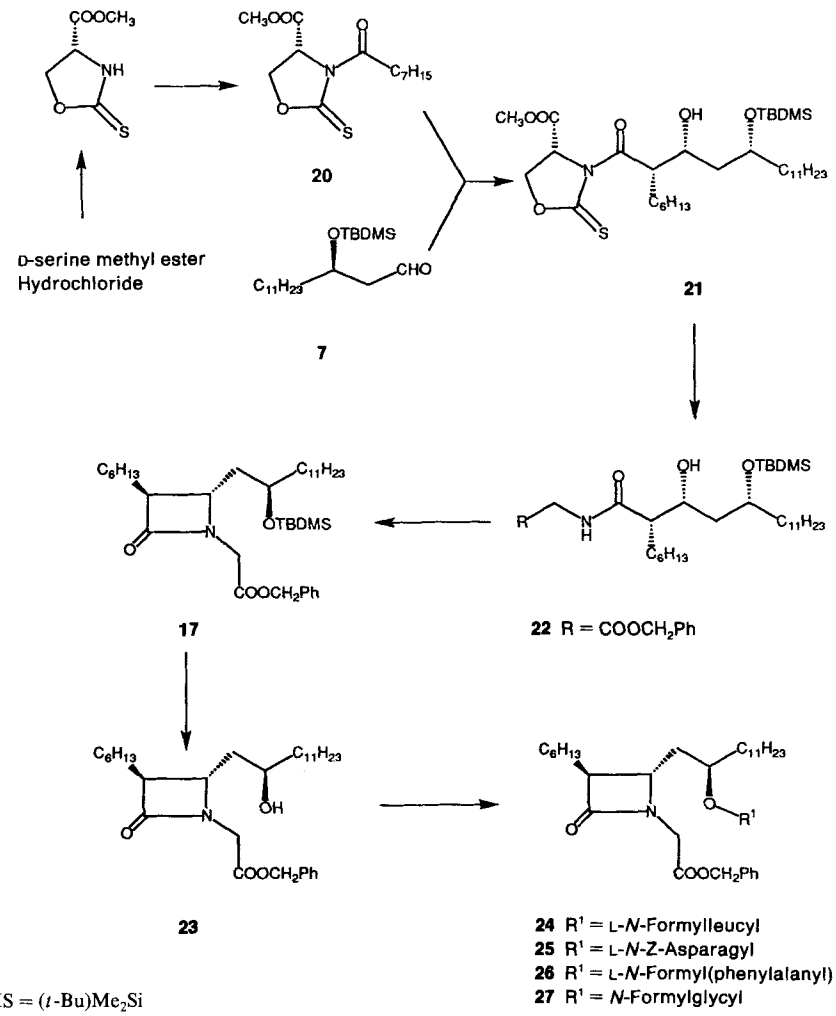
Although we completed the synthesis of azetidinone **17** and **19** in acceptable overall yield, the use of a large excess H_2O_2 for the aldol condensation oxidative workup and Me_3Al in the transamination step as well as the elevated number of steps encouraged us to look for a better procedure.

An improvement of this approach consisted in using the chiral auxiliary (4*R*)-2,3,4,5-tetrahydro-2-thioxo-1,3-oxazole-4-carboxylate reported by *Miller* and coworkers [20]. The usual dibutylboron-triflate-mediated aldol condensation is compatible with this chiral auxiliary but does not require oxidative workup. Furthermore, the acyloxazolidinethiones are reported as being easily removed by solvolysis or aminolysis in satisfactory yield.

In our synthesis, the use of this chiral auxiliary should yield the required *N*-substituted azetidinone **17** in only two steps from the aldol adduct: aminolysis using the required substituted amines followed by cyclization.

The synthesis of the *N*-adduct **22** was achieved as follows (*Scheme 5*). Acylation of the D-serine-derived dihydrooxazole-thione with caproyl chloride produced the optically pure aldol substrate **20**. Enolization of **20** with dibutylboryl triflate and $(i\text{-Pr})_2EtN$ [20] followed by reaction with the aldehyde **7** produced the '*syn*'-β-hydroxamide equivalent **21** diastereoselectively (< 10:1 routinely and, as a single detectable diastereoisomer). This process established the two asymmetric centers of the β-lactam moiety. Direct treatment of **21** with glycine benzyl ester hydrochloride produced the desired amide **22** in 69.4% yield.

Scheme 5



TBDMS = $(t\text{-Bu})Me_2Si$

Cyclization of β-hydroxyamides using the two methods described in the literature for deactivated *N*-substituted hydroxamides, namely *Mitsunobu*'s procedure, as well as displacement of halides by amide anions generated with strong bases (lithium dialkylamides or NaH) [21] proceeded with poor yield.

Due to the lack of a relatively strong acidic proton on the C-atom α to the N-atom, which is essential for the success of the reaction [22], secondary products from reactions such as β-elimination and/or pyrrolidone formation predominate. As expected when **22** was submitted to *Mitsunobu*'s or modified *Mitsunobu*'s conditions [23], no reaction occurred.

The method proposed by *Floyd et al.* [11] for the cyclization of β-hydroxy hydroxamate, namely mesylation of the β-OH group followed by cyclization using K_2CO_3 in acetone, has not been described so far for deactivated *N*-substituted β-hydroxy amides. No β-lactam was obtained when the methanesulfonate, prepared from **22**, was subjected to K_2CO_3 in acetone or using 1,2-dimethoxyethane as a solvent. However, with DMF at 120°, cyclization occurred readily. In addition, we explored this cyclization reaction using Cs^+. Cesium is reported to be a cyclization promoter probably due to ion-pairing phenomena [24]. Refluxing the methanesulfonate derived from **22** with Cs_2CO_3 in acetone, THF and/or MeCN, only very poor yield of cyclized product were obtained. Changing to 1,2-dimethoxyethane as a solvent, the cyclization proceeded smoothly to give a 65.8% yield of **17**.

The *trans*-β-lactam was cleanly formed as indicated by ^{1}H-NMR data, no epimerization could be detected. Furthermore, all the analytical data and the optical rotation of the compound obtained in this manner were identical to the material prepared from **11**; this proved the absolute configuration to be (3*S*,4*S*) and confirmed the absolute configuration of the precursor *syn*-aldol adduct **21** to be (2*S*,3*R*,5*R*). The easy isolation of the pure compound using this method is an advantage, if compared with the sometimes difficult chromatographic separations necessary when using *Mitsunobu*'s cyclization conditions.

Being able now to prepare the *N*-substituted azetidinone **17** in sufficient amounts, the synthesis of a series of THE *N*-substituted-β-lactam analogues was investigated. Removal of the (*t*-Bu)Me_2Si group using a 40% aqueous HF solution in MeCN, followed by esterification of the hydroxy-azetidinone **23** with various amino acids (*N*-Z-L asparagine, L-*N*-formylleucine, L-*N*-formyl(phenylalanine), *N*-formylglycine) using *Mitsunobu*'s conditions provided the pure β-lactam analogues **24**–**27** with (*S*,*S*,*S*,*S*) absolute configuration.

Our thanks are due to Mr. *M. Burn* and *M. Menzi* for their excellent technical assistance, and colleagues from Central Research for spectral data and elemental analyses.

Experimental Part

General. Column chromatography: *Merck* silica gel *60* (70–230 mesh ASTM). M.p.: *Totolli* 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 W M 250*. MS: *MS9-ZAB*, data system *SS 200*.

*(4S)-2,3,4,5-Tetrahydro-4-(1-methylethyl)-*N*-octanoyloxazol-2-one* (**3**). To a soln. of (4*S*)-2,3,4,5-tetrahydro-4-(1-methylethyl)oxazol-2-one (15 g, 0.116 mol) in dry THF (500 ml) at −78° under Ar was added a soln. of BuLi (0.116 mol). The mixture was stirred for 30 min, during which time the reaction was allowed to warm to −20°, and was subsequently cooled to −78°. Capryloyl chloride (19.88 ml, 0.116 mol) in THF (60 ml) was added with

stirring while allowing the mixture to slowly warm to r.t. The reaction mixture was quenched with phosphate buffer (pH 7), the product was extracted with Et_2O, the extract washed with distilled water and brine, and then dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave the crude product which was purified by bulb-to-bulb distillation (160°, 0.6 mm Hg) to give pure **3** as a colorless oil (26.12 g, 88.2%). $[\alpha]_D^{20} = +67.06$ ($c = 0.34$, $CHCl_3$). IR (film): 1780, 1702. ^{1}H-NMR ($CDCl_3$): 4.39–4.45 (*m*, H–C(4)); 4.16–4.29 (*m*, 2 H–C(5)); 2.77–3.04 (*m*, CH_2CO); 2.30–2.45 (*m*, Me_2CH); 1.58–1.67, 1.20–1.45 (2*m*, 2 H, 8 H, 5 CH_2); 0.83–0.96 (*m*, 3 Me). MS: 256 ($[M + H]^+$), 225 (M^+). Anal. calc. for $C_{14}H_{25}NO_3$ (255.38): C 65.85, H 9.87, N 5.49; found: C 65.97, H 10.15, N 5.74.

*Methyl (*R*)-3-[(*tert*-Butyl)dimethylsilyloxy]tetradecanoate* (**6**). To a soln. of **5** (25.84 g, 100 mmol), 4-(dimethylamino)pyridine (3.05 g, 25 mmol) and (*t*-Bu)Me_2SiCl (16.58 g, 110 mmol) in 100 ml of DMF was added Et_3N (20.91 ml, 150 mmol). The mixture was stirred 16 h at r.t. The salt formed was filtered, washed with DMF (25 ml) and pentane (4 times 25 ml). The pentane phase was separated, and the DMF was carefully extracted with additional pentane (4 × 50 ml). The combined pentane phase was washed with 1N HCl soln. distilled water, and brine, and dried ($MgSO_4$) and evaporated *in vacuo* to give **6** (39.33 g, 100%; practically pure), the crude compound **6** was purified on a flash column (alox A III, Et_2O/hexane, 1:19). IR (film): 1739, 1496. ^{1}H-NMR ($CDCl_3$): 4.12–4.02 (*m*, CHOSi); 3.67 (*s*, MeO); 2.60 (*dd*, $J = 15.7$, 7.5, 1 H), 2.45 (*dd*, $J = 15.7$, 7.5, 1 H) (CH_2CO); 1.50–1.47, 1.25–1.23 (2*m*, 2 H, 18 H, 10 CH_2); 0.90–0.85 (*m*, Me, *t*-Bu); 0.072 (*s*, 3 H), 0.055 (*s*, Me_2Si). MS: 372.

*(*R*)-3-[(*tert*-Butyl)dimethylsilyloxy]tetradecanal* (**7**). A soln. of **6** (21.7 g, 58.4 mmol) in Et_2O (170 ml) was cooled under stirring and Ar to −78°. A 1.2M DIBAH soln. in toluene (76.3 ml) was added dropwise within 2 h. The mixture was stirred an additional 2 h at −78°. i-PrOH (5 ml) was added. The temp. was allowed to warm up to 0°, and H_2O (17 ml) was added dropwise, followed by a 0.5M soln. of citric acid (170 ml). The resulting mixture was stirred vigorously 1 h at r.t. The org. phase was separated and the aq. phase extracted with Et_2O. The org. phases were combined and washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The oily residue was purified by flash chromatography (silica gel, hexane/Et_2O/Et_3N 19:1:0.1%. Before complete evaporation of the collected fraction, Et_3N was neutralized with citric acid) to give pure **7** (12.8 g, 65%). $[\alpha]_D^{20} = -2.6$ ($c = 0.9$, $CHCl_3$). IR (film): 2717, 1728, 1254, 836, 776, 721. ^{1}H-NMR ($CDCl_3$): 9.73 (*t*, $J = 2.5$, CHO); 4.17 (*tt*, $J = 4.75$, 4.75, CHOSi); 2.51 (*dd*, $J = 5.75$, 2.75, CH_2); 1.52–1.49 (*m*, 2 H), 1.26 (br. *s*, 18 H) (10 CH_2); 0.92–0.85 (*m*, CH_3, *t*-Bu); 0.071 (*s*, 3 H), 0.054 (*s*, 3 H) (Me_2Si). MS: 327, 285, 187, 131, 101. Anal. calc. for $C_{20}H_{42}O_2Si$ (342.637): C 70.71, H 12.36; found: C 70.71, H 12.53.

*(4*S*)-3-{(2*S*,3*R*,5*R*)-5-[(*tert*-Butyl)dimethylsilyloxy]-2-hexyl-3-hydroxyhexadecanoyl}-2,3,4,5-tetrahydro-4-isopropyloxazol-2-one* (**8**). To a stirred soln. of **3** (15.88 g, 63 mmol) in 240 ml of CH_2Cl_2 at 0° under Ar (internal temp.) was added dibutylboryl trifluoromethanesulfonate under Ar (69 mmol, 69 ml of a 1.0M soln. in CH_2Cl_2, *Aldrich*). After the mixture had been stirred for 5 min at 0°, Et(i-Pr)$_2$N (11.8 ml, 69 mmol) was added slowly. The internal temp. was carefully maintained at 0° during this process. The resulting soln. was stirred at 0° for another 30 min and then cooled to −78°, and **7** (23.6 g, 69 mmol) in 90 ml of CH_2Cl_2 was added. The mixture was stirred for 1 h at −78° and then allowed to warm to −30° over 30 min. The mixture was stirred at −30° for an additional h. The resulting soln. was quenched with a mixture of 320 ml of MeOH and 160 ml of phosphate buffer (pH 7) and the mixture stirred vigorously at 0° for 15 min. The resulting borate was oxidized by 30% H_2O_2 (160 ml) for 1 h at 0°, 225 ml of H_2O was added; and the mixture concentrated *in vacuo* to remove CH_2Cl_2 and most of MeOH. The residue was extracted twice with Et_2O and the combined Et_2O soln. washed with 5% aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The oily residue was a purified by column chromatography (silica gel, Et_2O/hexane 1:9 then 1:2) to provide **8** (28 g, 74%). Colorless oil. $[\alpha]_D^{20} = +45.13$ ($c = 0.74$, $CHCl_3$). IR (film): 1782, 1698, 1250, 837, 774. ^{1}H-NMR ($CDCl_3$): 4.44–4.38 (*m*, H–C(4)); 4.19–4.08 (*m*, 2 H–C(5)); 4.03–3.98 (*m*, 1 H, CHCO); 3.92–3.85 (*m*, 1 H, CHOH); 3.85–3.77 (*m*, CHOSi); 3.19 (*d*, $J = 2.3$, OH); 2.31–2.27 (*m*, Me_2CH); 1.77–1.72 (*m*, 1 H); 1.54–1.51 (*m*, 3 H); 1.40–1.35 (*m*, 2 H); 1.20–1.17 (*m*, 26 H) (16 CH_2); 0.95–0.71 (*m*, 4 Me and *t*-Bu); 0.09 (*s*, 3 H), 0.08 (*s*, 3 H) (Me_2Si). MS: 478, 367, 285. Anal. calc. for $C_{34}H_{67}NO_5Si$ (597.998): C 68.29, H 11.29, N 2.34; found: C 68.34, H 11.54, N 2.33.

*(2*S*,3*R*,5*R*)-5-[(*tert*-Butyl)dimethylsilyloxy]-2-hexyl-3-hydroxy-N-methoxyhexadecanamide* (**9**). To a suspension of *N*-methylhydroxylamine hydrochloride (9.28 g, 111.6 mmol) in 190 ml of THF at 0°, was slowly added a 2M soln. (58 ml, 111.6 mmol) of Me_3Al in toluene. After the addition was complete, the mixture was allowed to warm to r.t. and was stirred, until gas evolution has ceased (1–2 h). The aluminum-amide reagent formed was added to a soln. of **8** (31.8 g, 531 mmol) in 255 ml of THF at 0°. The soln. was stirred at r.t. for 3 h. The mixture was cooled to 0° carefully quenched with 5% HCl. The org. layer was separated and the aq. layer extracted with Et_2O. The combined org. extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford essentially pure **9** which was purified by silica-gel chromatography (Et_2O/hexane 1:2 then Et_2O) to give 25.7 g of pure **9** (93.9%). $[\alpha]_D^{20} = -13.79$ ($c = 0.29$, $CHCl_3$). IR (film): 3470, 3189, 1648, 1254, 836, 775. ^{1}H-NMR ($CDCl_3$): 8.85 (*s*, NH);

4.23 (*s*, OH); 3.95–3.82 (*m*, CHO, CHN); 3.76 (*s*, MeO); 2.28–2.16 (*m*, COCH); 1.75–1.20 (*m*, 16 CH_2); 0.90–0.85 (*m*, 2 Me, *t*-Bu); 0.12 (*s*, 3 H), 0.11 (*s*, 3 H) (Me_2Si). MS: 516 ($[M + H]^+$), 458, 384. Anal. calc. for $C_{29}H_{61}NO_4Si$ (515.896): C 67.52, H 11.92, N 2.72; found: C 67.46, H 12.24, N 2.73.

*(3S,4S)-4-{(R)-2-[(*tert*-Butyl)dimethylsilyloxy]tridecyl}-3-hexyl-1-methoxyazetidin-2-one* (**10**). A soln. of **9** (28 g, 54.36 mmol) in dry pyridine (60 ml) at 0° was treated with MsCl (5 ml, 65.2 mmol). The mixture was stirred at 0° for 3 h, then diluted with AcOEt and treated with 1N HCl (until acidic), followed by sat. $NaHCO_3$ and finally brine. The extracts were dried and evaporated to give the crude mesylate in quantitative yield. A soln. of the crude mesylate in dry acetone (750 ml) was heated at reflux temp. and treated with powdered K_2CO_3 (36.3 g, 263 mmol) with vigorous stirring. After refluxing for 1 h, the mixture was cooled, diluted with AcOEt, and filtered through *Celite* (washing with AcOEt). The solvent was evaporated to give a crude product which was purified by flash chromatography (Et_2O/hexane 1:2) to afford **10** in 80.8% yield (21.8 g). $[\alpha]_D^{20} = -14$ ($c = 0.1$, $CHCl_3$). IR (film): 1778, 1259, 836, 775. ^{1}H-NMR ($CDCl_3$): 3.88–3.78 (*m*, CHO); 3.78 (*s*, MeO); 3.705 (*dt*, $J = 8$, 2, CHN); 2.5 (*dt*, $J = 7.5$, 2.1, CHCO); 1.99–1.23 (*m*, 16 CH_2); 0.90–0.65 (*m*, 2 Me, *t*-Bu); 0.081 (*s*, 3 H), 0.075 (*s*, 3 H) (Me_2Si). MS: 497 (M^+), 440, 408, 240. Anal. calc. for $C_{29}H_{59}NO_3Si$ (497.881): C 69.96, H 11.95, N 2.81; found: C 69.73, H 11.70, N 2.95.

*(3S,4S)-4-{(R)-2-[(*tert*-Butyl)dimethylsilyloxy]tridecyl}-3-hexylazetidin-2-one* (**11**). To a soln. of Na (5.57 g, 241.5 mmol) in NH_3/*THF* 10:1 (500 ml) at −78°, a soln. of **10** (20 g, 40.24 mmol) in THF (100 ml) was added. The resulting blue soln. was stirred at −78° for 2 h, then solid NH_4Cl (29.1 g, 544 mmol) was added, and the resulting colorless soln. was diluted with Et_2O (500 ml). NH_3 was then distilled off, while the soln. was heated to r.t., and 500 ml of Et_2O was added to the white slurry. After filtration and washing of the solids with additional Et_2O, the org. phase was concentrated to give a crude product which was purified by flash chromatography (Et_2O/hexane 1:1) to give **11** in 83% yield (15.6 g). $[\alpha]_D^{20} = -25$ ($c = 0.1$, $CHCl_3$). IR (film): 3231, 1753, 1254, 836, 775. ^{1}H-NMR ($CDCl_3$): 5.77 (*s*, NH); 3.75–3.64 (*m*, CHO); 3.47–3.38 (*m*, CHN); 2.75–2.65 (*m*, COCH); 1.82–1.15 (*m*, 16 CH_2); 0.91–0.82 (*m*, 2 Me, *t*-Bu); 0.081 (*s*, 3 H), 0.073 (*s*, 3 H) (Me_2Si). MS: 410, 367, 229, 284. Anal. calc. for $C_{28}H_{57}NO_2Si$ (467.855): C 71.88, H 12.28, N 2.99; found: C 71.78, H 12.38, N 3.04.

(3S,4S)-3-Hexyl-4-[(R)-2-hydroxytridecyl]azetidin-2-one (**12**). To a soln. of **11** (8.2 g, 17.55 mmol) in a mixture of 200 ml of MeCN and 50 ml of THF at 0° was added 11.68 ml of 40% aq. HF. The mixture was stirred for 2 h and then diluted with Et_2O washed with H_2O, sat. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The white residue was crystallized from hexane to give **12** in 88% yield (5.45 g). M.p. 99.7–100.4°. $[\alpha]_D^{20} = -27.5$ ($c = 0.2$, $CHCl_3$). IR (film): 3268, 3223, 1711. ^{1}H-NMR ($CDCl_3$): 5.98 (br. *s*, NH); 3.77–3.66 (*m*, CHO); 3.59–3.50 (*m*, CHN); 2.85–2.73 (*m*, COCH); 1.86–1.22 (*m*, 16 CH_2); 0.97–0.82 (*m*, 2 Me). MS: 354 ($[M + H]^+$), 210, 185. Anal. calc. for $C_{22}H_{43}NO_2$ (353.591): C 74.73, H 12.26, N 3.98; found: C 74.57, H 12.38, N 3.98.

(S)-1-{[(2S,3S)-3-Hexyl-4-oxoazetidin-2-yl]methyl}dodecyl (S)-2-[(Benzyloxycarbonyl)amino]succinamate (**13**). A soln. of **12** (500 mg, 1.4 mmol), Ph_3P (428 mg, 1.633 mmol), and *N*-Z-L-asparagine (435 mg, 1.663 mmol) in THF (40 ml) was cooled with stirring to 0°. Diethyl azodicarboxylate (0.256 ml, 1.699 mmol) dissolved in 10 ml of THF was added slowly (1 h), and the mixture was stirred for 2 h at r.t. and evaporated. The residue was chromatographed on silica gel (Et_2O then Et_2O/MeOH 19:1) to give **12** in 55% yield (463 mg). $[\alpha]_D^{20} = +8$ ($c = 0.3$, $CHCl_3$). IR (KBr): 3347, 1766, 1725, 1700, 1659, 1544, 729, 696. ^{1}H-NMR ($CDCl_3$): 7.41–7.3 (*m*, 5 arom. H); 7.09 (br. *s*, NH); 6.29 (br. *s*, 1 H), 6.21 (br. *s*, 1 H) (NH_2); 5.94 (*d*, $J = 8$, NH); 5.12 (*s*, CH_2O); 5.08–4.96 (*m*, CHO); 4.56–4.44 (*m*, NCH); 3.39–3.29 (*m*, NCH); 2.91 (*ABX*, $J_{AB} = 36$, $J_{AX} = 5.76$, $J_{BX} = 4$, $COCH_2$); 2.70–2.61 (*m*, COCH); 1.98–1.18 (*m*, 16 CH_2); 0.90–0.65 (*t*, $J = 6.4$, 2 Me). MS: 602 ($[M + H]^+$), 468, 300, 210. Anal. calc. for $C_{34}H_{55}N_3O_6$ (601.829): C 67.86, H 9.21, N 6.28; found: C 67.64, H 9.20, N 6.93.

(S)-1-{[(2S,3S)-3-hexyl-4-oxoazetidin-2-yl]methyl}dodecyl (S)-2-(Formylamino)succinamate (**2**). A soln. of **13** (350 mg, 0.582 mmol) in THF (7 ml) was treated with 10% Pd/C (40 mg) and hydrogenated at r.t. under normal pressure. After 2 h, the reaction was completed. The catalyst was filtered off, the filtrate was evaporated and the residue at 0° treated dropwise with acetic formic anhydride (1 ml). The mixture was diluted with Et_2O and washed with a 2% aq. $NaHCO_3$ soln. and brine. The org. phase was dried ($MgSO_4$) and evaporated. The crude product was purified on a flash column (silica gel, Et_2O/MeOH 19:1) to give 100 mg (35% yield) of pure **2** as a colorless oil. $[\alpha]_D^{20} = -18.5$ ($c = 0.9$, MeOH). IR (film): 3289, 2925, 2854, 1741, 1.673, 1.511, 1.204. ^{1}H-NMR ($CDCl_3$): 8.22 (*s*, CHO); 7.01 (*s*, NH); 6.95 (*d*, $J = 8$, NH); 6.13 (br. *s*, NH_2); 5.12–5.01 (*m*, OCH); 4.35–4.25 (*m*, NCH); 3.45–3.35 (*m*, NCH); 2.88, 3.04 (*ABX*, $J_{AB} = 16$, $J_{AX} = 4$, $J_{BX} = 4.8$, $COCH_2$); 2.64–2.74 (*m*, COCH); 2.02–1.21 (*m*, 16 CH_2); 0.85–0.82 (*m*, 2 Me). MS: 496 ($[M + H]^+$), 468, 210. Anal. calc. for $C_{27}H_{49}N_3O_5$ (495.705): C 65.42, H 9.96, N 8.48; found: C 65.27, H 10.09, N 8.08.

*3-Hexyl-3,4,5,6-tetrahydro-4β-hydroxy-6-undecyl-2*H*-pyran-2-one* (**16**). To a precooled (0°) soln. of **8** (1 g unpurified material) dissolved in 120 ml of THF was added slowly dropwise with stirring an aq. lithium hydrogen peroxide soln. (prepared from 40 mg (1.67 mmol) of LiOH in 7 ml of H_2O, 0.849 ml (8.35 mmol) of 30% aq. H_2O_2,

and 12 ml of distilled H_2O). After stirring the clear soln. for 1 h at 0°, the reaction mixture was quenched by dropwise addition of an aq. soln. of sodium hydrogen sulfite (10 equiv., 1.736 g in 19 ml of distilled H_2O). After stirring the resulting mixture for 15 min at 0°, the org. solvent was removed *in vacuo*. The remaining aq. mixture was extracted 3 times with AcOEt. The combined org. phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the unpurified acid **15**. The unpurified acid was disolved in 15 ml of MeCN and treated with 1 ml of 40% aq. HF. The mixture was stirred for 1 h and then diluted with AcOEt, washed with H_2O, sat. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude material was purified on a flash column (silica gel, AcOEt/hexane 1:2) to give 300 mg of pure **16**. M.p. 66.5–67.4°. $[\alpha]_D^{20} = +20$ ($c = 0.35$, $CHCl_3$). IR (film): 3461, 2956, 2852, 1708, 1211, 1097. ^{1}H-NMR ($CDCl_3$): 4.60–4.53 (*m*, H–C(2)); 4.02–3.98 (*m*, H–C(4)); 2.48–2.43 (*m*, H–C(3)); 1.89 (br. *s*, OH); 1.89–1.25 (*m*, 16 CH_2); 0.93–0.86 (*m*, 2 Me). MS: 354 (M^+), 336, 318, 252. Anal. calc. for $C_{22}H_{42}O_3$ (354.575): C 74.52, H 11.94; found: C 74.27, H 11.96.

*Benzyl (2S,3S)-2-{(R)-2-[(*tert*-Butyl)dimethylsilyloxy]tridecyl}-3-hexyl-4-oxoazetidine-1-acetate.* (**17**). To a soln. of **11** (5 g, 10.7 mmol) in 1,2-dimethoxyethane (100 ml) was added Cs_2CO_3 (8.7 g, 26.7 mmol) and benzyliodoacetate (8.5 ml, 30 mmol). The suspension was stirred under vigorous stirring 4 h at 120°, filtered, and the filtrate evaporated under vacuum. The residue was purified on a flash column (silica gel, hexane/Et_2O 2:1, then 1:1) to give pure **17** as a yellowish oil (4.2 g, 63.8% yield). $[\alpha]_D^{20} = +7$ ($c = 0.1$, $CHCl_3$). IR (film): 1763, 1462, 1254, 1186, 1081, 835, 775, 696. ^{1}H-NMR ($CDCl_3$): 7.33 (*s*, arom. H); 5.16, 5.10 (*AB*, $J_{AB} = 14.6$, $PhCH_2$); 4.05, 3.97 (*AB*, $J_{AB} = 99.2$, NCH_2); 3.72–3.64 (*m*, CHOSi); 3.59 (*dt*, $J = 6, 2$, CHN); 2.77 (*dt*, $J = 8, 2$, CHCO); 1.91–1.16 (*m*, 16 CH_2); 0.94–0.79 (*m*, 2 Me, *t*-Bu); 0.034 (*s*, 3 H), 0.013 (*s*, Me_2Si). MS: 558, 480, 432, 299, 91. Anal. calc. for $C_{37}H_{65}NO_4Si$ (616.016): C 72.14, H 10.64, N 2.27; found: C 72.05, H 10.59, N 2.27.

*(2S,3S)-2-{(R)-2-[(*tert*-Butyl)dimethylsilyloxy]tridecyl}-3-hexyl-4-oxoazetidine-1-acetamide* (**18**). A mixture of **17** (3.59 g, 5.82 mmol) and NaCN (32 mg) in 8.5 ml of 11M ammonia in MeOH was heated to 45° in a sealed glass flask for 30 h. The solvent was evaporated and the residue purified on a flash column (silica gel, AcOEt/hexane 1:9) to give pure **18** as an oil (2.7 g, 88% yield). $[\alpha]_D^{20} = -5$ ($c = 0.4$, $CHCl_3$). IR (film): 3487, 3352, 3203, 1748, 1691, 1622, 1254, 1082, 855, 775. ^{1}H-NMR ($CDCl_3$): 6.22 (br. *s*, 1 H), 5.34 (br. *s*, 1 H) (NH_2); 3.83, 3.75 (*AB*, $J_{AB} = 30$, NCH_2); 3.75–3.54 (*m*, HCOSi); 3.48 (*dt*, $J = 6, 2$, CHN); 2.77 (*dt*, $J = 6, 2$, CHCO); 1.94–1.08 (*m*, 16 CH_2); 0.80–0.79 (*m*, 2 Me, *t*-Bu); 0.07 (*s*, Me_2Si). MS: 467, 367, 341, 157, 73. Anal. calc. for $C_{30}H_{60}N_2O_3Si$ (524.907): C 68.65, H 11.52, N 5.34; found: C 68.21, H 11.80, N 5.31.

*(2S,3S)-2-{(R)-2-[(*tert*-Butyl)dimethylsilyloxy]tridecyl}-3-hexyl-4-oxoazetidine-1-acetonitrile* (**19**). To a soln. of **18** (1.7 g, 3.24 mmol) in $CHCl_3$ (15 ml) was added Et_3N (6.8 ml) and the mixture cooled to 0°. Phosphorus oxychloride (0.826 ml, 8.77 mmol) was added dropwise with stirring and the soln. allowed to warm to r.t. for 1 h. The brown mixture was concentrated to dryness *in vacuo* and the residue dissolved in $CHCl_3$. This org. soln. was washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over silica gel (flash chromatography, AcOEt/hexane 1:9) to yield 1.3 g (80%) of pure **19** as an oil. $[\alpha]_D^{20} = -7.42$ ($c = 0.7$, $CHCl_3$). IR (film): 1765, 1254, 1079, 836, 776. ^{1}H-NMR ($CDCl_3$): 4.24, 4.16 (*AB*, $J_{AB} = 44$, NCH_2Ph); 3.91–3.79 (*m*, CHOSi); 3.58 (*dt*, $J = 6, 2$, CHN); 2.85 (*dt*, $J = 6, 2$, CHCO); 2.03–1.14 (*m*, 16 CH_2); 0.97–0.81 (*m*, 2 Me, *t*-Bu); 0.085 (*s*, Me_2Si). MS: 449, 324, 299. Anal. calc. for $C_{30}H_{58}N_2O_2Si$ (506.892): C 71.09, H 11.53, N 5.53; found: C 70.95, H 11.71, N 5.53.

Methyl 3-Heptanoyl-2,3,4,5-tetrahydro-2-thioxo-1,3-oxazole-4-carboxylate(**20**). To a soln. of methyl (4*R*)-2,3,4,5-tetrahydro-2-thioxo-1,3-oxazole-4-carboxylate [20] (10.81 g, 67.1 mmol) in 88.5 ml of CH_2Cl_2 at −78° under Ar was added pyridine (6.17 ml, 76.5 mmol). After the mixture was stirred for 5 min, a soln. of caproyl chloride (13.9 ml, 81.2 mmol) in 6 ml of CH_2Cl_2 was added dropwise. The mixture was stirred at −78° for 1 h, allowed to warm to r.t. over 30 min, and then stirred overnight. More CH_2Cl_2 was added (200 ml), and the mixture was extracted with H_2O, with 5% aq. oxalic acid, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The oily yellow residue was chromatographed on silica gel using AcOEt/hexane 1:2 to provide 18 g (93% yield) of **20** as a yellow oil. $[\alpha]_D^{20} = +31.4$ ($c = 0.5$, $CHCl_3$). IR (film): 1756, 1708, 1370, 1221. ^{1}H-NMR ($CDCl_3$): 5.15 (*dd*, $J = 8.4, 4$, 1 H, CH_2CHN); 4.69 (*dd*, $J = 8.4, 8.4$, 1 H); 4.53 (*dd*, $J = 8.4, 4$, 1 H) (CH_2CHN); 3.61 (*s*, MeO); 3.49–3.16 (*m*, $NCOCH_2$); 1.78–1.59 (*m*, 2 H), 1.47–1.14 (*m*, 8 H) (5 CH_2); 0.9 (*t*, $J = 7.6$, 2 Me). MS: 287 (M^+), 254, 162, 102. Anal. calc. for $C_{13}H_{21}NO_4S$ (287.374): C 54.33, H 7.37, N 4.87; found: C 54.83, H 7.62, N 4.59.

*Methyl (R)-3-{(2S,3R,5R)-5-[(*tert*-Butyl)dimethylsilyloxy]-2-hexyl-3-hydroxyhexadecanoyl}-2,3,4,5-tetrahydro-2-thioxooxazole-4-carboxylate* (**21**). To a stirred soln. of **20** (2.94 g, 10.23 mmol) in 42 ml of CH_2Cl_2 at 0° (internal temp.) under Ar was added dibutylboryl trifluoromethanesulfonate (10.91 mmol, 10.91 ml of a 1.0M soln. in CH_2Cl_2). After the mixture was stirred for 15 min at 0°, $(i\text{-}Pr)_2EtN$ (10.6 mmol, 1.84 ml) was added dropwise with a syringe. The internal temp. was carefully maintained at 0° during this process. The resulting light yellow soln. was stirred at 0° for another 30 min, and then cooled to −78°, and aldehyde **7** in 15 ml of CH_2Cl_2 (11.21 mmol, 3.84 g) was added. The mixture was stirred for 1.5 h at −78° and then allowed to warm to −30°. At this time, no starting

material could be detected by TLC. A phosphate buffer (47 ml, pH 7) was added, and the mixture was stirred vigorously at 0° for 10 min. The yellow CH_2Cl_2 soln. was separated, concentrated, and filtered through a silica-gel column with AcOEt to remove the boric-acid by-products. The filtrate was concentrated under reduced pressure and purified on flash chromatography (silica gel, AcOEt/hexane 1:2) to provide **21** (4.7 g, 73% yield) as a light yellow oil. $[\alpha]_D^{20} = -8.5$ ($c = 0.4$ $CHCl_3$). IR (film): 1757, 1703, 1254, 1194, 1084, 836, 776. ^{1}H-NMR ($CDCl_3$): 5.21 (*dd*, $J = 9.3, 4.05$, CH_2CHN); 5.02 (*dt*, $J = 8.8, 4.4$, NCOCH); 4.62 (*dd*, $J = 9.3, 9.3$, 1 H); 4.49 (*dd*, $J = 9.3, 4.05$, 1 H) (CH_2CHN); 4.15–4.07 (*m*, OCH); 3.98–3.70 (*m*, OCH); 3.60 (*s*, COOMe); 3.21 (*d*, $J = 2$, OH); 2.01–1.26 (*m*, 16 CH_2); 0.90–0.87 (*m*, 2 Me, *t*-Bu); 0.087 (*s*, Me_2Si). MS: 630 ($[M + H]^+$), 596, 162. Anal. calc. for $C_{33}H_{63}NO_6SSi$ (630.014): C 62.91, H 10.08, N 2.18; found: C 63.00, H 10.17, N 2.18.

N-{*(2S,3S,5R)-5-[(*tert*-Butyl)dimethylsilyloxy]-2-hexyl-3-hydroxyhexadecanoyl}glycine Benzyl Ester* (**22**). To a suspension of glycine benzyl ester hydrochloride (2.86 g, 14.2 mmol) in CH_2Cl_2 (70 ml) at 0° was added Et_3N (1.97 ml, 14.2 mmol). The mixture was stirred, until a clear soln. was obtained (15 min). Compound **21** (4.47 g, 7.09 mmol) dissolved in CH_2Cl_2 (20 ml) was added to the soln. and stirred for two days at r.t. The mixture was diluted with CH_2Cl_2, washed with 0.1M HCl, water, brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude residue was purified on a flash chromatography (silica gel, Et_2O/hexane 1:2) to give **22** (3.12 g) in 69.4% yield. $[\alpha]_D^{20} = -14.5$ ($c = 0.4$, $CHCl_3$). IR (film): 3312, 1752, 1651, 1537, 1255, 1189, 1081, 836, 776, 696. ^{1}H-NMR ($CDCl_3$): 7.35 (*s*, 5 arom. H); 6.70 (*t*, $J = 6$, NHCO); 5.17 (*s*, $COOCH_2$); 4.09, 4.07 (*AB*, $J_{AB} = 5.4$, NCH_2); 3.99 (br. *s*, OH); 3.98–3.82 (*m*, OCH); 2.38–2.28 (*m*, $CHOH$); 1.82–1.18 (*m*, 16 CH_2); 0.90–0.85 (*m*, 2 Me, *t*-Bu); 0.116 (*s*, 3 H), 0.10 (*s*, 3 H) (Me_2Si). MS: 638.5 ($[M + Na]^+$), 616.5 ($[M + H]^+$). Anal. calc. for $C_{37}H_{67}NO_5Si \cdot 1/3\ H_2O$ (639.364): C 69.44, H 10.58, N 2.18; found: C 69.28, H 10.71, N 2.15.

*Benzyl (2R,3S)-2-{(R)-2-[(*tert*-butyl)dimethylsilyloxy]tridecyl}-3-hexyl-4-oxoazetidine-1-acetate* (**17**). A soln. of **22** (3.5 g, 5.52 mmol) in dry pyridine (10.7 ml) at 0° was treated with MsCl (0.53 ml, 6.8 mmol). The mixture was stirred at 0° for 2 h followed by 1 h at r.t., then diluted with AcOEt and treated with 1N HCl (until acidic), sat. $NaHCO_3$ and finally brine. The extracts were dried ($MgSO_4$) and evaporated to give the crude methane sulfonate in quant. yield.

a) A soln. of the crude methane sulfonate in dry 1,2-dimethoxyethane (107 ml) was heated at reflux temp. and treated with Cs_2CO_3 (3.5 g) with vigorous stirring. After refluxing for 2 h, the mixture was cooled down, diluted with AcOEt, and filtered through *Celite* (washing with AcOEt). The solvent was evaporated to give a crude product which was purified by flash chromatography (AcOEt/hexane 1:6) to afford **17** in 65.8% yield (2.02 g). $[\alpha]_D^{20} = +7.02$ ($c = 0.1$, $CHCl_3$). Anal. data were identical to those of the material prepared from **11** (see above).

b) A soln. of the crude methane sulfonate (from 0.2 g **22**, 0.31 mmol) in dry DMF (5 ml) was heated at 120° and treated with anh. K_2CO_3 (0.1 g, 0.76 mmol) with vigorous stirring. After stirring for 2 h, the compound was isolated as described above.

Benzyl (2S,3S)-3-Hexyl-2-[(R)-2-hydroxytridecyl]-4-oxoazetidine-1-acetate (**23**). To a soln. of **17** (4 g, 6.5 mmol) in of 100 ml of MeCN at 0° was added 4.7 ml of 40% aq. HF. The mixture was stirred for 2 h and then diluted with AcOEt, washed with H_2O, sat. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude compound was purified on flash chromatography (silica gel, Et_2O/hexane 1:1) to give 3 g of pure **23** (91.9% yield). $[\alpha]_D^{20} = -10$ ($c = 0.5$, $CHCl_3$). IR (film): 3431, 1768, 1736, 1500, 1190, 999, 735. ^{1}H-NMR ($CDCl_3$): 7.35 (br. *s*, arom. H); 5.16 (*s*, NCH_2CO); 4.09, 4.02 (*AB*, $J_{AB} = 107.5$, $COOCH_2Ph$); 3.73–3.59 (*m*, CHN, CHOSi); 2.92–2.83 (*m*, CHCO); 1.92–1.21 (*m*, 16 CH_2); 0.98–0.83 (*m*, 2 Me). MS: 410, 366, 292, 192, 183, 91. Anal. calc. for $C_{31}H_{51}NO_4 \cdot 1/4\ H_2O$ (505.752); C 73.48, H 10.45, N 2.76; found: C 73.50, H 10.45, N 2.68.

(S)-1-{{(2S,3S)-1-[(Benzyloxycarbonyl)methyl]-3-hexyl-4-oxoazetidin-2-yl}methyl}dodecyl (S)-2-(Formylamino)-4-methylpentanoate (**24**). A soln. of **23** (1.4 g, 2.79 mmol), Ph_3P (1.1 g, 4.2 mmol), and L-*N*-formylleucin (0.66 g, 4.2 mmol) in THF (80 ml) was cooled with stirring to 0°. Diethyl azodicarboxylate (0.65 ml, 4.2 mmol) dissolved in 20 ml THF was added slowly (2 h), after complete addition the mixture was allowed to warm up slowly to r.t. and stirred overnight. The mixture was evaporated to dryness and the residue chromatographed on silica gel (hexane/Et_2O 1:1 than 1:2) to give **24** (1.1 g, 60%) and 0.24 g of the starting alcohol **23**. $[\alpha]_D^{20} = -4.5$ ($c = 0.2$, $CHCl_3$). IR (film): 3307, 1742, 1687, 1526, 1191, 735, 697. ^{1}H-NMR ($CDCl_3$): 8.22 (br. *s*, NCHO); 7.36 (br. *s*, 5 arom. H); 5.94–5.33 (*m*, NH); 5.16 (*s*, OCH_2); 4.95–4.81 (*m*, COOCH); 4.76–4.63 (*m*, NCHCOO); 4.24 (*d*, $J = 18$, 1 H), 3.81 (*d*, $J = 18$) (NCH_2); 3.57–3.45 (*m*, NCH); 2.86–2.74 (*m*, CHCO); 2.14–1.98 (*m*, 1 H); 1.82–1.18 (*m*, 35 H) (17 CH_2, $(CH_3)_2CH$); 1.04–0.82 (*m*, 4 Me). MS: 643 ($[M + H]^+$), 551, 507, 292, 114, 91. Anal. calc. for $C_{38}H_{62}N_2O_6$ (642.92): C 70.99, H 9.72, N 4.36; found: C 70.85, H 9.53, N 4.30.

(S)-1-{{(2S,3S)-1-[(Benzyloxycarbonyl)methyl]-3-hexyl-4-oxoazetidin-2-yl}methyl}dodecyl (S)-2-Amino-4-[(benzyloxycarbonyl)amino]-4-oxobutanoate (**25**). Compound **25** was prepared in 28% yield (0.64 g, 0.85 mmol) from **23** (1.5 g, 2.98 mmol) and L-*N*-Z-asparagin (1.19 g, 4.47 mmol) by the procedure used above for **24**. $[\alpha]_D^{20} = -3.3$ ($c = 0.3$, MeOH). IR (film): 3425, 3350, 3209, 1737, 1682, 1501, 1198, 735, 697. ^{1}H-NMR ($CDCl_3$):

7.35 (br. *s*, 10 arom. H); 6.6 (*d*, $J = 8$, 1 H, NH); 5.49 (br. *s*, 1 H), 5.28 (br. *s*, 1 H) (NH_2); 5.15 (*s*, 1 H), 5.11 (*s*, 1 H) (OCH_2Ph); 4.95–4.81 (*m*, OCH); 4.52 (*dt*, $J = 8, 4$, $NHCH$); 4.93, 3.96 (*AB*, $J_{AB} = 118$, NCH_2CO); 3.58–3.46 (*m*, NCH); 2.85, 2.78 (*ABX*, $J_{AB} = 48$, $J_{AX} = 4$, $J_{BX} = 4$, CH_2CO); 2.80–2.7 (*m*, CHCO); 2.08–1.11 (*m*, 16 CH_2); 0.98–0.79 (*m*, 2 Me). MS: 750 ($[M + H]^+$), 616, 358, 268. Anal. calc. for $C_{43}H_{63}N_3O_8$. 1/4 H_2O (754.4): C 68.46, H 8.41, N 5.56; found: C 68.45, H 8.69, N 5.56.

(S)-1-{{(2S,3S)-1-[(Benzyloxycarbonyl)methyl]-3-hexyl-4-oxoazetidin-2-yl}methyl}dodecyl (S)-2-(Formylamino)-3-phenylpropionate (**26**). Compound **26** was prepared in 63% yield (1.7 g, 2.5 mmol) from **17** (2 g, 3.98 mmol) and *N*-formyl-L-phenylalanine (1.15 g, 5.97 mmol) by the procedure used above for **24**. $[\alpha]_D^{20} = +11.28$ ($c = 0.7$, $CHCl_3$). IR (film): 3303, 1741, 1688, 1520, 1245, 741, 699. ^{1}H-NMR ($CDCl_3$): 8.16 (*s*, CHO); 7.40–7.11 (*m*, 10 arom. H); 5.96 (*d*, $J = 8$, NH); 5.14 (*s*, OCH_2Ph); 4.98–4.77 (*m*, CHNCHO, COOCH); 4.02, 3.95 (*AB*, $J_{AB} = 90$, NCH_2CO); 3.38 (*ddd*, $J = 2, 4, 8.4$, CHN); 3.14, 3.10 (*ABX*, $J_{AB} = 24$, $J_{AX} = 6$, $J_{BX} = 7.2$, CH_2Ph); 2.73 (*dt*, $J = 7, 2$, CHCO); 2.02–1.07 (*m*, 16 CH_2); 0.46–0.27 (*m*, 2 Me). MS: 677 ($[M + H]^+$), 649, 551, 358. Anal. calc. for $C_{41}H_{60}N_2O_6$ (676.939): C 72.73, H 8.93, N 4.14; found: C 72.33, H 8.80, N 4.22.

Benzyl (2S,3S)-2-{(2S)-2-[(Formylamino)acetoxy]tridecyl}-3-hexyl-4-oxoazetidine-1-acetate (**27**). Compound **27** was prepared in 44% yield (0.8 g, 0.53 g (34%) recovered starting material) from **17** (1.54 g, 3.06 mmol) and *N*-formylglycine (0.47 g, 4.6 mmol) by the procedure used above for **24**. $[\alpha]_D^{20} = +5.2$ ($c = 0.5$, $CHCl_3$). IR (film): 3323, 1746, 1688, 1521, 1195, 736, 698. ^{1}H-NMR ($CDCl_3$): 8.25 (*s*, CHO); 7.36 (*s*, arom. H); 6.11–5.98 (*m*, NH); 5.16 (*s*, $COOCH_2$); 5.01–4.87 (*m*, COOCH); 4.04, 3.97 (*AB*, $J_{AB} = 112$, NCH_2CO); 4.06, 4.02 (*ABX*, $J_{AB} = 27$, $J_{AX} = 5.2$, $J_{BX} = 4.8$, $NHCH_2CO$); 3.52–3.43 (*m*, NCH); 2.80 (*dt*, $J = 2, 8$, COCH); 2.12–1.12 (*m*, 16 CH_2); 0.97–0.79 (*m*, 2 Me). Anal. calc. for $C_{34}H_{54}N_2O_6 \cdot 1/4\ H_2O$ (591.314): C 69.06, H 9.29, N 4.73; found: C 68.90, H 9.33, N 4.78.

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