Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1503–1509

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of (5*S*,6*S*)- and (5*S*,6*R*)-aza-muricatacin from an L-glutamic acid derivative

José M. Andrés, Noemí de Elena, Rafael Pedrosa* and Alfonso Pérez-Encabo

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Doctor Mergelina s/n, 47011 Valladolid, Spain

Received 17 May 2001; accepted 30 May 2001

Abstract—A stereodivergent synthesis of *threo* and *erythro* aza-muricatacin, a non-natural aza-analogue of the bioactive annonaceous acetogenin muricatacin, is presented. The configuration of the C(5) stereocenter is controlled by diastereoselective alkylation of α-dibenzylamino aldehyde **1** or diastereoselective reduction of α-dibenzylamino ketone **3**. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Threo and *erythro* aza-muricatacin (Fig. 1) are 5-(α-hydroxy)-substituted pyrrolidin-2-ones with interesting cytotoxic activity;[1] they are related to muricatacin, a hydroxy lactone, isolated from *Annona muricata* which also has physiological activity.[2] (+)-Aza-muricatacin is also a component of the aza-solamine isolated from some species of Annonaceae with related cytotoxic activity.[3] As a consequence, the synthesis of different diastereoisomers of aza-muricatacin has attracted much attention. In this way, (+)-*syn*- and (−)-*anti*-aza-muricatacins have been prepared by diastereoselective reduction of a ketone obtained from a pyroglutamic acid derivative or diastereoselective condensation of tridecanal with a silyloxypyrrole derivative.[1a] *N*-Boc-*tert*-butyldimethylsilyloxypyrrole readily reacted with tridecanal enantioselectively to (+)-aza-muricatacin in the presence of (*R*)-Binol as catalyst[4] and the same pyrrole derivative has been used in a different diastereoselective approach to aza-muricatacin by condensation with a chiral α-hydroxy aldehyde.[5]

2. Results and discussion

Herein we report on the stereoselective preparation of enantiopure *syn*-(5*S*,6*S*)- and *anti*-(5*S*,6*R*)-aza-muricatacin starting from a common α-amino-δ-hydroxypentanal derivative obtained from L-glutamic acid.[6] The retrosynthetic approach (Scheme 1) used the stereoselective addition of different organometallic reagents to the chiral α-amino aldehyde structure previously described[7] to *vic*-amino alcohols **2** and further elaboration to the final 5-substituted pyrrolidin-2-one **10**.

The reaction of *N*,*N*-dibenzylamino aldehyde **1** with dodecylmagnesium bromide for 1.5 h at 0°C in diethyl

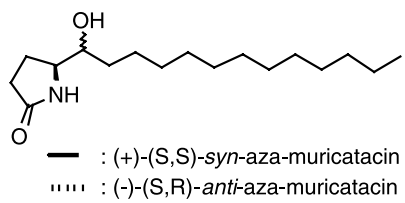
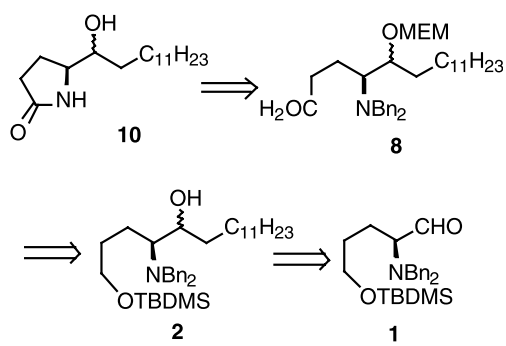


Figure 1.



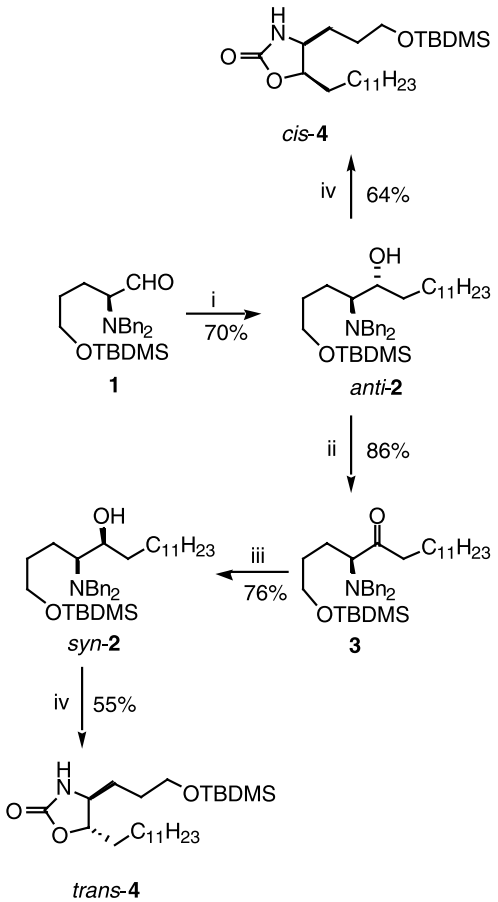
Scheme 1. Retrosynthetic analysis of (*S*,*S*)- and (*S*,*R*)-aza-muricatacin.

* Corresponding author.

PII: S0957-4166(01)00251-8

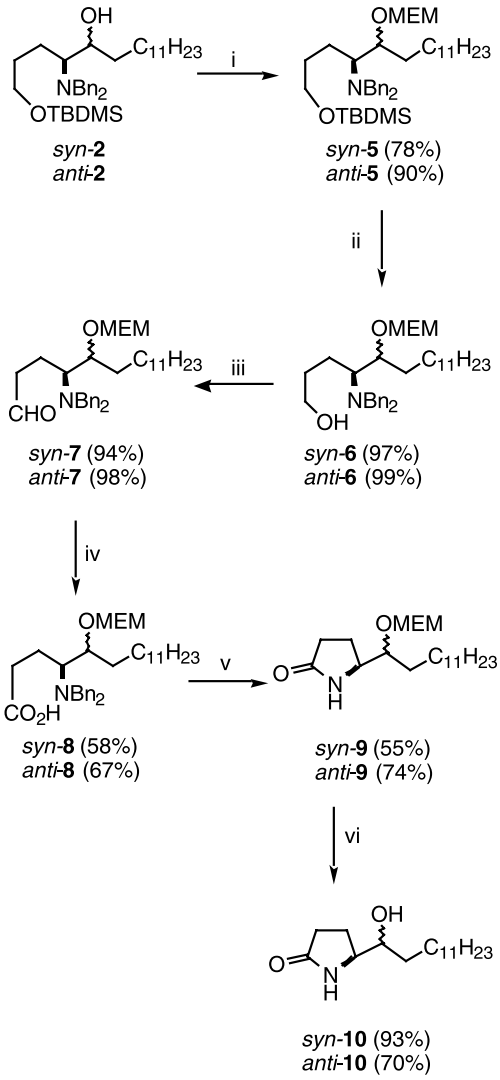
ether lead to the expected Felkin–Ahn *anti*-**2** addition compound[8] in 70% yield as a single diastereomer as demonstrated by the ^{1}H NMR analysis of the reaction mixture. Compound **1** was also treated with the zinc reagent derived from dodecyl bromide attempting to prepare *syn*-**2** but this compound was obtained in only low yield, probably due to the difficult formation of the zinc reagent, and very low stereoselection (a 6:4 mixture of *syn* and *anti* products was observed). Thus *syn*-**2** was prepared from *anti*-**2** in two steps. Swern oxidation of *anti*-**2** gave amino ketone **3** in 86% yield, which was transformed stereoselectively into *syn*-**2** (93:7 mixture, 86% d.e.) by reduction with sodium borohydride in methanol;[9] enantiopure *syn*-**2** was obtained in 76% yield from **3** after purification by flash chromatography on silica gel and hexane/ethyl acetate as eluent.

The stereochemistry of both *anti*-**2** and *syn*-**2** was assigned on the basis of previously published results,[7] and confirmed by transformation into the oxazolidinones *cis*-**4** and *trans*-**4**, respectively, by debenzylation and reaction with triphosgene (Scheme 2). The vicinal coupling constants between the protons at C(3) and C(4) in the rings were higher for *cis*-**4** ($J=7.2$ Hz) than for *trans*-**4** ($J=5.8$ Hz) and were consistent with previously reported data.[10]



Scheme 2. *Reagents and conditions*: (i) $BrMg(CH_2)_{11}CH_3$, Et_2O, 0°C; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; (iii) $NaBH_4$, MeOH/THF, −20°C; (iv) (1) H_2, $Pd(OH)_2$–C, MeOH, rt; (2) $(CCl_3O)_2CO$, iPr_2NEt, CH_2Cl_2.

The transformation of *anti*-**2** and *syn*-**2** into the corresponding enantiopure aza-muricatacins is summarized in Scheme 3. To this end, *anti*- and *syn*-**2** were transformed into the MEM derivatives *anti*- and *syn*-**5** in 90 and 78% yield, respectively, by reaction with MEM chloride in the presence of *N*-ethyldi-*iso*-propylamine in methylene chloride at rt for 4 h, then the primary hydroxy group was quantitatively deprotected to *anti*-**6** and *syn*-**6** by treatment with tetrabutylammonium fluoride in THF at 0°C for 10 h. Oxidation of the primary hydroxyl group to give the corresponding carboxylic acid was carried out in two steps. First, *anti*-**6** and *syn*-**6** were subjected to Swern oxidation leading to aldehydes *anti*-**7** and *syn*-**7** in 94 and 98% yield, respectively. Treatment of these aldehydes with sodium chlorite[11] gave *anti*-**8** and *syn*-**8** in 67 and 58% yield, respectively. These amino acids were quantitatively debenzylated by hydrogenolysis with palladium hydroxide on carbon and, without purification, the resulting



Scheme 3. *Reagents and conditions*: (i) MEMCl, iPr_2NEt, CH_2Cl_2, rt; (ii) TBAF, THF, 0°C; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; (iv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, tBuOH/CH_3CN, 0°C; (v) (1) H_2, $Pd(OH)_2$–C, MeOH, rt; (2) DCC, 4-PPY, CH_2Cl_2, 20°C; (vi) $TiCl_4$, CH_2Cl_2, 0°C.

γ-amino acids were directly ring closed[12] to *anti*-**9** and *syn*-**9**, in 74 and 55% yield, respectively, by treatment with DCC and 4-pyrrolidinepyridine in methylene chloride at rt.

Finally, *anti*-**9** and *syn*-**9** were transformed into enantiopure (5*S*,6*R*)-aza-muricatacin *anti*-**10** and (5*S*,6*S*)-aza-muricatacin *syn*-**10**, respectively, by removal of the MEM protective group. To this end, compounds *anti*-**9** and *syn*-**9** were treated with aqueous hydrochloric acid or zinc bromide as previously described[13] but the reaction was very slow and only degradation products were obtained. Attempts to cleave the ether by reaction with *B*-bromo catecholborane[14] were more successful, but the hydroxy derivatives were isolated in only 40% yield. Cleavage of the MEM group was easily achieved by treatment of solutions of *anti*-**9** and *syn*-**9** with 1 M $TiCl_4$ in methylene chloride at 0°C for 4 h;[13] under these conditions *anti*-**10** and *syn*-**10** were obtained in 70 and 93% yield, respectively.

The isolated (5*S*,6*R*)-aza-muricatacin *anti*-**10** and (5*S*,6*S*)-aza-muricatacin *syn*-**10** had concordant physical and spectroscopic data with those previously reported,[1a,5] thus confirming the assigned stereochemistry for all compounds and that stereochemical integrity was maintained during the transformations of *anti*-**2** to *anti*-**10** and *syn*-**2** to *syn*-**10**.

3. Conclusion

In summary, the synthesis of two enantiopure diastereoisomers of aza-muricatacin has been easily carried out from a common *N*,*N*-dibenzylamino aldehyde derived from L-glutamic acid.

4. Experimental

4.1. General procedures

The reactions were carried out in oven-dried glassware, under an argon atmosphere, and using anhydrous solvents. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC 300 or Bruker AMX 300, using TMS as the internal standard. IR spectra were recorded on a Philips PU 9706 spectrometer, as a film or a KBr dispersion. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 1 dm cell.

4.2. (4*S*,5*R*)-4-(*N*,*N*-Dibenzylamino)-1-(*tert*-butyldimethylsilyloxy)-5-heptadecanol *anti*-2

To a solution of $CH_3(CH_2)_{11}MgBr$ (60 mmol, 1.5 equiv.) in ether (60 mL) at 0°C was added dropwise a solution of amino aldehyde **1** (16.46 g, 40 mmol) in ether (150 mL). After stirring the mixture at this temperature for 1.5 h, saturated NH_4Cl (150 mL) was added and the mixture was extracted with ether (3× 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under vacuum. After flash chromatography (silica gel: hexane/EtOAc: 50/1), *anti*-**2** was obtained as a colorless oil (16.3 g, 28 mmol, 70%); $[\alpha]_D^{23}=+8.6$ (*c* 1.2, $CHCl_3$); IR (film): 3400, 1600, 1490, 1450, 1090, 740, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 3H, C$\underline{H}_3$Si), 0.05 (s, 3H, C$\underline{H}_3$Si), 0.89 (t, 3H, $J=6.4$ Hz, C$\underline{H}_3$CH$_2$), 0.90 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.25 (m, 20H, (C$\underline{H}_2$)$_{10}$CH$_3$), 1.46 (m, 4H, TBDMSOCH$_2$C$\underline{H}_2$, C$\underline{H}$HCHOH, C$\underline{H}$HCHN), 1.73 (m, 2H, CH$\underline{H}$CHOH, CH$\underline{H}$CHN), 2.20 (br s, 1H, O$\underline{H}$), 2.64 (m, 1H, C$\underline{H}$N), 3.58 (m, 2H, TBDMSOC$\underline{H}_2$), 3.67 (m, 4H, C$\underline{H}_2$Ph), 3.71 (m, 1H, C$\underline{H}$OH), 7.20–7.40 (m, 10H, $\underline{H}$arom.); ^{13}C NMR ($CDCl_3$): δ −5.3 (C$\underline{H}_3$Si), 14.1 (C$\underline{H}_3$CH$_2$), 18.3 (C$\underline{(}$CH$_3$)$_3$), 21.3 (C$\underline{H}_2$CH$_3$), 22.7 (C$\underline{H}_2$), 26.0 (C(C$\underline{H}_3$)$_3$), 26.6 (C$\underline{H}_2$), 29.4 (C$\underline{H}_2$), 29.6 (several C$\underline{H}_2$), 30.6 (C$\underline{H}_2$), 31.9 (C$\underline{H}_2$), 34.6 (C$\underline{H}_2$), 55.0 (C$\underline{H}_2$Ph), 60.7 (C$\underline{H}$N), 63.0 (TBDMSOC$\underline{H}_2$), 70.8 (C$\underline{H}$OH), 127.0, 128.3, 128.9 (C$\underline{H}$arom.), 140.0 (C$\underline{a}$rom.). Anal. calcd for $C_{37}H_{63}NO_2Si$: C, 76.36; H, 10.91; N, 2.41. Found: C, 76.06; H, 10.96; N, 2.44%.

4.3. (4*S*)-4-(*N*,*N*-Dibenzylamino)-1-(*tert*-butyldimethylsilyloxy)-5-heptadecanone 3

To a stirred solution of oxalyl chloride (1.95 mL, 22.35 mmol) in CH_2Cl_2 (50 mL) cooled to −78°C under argon was added dropwise DMSO (3.3 mL, 46.5 mmol). After stirring the mixture for 15 min, a solution of the amino alcohol *anti*-**2** (9.6 g 16.5 mmol) in CH_2Cl_2 (50 mL) was added, and the mixture was stirred for 30 min at −78°C before addition of triethylamine (6.6 mL, 47.4 mmol). Then, the reaction was allowed to warm to rt under stirring for 45 min and the mixture was quenched with water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (45 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and then concentrated to yield an oil which was purified by flash chromatography (silica gel, hexane/EtOAc: 60/1) (8.23 g, 14.2 mmol, 86%); $[\alpha]_D^{23}=-42.2$ (*c* 1.1, $CHCl_3$); IR (film): 1700, 1595, 1485, 1445, 1090, 740, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H, C$\underline{H}_3$Si), 0.88 (t, 3H, $J=7.1$ Hz, C$\underline{H}_3$CH$_2$), 0.90 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.38 (m, 18H, (C$\underline{H}_2$)$_9$CH$_3$), 1.42 (m, 4H, C$\underline{H}_2$CH$_2$CO and C$\underline{H}_2$CH$_2$CHN), 1.74 (m, 2H, C$\underline{H}_2$CHN), 2.34 (dt, 1H, $J_1=16.6$ Hz, $J_2=7.3$ Hz, C$\underline{H}$HCO), 2.53 (dt, 1H, $J_1=16.6$ Hz, $J_2=7.2$ Hz, CH$\underline{H}$CO), 3.23 (dd, 1H, $J_1=8.2$ Hz, $J_2=5.4$ Hz, C$\underline{H}$N), 3.55 (m, 2H, TBDMSOC$\underline{H}_2$), 3.57 (d, 2H, $J=13.7$ Hz, C$\underline{H}$HPh), 3.70 (d, 2H, $J=13.7$ Hz, CH$\underline{H}$Ph), 7.20–7.40 (m, 10H, $\underline{H}$arom.); ^{13}C NMR ($CDCl_3$): δ −5.3 (C$\underline{H}_3$Si), 14.1 (C$\underline{H}_3$CH$_2$), 18.3 (C$\underline{(}$CH$_3$)$_3$), 19.7 (C$\underline{H}_2$CH$_3$), 22.7 (C$\underline{H}_2$), 23.8 (C$\underline{H}_2$), 26.0 (C(C$\underline{H}_3$)$_3$), 29.4 (C$\underline{H}_2$), 29.5 (C$\underline{H}_2$), 29.6 (several C$\underline{H}_2$), 30.3 (C$\underline{H}_2$), 31.9 (C$\underline{H}_2$), 41.1 (C$\underline{H}_2$CO), 54.5 (C$\underline{H}_2$Ph), 62.7 (TBDMSOC$\underline{H}_2$), 65.6 (C$\underline{H}$N), 127.1, 128.3, 128.8 (C$\underline{H}$arom.), 139.6 (C$\underline{a}$rom.), 212.1 (C$\underline{O}$). Anal. calcd for $C_{37}H_{61}NO_2Si$: C, 76.62; H, 10.60; N, 2.41. Found: C, 76.47; H, 10.48; N, 2.37%.

4.4. (4*S*,5*S*)-4-(*N*,*N*-Dibenzylamino)-1-(*tert*-butyldimethylsilyloxy)-5-heptadecanol *syn*-2

To a stirred solution of ketone **3** (10.62 g, 18.3 mmol) in MeOH/THF (9:2, 110 mL), cooled to −20°C, was added sodium borohydride (3.12 g, 82.4 mmol, 4.5 equiv.). After stirring the mixture for 2 h, the mixture was quenched with H_2O and extracted several times with ether. The ethereal layer was washed with NaCl solution and dried over $MgSO_4$, the solvents were removed, and the residue was purified by flash chromatography (silica gel, hexane/EtOAc: 50/1) to afford a colorless oil (8.1 g, 13.9 mmol, 76%); $[\alpha]_D^{23}=+15.2$ (*c* 1.0, $CHCl_3$); IR (film): 3410, 1600, 1495, 1455, 1100, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.09 (2s, 6H, (CH_3)$_2$Si), 0.87 (t, 3H, $J=6.6$ Hz, CH_3CH_2), 0.94 (s, 9H, C(CH_3)$_3$), 1.23 (m, 22H, (CH_2)$_{10}CH_3$, CH_2CH_2CHN), 1.47 (m, 1H, CHHCHN), 1.65 (m, 2H, CHHCHN, CHHCHOH), 1.78 (m, 1H, CHHCHOH), 2.40 (m, 1H, CHN), 3.43 (d, 2H, $J=$ 13.2 Hz, CHHPh), 3.46 (m, 1H, CHOH), 3.63 (t, 2H, $J=6.1$ Hz, TBDMSOCH_2), 3.86 (d, 2H, $J=13.2$ Hz, CHHPh), 4.47 (br s, 1H, OH), 7.20–7.35 (m, 10H, Harom.); ^{13}C NMR ($CDCl_3$): δ −0.03 (CH_3Si), 14.1 (CH_3CH_2), 18.3 (C(CH_3)$_3$), 22.2 (CH_2), 22.7 (CH_2), 26.0 (C(CH_3)$_3$), 26.1 (CH_2), 29.3 (CH_2), 29.6 (several CH_2), 29.8 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 34.2 (CH_2), 54.0 (CH_2Ph), 63.0 (CHN, TBDMSOCH_2), 70.6 (CHOH), 127.2, 128.4, 129.1 (CHarom.), 139.0 (Carom.). Anal. calcd for $C_{37}H_{63}NO_2Si$: C, 76.36; H, 10.91; N, 2.41. Found: C, 76.53; H, 10.80; N, 2.52%.

4.5. (4*S*,5*R*)-4-[3-(*tert*-Butyldimethylsilyloxy)propyl]-5-dodecyloxazolidin-2-one *cis*-4

To a solution of *anti*-**2** (140 mg, 0.24 mmol) in methanol (4 mL) was added $Pd(OH)_2$–C (28 mg) in one portion. The mixture was stirred under hydrogen for 3.5 h and the catalyst was removed by filtration through Celite and washed with methanol. The filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and then di-*iso*-propylethylamine (94 μL, 0.54 mmol) and triphosgene (36 mg, 0.12 mmol) were added. The reaction solution was allowed to warm to rt with stirring for 12 h, H_2O (2 mL) and EtOAc (30 mL) were added to the mixture, and the organic phase was separated, dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (silica gel, hexane/EtOAc: 8/1) to afford a colorless oil (64 mg, 0.15 mmol, 64%); $[\alpha]_D^{23}=-5.1$ (*c* 1.0, $CHCl_3$); IR (film): 3250, 1740, 1240 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.06 (s, 6H, SiCH$_3$), 0.88 (t, 3H, $J=7.1$ Hz, CH_3CH_2), 0.89 (s, 9H, C(CH_3)$_3$), 1.26 (m, 19H), 1.63 (m, 7H), 3.65 (m, 2H, TBDMSOCH_2), 3.76 (m, 1H, CHN), 4.57 (m, 1H, CHO), 6.36 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ −5.4 (CH_3Si), 14.1 (CH_3CH_2), 18.2 (C(CH_3)$_3$), 22.7 (CH_2), 25.9 (C(CH_3)$_3$), 27.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (several CH_2), 31.9 (CH_2), 55.6 (CHN), 62.6 (TBDMSOCH_2), 80.3 (CHO), 159.6 (C=O). Anal. calcd for $C_{24}H_{49}NO_3Si$: C, 67.39; H, 11.55; N, 3.27. Found: C, 67.47; H, 11.66; N, 3.15%.

4.6. (4*S*,5*S*)-4-[3-(*tert*-Butyldimethylsilyloxy)propyl]-5-dodecyloxazolidin-2-one *trans*-4

Oxazolidinone *trans*-**4** was obtained from the amino alcohol *syn*-**2** (140 mg, 0.24 mmol) by the method described for *cis*-**4**, and purified by flash chromatography (silica gel, hexane/EtOAc: 8/1) to afford a colorless oil (56 mg, 0.13 mmol, 55%); $[\alpha]_D^{23}=-41.8$ (*c* 1.0, $CHCl_3$); IR (film): 3260, 1740, 1245 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.05 (s, 6H, (CH_3)$_2$Si), 0.88 (t, 3H, $J=7.1$ Hz, CH_3CH_2), 0.89 (s, 9H, C(CH_3)$_3$), 1.26 (m, 18H, CH_2), 1.56 (m, 8H, CH_2), 3.46 (m, 1H, CHN), 3.65 (t, 2H, $J=5.2$ Hz, TBDMSOCH_2), 4.14 (m, 1H, CHO), 6.34 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ −5.4 (CH_3Si), 14.1 (CH_3CH_2), 18.3 (C(CH_3)$_3$), 22.7 (CH_2CH_3), 24.8 (CH_2), 25.9 (C(CH_3)$_3$), 28.7 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (several CH_2), 31.9 (CH_2), 32.4 (CH_2), 34.8 (CH_2), 57.9 (CHN), 62.5 (TBDMSOCH_2), 82.7 (CHO), 159.3 (C=O). Anal. calcd for $C_{24}H_{49}NO_3Si$: C, 67.39; H, 11.55; N, 3.27. Found: C, 67.56; H, 11.67; N, 3.22%.

4.7. (4*S*,5*R*)-4-(*N*,*N*-Dibenzylamino)-1-(*tert*-butyldimethylsilyloxy)-5-[(2-methoxyethoxy)methoxy]-heptadecane *anti*-5

To a solution of *anti*-**2** (6.75 g, 11.6 mmol) and di-*iso*-propylethylamine (12.5 mL, 71.9 mmol) in CH_2Cl_2 (100 mL) at 0°C was added dropwise MEM chloride (7.95 mL, 69.6 mmol). After stirring the mixture for 4 h at rt, the reaction was quenched with saturated aqueous NH_4Cl (150 mL). The aqueous phase was extracted with CH_2Cl_2 (2×75 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed (silica gel, hexane/EtOAc: 25/1) to give *anti*-**5** as a colorless oil (6.99 g 10.4 mmol, 90%); $[\alpha]_D^{23}=-17.4$ (*c* 1.8, $CHCl_3$); IR (film): 1600, 1490, 1460, 1250, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.03 (s, 3H, SiCH$_3$), 0.04 (s, 3H, SiCH$_3$), 0.88 (t, 3H, $J=6.8$ Hz, CH_3CH_2), 0.89 (s, 9H, C(CH_3)$_3$), 1.22 (m, 18H, (CH_2)$_9$), 1.52 (m, 4H, CHHCHN, CHHCHOMEM, CH_2CH_2CHN), 1.76 (m, 2H, CHHCHN, CHHCHOMEM), 2.56 (m, 1H, CHN), 3.38 (s, 3H, OCH_3), 3.54 (m, 6H, OCH_2CH_2O and CHHPh), 3.70 (m, 2H, TBDMSOCH_2), 3.77 (d, 2H, $J=13.7$ Hz, CHHPh), 3.82 (m, 1H, CHOMEM), 4.73 (d, 1H, $J=7.0$ Hz, OCHHO), 4.78 (d, 1H, $J=7.0$ Hz, OCHHO), 7.15–7.40 (m, 10H, Harom.); ^{13}C NMR ($CDCl_3$): δ −5.3 (CH_3Si), 14.1 (CH_3CH_2), 18.3 (C(CH_3)$_3$), 21.9 (CH_2CH_3), 22.7 (CH_2), 25.1 (CH_2; 26.0 (C(CH_3)$_3$), 29.4 (CH_2), 29.6 (CH_2), 29.7 (several CH_2), 29.9 (CH_2), 31.3 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 54.3 (CH_2Ph), 58.6 (CHN), 59.0 (OCH_3), 63.2 (TBDMSOCH_2), 67.4 (OCH_2CH_2O), 71.8 (OCH_2CH_2O), 78.1 (CHOMEM), 95.1 (OCH_2O), 126.7, 128.0, 128.9 (CHarom.), 140.4 (Carom.). Anal. calcd for $C_{41}H_{71}NO_4Si$: C, 73.49; H, 10.68; N, 2.09. Found: C, 73.27; H, 10.81; N, 2.07%.

4.8. (4S,5S)-4-(*N*,*N*-Dibenzylamino)-1-(*tert*-butyldimethylsilyloxy)-5-[(2-methoxyethoxy)methoxy]-heptadecane *syn*-5

syn-**5** was obtained from the amino alcohol *syn*-**2** (3.80 g, 6.5 mmol) by the method described for *anti*-**5**, and purified by flash chromatography (silica gel, hexane/EtOAc: 30/1) to afford a colorless oil (3.40 g, 5.1 mmol, 78%); $[\alpha]_D^{23}=+16.8$ (*c* 1.1, $CHCl_3$); IR (film): 1600, 1490, 1450, 1250, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.07 (s, 6H, ($C\underline{H}_3)_2Si$), 0.89 (t, 3H, $J=7.5$ Hz, $C\underline{H}_3CH_2$), 0.93 (s, 9H, $C(C\underline{H}_3)_3$), 1.11 (m, 4H, $C\underline{H}_2$), 1.27 (m, 16H, $C\underline{H}_2$), 1.54 (m, 4H, $C\underline{H}HCHN$, $C\underline{H}HCHOMEM$, $C\underline{H}_2CH_2CHN$), 1.77 (m, 2H, $CH\underline{H}CHN$, $CH\underline{H}CHOMEM$), 2.51 (m, 1H, $C\underline{H}N$), 3.37 (s, 3H, $OC\underline{H}_3$), 3.43 (d, 2H, $J=13.4$ Hz, $C\underline{H}HPh$), 3.51 (m, 2H, $TBDMSOC\underline{H}_2$), 3.56 (m, 1H, $C\underline{H}OMEM$), 3.60 (m, 2H, $OC\underline{H}_2CH_2OCH_3$, $C\underline{H}OMEM$), 3.68 (m, 2H, $OCH_2C\underline{H}_2O$), 3.96 (d, 2H, $J=13.4$ Hz, $CH\underline{H}Ph$), 4.63 (d, 1H, $J=7.0$ Hz, $OC\underline{H}HO$), 4.70 (d, 1H, $J=7.0$ Hz, $OCH\underline{H}O$), 7.15–7.40 (m, 10H, $\underline{H}$arom.); ^{13}C NMR ($CDCl_3$): δ −5.2 ($\underline{C}H_3Si$), 14.1 ($\underline{C}H_3CH_2$), 18.4 ($\underline{C}(CH_3)_3$), 20.1 ($\underline{C}H_2CH_3$), 22.7 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 26.0 ($C(\underline{C}H_3)_3$), 29.4 ($\underline{C}H_2$), 29.7 (several $\underline{C}H_2$), 29.9 ($\underline{C}H_2$), 30.7 ($\underline{C}H_2$), 31.4 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 55.4 ($\underline{C}H_2Ph$), 58.0 ($\underline{C}HN$), 59.0 ($\underline{C}H_3O$), 63.2 ($TBDMSO\underline{C}H_2$), 67.2 ($O\underline{C}H_2CH_2O$), 71.8 ($OCH_2\underline{C}H_2O$), 80.0 ($\underline{C}HOMEM$), 95.1 ($O\underline{C}H_2O$), 126.6, 128.0, 129.2 ($\underline{C}$Harom.), 140.9 ($\underline{C}$arom.). Anal. calcd for $C_{41}H_{71}NO_4Si$: C, 73.49; H, 10.68; N, 2.09. Found: C, 73. 34; H, 10.64; N, 2.04%.

4.9. (4*S*,5*R*)-4-(*N*,*N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]-1-heptadecanol *anti*-6

To a solution of *anti*-**5** (6.53 g, 9.7 mmol) in THF (90 mL) at 0°C was slowly added a solution of tetrabutylammonium fluoride (4.61 g, 14.6 mmol) in THF (45 mL). The mixture was stirred for 10 h at 0°C, and the reaction was quenched by addition of water (90 mL). The aqueous phase was extracted with ether (2×75 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and chromatographed (silica gel, AcOEt/hexane: 1/4) to yield *anti*-**6** as a colorless oil (5.36 g, 9.6 mmol, 99%); $[\alpha]_D^{23}=-33.7$ (*c* 1.1, $CHCl_3$); IR (film): 3420, 1600, 1490, 1450, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (t, 3H, $J=6.7$ Hz, $C\underline{H}_3CH_2$), 1.24 (m, 18H, ($C\underline{H}_2)_9$), 1.55 (m, 5H), 1.80 (m, 3H), 2.60 (m, 1H, $C\underline{H}N$), 3.39 (s, 3H, $OC\underline{H}_3$), 3.54 (m, 6H, $OC\underline{H}_2CH_2O$, $C\underline{H}HPh$ and $C\underline{H}_2OH$), 3.72 (m, 2H, $OCH_2C\underline{H}_2O$), 3.80 (d, 2H, $J=13.8$ Hz, $CH\underline{H}Ph$), 3.86 (m, 1H, $C\underline{H}OMEM$), 4.74 (d, 1H, $J=7.0$ Hz, $OC\underline{H}HO$), 4.80 (d, 1H, $J=7.0$ Hz, $OCH\underline{H}O$), 7.20–7.40 (m, 10H, $\underline{H}$arom.); ^{13}C NMR ($CDCl_3$): δ 14.1 ($\underline{C}H_3CH_2$), 22.2 ($\underline{C}H_2CH_3$), 22.7 ($\underline{C}H_2$), 25.1 ($\underline{C}H_2$), 29.4 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.7 (several $\underline{C}H_2$), 29.9 ($\underline{C}H_2$), 31.3 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 32.5 ($\underline{C}H_2$), 54.3 ($\underline{C}H_2Ph$), 58.8 ($\underline{C}HN$), 59.0 ($O\underline{C}H_3$), 63.0 ($\underline{C}H_2OH$), 67.6 ($O\underline{C}H_2CH_2O$), 71.8 ($OCH_2\underline{C}H_2O$), 77.9 ($\underline{C}HOMEM$), 95.1 ($O\underline{C}H_2O$), 126.8, 128.1, 129.0 ($\underline{C}$Harom.), 140.2 ($\underline{C}$arom.). Anal. calcd for $C_{35}H_{57}NO_4$: C, 75.63; H, 10.34; N, 2.52. Found: C, 75.76; H, 10.30; N, 2.45%.

4.10. (4*S*,5*S*)-4-(*N*,*N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]-1-heptadecanol *syn*-6

The amino alcohol *syn*-**6** was obtained from *syn*-**5** (3.3 g, 4.9 mmol) by the method described for *anti*-**6** and purified by flash chromatography (silica gel, hexane/EtOAc: 2/1) to afford a colorless oil (2.64 g, 4.7 mmol, 97%); $[\alpha]_D^{23}=+40.7$ (*c* 1.2, $CHCl_3$); IR (film): 3420, 1600, 1490, 1450, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.60 (m, 1H, $C\underline{H}HH$), 0.85 (m, 1H, $CH\underline{H}$), 0.89 (t, 3H, $J=7.1$ Hz, $C\underline{H}_3CH_2$), 1.11 (m, 4H, $C\underline{H}_2$), 1.27 (m, 14H, $C\underline{H}_2$), 1.50 (m, 2H, $C\underline{H}_2CH_2CHN$), 1.75 (m, 4H, $C\underline{H}H$-CHOMEM, $C\underline{H}HCHN$), 2.25 (br s, 1H, $O\underline{H}$), 2.52 (m, 1H, $C\underline{H}N$), 3.39 (s, 3H, $OC\underline{H}_3$), 3.43 (d, 2H, $J=13.4$ Hz, $C\underline{H}HPh$), 3.56 (m, 5H, $OC\underline{H}_2C\underline{H}_2O$, and $C\underline{H}OMEM$), 3.70 (m, 1H, $C\underline{H}HOH$), 3.85 (m, 1H, $CH\underline{H}OH$), 3.99 (d, 2H, $J=13.4$ Hz, $CH\underline{H}Ph$), 4.62 (d, 1H, $J=7.1$ Hz, $OC\underline{H}HO$), 4.71 (d, 1H, $J=7.1$ Hz, $OCH\underline{H}O$), 7.15–7.40 (m, 10H, $\underline{H}$arom.); ^{13}C NMR ($CDCl_3$): δ 14.1 ($\underline{C}H_3CH_2$), 20.2 ($\underline{C}H_2CH_3$), 22.7 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 29.4 ($\underline{C}H_2$), 29.7 (several $\underline{C}H_2$), 29.9 ($\underline{C}H_2$), 30.7 ($\underline{C}H_2$), 31.2 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 55.4 ($\underline{C}H_2Ph$), 58.1 ($\underline{C}HN$), 59.1 ($O\underline{C}H_3$), 63.1 ($\underline{C}H_2OH$), 67.6 ($O\underline{C}H_2CH_2O$), 72.0 ($OCH_2\underline{C}H_2O$), 79.9 ($\underline{C}HOMEM$), 95.1 ($O\underline{C}H_2O$), 126.7, 128.0, 129.2 ($\underline{C}$Harom.), 140.9 ($\underline{C}$arom.). Anal. calcd for $C_{35}H_{57}NO_4$: C, 75.63; H, 10.34; N, 2.52. Found: C, 75.49; H, 10.47; N, 2.66%.

4.11. (4*S*,5*R*)-4-(*N*,*N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]heptadecanal *anti*-7

The amino aldehyde *anti*-**7** was obtained from the amino alcohol *anti*-**6** (3.06 g, 5.5 mmol) by Swern oxidation, as described for compound **3**, as a colorless oil (2.98 g, 5.4 mmol, 98%); $[\alpha]_D^{23}=-37.4$ (*c* 1.6, $CHCl_3$); IR (film): 1720, 1600, 1495, 1455, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J=7.0$ Hz, $C\underline{H}_3CH_2$), 0.94 (m, 2H, $C\underline{H}_2$), 1.16 (m, 18H, $C\underline{H}_2$), 1.40 (m, 1H, $C\underline{H}HCHOMEM$), 1.63 (m, 2H, $C\underline{H}HCHN$, $CH\underline{H}CHOMEM$), 1.93 (m, 1H, $CH\underline{H}CHN$), 2.45 (m, 2H, $C\underline{H}N$ and $C\underline{H}HCHO$), 2.58 (m, 1H, $CH\underline{H}CHO$), 3.30 (s, 3H, $OC\underline{H}_3$), 3.41 (d, 2H, $J=13.8$ Hz, $C\underline{H}HPh$), 3.47 (m, 2H, $OC\underline{H}_2CH_2O$), 3.64 (m, 2H, $OCH_2C\underline{H}_2O$), 3.74 (d, 2H, $J=13.8$ Hz, $CH\underline{H}Ph$), 3.81 (m, 1H, $C\underline{H}OMEM$), 4.68 (d, 1H, $J=7.0$ Hz, $OC\underline{H}HO$), 4.74 (d, 1H, $J=7.0$ Hz, $OCH\underline{H}O$), 7.10–7.30 (m, 10H, $\underline{H}$arom.), 9.60 (s, 1H, $C\underline{H}O$); ^{13}C NMR ($CDCl_3$): δ 14.1 ($\underline{C}H_3CH_2$), 18.2 ($\underline{C}H_2CH_3$), 22.7 ($\underline{C}H_2CHN$), 25.1 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 29.7 (several $\underline{C}H_2$), 29.9 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 32.5 ($\underline{C}H_2$), 42.3 ($\underline{C}H_2CHO$), 54.1 ($\underline{C}H_2Ph$), 58.4 ($\underline{C}HN$), 59.0 ($O\underline{C}H_3$), 67.6 ($O\underline{C}H_2CH_2O$), 71.7 ($OCH_2\underline{C}H_2$), 76.6 ($\underline{C}HOMEM$), 95.0 ($O\underline{C}H_2O$), 126.9, 128.2, 128.9 ($\underline{C}$Harom.), 140.0 ($\underline{C}$arom.), 202.9 ($\underline{C}HO$). Anal. calcd for $C_{35}H_{55}NO_4$: C, 75.91; H, 10.01; N, 2.53. Found: C, 75.75; H, 10.19; N, 2.61%.

4.12. (4*S*,5*S*)-4-(*N*,*N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]heptadecanal *syn*-7

The amino aldehyde *syn*-**7** was obtained from the amino alcohol *syn*-**6** (5.38 g, 9.7 mmol) by Swern oxidation, as described for compound **3**, as a colorless

oil (5.04 g, 9.1 mmol, 94%); $[\alpha]_D^{23}=+14.6$ (*c* 0.8, $CHCl_3$); IR (film): 1715, 1600, 1490, 1450, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.82 (t, 3H, $J=6.7$ Hz, CH_3CH_2), 1.14 (m, 20H, CH_2), 1.47 (m, 1H, CHHCHOMEM), 1.68 (m, 1H, CHHCHN), 1.88 (m, 2H, CHHCHOMEM, CHHCHN), 2.38 (m, 1H, CHN), 2.47 (m, 2H, CH_2CHO), 3.30 (s, 3H, OCH_3), 3.46 (m, 5H, OCH_2CH_2O, CHOMEM and CHHPh), 3.57 (m, 1H, OCH_2CHHO), 3.67 (m, 1H, OCH_2CHHO), 3.85 (d, 2H, $J=13.4$ Hz, CHHPh), 4.57 (d, 1H, $J=7.1$ Hz, OCHHO), 4.64 (d, 1H, $J=7.1$ Hz, OCHHO), 7.10–7.30 (m, 10H, Harom.), 9.67 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3CH_2), 16.9 (CH_2CH_3), 22.6 (CH_2CHN), 25.4 (CH_2), 29.3 (CH_2), 29.6 (several CH_2), 29.8 (CH_2), 31.3 (CH_2), 31.8 (CH_2), 41.6 (CH_2CHO), 55.0 (CH_2Ph), 57.6 (CHN), 58.9 (OCH_3), 67.5 (OCH_2CH_2O), 71.6 (OCH_2CH_2O), 79.3 (CHOMEM), 94.9 (OCH_2O), 126.7, 128.0, 129.0 (CHarom.), 140.4 (Carom.), 202.2 (CHO). Anal. calcd for $C_{35}H_{55}NO_4$: C, 75.91; H, 10.01; N, 2.53. Found: C, 75.80; H, 10.13; N, 2.59%.

4.13. (4*S*,5*R*)-4-(*N*,*N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]heptadecanoic acid *anti*-8

To a solution of amino aldehyde *anti*-**7** (5.0 g, 9 mmol) and 2-methyl-2-butene (11.4 mL, 108 mmol, 12 equiv.) in *t*-BuOH/CH_3CN (5/3, 120 mL) was added dropwise a solution containing 80% $NaClO_2$ (6.1 g, 54 mmol, 6 equiv.) and $NaH_2PO_4{\cdot}2H_2O$ (8.4 g, 54 mmol, 6 equiv.) in H_2O (100 mL) at 0°C. The resulting solution was stirred at 0°C for 30 min and quenched by addition of a 5% aqueous $Na_2S_2O_5$ solution (100 mL). The solution was adjusted to pH 6 and the mixture was extracted with EtOAc (3×50 mL), the combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was evaporated. The product was purified by flash chromatography (silica gel, hexane/EtOAc: 4/1) yielding *anti*-**8** as a colorless oil (3.44 g, 6 mmol, 67%); $[\alpha]_D^{23}=-17.3$ (*c* 1.0, $CHCl_3$); IR (film): 3600–2400, 1740–1700, 1600, 1495, 1445, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (t, 3H, $J=6.7$ Hz, CH_3CH_2), 1.02 (m, 2H, CH_2), 1.24 (m, 18H, CH_2), 1.46 (m, 1H, CHHCHOMEM), 1.65 (m, 1H, CHHCHOMEM), 1.82 (m, 1H, CHHCHN), 2.08 (m, 1H, CHHCHN), 2.49 (t, 2H, $J=7.2$ Hz, CH_2CO_2H), 2.67 (m, 1H, CHN), 3.38 (s, 3H, OCH_3), 3.57 (m, 4H, OCH_2CH_2O and CHHPh), 3.72 (m, 2H, OCH_2CH_2O), 3.93 (d, 2H, $J=13.8$ Hz, CHHPh), 3.98 (m, 1H, CHOMEM), 4.77 (d, 1H, $J=7.0$ Hz, OCHHO), 4.84 (d, 1H, $J=7.0$ Hz, OCHHO), 7.20–7.40 (m, 10H, Harom.); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3CH_2), 20.5 (CH_2CH_3), 22.7 (CH_2CHN), 25.2 (CH_2CO_2H), 29.3 (CH_2), 29.5 (CH_2), 29.6 (several CH_2), 29.8 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 32.9 (CH_2), 54.2 (CH_2Ph), 59.0 (OCH_3), 59.4 (CHN), 67.7 (OCH_2CH_2O), 71.7 (OCH_2CH_2O), 76.3 (CHOMEM), 94.8 (OCH_2O), 127.3, 128.3, 129.3 (CHarom.), 138.5 (Carom.), 179.0 (CO_2H). Anal. calcd for $C_{35}H_{55}NO_5$: C, 73.78; H, 9.73; N, 2.46. Found: C, 73.57; H, 9.78; N, 2.30%.

4.14. (4*S*,5*S*)-4-(*N*,*N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]heptadecanoic acid *syn*-8

The amino acid *syn*-**8** was obtained from *syn*-**7** (2.55 g, 4.6 mmol) by the procedure described for *anti*-**8** and purified by flash chromatography (silica gel, hexane/EtOAc: 4/1) to afford a colorless oil (1.52 g, 2.67 mmol, 58%); $[\alpha]_D^{23}=+23.1$ (*c* 0.6, $CHCl_3$); IR (film): 3600–2400, 1720, 1600, 1490, 1450, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (m, 1H, CHH), 0.89 (t, 3H, $J=6.6$ Hz, CH_3CH_2), 0.95 (m, 1H, CHH), 1.22 (m, 18H, CH_2), 1.52 (m, 1H, CHHCHOMEM), 1.78 (m, 1H, CHHCHOMEM), 1.90 (m, 1H, CHHCHN), 2.03 (m, 1H, CHHCHN), 2.30 (m, 1H, CHHCHO), 2.46 (m, 1H, CHHCHO), 2.65 (m, 1H, CHN), 3.38 (s, 3H, OCH_3), 3.54 (m, 2H, OCH_2CH_2O), 3.60 (d, 2H, $J=13.2$ Hz, CHHPh), 3.63 (m, 1H, CHOMEM), 3.68 (m, 1H, OCH_2CHHO), 3.77 (m, 1H, $OCH_2CHHOCH_3$), 3.94 (d, 2H, $J=13.2$ Hz, CHHPh), 4.68 (d, 1H, $J=7.1$ Hz, OCHHO), 4.74 (d, 1H, $J=7.1$ Hz, OCHHO), 7.20–7.40 (m, 10H, Harom.); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3CH_2), 20.0 (CH_2CH_3), 22.7 (CH_2CHN), 25.2 (CH_2CO_2H), 29.3 (CH_2), 29.7 (several CH_2), 29.9 (CH_2), 31.3 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 55.0 (CH_2Ph), 58.1 (CHN), 59.0 (OCH_3), 67.6 (OCH_2CH_2O), 71.7 (OCH_2CH_2O), 78.9 (CHOMEM), 94.9 (OCH_2O), 127.0, 128.2, 129.4 (CHarom.), 139.6 (Carom.), 178.8 (CO_2H). Anal. calcd for $C_{35}H_{55}NO_5$: C, 73.78; H, 9.73; N, 2.46. Found: C, 73.99; H, 9.90; N, 2.55%.

4.15. (5*S*,6*R*)-5-[1-(2-Methoxyethoxymethoxy)tridecyl]-pyrrolidin-2-one *anti*-9

To a solution of *N*,*N*-dibenzylamino acid *anti*-**8** (1.71 g, 3 mmol) in methanol (30 mL) was added 20% $Pd(OH)_2$–C (425 mg) in one portion. The mixture was stirred under hydrogen at atmospheric pressure and the reaction was monitored by TLC. After 2 h, when reaction had reached completion, the catalyst was removed by filtration through Celite and washed with methanol. The filtrate was concentrated under reduced pressure to afford the crude acid which was dissolved in CH_2Cl_2 (30 mL) and stirred at rt during addition of DCC (705 mg, 3.42 mmol) and 4-PPY (48 mg, 0.32 mmol). The resultant solution was stirred for 5 h at rt (reaction complete by TLC) and the precipitated DCU was filtered off. The filtrate was washed twice with water, once with 5% aqueous acetic acid, and once with water. The organic phase was dried over $MgSO_4$ and then concentrated to yield a residue, which was purified by flash chromatography (silica gel, EtOAc) to afford a colorless oil (825 mg, 2.22 mmol, 74%); $[\alpha]_D^{23}=-10.0$ (*c* 0.7, $CHCl_3$); IR (film): 3200, 3060, 1685, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $J=6.7$ Hz, CH_3CH_2), 1.24 (m, 22H, CH_2), 2.02 (m, 2H), 2.27 (m, 2H, CH_2CONH), 3.38 (s, 3H, OCH_3), 3.58 (m, 4H, OCH_2CH_2O, OCH_2CHH, CHN), 3.79 (m, 2H, CHOMEM, OCH_2CHHO), 4.70 (d, 1H, $J=7.2$ Hz, OCHHO), 4.74 (d, 1H, $J=7.2$ Hz, OCHHO), 6.31 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3CH_2), 21.4 (CH_2CH_3), 22.6 (CH_2), 25.6 (CH_2), 29.3 (CH_2), 29.6 (several CH_2), 29.7 (CH_2), 30.0

($\underline{C}H_2$), 30.3 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 56.6 ($\underline{C}HN$), 59.0 ($O\underline{C}H_3$), 67.1 ($O\underline{C}H_2CH_2O$), 71.7 ($OCH_2\underline{C}H_2O$), 78.7 ($\underline{C}HOMEM$), 94.7 ($O\underline{C}H_2O$), 178.4 ($\underline{C}ONH$). Anal. calcd for $C_{21}H_{41}NO_4$: C, 67.88; H, 11.12; N, 3.77. Found: C, 67.96; H, 11.01; N, 3.90%.

4.16. (5*S*,6*S*)-5-[1-(2-Methoxyethoxymethoxy)tridecyl]-pyrrolidin-2-one *syn*-9

The lactam *syn*-**9** was obtained from *syn*-**8** (1.42 g, 2.5 mmol) by debenzylation and cyclization as described for compound *anti*-**9**. The product was purified by flash chromatography (silica gel, EtOAc) to afford a colorless solid (511 mg, 1.4 mmol, 55%); mp 38–40°C (from hexane); $[\alpha]_D^{23}=+38.1$ (*c* 0.5, $CHCl_3$); IR (Nujol): 3400, 3160, 1690, 1450, 790 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J=6.7$ Hz, $C\underline{H}_3CH_2$), 1.12–1.50 (m, 22H, $(C\underline{H}_2)_{11}CH_3$), 1.63 (m, 1H, $C\underline{H}HCHN$), 2.05 (m, 1H, $CH\underline{H}CHN$), 2.28 (m, 2H, $C\underline{H}\underline{H}CONH$), 3.27 (m, 1H, $C\underline{H}OMEM$), 3.36 (s, 3H, $OC\underline{H}_3$), 3.51 (m, 2H, $OC\underline{H}\underline{H}CH_2OCH_3$), 3.59 (m, 2H, $OCH_2C\underline{H}HOCH_3$, $C\underline{H}N$), 3.74 (m, 1H, $OCH_2CH\underline{H}OCH_3$), 4.67 (d, 1H, $J=7.3$ Hz, $OC\underline{H}HO$), 4.72 (d, 1H, $J=7.3$ Hz, $OCH\underline{H}O$), 6.70 (br s, 1H, $N\underline{H}$); ^{13}C NMR ($CDCl_3$): δ 14.0 ($\underline{C}H_3CH_2$), 22.6 ($\underline{C}H_2CH_3$), 24.2 ($\underline{C}H_2$), 24.6 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 29.5 ($\underline{C}H_2$), 29.6 (several $\underline{C}H_2$), 30.6 ($\underline{C}H_2$), 30.8 ($\underline{C}H_2$), 31.8 ($\underline{C}H_2$), 57.6 ($\underline{C}HN$), 58.9 ($O\underline{C}H_3$), 67.7 ($O\underline{C}H_2CH_2O$), 71.5 ($OCH_2\underline{C}H_2O$), 84.1 ($\underline{C}HOMEM$), 95.9 ($O\underline{C}H_2O$), 177.5 ($\underline{C}ONH$). Anal. calcd for $C_{21}H_{41}NO_4$: C, 67.88; H, 11.12; N, 3.77. Found: C, 67.88; H, 10.96; N, 3.89%.

4.17. (5*S*,6*R*)-5-(1-Hydroxytridecyl)pyrrolidin-2-one, *erythro* aza-muricatacin *anti*-10[1a]

A cold solution (0°C) of lactam *anti*-**9** (65 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was treated with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.26 mL, 0.26 mmol) and the resultant mixture stirred at 0°C for 4 h. After hydrolysis with a saturated $NaHCO_3$ solution, the mixture was extracted with EtOAc (2×5 mL). The combined organic layers were dried over $MgSO_4$, concentrated and the residue purified by flash chromatography (silica gel, EtOAc) to provide *anti*-**10** as a colorless solid (34 mg 0.12 mmol, 70%); mp 86–88°C (from hexane/CH_2Cl_2); $[\alpha]_D^{23}=+4.9$ (*c* 0.9, $CHCl_3$); IR (KBr): 3600–3100, 1680, 1460 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, $J=6.6$ Hz, $C\underline{H}_3CH_2$), 1.26 (m, 20H, $(C\underline{H}_2)_{10}CH_3$), 1.50 (m, 2H, $C\underline{H}_2$), 2.06 (m, 2H, $C\underline{H}\underline{H}CHN$), 2.33 (m, 2H, $C\underline{H}_2CONH$), 3.54 (br s, 1H, $O\underline{H}$), 3.66 (m, 2H, $C\underline{H}N$, $C\underline{H}OH$), 7.19 (br s, 1H, $N\underline{H}$); ^{13}C NMR ($CDCl_3$): δ 14.1 ($\underline{C}H_3CH_2$), 19.8 ($\underline{C}H_2CH_3$), 22.7 ($\underline{C}H_2$), 26.1 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 29.6 (several $\underline{C}H_2$), 30.6 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 32.5 ($\underline{C}H_2$), 59.3 ($\underline{C}HN$), 72.3 ($\underline{C}HOH$), 180.0 ($\underline{C}ONH$). Anal. calcd for $C_{17}H_{33}NO_2$: C, 72.04; H, 11.73; N, 4.94. Found: C, 69.68; H, 10.66; N, 6.61%.

4.18. (5*S*,6*S*)-5-(1-Hydroxytridecyl)pyrrolidin-2-one, *threo* aza-muricatacin *syn*-10

This compound was obtained from *syn*-**9** (74 mg, 0.2 mmol) by the procedure described for *anti*-**10** as a colorless solid (53 mg, 0.19 mmol, 93%); mp 73–74°C (from hexane); $[\alpha]_D^{23}=+9.3$ (*c* 1.0, $CHCl_3$); [Lit.[5] mp 63–64°C; $[\alpha]_D^{23}=+10.3$ (*c* 0.4, $CHCl_3$)]; IR (KBr): 3400, 3200, 1670, 1370 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, $J=6.7$ Hz, $C\underline{H}_3CH_2$), 1.26 (m, 20H, $(C\underline{H}_2)_{10}CH_3$), 1.47 (m, 2H, $C\underline{H}_2$), 1.78 (m, 1H, $C\underline{H}HCHN$), 2.13 (m, 1H, $CH\underline{H}CHN$), 2.35 (m, 2H, $C\underline{H}\underline{H}CONH$), 3.34 (m, 1H, $C\underline{H}N$), 3.53 (q, 1H, $J=7.1$ Hz, $C\underline{H}OH$), 4.12 (bs, 1H, $O\underline{H}$), 7.39 (br s, 1H, $N\underline{H}$); ^{13}C NMR ($CDCl_3$): δ 14.1 ($\underline{C}H_3CH_2$), 22.6 ($\underline{C}H_2CH_3$), 23.7 ($\underline{C}H_2$), 25.5 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 29.6 (several $\underline{C}H_2$), 30.6 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 33.3 ($\underline{C}H_2$), 59.9 ($\underline{C}HN$), 75.1 ($\underline{C}HOH$), 179.1 ($\underline{C}ONH$). Anal. calcd for $C_{17}H_{33}NO_2$: C, 72.04; H, 11.73; N, 4.94. Found: C, 71.90; H, 11.59; N, 5.08%.

Acknowledgements

The authors would like to thank the Spanish DGESYC (Project PB98-0361) and Junta de Castilla y León (Project VA67/99) for financial support.

References

1. (a) Baussanne, I.; Schwardt, O.; Royer, J.; Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett*. **1997**, *38*, 2259–2262; (b) Cavé, A.; Chaboche, C.; Figadére, B.; Harmange, J.-C.; Laurens, A.; Peyrat, J. F.; Pichon, M.; Szlosek, M.; Cotte-Lafitte, J.; Quéro, A. M. *Eur. J. Med. Chem*. **1997**, *32*, 617–623.
2. Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett*. **1991**, *32*, 1137–1140.
3. Pichon, M.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett*. **1999**, *40*, 8567–8570 and references cited therein.
4. Pichon, M.; Jullian, J.-C.; Figadère, B.; Cavé, A. *Tetrahedron Lett*. **1998**, *39*, 1755–1758.
5. Rassu, G.; Pinna, L.; Spanu, P.; Zanardi, F.; Battistini, L.; Casiraghi, G. *J. Org. Chem*. **1997**, *62*, 4513–4517.
6. Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett*. **1998**, *39*, 1745–1748.
7. (a) Andrés, J. M.; Barrio, R.; Martínez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *J. Org. Chem*. **1996**, *61*, 4210–4213; (b) Andrés, J. M.; Pedrosa, R. *Tetrahedron* **1998**, *54*, 5607–5616; (c) Andrés, J. M.; Pedrosa, R. *Tetrahedron: Asymmetry* **1998**, *9*, 2493–2498; (d) Andrés, J. M.; de Elena, N.; Pedrosa, R. *Tetrahedron* **2000**, *56*, 1523–1531.
8. Reetz, M. T. *Chem. Rev*. **1999**, *99*, 1121–1162.
9. Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375–378.
10. (a) Dufour, M. N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1895–1899; (b) Yamazaki, T.; Iwatsubo, H.; Kitazume, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1823–1830.
11. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
12. Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619–624.
13. Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett*. **1976**, *11*, 809–812.
14. Boeckman, R. K; Potenza, J. C. *Tetrahedron Lett*. **1985**, *26*, 1411–1414.