Pergamon

Tetrahedron, Vol. 53, No. 21, pp. 7255-7266, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00428-6

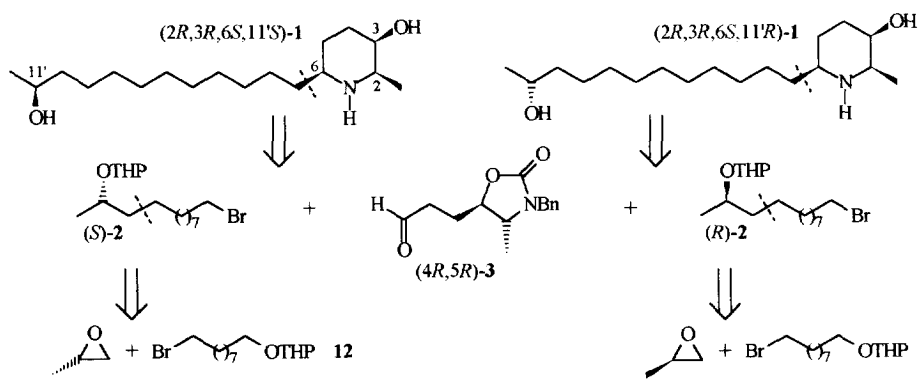
Diastereoselective and Convergent Synthesis of Both 11'-Epimers of (–)-(2*R*,3*R*,6*S*)-Carnavaline

Axel Pahl, Jörg Oetting, Jens Holzkamp and Hartmut H. Meyer*

Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

Abstract: Enantio- and diastereoselective syntheses of both 11'-epimers of (–)-carnavaline **1** have been achieved. Since the configuration of the remote chiral centre in the C-12 side chain of naturally occurring (–)-carnavaline had been unknown and spectroscopic data were not conclusive, an assignment of the 11'*S*-epimer to the natural product by comparison of the melting points is discussed and complete spectroscopic data are given. © 1997 Elsevier Science Ltd.

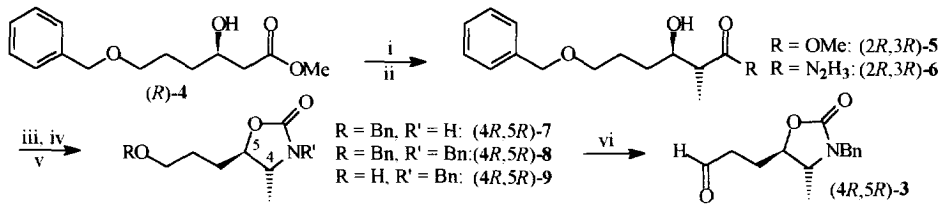
Carnavaline **1**, a 2,6-disubstituted 3-piperidinol-alkaloid isolated from the leaves of *Cassia carnaval* and *Cassia leptophylla*[1] displays interesting biological activities.[1b,2] Because spectroscopic and configurational data of natural carnavaline are incomplete – the absolute configuration of the piperidinol ring is known but the configuration of the C-12 side chain secondary alcohol and optical rotary powers have not yet been published[1] – we first tried to elucidate the structure by reducing synthetic (–)-cassine (2*R*,3*R*,6*S*)-**21** with sodium borohydride as described below. The resulting mixture of 11'-epimers as well as their triacetates could not be characterized by spectroscopic methods nor could they be separated by chromatography or preparative means. Since the formation of only one epimer due to intramolecular effects could not be excluded either,[3] the synthesis of both 11'-epimers of (–)-carnavaline was carried out (Scheme 1).



Scheme 1. Retrosynthetic approach to the 11'-epimers of (–)-carnavaline.

Synthesis

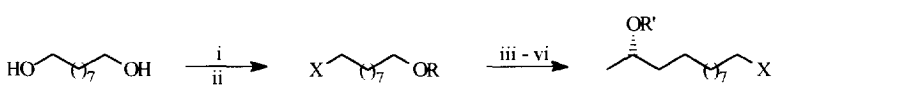
The enantiomeric purity and absolute configuration of the side chain building block **2** was of special importance and it was introduced by optically active (*S*)- resp. (*R*)-propylene oxide. Based on preceding work[4] the 2-oxazolidinone-aldehyde (4*R*,5*R*)-**3** served as very stable precursor[5] to the *all-cis*-2,6-disubstituted 3-piperidinol ring.



i) LDA, MeI, THF/*n*-hexane, -78°C → RT. ii) N_2H_4, cat. DMAP, MeOH, 16h, 100°C, cryst. (EtOH). iii) 6N HCl, $NaNO_2$, MeOH, 0°C → RT. iv) BnBr, NaH, DMF, 0°C → RT, FC. v) Pd/C, H_2, MeOH, FC. vi) $(COCl)_2$, DMSO, Et_3N, DCM, -70°C → RT, FC.

Scheme 2. Synthesis of the 2-oxazolidinone building block (4*R*,5*R*)-**3**.

The β-hydroxy ester (*R*)-**4** was obtained via kinetic enzymatic resolution of the corresponding racemic ethyl ester with PPL (porcine pancreas lipase), crystallization of the resulting acid with (1*R*,2*S*)-ephedrine and esterification with diazomethane. Diastereoselective alkylation supplied (2*R*,3*R*)-**5**, (*anti* : *syn* ~ 9:1)[4] which was heated with hydrazine-hydrate without purification. Diastereomeric enrichment by crystallization of the hydrazide from EtOH afforded pure (2*R*,3*R*)-**6** which was subjected to a Curtius rearrangement to give 2-oxazolidinone (4*R*,5*R*)-**7** with complete retention of the configuration. Protection of the nitrogen with the benzyl group has proved to be highly useful for the required Grignard addition in the convergent step. O-Debenzylation and Swern oxidation provided the aldehyde (4*R*,5*R*)-**3**.

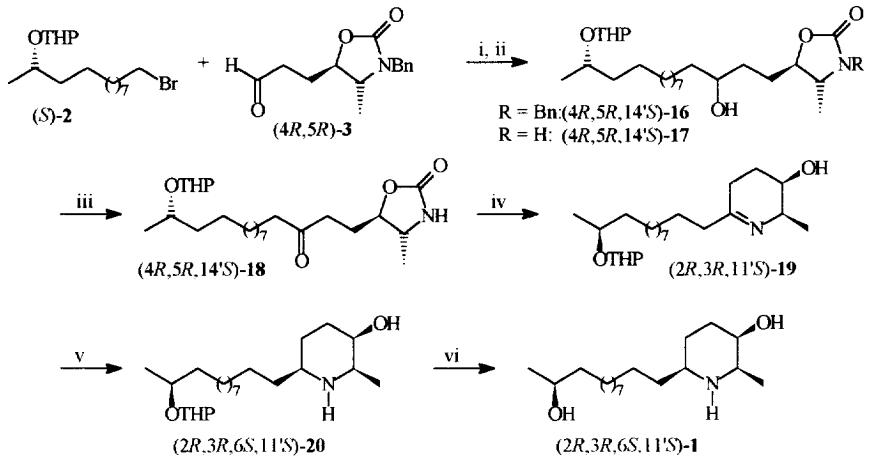


10 X = Br, R = H: **11** R' = H, X = OTHP: (*S*)-**13** R' = H, X = Br: (*S*)-**15**
X = Br, R = THP: **12** R' = H, X = OH: (*S*)-**14** R' = THP, X = Br: (*S*)-**2**

i) 48% HBr, cont. extraction with *n*-heptane, FC. ii) DHP, cat. *p*-TsOH, Et_2O, FC. iii) Mg, THF, RF, (*S*)-propylene oxide, cat. 1,5-cyclooctadiene-$Cu^{I}Cl$, THF, -78°C → RT. iv) MeOH, 6N HCl, RF, FC. v) CBr_4, PPh_3, DCM, FC. vi) DHP, cat. *p*-TsOH, Et_2O, FC. Enantiomeric (*R*)-**2** was synthesized likewise.

Scheme 3. Synthesis of the side chain (*S*)-**2**.

The side chain was built from nonanediol and chiral propylene oxide. The diol **10** was monobrominated in a continuous extractor (perforator) according to the literature,[6] followed by protection of the remaining alcohol function as THP ether to give **12**. Cu^{I}-mediated Grignard addition of the bromide **12** to (*S*)- resp. (*R*)-propylene oxide[7] and subsequent deprotection of the primary alcohol, selective bromination with CBr_4 and PPh_3[8] and protection of the secondary alcohol as THP ether, supplied the side chain building blocks (*S*)- and (*R*)-**2** with the desired configuration.[9]

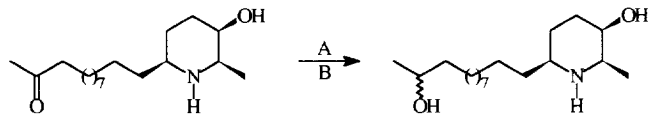


i) (*S*)-**2**, Mg, THF, RF → RT. (4*R*,5*R*)-**3**, RT, FC. ii) Li, ^{t}BuOH, THF, $EtNH_2$, -78°C → RT, FC. iii) Joncs' reagent, acetone, 0°C, FC. iv) 2N NaOH, EtOH, RF. v) Pd/C, H_2, MeOH, RT, FC. vi) 2N HCl, MeOH, RF, FC, cryst. (MTBE). (2*R*,3*R*,6*S*,11'*R*)-**1** was synthesized likewise with (*R*)-**2** and (4*R*,5*R*)-**3**.

Scheme 4. Synthesis of both 11'-epimer (–)-carnavalines.

The Grignard reagent of bromide (*S*)-**2** was added to aldehyde (4*R*,5*R*)-**3** to form the secondary alcohol (4*R*,5*R*,14'*S*)-**16**. After debenzylation under Birch conditions and Jones oxidation of the secondary alcohol to ketone (4*R*,5*R*,14'*S*)-**18**, alkaline hydrolysis of the oxazolidinone function was performed, followed by spontaneous cyclization to imine (2*R*,3*R*,11'*S*)-**19**, which was hydrogenated stereospecifically to piperidinol (2*R*,3*R*,6*S*,11'*S*)-**20** without purification analogous to previous results.[4] Finally deprotection of the alcohol in the side chain supplied (2*R*,3*R*,6*S*,11'*S*)-carnavaline.

In addition to these experiments, synthetic (–)-cassine (2*R*,3*R*,6*S*)-**21**[4] was reduced with $NaBH_4$ resp. BH_3·THF to crosscheck the above mentioned possibility of intramolecular interaction. These experiments provided only mixtures of epimers (Scheme 5).



A) 7 eq BH_3·THF, THF, 2.5h, -30°C → RT. B) 1 eq $NaBH_4$, isopropanol, 2h, RT.

Scheme 5. Reduction of (–)-cassine (2*R*,3*R*,6*S*)-**21**.

RESULTS AND DISCUSSION

Both 11'-epimers of (–)-carnavaline have been synthesized. Their spectroscopic data were identical, even the triacetates could not be distinguished by NMR. Only the optical rotary powers and melting points of (2*R*,3*R*,6*S*,11'*S*)-**1** and (2*R*,3*R*,6*S*,11'*R*)-**1** differed. Since the optical rotation of carnavaline has not yet been

published, the configuration of the side chain in the natural product can only be assigned on the basis of the reported melting points. The published melting point for natural carnavaline isolated from *cassia carnaval* is 60.7-61.2°C. The 11'*R*-epimer synthesized by us melted at 72°C, the 11'*S*-epimer at 63.5°C. So the natural product is more likely to be the lower melting (2*R*,3*R*,6*S*,11'*S*)-**1**-epimer.

The reduction experiments of cassine provided mixtures of the 11'-epimers, only slightly differing from the statistical value [ratio of (2*R*,3*R*,6*S*,11'*S*)-**1** : (2*R*,3*R*,6*S*,11'*R*)-**1** approx. 55:45 (method A) resp. 64:36 (method B), determined by optical rotation] therefore dominating intramolecular effects by complexation of boron could be excluded in this example. Table 1 gives a summary of the results.

Table 1. Melting Points and $[\alpha]_D^{20}$ of Synthesized and Natural Carnavaline and of Reduced Cassine.

	carnavaline isol. from NP	(2*R*,3*R*,6*S*, 11'*S*)-**1**	(2*R*,3*R*,6*S*, 11'*R*)-**1**	(2*R*,3*R*,6*S*, 11'*RS*)-**22** (A)	(2*R*,3*R*,6*S*, 11'*RS*)-**22** (B)
$[\alpha]_D^{20}$ ($CHCl_3$)	–	-5.63° (c = 0.675)	-14.71° (c = 1.14)	-9.76° (c = 0.82)	-8.93° (c = 0.84)
m.p.	60.7-61.2°C[1a]	63.5°C	72°C	60°C	58°C

EXPERIMENTAL

General Experimental Procedures. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY respectively on a Bruker AM 400 spectrometer with tetramethylsilane as internal standard. ^{13}C NMR spectra were measured with the APT (WP 200, 50MHz) resp. DEPT (AM 400, 100MHz) technique. IR spectra were recorded with a Perkin-Elmer electrophotometer 580 or a fourier transformation spectrometer 1710. Mass spectra were obtained with a Finnigan MAT 312 instrument (low resolution) and a VG Autospec (high resolution). Microanalyses were carried out on a Heraeus CHN-Rapid. Optical rotations were determined on a Perkin-Elmer polarimeter 241. Melting points were measured in a Tottoli apparatus and are not corrected. Column chromatographies were performed on silica gel from J.T. Baker (0.05-0.2mm) using gradients of mixtures of petrol ether, Et_2O and MeOH. For chromatographies of the free piperidinol bases an amount of 1-2% Et_3N was added to the eluents. Jones' reagent was prepared by dissolving 26.7g CrO_3 in 23ml concentrated H_2SO_4 at 0°C and addition of water to the resulting mixture to a total volume of 100ml [$c(Cr^{VI})$= 2.67M, $c(H^+)$= 8.3M].

Remarks. Diastereomers resulting from the THP-protecting group were not considered in the chemical names. In the experimental part below is described the synthesis of the side chain building block (*S*)-**2**, the oxazolidinone building block (4*R*,5*R*)-**3**, the formation of (2*R*,3*R*,6*S*,11'*S*)-carnavaline [(2*R*,3*R*,6*S*,11'*S*)-**1**] from (*S*)-**2** and (4*R*,5*R*)-**3** and the reduction experiments with (2*R*,3*R*,6*S*)-cassine. (*R*)-**2** and (2*R*,3*R*,6*S*,11'*R*)-**1** were synthesized accordingly. Since their spectroscopic data were identical to the enantiomeric resp. diastereomeric compounds only the optical rotations and melting points are reported herein.

(2*R*,3*R*)-6-Benzyloxy-3-hydroxy-2-methyl-hexanoic acid hydrazide (2*R*,3*R*)-6. 164.6ml *n*-butyllithium (1.64M in hexane, 270.1mmol, 2.2eq) were added dropwise to a solution of 38.0ml diisopropyl amine (270.1mmol, 2.2eq) in 120ml dry THF under nitrogen at -50 - -40°C. After stirring for 30min at -40°C a solution of 31.0g (122.8mmol, 1eq) (*R*)-6-benzyloxy-3-hydroxy-hexanoic acid methylester[4] (*R*)-**4** in 35ml dry THF was added below -65°C. The mixture was allowed to warm to -40°C over a period of 1.5h and was stirred for 3h at this temperature to complete the formation of the dianion. The solution was cooled to -78°C again, 19.2ml

(307.0mmol, 2.5eq) MeI were added and the reaction mixture was allowed to warm to ambient temperature over night. The reaction was quenched by addition of 200ml diethyl ether and 200ml 2N sulfuric acid at 0°C. After separation of the organic layer the aqueous layer was extracted three times with 200ml diethyl ether. The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuum to afford 32.48g of a yellow oil which was converted to the hydrazide without purification.

32.48g crude ester (2*R*,3*R*)-**5** were dissolved in 70ml MeOH, treated with 27.4ml hydrazine-hydrate and 410mg 4-(dimethylamino)-pyridine (DMAP) and refluxed over night. The volatile components were evaporated under reduced pressure and the solid residue was recrystallized three times from EtOH to afford 21.65g (66% over two steps) diastereomeric pure hydrazide (2*R*,3*R*)-**6** free from *syn*-epimer. ^{1}H NMR (200MHz, CD_3OD): δ= 1.09 (d, J=7.25Hz, 3H, 2-CCH_3), 1.29-1.50 (m, 2H, 5-CH_2), 1.53-1.86 (m, 2H, 4-CH_2), 2.28 (quint, J=7.25Hz, 1H, 2-CH), 3.51 (t, J=6Hz, 2H, 6-OCH_2), 3.59-3.69 (m, 1H, 3-CHO), 4.49 (s, 2H, Bn-CH_2), 7.25-7.36 (m, 5H, Ar-H) ppm; IR (KBr): 3289 vs, 3166 m, 2906 w, 2874 m, 2800 w, 1627 vs, 1545 m, 1455 m, 1359, 1257, 1232 w, 1123, 1096 s cm^{-1}; MS (120°C): m/e= 267 (6, M^++1), 249 (2), 235 (3), 188 (2), 178 (2), 158 (6), 157 (6), 156 (5), 142 (10), 122 (20), 117 (19), 111 (18), 107 (8), 92 (27), 91 (100); Analysis: calc. for $C_{14}H_{22}N_2O_3$: C 63.14 H8.33 N 10.52; found: C 62.86 H 8.04 N 10.31; m.p.: 127°C, $[\alpha]_D^{20}$= -9.19° (c= 0.870, MeOH).

(4*R*,5*R*)-5-(3'-Benzyloxypropyl)-4-methyl-2-oxazolidinone (4*R*,5*R*)-7. To 21.65g (81.3mmol, 1eq) hydrazide (2*R*,3*R*)-**6** dissolved in 300ml MeOH were added 81ml (486mmol, 6eq) 6N H_2SO_4 under magnetical stirring at 0°C. A solution of 15.42g (223.5mmol, 2.75eq) sodium nitrite in 125ml water was then added within 60min under ice cooling. The mixture was stirred at 0°C for further 30min then over night at room temperature. The reaction mixture was cooled to 0°C again and the pH was adjusted to 5-7 by addition of 110ml 2N NaOH. The organic components were evaporated and the aqueous residue was extracted four times with DCM. The combined extracts were dried over $MgSO_4$ and concentrated in vacuum to yield 20.92g crude oxazolidinone (4*R*,5*R*)-**7** as yellow oil, which was used in the next step without further purification. A small amount was purified by chromatography over SiO_2 to obtain an analytical sample. For spectroscopic data see Lit.[4] $[\alpha]_D^{20}$= +43.49° (c= 1.06, $CHCl_3$).

(4*R*,5*R*)-3-Benzyl-5-(3'-benzyloxypropyl)-4-methyl-2-oxazolidinone (4*R*,5*R*)-8. A magnetically stirred solution of 20.27g (81.3mmol, 1eq) (4*R*,5*R*)-**7** in 81ml DMF under nitrogen was treated with 11.40ml (95.9mmol, 1.18eq) benzyl bromide. The solution was cooled to 0°C and 3.41g (85.4mmol, 1.05eq) NaH (60% suspension in mineral oil) were added in three portions in intervalls of 30min. The mixture was allowed to warm to room temperature and stirring was continued for three hours. The reaction solution was neutralized with acetic acid, transferred to a one-neck flask and the main amount of DMF was removed in vacuum. The cloudy yellow oil was suspended in 300ml half saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography to afford 25.95g (94% over two steps) of (4*R*,5*R*)-**8** as a colourless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.17 (d, J=6.25Hz, 3H, 4-CCH_3), 1.57-1.83 (m, 4H, 1'-CH_2–2'-CH_2), 3.23 (quint, J=6.25Hz, 1H, 4-CHN), 3.40-3.56 (m, 2H, 3'-OCH_2), 3.96-4.05 (m, 1H, 5-CHO), 4.09 (d, J=15.5Hz, 1H, NBn-CH_2), 4.48 (s, 2H, OBn-CH_2), 4.77 (d, J=15.5 Hz, 1H, NBn-CH_2), 7.22-7.39 (m, 10H, Ar-H) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 17.81 (4-CCH_3), 25.19, 30.81 (1'-CH_2–2'-CH_2), 45.60 (NBn-CH_2), 55.62 (4-CHN), 69.36 (3'-OCH_2), 72.82 (OBn-CH_2), 80.96 (5-CHO), 127.58 (3×Ar-CH), 127.79 (Ar-CH), 128.00 (2×Ar-CH), 128.34 (2×Ar-CH), 128.74 (2×Ar-CH), 135.98 (Ar-C), 138.33 (Ar-C), 157.84 (2-C=O) ppm; IR (neat): 2931 w, 2861 w, 1747 vs, 1496 w, 1455 w, 1416, 1362, 1247, 1203, 1103, 1028 cm^{-1}; MS (150°C): m/e= 339 (5, M^+), 248

(2), 234 (14), 204 (10), 188 (6), 160 (5), 150 (5), 147 (9), 142 (16), 106 (6), 91 (100), 65 (15); HRMS: calc. for $C_{21}H_{25}NO_3$: 339.1834; found: 339.1831; $[\alpha]_D^{20}$ = +65.40° (c= 1.13, $CHCl_3$).

(4*R*,5*R*)-3-Benzyl-5-(3'-hydroxypropyl)-4-methyl-2-oxazolidinone (4*R*,5*R*)-9. 25.95g (76.4mmol) (4*R*,5*R*)-**8** were dissolved in 300ml MeOH under magnetical stirring and hydrogenated with 640mg Pd/C (10%) at 3.7bar H_2 over night. Evaporation of the solvent and filtration over a SiO_2 column yielded 18.22g (96%) colourless oily (4*R*,5*R*)-**9**. ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.18 (d, J=6Hz, 3H, 4-CC$\underline{H}_3$), 1.54-1.76 (m, 4H, 1'-CH_2–2'-CH_2), 2.77 (s, OH), 3.26 (quint, J=6Hz, 1H, 4-CHN), 3.54-3.70 (m, 2H, 3'-OCH_2), 3.99-4.08 (m, 1H, 5-CHO), 4.09 (d, J=15Hz, 1H, Bn-CH_2), 4.73 (d, J=15Hz, 1H, Bn-CH_2), 7.22-7.39 (m, 5H, Ar-H) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 17.84 (4-C$\underline{C}H_3$), 27.99, 30.43 (1'-CH_2–2'-CH_2), 45.65 (Bn-CH_2), 55.82 (4-CHN), 61.74 (3'-OCH_2), 81.28 (5-CHO), 127.87 (Ar-CH), 127.99 (2×Ar-CH), 128.80 (2×Ar-CH), 135.87 (Ar-C), 158.06 (2-C=O) ppm; IR (neat): 3033 w, 2932 w, 1747 vs, 1718 vs, 1602, 1602, 1585, 1496, 1452, 1417, 1385 cm^{-1}; MS (80°C): m/e= 249 (7, M^+), 234 (3), 205 (5), 190 (3), 160 (4), 158 (5), 132 (6), 106 (33), 100 (100); HRMS: calc. for $C_{14}H_{19}NO_3$: 249.1365; found: 249.1372; $[\alpha]_D^{20}$ = 87.85° (c= 1.045, $CHCl_3$).

(4*R*,5*R*)-3-Benzyl-4-methyl-5-(3'-oxopropyl)-2-oxazolidinone (4*R*,5*R*)-3. Swern oxidation: To a magnetically stirred solution of 3.77ml (44.0mmol, 1.1eq) oxalyl chloride in 60ml dry DCM were added 6.25ml (88.0mmol, 2.2eq) DMSO below -60°C. Stirring was continued for 10min before a solution of 9.97g (40.0mmol, 1eq) (4*R*,5*R*)-**9** in 10ml dry DCM was added at -70°C whereupon the reaction mixture turned white and cloudy. The mixture was stirred for further 30min prior to the addition of 27.72ml (200.0mmol, 5eq) triethylamine at -70°. After 10min the mixture was allowed to warm to 0°C and stirring was continued for further 60min. The reaction was quenched by the addition of 40ml water, separation of the organic layer and further extraction with DCM for two times. The combined organic extracts were washed successively with 30ml 2N HCl, 30ml 1N HCl and 20ml sat. $NaHCO_3$ (aq), dried over $MgSO_4$, concentrated in vacuum and purified by column chromatography to supply 8.90g (90%) of the very stable[5] (4*R*,5*R*)-**3** as a colourless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.22 (d, J=6Hz, 3H, 4-CC$\underline{H}_3$), 1.64 (m, 1H, 1'-CH_2), 2.08 (m, H, 1'-CH_2), 2.67 (t, J=7Hz, 2H, 2'-CH_2), 3.24 (dq, J_1= 4.5Hz, J_2= 6Hz, 1H, 4-CHN), 4.04 (m, 1H, 5-CHO), 4.07 (d, J=16Hz, 1H, Bn-CH_2), 4.77 (d, J=16Hz, 1H, Bn-CH_2), 7.21-7.42 (m, 5H, Ar-H), 9.78 (s, 1H, 3'-CHO) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 17.69 (4-C$\underline{C}H_3$), 26.09 (1'-CH_2), 39.21 (2'-CH_2), 55.70 (4-CHN), 79.95 (5-CHO), 127.93, 128.01, 128.83 (5×Ar-CH), 135.78 (Ar-C), 157.55 (2-C=O), 200.68 (3'-CHO) ppm; IR (neat): 3032 w, 2972 w, 2731 w, 1747 vs, 1605 w, 1497 w, 1417 s, 1385, 1360, 1244, 1204 1112, 1065 s cm^{-1}; MS (RT): m/e= 247 (12, M^+), 232 (3), 219 (2), 203 (3), 178 (4), 150 (29), 129 (11), 106 (24), 91 (100); HRMS: calc. for $C_{14}H_{17}NO_3$: 247.1182; found: 247.1208; $[\alpha]_D^{20}$ = +106.34° (c= 1.025, $CHCl_3$).

9-Bromo-nonane-1-ol 11. According to the literature[6] 150ml (1.322mol, 6eq) HBr (aq, 48%) were added to 35.58g (222.0mmol, 1eq) 1,9-nonanediol **10** in a continuous extractor (volume: 300ml). The extractor was filled up with 150ml *n*-heptane and heated to 80°C. The distillation flask was filled with 200ml *n*-heptane and heated to 150°C so that 100-200 drops of the solvent per minute passed through the aqueous layer. After 6h the organic extract in the distillation flask was replaced by 200ml of fresh *n*-heptane and heating was continued. After 24h no further organic material was extracted (confirmed by TLC of the organic layer in the extractor) and the combined organic extracts were washed with 30ml sat. $NaHCO_3$ (aq) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography to give 46.27g (93%) of **11** as colourless crystals.

1-Bromo-9-(tetrahydropyran-2'-yloxy)-nonane 12. 46.27g (207.3mmol, 1eq) **11** were dissolved in 50ml diethyl ether and cooled to 0°C. 24.4ml (269.5mmol, 1.3eq) Dihydropyrane and 500mg *p*-toluenesulphonic acid were added under magnetical stirring. After 10min the ice bath was removed and stirring was continued for 2h. The reaction solution was diluted with 30ml Et_2O and washed with 30ml half saturated $NaHCO_3$ (aq). The aqueous layer was backextracted two times with Et_2O and the combined organic extracts were dried over $MgSO_4$. The residue which in this case was not concentrated to complete dryness[10] was purified by column chromatography to yield 62.83g **12** as colourless oil. Spectroscopic data were in accordance with the literature.[11]

(*S*)-12-(Tetrahydropyran-2'-yloxy)-dodecane-2-ol (*S*)-13. The reaction was performed analogous to the literature.[8] To 1.00g (40.8mmol, 1.4eq) Mg shavings under nitrogen were added 30ml dry THF und one drop of 1,2-dibromoethane. The suspension was heated to reflux under magnetical stirring and a solution of 11.41g (37.1mmol, 1.3eq) **12** in 40ml dry THF was added dropwise so that after the reaction had started the mixture boiled steadily. After the addition heating was continued for one hour then the mixture was cooled to 0°C and added via syringe to a magnetically stirred slurry of 864mg 1,5-cyclooctadiene · $Cu^{I}Cl$ [12] and 2.00ml (28.6mmol, 1eq) (*S*)-propylene oxide[7] in 60ml dry THF at -78°C within 10min, whereupon the colour of the slurry changed from white to orange and dark brown. The mixture was allowed to warm to room temperature and stirring was continued over night whereupon the colour lightened up again. The reaction was quenched by addition of 100ml sat. NH_4Cl (aq) and 75ml Et_2O at 0°C. Stirring must be continued at this temperature for at least 20min to complete hydrolysis. The organic phase was separated and the aqueous layer was extracted two times with Et_2O. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting oil was purified by column chromatography and 7.03g (86%) (*S*)-**13** were obtained as colourless oil. ^1H NMR (200MHz, $CDCl_3$): δ= 1.18 (d, J=6Hz, 3H, 1-CH_3), 1.21-1.94 (m, 24H, 3-CH_2–11-CH_2, 3'-CH_2–5'-CH_2), 3.38, 3.73 (2dt, J_1=10Hz, J_2=6.7Hz, 2H, 12-CH_2), 3.43-3.57 (m, 1H, 6'-CH_2), 3.76-3.94 (m, 2H, 2-CH, 1H at 6'-CH_2), 4.58 (m, 1H, 2'-CH_2) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 19.65 (CH_2), 23.47 (1-CH_3), 25.52, 25.80, 26.24 (3×CH_2), 29.49, 29.55, 29.58, 29.62, 29.67, 29.75 (6×CH_2), 30.78, 39.39 (2×CH_2), 62.26 (12-CH_2), 67.69 (6'-CH_2), 68.03 (2-CH), 98.79 (2'-CH) ppm; IR (neat): 3400 b (OH), 2930 s, 2855, 1137, 1122, 1078, 1034, 1024 cm^{-1}; MS (RT): m/e= 286 (1, M^+), 111 (6), 101 (36), 85 (100, $C_5H_9O^+$ (THP-residue)); HRMS: calc. for $C_{17}H_{34}O_3$: 286.2508; found: 286.2482; $[\alpha]_D^{20}$= +4.03° (c=1.315, $CHCl_3$; mixture of diastereomers).

(*S*)-1,11-Dodecanediol (*S*)-14. 6.87g (24.0mmol, 1eq) (*S*)-**13** were dissolved in 90ml MeOH, treated with 9ml of 6N HCl and refluxed for three hours. The solution was neutralized with 5g $NaHCO_3$ and the solvent was evaporated. The residue was taken up with 75ml water and extracted three times with a total of 200ml Et_2O. The extracts were dried ($MgSO_4$), concentrated and the crude crystalline diol was purified by column chromatography to afford 4.64g (95%) (*S*)-**14** as white waxy crystals. ^1H NMR (200MHz, $CDCl_3$): δ= 1.18 (d, J=6Hz, 3H, 12-CH_3), 1.21-1.65 (m, 18H, 2-CH_2–10-CH_2), 3.64 (t, J=6.5Hz, 2H, 1-CH_2), 3.70-3.87 (m, 1H, 11-CH) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 23.34 (12-CH_3), 25.79 (CH_2), 29.46-29.68 (6×CH_2), 32.71 (CH_2), 39.30 (CH_2), 62.62 (1-CH_2), 67.95 (11-CH) ppm; IR (KBr): 3390 (sb, OH), 2925 s, 2850 m, 1470 w, 1060 w cm^{-1}; MS (70°C): m/e= 201 (1), 189 (1), 188 (11), 166 (11), 140 (52), 138 (21), 124 (11), 69 (100); Analysis: calc. for $C_{12}H_{26}O_2$: C 71.23 H 12.95; found: C 71.22 H 12.62; m.p.: 46°C; $[\alpha]_D^{20}$= +5.37° (c= 1.08, $CHCl_3$).

(*S*)-12-Bromo-dodecane-2-ol (*S*)-15. 4.64g (22.8mmol, 1eq) (*S*)-**14** and 8.35g (25.2mmol, 1.1eq) tetrabromomethane were dissolved in 51ml dry DCM under nitrogen and cooled to 0°C whereupon part of the

diol crystallized again from the solution. 6.90g (26.3mmol, 1.15eq) triphenylphosphine PPh_3 in 30ml dry DCM were then added within 1.5h at 0°C and the resulting homogenous solution was stirred for further 60min. The reaction mixture was diluted with 100ml petrol ether and the reactants were separated by filtration over a column of 110g SiO_2.(eluent: DCM : PE – 1 : 1.2 to PE : EtOAc – 2 : 1). After evaporation of the solvent the crude oil was purified by column chromatography to give 5.08g (84%) (*S*)-**15** as colourless oil. $[\alpha]_D^{20}$ = +3.29° (c= 1.215, $CHCl_3$).[9] Spectroscopic data were identical to the literature.[13]

(*S*)-1-Bromo-11-(tetrahydropyran-2'-yloxy)-dodecane (*S*)-2. 4.80g (18.1mmol, 1eq) (*S*)-**15** and 4.1ml (45.3mmol, 2.5eq) DHP dissolved in 25ml dry Et_2O were cooled to 0°C and 75mg *p*-toluenesulphonic acid were added under magnetical stirring. After 10min the ice bath was removed and stirring was continued for further 3h. The reaction was quenched by the addition of 20ml sat. $NaHCO_3$ (aq) at 0°C. The organic layer was separated and the aqueous phase was extracted two times with Et_2O. The combined extracts were dried over $MgSO_4$, concentrated again not to complete dryness[10] and purified by column chromatography to yield 6.14g (97%) of the side chain building block (*S*)-**2** as colourless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.10, 1.21 (2d, J=6Hz, ~1:1, 12-CH_3), 1.24-1.93 (m, 24H, 2-CH_2–10-CH_2, 3'-CH_2–5'-CH_2), 3.40 (t, J=7Hz, 2H, 1-CH_2), 3.45-3.55, 3.84-3.99 (2m, 2H, 6'-CH_2), 3.66-3.83 (m, 1H, 11-CH), 4.63, 4.71 (2m, 1H, 2'-CH) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 19.10, 21.60 (12-CH_3), 19.79, 20.12 (CH_2), 25.47, 25.55, 25.61, 25.86 (CH_2), 28.18, 28.76 (1×CH_2), 29.43, 29.47, 29.51, 29.57, 29.58, 29.70, 29.74 (CH_2), 31.23, 31.26 (1×CH_2), 32.84, 33.98 (1×CH_2), 36.52, 37.56 (1×CH_2), 62.44, 62.81 (1-CH_2), 71.12, 73.89 (11-CH), 95.59, 98.59 (2'-CH) ppm; IR (neat): 2930 s, 2855 m; 1135, 1080, 1030, 1024, 995 cm^{-1}; MS (60°C): m/e= 350 (1), 349 (1), 348 (2, M^+), 305 (4), 303 (4), 2449 (5), 129 (19), 102 (19), 85 (100, $C_5H_9O^+$); HRMS: calc. for $C_{17}H_{33}BrO_2$: 348.1664; found: 348.1642; $[\alpha]_D^{20}$ = -1.09° (c= 1.005, $CHCl_3$; mixture of diastereomers).

(4*R*,5*R*,14'*S*)-3-Benzyl-5-[3'-hydroxy-14'-(tetrahydropyran-2''-yloxy)-pentadecyl]-4-methyl-2-oxazolidinone (4*R*,5*R*,14'*S*)-16. To 374mg (15.4mmol, 1.54eq) magnesium under nitrogen were added 10ml dry THF and one drop of 1,2-dibromoethane. The suspension was heated to reflux and a solution of 4.89g (14.0mmol, 1.4eq) (*S*)-**2** in 20ml dry THF was added under magnetical stirring so that after the start of the reaction the mixture boiled constantly. Heating was continued for one hour, then the mixture was cooled to RT. Within 15min a solution of 2.47g (10.0mmol, 1eq) (4*R*,5*R*)-**3** in 10ml dry THF was then added and stirring was continued for further 45min. The reaction was quenched by the addition of 50ml sat. NH_4Cl (aq) at 0°C, separation of the organic layer and further extraction with Et_2O for two times. The combined organic layers were dried ($MgSO_4$), concentrated and the residue was purified by column chromatography to give 4.44g (86%) of the secondary alcohol (4*R*,5*R*,14'*S*)-**16** as colourless oil. ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.10, 1.21 (2d, J=6Hz, 3H, 15'-CH_3), 1.18 (d, J=6.25Hz, 3H, 4-CCH_3), 1.23-1.98 (m, 30H, 1'-CH_2–2'-CH_2, 4'-CH_2–13'-CH_2, 3''-CH_2–5''-CH_2), 3.24 (dquint, J_1=6.25Hz, J_2=2Hz, 1H, 4-CHN), 3.42-3.63 (m, 2H, 1H at 6''-CH_2, 3'-CHO), 3.66-3.83 (m, 1H, 14'-CHO), 3.83-4.11 (m, 2H, 1H at 6''-CH_2, 5-CHO), 4.09 (d, J=15Hz, 1H, Bn-CH_2), 4.63, 4.71 (2m, 1H, 2''-CH), 4.76 (d, J=15Hz, 1H, Bn-CH_2), 7.22-7.40 (m, 5H, Ar-H) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 17.86, 17.89 (4-CCH_3), 19.10, 21.59 (15'-CH_3), 19.74, 20.09 (CH_2), 25.47, 25.52, 25.58, 25.61, 25.87 (CH_2), 29.58, 29.64, 29.72, 29.74, 29.84 (CH_2), 30.58, 31.22, 32.08, 32.79 (CH_2), 36.51, 37.55, 37.64, 37.81 (CH_2), 45.66 (NBn-CH_2), 55.53, 55.82 (4-CHN), 62.41, 62.82 (6''-CH_2), 70.89, 71.40 (3'-CHO), 71.14, 73.91 (14'-CHO), 80.99, 81.65 (5-CHO), 95.56, 98.58 (2''-CH), 127.83, 128.05, 128.77 (5×Ar-C), 135.93 (Ar-C), 157.92 (2-C=O) ppm; IR (neat): 3450 b (OH), 2930, 2855, 1750, 1497, 1120, 1075, 1024, 705 cm^{-1}; MS (100°C): m/e= 247 (42), 150 (39), 106 (11), 92 (16), 91 (100), 85 (4, $C_5H_9O^+$), 65 (11); $[\alpha]_D^{20}$ = +55.67° (c= 0.970, $CHCl_3$; mixture of diastereomers).

(4*R*,5*R*,14'*S*)-5-[3'-Hydroxy-14'-(tetrahydropyran-2''-yloxy)-pentadecyl]-4-methyl-2-oxazolidinone (4*R*,5*R*,14'*S*)-17. Birch reduction: To 85ml $EtNH_2$ at -30°C under nitrogen were added 4.21g (8.1mmol, 1eq) (4*R*,5*R*,14'*S*)-**16** and 7.23g (97.5mmol, 12eq) *tert.*-butanol in 20ml dry THF under magnetical stirring. The solution was cooled to -78°C and 564mg (81.3mmol, 10eq) Li were added. Soon after the addition blue streaks showed on the surface of the metal and after 1.5h the blue colour of the whole solution indicated the completion of the reaction. The mixture was treated with 10ml MeOH at -78°C to remove excess lithium and then warmed to RT in a water bath to evaporate the main amount of the ethylamine. 30g NH_4Cl and 75ml water were added and extraction with DCM for three times, drying over $MgSO_4$, removal of the solvent in vacuum and column chromatography supplied 3.34g (96%) colourless oily (4*R*,5*R*,14'*S*)-**17**. ^1H NMR (200MHz, $CDCl_3$): δ= 1.11, 1.22 (2d, J=6Hz, 3H, 15'-CH_3), 1.27 (d, J=6Hz, 3H, 4-CC$\underline{H}_3$), 1.22-2.09 (m, 31H, 1'-CH_2–2'-CH_2, 4'-CH_2–13'-CH_2, 3''-CH_2–5''-CH_2, OH), 3.42-4.00 (m, 5H, 4-CHN, 6''-CH_2, 3'-CHO, 14'-CHO), 4.05-4.20 (m, 1H, 5-CHO), 4.64, 4.71 (2m, 1H, 2''-CH), 6.21 (s, 1H, NH) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 19.09, 21.59 (15'-CH_3), 19.76, 20.09 (CH_2), 20.56, 20.60 (4-C$\underline{C}H_3$), 25.47, 25.52, 25.57, 25.65, 25.87 (CH_2), 29.58, 29.64, 29.71, 29.74 (CH_2), 30.03, 30.67, 31.22, 32.21, 32.82 (CH_2), 36.50, 37.54, 37.62, 37.78 (CH_2), 53.61, 53.82 (4-CHN), 62.45, 62.84 (6''-CH_2), 71.06, 71.49 (3'-CHO), 71.18, 73.92 (14'-CHO), 83.98, 84.58 (5-CHO), 95.60, 98.59 (2''-CH), 159.29 (2-C=O) ppm; IR (neat): 3350 b (OH), 2930 s, 2855 s, 1750 s, 1135, 1078, 1024 cm^{-1}; MS (160°C): m/e= 326 (22), 282 (21), 158 (33), 129 (35), 114 (18), 85 (100, $C_5H_9O^+$) $[\alpha]_D^{20}$= +24.42° (c= 0.99, $CHCl_3$; mixture of diastereomers).

(4*R*,5*R*,14'*S*)-4-Methyl-5-[3'-oxo-14'-(tetrahydropyran-2''-yloxy)-pentadecyl]-2-oxazolidinone (4*R*,5*R*,14'*S*)-18. 3.34g (7.8mmol, 1eq) (4*R*,5*R*,14'*S*)-**17** were dissolved in 120ml acetone. 1.93ml (5.2mmol, 0.67eq) Jones' reagent were then added rapidly at 0°C under magnetical stirring. As long as Cr^{VI} was reduced the solution remained green, an orange shade in the colour indicated the completion of the reaction. Stirring was continued for 30 seconds (!) then 1ml isopropanol was added to reduce excess Cr^{VI} whereupon the slurry turned green again. 10ml sat. $NaHCO_3$ (aq) were added shortly afterwards and the mixture was stirred for 10min at 0°C (Addition of Jones' reagent, *iso*-propanol and $NaHCO_3$ (aq) was completed within 2min overall). The acetone was removed under reduced pressure and the residue was treated with 75ml water. Precipitated chromium hydroxide was filtered off through a suction funnel and washed with DCM. The filtrate was extracted with DCM three times, the combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuum. Column chromatography afforded 2.79g (84%) (4*R*,5*R*,14'*S*)-**18** as white crystals. ^1H NMR (200MHz, $CDCl_3$): δ= 1.10, 1.22 (2d, J=6Hz, 3H, 15'-CH_3), 1.28 (d, J=6Hz, 3H, 4-CC$\underline{H}_3$), 1.22-2.15 (m, 26H, 1'-CH_2, 5'-CH_2–13'-CH_2, 3''-CH_2–5''-CH_2), 2.42 (t, J=7.5Hz, 2H, 2'-CH_2), 2.64 (t, J=7Hz, 2H, 4'-CH_2), 3.42-3.99 (m, 3H, 6''-CH_2, 14'-CHO), 3.57 (quint, J=6Hz, 1H, 4-CHN), 4.11 (ddd, J_1=9.5Hz, J_2=6Hz, J_3=3.5Hz, 1H, 5-CHO), 4.63, 4.71 (2m, 1H, 2''-CH), 6.51 (s, 1H, NH) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 19.10, 21.59 (15'-CH_3), 19.77, 20.12 (CH_2), 20.37 (4-C$\underline{C}H_3$), 23.83 (CH_2), 25.47, 25.53, 25.58, 25.86 (CH_2), 27.80 (CH_2), 29.20, 29.37, 29.43, 29.57, 29.70, 29.74 (CH_2), 31.24 (CH_2), 36.51, 37.55, 37.62 (CH_2), 42.99 (CH_2), 53.85 (4-CHN), 62.44, 62.85 (6''-CH_2), 71.15, 73.92 (14'-CHO), 83.12 (5-CHO), 95.59, 98.62 (2''-CH), 159.22 (2-C=O), 209.96 (3'-C=O) ppm; IR (KBr): 2927 s, 1739, 1714, 1135, 1079, 1025 cm^{-1}; MS (150°C): m/e= 425 (1, M^+), 324 (100), 280 (11), 237 (18), 209 (23), 191 (14), 171 (13), 114 (18), 110 (18), 85 (71); analysis: calc. for $C_{24}H_{43}NO_5$: C 67.73 H 10.18 N 3.29; found: C 67.75 H 9.96 N 3.55; m.p.: 41.5°C $[\alpha]_D^{20}$= +46.63° (c= 0.965, $CHCl_3$; mixture of diastereomers).

(2*R*,3*R*,6*S*,11'*S*)-2-Methyl-6-[11'-(tetrahydropyran-2''-yloxy)-dodecyl]-piperidine-3-ol (2*R*,3*R*,6*S*,11'*S*)-20. 1.702g (4.0mmol, 1eq) (4*R*,5*R*,14'*S*)-**18** in 20ml EtOH and 20ml (40mmol, 10eq) 2N NaOH were heated to reflux (100°C) for 3h. The solvent was evaporated and the resulting aqueous residue was

diluted with 30ml water and extracted with DCM three times. The combined organic layers were dried over $MgSO_4$ and removal of the solvent in vacuum to supply the crude imine (2*R*,3*R*,11'*S*)-**19** as yellow oil which was hydrogenated over night with 150mg Pd/C (10%) at 1atm H_2 in 32ml MeOH without further purification. Filtration of the catalyst, concentration of the filtrate under reduced pressure and purification by column chromatography gave 1.22g (80% over two steps) (2*R*,3*R*,6*S*,11'*S*)-**20** as pale oil. ^1H NMR (200MHz, $CDCl_3$): δ= 1.10, 1.22 (2d, J=6Hz, 3H, 12'-CH_3), 1.12 (d, J=6Hz, 3H, 2-CC$\underline{H}_3$), 1.22-1.95 (m, 30H, 4-CH_2–5-CH_2, 1'-CH_2–10'-CH_2, 3''-CH_2–5''-CH_2), 2.50-2.61 (m, 1H, 6-CH_{ax}N), 2.78 (dq, J_1=6Hz, J_2=1.5Hz, 1H, 2-CH_{ax}N), 3.44-3.54 (m, 1H, 1H at 6''-CH_2), 3.56 (sb, 1H, 3-CH_{eq}O), 3.66-3.83 (m, 1H, 11'-CHO), 3.86-3.97 (m, 1H, 1H at 6''-CH_2), 4.63, 4.71 (2m, 1H, 2''-CH) ppm; ^{13}C NMR (50MHz, $CDCl_3$): δ= 19.10, 21.59 (12'-CH_3), 18.64 (2-C$\underline{C}H_3$), 19.79, 20.10 (CH_2), 25.49, 25.57, 25.62, 25.82, 26.09 (CH_2), 29.59, 29.75, 29.80 (CH_2), 31.26, 32.06 (CH_2), 36.55, 36.94, 37.58 (CH_2), 55.88 (6-CHN), 57.30 (2-CHN), 62.46, 62.81 (6''-CH_2), 67.95 (3-CHO), 71.20, 73.92 (11'-CHO), 95.67, 98.59 (2''-CH) ppm; IR (neat): 3436 b, 2927, 2854, 1133, 1078, 1023, 995 cm^{-1}; MS (80°C): m/e= 383 (3, M^+), 368 (1), 339 (1), 323 (2), 282 (25), 267 (3), 119 (6), 114 (100), 85 (23); HRMS: calc. for $C_{23}H_{45}NO_3$: 383.3399; found: 383.3384; $[\alpha]_D^{20}$= -3.94° (c= 0.99, $CHCl_3$; mixture of diastereomers).

(2*R*,3*R*,6*S*,11'*S*)-6-(11'-Hydroxy-dodecyl)-2-methyl-piperidine-3-ol [(–)-(11'*S*)-carnavaline] (2*R*,3*R*,6*S*,11'*S*)-1. 1.20 g (3.1mmol) (2*R*,3*R*,6*S*,11'*S*)-**20** were dissolved in 30ml MeOH and 4.6ml 2N HCl and refluxed for one hour. The pH of the solution was increased to 8-9 by the addition of 5ml 2N NaOH. The MeOH was removed under reduced pressure, 20ml water were added to the remaining residue and the aqueous layer was extracted with DCM three times. The combined extracts were dried over $MgSO_4$, the solvent was evaporated and the crude product was purified by column chromatography followed by crystallization from MTB-ether to yield 888mg (96%) (–)-(11'*S*)-carnavaline (2*R*,3*R*,6*S*,11'*S*)-**1** as white crystals. ^1H NMR (400MHz, $CDCl_3$): δ= 1.10 (d, J=6.6Hz, 3H, 2-CC$\underline{H}_3$), 1.18 (d, J=6Hz, 3H, 12'-CH_3), 1.22-1.54 (m, 23H, 4-CH_{ax}, 5-CH_2, 1'-CH_2–10'-CH_2), 1.86-1.93 (m, 1H, 4-CH_{eq}), 2.48-2.56 (m, 1H, 6-CH_{ax}N), 2.76 (dq, J_1=6.6Hz, J_2=1.5Hz, 1H, 2-CH_{ax}N), 3.54 (sb, 1H, 3-CH_{eq}), 3.78 (m, 1H, 11'-CHO) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ= 18.77 (2-C$\underline{C}H_3$), 23.50 (12'-CH_3), 25.77 (CH_2), 25.81, 26.22 (2×CH_2), 29.55, 29.58, 29.63, 29.80 (6×CH_2), 32.11 (4-CH_2), 37.08 (1'-CH_2), 39.38 (10'-CH_2), 55.77 (6-CHN), 57.21 (2-CHN), 68.03, 68.04 (3-CHO, 11'-CHO) ppm; IR ($CHCl_3$): 3616, 3364 b, 2928, 2856, 1600, 1464, 1380, 1320, 1240, 1120, 1008, 964 cm^{-1}; MS (60°C): m/e= 299 (1, M^+), 284 (3), 267 (1), 240 (2), 140 (1), 114 (100), 96 (6); HRMS: calc. for $C_{18}H_{37}NO_2$: 299.2824; found: 299.2834; Analysis: calc.: C 72.19 H 12.45 N 4.68; found: C 71.83 H 12.17 N 4.84; m.p.: 63.5°C; $[\alpha]_D^{20}$= -5.63° (c= 0.675, $CHCl_3$).

(*R*)-12-(Tetrahydropyran-2'-yloxy)-dodecane-2-ol (*R*)-13. $[\alpha]_D^{20}$= -5.37° (c=1.005, $CHCl_3$; mixture of diastereomers).

(*R*)-1,11-Dodecanediol (*R*)-14. $[\alpha]_D^{20}$= -6.21° (c= 1.03, $CHCl_3$).

(*R*)-12-Bromo-dodecane-2-ol (*R*)-15. $[\alpha]_D^{20}$= -4.82° (c= 1.12, $CHCl_3$).[9]

(*R*)-1-Bromo-11-(tetrahydropyran-2'-yloxy)-dodecane (*R*)-2. $[\alpha]_D^{20}$= -5.78° (c= 1.09, $CHCl_3$; mixture of diastereomers).

(4*R*,5*R*,14'*R*)-3-Benzyl-5-[3'-hydroxy-14'-(tetrahydropyran-2''-yloxy)-pentadecyl]-4-methyl-2-oxazolidinone (4*R*,5*R*,14'*R*)-16. $[\alpha]_D^{20}$ = +48.22° (c= 1.095, $CHCl_3$; mixture of diastereomers).

(4*R*,5*R*,14'*R*)-5-[3'-Hydroxy-14'-(tetrahydropyran-2''-yloxy)-pentadecyl]-4-methyl-2-oxazolidinone (4*R*,5*R*,14'*R*)-17. $[\alpha]_D^{20}$ = +24.82° (c= 0.995, $CHCl_3$; mixture of diastereomers).

(4*R*,5*R*,14'*R*)-4-Methyl-5-[3'-oxo-14'-(tetrahydropyran-2''-yloxy)-pentadecyl]-2-oxazolidinone (4*R*,5*R*,14'*R*)-18. $[\alpha]_D^{20}$ = +32.64° (c= 1.10, $CHCl_3$; mixture of diastereomers).

(2*R*,3*R*,6*S*,11'*R*)-2-Methyl-6-[11'-(tetrahydropyran-2''-yloxy)-dodecyl]-piperidine-3-ol (2*R*,3*R*,6*S*,11'*R*)-20. $[\alpha]_D^{20}$ = -13.71° (c= 0.795, $CHCl_3$; mixture of diastereomers).

(2*R*,3*R*,6*S*,11'*R*)-6-(11'-Hydroxy-dodecyl)-2-methyl-piperidine-3-ol [(–)-(11'*R*)-carnavaline] (2*R*,3*R*,6*S*,11'*R*)-1. m.p.: 72°C; $[\alpha]_D^{20}$ = -14.71° (c= 1.14, $CHCl_3$).

(2*R*,3*R*,6*S*,11'*RS*)-6-(11'-Hydroxy-dodecyl)-2-methyl-piperidine-3-ol (2*R*,3*R*,6*S*,11'*RS*)-22. Method A: 45mg (–)-(2*R*,3*R*,6*S*)-Cassine[4] (0.15mmol, 1eq) were dissolved in 2ml dry THF under nitrogen. Under magnetical stirring 1ml (1.00mmol, 7eq) BH_3 · THF was added at -30°C. Stirring was continued for 30min then the solution was allowed to warm to RT and was stirred for further 1.5h. The reaction was quenched by the addition of 4ml 2N HCl and stirred for 2h at 0°C. The solution was made alkaline with 5ml 2N NaOH and extracted with Et_2O three times. The organic layers were combined, dried over $MgSO_4$, the solvent removed under reduced pressure and the residue purified by column chromatography to afford 41mg (91%) (2*R*,3*R*,6*S*,11'*RS*)-**22** as white crystals. m.p.: 60°C; $[\alpha]_D^{20}$ = -9.76° (c= 0.82, $CHCl_3$).

(2R,3R,6S,11'*RS*)-6-(11'-Hydroxy-dodecyl)-2-methyl-piperidine-3-ol (2*R*,3*R*,6*S*,11'*RS*)-22. Method B: 50mg (–)-(2R,3R,6S)-Cassine[4] (0.17mmol, 1eq) were dissolved in 2ml isopropanol and treated with 6mg (0.17mmol, 1eq) $NaBH_4$ and stirred for 2h. The reaction was quenched with 1ml 2N HCl at 0°C for 30min. The mixture was made alkaline by the addition of 1.5ml 1N NaOH and was extracted with Et_2O three times. The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuum. After column chromatography 45mg (90%) (2*R*,3*R*,6*S*,11'*RS*)-**22** were obtained as white crystals. m.p.: 58°C; $[\alpha]_D^{20}$ = -8.93° (c= 0.84, $CHCl_3$).

References And Notes

1. (a) Lythgoe, D.; Vernengo, M.J.; *Tetrahedron Lett.* **1967**, 1133. (b) Bolzani, V.d.S.; Gunatilaka, A.A.L.; Kingston, D.G.I.; *Tetrahedron* **1995**, 51(21), 5929.
2. (a) Strunz, G.M.; Findlay, J. A. in: *The Alkaloids*; Brossi, A., Ed; Academic Press: New York **1985**; Vol.26, 89. (b) Wang, C.-L.J.; Wuonola, M.A.; *Org. Prep. Proc. Int.* **1992**, 24, 585. (c) Pinder, A.R.; *Nat. Prod. Rep.* **1992**, 9, 17. (d) Pinder, A.R.; *Nat. Prod. Rep.* **1992**, 9, 491.
3. For enantioselective reduction of ketones with BH_3 and chiral 1,2-aminoalcohols see e.g.: Corey, E.J.; Bakshi, R.K; Shibata, S.; *J. Am. Chem. Soc.* **1987**, 109, 5551.
4. Meyer, H.H.; Holzkamp, J.; Oetting, J.; Pahl, A.; *Tetrahedron Asymm.* **1997**, 8(3), 477.

5. No sign of decomposition appeared after storage for 1 year under nitrogen at -16°C.
6. Camps, F.; Casamor,. J.M.; Coll, J.; Guerrero, A.; Riba, M.; *Org. Prep. Proc. Int.* **1983**, 15(1-2), 63.
7. (*S*)- and (*R*)-propylene oxide were purchased from Fluka.
8. Quinkert, G.; Fernholz, E.; Eckes, P.; Neumann, D.; Dürner, G.; *Helv. Chim. Acta* **1989**, 72, 1753.
9. The absolute values of the optical rotations of (*S*)-**15** and enantiomeric (*R*)-**15** were not identical, probably due to an optically active impurity. The enantiomeric purity of **2** was therefore confirmed via Mosher esters of **15** and by shift experiments with (+)-Eu(hfc)$_3$ of the acetates of **15**, and was determined to be higher than 98% ee.
10. Due to the risk resulting from the possible presence of peroxides.
11. Quinkert, G.; Billhardt, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J.W.; Dürner, G.; Zimmermann, G.; Kessler, H.; *Helv. Chim. Acta* **1987**, 70, 771.
12. Cook, W.; Miller, R.G.J.; Todd, P.F.; *J. Organomet. Chem.* **1969**, 19, 421.
13. Baldwin, J.E; Adlington, R.M; Ramcharitar, S.H.; *Tetrahedron* **1992**, 48(16), 3413.

(*Received in Germany* 6 *January* 1997; *revised* 14 *April* 1997; *accepted* 15 *April* 1997)