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Synthesis of (±)-Tetrahydromyricoidine

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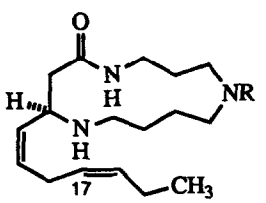
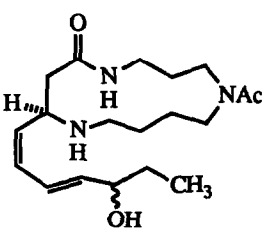
Abstract: A total synthesis of the spermidine alkaloid (±)-tetrahydromyricoidine (**6**) was achieved by using two ring enlargement reactions. The difficulties experienced in the second ring enlargement step, a transamidation reaction with a medium ring sized lactam bearing two bulky groups are discussed. These were overcome by altering the reaction sequence and the transamidation reaction was successfully carried out by at first deprotection of the Boc function.

Introduction

(+)-Loesenerine (**1**), (+)-17,18-didehydroloesenerine (**2**), and (+)-16,17-didehydroloesenerine-18-ol (**3**) were isolated from the leaves of *Maytenus loeseneri* Urb. (Celastraceae)[1,2] in 1987 and 1988. (+)-Myricoidine (**4**) together with (+)-dihydromyricoidine (**5**) were isolated from *Clerodendrum myricoides* (Verbenaceae)[3] in 1988. The five alkaloids contain 13-membered lactam rings and are structurally related to that of palustrine,[4] differing only in the arrangement of the spermidine chain within the lactam ring. Their structures had been elucidated mainly by spectroscopic methods and partly by chemical reactions. (+)-Myricoidine (**4**) and its dihydro derivative **5** were correlated with (+)-tetrahydromyricoidine by hydrogenation.[3] The absolute configuration at C(13) was assigned to be (*R*) initially by comparing the optical rotation of (+)-**1** with that of (*R*)-(+)-3-methoxy-1-butene.[1]



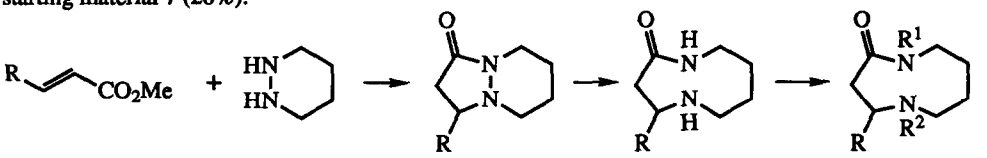
R = Ac, 17,18 = H,H (+)-loesenerine (**1**)
R = Ac (+)-17,18-didehydroloesenerine (**2**)
R = H (+)-myricoidine (**4**)
R = H, 17,18 = H, H (+)-dihydromyricoidine (**5**)



(+)-16,17-didehydroloesenerine-18-ol (**3**)

Results and Discussion

The synthesis of the alkaloid (±)-tetrahydromyricoidine (**6**) was done starting from the lactam **7** by two ring enlargement reactions. For the construction of the bicyclic lactam the method of *Wasserman* and co-workers[5] was used. This method includes conjugate addition of perhydropyridazine (**8**) to an α,β-unsaturated ester to give the bicyclic product. Thus, treatment of methyl (*E*)-2-decenoate (**9**)[6] with **8**[7,8] by heating in toluene for 30 h gave 9-heptyl-1,6-diazabicyclo[4.3.0]nonan-7-one (**7**) in a yield of 91%. The cleavage of the bridging N-N bond of the bicyclic compound with sodium in liquid ammonia has been carried out according to the method of *Kemp* and co-workers.[9] Compound **10** was thus obtained in 62% yield along with recovered starting material **7** (20%).[10]



9 **8** **7** **10**

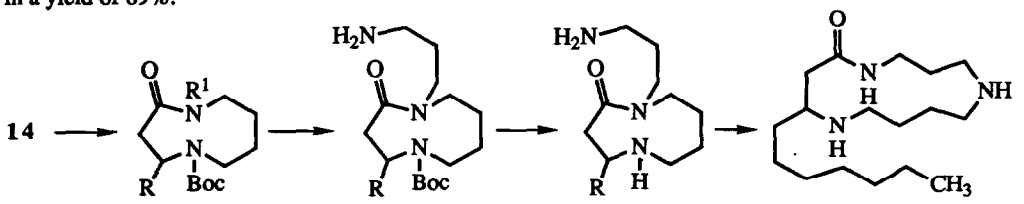
11 $R^1 = R^2 = Ac$
12 $R^1 = H$; $R^2 = Ac$
13 $R^1 = H$; $R^2 = Ts$
14 $R^1 = H$; $R^2 = Boc$

R = -$(CH_2)_6$Me

Scheme 1. First ring enlargement.

Attempts to protect the secondary amino group in lactam **10** by treatment with Ph_3CCl failed. This is probably due to the bulkiness of the triphenylmethyl group, which could no more be attached to the substituted medium sized ring. In order to characterize compound **10**, it was acetylated under standard reaction conditions. Thus, treatment of lactam **10** with acetic anhydride in the presence of pyridine at room temperature for 30 h brought the di-acetylated product **11**, and when lactam **10** was exposed under the same condition but for a shorter time (5 h) only the mono-acetylated product was formed in a yield of 86%. Tosylation of lactam **10** with TsCl the mono-tosylated compound **13** was obtained in 50% yield only, besides decomposition products.

The amino group in lactam **10** could be successfully protected by the Boc group.[11,12] Thus, treatment of lactam **10** with Boc_2O in the presence of catalytic amounts of 4-(dimethylamino)-pyridine afforded compound **14** in a yield of 89%.



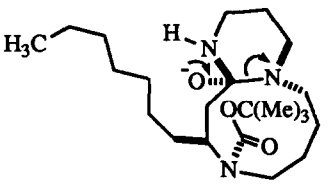
15 $R^1 = -(CH_2)_3NPhth$ **16** **18** (±)-**6**
17 $R^1 = -(CH_2)_2CN$

R = -$(CH_2)_6$Me

Scheme 2. Second ring enlargement.

To introduce the C_3-amino moiety at N(1) of compound **14**, required for the second ring enlargement step, we used two procedures. Treatment of lactam **14** with NaH followed by addition of *N*-(3-bromopropyl)-phthalimide[13] gave the tertiary amide **15** (38%) along with considerable recovered precursor **14** (46%). Removal of the phthalimide with ethanolic hydrazine generated the triamine **16** in a yield of 86%. Being aware of the Boc function labile towards acidic conditions, *Eschenmoser* basic work-up procedure[14,15] was used.

Alternatively, treatment of the sodium salt of lactam **14** with acrylonitrile, followed by catalytic reduction of the nitrile function in compound **17**, gave also the amine **16**. Because of the labile Boc function again acidic conditions were avoided in the hydrogenation steps,[16] and NH_4OH in EtOH was used as solvents. Although the yield of the reduction step was too low, only 42%, the alkylation of amide went nearly quantitatively. The overall yield was better than that of using the first method (42% to 33%, without considering the recovered starting material).



The suggested transition state for ring enlargement of **16**

With the compound **16** in hand, we tried to use the normal basic ring enlargement conditions, but treatment of **16** with refluxing 2,4-lutidine afforded no ring enlargement product, only slow decomposition of starting material was observed by means of TLC. It seems reasonable to assume that the *n*-heptyl and the Boc groups are in *trans* relationship to each other, so that both faces of the important amide function suffer steric shielding by *n*-heptyl and Boc.

Once this was recognized, we considered the possibility to remove the Boc function first and enlarge the ring afterwards. Deprotection of the secondary amine leading to **18** was readily accomplished upon exposuring of compound **16** to TFA. The synthesis of the target molecule (±)-tetrahydromyricoidine (**6**) was now performed as follows: treatment of **16** with TFA at 20° for 10 min, evaporation of the TFA, the residue was dissolved in 2,4-lutidine and the solution for 1.5 h refluxed to give **6** in yield of 62%. The ^{1}H-NMR and mass spectra of synthetic (±)-**6** were identical with those reported in the literature.[3] Enantioselective synthesis of naturally occurring spermidine alkaloids of this (+)-loesenerine type are in progress.[17]

EXPERIMENTAL

General Procedure : Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Merck silica gel 60 (0.04 - 0.06 mm) was used for column chromatography. Merck-Si_{F254} pre-coated aluminium plates were used for TLC. Glass sheets (*Merck*)were used for preparative TLC. Melting points were measured on a *Mettler FP-52* apparatus. IR spectra, in cm^{-1}, were recorded on a *Perkin Elmer-781* spectrophotometer. ^{1}H-NMR measurements were carried out on a *Bruker AM-300* (300 MHz) or, as stated, on a *Bruker AM-400* (400 MHz). ^{13}C-NMR measurements were carried out on a *Varian*

XL-200 (50 MHz). Chemical shifts are given in ppm (J in Hz) relative to the deuterated solvents used. EI-MS (70 eV) and CI-MS (NH_3 or isobutane, 150 eV) data, given in m/z (rel. %), were measured on a *Varian MAT 112S* or a *Finnigan MAT 90* mass spectrometer.

Synthesis of Methyl(Ethyl) (*E*)-2-Decenoate.

(E)-2-Decenic acid (**19**).[6] Octanal (20 g, 0.156 mol) gave 21 g of **19** (0.156 mol, 79%) as a colorless liquid of b.p. 98°/0.075 mm. IR (film): 3500-2500 (*br.*), 1698, 1650, 1460, 1420, 1308, 1285, 1224, 980, 938. ^{1}H-NMR ($CDCl_3$): 13.0-8.0 (*br.*, OH, D_2O exchangeable); 7.08 (*td*, J=7.0, 15.5, H-C(3)); 5.82 (*td*, J=1.5, 15.5, H-C(2)); 2.23 (*dq*, J=1.5, 7.0, 2H-C(4)); 1.47 (*quint.*, J=7.2, 2H-C(5)); 1.40-1.20 (*m*, 8H); 0.88 (*t*, J=7.2, CH_3). CI-MS: 172 (50), 171 (100, $[M+1]^+$), 153 (34).

Methyl (E)-2-decenoate (**9**). To a solution of **19** (15.26 g, 89.6 mmol) in 10 ml benzene was added $SOCl_2$ (10 ml). After the mixture had been heated for 2 h under reflux, it was evaporated, dry MeOH (20 ml) added dropwise to the ice bath cooled residue and the solution then heated to reflux for 30 min. The solvent was removed in vacuo and the residue was distilled to give 14.85 g of **9** (80.6 mmol, 90%) as a colorless liquid of b.p. 126-8°/15 mm. IR (film): 2930, 2855, 1728, 1658, 1460, 1435, 1312, 1270, 1196, 1169, 1128, 1040, 980. ^{1}H-NMR ($CDCl_3$): 6.97 (*td*, J=7.0, 15.5, H-C(3)); 5.81 (*td*, J=1.5, 15.5, H-C(2)); 3.72 (*s*, CH_3); 2.19 (*dq*, J=1.5, 7.0, 2H-C(4)); 1.44 (*quint.*, J=7.3, 2H-C(5)); 1.38-1.20 (*m*, 8H); 0.87 (*t*, J=7.3, CH_3). GC/MS(CI, NH_3): 202 (100, $[M+18]^+$), 185 (10, $[M+1]^+$).

Ethyl (E)-2-decenoate (**20**). Reaction was carried out as described as in **9** to give **20** (90%) as a colorless liquid of b.p. 130-2°/15 mm. IR ($CHCl_3$): 2930, 2855, 1710, 1652, 1465, 1370, 1305, 1275, 1185, 1128, 1035, 980. ^{1}H-NMR ($CDCl_3$): 6.96 (*td*, J=7.0, 15.5, H-C(3)); 5.80 (*td*, J=1.5, 15.5, H-C(2)); 4.17 (*q*, J=7.1, OCH_2); 2.18 (*dq*, J=1.5, 7.0, 2H-C(4)); 1.44-1.48 (*m*, 2H-C(5)); 1.35-1.20 [*m*, 11H, where 1.28 (*t*, J=7.1, OCH_2CH_3)]; 0.87 (*t*, J=7.0, CH_3). EI-MS: 199 (47, $[M+1]^+$), 153 (72), 142 (20), 139 (18), 127 (45), 123 (45), 115 (22), 110 (48), 99 (63), 88 (42), 81 (46), 73 (63), 69 (68), 55 (77), 43 (98), 41 (100).

Synthesis of Perhydropyridazine (8).[7,8]

1,2-Bis(ethoxycarbonyl)-1,2,3,6-tetrahydropyridazine (**21**). Diethyl azodicarbooxylate (113 g, 649 mmol) gave 144 g of **21** (630 mmol, 97%) by *Diels-Alder* reaction a colorless oil of b.p. 87°/0.1 mm. IR (film): 3048, 2980, 2910, 2858, 1710, 1468, 1420, 1378, 1343, 1274, 1228, 1212, 1172, 1148, 1120, 1072, 1025, 758. ^{1}H-NMR ($CDCl_3$): 5.79 (*s*, H-C(4), H-C(5)); 4.43 (*br.*, H-C(3), H-C(6)); 4.19 (*m*, $2OCH_2$); 3.81 (*br.*, H-C(3), H-C(6)); 1.26 (*t*, J=7.0, $2CH_3$). CI-MS: 230 (16), 229 (100, $[M+1]^+$), 197 (3), 183 (5).

1,2-Bis(ethoxycarbonyl)-perhydropyridazine (**22**). Compound **21** (58.7 g, 257 mmol) gave 58.6 g of **22** (254 mmol, 99%) by hydrogenation with Pt_2O as catalysator as a colorless oil of b.p. 95°/0.08 mm. IR (film): 2980, 2940, 2860, 1717, 1468, 1450, 1420, 1380, 1350, 1257, 1186, 1140, 1058, 758. ^{1}H-NMR ($CDCl_3$): 4.20-4.00 (*m*, $2OCH_2$, H-C(3), H-C(6)); 2.85 (*br.*, H-C(3), H-C(6)); 1.65-1.50 (*br.*, 2H-C(4), 2H-C(5)); 1.19 (*m*, $2CH_3$). CI-MS: 232 (19), 231 (100, $[M+1]^+$), 230 (6).

1,2-Bis(isopropoxycarbonyl)-1,2,3,6-tetrahydropyridazine (**23**). Diisopropyl azodicarboxylate (38.8 g, 0.192 mol) gave 43.9 g of **23** (0.171 mol, 89%) by *Diels-Alder* reaction as a colorless oil of b.p. 102°/0.075 mm. IR ($CHCl_3$): 2982, 2935, 1715, 1468, 1408, 1388, 1375, 1308, 1182, 1148, 1108, 1070, 1048, 930. ^{1}H-NMR ($CDCl_3$): 5.78 (*s*, H-C(4), H-C(5)); 4.96 (*quint*, J=6.2, $2CH$); 4.43 (*br.*, H-C(3), H-C(6)); 3.77 (*br.*, H-C(3), H-C(6)); 1.25 (*t*, J=6.2, $4CH_3$). CI-MS: 258 (14), 257 (100, $[M+1]^+$), 171 (6), 170 (12).

1,2-Bis(isopropoxycarbonyl)-perhydropyridazine (**24**). Compound **23** (24.1 g, 94.0 mmol) gave 23.1 g of **24** (89.3 mmol, 95%) by hydrogenation with Pt_2O as catalysator as a colorless oil of b.p. 98°/0.055 mm. IR ($CHCl_3$): 2982, 2940, 2870, 1700, 1470, 1454, 1410, 1387, 1260, 1195, 1182, 1144, 1110, 1055, 930. ^{1}H-NMR ($CDCl_3$): 4.95 (*m*, 2C*H*); 4.25-4.05 (*br.*, H-C(3), H-C(6)); 3.10-2.80 (*br.*, H-C(3), H-C(6)); 1.75-1.60 (*m*, 2H-C(4), 2H-C(5)); 1.19 (*m*, 4CH_3). CI-MS: 260 (14), 259 (100, $[M+1]^+$), 258 (7), 173 (13), 172 (8).

Perhydropyridazine (**8**). Compound **23** (40.0 g, 156 mmol) per **24** in two steps gave 11.7 g of **8** (136 mmol, 87%) as a colorless liquid of b.p. 40-45°/15 mm. ^{1}H-NMR (C_6D_6): 2.55 (*m*, 2H-C(3), 2H-C(6)); 1.24 (*m*, 2H-C(4), 2H-C(5)). ^{1}H-NMR (CD_3OD): 2.73 (*m*, 2H-C(3), 2H-C(6)); 1.52 (*m*, 2H-C(4), 2H-C(5)). GC/MS(EI): 87 (6), 86 (100, M^+), 85 (10), 57 (1).

Perhydropyridazine hydrochloride (**8**·HCl). ^{1}H-NMR (CD_3OD): 2.13 (*s*, 2H-C(3), 2H-C(6)); 1.80 (*s*, 2H-C(4), 2H-C(5)). ^{1}H-NMR (CD_3SOCD_3): 11.0-8.5 (*br.*, 2N*H*); 2.48 (*s*, 2H-C(3), 2H-C(6)); 1.65 (*s*, 2H-C(4), 2H-C(5)). ^{13}C-NMR (CD_3OD): 46.9 , 22.8 (2*t*, 4CH_2). EI-MS: 86 (100, M^+, free base), 57 (83), 36 (94).

9-Heptyl-diazabicyclo[4.3.0]nonan-7-one (**7**). A solution of **9** (2.00 g, 10.85 mmol) und **8** (1.80 g, 20.90 mmol) in 8 ml toluene was heated to reflux for 30 h under an argon atmosphere. It was concentrated in vacuo and the oil thus obtained was chromatographed (Et_2O/hexane 1:1; then Et_2O/EtOH/NH_4OH (25%) 50:2:1) to give in addition of 0.12 g of **9** (0.65 mmol, 6%) 2.35 g of **7** (9.87 mmol, 91%) as a pale yellow oil. IR ($CHCl_3$): 3000, 2930, 2860, 1673, 1450, 1420, 1270, 1184. ^{1}H-NMR (400 MHz, $CDCl_3$; assignment according to the decoupling experiments): 4.09 (*br.*, H_a-C(5)); 3.13 (*br.*, H-C(9)); 2.82 (*br.*, H_b-C(5), H_a-C(2)); 2.68 (*dd*, *J*=8.5, 16.4, H_a-C(8)); 2.28 (*br.*, H_b-C(2)); 2.14 (*ddd*, *J*=1.3, 9.2, 16.4, H_b-C(8)); 1.85-1.55 (*m*, 4H); 1.50-1.10 (*m*, 12H); 0.87 (*t*, *J*=6.8, CH_3). ^{13}C-NMR ($CDCl_3$): 168.6 (*s*, C(7)); 62.5 (*s*, C(9)); 55.8, 41.3, 36.3, 33.5, 31.5, 29.3, 28.9, 25.8, 23.9, 22.8, 22.4 (11*t*, 11CH_2); 13.8 (*q*, CH_3). EI-MS: 238 (15, M^+), 139 (100), 111 (5), 85 (4), 56 (7). Anal. calc. for $C_{14}H_{26}N_2O$ (238.37): C 70.54, H 11.00, N 11.76; found: C 70.68, H 11.12, N 11.99.

4-Heptyl-1,5-diazacyclononan-2-one (**10**). Dry NH_3 (ca. 20 ml) was condensed in a three-necked flask containing 2.00 g of **7** (8.39 mmol). Sodium metal was added to the mixture at stirring and refluxing until a permanent blue color develops. NH_4Cl was added carefully, and the solvent was evaporated, the residue was extracted with Et_2O, and the solution filtered. The product obtained by evaporation of the solvent was purified by column chromatography ($CHCl_3$/acetone/NH_4OH (25%) 200:4:0.1) to give 0.40 g of **7** (1.68 mmol, 20%) und 1.26 g of **10** (5.26 mmol, 63%; or 78% based on converted starting material) as a solid. A sample was crystallized from hexane as colorless crystals of m.p. 49.5-50.5° for analysis. IR (KBr): 3380, 3305, 2950, 2920, 2855, 1645, 1550, 1445, 1358, 1330, 1178, 1148, 810, 752. ^{1}H-NMR ($CDCl_3$): 6.91 (*d*, *J*=9.8, H-N(1)); 3.74-3.61 (*m*, H_a-C(9)); 2.90-2.65 (*br.*, H_a-C(6), H-N(5), H-C(4)); 2.48 (*br.*, H_b-C(9)); 2.20 (*dd*, *J*=2.5, 11.7, H_a-C(3)); 1.94 (*t*, *J*=11.7, H_b-C(3)); 1.88 (*br.*, H_b-C(6)); 1.65-1.20 (*br.*, 16H); 0.88 (*t*, *J*=6.7, CH_3). ^{13}C-NMR ($CDCl_3$): 176.7 (*s*, C(2)); 57.0 (*s*, C(4)); 51.6, 45.6, 40.0, 38.2, 31.5, 29.3, 29.0, 28.9, 25.9, 25.7, 22.3 (11*t*, 11CH_2); 13.8 (*q*, CH_3). CI-MS (isobutane): 242 (15), 241 (100, $[M+1]^+$), 240 (4), 182 (4), 169 (3). Anal. calc. for $C_{14}H_{28}N_2O$ (240.39): C 69.95, H 11.74, N 11.66; found: C 70.05, H 12.00, N 11.41.

1,5-Diacetyl-4-heptyl-1,5-diazacyclononan-2-one (**11**). In dry pyridine (2 ml) 72 mg of **10** (0.30 mmol) were acetylated with Ac_2O (2 ml) for 30 h at room temperature. A sample of **11** was purified for analysis by preparative silica plates chromatography (Et_2O/acetone). IR ($CHCl_3$): 3000, 2930, 2860, 1690, 1632, 1446, 1422, 1370, 1338, 1280, 1260, 1190, 1162, 980, 910. ^{1}H-NMR ($CDCl_3$): 4.30-2.00 [*br. m*, 13H, where 2.44 (*s*,

CH_3CO-N(5)); 2.17 and 2.11 (2*s*, CH_3CO-N(1))]; 1.90-1.45 (*br. m*, 6H); 1.37-1.17 (*br.* 10H); 0.88 (*t*, *J*=6.7, CH_3). EI-MS: 324 (6, M^+), 281 (34), 253 (5), 239 (11), 225 (32), 207 (10), 183 (36), 124 (39), 70 (21), 43 (100).

5-Acetyl-4-heptyl-1,5-diazacyclononan-2-one (**12**). In dry pyridine (1 ml) 50 mg of **10** (0.21 mmol) were acetylated with Ac_2O (1 ml) for 5 h at room temperature. The residue left after evaporation was purified by column chromatography (Et_2O/acetone from 1:1 to 0:1) to afford 51 mg of **12** (0.18 mmol, 86%). IR ($CHCl_3$): 3395, 3000, 2930, 2860, 1640, 1518, 1468, 1445, 1368, 1240. ^{1}H-NMR ($CDCl_3$): 6.38-5.18 (*br. m*, H-N(1)); 4.28-2.03 [*br. m*, 10H, where 2.13, 2.11 and 2.08 (3*s*, $COCH_3$)]; 1.93-1.43 (*br. m*, 6H); 1.28-1.08 (*br. m*, 10H); 0.84 (*m*, CH_3). EI-MS: 282 (5, M^+), 239 (66), 212 (7), 197 (8), 183 (51), 169 (30), 157 (14), 141 (71), 70 (98), 43 (100).

4-Heptyl-5-tosyl-1,5-diazacyclononan-2-one (**13**). To a solution of **10** (104 mg, 0.44 mmol) in dry CH_3CN (2 ml) was added 106 mg of TsCl (0.56 mmol), 15 mg of 4-(dimethylamino)-pyridine (0.12 mmol), and 95 mg of K_2CO_3 (0.687 mmol). After stirring for 36 h at room temperature, the mixture was filtered. The residue after evaporation was purified by column chromatography (Et_2O/MeOH 30:1) to give 86 mg of **13** (0.22 mmol, 50%). IR ($CHCl_3$): 3420, 3390, 3000, 2930, 2860, 1660, 1523, 1468, 1335, 1238, 1155, 1090, 920, 850, 810 ^{1}H-NMR ($CDCl_3$): 7.75-7.65 (*m*, 2 arom. *H*); 7.35-7.25 (*m*, 2 arom. *H*); 5.90 and 5.40 (2*s*, CON*H*); 4.00-2.10 [*br. m*, 10H, where 2.42 and 2.43 (2*s*, arom. CH_3)]; 2.00-1.45 (*br. m*, 7H); 1.25-0.90 (*br. m*, 9H); 0.84 (*t*, *J*=6.6, CH_3). CI-MS: 395 (100, $[M+1]^+$), 239 (21), 157 (22), 142 (7).

*5-(*tert*-Butoxycarbonyl)-4-heptyl-1,5-diazacyclononan-2-one* (**14**). To a solution of **10** (866 mg, 3.60 mmol) in dry CH_3CN (1 ml) was added 88 mg of 4-(dimethylamino)-pyridine (0.72 mmol) and 950 mg of Boc_2O (4.35 mmol). After stirring for 48 h at room temperature, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc) to give 1.10 g of **14** (3.22 mmol, 89.3%). IR ($CHCl_3$): 3430, 3395, 3000, 2935, 2860, 1675, 1520, 1470, 1434, 1370, 1330, 1272, 1254, 1165. ^{1}H-NMR ($CDCl_3$): 5.40-4.70 (*br. m*, H-N(1)); 3.50-2.40 (*br. m*, 5H); 2.35-1.35 [*m*, 17H, where 1.49 and 1.47 (2*s*, 3CH_3)]; 1.34-1.15 (*br. m*, 10H); 0.87 (*t*, *J*=6.6, CH_3). EI-MS: 340 (0.6, M^+), 284 (7), 267 (3), 240 (16), 212 (5), 197 (13), 185 (15), 169 (100). Anal. calc. for $C_{19}H_{36}N_2O_3$ (340.50): C 67.02, H 10.66, N 8.23; found: C 66.85, H 10.68, N 8.24.

Synthesis of 1-(3-Aminopropyl)-5-(*tert*-butoxycarbonyl)-4-heptyl-1,5-diazacyclononan-2-one (16).

Method 1: *5-(*tert*-Butoxycarbonyl)-4-heptyl-1-(3-phthalimidopropyl)-1,5-diazacyclononan-2-one* (**15**). The amount of 87 mg of NaH (55% in oil; 1.93 mmol) was added to dry DMF (7 ml) containing 598 mg of **14** (1.76 mmol). The mixture was stirred for 40 min at room temperature, a solution of *N*-(3-brompropyl)-phthalimide (472 mg, 1.76 mmol) in dry DMF (6 ml) was added dropwise, and it was stirred for another 2.5 h at room temperature. The residue left after evaporation of the solvent was purified by column chromatography (Et_2O) to give 274 mg of **14** (46%) and 354 mg of **15** (0.67 mmol, 38%, or 70% based on convented starting material; first eluted): IR ($CHCl_3$): 3000, 2935, 2860, 1775, 1715, 1682, 1625, 1470, 1435, 1400, 1370, 1344, 1288, 1255, 1164, 1030, 892. ^{1}H-NMR ($CDCl_3$): 7.84 (*m*, 2 arom. *H*); 7.72 (*m*, 2 arom. *H*); 4.30-2.70 (*br. m*, 9H); 2.40-1.65 (*br. m*, 6H); 1.60-1.20 [*m*, 23H, where 1.49 and 1.47 (2*s*, 3CH_3)]; 0.88 (*t*, *J*=6.7, CH_3). CI-MS:

528 (46, $[M+1]^+$), 472 (100), 428 (57). Anal. calc. for $C_{30}H_{45}N_3O_5$ (527.68): C 68.28, H 8.60, N 7.96; found: C 68.26, H 8.40, N 7.85%.

*1-(3-Aminopropyl)-5-(*tert*-butoxycarbonyl)-4-heptyl-1,5-diazacyclononan-2-one* (**16**). To a solution of **15** (331 mg, 0.62 mmol) in 8 ml of EtOH was added 270 mg of $N_2H_4 \cdot H_2O$ (5.39 mmol) and the solution was heated to reflux for 1 h. Then cooled (ice bath), the solution was diluted with 250 ml of Et_2O, and then NH_4OH (25%) was added dropwise until the precipitate dissolved. The solution was washed with H_2O (3 x 60 ml) and the H_2O layer was extracted with Et_2O (2 x 100 ml). The combined organic layers were dried over K_2CO_3 and evaporated. The residue was purified by column chromatography (Et_2O/EtOH/NH_4OH (25%) 20:10:1) to give 215 mg of **16** (0.54 mmol, 86%). IR ($CHCl_3$): 3380, 3000, 2930, 2860, 1680, 1620, 1465, 1370, 1344, 1288, 1250, 1164, 895, 860. ^{1}H-NMR ($CDCl_3$): 4.30-1.35 [*br. m*, 30H, where 2.67 (*dt*, *J*=2.2, 6.6, C*H*$_2$N); 1.67 (*quint.*, *J*=6.9, C*H*$_2$); 1.49 and 1.47 (2*s*, 3C*H*$_3$)]; 1.34-1.15 (*br. m*, 10H); 0.88 (*m*, C*H*$_3$). CI-MS: 398 (100, $[M+1]^+$), 384 (9), 382 (7), 343 (11), 342 (57), 298 (60), 211 (28), 171 (35), 153 (15). Anal. calc. for $C_{22}H_{43}N_3O_3$ (397.58): C 66.46, H 10.90, N 10.57; found: C 66.30, H 11.04, N 10.78.

Method 2: *5-(*tert*-Butoxycarbonyl)-1-(2-cyanoethyl)-4-heptyl-1,5-diazacyclononan-2-one* (**17**). To a solution of EtONa (37 mg, 0.57 mmol) in 5 ml of EtOH was added 124 mg of **14** (0.36 mmol) and the solution was stirred for 30 min at room temperature. The solvent was evaporated in vacuo and the residue was dissolved in 5 ml of dry toluene. To this solution was carefully added first 0.37 ml (298 mg, 5.62 mmol) and after 1.5 h 0.15 ml of freshly distilled acrylonitrile was carefully added. It was stirred at room temperature for 3 h. The residue left after evaporation was purified by column chromatography (Et_2O) to give143 mg of **17** (quantitative). IR ($CHCl_3$): 3000, 2930, 2860, 2255 (CN), 1684, 1635, 1462, 1430, 1370, 1344, 1162, 910. ^{1}H-NMR ($CDCl_3$): 4.40-2.15 (*br. m*, 11H); 1.70-1.15 [*br. m*, 25H, where 1.49 and 1.47 (2*s*, 3C*H*$_3$)]; 0.89 (*m*, C*H*$_3$). EI-MS: 293 (5, $[M-100]^+$), 250 (5), 222 (3), 194 (55), 182 (4), 168 (11), 152 (5), 140 (9), 123 (13). CI-MS: 394 (5, $[M+1]^+$), 338 (15), 337 (13), 294 (78), 276 (17), 268 (13), 267 (100), 98 (16).

Second preparation of **16**. A mixture of **17** (109 mg, 0.28 mmol) and 200 mg of PtO_2 in 100 ml of EtOH (95%), and 10 ml of NH_4OH (25%) was shaken overnight under H_2 atmosphere (50 psi) at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by column chromatography (Et_2O, then Et_2O/EtOH/NH_4OH (25%) 25:5:1) to give 47 mg of **16** (0.12 mmol, 42%), its spectra see above.

1-(3-Aminopropyl)-4-heptyl-1,5-diazacyclononan-2-one (**18**). A solution of 10 mg of **16** (0.025 mmol) in 0.5 ml of TFA was stirred for 10 min at room temperature. After evaporation of the TFA, the residue was diluted with CH_2Cl_2 and then the pH was adjusted to 8.5 by addition of a solution of Na_2CO_3. The organic layer was dried over K_2CO_3 and evaporated to give crude **18** as a syrup. ^{1}H-NMR ($CDCl_3$): 4.54 (*br.*, 1H); 3.87 (*br.*, 1H); 3.20 (*br.*, 1H); 2.95 (*br.*, 1H); 2.81 (*t*, *J*=5.9, 2H); 2.80-2.60 (*br. m*, 4H); 2.61 (*dd*, *J*=9.2, 11.1, H_a-C(3)); 2.37 (*d*, *J*=11.1, H_b-C(3)); 1.73 (*quint.*, *J*=6.7, 2H-C(2')); 1.60-1.20 (*br. m*, 18H); 0.89 (*t*, *J*=6.7, C*H*$_3$). EI-MS: 297 (9, M^+), 281 (6), 267 (17), 238 (9), 225 (7), 211 (5), 198 (27), 182 (35), 168 (29), 139 (100).

(±)-Tetrahydromyricoidin (=(±)-2-heptyl-1,5,9-triazacyclotridecan-4-one) (**6**). A solution of 14 mg of **16** (0.035 mmol) was dissolved in 0.5 ml of TFA and stirred for 10 min at room temperature. After evaporation of the TFA, the residue was dissolved in 1 ml of 2,4-lutidine and heated to reflux for 1.5 h. The residue left after evaporation was purified by column chromatography (Et_2O/EtOH/NH_4OH (25%) 10:5:2) to give 6.5 mg

of (±)-**6** (0.022 mmol, 62%) as a syrup. ^{1}H-NMR ($CDCl_3$): 8.42 (*br.*, H-N(5)); 3.66 (*br.*, 1H); 3.45 (*br.*, 1H); 3.28 (*br.*, 1H); 3.15-2.40 (*br. m*, 8H); 2.15-1.15 (*br. m*, 20H); 0.88 (*t*, *J*=6.7, CH_3). EI-MS: 297 (7, $M^{+\cdot}$), 280 (14), 254 (19), 239 (14), 226 (5), 211 (8), 198 (100), 182 (17), 168 (38), 155 (31), 153 (14).

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