

166. Total Synthesis of (–)-(2*R*)-Dihydromyricoidine

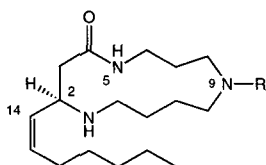
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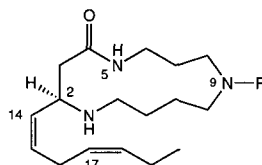
(2. VIII. 96)

An asymmetric synthesis of the spermidine alkaloid (–)-(2*R*)-dihydromyricoidine (**5**) was performed by employing two ring-enlargement reactions. The chiral center was introduced by a diastereoselective *Michael* addition of perhydropyridazine (**7**) to the α,β -unsaturated ester **6**. The (*Z*)-C=C bond was obtained by a selective *Wittig* reaction. The synthetic compound **5** was found to have a negative value for the specific rotation. This is in contrast to that of the natural product reported in the literature. Therefore, as an outcome of this synthesis, the absolute configuration of the natural alkaloid should be inverted to be as shown in structure **V**.

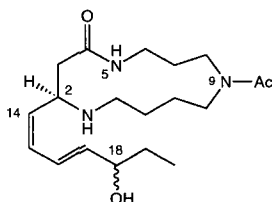
1. Introduction. – The spermidine alkaloids (+)-loesenerine (**1**), (+)-17,18-didehydroloesenerine (**2**), and (+)-16,17-didehydroloesenerin-18-ol (**3**)³⁾ have previously been isolated from *Maytenus loeseneri* URB. (Celastraceae) [1] [2]. Their structures were elucidated mainly by spectroscopic means, particularly by interpretation of the fragmentation patterns observed in their (electron impact) mass spectra as well as by ¹H- and ¹³C-NMR spectra.



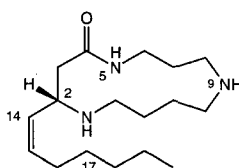
1 R = Ac (*R*)-Loesenerine
5 R = H (*R*)-Dihydromyricoidine



2 R = Ac (*R*)-17,18-Didehydroloesenerine
4 R = H (*R*)-Myricoidine



3 (*R*)-16,17-Didehydroloesenerin-18-ol



V (+)-(S)-Dihydromyricoidine with the corrected absolute configuration

¹⁾ Part of the planned Ph. D. thesis of U. A. H.

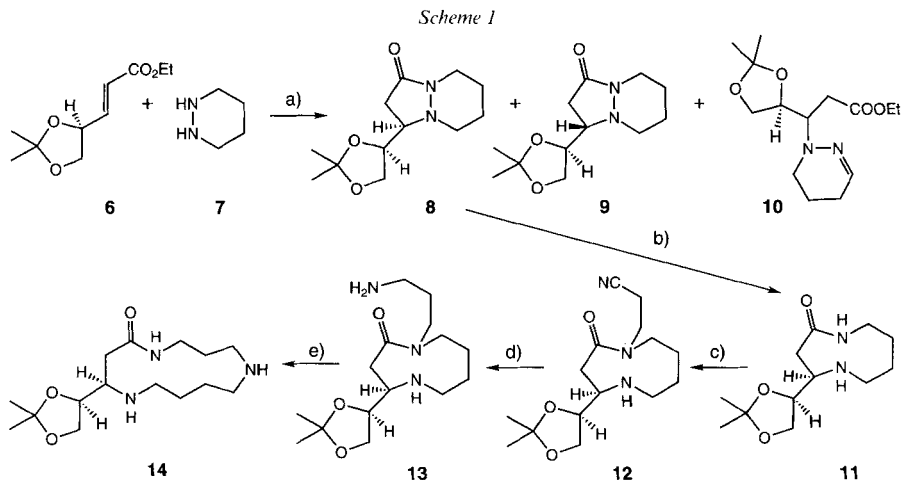
²⁾ Part of the Ph. D. thesis of J. S., University of Zürich, 1993.

At the same time, (+)-myricoidine (**4**) and (+)-dihydromyricoidine (**5**)³ were reported as constituents of *Clerodendrum myricoides* VATKE (Verbenaceae) [3].

The alkaloids **1–5** consist of the same 13-membered macrocyclic lactam ring formed by spermidine and a C₁₀-fatty acid. The chiral center C(2) of (+)-loesenerine (**1**) was assumed to have the (*R*)-configuration by comparison of the specific rotation of **1** with that of (+)-(*R*)-3-methoxybut-1-ene. The absolute configurations of **2** and **3** were determined by comparison of their *Cotton* effects with that of **1**. The chiral centers of **4** and **5** also have the (*R*)-configuration, because the specific rotation of samples of *N,N'*-diacetyldihydromyricoidine prepared from **4**, **5**, and **1** were the same. The (*R*)-configuration at the chiral center C(2) of these five alkaloids contrasts with the absolute configurations of all other structurally related, naturally occurring spermine and spermidine alkaloids, which have the (*S*)-configuration [4].

To verify the structures proposed in the literature [1] [3], we synthesized (2*R*)-dihydromyricoidine (**5**) by an enantioselective synthesis. Comparison of the specific rotations of the synthesized products with those reported for the natural products [1] [3] should allow the unambiguous assignment of the absolute configurations of the natural alkaloids.

2. Synthesis and Discussion. – The (*R*)-configured center was introduced directly by a diastereoselective *Michael* addition of perhydropyridazine (**7**) to the (*S*)-ester **6** [5], followed by subsequent cyclization to give the corresponding lactam **8** (88%) (*Scheme 1*). In other experiments, not only **8** was isolated (81%), but the two side-products **9** (7%) and **10** (4%) were also obtained [6].



a) Toluene, Ar, 20°, 5 d. b) THF, Na/NH₃ (l), 70%. c) i) EtONa/EtOH, r.t., 30 min; ii) CH₂=CHCN, toluene, r.t., 99%. d) H₂/Raney-Ni, 50 psi, 25% NH₃/EtOH, r.t., 6 h, 76%. e) 1*N* Ethanolic NaOH, 50–60°, 14 d, 83%.

³) The IUPAC-conform systematic names of these compounds are: **1**: (2*R*)-9-Acetyl-2-[(*Z*)-hept-1-enyl]-1,5,9-triazacyclotridecan-4-one; **2**: (2*R*)-9-acetyl-2-[(1*Z*,4*Z*)-hepta-1,4-dienyl]-1,5,9-triazacyclotridecan-4-one; **3**: (2*R*)-9-acetyl-2-[(1*Z*,3*E*)-5-hydroxyhepta-1,3-dienyl]-1,5,9-triazacyclodecan-4-one; **4**: (2*R*)-2-[(1*Z*,4*Z*)-hepta-1,4-dienyl]-1,5,9-triazacyclotridecan-4-one; **5**: (2*R*)-2-[(*Z*)-hept-1-enyl]-1,5,9-triazacyclotridecan-4-one.

The diastereoselectivity of this reaction is induced by the (*S*)-configured center of **6** [7–9], which was synthesized from D-mannitol according to a known procedure [10]. The relative configuration of **8** was determined by X-ray crystal-structure analysis (*Fig.*) and, based on the known configuration of the D-mannitol, the absolute configurations at the two chiral centers, C(9) and C(4'), could then be assigned as (*R*) and (*S*), respectively.

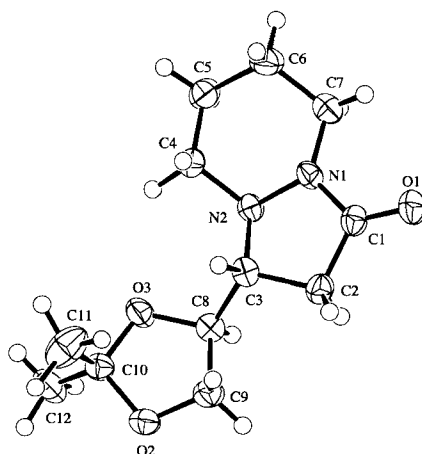


Figure. ORTEP Plot of (9*R*)-9-[(4'*S*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-1,6-diazacyclo[4.3.0]nonan-7-one (**8**)

The ring enlargement of **8** by treatment with Na in liquid NH₃ [11] led to the nine-membered ring component **11** in 70% yield. Subsequently, the 3-aminopropyl side chain, necessary for the second ring-enlargement reaction, was introduced by a regioselective cyanoethylation of **11** using acrylonitrile in toluene.

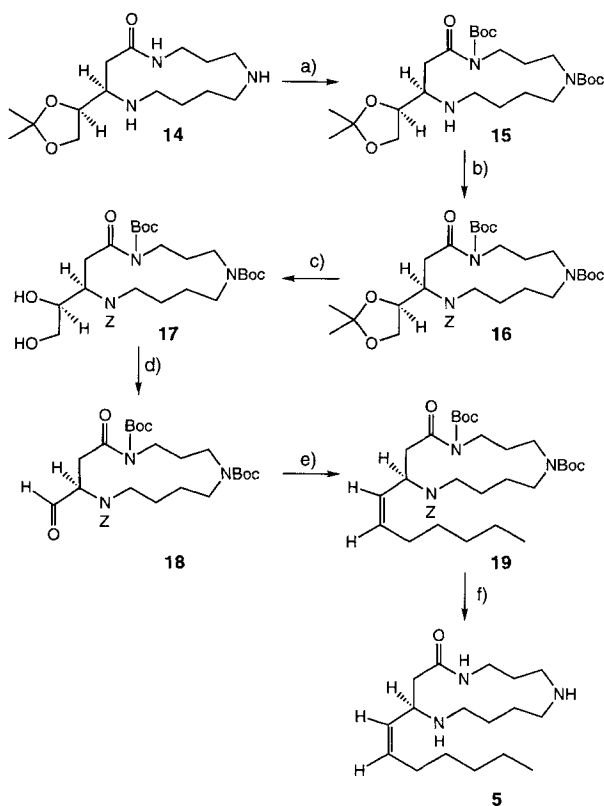
The reduction of the nitrile **12** then yielded the amine **13** in 76% yield, when the hydrogenation was carried out with *Raney*-Ni in 25% NH₃/EtOH. If 1*N* ethanolic NaOH was used instead, reductive cleavage of the lactam occurred with only 50% yield [12]. Finally, the 13-membered lactam **14** was obtained by treatment of **13** with 1*N* ethanolic NaOH at 50–60° for 14 days.

After the synthesis of the ring skeleton containing the chiral center C(2), the side chain with the (*Z*)-C=C bond was introduced by a (*Z*)-selective *Wittig* reaction with an unstable ylide at low temperature (*Scheme 2*) [13].

Studies on this *Wittig* reaction showed that all N-atoms required protection, because all experiments with unprotected or partially protected compounds failed completely: experiments with the corresponding aldehydes of **11** and **14** showed that, in both cases, unprotected N(5) attacked the aldehyde group intramolecularly to give bicyclic amino-semiacetals of lactams. The atoms N(1) and N(9) had to be protected, since they underwent side reactions. Choosing a suitable protecting group was rather tricky: the (4-nitrobenzoyloxy)carbonyl group was easily introduced but failed to be cleaved without reducing the C=C bond. The (trichloromethoxy)carbonyl group could be introduced in **11**, but the corresponding diol reacts with this protecting group intramolecularly [6]. In our case, the most suitable protecting groups appeared to be the combination of Boc and Z groups (Boc = (*tert*-butoxy)carbonyl, Z = (benzoyloxy)carbonyl) [14], both of which

could easily be introduced and subsequently removed. Therefore, the Boc group was introduced at N(5) and N(9) by treatment of **14** with (Boc)₂O, Et₃N, and 4-(dimethylamino)pyridine (DMAP) in CH₂Cl₂. Afterwards, **15** was treated with Z-Cl and Hünig base ((i-Pr)₂NEt) in THF to give the fully protected lactam **16**. Cleavage of the acetonide protecting group was achieved by treatment of **16** with (±)-camphor-10-sulfonic acid (CSA) in MeOH. Removal of the Boc groups was achieved by treatment of **17** with TFA in MeOH. Finally, the aldehyde **18** was treated with H₃C(CH₂)₄CHP(Ph)₃ to give the alkene **19**. Finally, deprotection of **19** with Me₃SiI and TFA yielded the desired dihydromyricoidine (**5**).

Scheme 2



a) (Boc)₂O/Et₃N, DMAP, CH₂Cl₂, 0°, 15 h, 66%. b) ZCl, (i-Pr)₂NEt, THF, Ar, r.t., 4 h, 93%. c) CSA, MeOH, r.t., 5 h, 86%. d) NaIO₄, MeOH, Ar 3 h, 93%. e) H₃C(CH₂)₄CHP(Ph)₃, toluene, –80°, 18 h, 66%. f) i) Me₃SiI, CH₂Cl₂; ii) TFA, 37%.

The oxidative cleavage of the diol **17** to the corresponding aldehyde **18** with NaIO₄ and the subsequent Wittig reaction proved to be difficult. Since the aldehyde **18** tended to racemize, it was isolated for analytical purposes only. Otherwise, **18** was treated directly with freshly generated ylide to obtain **19** in 66% yield. Final deprotection yielded the desired dihydromyricoidine (**5**). This was achieved by treatment of **19** with Me₃SiI to deprotect N(1) and subsequent addition of TFA to cleave the Boc groups.

Dihydromyricoidine (**5**) was characterized by IR, ¹H-NMR, ¹³C-NMR, TOCSY, ¹H, ¹³C-COSY, and mass spectra (electron impact (EI) well as chemical ionization (CI)).

The IR and the EI mass spectra of the synthetic and natural products were identical. The few signals of the ^1H -NMR spectrum reported in the literature [3] also appear in our spectrum. With a TOCSY and ^1H , ^{13}C -COSY spectrum, it was possible to assign all signals. The synthetic compound **5** has a specific rotation of $[\alpha]_{\text{D}}^{21} = -65$. In contrast, $[\alpha]_{\text{D}}^{21} = +77$ was reported for the natural product. The smaller absolute value of $[\alpha]_{\text{D}}^{21}$ obtained for the synthetic compound can readily be attributed to the tendency of **18** to racemize. In consideration of these results, we suppose that the absolute configuration of (+)-dihydromyricoidine (**5**) was proposed incorrectly in the literature [3]. On the basis of this synthesis of (–)-(*R*)-dihydromyricoidine, we propose that the opposite absolute configuration be assigned to C(2), namely (*S*) (shown by structure **V**), which is in accordance with all other structurally known macrocyclic spermidine alkaloids. This result is also suggestive that the hitherto assumed absolute configurations of the alkaloids **1–4** has to be reversed as well.

We thank the *Swiss National Science Foundation* for financial support, the analytical department of the University of Zürich for IR, NMR, and mass spectra, and *A. Guggisberg* for practical advice.

Experimental Part

General. All reactions were carried out under an Ar atmosphere and with abs. solvents. Hydrogenations: apparatus *Parr Instruments Company Inc.* DC: Silica gel 60 F_{254} (*Merck*). Column chromatography (CC): silica gel 60 *F* (*Merck*; 0.040–0.063 mm). M.p.: *Mettler Fp 5*. IR: *Perkin-Elmer 297*, in cm^{-1} ; ^1H -NMR: *Bruker ARX 300* (300 MHz) or *Bruker AMX 600* (600 MHz), in CDCl_3 , δ in ppm relative to CDCl_3 as internal standard ($\delta(\text{H}) = 7.26$ ppm) or in $(\text{D}_6)\text{DMSO}$ δ in ppm relative to CDCl_3 as internal standard ($\delta(\text{C}) = 2.49$ ppm); ^{13}C -NMR: *Bruker ARX 300* (75.5 MHz) or *Bruker AMX 600* (150.9 MHz), in CDCl_3 , δ in ppm relative to CDCl_3 as internal standard ($\delta(\text{C}) = 77.0$ ppm) or in $(\text{D}_6)\text{DMSO}$ δ in ppm relative to CDCl_3 as internal standard ($\delta(\text{C}) = 40.3$ ppm); multiplicity with DEPT experiments. EI- and CI-MS (NH_3): *Finnigan SSQ MAT 700* or *Finnigan 90*, in m/z (rel. %); ESI-MS: *Finnigan TSQ 700* in m/z (rel. %).

(9*R*)-9-[(4'*S*)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-1,6-diazabicyclo[4.3.0]nonan-7-one (**8**). To a soln. of 46.55 g (0.25 mol) of **6** in 500 ml of toluene were added 25.68 g (0.3 mol) of **7**. The soln. was stirred for 5 d, the solvent evaporated, and the residue chromatographed (Et_2O /acetone 3:1). Crystallization (Et_2O) led to 53.19 g (88 %) of colorless needles. M.p. 105–106°. $[\alpha]_{\text{D}}^{21} = +64.4$ ($c = 0.99$, CHCl_3). CD (95% EtOH): 229.2 ($A_{\text{E}} = +11.10$); 213.8 ($A_{\text{E}} = 0$); 205.4 ($A_{\text{E}} = -7.84$). UV ($c = 1.61 \cdot 10^{-4}$ M, 95% EtOH): 229 (3.70). IR (KBr): 2980s, 2950s, 2940s, 2870s, 2850m, 2820s, 1690s, 1665s, 1480m, 1430s, 1420s, 1410s, 1400m, 1380s, 1365s, 1325m, 1295m, 1255s, 1240s, 1220s, 1210s, 1200s, 1180s, 1160m, 1145s, 1120s, 1070s, 1055s, 1005s, 965m, 955m, 940m, 925m, 910m, 845s, 835s, 795w, 660w. ^1H -NMR: 4.18 (dd, $J = 13.5, 6.5$, H-C(4')); 4.12 (dd, $J = 13.1, 4.3$, H-C(5)); 4.06 (dd, $J = 8.5, 6.5$, H-C(5')); 3.65 (dd, $J = 8.5, 6.2$, H-C(5')); 3.34 (br. d, $J = 10.7$, H-C(2)); 3.06 (dd, $J = 16.8, 8.6$, H-C(9)); 2.91 (t, $J = 12.2$, H-C(5)); 2.64 (dd, $J = 16.8, 9.4$, H-C(8)); 2.41 (dd, $J = 15.0, 10.7$, H-C(2)); 2.20 (ddd, $J = 16.8, 8.5, 1.4$, H-C(8)); 1.82–1.61 (m, 3 H); 1.51–1.31 (m, 1 H); 1.41, 1.35 (2s, 2 Me). ^{13}C -NMR: 167.0 (s, C(7)); 109.8 (s, C(2')); 77.4 (d, C(4')); 66.1 (t, C(5')); 63.9 (d, C(9)); 57.3, 41.4, 32.1 (3t, 3 CH_2); 26.5, 25.1 (2q, 2 Me); 24.0, 22.7 (2t, 2 CH_2). CI-MS: 271 (18), 241 (100, $[M + 1]^+$). Anal. calc. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_3$ (240.302): C 59.98, H 8.39, N 11.66; found: C 60.07, H 8.35, N 11.48.

Crystal-Structure Determination of **8** (see the Table and the Fig.)⁴⁾. All measurements were conducted at low temp. on a *Nicolet R3* diffractometer using graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å). The intensities were collected using *Wyckoff ω* scans. Three standard reflections measured every 150 reflections showed negligible variation in intensity. The intensities were corrected for *Lorentz* and polarization effects. The structure

⁴⁾ Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-10/24. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: teched@chemcrs.cam.ac.uk).

was solved by direct methods using SHELXS86 [15] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were located in a difference electron-density map and were refined isotropically. All refinements were carried out on F using full-matrix least-squares procedures, which minimized the function $\sum w(|F_o| - |F_c|)^2$, where $w = [\sigma^2(F_o) + (0.02F_o)^2]^{-1}$. A correction for secondary extinction was applied. Data collection and refinement parameters are given in the Table. The enantiomorph was chosen to correspond with the known (*S*)-chirality of the dioxolane ring.

Table. Crystallographic Data for Compound 8

Crystallized from	Et ₂ O
Empirical formula	C ₁₂ H ₂₀ N ₂ O ₃
Formula weight	240.30
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	0.18 × 0.27 × 0.48
Temp. [K]	193 (1)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Z	4
Reflections for cell determination	25
2θ range for cell determination [°]	28–32
Unit cell parameters a [Å]	5.3264 (8)
b [Å]	8.726 (1)
c [Å]	27.064 (3)
V [Å ³]	1257.9 (3)
D_x [g cm ⁻³]	1.269
μ MoK α [mm ⁻¹]	0.0854
$2\theta_{\text{(max)}}$ [°]	55
Total reflections measured	2020
Symmetry independent reflections	1922
Reflections used [$I > 2\sigma(I)$]	1341
Parameters refined	235
R	0.0511
wR	0.0529
Goodness of fit	1.441
Secondary extinction coefficient	1.6×10^{-7}
Final $\Delta_{\text{max}}/\sigma$	0.0001
$\Delta\rho$ (max; min) [e Å ⁻³]	0.24; -0.27

Neutral atom scattering factors for non-H-atoms were taken from [16a] and the scattering factors for H-atoms from [17]. Anomalous dispersion effects were included in F_c [18]; the values for f' and f'' were taken from [16b]. All calculations were performed using the TEXSAN crystallographic software package [19].

(2*R*)-4-[*(4'S)*-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-1,5-diazacyclononan-2-one (**11**). In 250 ml liquid NH₃, 6.7 g (0.29 mol) of Na were dissolved and 24.04 g (0.1 mol) of **8** in 100 ml of THF were added. The soln. was stirred for 15 min and quenched with NH₄Cl (color change from blue to white). NH₃ was evaporated and the residue dissolved in acetone. The soln. was filtered through *Celite* and the solvent evaporated. Chromatography (Et₂O/MeOH 25:1) gave 16.96 g (70%) of colorless cubic crystals. M.p. 107.1–107.4° (acetone). $[\alpha]_D^{25} = +70.4$ ($c = 0.778$, CHCl₃). IR (KBr): 3380s, 3260s, 3090s, 2990s, 2980s, 2930s, 2920s, 2900s, 2850s, 1630s, 1550s, 1450s, 1440s, 1370s, 1360m, 1345s, 1335s, 1320m, 1300m, 1265s, 1240m, 1210s, 1200s, 1175s, 1150s, 1135s, 1115m, 1090m, 1040s, 990m, 960m, 940w, 915w, 870w, 850s, 830w, 800w, 750m, 730w, 660w. ¹H-NMR: 6.71 (*d*, $J = 10.4$, HN(5)); 4.14–4.00 (*m*, H–C(4'), H–C(5')); 3.75–3.62 (*m*, H–C(5'), H–C(6)); 2.87–2.78 (*m*, H–C(2), H–C(9)); 2.70–2.56 (*m*, H–C(9), H–C(6)); 2.19 (*t*, $J = 11.7$, H_a–C(3)); 2.08 (*dd*, $J = 11.7$, 2.8, H–C(3)); 1.94–1.84 (*m*, CH₂(7)); 1.63–1.20 (*m*, 3 H); 1.44, 1.34 (2s, 2 Me). ¹³C-NMR: 176.0 (*s*, C(4)); 109.2 (*s*, C(2)); 79.8 (*d*, C(4')); 66.9 (*t*, C(5')); 57.7 (*d*, C(2)); 49.8, 42.3, 40.3, 29.9 (4t, 4 CH₂); 26.5, 24.8 (2q, 2 Me); 22.5 (*t*, CH₂). CI-MS: 243 (100, $[M + 1]^+$), 185 (10), 141 (34).

(4*R*)-1-(2'-Cyanoethyl)-4-[*(4'S)*-2'',2''-dimethyl-1'',3''-dioxolan-4''-yl]-1,5-diazacyclononan-2-one (**12**). To a soln. of 1.4 g (60 mmol) of Na in 100 ml of EtOH, 12.12 g (50 mmol) of **11** were added and after stirring for 30 min,

the solvent was evaporated overnight under high vacuum. The residue was dissolved in 250 ml of toluene. At 0°, 6 ml (90 mmol) of acrylonitrile in 50 ml of toluene were added dropwise during 75 min, and the soln. was stirred at 0° for 2 h. Another 6 ml (90 mmol) of acrylonitrile in 50 ml of toluene were added during 75 min. After stirring for 2 h, the soln. was poured onto ice-water and extracted with CH₂Cl₂. The org. layer was washed twice with H₂O, dried (MgSO₄), and the solvent evaporated. Chromatography (CH₂Cl₂/MeOH/25% (NH₃/H₂O) 85:15:1) and recrystallization (Et₂O) gave 14.62 g (99%) of pale-yellow crystals. M.p. 91.8–93.5°. $[\alpha]_D^{25} = +49.8$ ($c = 1$, CHCl₃). IR (KBr): 3360w, 2980m, 2930m, 1630s, 1460m, 1420m, 1370m, 1350m, 1330w, 1260m, 1235m, 1210m, 1180m, 1160m, 1120m, 1100m, 1070m, 970w, 915w, 845m, 790m, 730s, 700w, 650m. ¹H-NMR: 4.72 (t, $J = 12.0$, H–C(9)); 4.12–4.03 (m, H–C(4''), H–C(5'')); 3.92–3.83 (m, H–C(1'')); 3.99 (dd, $J = 7.4, 5.4$, H–C(5'')); 3.34 (ddd, $J = 14.4, 9.2, 1.9$, H–C(9)); 3.18–3.09 (m, H–C(1'')); 2.93–2.78 (m, H–C(2'), CH₂(6)); 2.76–2.63 (m, H–C(4), H–C(3)); 2.58 (ddd, $J = 16.6, 6.5, 5.0$, H–C(2'')); 2.34 (d, $J = 11.4$, H–C(3)); 1.93–1.82 (m, H–C(8)); 1.57 (tt, $J = 13.5, 1.9$, H–C(8)); 1.43, 1.33 (2s, 2 Me); 1.43–1.20 (m, 3 H). ¹³C-NMR: 174.1 (s, C(2)); 118.4 (s, CN); 109.4 (s, C(2'')); 79.8 (d, C(4'')); 66.9 (t, C(5'')); 58.0 (d, C(4)); 50.2, 49.0, 43.6, 42.3 (4t, 4 CH₂); 26.5 (q, Me); 26.3 (t, CH₂); 24.8 (q, Me); 22.0, 16.0 (2t, 2 CH₂). CI-MS: 296 ($[M + 1]^+$).

(4R)-1-(3'-Aminopropyl)-4-[(4'S)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-1,5-diazacyclononan-2-one (13). To 134 ml of EtOH and 66 ml of 25% NH₃, 3 g of Raney-Ni and 5.90 g (20 mmol) of **12** were added. The soln. was hydrogenated at 50 psi 6 h, filtered through Celite, and the solvent was evaporated. The residue was chromatographed (CH₂Cl₂/MeOH/25% (NH₃/H₂O) 90:10:0.5) to give 4.56 g (76%) of a pale-yellow oil. $[\alpha]_D^{25} = +17.2$ ($c = 1$, CHCl₃). IR (film): 3360m, 3050w, 2980m, 2930s, 2860m, 2800m, 1620s, 1460m, 1420m, 1380m, 1370m, 1345w, 1320w, 1260m, 1230m, 1210m, 1175m, 1150m, 1115w, 1090m, 1070s, 970w, 900w, 845m, 790w, 775w, 730m, 700w. ¹H-NMR: 4.55 (br. t, $J = 14.2$, H–C(9)); 4.11–4.03 (m, H–C(4''), H–C(5'')); 3.88–3.81 (m, H–C(1'')); 3.73–3.69 (m, H–C(5'')); 3.20 (dd, $J = 14.2, 5.2$, H–C(9)); 2.91–2.77 (m, H–C(1'), CH₂(6)); 2.70–2.66 (m, CH₂(3'), H–C(3)); 2.30–2.27 (m, H–C(3)); 1.90–1.70 (m, CH₂(2'')); 1.72–1.33 (m, 7 H); 1.43, 1.33 (2s, 2 Me). ¹³C-NMR: 173.6 (s, C(2)); 109.3 (s, C(2'')); 79.9 (d, C(4'')); 67.0 (t, C(5'')); 58.1 (d, C(4)); 50.1, 47.1, 43.3, 40.8, 39.2, 30.5 (6t, 6 CH₂); 24.5 (q, Me); 26.0 (t, CH₂); 24.8 (q, Me); 22.0 (t, CH₂). CI-MS: 300 (100, $[M + 1]^+$), 198 (52), 155 (18), 146 (67). EI-MS: 300 (10, $[M + 1]^+$), 198 (52), 180 (12), 155 (88), 124 (27), 113 (61), 98 (100), 84 (68), 70 (59), 56 (71).

(2R)-2-[(4'S)-2',2'-Dimethyl-1',3'-dioxolan-4'-yl]-1,5,9-triazacyclotridecan-4-one (14). In 50 ml of EtOH and 2.02 g (6.7 mmol) of **13** were stirred for 14 d at 50–60°. After evaporation of the solvent, the residue was chromatographed (CH₂Cl₂/MeOH/25% (NH₃/H₂O) 80:19:1) to give 1.667 g (83%) of white crystals. M.p. 52–53°. $[\alpha]_D^{25} = -5.3$ ($c = 1$, CHCl₃), $[\alpha]_D^{25} = -18.6$ ($c = 1$, MeOH). IR (film): 3280m, 2990m, 2920s, 1640s, 1550m, 1455m, 1430m, 1380m, 1370m, 1260m, 1210m, 1155m, 1125m, 1065s, 920w, 865m, 750s, 660w. ¹H-NMR: 8.80 (s, H–N(5)); 4.17–4.13 (m, H–C(4''), H–C(5'')); 3.73–3.71 (m, H–C(5'')); 3.53–3.46 (m, H–C(6)); 3.29–3.25 (m, H–C(6)); 2.95–2.70 (m, H–C(2), CH₂(8), CH₂(10), CH₂(13)); 2.42 (dd, $J = 14.9, 3.1$, H–C(3)); 2.07 (dd, $J = 14.9, 6.2$, H–C(3)); 1.74–1.45 (m, 8 H); 1.40, 1.34 (2s, 2 Me). ¹³C-NMR: 170.5 (s, C(4)); 109.2 (s, C(2'')); 77.5 (d, C(4'')); 67.0 (t, C(5'')); 59.7 (d, C(2)); 49.2, 49.0, 46.0, 39.3, 37.0, 28.7, 27.3 (7t, 7 CH₂); 26.8 (q, Me); 26.2 (t, CH₂); 25.4 (q, Me). CI-MS: 300 (100, $[M + 1]^+$), 198 (34), 190 (15), 173 (60), 146 (50). EI-MS: 300 (1, $[M + 1]^+$), 198 (82), 155 (41), 129 (30), 124 (57), 113 (19), 110 (40), 98 (100), 84 (94), 70 (73), 56 (59).

(2R)-5,9-Bis[(tert-butoxy)carbonyl]-2-[(4'S)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-1,5,9-triazacyclotridecan-4-one (15). To a soln. of 30 ml of CH₂Cl₂, 3 ml of Et₃N and 1.06 g (3.5 mmol) of **14** at 0°, first 1.71 g (14 mmol) of DMAP in 20 ml of CH₂Cl₂ and then 9.17 g (42 mmol) of (Boc)₂O in 20 ml of CH₂Cl₂ were added. The mixture was stirred overnight. The solvent was evaporated and the residue chromatographed (CH₂Cl₂/MeOH/25% (NH₃/H₂O) 99:1:0.2) to give 1.168 g (66%) of a pale-yellow oil. $[\alpha]_D^{25} = +4.5$ ($c = 1$, CHCl₃). IR (film): 3320m, 2970s, 2920s, 1725s, 1690s, 1610w, 1475s, 1415s, 1360s, 1290s, 1210s, 1140s, 1055s, 955w, 890m, 850s, 770m, 745w, 720w. ¹H-NMR (DMSO, 90°): 4.16 (ddd, $J = 11.7, 6.6, 6.5$, H–C(4'')); 3.97 (ddd, $J = 8.3, 6.5, 0.7$, H–C(5'')); 3.80–3.58 (m, H–C(2), H–C(6)); 3.30–3.07 (m, H–C(5'), H–C(6), H–C(8), H–C(13)); 3.05–2.99 (m, H–C(10)); 2.98–2.55 (m, H–C(3), H–C(8), H–C(10), H–C(13)); 2.59 (ddd, $J = 11.8, 8.4, 4.8$, H–C(3)); 1.95–1.28 (m, CH₂(7), CH₂(11), CH₂(12), NH); 1.52, 1.40 (2s, 2 *t*-Bu); 1.36, 1.30 (2s, 2 Me). ¹³C-NMR (DMSO, 90°): 174.6 (s, N–C=O); 155.2, 153.8 (2s, 2 N–CO₂); 108.7 (s, Me₂C); 83.3 (s, 2 Me₂C); 79.2 (d, C(4'')); 66.1 (t, C(5'')); 58.5 (d, C(2)); 46.2, 45.8, 45.6, 44.3, 43.4 (5t, C(3), C(6), C(8), C(10), C(13)); 28.6, 28.0 (2q, 2 Me₂C); 26.7, 25.5 (2q, 2 Me); 26.1, 24.6, 24.0 (3t, C(7), C(11), C(12)). CI-MS: 500 (25, $[M + 1]^+$), 398 (25), 298 (13), 198 (110). Anal. calc. for C₂₅H₄₅N₃O₇ (499.646): C 60.10, H 9.08, N 8.41; found: C 60.28, H 9.03, N 8.14.

(2R)-1-[(Benzyloxy)carbonyl]-5,9-bis[(tert-butoxy)carbonyl]-2-[(4'S)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-1,5,9-triazacyclotridecan-4-one (16). To a soln. of 1.16 g (2.32 mmol) of **15** and 2.1 ml (23.2 mmol) of (i-Pr)₂NEt in 80 ml of THF at r.t., 328 μ l (2.32 mmol) of Z-Cl in 20 ml of THF were added. The mixture was stirred for 4 h. The solvent was then evaporated and the crude product purified by chromatography (CH₂Cl₂/MeOH/25%

(NH₃/H₂O) 98:2:0.3) to give 1.372 g (93%) of a pale-yellow oil. $[\alpha]_D^{25} = +18.8$ ($c = 1.021$, CHCl₃). IR (film): 3000m, 2980m, 2940m, 2870m, 1740s, 1680s, 1480s, 1455m, 1420s, 1395m, 1380s, 1370s, 1295s, 1240s, 1150s, 1070s, 1005w, 980w, 955w, 895w, 850m, 700m, 660w. ¹H-NMR (DMSO, 90°): 7.39–7.25 (m, 5 arom. H); 5.12 (dd, $J = 12.0$, 20.8, PhCH₂); 4.47–4.36 (m, H–C(4'')); 3.97 (dd, $J = 8.4$, 6.5, H–C(5'')); 3.93–3.87 (m, H–C(2), H–C(6)); 3.69 (ddd, $J = 8.5$, 6.5, 4.3, H–C(5'')); 3.63–3.47 (m, H–C(6), H–C(13)); 3.46–3.17 (m, H–C(8), H–C(10)); 3.13–3.00 (m, H–C(10), H–C(13)); 2.99–2.68 (m, H–C(3), H–C(8)); 2.07 (dd, $J = 15.2$, 2.6, H–C(3)); 1.88–1.79 (m, CH₂(7)); 1.53–1.16 (m, CH₂(11), CH₂(12)); 1.52, 1.41 (2s, 2 *t*-Bu); 1.35, 1.26 (2s, 2 Me). ¹³C-NMR (DMSO, 90°): 173.6 (s, N–C=O); 156.1, 155.4, 153.6 (3s, 3 N–CO₂); 137.5 (s, arom. C); 128.5, 128.4, 127.8, 127.7, 127.6 (5d, arom. C); 108.8 (s, Me₂C); 83.7, 78.7 (2s, 2 Me₃C); 76.6 (d, C(4'')); 66.8 (t, C(5'')); 66.5 (t, PhCH₂); 60.6 (d, C(2)); 47.9 (t, C(13)); 44.8 (t, C(8)); 44.2 (t, C(10)); 42.4 (t, C(6)); 37.0 (t, C(3)); 29.1 (t, C(7)); 28.6, 28.0 (2q, Me₃C); 27.5, 26.9 (2t, C(11), C(12)); 26.7, 25.5 (2q, 2 Me). CI-MS: 634 (10, [M + 1]⁺), 534 (100), 434 (51).

(2R)-1-[(Benzyloxy)carbonyl]-5,9-bis[(tert-butoxy)carbonyl]-2-[(1'S)-1',2'-dihydroxyethyl]-1,5,9-triazacyclotridecan-4-one (17). A soln. of 120 ml of MeOH, 730 mg (1.17 mmol) of 16, 2.728 g (11.7 mmol) of CSA and ~ 500 grains of molecular sieve was stirred for 5 h at r.t. and filtered through Celite. Evaporation of the solvent and purification by chromatography (CH₂Cl₂/MeOH/25% (NH₃/H₂O) 95:5:0.5) led to 598 mg (86%) of 17 of a pale-yellow oil. $[\alpha]_D^{25} = +25.2$ ($c = 0.99$, CHCl₃). IR (CHCl₃): 3400w, 2970s, 2930s, 2870m, 1725s, 1670s, 1460s, 1420s, 1360s, 1290s, 1240s, 1145s, 1070s, 1030m, 960w, 850m, 820w, 690m, 640w. ¹H-NMR (DMSO, 100°): 7.27–7.23 (m, 5 arom. H); 5.09 (dd, $J = 12.0$, 21.8, PhCH₂); 4.18–4.12 (m, H–C(1'')); 3.91 (dt, $J = 14.0$, 5.0, H–C(2)); 3.81–3.75 (m, 1 H); 3.59–3.27 (m, 6 H); 3.14–3.09 (m, 2 H); 2.99–2.79 (m, 3 H); 1.87–1.78 (m, CH₂(7)); 1.54–1.27 (m, CH₂(11), CH₂(12)); 1.51, 1.40 (2s, 2 *t*-Bu). ¹³C-NMR (DMSO, 100°): 174.2 (s, N–C=O); 156.8, 155.4, 153.6 (3s, N–CO₂); 137.6 (s, arom. C); 128.4, 127.7, 127.6 (3d, 5 arom. C); 83.5, 79.5 (2s, 2 Me₃C); 73.4 (d, C(1'')); 66.6 (t, PhCH₂); 64.3 (t, C(2'')); 59.0 (d, C(2)); 48.8, 44.9, 42.4, 39.4, 37.4 (5t, C(3), C(6), C(8), C(10), C(13)); 29.2, 27.7, 26.6 (3t, C(7), C(11), C(12)); 28.6, 28.1 (2q, 2 Me₃C). ESI-MS: 616 ([M + Na]⁺).

(2R)-1-[(Benzyloxy)carbonyl]-5,9-bis[(tert-butoxy)carbonyl]-2-formyl-1,5,9-triazacyclotridecan-4-one (18). To a soln. of 165 mg (0.28 mmol) of 17 in 10 ml of MeOH under an Ar atmosphere at –10° 203 mg (0.912 mmol) of NaIO₄ were added, and the mixture was stirred for 3 h (→ r.t.). The soln. was directly filtered through Alox and eluted with hexane/Et₂O 3:2 to give 140 mg (93%) of 18 as a yellow oil. $[\alpha]_D^{25} = +16.7$ ($c = 0.072$, CHCl₃). IR (CHCl₃): 2980s, 2930s, 2860m, 2820m, 2720w, 1725s, 1670s, 1585w, 1540w, 1450s, 1415s, 1340s, 1290s, 1240s, 1220s, 1140s, 1070s, 1030m, 995m, 965m, 845m, 770m. ¹H-NMR: 9.44 (d, $J = 9.4$, CHO); 7.36–7.20 (m, 5 arom. H); 5.09 (d, $J = 12.8$, PhCH₂); 4.92–2.53 (m, 11 H); 1.98–1.66 (m, CH₂(7)); 1.58–1.13 (m, CH₂(11), CH₂(12)); 1.45, 1.38 (2s, 2 *t*-Bu). ¹³C-NMR: 197.4 (s, CHO); 174.4 (s, N–C=O); 155.7, 153.3 (2s, 3 NCO₂); 136.6 (s, arom. C); 128.5, 128.2, 127.9 (3d, 5 arom. C); 83.9, 79.5 (2s, 2 Me₃C); 67.6 (t, PhCH₂); 50.7 (d, C(2)); 48.6, 45.5, 42.4, 39.0, 38.3 (5t, C(3), C(6), C(8), C(10), C(13)); 28.9, 27.4, 26.9 (3t, C(7), C(11), C(12)); 28.4, 27.9 (2q, 2 Me₃C). CI-MS: 562 (9, [M + 1]⁺), 462 (98), 362 (100).

(2R)-1-[(Benzyloxy)carbonyl]-5,9-bis[(tert-butoxy)carbonyl]-2-[(Z)-hept-1-enyl]-1,5,9-triazacyclotridecan-4-one (19). To a soln. of 185 mg (0.31 mmol) of 17 in 10 ml of MeOH under an Ar atmosphere at –10° 203 mg (0.912 mmol) of NaIO₄ were added, and the mixture was stirred for 6 h (→ r.t.). The soln. was directly filtered through Alox and eluted with hexane/Et₂O 1:2 to give 173 mg (quant.) of 18, which were dried overnight at 10^{–5} mbar and dissolved in 15 ml of toluene.

To a soln. of 174 mg (1.55 mmol) of freshly sublimed *t*-BuOK in 20 ml of toluene were added 662 mg (1.55 mmol) of (hexyl)(triphenyl) phosphonium bromide. The mixture was stirred for 1 h to give a 0.078M soln. of (hexyl)(triphenyl)phosphonium ylide.

At –80°, 4 ml (0.31 mmol) of this ylide soln. were added dropwise under an Ar atmosphere to the above soln. and stirred for 18 h. The cold soln. (0°) was filtered through Alox and eluted with hexane/Et₂O 3:2 to give 129 mg (66%) of 19 of a yellow oil. $[\alpha]_D^{25} = -23$ ($c = 1.1$, CHCl₃). IR (CHCl₃): 3450w, 3080w, 3060w, 3030m, 2970s, 2930s, 2870s, 2850s, 1730s, 1680s, 1550w, 1470s, 1420s, 1390s, 1370s, 1310s, 1295s, 1240s, 1140s, 1070s, 1030m, 1000m, 960m, 910w, 885w, 850m, 830w, 695m, 660w, 640w. ¹H-NMR (DMSO, 70°): 7.28–7.20 (m, 5 arom. H); 5.62 (dd, $J = 10.6$, 9.8, H–C(14)); 5.42 (dt, $J = 10.6$, 7.4, H–C(15)); 5.09 (dd, $J = 12.3$, 25.8, PhCH₂); 4.96 (dt, $J = 2.7$, 8.0, H–C(2)); 3.87 (dt, $J = 13.4$, 5.3, H–C(6)); 3.66–3.49 (m, H–C(3), H–C(6)); 3.39–3.23 (m, H–C(8), CH₂(10)); 3.01–2.88 (m, H–C(8), CH₂(13)); 2.75 (dd, $J = 16.1$, 2.7, H–C(3)); 2.12–2.06 (m, CH₂(16)); 1.85–1.76 (m, CH₂(7)); 1.55–1.23 (m, CH₂(11), CH₂(12), CH₂(17), CH₂(18), CH₂(19)); 1.51, 1.39 (2s, 2 *t*-Bu); 0.83 (t, $J = 6.4$, Me). ¹³C-NMR (DMSO, 70°): 173.3 (s, N–C=O); 156.0, 155.3, 153.6 (3s, 3 NCO₂); 137.4 (s, arom. C); 131.4 (d, C(14)); 128.5 (d, C(15)); 128.5, 127.9, 127.7 (3d, 5 arom. C); 83.6, 78.8 (2s, 2 Me₃C); 66.5 (PhCH₂); 53.4 (d, C(2)); 48.3, 46.6, 44.9, 42.7, 42.2 (5t, C(3), C(6), C(8), C(10), C(13)); 31.2, 29.3, 29.0, 27.7, 27.4, 26.5, 22.1 (7t, C(7), C(11), C(12), C(16), C(17), C(18), C(19)); 28.5, 28.0 (2q, 2 Me₃C); 27.5, 26.9 (2t, C(11), C(12)); 14.0 (q, Me). CI-MS: 630 (29, [M + 1]⁺), 530 (100), 496 (6), 430 (19), 396 (3), 296 (4).

(2R)-2-[(Z)-Hept-1-enyl]-1,5,9-triazacyclotridecan-4-one (= Dihydromyricoidine, **5**). To a soln. of 129 mg (0.203 mmol) of **19** in 15 ml of MeCN at -10° 277 μ l (2.03 mmol) of Me₃SiI were added, and, after 45 min stirring, 5 ml of CF₃COOH were also added. After 2 h, the solvent was evaporated and purified several times by chromatography (CHCl₃/MeOH 19:1) to give 22 mg (37%) of **5** as a colorless oil. $[\alpha]_D^{25} = -65$ ($c = 0.52$, MeOH). IR (CHCl₃): 3530w, 3430m, 3410m, 3080w, 3060w, 3030w, 2960s, 2930s, 2860m, 1680s, 1595m, 1520m, 1465m, 1450m, 1420m, 1370m, 1340m, 1310m, 1285m, 1250m, 1130m, 1070m, 995m, 910s, 860w, 830w, 695w, 650w. ¹H-NMR (600 MHz): 7.98 (t, $J = 6.2$, HN–C=O); 5.61 (dt, $J = 10.6, 7.5$, H–C(15)); 5.17 (dt, $J = 10.6, 6.9$, H–C(14)); 4.03 (dt, $J = 3.6, 10.6$, H–C(2)); 3.75–3.70 (m, H–C(6)); 3.29–3.28 (m, H–C(8)); 3.25–3.24 (m, H–C(8)); 3.16–3.13 (m, H–C(6)); 3.07–3.04 (m, H–C(10)); 2.89–2.86 (m, H–C(10), H–C(13)); 2.59–2.54 (m, H–C(3), H–C(13)); 2.38 (dd, $J = 13.2, 8.3$, H–C(3)); 2.20–2.17 (m, CH₂(7)); 2.09–2.00 (m, H–C(11), CH₂(16)); 1.95–1.90 (m, H–C(11)); 1.80–1.71 (m, CH₂(12), NH); 1.39–1.22 (m, CH₂(17), CH₂(18), CH₂(19)); 0.89 (t, Me). ¹³C-NMR (600 MHz): 172.1 (s, N–C=O); 134.5 (d, C(15)); 129.3 (d, C(14)); 52.6 (d, C(2)); 50.0 (t, C(10)); 49.2 (t, C(8)); 45.1 (t, C(13)); 43.0 (t, C(3)); 38.6 (t, C(6)); 31.5 (t, C(18)); 31.5 (t, C(17)); 29.3 (t, C(16)); 27.7 (t, C(11)); 26.8 (t, C(7)); 26.3 (t, C(12)); 22.5 (t, C(19)); 14.0 (q, Me). CI-MS: 296 (100, [$M + 1$]⁺). EI-MS: 296 (23, [$M + 1$]⁺), 278 (51, [$M + 1 - H_2O$]⁺), 221 (26), 180 (19), 168 (18), 152 (41), 138 (12), 128 (27), 110 (39), 98 (35), 84 (100), 70 (73), 56 (32), 41 (38).

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