Synthesis of the Spermidine Alkaloid (−)-(4*R*)-Dihydroisomyricoidine

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An asymmetric synthesis of (−)-(4*R*)-dihydroisomyricoidine (**28**), a 13-membered amino lactam of type A, was performed by a diastereoselective *Michael* addition between the spermidine derivative **3** and the commercially available optically active ethyl carboxylate **4**, and the cyclization of the resulting ω-amino acid **7** using diethyl phosphorocyanidate ($(EtO)_2POCN$), followed by a *Wittig* reaction to introduce the (*Z*)-side chain. Some side reactions are also discussed.

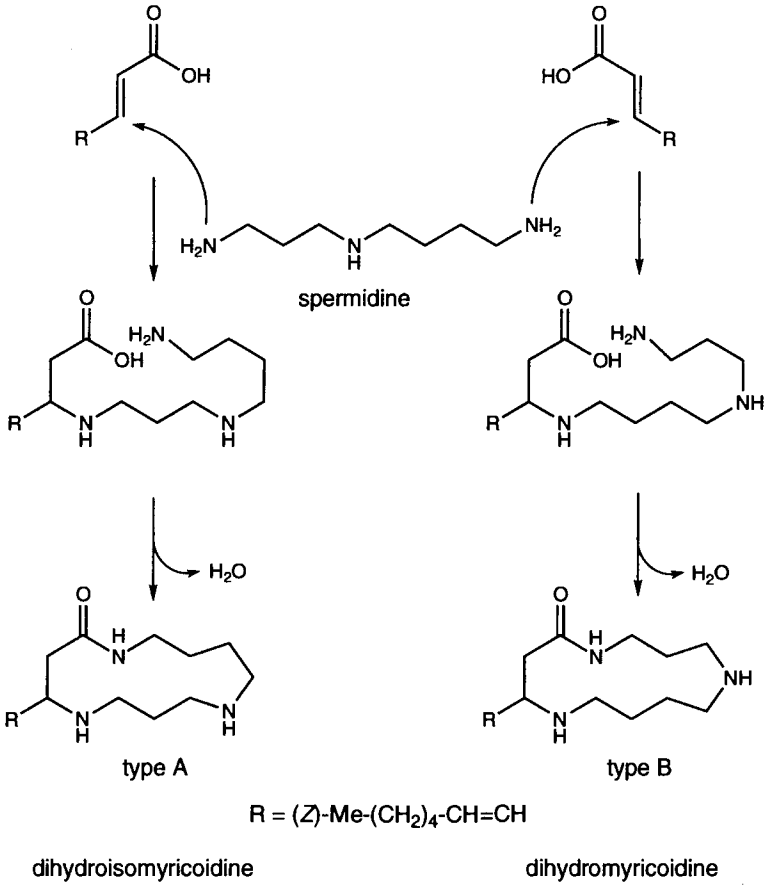
Introduction. – In 1936, the first spermidine alkaloid, containing a 13-membered ring, was isolated from the plant material of *Equisetum palustre* L. [1]. Since then, more than 30 different natural products, which contain a 13-membered ring system, built up from spermidine and a fatty or a cinnamic-acid unit, have been extracted from plants [2]. Due to the non-asymmetric structure of spermidine, two constitutionally different ring systems are possible and, in fact, both are found in nature. Although the biomimetic pathway is not yet well understood, we propose, that it follows a *Michael* addition of spermidine to an α,β-unsaturated fatty acid, followed by an intramolecular cyclization with the loss of H_2O (*Scheme 1*). Recently, we reported the enantioselective synthesis of (−)-(2*R*)-dihydromyricoidine [3], a type-B alkaloid, which was isolated from *Maytenus loeseneri* URB. (Celastraceae) [4] and *Clerodendrum myricoides* VATKE (Verbenaceae) [5]. It was in our interest to synthesize the isomeric compound of dihydromyricoidine, dihydroisomyricoidine, in which a ring system of type A is present, and which has not yet been found in Nature.

Synthesis and Discussion. – *Synthesis of the 13-Membered Ring System. N*-Benzyl-*N*-[(*tert*-butoxy)carbonyl]propane-1,3-diamine (**1**) was prepared from propane-1,3-diamine according to the procedure of *Huang et al.* [6]. *N*-Alkylation with 4-bromobutyronitrile in boiling THF in the presence of Et_3N led to the spermidine derivative **2** in 76% yield (*Scheme 2*). The (*tert*-butoxy)carbonyl (Boc) protecting group was cleaved by treatment with CF_3COOH (TFA). The subsequent *Michael* addition to the α,β-unsaturated ethyl carboxylate **4** could be achieved in THF at room temperature by the addition of an excess of LiCl[2]), resulting in a 13:2 mixture (determined by ^{1}H-NMR) of the main product **5** and its diastereoisomer. Separation by column chromatography on silica gel afforded the pure (3*R*)-isomer **5** in 71% yield. The configuration at C(3) was determined by an X-ray analysis of compound **8**, in which the configuration at C(4') was already known (*Fig.*). The reduction of the CN group of **5** with H_2 and *Raney*-Ni as a catalyst in a solvent

[1]) Part of the Ph. D. thesis of *A. H.*, Universität Zürich, 1997.

[2]) In the absence of LiCl the reaction failed. We assume that a complexation between the Li^+ cation and the carbonyl system of **4** enhances the electrophilicity at the β-position of **4**.

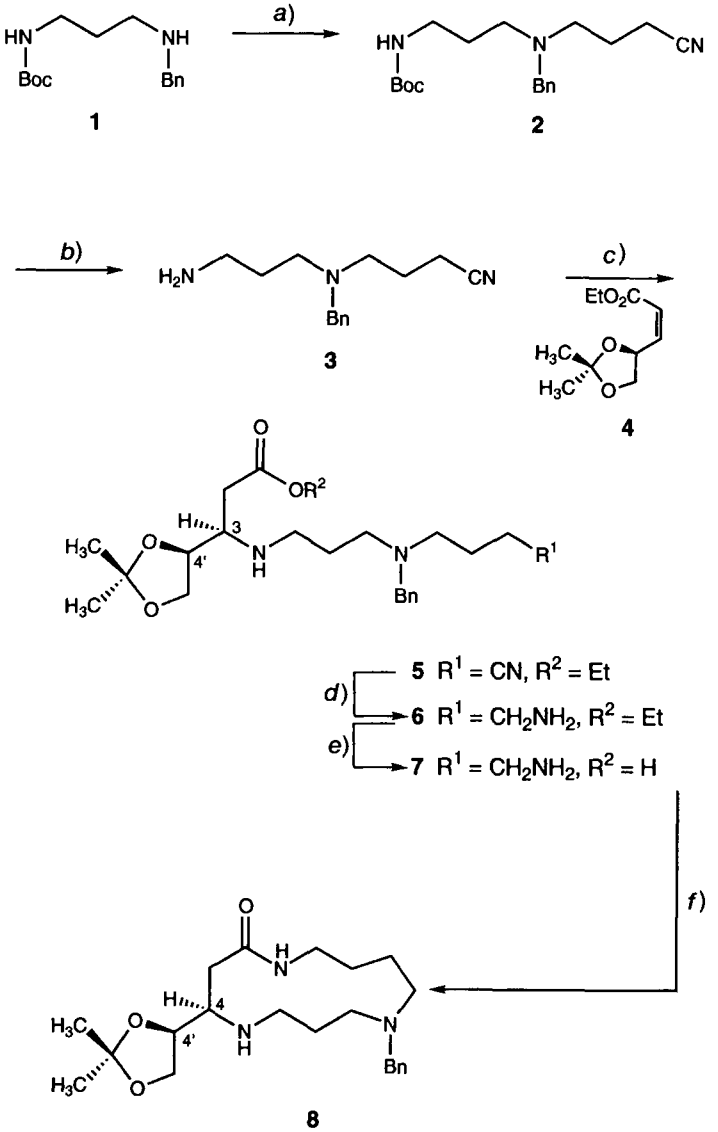
Scheme 1. *Proposed Biomimetic Pathway for 13-Membered Cyclic Spermidine Alkaloids*



mixture of aqueous 25% NH_4OH solution/EtOH provided the primary amine **6** in 77% yield, which was converted to the amino acid **7** by saponification with LiOH in THF/MeOH/H_2O 3:1:1. The cyclization of **7** with diethyl phosphorocyanidate ($(EtO)_2$-POCN) [8] in the presence of Et_3N in DMF furnished, after column chromatography and crystallization, the secondary 13-membered amino lactam **8** in 63% yield. The cyclization of the amino ester **6** with $B(NMe_2)_3$ according to the method of *Yamamoto* and *Maruoka* [9] failed; after workup the starting material was re-isolated.

The Periodate Cleavage. Treatment of the amino lactam **8** with 1N aqueous HCl in THF led to the cleavage of the acetal in 95% yield (*Scheme 3*). In an attempt to obtain the hydroxy compound **10**, $NaIO_4$ was initially added to the MeOH solution of the 1,2-diol **9**, followed, after 1 h stirring at 0°, by an excess of $NaBH_4$. After aqueous workup and column chromatography on silica gel, not the desired alcohol **10**, but, instead, compound **11** with no substituent at C(4) was isolated. Under the oxidative and then reductive conditions used in this procedure, the substituent at C(4) was cleaved from the 13-membered ring system, probably because of the secondary N(5)-atom, which

Scheme 2



a) 4-Bromobutyronitrile, Et_3N, THF, reflux; 76%. *b*) CF_3COOH, CH_2Cl_2, r.t.; 95%. *c*) LiCl, THF, r.t.; 71%. *d*) H_2, *Raney*-Ni, 25% aq. NH_4OH soln., EtOH, r.t.; 77%. *e*) LiOH, THF/MeOH/H_2O 3:1:1, r.t.; 80%. *f*) $(EtO)_2POCN$, Et_3N, DMF, r.t.; 63%.

reacted with $NaIO_4$ to form an imine. Reduction of the imine to a secondary amino group led to **11** (*Scheme 4*).

The N(5)-Protecting Group. To prevent the cleavage of the substituent at C(4) of the ring system, the N(5)-atom had to be converted into a non-nucleophilic group. As a protecting group, Boc was chosen. To introduce the Boc group, the amino lactam **8** was

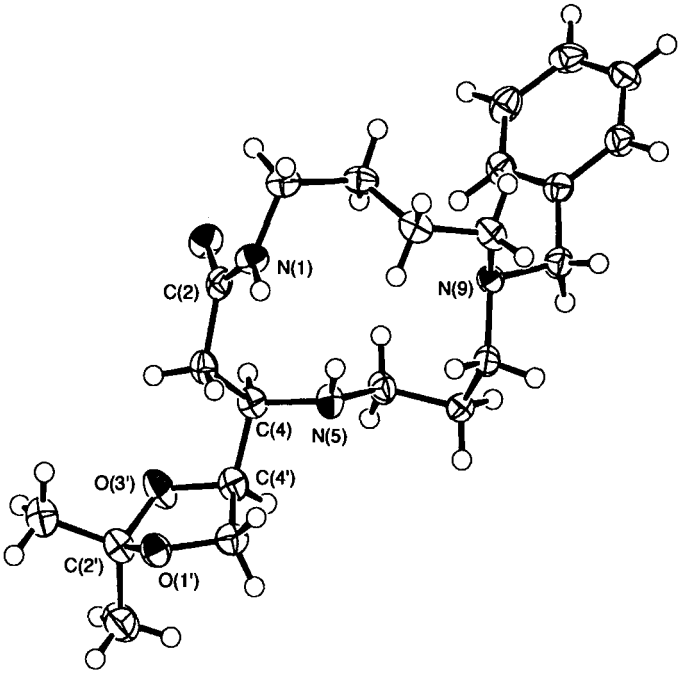
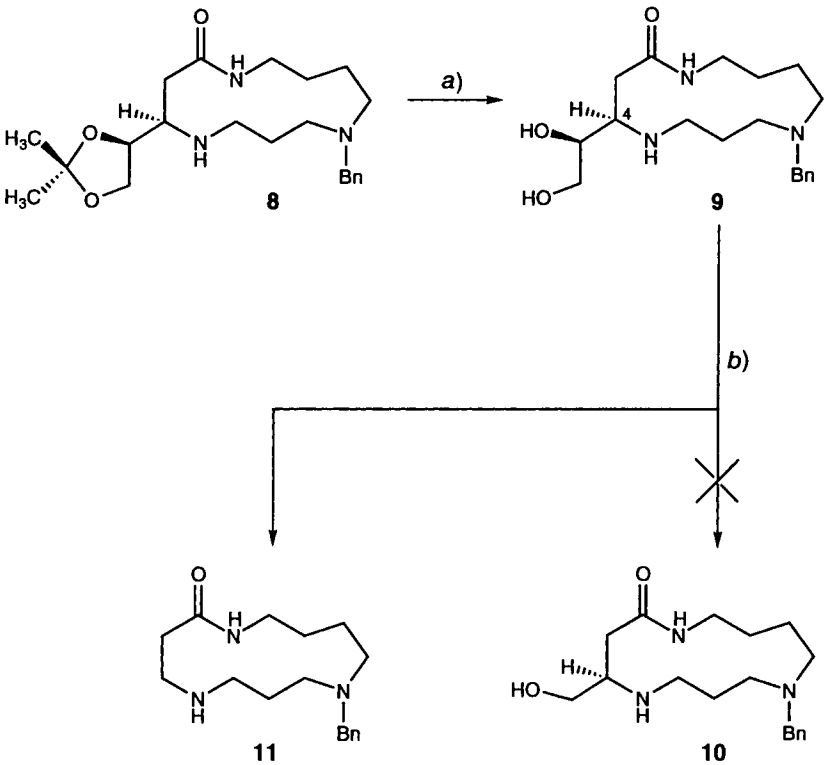


Figure. *ORTEP Plot* [7] *with 50% probability ellipsoids of the crystal structure of* **8**

heated to reflux with an excess of di(*tert*-butyl) dicarbonate (Boc_2O) in dioxane (*Scheme 5*). After column chromatography (silica gel), the *N*(5)-Boc protected compound **12** was isolated in 76% yield. Cleavage of the acetal moiety of **12** was accomplished in MeOH with the addition of 1.5 equiv. of camphorsulfonic acid (CSA) (77%). The 1,2-dihydroxy compound **13** was then treated with $NaIO_4$, followed by an excess of $NaBH_4$, which led to the alcohol **14** in almost quantitative yield. After transformation of the OH group in **14** to a halide and then to a phosphonium salt, *Wittig* reaction with a C_6-aldehyde should allow the introduction of the desired side chain. Thus, **14** was heated in CCl_4 in the presence of Ph_3P to give the chloride **15**; but when **15** was purified by column chromatography (silica gel), the *retro* reaction to the alcohol **14** took place. In an attempt to exchange the Cl-atom of crude **15** for a Br-atom by using LiBr in boiling acetone, only the bicyclic carbamate **16** could be isolated. The same product **16** was also isolated when the alcohol **14** was tosylated in pyridine or treated with CBr_4 or *N*-bromosuccinimide (NBS) in the presence of Ph_3P in MeCN and CH_2Cl_2, respectively. Similar cyclization reactions were observed by *Song* [10], when *N*-(2,2,2-trichloroethoxy)-carbonyl-protected *β*-amino alcohols were purified over silica gel.

The Formation of the Amido Acetal. To avoid the cleavage of the *tert*-butyl cation (→ **16**), we decided to reverse the *Wittig* reaction, which requires the presence of an aldehyde group at C(4) of the 13-membered ring system. When the 1,2-diol **13** was treated with $NaIO_4$, a compound was isolated with the correct molecular weight (*M* 417) for the desired aldehyde **17** (*Scheme 6*). However, in the ^{1}H-NMR spectra, the signals for the amide and the aldehyde protons at low field, as well as those for the carbonyl group

Scheme 3

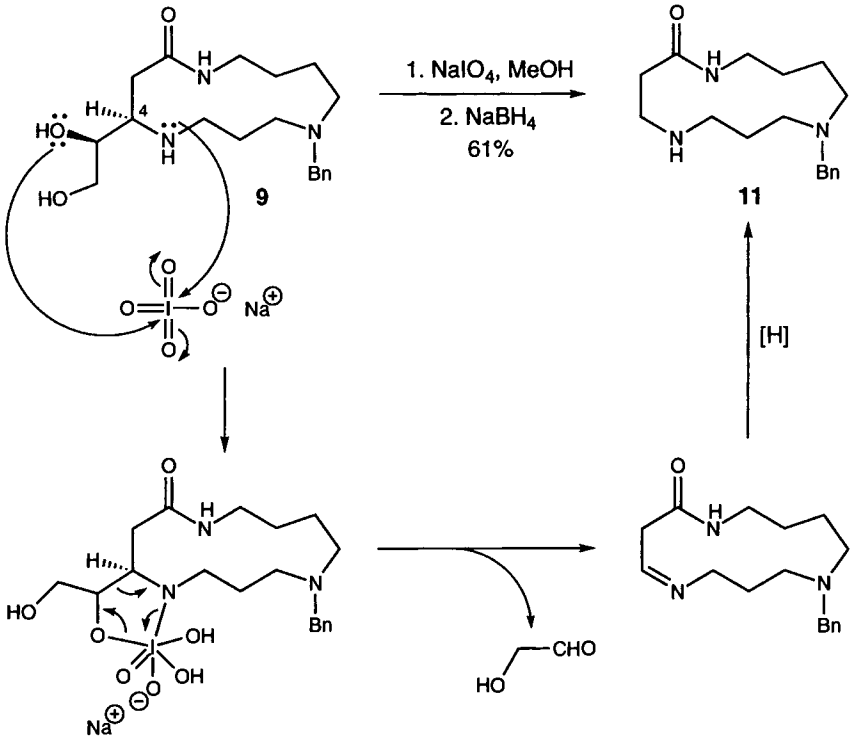


a) 1N aq. HCl, THF, reflux; 95%. *b*) 1. $NaIO_4$, MeOH, 0°; 2. $NaBH_4$; 61%.

of the aldehyde in the ^{13}C-NMR spectra, were missing. Therefore, the expected aldehyde **17** is present in the corresponding bicyclic hemiaminal form **18**. The nucleophilic attack of the lactam N-atom at the aldehyde carbonyl group was also observed by *Song* [10] on treatment of secondary amino lactams containing a side chain with an aldehyde group under basic conditions. In an attempt to introduce a C_6 side chain, **18** was treated with the phosphonium salt **19** under basic conditions. However, after workup, the starting material was re-isolated in almost quantitative yield.

Synthesis of the Fully Protected Amino Lactam and the Reaction to Dihydroisomyricoidine (**28**). To introduce the C_6 side chain, we envisaged adding different protecting groups at N(5) and N(1). Instead of the Boc group at N(5), the (benzyloxy)carbonyl group (Z) and, for the amide N-atom, the Boc group were chosen. The Z group was introduced in 89% yield by treatment of compound **8** with (benzyloxy)carbonyl chloride (Z–Cl) in boiling THF (→ **20**; *Scheme 7*). Introduction of the Boc group took place with a 76% yield in a mixture of NaH/4-(dimethylamino)pyridine(DMAP)/Boc_2O in THF at room temperature, leading to **21**. The conversion of the fully protected amino lactam **21** to the 1,2-dihydroxy compound **22** was achieved with camphorsulfonic acid (CSA) in MeOH. Treatment of **22** with $NaIO_4$ afforded **23**, which was, to avoid racemization, directly converted at −78° to the *Wittig* product **25** by treatment with 3 equiv. of the

Scheme 4. *Proposed Mechanism for the Cleavage of the Substituent from the 13-Membered Ring System*



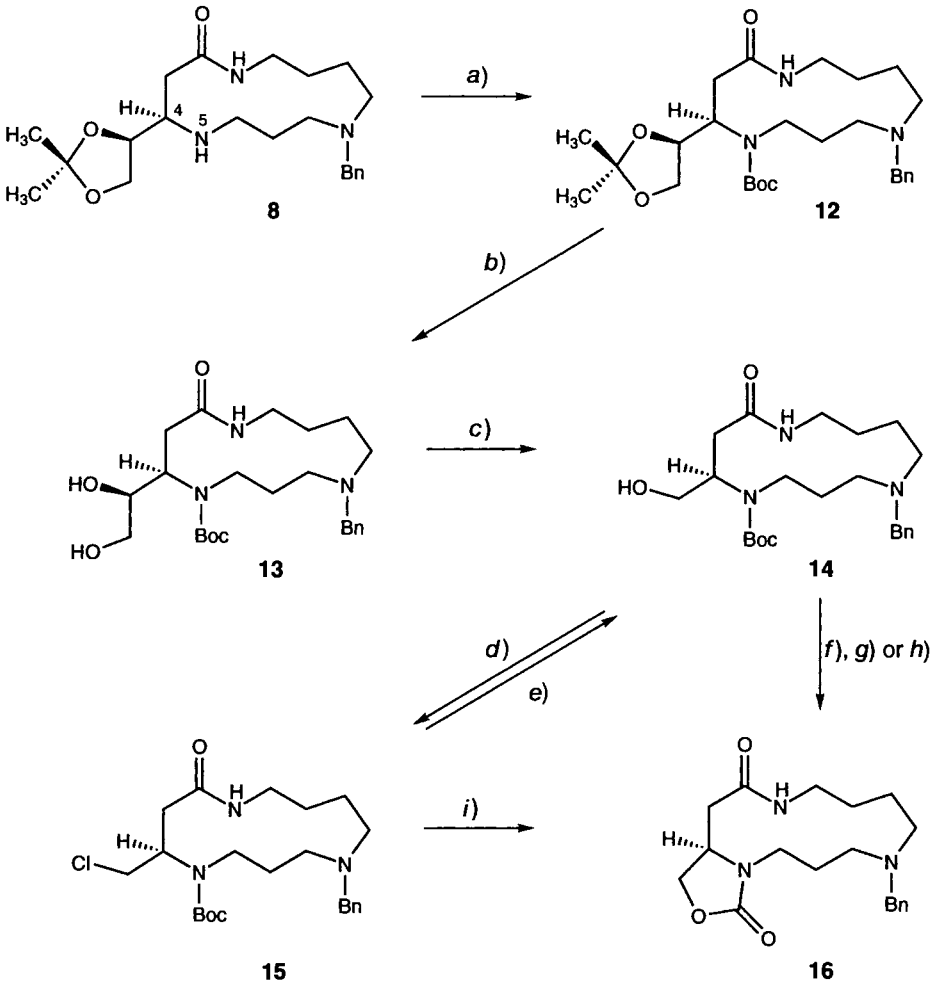
freshly prepared ylide from **24**. The synthesis was completed by removing the N-protecting groups: the secondary amide **26** was obtained in 90% yield with the assistance of TFA, the Bn group was cleaved in refluxing $CHCl_3$ with an excess of 1-chloroethyl carbonochloridate (55%) and the Z group was cleaved by treatment of compound **27** with Me_3SiI in MeCN to give the title compound (–)-(4*R*)-dihydroisomyricoidine (**28**) in 60% yield.

We thank the analytical departments of our institute for measurements and the *Swiss National Science Foundation* for the financial support.

Experimental Part

General. Hydrogenation: *Parr-Instruments Company Inc.* and *Büchi* (Laborautoklav *BEP 280*). For the slow addition of **7**, an infusion pump (*Precidor 5003, Infors AG*, Switzerland) was used. Column chromatography (CC): *Merck* silica gel *60* (40–60 μ). TLC: *Merck* silica gel $60F_{254}$. M.p.: *Mettler FP5*. Optical rotation: *Perkin-Elmer 241*; $[\alpha]_D^{21}$ at 589 nm and 21°. IR: *Perkin-Elmer 297*; measured as film, unless otherwise stated; in cm^{-1}. ^{1}H-NMR: *Bruker ARX 300* (300 MHz) and *Bruker AMX 600* (600 MHz); in $CDCl_3$; unless otherwise stated; chemical shifts δ in ppm using $SiMe_4$ (= 0 ppm) as internal standard, coupling constants J in Hz. ^{13}C-NMR: *Bruker ARX 300* (75 MHz) and *Bruker AMX 600* (150 MHz); in $CDCl_3$, unless otherwise stated. MS: *Finnigan SSQ 700*, *Finnigan MAT 90*, or *Finnigan TSQ 700*.

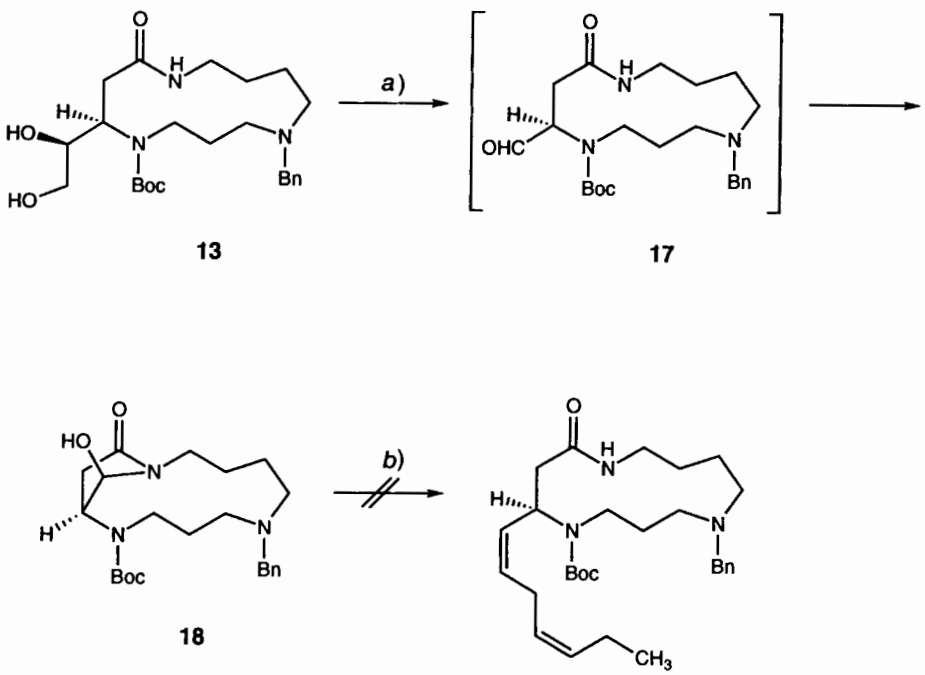
Scheme 5



a) Boc_2O, dioxane, Et_3N, 80°; 76%. *b*) CSA, MeOH, r.t.; 77%. *c*) 1. $NaIO_4$, MeOH, H_2O, 0°; 2. $NaBH_4$; 99%. *d*) Ph_3P, CCl_4. *e*) SiO_2. *f*) TsCl, pyridine, r.t.; 82%. *g*) NBS, Ph_3P, CH_2Cl_2, 0° → r.t.; 65%. *h*) Ph_3P, CBr_4, MeCN, 0° → r.t.; 52%. *i*) LiBr, acetone, reflux; 66%.

*5-Benzyl-8-{[(*tert*-butoxy)carbonyl]amino}-5-azaoctanenitrile* (= *4-{Benzyl{3-{[(*tert*-butoxy)carbonyl]amino}-propyl}amino}butanenitrile*; **2**). To a soln. of *N*-benzyl-*N*-[(*tert*-butoxy)carbonyl]propane-1,3-diamine (**1**; 41.091 g, 155 mmol) and Et_3N (100 ml) in THF (250 ml), 4-bromobutyronitrile (16 ml, 161 mmol) were added. The mixture was refluxed for 36 h. After 12 and after 24 h, 4-bromobutyronitrile (2.5 ml, 25.2 mmol) was added. After evaporation, the residue was purified by CC (SiO_2 (800 g), AcOEt/hexane 1:2): 38.996 g (76%) of **2**. Colorless oil. IR: 3350*m*, 3080*w*, 3060*m*, 3020*m*, 2970*s*, 2930*s*, 2860*s*, 2800*s*, 2240*m*, 1700*s*, 1510*s*, 1450*s*, 1390*s*, 1360*s*, 1270*s*, 1250*s*, 1170*s*, 1130*s*, 1070*s*, 1030*s*, 1000*m*, 970*m*, 910*w*, 860*m*, 820*w*, 780*m*, 730*s*, 700*s*. ^{1}H-NMR: 7.3–7.25 (*m*, 5 arom. H); 5.29 (br. *s*, BocN*H*); 3.53 (*s*, PhCH_2N); 3.15–3.1 (*m*, CH_2(8)); 2.55–2.45 (*m*, CH_2(4), CH_2(6)); 2.37 (*t*, *J* = 7.3, CH_2(2)); 1.78 (*quint.*, *J* = 6.9, CH_2(3) or CH_2(7)); 1.66 (*quint.*, *J* = 6.6, CH_2(3) or CH_2(7)); 1.44 (*s*, *t*-Bu). ^{13}C-NMR: 155.9 (*s*, C=O); 138.9 (*s*, arom. C); 128.8, 128.4, 127.3 (3*d*, 5 arom. CH); 119.7 (*s*, CN); 78.9 (*s*, Me_3C); 58.8 (*t*, PhCH_2N); 52.3, 52.1 (2*t*, C(4), C(6)); 39.2 (*t*, C(8)); 28.4 (*q*, Me_3C); 26.9, 23.4 (2*t*, C(3), C(7)); 14.9 (*t*, C(2)). CI-MS: 333 (13), 332 (100, $[M + 1]^+$), 276 (5), 187 (3), 91 (4).

Scheme 6

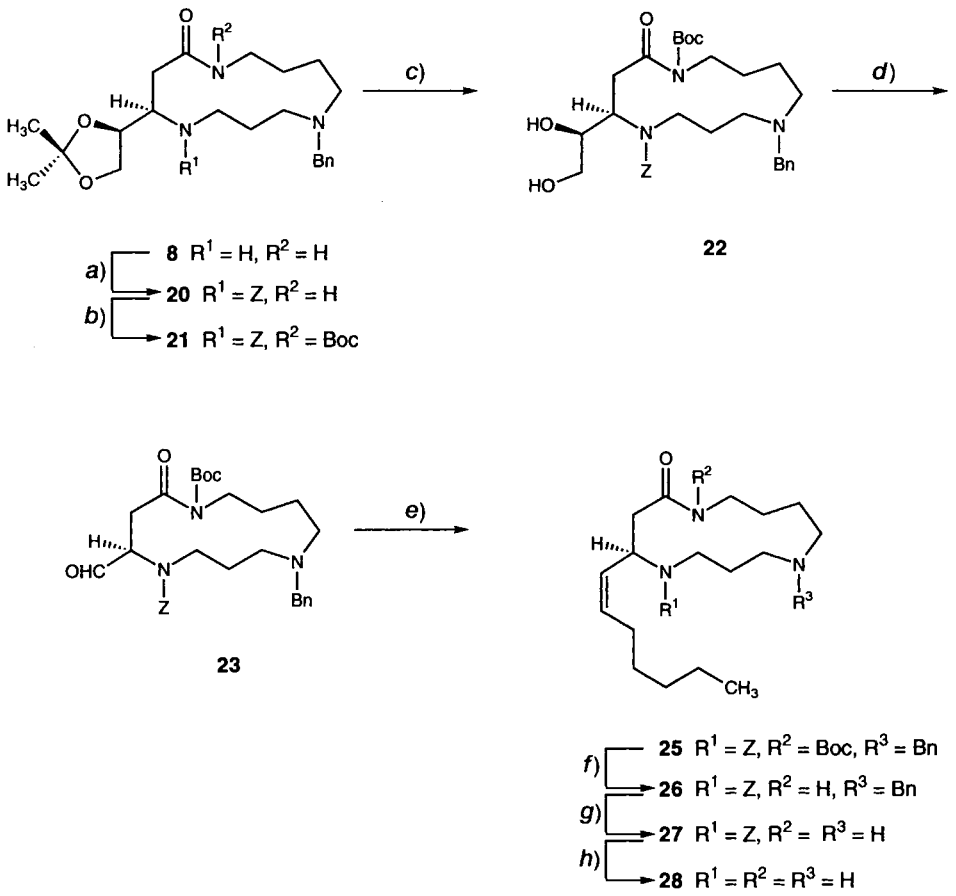


a) $NaIO_4$, MeOH, H_2O, 0°; 99%. *b*) [(*Z*)-$MeCH_2CH{=}CH(CH_2)_2PPh_3$]I (**19**), KO'Bu, BuLi or NaH, THF, −78° → −40°.

8-Amino-5-benzyl-5-azaoctanenitrile (= *4-[(3-Aminopropyl)amino]butanenitrile*; **3**). A soln. of **2** (1.313 g, 3.96 mmol) in CH_2Cl_2 (25 ml) was cooled to 0°, and CF_3COOH (16 ml) was added slowly. After warming up to r.t., stirring was continued for 2 h. Then H_2O (20 ml) was added and the pH value adjusted to 10 by adding solid Na_2CO_3. The org. layer was separated and the aq. soln. extracted with CH_2Cl_2. Evaporation of the combined org. layers gave 818 mg (95%) of **3**. Colorless oil. IR: 3370*m*, 3080*w*, 3060*m*, 3020*m*, 2940*s*, 2810*s*, 2240*m*, 1600*w*, 1490*m*, 1450*s*, 1420*m*, 1370*m*, 1300*w*, 1250*w*, 1210*w*, 1130*m*, 1070*m*, 1030*m*, 910*m*, 820*m*, 735*s*, 700*s*. ^{1}H-NMR: 7.35–7.2 (*m*, 5 arom. H); 3.53 (*s*, PhCH_2N); 2.70 (*t*, *J* = 6.9, CH_2(8)); 2.55, 2.52 (2*t*, *J* = 6.5, CH_2(4), CH_2(6)); 2.37 (*t*, *J* = 7.2, CH_2(2)); 1.76, 1.61 (2 *quint.*, *J* = 6.9, CH_2(3), CH_2(7)); 1.30 (*s*, NH_2). ^{13}C-NMR: 139.3 (*s*, arom. C); 128.9, 128.3, 127.1 (3*d*, 5 arom. CH); 119.9 (*s*, CN); 58.7 (*t*, PhCH_2N); 52.0, 51.4 (2*t*, C(4), C(6)); 40.2 (*t*, C(8)); 30.8, 23.5 (2*t*, C(3), C(7)); 14.8 (*t*, C(2)). CI-MS: 187 (9, $[M - C_2H_6N]^+$), 173 (13), 140 (14), 111 (21), 97 (9), 91 (100, $[C_7H_7]^+$).

Ethyl (3R,4'S)-8-Benzyl-11-cyano-3-(2',2'-dimethyldioxolan-4'-yl)-4,8-diazaundecanoate (= *Ethyl (3R)-3-{{3-[Benzyl(3-cyanopropyl)amino]propyl}amino}-3-[(4S)-2,2-dimethyldioxolan-4-yl]propanoate*; **5**). A soln. of **3** (666 mg, 2.879 mmol) in THF (10 ml) was added to **4** (577 mg, 2.882 mmol) and LiCl (1.222 g, 28.8 mmol) in THF (50 ml) within 15 min at 0°. The mixture was allowed to warm to r.t. and stirred for 10 d. After evaporation, the residue was taken up in H_2O and extracted with CH_2Cl_2. The combined org. layer was evaporated and the residue purified by CC (SiO_2, Et_2O → CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:10:1): 883 mg (71%) of **5**. Colorless oil. $[\alpha]_D^{21} = -2.26$ (*c* = 1.107, MeOH). IR: 2980*s*, 2930*s*, 2700*m*, 2220*m*, 1730*s*, 1600*w*, 1490*m*, 1450*s*, 1370*s*, 1350*m*, 1210*s*, 1180*s*, 1150*s*, 1060*s*, 940*w*, 910*w*, 860*m*, 790*w*, 730*s*, 700*s*. ^{1}H-NMR: 7.35–7.2 (*m*, 5 arom. H); 4.13 (*q*, *J* = 7.0, MeCH_2O); 4.1–4.05 (*m*, H–C(4')); 3.97 (*dd*, *J* = 7.9, 6.5, H_a–C(5')); 3.73 (*dd*, *J* = 7.7, 7.4, H_b–C(5')); 3.53 (*s*, PhCH_2N); 3.05 (*t*, *J* = 5.9, H–C(3)); 2.7–2.3 (*m*, CH_2(2), CH_2(5), CH_2(7), CH_2(9), CH_2(11)); 1.8–1.6 (*m*, CH_2(6), CH_2(10)); 1.39, 1.33 (2*s*, Me_2C(2')); 1.26 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR: 172.1 (*s*, C=O); 139.3 (*s*, arom. C); 128.8, 128.3, 127.1 (3*d*, 5 arom. CH); 119.9 (*s*, CN); 109.2 (*s*, C(2')); 77.6 (*d*, C(4')); 66.2 (*t*, C(5')); 58.6 (*t*, PhCH_2N); 56.5 (*d*, C(3)); 52.1, 51.9 (2*t*, C(5), C(7)); 45.4 (*t*, C(9)); 36.1 (*t*, C(6)); 27.6

Scheme 7



a) Z–Cl, (i-Pr)$_2$EtN, THF, reflux; 89%. *b*) Boc$_2$O, NaH, DMAP, THF, r.t.; 76%. *c*) CSA, MeOH; 73%. *d*) NaIO$_4$, MeOH, 0° → r.t.; 84%. *e*) [Me(CH$_2$)$_5$PPh$_3$]Br (**24**), KO^{t}Bu, THF, –78° – 40°; 32%. *f*) CF$_3$COOH, CHCl$_3$, 0° → r.t.; 97%. *g*) 1. ClCO$_2$CHClMe, CHCl$_3$, reflux; 2. MeOH, reflux; 55%. *h*) 1. Me$_3$SiI, MeCN; 2. MeOH, reflux; 60%.

(*t*, C(10)); 26.4, 25.1 (2*q*, *Me*$_2$C(2')); 23.5 (*t*, MeCH$_2$O); 14.7 (*t*, CH$_2$CN); 14.1 (*q*, *Me*CH$_2$O). CI-MS: 433 (28), 432 (100, [*M* + 1]$^+$), 232 (6).

Ethyl (3R,4'S)-12-Amino-8-benzyl-3-(2',2'-dimethyldioxolan-4'-yl)-4,8-diazadodecanoate (= Ethyl (3R)-3-{{3-[(4-Aminobutyl)benzylamino]propyl}amino}-3-[(4S)-2,2-dimethyldioxolan-4-yl]propanoate; **6**). A suspension of **5** (4.259 g, 9.87 mmol) and *Raney*-Ni (3 g) in EtOH (250 ml) and 25% aq. NH$_4$OH soln. (70 ml) was hydrogenated overnight at r.t. and 4 atm. The catalyst was filtered off, the filtrate evaporated, and the residue purified by CC (SiO$_2$ (200 g), CH$_2$Cl$_2$/MeOH/25% aq. NH$_4$OH soln. 100:10:1): 3.310 g (77%) of **6**. Colorless oil. $[\alpha]_D^{21} = -3.92$ (*c* = 1.046, MeOH). IR: 3330*w*, 3080*w*, 3060*w*, 3020*m*, 2980*s*, 2930*s*, 2860*m*, 2800*m*, 1730*s*, 1490*m*, 1450*s*, 1250*s*, 1210*s*, 1150*s*, 1060*s*, 855*m*, 730*m*, 700*s*. ^{1}H-NMR: 7.3–7.2 (*m*, 5 arom. H); 4.12 (*q*, *J* = 7.1, MeC*H*$_2$O); 3.96 (*t*, *J* = 7.3, H$_a$–C(5')); 3.74 (*dd*, *J* = 7.6, 7.3, H$_b$–C(5')); 3.53 (*s*, PhC*H*$_2$N); 3.06 (*q*, *J* = 6.0, H–C(3)); 2.7–2.3 (*m*, CH$_2$(2), CH$_2$(5), CH$_2$(7), CH$_2$(8), CH$_2$(9), CH$_2$(12)); 1.62 (*quint.*, *J* = 7.0, CH$_2$(6)); 1.5–1.4 (*m*, CH$_2$(10), CH$_2$(11), NH$_2$, NH); 1.39, 1.33 (2*s*, Me$_2$C(2')); 1.25 (*t*, *J* = 7.0, *Me*CH$_2$O). ^{13}C-NMR: 172.2 (*s*, C=O); 140.0 (*s*, arom. C); 128.8, 128.1, 126.7 (3*d*, 5 arom. CH); 109.1 (*s*, C(2')); 77.4 (*d*, C(4')); 66.1 (*t*, C(5')); 60.4 (*t*, MeCH$_2$O); 58.6 (*t*, PhCH$_2$N); 56.4 (*d*, C(3)); 53.6, 51.7 (2*t*, C(5), C(7)); 45.6, 42.0 (2*t*, C(9), C(12)); 36.1,

31.5, 27.7, 24.3 (4*t*, C(6), C(10), C(11), C(12)); 26.4, 25.1 (2*q*, *Me*$_2$C(2')); 14.1 (*q*, *Me*CH$_2$O). CI-MS: 437 (27), 436 (100, $[M + 1]^+$), 236 (7).

*(3*R*,4'*S*)-12-Amino-8-benzyl-3-(2',2'-dimethyldioxolan-4'-yl)-4,8-diazadodecanoic Acid (= (3*R*)-3-{{3-[(4-Aminobutyl)butylamino]propyl}amino}-3-[(4*S*)-2,2-dimethyldioxolan-4-yl]propanoate*; **7**). A soln. of **6** (2.453 g, 5.631 mmol) and LiOH · H$_2$O (500 mg, 11.92 mmol) in THF/MeOH/H$_2$O 3:1:1 (30 ml) was stirred at r.t. for 4 h. The solvent was evaporated and the residue purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 78:17:3): 1.967 g (80%) of **7**. Colorless oil. $[\alpha]_D^{21} = +2.68$ (*c* = 0.8224, MeOH). IR ($CHCl_3$): 2980*s*, 2940*s*, 2810*s*, 1570*s*, 1450*s*, 1380*s*, 1230*m*, 1150*m*, 1065*s*, 850*m*. ^{1}H-NMR: 8.41 (*s*, NH_3^+); 7.3–7.2 (*m*, 5 arom. H); 4.34 (*q*, *J* = 6.9, H–C(4')); 4.05 (*t*, *J* = 7.2, H$_a$–C(5')); 3.65–2.85 (*m*, H$_b$–C(5'), H–C(3), PhC*H*$_2$N, CH$_2$(5), CH$_2$(7)); 2.45–2.3 (*m*, CH$_2$(2), CH$_2$(9), CH$_2$(12), NH); 1.85–1.4 (*m*, CH$_2$(6), CH$_2$(10), CH$_2$(11)); 1.36, 1.32 (2*s*, Me$_2$C(2')). ^{13}C-NMR: 175.7 (*s*, C=O); 138.5 (*s*, arom. C); 129.2, 128.3, 127.2 (3*d*, 5 arom. CH); 109.9 (*s*, C(2')); 76.1 (*d*, C(3)); 66.8 (*t*, C(5')); 58.9 (*d*, C(4')); 58.8 (*t*, PhC*H*$_2$N); 53.0, 51.1, 45.4 (3*t*, C(5), C(7), C(9)); 39.2, 35.3, 34.6 (3*t*, C(6), C(11), C(12)); 26.5, 25.5 (2*q*, *Me*$_2$C(2')); 24.3 (*t*, C(2)). ESI-MS: 420 (100, $[M - H + 2Li]^+$), 408 (95, $[M + 1]^+$).

*(4*R*,4'*S*)-9-Benzyl-4-(2',2'-dimethyldioxolan-4'-yl)-1,5,9-triazacyclotridecan-2-one* (**8**). To a soln. of (EtO)$_2$POCN (922 mg, 5.652 mmol) and Et$_3$N (4 ml) in DMF (200 ml) at r.t., a soln. of **7** (1.537 g, 3.77 mmol) in DMF (20 ml) was added within 24 h. After additional 24 h stirring at r.t., the solvent was evaporated, the residue taken up in sat. aq. $NaHCO_3$ soln., the mixture extracted with CH_2Cl_2, the combined org. phase evaporated, and the crude product purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:5:1) and crystallization from CH_2Cl_2/pentane yielded 925.2 mg (63%) of **8**. Colorless crystals. M.p. 135.6–137.7°. $[\alpha]_D^{21} = -51.1$ (*c* = 0.9949, MeOH). IR ($CHCl_3$): 2980*m*, 2940*m*, 2800*m*, 1640*s*, 1540*m*, 1450*m*, 1420*m*, 1380*m*, 1370*m*, 1210*s*, 1150*m*, 1060*s*, 930*m*, 880*w*, 850*m*, 790*s*, 720*s*, 620*m*, 590*m*. ^{1}H-NMR (600 MHz): 8.61 (br. *s*, H–N(1)); 7.3–7.2 (*m*, 5 arom. H); 4.1–4.05 (*m*, H–(4'), H$_a$–C(5')); 3.68 (*t*, *J* = 9.4, H$_b$–C(5')); 3.63 (*AB*, *J* = 13.3, PhC*H*$_A$N); 3.25–3.2 (*m*, H$_a$–C(13)); 3.23 (*AB*, *J* = 13.3, PhC*H*$_B$N); 3.0–2.75 (*m*, H–C(4), H$_a$–C(6), H$_a$–C(8), H$_b$–C(13)); 2.75–2.7 (*m*, H$_b$–C(6)); 2.48 (*dd*, *J* = 15.9, 3.6, H$_a$–C(3)); 2.35–2.25 (*m*, H$_b$–C(8), H$_a$–C(10)); 2.2–2.15 (*m*, H$_b$–C(10)); 2.08 (*dd*, *J* = 15.9, 6.7, H$_b$–C(3)); 1.9–1.85 (*m*, H$_a$–C(7)); 1.65–1.6 (*m*, H$_b$–C(7)); 1.55–1.4 (*m*, H–N(5), CH$_2$(11), CH$_2$(12)); 1.41, 1.36 (2*s*, Me$_2$C(2'')). ^{13}C-NMR (150 MHz): 170.5 (*s*, C(2)); 139.3 (*s*, arom. C); 129.6, 128.4, 127.2 (3*d*, 5 arom. CH); 109.6 (*s*, C(2')); 77.9 (*d*, C(4')); 67.5 (*t*, C(5')); 59.0 (*d*, C(4)); 58.9 (*t*, PhC*H*$_2$N); 54.3 (*t*, C(10)); 50.9 (*t*, C(8)); 43.4 (*t*, C(6)); 38.0 (*t*, C(13)); 36.3 (*t*, C(3)); 27.5 (*t*, C(7)); 27.1 (*t*, C(11)); 27.1, 25.9 (2*q*, *Me*$_2$C(2')); 24.2 (*t*, C(12)). CI-MS: 309 (8), 308 (100), 291 (36), 169 (5). ESI-MS: 390 ($[M + 1]^+$).

*(4*R*,1'*S*)-9-Benzyl-4-(1',2'-dihydroxyethyl)-1,5,9-triazacyclotridecan-2-one* (**9**). A mixture of **8** (22.1 mg, 0.0567 mmol), THF (4 ml), and 1N aq. HCl (1 ml) was stirred at r.t. for 1 h and then refluxed for 2 h. After evaporation, the residue was taken up in sat. aq. Na_2CO_3 soln., extracted with CH_2Cl_2, and the combined org. phase evaporated: 18.8 mg (95%) of **9**. Colorless oil. $[\alpha]_D^{21} = -12.74$ (*c* = 1.060, MeOH). IR ($CHCl_3$): 3320*m*, 3000*s*, 2940*s*, 2860*s*, 2800*s*, 1735*w*, 1640*s*, 1550*m*, 1490*m*, 1450*s*, 1370*m*, 1350*m*, 1290*m*, 1200*m*, 1080*m*, 1030*m*, 960*w*, 910*w*, 880*w*, 870*w*, 840*w*, 690*m*. ^{1}H-NMR ((D$_6$)DMSO, 333 K): 7.95 (br. *s*, H–N(1)); 7.3–7.2 (*m*, 5 arom. H); 3.62 (*AB*, *J* = 13.3, PhC*H*$_A$N); 3.5–3.1 (*m*, H–C(4), H$_a$–C(13), H–C(1'), CH$_2$(2'), 2 OH); 3.05 (*AB*, *J* = 13.3, PhC*H*$_B$N); 2.95–2.8 (*m*, H$_b$–C(13)); 2.8–2.6 (*m*, CH$_2$(8)); 2.6–2.45 (*m*, CH$_2$(6)); 2.25–1.9 (*m*, CH$_2$(3), H$_a$–C(7), CH$_2$(10)); 1.7–1.4 (*m*, H$_b$–C(7), CH$_2$(12)); 1.4–1.2 (*m*, NH(5)); 1.2–0.9 (*m*, CH$_2$(11)). ^{13}C-NMR ((D$_6$)DMSO, 333 K): 171.9 (*s*, C(2)); 140.1 (*s*, arom. C); 129.1, 128.3, 127.0 (3*d*, 5 arom. CH); 72.8 (*d*, C(1')); 63.5 (*t*, C(2')); 59.1 (*t*, PhC*H*$_2$N); 58.5 (*d*, C(4)); 53.5, 49.8, 45.5 (3*t*, C(6), C(8), C(10)); 39.1, 38.2 (2*t*, C(3), C(13)); 27.8, 26.8, 24.1 (3*t*, C(7), C(11), C(12)). ESI-MS: 369 (10), 350 (100, $[M + 1]^+$), 338 (19), 312 (11).

9-Benzyl-1,5,9-triazacyclotridecan-2-one (**11**). To a stirred ice-cooled soln. of **9** (24.1 mg, 0.0702 mmol) in MeOH (10 ml), $NaIO_4$ (40 mg, 0.187 mmol) and H_2O (0.2 ml) were added. The mixture was stirred for 45 min, then $NaBH_4$ (150 mg, 3.97 mmol) was added in small portions. After warming up to r.t., stirring was continued for an additional 60 min, the mixture evaporated, the residue taken up in aq. 2N NaOH and extracted with CH_2Cl_2. Removal of the solvent and purification by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:5:1) gave 12.3 mg (61%) of **11**. Colorless oil. IR ($CHCl_3$): 3660*w*, 3180*s*, 3060*s*, 2980*s*, 2930*s*, 2800*s*, 1650*s*, 1560*s*, 1490*s*, 1450*s*, 1430*m*, 1370*m*, 1350*m*, 1340*s*, 1280*m*, 1240*s*, 1180*m*, 1140*s*, 1120*s*, 1070*m*, 1020*m*, 960*m*, 910*m*, 890*m*, 840*m*, 700*m*, 660*m*, 610*m*. ^{1}H-NMR: 8.65 (br. *s*, NH); 7.35–7.2 (*m*, 5 arom. H); 3.43 (*s*, PhC*H*$_2$N); 3.2–3.1 (*m*, CH$_2$(4)); 3.93 (*t*, *J* = 5.4, CH$_2$(12)); 2.80 (*t*, *J* = 5.6, CH$_2$(6) or CH$_2$(8)); 2.58 (*t*, *J* = 5.9, CH$_2$(6) or CH$_2$(8)); 2.30 (*t*, *J* = 5.5, H–C(10)); 2.25–2.2 (*m*, CH$_2$(3)); 1.8–1.7 (*m*, CH$_2$(7)); 1.7–1.4 (*m*, CH$_2$(11), CH$_2$(12), NH). ^{13}C-NMR: 173.1 (*s*, C=O); 139.2 (*s*, arom. C); 129.1, 128.1, 126.8 (3*d*, 5 arom. CH); 58.6 (*t*, PhC*H*$_2$N); 53.8, 49.7, 46.0, 45.8 (4*t*, C(4), C(6), C(9), C(11)); 38.4, 35.7 (2*t*, C(3), C(13)); 26.8, 26.1, 24.0 (3*t*, C(7), C(11), C(12)). CI-MS: 291 (18), 290 (100, $[M + 1]^+$).

*(4R,4'S)-9-Benzyl-5-[(*tert*-butoxy)carbonyl]-4-(2',2'-dimethyldioxolan-4'-yl)-1,5,9-triazacyclotridecan-2-one* (**12**). A mixture of **8** (513 mg, 1.32 mmol), Et_3N (1.5 ml) and Boc_2O (356 mg, 1.63 mmol) in dioxane (25 ml) was heated at 80° for 29 h. After 5, 11, and 24 h, 150 mg (0.687 mmol), 130 mg (0.596 mmol), and 110 mg (0.504 mmol) of Boc_2O, respectively, were added. After evaporation, the residue was taken up in sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The combined org. phase was evaporated and the residue purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:5:1): 489.6 mg (76%) of **12**. Amorphous solid. M.p. 155.7–157.9°. $[\alpha]_D^{21} = +5.72$ ($c = 1.015$, MeOH). IR ($CHCl_3$): 3440*m*, 2980*s*, 2940*s*, 2860*s*, 2800*m*, 1670*s*, 1510*s*, 1450*s*, 1420*s*, 1380*s*, 1365*s*, 1320*s*, 1250*s*, 1160*s*, 1060*s*, 970*m*, 910*w*, 860*m*, 695*w*. ^{1}H-NMR: 7.3–7.2 (*m*, 5 arom. H); 5.93 (br. *s*, H–N(1)); 4.55–4.35 (*m*, H–C(4')); 4.05–3.95 (*m*, H_a–C(5')); 3.95–3.45 (*m*, H_b–C(5'), PhCH_AN, CH_2(13)); 3.45–3.25 (*m*, PhCH_BN); 3.25–2.75 (*m*, H_a–C(3), H–C(4), H_a–C(6), H_a–C(8)); 2.75–2.35 (*m*, H_b–C(8), H_a–C(10)); 2.1–2.0 (*m*, H_b–C(3)); 1.95–1.5 (*m*, CH_2(7), CH_2(11), CH_2(12)); 1.47 (*s*, *t*-Bu); 1.45, 1.39 (2*s*, Me_2C(2')). ^{13}C-NMR[3]): 170.5 (*s*, C(2)); 156.0 (*s*, OCON); 139.5 (*s*, arom. C); 129.0, 128.2, 126.9 (3*d*, 5 arom. CH); 109.1 (*s*, C(2')); 80.0 (*s*, Me_3C); 76.1 (*d*, C(4')); 67.4 (*t*, C(5')); 59.9 (*t*, PhCH_2N); 51.8, 49.1, 48.0 (3*t*, C(6), C(8), C(10)); 38.8, 37.4 (2*t*, C(3), C(13)); 28.5 (*q*, Me_3C); 26.6, 25.5 (2*q*, Me_2C(2')); 25.1, 21.8 (2*t*, C(11), C(12)). ESI-MS: 490 ($[M + 1]^+$).

*(4R,1'S)-9-Benzyl-5-[(*tert*-butoxy)carbonyl]-4-(1',2'-dihydroxyethyl)-1,5,9-triazacyclotridecan-2-one* (**13**). A mixture of **12** (489.6 mg, 1.0 mmol), CSA (352 mg, 1.52 mmol), and 10 grains of molecular sieve (4 Å) in MeOH (20 ml) was stirred at r.t. for 24 h. The solvent was evaporated and the residue purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:10:1): 346 mg (77%) of **13**. Colorless amorphous solid. M.p. 59.2–60.3° (CH_2Cl_2/hexane). $[\alpha]_D^{21} = +11.40$ ($c = 1.0352$, MeOH). IR ($CHCl_3$): 3430*m*, 3320*m*, 2970*m*, 2930*s*, 2860*m*, 2790*m*, 1655*s*, 1510*m*, 1475*s*, 1450*m*, 1420*s*, 1390*m*, 1365*s*, 1200*s*, 1170*s*, 1140*m*, 1030*m*, 960*w*, 930*m*, 910*m*, 870*w*, 730*s*, 660*s*, 620*m*. ^{1}H-NMR: 7.4–7.2 (*m*, 5 arom. H); 6.06 (br. *s*, H–N(1)); 4.0–3.25 (*m*, H–C(1'), CH_2(2'), PhCH_2N, CH_2(6), CH_2(8)); 3.05–2.8 (*m*, H–C(4), H_a–C(13)); 2.8–2.0 (*m*, CH_2(3), H_b–C(13), CH_2(10)); 1.9–1.5 (*m*, CH_2(11) or CH_2(12), CH_2(7), 2 OH); 1.45 (*s*, *t*-Bu); 1.45–1.2 (*m*, CH_2(11) or CH_2(12)). ^{13}C-NMR[3]): 171.8 (*s*, C(2)); 129.0, 128.2, 127.0 (3*d*, 5 arom. CH); 80.9 (*s*, Me_3C); 64.1, 60.1 (2*t*); 28.4 (*q*, Me_3C). ESI-MS: 472 (10, $[M + Na]^+$), 450 (100, $[M + 1]^+$), 394 (61, $[M + 1 - C_4H_8]^+$), 350 (20, $[M + 1 - Boc]^+$).

*(4R)-9-Benzyl-5-[(*tert*-butoxy)carbonyl]-4-(hydroxymethyl)-1,5,9-triazacyclotridecan-2-one* (**14**). To a suspension of **13** (85.7 mg, 0.191 mmol) and $NaIO_4$ (131 mg, 0.612 mmol) in MeOH (15 ml), H_2O (0.3 ml) was added at 0°. The mixture was stirred for 90 min and $NaBH_4$ (300 mg, 7.93 mmol) was added in small portions. After warming up to r.t., stirring was continued for an additional 60 min. The solvent was evaporated and the residue taken up in sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2: 78.3 mg (99%) of **14**. Amorphous solid. M.p. 61.8–62.5° (Et_2O). $[\alpha]_D^{21} = +4.29$ ($c = 1.235$, $CHCl_3$). IR ($CHCl_3$): 3435*s*, 2970*s*, 2920*s*, 2860*s*, 2800*m*, 1665*s*, 1510*s*, 1470*s*, 1450*s*, 1420*s*, 1390*s*, 1365*s*, 1250*s*, 1160*s*, 1140*s*, 1070*s*, 995*m*, 960*m*, 910*w*, 880*w*, 850*m*, 695*w*, 655*w*. ^{1}H-NMR: 7.3–7.2 (*m*, 5 arom. H); 6.39 (br. *s*, H–N(1)); 4.0–3.8 (*m*, CH_2(1'), H_a–C(13), OH); 3.68 (*AB*, $J = 13.3$, PhCH_AN); 3.52 (*t*, $J = 11.1$, H_b–C(13)); 3.37 (*AB*, $J = 13.3$, PhCH_BN); 3.1–2.8 (*m*, H–C(2), H_a–C(6), CH_2(8)); 2.8–2.6 (*m*, H_b–C(6)); 2.6–2.45 (*m*, H_a–C(10)); 2.39 (*d*, $J = 14.0$, H_a–C(3)); 2.3–2.15 (*m*, H_b–C(3), H_b–C(10)); 1.9–1.5 (*m*, CH_2(7), CH_2(12)); 1.5–1.2 (*m*, CH_2(11)); 1.46 (*s*, *t*-Bu). ^{13}C-NMR: 171.9 (*s*, C(2), 156.6 (*s*, OCON); 139.6 (*s*, arom. C); 129.0, 128.2, 126.8 (3*d*, 5 arom. CH); 80.3 (*s*, Me_3C); 64.5, 60.0 (2*t*, PhCH_2N, C(1')); 52.0, 49.4, 47.6 (3*t*, C(6), C(8), C(10)); 38.9, 37.3 (2*t*, C(3), C(13)); 28.5 (*q*, Me_3C); 26.8, 25.2, 22.1 (3*t*, C(7), C(11), C(12)). ESI-MS: 450 (18), 420 (100, $[M + 1]^+$), 394 (10), 364 (79, $[M + 1 - C_4H_8]^+$), 320 (38, $[M + 1 - Boc]^+$).

*(11R)-6-Benzyl-10-[(*tert*-butoxy)carbonyl]-14-hydroxy-1,6,10-triazabicyclo[9.2.1]tetradecan-13-one* (**18**). A suspension of **13** (23.3 mg, 0.0518 mmol), $NaIO_4$ (27.9 mg, 0.130 mmol, 2.5 equiv.), and H_2O (0.1 ml) in MeOH (10 ml) was stirred at 0° for 1 h. The mixture was filtered through *Celite*, the filtrate evaporated, and the residue taken up in H_2O and extracted with CH_2Cl_2. Removal of the solvent gave 21.4 mg (99%) of **18**. Colorless oil. $[\alpha]_D^{21} = +12.32$ ($c = 0.495$, MeOH). IR ($CHCl_3$): 3360*m*, 3000*m*, 2980*m*, 2920*s*, 2860*m*, 2800*m*, 1680*s*, 1600*m*, 1490*m*, 1470*m*, 1450*s*, 1410*s*, 1395*s*, 1370*s*, 1345*m*, 1300*m*, 1250*s*, 1160*s*, 1040*m*, 1010*m*, 960*w*, 950*m*, 910*w*, 880*w*, 850*w*, 700*w*, 660*w*. ^{1}H-NMR: 7.3–7.25 (*m*, 5 arom. H); 5.21 (*d*, $J = 6.3$, H–C(14)); 4.9–4.85 (*m*, H–C(11)); 3.95–3.8 (*m*, H_a–C(9)); 3.8–3.65 (*m*, H_a–C(5)); 3.61 (*s*, PhCH_2N); 3.05–2.95 (*m*, H_a–C(2)); 2.8–2.3 (*m*, H_a–C(5), H_b–C(7), H_b–C(9), CH_2(12)); 2.25–2.15 (*m*, H_b–C(12)); 2.1–1.9 (*m*, H_b–C(2)); 1.9–1.65 (*m*, CH_2(4), CH_2(8)); 1.6–1.2 (*m*, CH_2(3), OH); 1.43 (*s*, *t*-Bu). ^{13}C-NMR: 173.0 (*s*, C(13)); 156.4 (*s*, OCON); 135.8 (*s*, arom. C); 130.5, 128.5, 127.5 (3*d*, 5 arom. CH); 86.7 (*d*, C(14)); 80.3 (*s*, Me_3C); 59.1 (*t*, PhCH_2N); 54.0,

[3]) Because of many conformers, not all signals were detected.

53.5 (2*t*, C(5), C(7)); 52.1 (*d*, C(11)); 43.6, 43.2 (2*t*, C(2), C(9)); 34.7 (*t*, C(12)); 28.4 (*q*, Me_3C); 27.6, 25.8, 23.8 (3*t*, C(3), C(4), C(8)). ESI-MS: 418 (100, $[M + 1]^+$), 362 (60, $[M + 1 - C_4H_8]^+$).

*(4*R*)-9-Benzyl-5-[(*tert*-butoxy)carbonyl]-4-(chloromethyl)-1,5,9-triazacyclotridecan-2-one* (**15**). A mixture of **14** (10.3 mg, 0.0245 mmol) and Ph_3P (8.6 mg, 0.0328 mmol) in THF (3 ml) was refluxed for 2 h. The mixture was evaporated and the residue purified by CC (SiO_2 (500 mg), CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:5:1): 7.9 mg of a compound whose spectroscopic data were identical with those of **14**. The structure of **15** was elucidated by ESI-MS measurements of the crude chloride before CC. ESI-MS/MS: 438 (20, $[M + 1]^+$), 382 (60, $[M + 1 - C_4H_8]^+$), 338 (100, $[M + 1 - Boc]^+$), 233 (20).

*(13*R*)-5-Benzyl-15-oxa-1,5,10-triazabicyclo[11.3.0]hexadecan-11,16-dione* (**16**). 1) A soln. of crude **15** (8.3 mg, 0.0189 mmol) and LiBr (17.7 mg, 0.204 mmol) in acetone (3 ml) was refluxed overnight. The solvent was evaporated and the residue purified by CC (SiO_2, CH_2Cl_2 → CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:10:1): 4.3 mg (66%) of **16**. Colorless oil.

2) To a mixture of **14** (14.0 mg, 0.0334 mmol) and Ph_3P (11.1 mg, 0.0423 mmol) in MeCN (3 ml), a soln. of CBr_4 (12.1 mg, 0.0365 mmol) in MeCN (0.4 ml) was added at 0°. After warming to r.t., the mixture was stirred for 48 h. Evaporation and CC (see above) gave 6.0 mg (52%) of **16**. Colorless oil.

3) A soln. of NBS (8.9 mg, 0.050 mmol) in CH_2Cl_2 (4 ml) was added dropwise at 0° to a soln. of **14** (18.3 mg, 0.0436 mmol) and Ph_3P (13.1 mg, 0.0499 mmol) in CH_2Cl_2 (4 ml). The mixture was allowed to warm to r.t. and stirred for 4 h. After evaporation, the residue was purified by CC (see above): 8.2 mg (65%) of **16**.

4) To a soln. of **4** (27.0 mg, 0.0644 mmol) and 3 drops of Et_3N in CH_2Cl_2 (3 ml), TsCl (15.8 mg, 0.0829 mmol, 1.3 equiv.) was added in one portion at r.t. The mixture was stirred overnight and evaporated. The residue was taken up in sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2, the combined org. phase evaporated, and the crude product purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. Na_4OH soln. 100:5:1): 18.3 mg (82%) of **16**. Colorless oil. IR ($CHCl_3$): 3440*w*, 3330*w*, 2980*m*, 2940*m*, 2860*m*, 2810*m*, 1740*s*, 1660*s*, 1600*w*, 1550*m*, 1520*m*, 1490*m*, 1480*m*, 1450*m*, 1420*m*, 1370*m*, 1260*m*, 1180*s*, 1140*m*, 1090*m*, 1070*m*, 1040*m*, 1030*w*, 1000*w*, 950*w*, 830*w*, 700*w*, 660*w*. ^{1}H-NMR: 7.49 (br. *s*, NH); 7.3–7.25 (*m*, 5 arom. H); 4.3–4.1 (*m*, CH_2O); 3.9–3.75 (*m*, H–C(13)); 3.75–3.5 (*m*, H_a–C(9)); 3.53 (*s*, PhCH_2N); 3.25–3.1 (*m*, H_b–C(9), H_a–C(4)); 2.65–2.4 (*m*, CH_2(2), H_b–C(4), CH_2(6)); 2.28 (*dd*, *J* = 15.4, 8.5, H_a–C(12)); 1.95–1.5 (*m*, CH_2(3), CH_2(7), CH_2(8), H_b–C(12)). ^{13}C-NMR: 168.8 (*s*, C(11)); 158.3 (*s*, OCON); 129.5, 128.3, 127.4 (3*d*, 5 arom. CH); 66.9 (*t*, C(14)); 59.9 (*t*, PhCH_2N); 53.4 (*d*, C(13)); 52.5, 51.2 (2*t*, C(4), C(6)); 41.6, 41.5 (2*t*, C(2), C(9)); 39.4 (*t*, C(12)); 26.0, 25.5 (2*t*, C(3), C(7), C(8)). ESI-MS: 368 (9, $[M + Na]^+$), 346 (100, $[M + 1]^+$). ESI-MS/MS: 346 (100, $[M + 1]^+$), 245 (21), 162 (61), 138 (70), 91 (45, $C_7H_7^+$).

*(4*R*,4′*S*)-9-Benzyl-5-[(benzyloxy)carbonyl]-4-(2′,2′-dimethyldioxolan-4′-yl)-1,5,9-triazacyclotridecan-2-one* (**20**). A mixture of **8** (433 mg, 1.11 mmol), (i-Pr)$_2$EtN (0.5 ml), and Z-Cl (213 mg, 1.25 mmol) in THF (10 ml) was refluxed for 4 h. After evaporation, the residue was purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 200:5:1): 519 mg (89%) of **20**. Colorless oil. IR: 3300*s*, 2980*s*, 2940*s*, 2820*m*, 1680*s*, 1550*m*, 1470*m*, 1450*s*, 1420*s*, 1380*m*, 1370*m*, 1300*m*, 1220*s*, 1160*m*, 1140*s*, 1060*s*, 1030*s*, 850*m*, 800*m*, 770*m*, 740*m*, 700*s*, 600*s*. ^{1}H-NMR ((D$_6$)DMSO, 360 K): 7.64 (*s*, H–N(1)); 7.4–7.2 (*m*, 10 arom. H); 5.19, 5.07 (*AB*, *J* = 12.7, PhCH_2O); 4.55–4.45 (*m*, H–C(4′)); 4.03 (*dd*, *J* = 8.4, 6.4, H_a–C(5′)); 3.81 (*t*, *J* = 8.3, H–C(4)); 3.68 (*dd*, *J* = 8.4, 6.6, H_b–C(5′)); 3.6–3.45 (*m*, H_a–C(6), H_a–C(13), PhCH_2N); 3.1–2.8 (*m*, H_a–C(3), H_b–C(6), H_b–C(13)); 2.6–2.45 (*m*, H_a–C(8), H_a–C(10)); 2.3–2.2 (*m*, H_b–C(8), H_b–C(10)); 2.05 (*dd*, *J* = 14.9, 1.8, H_b–C(3)); 1.8–1.4 (*m*, CH_2(7), CH_2(11), CH_2(12)); 1.37, 1.28 (2*s*, Me_2C(2′)). ^{13}C-NMR ((D$_6$)DMSO, 360 K): 169.4 (*s*, C(2)); 155.0 (*s*, OCON); 139.6, 136.5 (2*s*, 2 arom. C); 127.8, 127.7, 127.3, 127.0, 126.9, 125.9 (6*d*, 10 arom. CH); 107.8 (*s*, C(2′)); 75.2 (*d*, C(4′)); 66.3 (*t*, C(5′)); 65.5 (*t*, PhCH_2O); 59.7 (*d*, C(4)); 59.1 (*t*, PhCH_2N); 51.1 (*t*, C(10)); 49.1 (*t*, C(8)); 46.9 (*t*, C(6)); 37.0 (*t*, C(13)); 35.8 (*t*, C(3)); 26.1 (*t*, C(7)); 26.0, 24.7 (2*q*, Me_2C(2′)); 24.0 (*t*, C(11)); 21.3 (*t*, C(12)). ESI-MS: 524 ($[M + 1]^+$).

*(4*R*,4′*S*)-9-Benzyl-5-[(benzyloxy)carbonyl]-1-[(*tert*-butoxy)carbonyl]-4-(2′,2′-dimethyldioxolan-4′-yl)-1,5,9-triazacyclotridecan-2-one* (**21**). A suspension of **20** (2.772 g, 5.29 mmol), NaH (237.7 mg, 5.45 mmol), DMAP (634 mg, 5.189 mmol), and Boc_2O (5.92 g, 2.71 mmol) in THF (50 ml) was stirred at r.t. for 24 h. The solvent was removed and the crude product purified by CC (SiO_2, CH_2Cl_2 → CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:5:1): 2.506 g (76%) of **21**. Colorless oil. $[\alpha]_D^{21} = +20.3$ (*c* = 1.315, MeOH). IR: 3080*w*, 3060*w*, 3030*m*, 2980*s*, 2920*s*, 2860*s*, 1735*s*, 1690*s*, 1600*w*, 1580*w*, 1450*s*, 1420*s*, 1370*s*, 1330*s*, 1280*s*, 1250*s*, 1150*s*, 1060*s*, 1000*m*, 950*m*, 920*w*, 850*s*, 790*m*, 770*m*, 700*s*. ^{1}H-NMR: 7.35–7.15 (*m*, 10 arom. H); 5.16, 5.04 (*AB*, *J* = 12.7, PhCH_2O); 4.45 (*t*, *J* = 6.9, H–C(4′)); 4.1–3.95 (*m*, H–C(4), CH_2(5′)); 3.75–3.65 (*m*, H_a–C(6), H_a–C(8)); 3.55–3.45 (*m*, PhCH_2N, H_a–C(10), H_a–C(13)); 3.15–3.05 (*m*, H_b–C(13)); 2.75 (*dd*, *J* = 17.2, 2.4, H_a–C(3)); 2.5–2.2 (*m*, H_b–C(3), H_b–C(6), CH_2(7), H_b–C(8), H_b–C(10)); 1.75–1.55 (*m*, CH_2(11), CH_2(12)); 1.51 (*s*, *t*-Bu); 1.34, 1.27 (2*s*, Me_2C(2′)). ^{13}C-NMR: 172.6 (*s*, C(2)); 155.2, 152.5 (2*s*, 2 OCON); 139.5, 136.5 (2*s*, 2 arom. C); 128.4,

127.7, 127.5, 127.2, 126.8, 125.9 (6*d*, 10 arom. CH); 107.8 (*s*, C(2')); 82.4 (*s*, Me_3C); 75.5 (*d*, C(4')); 66.9, 66.7 (2*t*, C(5'), $PhCH_2O$); 60.0 (*t*, $PhCH_2N$); 58.8 (*d*, C(4)); 52.4, 50.0, 46.9 (3*t*, C(6), C(8), C(10)); 43.4 (*t*, C(13)); 38.6 (*t*, C(3)); 28.8 (*q*, Me_3C); 27.1 (*t*, C(7)); 26.9, 25.0 (2*q*, $Me_2C(2')$); 24.6 (*t*, C(11)); 22.5 (*t*, C(12)). ESI-MS: 662 (10, $[M + K]^+$), 646 (20, $[M + Na]^+$), 624 (100, $[M + 1]^+$), 524 (60, $[M + 1 - Boc]^+$).

*(1R,2'S)-9-Benzyl-5-[(benzyloxy)carbonyl]-1-[(*tert*-butoxy)carbonyl]-4-(1',2'-dihydroxyethyl)-1,5,9-triazacyclotridecan-2-one* (**22**). To a soln. of **21** (903 mg, 1.448 mmol) in MeOH (15 ml), CSA (1.029 g, 4.430 mmol, 3.06 equiv.) was added at 0° in one portion. The mixture was allowed to warm to r.t. After 24 h, the mixture was poured into ice-cooled sat. aq. $NaHCO_3$ soln. and diluted with CH_2Cl_2 (50 ml). The aq. soln. was extracted with CH_2Cl_2, the combined org. phase dried (Na_2SO_4) and evaporated, and the residue purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:5:1): 617 mg (69%) of **22**. Colorless oil. $[\alpha]_D^{21} = +22.91$ (*c* = 1.17, MeOH). IR: 3380*m*, 3080*w*, 3060*m*, 3020*m*, 2930*s*, 2860*m*, 2800*m*, 1780*m*, 1730*s*, 1690*s*, 1600*w*, 1580*w*, 1480*s*, 1450*s*, 1370*s*, 1250*s*, 1200*s*, 1150*s*, 1080*s*, 1040*m*, 1030*m*, 960*w*, 910*w*, 850*m*, 770*m*, 740*s*, 700*s*. ^{1}H-NMR ((D$_6$)DMSO, 358 K): 7.45–7.1 (*m*, 10 arom. H); 5.16, 5.07 (*AB*, *J* = 12.7, $PhCH_2O$); 4.45–4.4 (*m*, H–C(1')); 4.25–4.0 (*m*, H–C(4), $CH_2(2')$); 3.9–3.8 (*m*, H_a–C(8)); 3.8–3.6 (*m*, H_a–C(6)); 3.6–3.35 (*m*, $PhCH_2N$, H_a–C(10), H_a–C(13), 2 OH); 3.2–2.9 (*m*, H_a–C(3), H_b–C(6), H_b–C(13)); 2.55–2.25 (*m*, H_b–C(3), $CH_2(7)$, H_b–C(8), H_b–C(10)); 1.75–1.25 (*m*, $CH_2(11)$, $CH_2(12)$); 1.50 (*s*, *t*-Bu). ^{13}C-NMR ((D$_6$)DMSO, 358 K)[4]: 174.2 (*s*, C(2)); 153.4 (*s*, OCON); 140.4 (*s*, arom. C); 128.6, 128.6, 128.4, 127.9, 127.2, 126.9 (6*d*, 10 arom. CH); 83.0 (*s*, Me_3C); 72.4 (*d*, C(1')); 66.1 (*t*, C(2')); 63.5 (*t*, $PhCH_2O$); 59.5 (*t*, $PhCH_2N$); 55.2 (*d*, C(4)); 51.0, 48.0 (3*t*, C(6), C(8), C(10)); 42.9 (*t*, C(13)); 38.0 (*t*, C(3)); 27.8 (*q*, Me_3C); 23.5 (*t*, C(11) or C(12)). ESI-MS: 606 (25, $[M + Na]^+$), 584 (100, $[M + 1]^+$), 484 (73, $[M + 1 - Boc]$).

*(4R)-9-Benzyl-5-[(benzyloxy)carbonyl]-1-[(*tert*-butoxy)carbonyl]-2-oxo-1,5,9-triazacyclotridecan-4-carboxaldehyde* (**23**). A mixture of **22** (389.5 mg, 0.667 mmol) and $NaIO_4$ (633 mg, 2.96 mmol, 4.4 equiv.) in MeOH (12 ml) was stirred at r.t. for 4 h. The solvent was evaporated and the residue purified by CC (SiO_2, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH/25% aq. NH_4OH soln. 100:5:1): 309.1 mg (84%) of **23**. Colorless oil. $[\alpha]_D^{21} = +12.96$ (*c* = 0.702, MeOH). IR ($CHCl_3$): 3260*m*, 2990*s*, 2940*s*, 2860*m*, 2820*m*, 1660*s*, 1630*s*, 1590*s*, 1550*s*, 1450*s*, 1420*m*, 1380*s*, 1370*s*, 1340*s*, 1300*m*, 1270*s*, 1160*m*, 1070*s*, 1020*s*, 860*m*, 840*m*, 700*s*, 660*w*. ^{1}H-NMR: 9.52 (*d*, *J* = 8.2, CHO); 7.35–7.2 (*m*, 10 arom. H); 5.12 (*s*, $PhCH_2O$); 4.39 (*dd*, *J* = 16.5, 8.2, H–C(4)); 4.15–4.0 (*m*, H_a–C(13)); 3.65–3.45 (*m*, $PhCH_2N$, H_a–C(6), $CH_2(8)$, H_b–C(13)); 3.2–3.0 (*m*, H_b–C(6)); 2.65–2.25 (*m*, $CH_2(3)$, $CH_2(10)$); 1.95–1.3 (*m*, $CH_2(7)$, $CH_2(11)$, $CH_2(12)$); 1.53 (*s*, *t*-Bu). ^{13}C-NMR: 198.3 (*s*, CHO); 174.0 (*s*, C(2)); 156.6, 153.1 (2*s*, 2 OCON); 139.9, 136.0 (2*s*, 2 arom. C); 128.5, 128.4, 128.1, 127.8, 126.7 (5*d*, 10 arom. CH); 83.6 (*s*, Me_3C); 67.5 (*t*, $PhCH_2O$); 64.9 (*d*, C(4)); 59.8 (*t*, $PhCH_2N$); 51.0, 49.3, 47.6 (3*t*, C(6), C(8), C(10)); 43.0 (*t*, C(13)); 38.1 (*t*, C(3)); 27.9 (*q*, Me_3C); 25.4, 24.1 (2*t*, C(7), C(11), C(12)). ESI-MS: 552 (62, $[M + 1]^+$), 452 (100, $[M + 1 - Boc]^+$).

*(4R)-9-Benzyl-5-[(benzyloxy)carbonyl]-1-[(*tert*-butoxy)carbonyl]-4-[(Z)-hept-1'-enyl]-1,5,9-triazacyclotridecan-2-one* (**25**). To a suspension of hexyltriphenylphosphonium bromide (**24**, 501.65 mg, 1.17 mmol) in THF (30 ml), KO^{t}Bu (130.7 mg, 1.16 mmol; freshly sublimed) were added in one portion. The corresponding orange suspension was stirred overnight at r.t. At −78°, this soln. (3.6 ml, 1.404 mmol) was added dropwise to **23** (67.7 mg, 0.1225 mmol) in THF (5 ml). The mixture was stirred for 2 h at −78° and then allowed to warm to −40° where it was kept for an additional 24 h. The solvent was removed and the residue purified by CC (SiO_2, Et_2O/hexane 2:3): 25 mg (33%) of **25**. Colorless oil. $[\alpha]_D^{21} = -16.97$ (*c* = 0.831, MeOH). IR: 3080*w*, 3060*w*, 3020*m*, 2960*s*, 2920*s*, 2860*s*, 2800*w*, 1730*s*, 1690*s*, 1600*w*, 1490*m*, 1450*s*, 1420*s*, 1390*s*, 1340*s*, 1310*s*, 1270*s*, 1230*s*, 1150*s*, 1080*s*, 1020*m*, 1000*m*, 980*m*, 850*m*, 780*m*, 730*s*, 700*s*. ^{1}H-NMR: 7.3–7.15 (*m*, 10 arom. H); 5.95–5.65 (*m*, H–C(2')); 5.5–5.35 (*m*, H–C(1')); 5.25–5.0 (*m*, $PhCH_2O$); 4.2–4.0 (H–C(4), H_a–C(13)); 3.8–3.35 (*m*, $CH_2(6)$, H_a–C(8), H_a–C(10), $PhCH_2N$); 3.05–2.85 (*m*, H_b–C(13)); 2.82 (*d*, *J* = 16.0, H_a–C(3)); 2.6–2.05 (*m*, H_b–C(3), $CH_2(7)$, H_b–C(10), $CH_2(3')$); 1.85–1.75 (*m*, H_b–C(8)); 1.75–1.55 (*m*, $CH_2(12)$); 1.49 (*s*, *t*-Bu); 1.4–1.15 (*m*, $CH_2(4')$, $CH_2(5')$, $CH_2(6')$); 0.85 (*t*, *J* = 7.5, Me(7')). ^{13}C-NMR: 173.9 (*s*, C(2)); 153.6, 151.1 (2*s*, 2 OCON); 137.0, 131.9 (2*d*, C(1'), C(2')); 128.7, 128.4, 128.1, 128.0, 127.8, 126.7 (6*d*, 10 arom. CH); 83.6 (*s*, Me_3C); 66.9, 66.8 (2*t*, $PhCH_2O$, $PhCH_2N$); 60.0 (*t*, C(6)); 54.0 (*d*, C(4)); 51.4, 48.9, 45.7 (3*t*, C(8), C(10), C(13)); 43.2 (*t*, C(3)); 31.5, 29.3 (*t*, C(7), C(3')); 28.0 (*q*, Me_3C); 27.6, 24.9, 23.8, 22.5, 20.6 (5*t*, C(11), C(12), C(4'), C(5'), C(6')); 14.0 (*q*, C(7')). ESI-MS: 642 (12, $[M + Na]^+$), 620 (100, $[M + 1]^+$), 520 (30, $[M + 1 - Boc]^+$).

(4R)-9-Benzyl-5-[(benzyloxy)carbonyl]-4-[(Z)-hept-1'-enyl]-1,5,9-triazacyclotridecan-2-one (**26**). To a soln. of **25** (80.0 mg, 0.129 mmol) in $CHCl_3$ (3 ml), CF_3COOH (3 ml) was added at 0°. The mixture was allowed to warm to r.t. and stirred for 3 h. After cooling to 0°, the pH was adjusted to 10 by adding 10% aq. NaOH soln. The aq.

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[4]) The signals of OCON, C(7), and C(11) or C(12) were not detected.

phase was extracted with CH_2Cl_2 and the combined org. phase dried (Na_2SO_4) and evaporated: 65.0 mg (97%) of **26**. Colorless oil. $[\alpha]_D^{21} = -29.32$ ($c = 0.59$, MeOH). IR: 3300*s*, 3080*m*, 3060*m*, 3020*s*, 2920*s*, 2860*s*, 2800*s*, 1690*s*, 1650*s*, 1600*m*, 1590*m*, 1540*s*, 1495*s*, 1465*s*, 1450*s*, 1420*s*, 1400*s*, 1360*s*, 1340*s*, 1320*s*, 1280*s*, 1260*s*, 1230*s*, 1170*s*, 1130*s*, 1110*s*, 1060*s*, 1025*s*, 1000*s*, 905*w*, 770*s*, 730*s*, 700*s*. ^{1}H-NMR: 7.35–7.2 (*m*, 10 arom. H); 5.85 (br. *s*, NH); 5.8–5.65 (*m*, H–C(2')); 5.45 (*dt*, $J = 10.7$, 7.5, H–C(1')); 5.3–5.0 (*m*, PhCH_2O); 3.75–3.45 (*m*, H–C(4), H_a–C(13)); 3.62, 3.39 (*AB*, $J = 3.4$, PhCH_2N); 3.3–3.1 (*m*, H_a–C(8)); 2.95–2.85 (*m*, H_b–C(13)); 2.85–2.5 (*m*, CH_2(6)); 2.5–2.35 (*m*, H_b–C(8), H_a–C(10)); 2.35–2.2 (*m*, H_a–C(3)); 2.2–2.05 (*m*, CH_2(7), H_b–C(10)); 2.16 (*dd*, $J = 14.0$, 2.9, H_b–C(3)); 1.75–1.55 (*m*, CH_2(11), CH_2(12)); 1.45–1.1 (*m*, CH_2(3'), CH_2(4'), CH_2(5'), CH_2(6')); 0.87 (*t*, $J = 6.7$, Me(7')). ^{13}C-NMR: 170.9 (*s*, C(2)); 156.6 (*s*, OCON); 136.7 (*d*, C(2')); 132.4 (*d*, C(1')); 129.0, 128.6, 128.5, 128.0, 127.5, 126.8 (6*d*, 10 arom. CH); 66.8 (*t*, PhCH_2O); 59.6 (*t*, PhCH_2N); 58.8, 53.3, 48.8 (3*t*, C(6), C(8), C(10)); 46.1 (*t*, C(13)); 39.2 (*t*, C(3)); 31.8, 29.2, 28.1 (C(7), C(11), C(12)); 25.0, 24.4, 22.4, 21.9 (4*t*, C(3'), C(4'), C(5'), C(6')); 13.9 (*q*, C(7')). ESI-MS: 520 ($[M + 1]^+$).

*(4*R*)-5-[(Benzyloxy)carbonyl]-4-[(Z)-hept-1'-enyl]-1,5,9-triazacyclotridecan-2-one* (**27**). A mixture of **25** (69.9 mg, 0.134 mmol) and 1-chloroethyl carbonochloridate (0.2 ml, 2.45 mmol) in $CHCl_3$ (2 ml) was refluxed for 18 h. The solvent was evaporated and the residue dissolved in MeOH (5 ml) and refluxed for an additional 4 h. After evaporation, the residue was purified by CC (SiO_2, CH_2Cl_2/MeOH/25% aq. NH_4OH soln. 100:1:1): 31.8 mg (55%) of **27**. Colorless oil. $[\alpha]_D^{21} = -26.79$ ($c = 0.84$, MeOH). IR ($CHCl_3$): 3440*m*, 2980*s*, 2950*s*, 2920*s*, 2860*s*, 1680*s*, 1510*s*, 1450*s*, 1415*s*, 1360*m*, 1340*m*, 1300*s*, 1260*s*, 1240*s*, 1130*m*, 1000*m*, 910*m*, 690*w*. ^{1}H-NMR: 7.4–7.3 (*m*, 5 arom. H); 5.55–5.4 (*m*, H–C(1'), H–C(2')); 5.22 (*AB*, $J = 12.2$, PhCH_AO); 5.1–5.05 (*m*, H–N(1)); 5.06 (*AB*, $J = 12.2$, PhCH_BO); 3.8–3.05 (*m*, H–C(4), CH_2(6), CH_2(8), CH_2(10), CH_2(13)); 2.8–2.35 (*m*, H_a–C(3)); 2.21 (*dd*, $J = 14.3$, 2.5, H_b–C(3)); 2.0–1.15 (*m*, CH_2(7), CH_2(11), CH_2(12), CH_2(3'), CH_2(4'), CH_2(5'), CH_2(6'), NH); 0.89 (*t*, $J = 7.0$, Me(7')). ^{13}C-NMR: 170.5 (*s*, C(2)); 157.0 (*s*, OCON); 136.6, 134.1 (2*d*, C(1'), C(2')); 128.5, 125.5, 127.2 (3*d*, 5 arom. CH); 67.1 (*t*, PhCH_2O); 52.8 (*d*, C(4)); 49.4, 48.4, 47.2 (3*t*, C(6), C(8), C(10)); 44.7 (*t*, C(13)); 39.4 (*t*, C(3)); 32.9, 31.4, 28.6, 28.2, 27.8, 26.3, 22.4 (7*t*, C(7), C(11), C(12), C(3'), C(4'), C(5'), C(6')); 14.0 (*q*, C(7')). ESI-MS: 430 ($[M + 1]^+$).

*(4*R*)-4-[(Z)-Hept-1'-enyl]-1,5,9-triazacyclotridecan-2-one* (= *(4*R*)-Dihydroisomyricoidine*; **28**). To a soln. of **27** (29.7 mg, 0.0691 mmol) in MeCN (4 ml), Me_3SiI (0.1 ml, 0.570 mmol, 8.2 equiv.) was added at 0°. After 4 h, MeOH (2 ml) was added and the mixture allowed to warm to r.t. The solvent was evaporated and the residue purified by CC (SiO_2, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH/25% aq. NH_4OH soln. 100:5:1): 12.3 mg (60%) of **28**. $[\alpha]_D^{21} = -36.32$ ($c = 0.62$, MeOH). IR ($CHCl_3$): 3300*m*, 2950*s*, 2850*m*, 1660*s*, 1600*m*, 1530*m*, 1460*m*, 1260*s*, 1200*m*, 1110*w*, 1010*w*, 980*w*, 895*w*. ^{1}H-NMR: 7.60 (*t*, $J = 5.9$, H–N(1)); 5.61 (*dt*, $J = 10.8$, 7.5, H–C(2')); 5.16 (*t*, $J = 10.1$, H–C(1')); 4.15–4.0 (*m*, H–C(4)); 3.7–3.55 (*m*, H_a–C(13)); 3.45–3.3 (*m*, H_a–C(8)); 3.3–3.0 (*m*, H_a–C(6), H_b–C(8), H_a–C(10), H_b–C(13), NH); 2.7–2.5 (*m*, H_a–C(3), H_b–C(6), H_b–C(10)); 2.37 (*dd*, $J = 13.3$, 3.1, H_b–C(3)); 2.25–2.18 (*m*, CH_2(7), CH_2(11), CH_2(12), CH_2(3'), NH); 1.4–1.2 (*m*, CH_2(4'), CH_2(5'), CH_2(6')); 0.89 (*t*, $J = 6.7$, Me(7')). ^{13}C-NMR: 171.9 (*s*, C=O); 134.1, 129.3 (2*d*, C(1'), C(2')); 53.2 (*d*, C(4)); 51.8, 48.9, 47.0, 43.7, 39.3 (5*t*, C(3), C(6), C(8), C(10), C(13)); 31.5, 29.4, 27.8, 26.0, 24.7, 24.2, 22.5 (7*t*, C(7), C(11), C(12), C(3'), C(4'), C(5'), C(6')); 14.0 (*q*, C(7')). EI-MS: 296 (11, $[M + 1]^+$), 219 (15), 151 (39, $C_{10}H_{15}O^+$), 128 (37, $C_7H_{16}N_2^+$), 127 (31), 112 (11), 110 (11), 99 (11), 98 (17), 96 (17), 95 (17), 87 (11), 85 (30), 84 (28), 83 (17), 82 (15), 81 (79), 77 (12), 72 (26), 71 (30), 70 (95, $C_4H_8N^+$), 69 (58), 67 (37), 66 (20), 65 (10), 58 (67), 57 (46), 56 (50), 53 (32), 46 (23), 45 (100). ESI-MS: 296 ($[M + 1]^+$).

Crystal-Structure Determination of Compound **8**[5]. The data collection and refinement parameters are summarized in the *Table*, and a view of the molecule is shown in the *Figure*. All measurements were conducted on a *Rigaku-AFC5R* diffractometer fitted to a 12 kW rotating anode generator. The intensities were collected using $\omega/2\theta$ scans, and three standard reflections measured after every 150 reflections showed negligible variation in intensity. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections, other than *Friedel* pairs, were merged. The structure was solved by direct methods using SHELXS86 [11] which revealed the positions of all non-H-atoms. The enantiomorph was chosen to agree with the known (*S*)-configuration at C(4'). The non-H-atoms were refined anisotropically. All of the amine and lactam H-atoms were placed in the positions indicated by a difference electron density map, and their positions were allowed to refine. All other H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å). Individual isotropic

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[5]) 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-101347. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-(0)1223-336033; email: deposit(*a*)ccdc.cam.ac.uk).

Table. *Crystallographic Data for Compound* **8**

Crystallized from	CH_2Cl_2/pentane
Empirical formula	$C_{22}H_{35}N_3O_3$
Formula weight	389.54
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	$0.20 \times 0.20 \times 0.50$
Temperature [K]	173(1)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Z	4
Reflections for cell determination	25
2θ range for cell determination [°]	24–26
Unit cell parameters a [Å]	13.391(5)
b [Å]	17.813(8)
c [Å]	9.182(4)
V [Å^3]	2190(1)
D_x [g cm^{-3}]	1.181
$\mu(MoK_\alpha)$ [mm^{-1}]	0.0787
$2\theta_{(max)}$ [°]	60
Total reflections measured	4207
symmetry-independent reflections	4078
Reflections used [$I > 2\sigma(I)$]	2487
Variables	294
R	0.0511
wR	0.0405
Goodness of fit s	1.375
Final Δ_{max}/σ	0.0003
$\Delta\rho$(max; min) [e Å^{-3}]	0.27; −0.24
$\sigma(d(C-C))$ [Å]	0.004–0.005

displacement parameters were refined for all of the H-atoms. A correction for secondary extinction was not applied. All refinements were carried out on F using full-matrix least-squares procedures which minimized the function $\sum\omega(|F_o|-|F_c|)^2$, where $1/\omega = [\sigma^2(F_o) + (0.005F_o)^2]$. Neutral atom scattering factors for non-H-atoms were taken from [12a], and the scattering factors for H-atoms from [13]. Anomalous dispersion effects were included in F_c [14]; the values for f' and f'' were taken from [12b]. All calculations were performed using the TEXSAN [15] crystallographic software package

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