A Novel Synthesis of the Macrocyclic Spermidine Alkaloid (+)-(*S*)-Dihydroperiphylline

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A novel, short, and highly stereoselective synthesis of the macrocyclic spermidine alkaloid (+)-(*S*)-dihydroperiphylline (**15**) is described. The key synthetic steps were the stereoselective addition of the chiral amine **1** to the cinnamate **2** and cyclization of the bis[toluene-4-sulfonamide] precursor **12** in the presence of Cs_2CO_3 as a template. Unambiguous assignments of the signals in both the ^{1}H- and ^{13}C-NMR spectra of **15** were achieved by 2D NMR spectra.

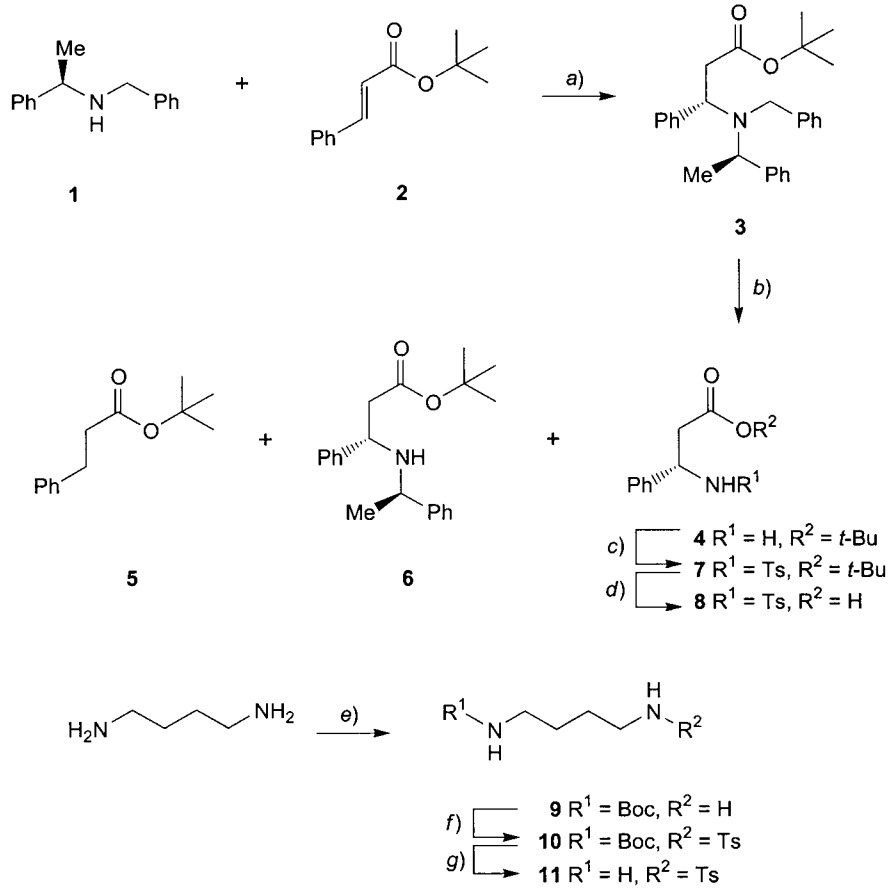
1. Introduction. – Macrocyclic lactams, derived from spermidine or spermine, are ubiquitous in nature. They have attracted the interest of organic chemists as synthetic targets due to a broad spectrum of biological activity [1]. Dihydroperiphylline (**15**) is an alkaloid isolated from leaves of the New Caledonian endemic plant *Peripterygia marginata* [2]. The single chiral center in **15** was assumed to have (*S*)-configuration. Racemic **15** was synthesized by *Wasserman* and *Matsuyama* [3]. The first enantioselective route, based on a 15-step preparation of *N*-Boc-(*S*)-*β*-phenyl-*β*-alanine from diethyl L-tartrate, was performed by *Kaseda et al.* [4], confirming the (*S*)-configuration. More recently, alternative syntheses of (*S*)-**15** by cyclization of methyl (*S*)-12-amino-4,8-diazadodecanoate in the presence of $(Me_2N)_3B$ [5] or by ring expansion of (*S*)-4-phenyl-2-azetidinone [6] were reported. In the present paper, we report a novel, short, and highly efficient approach to **15**, based on metal-templated macrocyclization as the key step.

2. Results and Discussion. – Our synthetic strategy is outlined in *Schemes 1* and *2*. A highly stereoselective preparation of the chiral *β*-phenyl-*β*-alanine derivative **3** was performed according to the method of *Davies et al.* [7]. Thus, addition of the *in situ* generated Li derivative of the optically pure amine **1** (prepared from commercially available (*R*)-*α*-methylbenzylamine, 94% ee, *Fluka* [8]) to *tert*-butyl 3-phenylpropenoate **2** (prepared by a modification of the published procedure [9]) gave the corresponding *β*-phenyl-*β*-alanine derivative **3** in nearly quantitative yield. Both the *N*-benzyl- and N-*α*-methylbenzyl groups were removed by catalytic hydrogenation [7b] in the presence of *Pearlman*'s catalyst, and the deprotected amino ester **4** was isolated in 63% yield after column chromatography. In addition, two side-products were isolated: *tert*-butyl 3-phenylpropanoate (**5**; 14%) and the aminoester **6** (13%). Formation of the latter indicates the much higher resistance of the *N*-*α*-methylbenzyl residue to reductive removal compared to unsubstituted *N*-benzyl group, a finding that is

[1]) Part of the Ph. D. Thesis of *S. A. S.*, University of Zürich, in preparation.

consistent with the observation of *Li et al.* [8]. The amino ester **4** was obtained in 92% ee, which was determined by ^{1}H-NMR *via* derivatization with *Mosher*'s (*R*)-acid chloride [10] (see *Exper. Part*). The amino ester **4** was tosylated to give **7** (84% yield). Subsequent ester hydrolysis was quantitatively accomplished with CF_3COOH (TFA) at ambient temperature to yield the chiral building block **8** (53% overall yield from **2**; *Scheme 1*).

Scheme 1



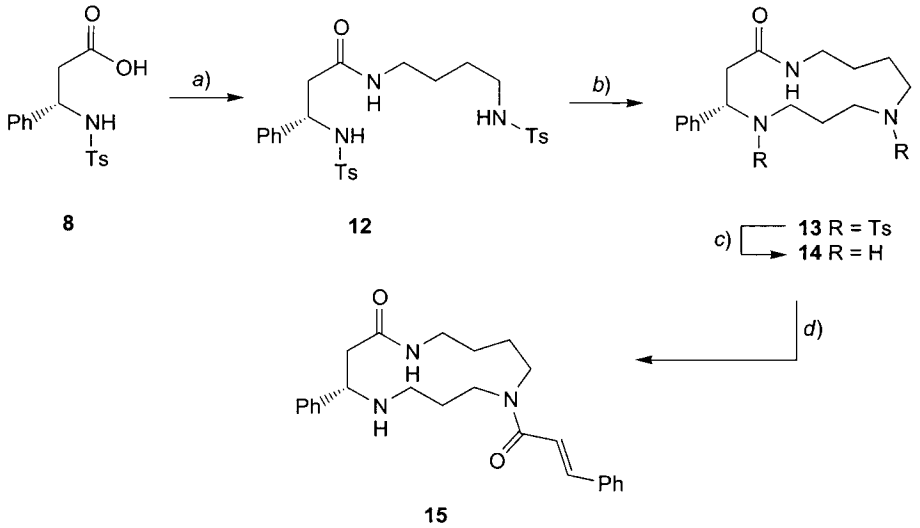
a) 1. BuLi, THF, −80°; quant. *b)* H_2, 3.8 bar, 10% $Pd(OH)_2$/C, EtOH; 63%. *c)* TsCl, Et_3N, CH_2Cl_2, −10°; 84%. *d)* TFA, r.t.; quant. *e)* Boc_2O, dioxane, r.t.; 85%. *f)* TsCl, Et_3N, CH_2Cl_2, −10°; 87%. *g)* 1. TFA, CH_2Cl_2, r.t.; 2. aq. Na_2CO_3; 90%.

The synthesis of **15** also required the preparation of monotosylated butane-1,4-diamine **11**. Difficulties arising during a direct monoderivatization of putrescine, however, are well-documented [11]. Putrescine tends to react at both amino groups to give symmetric bifunctional derivatives even in the presence of a large excess of the diamine relative to the functionalizing reagent. However, *N*-Boc derivatives have been prepared from terminal aliphatic diamines in high yields [12]. Following the procedure

in [12], we prepared *N*-Boc-butane-1,4-diamine (**9**) by reaction of Boc_2O with an excess of putrescine in dioxane (*Scheme 1*). The reaction of **9** with TsCl afforded *N*-Boc-*N'*-(toluene-4-sulfonyl)butane-1,4-diamine (**10**). The Boc group was finally cleaved with TFA to give the compound **11**.

To perform the coupling between the two key components, **8** and **11**, the protected amino acid **8** was first converted to the corresponding acyl chloride by the action of an excess of $SOCl_2$ in the presence of catalytic amounts of DMF. Subsequent reaction with **11** in the presence of Et_3N gave the amide **12** in 85% yield (*Scheme 2*).

Scheme 2



a) 1. $SOCl_2$, DMF (cat.); 2. **11**, Et_3N, CH_2Cl_2; −10°; 85%. *b)* $X(CH_2)_3X$, Cs_2CO_3, DMF; X = OTs, 50°, 24 h; 56%; X = OMs, r.t., 72 h; 78%). *c)* electrolysis, EtOH/DMF; quant. *d)* PhCH=CHCOCl, DMAP, CH_2Cl_2, −80°; 94%.

Cyclization reactions, mediated by alkali-metal carbonates in polar aprotic solvents like DMF or MeCN are known to be effective for the synthesis of a variety of macrocyclic compounds [13]. This strategy was also successfully applied in our laboratory to obtain some macrocyclic lactams in moderate to high yields [14]. In the present case, slow addition of a solution of equimolar amounts of 1,3-bis(tosyloxy)propane [15] and **12** to a suspension of Cs_2CO_3 in DMF at 50° resulted in the formation of the desired macrocycle **13** in 56% yield. When the more reactive 1,3-bis(methylsulfonyl)propane [16] was used, cyclization proceeded even at ambient temperature, and the yield of **13** increased to 78%. It should be noted that the order of addition is important. For example, slow addition of the alkylating agent to a mixture of Cs_2CO_3 and **12** resulted in a lower yield of **13**.

Among various methods for deprotecting tosyl-protected amines [17], electrochemical reduction was shown to be the most convenient procedure [18]. In our case, voltage-controlled electrolysis of **13** gave the corresponding macrocyclic lactam **14** in quantitative yield. Finally, **14** was selectively acylated [5] with 1 equiv. of 3-phenylpropenoyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) at low

temperature to afford (*S*)-dihydroperiphylline (**15**) in 94% yield. No acylation at the more hindered N-atom was observed, and the spectral and optical properties of **15** were in agreement with previously published data [4][5].

In the ^{1}H-NMR spectra of **15** in $CDCl_3$ or (D_6)DMSO, many signals were broad at ambient temperature due to restricted rotations in the disubstitued cinnamoyl amide, and in the ^{13}C-NMR spectra many signals were either broad or doubled. This problem could be overcome by recording the NMR spectra at 373 K in (D_6)DMSO. Using two dimensional ^{1}H,^{1}H (COSY) and ^{1}H,^{13}C (HMBC, HSQC) correlation spectra, we were able to make unambiguous assignments of all ^{1}H and ^{13}C signals (see *Exper. Part*).

We thank Mr. *A. Guggisberg* for electrochemical experiments, Dr. *N. A. Khanjin* for helpful discussions and the *Swiss National Science Foundation* for financial support of this work.

Experimental Part

General. All chemicals and solvents were obtained from commercial sources (*Fluka, Aldrich, Merck*) and used without further purification unless stated otherwise. Technical-grade solvents were distilled prior to use. DMF was stored over flame-dried molecular sieves (4 Å). THF was distilled over Na/benzophenone. (*R*)-*N*-Benzyl-α-methylbenzylamine [8], 1,3-bis(tosyloxy)propane [15] and 1,3-bis(methylsulfonyloxy)propane [16] were prepared according to published procedures. CC: SiO_2, *Merck 60* (40–63 μm). TLC: precoated SiO_2 plates, *Merck 60* F_{254}; detection by UV at 254 nm; *Fluram* reagent (*Fluka*) in acetone, fluorescence at 366 nm (for primary amines), *Schlittler* reagent [19] (for amines and polyamines). M.p.: *Mettler FP-5*. ORD: *Perkin-Elmer 241* polarimeter. IR (cm^{-1}): *Perkin-Elmer Spectrum One*; KBr pellets or neat substance. ^{1}H-NMR: *Bruker ARX-300* (300 MHz) or *AMX-600* (600 MHz); chemical shifts δ in ppm relative to Me_4Si as internal standard; *J* values in Hz. ^{13}C-NMR: *Bruker ARX-300* (75 MHz) or *AMX-600* (150 MHz); chemical shifts δ in ppm relative to Me_4Si, signals multiplicity determined from DEPT experiments. CI-MS (NH_3 as reactant gas): *Finnigan MAT 90*. ESI-MS (NaI/MeOH/CH_2Cl_2): *Finnigan TSQ 700*; *m*/*z* and relative intensities (% of base peak) are given.

tert-*Butyl (*E*)-3-Phenylprop-2-enoate* (**2**). 3-Phenylprop-2-enoyl chloride (49.8 g, 0.30 mol) was added in portions to a vigorously stirred mixture of *t*-BuOH (32.8 ml, 0.35 mol) and Et_3N (48.4 ml, 0.45 mol). The mixture was stirred at 90° for 12 h (a white solid precipitated), then cooled to r.t., Et_2O (100 ml) and H_2O (50 ml) were added, and stirring was continued until all the solid was dissolved. The org. layer was separated, washed with 1N aq. HCl (3 × 50 ml), sat. aq. $NaHCO_3$ (50 ml), H_2O (50 ml), dried ($MgSO_4$) and concentrated. Distillation of the residue *in vacuo* afforded 44.8 g (73%) of **2**. Colorless liquid. B.p. 72–73°/0.1 Torr ([20]: 80–81°/0.3 Torr). For IR, MS, ^{1}H- and ^{13}C-NMR spectra, see [20].

tert-*Butyl (3*S,αR*)-3-[*N*-Benzyl*-N*-(1-phenylethyl)amino]-3-phenylpropanoate* (**3**). A stirred soln. of (*R*)-*N*-benzyl-α-methylbenzylamine (15.8 g, 75 mmol) in dry THF (150 ml) was cooled to −80° and treated dropwise with BuLi (1.6M soln. in hexane, 44 ml, *ca*. 70 mmol). The resulting red soln. was stirred for 1 h. Then, a soln. of **2** (10.2 g, 50 mmol) in dry THF (40 ml) was added dropwise. Stirring was continued for 1 h. Sat. aq. NH_4Cl (60 ml) was added, and the mixture was allowed to reach r.t. THF was removed *in vacuo*, and the residue was partitioned between H_2O (50 ml) and CH_2Cl_2 (150 ml). The org. phase was washed with 10% citric acid (2 × 100 ml), H_2O (50 ml), dried ($MgSO_4$), and evaporated to give nearly pure **3** (20.8 g, 100%), which was used without further purification. Yellow oil. R_f 0.82 (CH_2Cl_2). IR (neat): 3085*m*, 3002*m*, 3062*m*, 3028*s*, 2976*s*, 2932*m*, 1948*w*, 1877*w*, 1807*w*, 1727*s*, 1601*m*, 1493*s*, 1478*m*, 1453*s*, 1367*s*, 1301*m*, 1237*m*, 1152*s*, 1083*m*, 1057*w*, 1028*m*, 962*m*, 912*m*, 749*s*, 699*s*, 647*w*, 549*w*. ^{1}H-NMR ($CDCl_3$): 1.20 (*s*, *t*-Bu); 1.24 (*d*, *J* = 6.8, Me); 2.48 (*dd*, *J* = 14.6, 9.4, 1 H, CH_2CO); 2.55 (*dd*, *J* = 14.6, 5.8, 1 H, CH_2CO); 3.67 (*s*, PhCH_2); 3.98 (*q*, *J* = 6.8, MeC*H*); 4.40 (*dd*, *J* = 9.4, 5.8, CH_2CH); 7.15–7.32 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 16.34 (*q*, Me); 27.77 (*q*, *Me*$_3$C); 38.50 (*t*, *C*H_2CO); 50.86 (*t*, PhCH_2); 57.10, 59.68 (2*d*, 2 CH); 80.05 (*s*, Me$_3$*C*); 126.45, 126.76, 127.03 (3*d*, 3 arom. CH); 127.80–128.25 (several *d*, 12 arom. CH); 141.66, 141.80, 144.15 (3*s*, 3 arom. C); 171.03 (*s*, C=O). CI-MS: 416 (100, [*M* + 1]$^+$), 300 (12).

tert-*Butyl (*S*)-3-Amino-3-phenylpropanoate* (**4**). A soln. of **3** (20.8 g, 50 mmol) in dry EtOH (200 ml) was placed in a pressure-resistant bottle. The bottle was purged with N_2, and *Pearlman*'s catalyst (10% $Pd(OH)_2$ on charcoal, 4.0 g) was added. The pressure head was adjusted, the bottle was placed in a *Parr* apparatus, evacuated, purged with N_2, and, then, 3 times with H_2. The pressure was set to 3.8 bar, and the bottle was vigorously shaken

for 72 h. Then, the pressure was released, the mixture was filtered through *Celite*, and EtOH was evaporated. CC (CH_2Cl_2, then CH_2Cl_2/MeOH 20:1) afforded **4** (6.96 g, 63%) as well as **5** (1.48 g, 14%) and **6** (2.11 g, 13%).

Data of **4**: colorless oil. R_f 0.60 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D = -19.3$ ($c = 1.06$, $CHCl_3$). IR (neat): 3382*m*, 3314*m*, 3063*m*, 3029*m*, 2978*s*, 2931*m*, 1953*w*, 1725*s*, 1604*m*, 1494*m*, 1479*w*, 1454*m*, 1392*m*, 1368*s*, 1319*m*, 1256*m*, 1209*m*, 1150*s*, 1028*w*, 1015*w*, 955*m*, 909*w*, 846*m*, 755*m*, 700*s*, 593*w*. ^{1}H-NMR ($CDCl_3$): 1.41 (*s*, *t*-Bu); 1.77 (br. *s*, NH_2); 2.58 (*d*, $J = 6.9$, CH_2CO); 4.37 (*t*, $J = 6.9$, C*H*N); 7.24–7.37 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 27.95 (*q*, $C(CH_3)_3$); 45.23 (*t*, CH_2); 52.69 (*d*, CHN); 80.60 (*s*, $C(CH_3)_3$); 126.20 (*d*, 2 arom. CH); 127.16 (*d*, 1 arom. CH); 128.41 (*d*, 2 arom. CH); 144.64 (*s*, 1 arom. C); 171.20 (*s*, C=O). CI-MS: 443 (24, $[2M+1]^+$), 222 (100, $[M+1]^+$). ^{1}H-NMR of *Mosher*'s amide of **4** (selected signals): (*S*,*S*)-isomer: 3.32 (*q*, ^5J(H,F) = 1.4, OCH_3); (*S*,*R*)-isomer: 3.40 (*q*, ^5J(H,F) = 1.4, OCH_3); integral ratio (*S*,*S*)/(*S*,*R*) = 23.6:1, corresponding to ee 92%.

Data of **5**: colorless liquid. ^{1}H-NMR: 1.41 (*s*, *t*-Bu); 2.54 (*t*, $J = 7.8$, CH_2CO); 2.91 (*t*, $J = 7.8$, PhCH_2); 7.18–7.27 (*m*, 5 arom. H). CI-MS: 224 (72, $[M+NH_4]^+$), 168 (100, $[(M-C_4H_8)+NH_4]^+$).

Data of **6**: colorless oil. R_f 0.62 (CH_2Cl_2/MeOH 20:1). IR (neat): 3328*w*, 3062*w*, 3028*m*, 2976*m*, 2930*m*, 1950*w*, 1726*s*, 1602*w*, 1493*m*, 1453*m*, 1367*s*, 1296*m*, 1258*m*, 1151*s*, 1079*w*, 1028*w*, 957*m*, 911*w*, 845*m*, 761*m*, 699*s*, 665*w*. ^{1}H-NMR ($CDCl_3$): 1.34 (*d*, $J = 6.5$, Me); 1.36 (*s*, *t*-Bu); 1.85 (br. *s*, NH); 2.59 (*dd*, $J = 10.7, 7.1$, CH_2); 3.66 (*q*, $J = 6.5$, MeC*H*); 4.15 (*dd*, $J = 7.7, 6.3$, CHN); 7.18–7.32 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 22.19 (*q*, Me); 27.90 (*q*, Me_3C); 43.84 (*t*, CH_2); 54.48, 57.03 (2*t*, 2 CHN); 80.35 (*s*, Me_3C); 126.46–127.02 (several *d*, 6 arom. CH); 128.20, 128.27 (2*d*, 2 × 2 arom. CH); 142.77, 145.97 (2*s*, 2 arom. C); 170.86 (*s*, C=O). CI-MS: 326 ($[M+1]^+$).

tert-*Butyl (*S*)-3-[[(4-Methylphenyl)sulfonyl]amino}-3-phenylpropanoate* (**7**). A stirred soln. of **4** (3.09 g, 14 mmol) and Et_3N (2.8 ml, 20 mmol) in CH_2Cl_2 (50 ml) was cooled to −10° and treated dropwise with TsCl (2.67 g, 14 mmol) in CH_2Cl_2 (20 ml), stirred for 30 min at −10° and another 30 min at r.t. The resulting mixture was washed with 10% citric acid (20 ml), H_2O (2 × 20 ml), dried ($MgSO_4$), and concentrated *in vacuo*. CC (CH_2Cl_2/AcOEt 20:1) afforded **7** (4.43 g, 84%). White solid. R_f 0.52 (CH_2Cl_2/AcOEt 20:1). M.p. 71–72°. $[\alpha_D = -35.6$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3250*s*, 3033*m*, 3062*m*, 2988*s*, 2753*w*, 2642*w*, 2293*w*, 1900*w*, 1717*s*, 1686*s*, 1600*m*, 1496*m*, 1456*s*, 1427*s*, 1326*s*, 1303*s*, 1252*m*, 1207*m*, 1159*s*, 1096*s*, 1060*s*, 968*s*, 858*m*, 809*m*, 771*m*, 703*s*, 665*s*, 603*m*, 555*s*, 534*s*, 467*m*. ^{1}H-NMR ($CDCl_3$): 1.30 (*s*, *t*-Bu); 2.34 (*s*, Me); 2.63 (*dd*, $J = 15.4, 6.5$, 1 H, CH_2CO); 2.73 (*dd*, $J = 15.4, 6.5$, 1 H, CH_2CO); 4.70 (*dt*, $J = 7.8, 6.5$, CHN); 5.97 (*d*, $J = 7.8$, NH); 7.08–7.18 (*m*, 5 H of Ph, 2 H of Ts); 7.57 (*d*, $J = 8.3$, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.30 (*q*, Me); 27.75 (*q*, Me_3C); 42.36 (*t*, CH_2); 54.61 (*d*, CHN); 81.47 (*s*, Me_3C); 126.49, 126.97 (2*d*, 2 × 2 arom. CH); 127.43 (*d*, 1 arom. CH); 129.24, 130.13 (2*d*, 2 × 2 arom. CH); 137.55, 139.33, 142.92 (3*s*, 3 arom. C); 169.82 (*s*, C=O). CI-MS: 393 (18, $[M+NH_4]^+$), 337 (100, $[(M-C_4H_8)+NH_4]^+$), 189 (6).

*(*S*)-3-[[(4-Methylphenyl)sulfonyl]amino}-3-phenylpropanoic Acid* (**8**). A mixture of **7** (2.14 g, 5.71 mmol) and TFA (5 ml) was stirred at r.t. for 3 h. Evaporation of volatile materials and drying of the residue *in vacuo* afforded **8** (1.82 g, 100%). White solid. R_f 0.31 (CH_2Cl_2/MeOH 10:1). M.p. 148–150°. $[\alpha]_D = -33.1$ ($c = 1.0$, MeOH). IR (KBr): 3270*s*, 3063*m*, 3028*m*, 2980*m*, 2917*m*, 2679*m*, 2577*m*, 1960*w*, 1907*w*, 1710*s*, 1598*m*, 1495*m*, 1460*m*, 1447*m*, 1414*m*, 1379*w*, 1352*m*, 1326*s*, 1306*s*, 1211*m*, 1162*s*, 1086*m*, 1064*m*, 1028*w*, 1019*w*, 955*m*, 843*m*, 810*m*, 763*m*, 703*s*, 670*s*, 616*m*, 573*m*, 551*m*, 527*m*, 477*m*. ^{1}H-NMR ($CDCl_3$): 2.37 (*s*, Me); 2.81 (*dd*, $J = 16.4, 6.2$, 1 H, CH_2); 2.92 (*dd*, $J = 16.4, 6.2$, 1 H, CH_2); 4.73 (*dt*, $J = 7.6, 6.2$, CHN); 5.67 (*d*, $J = 7.6$, NH); 7.08–7.21 (*m*, 5 H of Ph, 2 H of Ts); 7.59 (*d*, $J = 8.3$, 2 H of Ts); 11.5–12.5 (very br. *s*, COOH). ^{13}C-NMR ((D$_6$)DMSO): 20.74 (*q*, Me); 42.00 (*t*, CH_2); 54.38 (*d*, CHN); 126.19, 126.51 (2*d*, 2 × 2 arom. CH); 126.86 (*d*, 1 arom. CH); 127.86, 128.96 (2*d*, 2 × 2 arom. CH); 138.38, 140.57, 141.91 (3*s*, 3 arom. C); 170.86 (*s*, C=O). ESI-MS: 342 ($[M+Na]^+$).

tert-*Butyl (4-[[(4-Methylphenyl)sulfonyl]amino}butyl)carbamate* (**10**). A stirred soln. of **9** (4.00 g, 21.3 mmol) and Et_3N (5.5 ml, 40 mmol) in CH_2Cl_2 (100 ml) was cooled to −10°, and treated dropwise with a soln. of TsCl (4.19 g, 22 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred for 30 min at 0° and another 30 min at r.t. The resulting mixture was washed with 10% citric acid (25 ml), H_2O (2 × 25 ml), dried ($MgSO_4$), and evaporated. Extraction of the residue with hexane (3 × 50 ml) gave 7.25 g of crude product, which solidified upon standing. Crystallization from hexane/AcOEt gave pure **10** (6.30 g, 87%). White solid. R_f 0.19 (CH_2Cl_2/AcOEt 10:1). M.p. 85–87° ([21]: 87.5–88.5°). For IR, ^{1}H- and ^{13}C-NMR spectra, see [21]. ESI-MS: 365 (84, $[M+Na]^+$), 309 (39, $[(M-C_4H_8)+Na]^+$), 265 (10, $[(M-C_4H_8-CO_2)+Na]^+$), 243 (100, $[(M-C_4H_8-CO_2)+1]^+$).

N-*(4-Aminobutyl)-4-methylbenzenesulfonamide* (**11**). A stirred soln. of **10** (3.42 g, 10 mmol) in CH_2Cl_2 (25 ml) was treated with TFA (3.8 ml, 50 mmol) in one portion and stirred for 1 h at r.t. The acid was evaporated, the residue was treated with 10% aq. Na_2CO_3 (50 ml) and extracted with CH_2Cl_2 (5 × 75 ml). The combined extracts were dried ($MgSO_4$) and evaporated to afford **11** (2.15 g, 89%), which solidified upon standing. Slightly yellow solid. R_f 0.41 (CH_2Cl_2/MeOH/25% aq. NH_3 70:30:3). M.p. 64–66° ([22]: 65–68°). IR

(neat): 3583*m*, 3362*m*, 3276*s*, 3064*s*, 2936*s*, 1867*s*, 1924*w*, 1688*m*, 1598*m*, 1495*m*, 1452*m*, 1323*s*, 1201*m*, 1157*s*, 1094*s*, 1019*w*, 916*w*, 816*m*, 737*w*, 707*m*, 660*s*, 618*w*, 572*m*, 551*s*. ^{1}H-NMR ($CDCl_3$): 1.38–1.58 (*m*, 2 CH_2CH$_2$N); 2.42 (*s*, Me); 2.66 (*t*, *J* = 6.3, CH$_2$N); 2.92 (*t*, *J* = 6.5, CH$_2$N); 3.8 (br. *s*, 3 H, NH$_2$ + NH); 7.29 (*d*, *J* = 8.1, 2 arom. H); 7.74 (*d*, *J* = 8.1, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 21.33 (*q*, Me); 27.05, 29.53 (2*t*, 2 *C*H$_2$CH$_2$N); 40.90, 42.80 (2*t*, 2 CH$_2$N); 126.89, 129.49 (2*d*, 2 × 2 arom. CH); 137.17, 142.95 (2*s*, 2 arom. C). ESI-MS: 485 (38, [2*M* + 1]$^+$), 265 (21, [*M* + Na]$^+$), 243 (100, [*M* + 1]$^+$).

*(*S*)-3-[(4-Methylphenyl)sulfonylamino]-*N*-{4-[(4-methylphenyl)sulfonyl]aminobutyl}-3-phenylpropanamide* (**12**). To **8** (1.276 g, 4 mmol) was added $SOCl_2$ (4 ml) followed by DMF (*ca.* 0.05 ml). The resulting mixture was stirred at r.t. for 2 h. The excess of $SOCl_2$ was evaporated to give the corresponding acyl chloride which was dissolved in CH_2Cl_2 (20 ml) and added dropwise to stirred soln. of **11** (1.09 g, 4.5 mmol) and Et_3N (0.83 ml, 6 mmol) in CH_2Cl_2 (30 ml) at −10°. Stirring was continued for 30 min at −10° and for another 30 min at r.t. The resulting soln. was washed with 10% citric acid (20 ml), H_2O (2 × 20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by CC (CH_2Cl_2/MeOH 20:1) afforded **12** (1.85 g, 85%). White solid. R_f 0.57 (CH_2Cl_2/MeOH 10:1). M.p. 138–139°. $[\alpha]_D = -26.5$ (*c* = 1.00, MeOH). IR (KBr): 3744*w*, 3287*m*, 2928*m*, 2866*w*, 1914*w*, 1805*w*, 1647*s*, 1598*m*, 1542*s*, 1495*m*, 1455*m*, 1423*m*, 1322*s*, 1211*w*, 1155*s*, 1092*s*, 1067*m*, 967*w*, 842*w*, 813*m*, 744*w*, 703*m*, 671*s*, 604*w*, 573*m*, 551*s*. ^{1}H-NMR ($CDCl_3$): 1.44 (*m*, 2 CH_2CH$_2$N); 2.30, 2.41 (2*s*, 2 Me); 2.50 (*dd*, *J* = 14.4, 5.2, 1 H, CH$_2$CO); 2.58 (*dd*, *J* = 14.4, 8.0, 1 H, CH$_2$CO); 2.85 (*m*, CH_2NHTs); 3.03 (*m*, 1 H, CH_2NHCO); 3.21 (*m*, 1 H, CH_2NHCO); 4.74 (*ddd*, *J* = 8.1, 5.2, 8.0, CHN); 5.42 (*t*, *J* = 6.1, CH$_2$N*H*Ts); 6.30 (*t*, *J* = 5.7, CH$_2$N*H*CO); 6.72 (*d*, *J* = 8.1, CHN*H*Ts); 7.01–7.06 (*m*, 5 H of Ph, 2 H of Ts); 7.29 (*d*, *J* = 8.0, 2 H of Ts); 7.48 (*d*, *J* = 8.3, 2 H of Ts); 7.73 (*d*, *J* = 8.3, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.26, 21.38 (2*q*, 2 Me); 26.14, 26.40 (2*t*, 2 *C*H$_2$CH$_2$N); 38.66 (*t*, CH$_2$CO); 42.77, 43.38 (2*t*, 2 CH$_2$N); 55.43 (*d*, CHN); 126.39, 126.89, 126.96 (3*d*, 3 × 2 arom. CH); 127.15 (*d*, 1 arom. CH); 128.18, 129.10, 129.64 (3*d*, 3 × 2 arom. CH); 136.54, 137.45, 139.75, 142.74, 143.33 (5*s*, 5 arom. C); 170.09 (*s*, C=O). CI-MS: 561 (45, [*M* + NH$_4$]$^+$), 544 (81, [*M* + 1]$^+$), 390 (38, [(*M* − TsNH$_2$) + NH$_4$]$^+$), 373 (100, [(*M* − TsNH$_2$) + 1]$^+$), 189 (80).

*(*S*)-5,9-Bis[(4-methylphenyl)sulfonyl]-4-phenyl-1,5,9-triazacyclotridecan-2-one* (**13**). *Method A*. A stirred suspension of Cs_2CO_3 (0.717 g, 2.2 mmol) in dry DMF (30 ml) was warmed to 50° and treated dropwise with a soln. of **12** (0.543 g, 1.0 mmol) and 1,3-bis(tosyloxy)propane (0.384 g, 1.0 mmol) in dry DMF (40 ml) during 2 h. After the addition was completed, stirring was continued for 24 h, then the reaction mixture was cooled to r.t. The solvent was evaporated *in vacuo* and the residue was partitioned between CH_2Cl_2 (50 ml) and H_2O (20 ml). The org. layer was washed with H_2O (2 × 20 ml), dried ($MgSO_4$), and concentrated *in vacuo*. CC of the residue (CH_2Cl_2/AcOEt 4:1) afforded **13** (0.328 g, 56%). White foam. R_f 0.53 (CH_2Cl_2/AcOEt 1:1). $[\alpha]_D = +1.3$ (*c* = 1.27, $CHCl_3$). IR (KBr): 3380*m*, 3062*w*, 3030*w*, 2927*m*, 2866*m*, 1918*w*, 1751*m*, 1667*s*, 1598*m*, 1535*m*, 1495*m*, 1452*m*, 1335*s*, 1215*m*, 1155*s*, 1121*m*, 1089*m*, 1035*w*, 996*w*, 952*w*, 919*w*, 815*m*, 763*m*, 701*m*, 726*m*, 687*m*, 655*m*, 607*w*, 568*m*, 549*s*. ^{1}H-NMR ($CDCl_3$): 1.42, 1.56 (2*m*, 2 H, CH_2CH$_2$N); 1.76–2.03 (*m*, 3 H, CH_2CH$_2$N); 2.11 (*m*, 1 H, CH_2CH$_2$N); 2.26, 2.41 (2*s*, 2 Me); 2.69 (*dd*, *J* = 14.6, 2.0, 1 H, CH$_2$CO); 2.92 (*m*, 1 H, CH_2NHCO); 3.11–3.38 (*m*, 6 H, 3 CH_2NHTs); 3.67 (*dd*, *J* = 14.6, 11.6, 1 H, CH$_2$CO); 3.90 (*m*, 1 H, CH_2NHCO); 5.07 (*dd*, *J* = 11.6, 2.0, CHN); 6.26 (*dd*, *J* = 8.6, 3.4, CH$_2$N*H*CO); 6.89 (*d*, *J* = 8.3, 2 H of Ts); 6.98–7.21 (*m*, 5 H of Ph, 2 H of Ts); 7.28 (*d*, *J* = 8.4, 2 H of Ts); 7.68 (*d*, *J* = 8.3, 2 H of Ts). ^{13}C-NMR ($CDCl_3$): 21.16, 21.34 (2*q*, 2 Me); 22.42, 24.73, 28.52 (3*t*, 3 *C*H$_2$CH$_2$N); 38.48 (*t*, CH$_2$CO); 41.86, 44.28, 46.75, 48.03 (4*t*, 4 CH$_2$N); 62.21 (*d*, CHN); 127.03–128.29 (several *d*, 9 arom. CH); 128.78, 129.53 (2*d*, 2 × 2 arom. CH); 136.65, 136.92, 137.73, 142.47, 142.88 (5*s*, 5 arom. C); 170.64 (*s*, C=O). ESI-MS: 1189 (17, [2*M* + Na]$^+$), 606 (100, [*M* + Na]$^+$), 584 (13, [*M* + 1]$^+$).

Method B. A stirred suspension of Cs_2CO_3 (0.717 g, 2.2 mmol) in dry DMF (30 ml) was treated dropwise at r.t. with a soln. of **12** (0.543 g, 1.0 mmol) and 1,3-bis(methylsulfonyloxy)propane (0.384 g, 1.0 mmol) in dry DMF (40 ml) during 2 h. After the addition was complete, stirring was continued for 72 h. The same workup as above afforded **13** (0.457 g, 78%).

*(*S*)-4-Phenyl-1,5,9-triazacyclotridecan-2-one* (**14**). A soln. of **13** (0.419 g, 0.72 mmol) in a minimal amount of DMF was added to a 0.1M soln. of Me_4NCl in EtOH (100 ml). The resulting soln. was subjected to electrolysis under Ar at −2.25 V in a three-electrode cell with a Hg cathode, graphite-rod anode, and standard calomel electrode as reference electrode (see [18] for detailed procedure). After the electrolysis was complete, the solvents were removed *in vacuo*, the remainder was dissolved in 20% aq. K_2CO_3 (10 ml) and extracted with CH_2Cl_2 (4 × 50 ml). The combined extracts were dried and evaporated to afford **14** (0.198 g, 100%). Colorless oil. R_f 0.20 (CH_2Cl_2/MeOH/25% aq. NH_3 70:30:3). $[\alpha]_D = -5.2$ (*c* = 0.89, $CHCl_3$). IR (KBr): 3269*s*, 3025*m*, 3061*m*, 2927*s*, 2855*s*, 2803*m*, 1952*w*, 1881*w*, 1812*w*, 1657 (sh), 1636*s*, 1554*s*, 1491*m*, 1453*m*, 1436*m*, 1356*m*, 1308*m*, 1272*w*, 1233*m*, 1185*m*, 1130*m*, 1069*m*, 1028*m*, 960*m*, 925*w*, 844*w*, 799*w*, 763*m*, 703*s*, 646*w*, 619*w*, 595*m*, 569*w*, 543*m*, 521*m*. ^{1}H-NMR ($CDCl_3$): 1.69–1.88 (*m*, 6 H, 3 CH_2CH$_2$N); 2.38–2.54 (*m*, CH$_2$); 2.60–2.84 (*m*, 4 H,

CH_2 + 2 NH); 3.00–3.10 (*m*, CH_2); 3.48–3.69 (*m*, 2 CH_2N); 4.01 (*dd*, *J* = 11.5, 2.8, CHN); 7.21–7.35 (*m*, 5 H, Ph); 8.52 (br. *t*, CONH). ^{13}C-NMR: 26.33, 26.61, 27.41 (3*t*, 3 *C*H_2*C*H_2N); 39.53 (*t*, *C*H_2CO); 44.33, 45.14, 48.19, 49.00 (4*t*, 4 CH_2N); 59.99 (*d*, CHN); 126.23 (*d*, 2 arom. CH); 127.18 (*d*, 1 arom. CH); 128.56 (*d*, 2 arom. CH); 142.71 (*s*, 1 arom. C); 171.84 (*s*, C=O). CI-MS: 276 (100, $[M+1]^+$), 91 (22, $[C_7H_7]^+$).

*(*S*)-4-Phenyl-9-(3-phenylprop-2-enoyl)-1,5,9-triazacyclotridecan-2-one* (=*(*S*)-Dihydroperiphylline*; **15**). A stirred soln. of **14** (0.169 g, 0.61 mmol) and DMAP (0.223 g, 1.83 mmol) in CH_2Cl_2 (15 ml) was cooled to −80° and treated dropwise with a soln. of cinnamoyl chloride (101.5 mg, 0.60 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred for 1 h at −80°, allowed to reach r.t., washed with H_2O (2 × 10 ml) and concentrated. CC of the residue (CH_2Cl_2/MeOH 10:1) afforded **15** (230 mg, 94%). White solid. R_f 0.40 (CH_2Cl_2/MeOH 10:1). M.p. 81–82° ([4]: 82.5–83.5°). $[\alpha]_D = +3.2$ (*c* = 0.5, $CHCl_3$). IR (KBr): 3744*w*, 3400*m*, 3296*m*, 3060*m*, 3026*m*, 2926*m*, 2856*m*, 1952*w*, 1885*w*, 1825*w*, 1646*s*, 1597*s*, 1552*m*, 1495*m*, 1452*s*, 1427*s*, 1375*m*, 1327*m*, 1304*m*, 1254*w*, 1192*m*, 1174*m*, 1114*m*, 1073*m*, 1028*w*, 976*m*, 911*w*, 855*m*, 763*s*, 702*s*, 588*w*, 555*m*, 534*m*. ^{1}H-NMR ((D_6)DMSO, 373 K): 1.48–1.62/1.70–1.88 (2*m*, CH_2(7), CH_2(11), CH_2(12)); 2.24 (*ddd*, *J* = 12.4, 8.8, 3.7, 1, H–C(6)); 2.28 (*dd*, *J* = 13.3, 4.3, 1 H–C(3)); 2.37 (*dd*, *J* = 13.3, 10.4, 1 H–C(3)); 2.51 (*m*, H–N(5)); 2.55 (*ddd*, *J* = 12.4, 7.0, 3.8, 1 H–C(6)); 3.22, 3.35 (2*m*, 2 H, CH_2(13)); 3.47–3.66 (*m*, CH_2(8), CH_2(10)); 3.98 (*dd*, *J* = 10.4, 4.3, CHN); 7.00 (*d*, *J* = 15.4, CH=C*H*CO); 7.21 (*m*, 1 arom. H); 7.30–7.43 (*m*, 7 arom. H); 7.45 (*d*, *J* = 15.4, C*H*=CHCO); 7.61 (*m*, 2 H of CH=CH*Ph*); 7.72 (br. *t*, CONH). ^{13}C-NMR ((D_6)DMSO, 373 K): 24.64 (2 overlapping *t*, C(11), C(12)); 29.00 (*t*, C(7)); 37.36 (*t*, C(13)); 42.25 (*t*, C(6)); 43.22 (*t*, C(10)); 45.33 (*t*, C(3)); 47.50 (*t*, C(8)); 59.24 (*d*, C(4)); 119.07 (*d*, CH=*C*HCO); 125.80 (*d*, 2 arom. CH); 126.06 (*d*, 1 arom. CH); 127.11, 127.70, 128.10 (3*d*, 3 × 2 arom. CH); 128.55 (*d*, 1 arom. CH); 135.02 (*s*, 1 arom. CH); 139.85 (*d*, *C*H=CHCO); 143.85 (*s*, 1 arom. C); 164.79 (*s*, CH=CH*C*O); 170.33 (CONH). CI-MS: 406 (100, $[M+1]$, 276 (8).

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Received July 7, 2001