Synthesis of the Macrocyclic Spermidine Alkaloid (±)-(2*R**,3*R**)-3-Hydroxycelacinnine

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Dedicated to *Edgar Heilbronner* on the occasion of his 80th birthday

The macrocyclic lactam alkaloid (±)-(2*R**,3*R**)-3-hydroxycelacinnine (**1**) derived from spermidine was synthesized *via* stereoselective epoxide-ring opening with magnesium azide and cesium carbonate promoted macrocyclization of the ditosylated diamino precursor **12** with 1,4-dibromobutane in the two key steps (*Scheme 2*). ^{1}H- and ^{13}C-NMR Signal assignments from COSY, HSQC, and HMBC 2D NMR data of the synthesized **1** were compared with the earlier-described data of the natural 3-hydroxycelacinnine. The similarity of their ^{13}C-NMR spectra point to the correctness of the proposed constitutional formula for natural 3-hydroxycelacinnine; however, different ^{1}H-NMR chemical shifts and coupling constants ($J(2,3) = 9.0$ *vs.* 1.2 Hz, resp.) in the α-hydroxy-β-amino lactam moiety suggest that natural 3-hydroxycelacinnine is the 2,3-*cis*-epimer of one synthetic (±)-**1**.

Introduction. – Macrocyclic lactams derived from polyamines are of particular interest as synthetic targets for organic chemists due to their structural complexity and broad biological activity [1][2]. *Séguineau et al.* have isolated several novel hydroxylated spermidine alkaloids from the leaves of a New Caledonian Celastraceae, *Pleurostylia opposita* (WALL.) MERRILL-METCALF [3][4]. Their proposed structures for 3-hydroxycelacinnine (**1**) (originally named 7-hydroxycelacinnine [3]), 7-hydroxypleurostyline (**2**), and 7-hydroxypleurocorine (**3**) are shown in *Scheme 1*[1]). The presence of an OH group at the α-position to the lactam carbonyl group represents a new feature in such alkaloids. A biosynthetic pathway of their formation involving an epoxy precursor has been suggested [3][4] (*Scheme 1*)[2]). We are interested in the structure verification and biosynthesis of these alkaloids.

In this paper, we report the stereoselective synthesis of (±)-**1**. A large difference between coupling constants (9.0 *vs.* 1.2 Hz) as well as a significant difference between ^{1}H-NMR chemical shifts in the H–C(2)–C(3)–H moiety of the synthesized **1** and the natural 3-hydroxycelacinnine [3][4] suggest that the proposed relative *trans*-configuration (2*R**,3*R**) for the natural alkaloid should be changed to the corresponding *cis*-configuration (2*R**,3*S**). Also, the same conclusion holds for **2** and **3**, as well, since all three natural alkaloids had almost identical ^{1}H- and ^{13}C-NMR data for this moiety [3][4].

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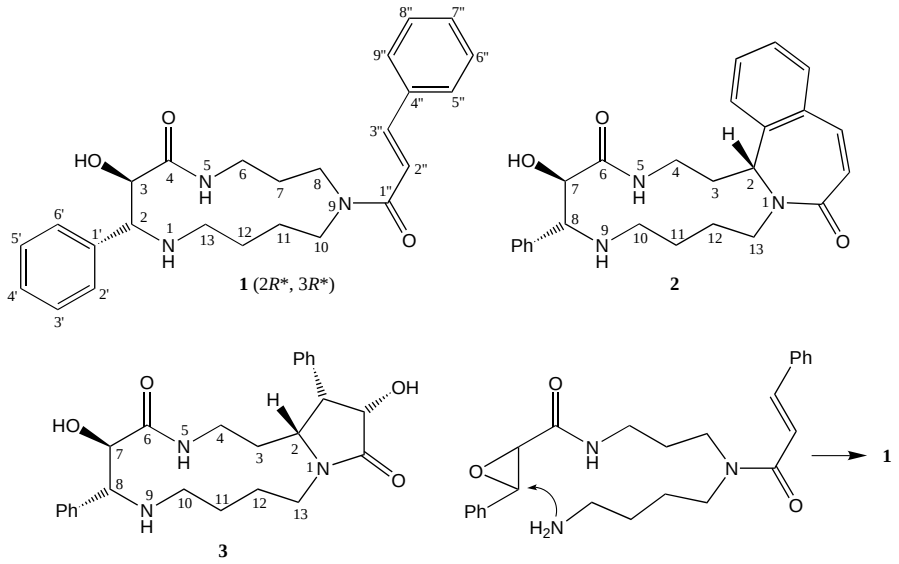
[1]) To have the same atom numbering for **1**–**3**, *Séguineau et al.* proposed the name 7-hydroxycelacinnine for **1** [3]. However, in this paper, we use the name 3-hydroxycelacinnine according to the IUPAC rules for atom numbering, as shown in *Scheme 1*. For systematic names, see *Exper. Part*.

[2]) In the light of the results disscussed below, the alleged precursor for natural 3-hydroxycelacinnine should be the (*Z*)-epoxide.

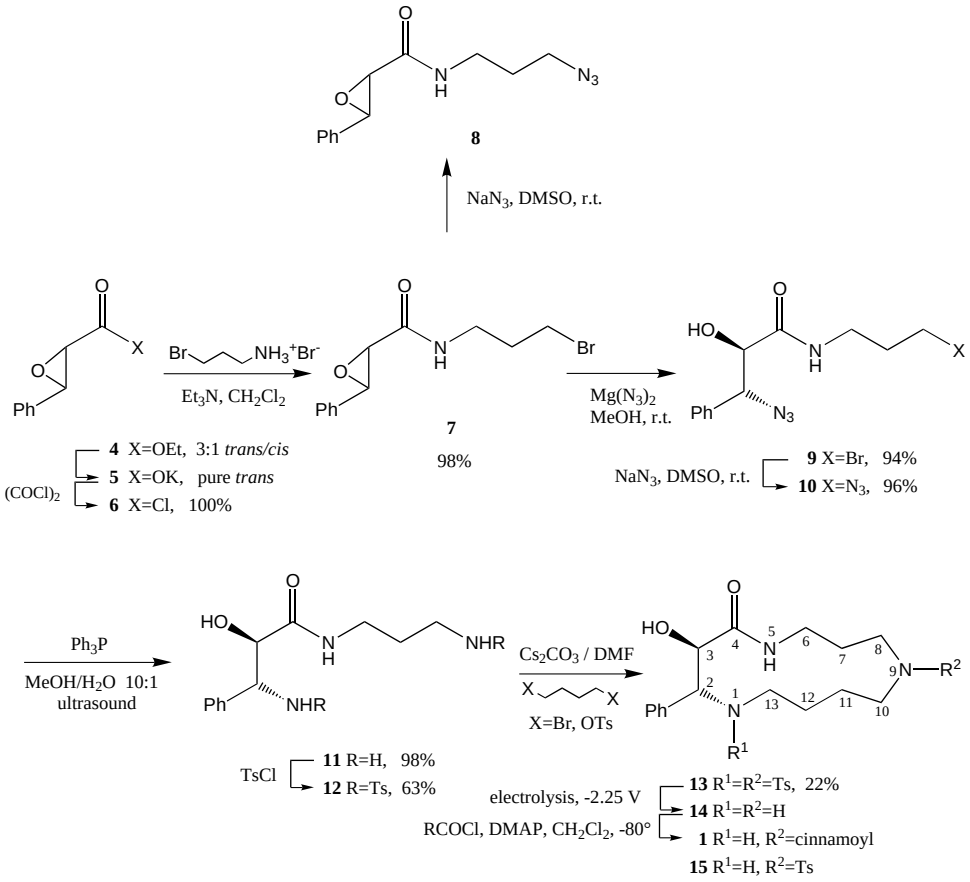
Scheme 1. *Proposed Structures of Novel Hydroxylated Alkaloids 3-Hydroxycelacinnine* (**1**)[1], *7-Hydroxypleurostyline* (**2**), *and 7-Hydroxypleurocorine* (**3**) *Isolated from* Pleurostylia opposita *and the Proposed Biosynthetic Formation of* **1** [3][4]



Synthesis. – For the synthesis of **1**, the commercially available *ca.* 3 : 1 mixture of the *cis*- and *trans*-ethyl phenylglycidate (= ethyl 3-phenyloxiranecarboxylate; **4**) was saponified to its potassium salt [5], which gave pure potassium *trans*-oxiranecarboxylate **5** after crystallization from aqueous EtOH, as described for the sodium salt [6] (*Scheme 2*). Potassium carboxylate **5** was converted to its acid chloride **6** [7] according to the procedure described for the sodium salt. Coupling of **6** with 3-bromopropanamine hydrobromide promoted by Et_3N in CH_2Cl_2 provided the amide **7** in 98% yield from **5**.

Direct coupling of the bromo epoxy amide **7** with deprotonated $TsNH_2$ led to a complex product mixture containing only traces of the ditosylate **12**. Thus, longer routes from **7** to **12** had to be investigated. We found that the epoxide or bromide functionalities in **7** can be selectively cleaved by the azide ion under specific conditions keeping the other functionality intact. Following the procedure of *Behrens* and *Sharpless* for the stereo- and regioselective preparation of β-azido-α-hydroxy-amides [8][9], we obtained the monoazido derivative **9** in 94% yield by stirring a MeOH solution of **7** with an *in situ* ($MgSO_4 + NaN_3$) preparation of $Mg(N_3)_2$. In this particular case, the Ph-substituent at the β-position greatly facilitated the epoxide opening, and the reaction proceeded to a full completion after 2 h at room temperature. An attempted direct formation of the diazido derivative **10** from **7** required higher temperatures, which led to the formation of by-products. Also, the formation of the C(α) ring-opened isomer was below detectable level, which has to be compared to the 10 : 1 regioselectivity observed in the case of epoxyamides with aliphatic substituents after reflux in methanolic $Mg(N_3)_2$ for several hours, the conditions applied in the original work of *Behrens* and *Sharpless* [9]. The facile conversion of azidobromido-

Scheme 2



amide **9** into diazido derivative **10** was achieved in 96% yield by treating the former with an excess of NaN_3 in DMSO at room temperature for 2 h according to a described general procedure [10]. Under these conditions, bromoepoxyamide **7** can be selectively converted into azido epoxy amide **8**. Keeping the reaction mixture at room temperature for a longer time (several days) led to only partial epoxide cleavage of **8**, with the formation of diazido derivative **10** as well as several unidentified by-products, according to the ^{1}H- and ^{13}C-NMR analysis of the reaction mixture in (D_6)DMSO.

The general procedure for the facile azide reduction with Ph_3P in aqueous THF at room temperature [11] required a longer reaction time (>24 h) in the case of diazido derivative **10** and furnished a low yield of diaminoamide **11**. A temperature increase to 50° facilitated the reduction. However, a small amount of by-product was always detected due, perhaps, to the slow reduction of the more hindered azido group at the secondary C(3) atom and the presence of the vicinal OH–C(2), which may lead to several by-products [11]. Therefore, the reaction was studied by ^{1}H-NMR in various

aqueous deuterated solvents. The reduction of diazido derivative **10** with Ph_3P in MeOH/H_2O 10:1 was best achieved by sonication of the suspension for 1 h to give **11** in 98% yield. For comparison, the reduction of **10** in aqueous DMSO under the same conditions proceeded much slower and with the formation of by-products.

Diaminohydroxyamide **11** was then selectively converted into ditosylate **12** with TsCl (2 equiv.), promoted by Na_2CO_3 in aqueous dioxane, in 63% yield after recrystallization. Tosylation of **11** in CH_2Cl_2 in the presence of Et_3N also led to **12** contaminated with a small amount of tritosylated product.

Several bimolecular [12–16] and intramolecular [17–20] macrocyclization reactions have been described based on the alkylation of *N*-monosubstituted sulfonamides promoted by Cs_2CO_3 in DMF [12–17] or K_2CO_3 in MeCN [18][19], or under *Mitsunobu* conditions [20]. According to previous studies, macrocyclization [12][13] as well as alkylation of tosylamides in general [13] proceeded better when Cs_2CO_3/DMF was used, and high dilution was not usually required to achieve the best yields. With this method, we already have obtained several 13-membered spermidine-derived lactam alkaloids in up to 90% yield [21][22]. Thus, we prepared the ditosylated lactam **13** by Cs_2CO_3-promoted coupling between **12** and a 1,4-disubstituted butane derivative. To evaluate effectiveness of this method for the preparation of similar macrocyclic lactams, we investigated the macrocyclization reaction between **12** and 1,4-dibromobutane under various conditions (see *Table 1* and *Scheme 3*).

First, the reaction was run at room temperature with a slight excess of 1,4-dibromobutane (1.2 equiv.) and Cs_2CO_3 (2.5 equiv.) at moderate dilution ([**12**] = 0.01M) (*Table 1*, *Entry 1*). Macrocyclic **13** was isolated in only 9% yield after 48 h together with the less hindered monosubstituted **16** (56%) as the major product and **24** (25%). The latter resulted from alkylation of the less hindered N-atoms of two molecules of **12** with one molecule of 1,4-dibromobutane. Presumably, **13** was formed from the more hindered monoadduct **17**, which was not detected in the reaction mixture due to its facile cyclization into **13**.

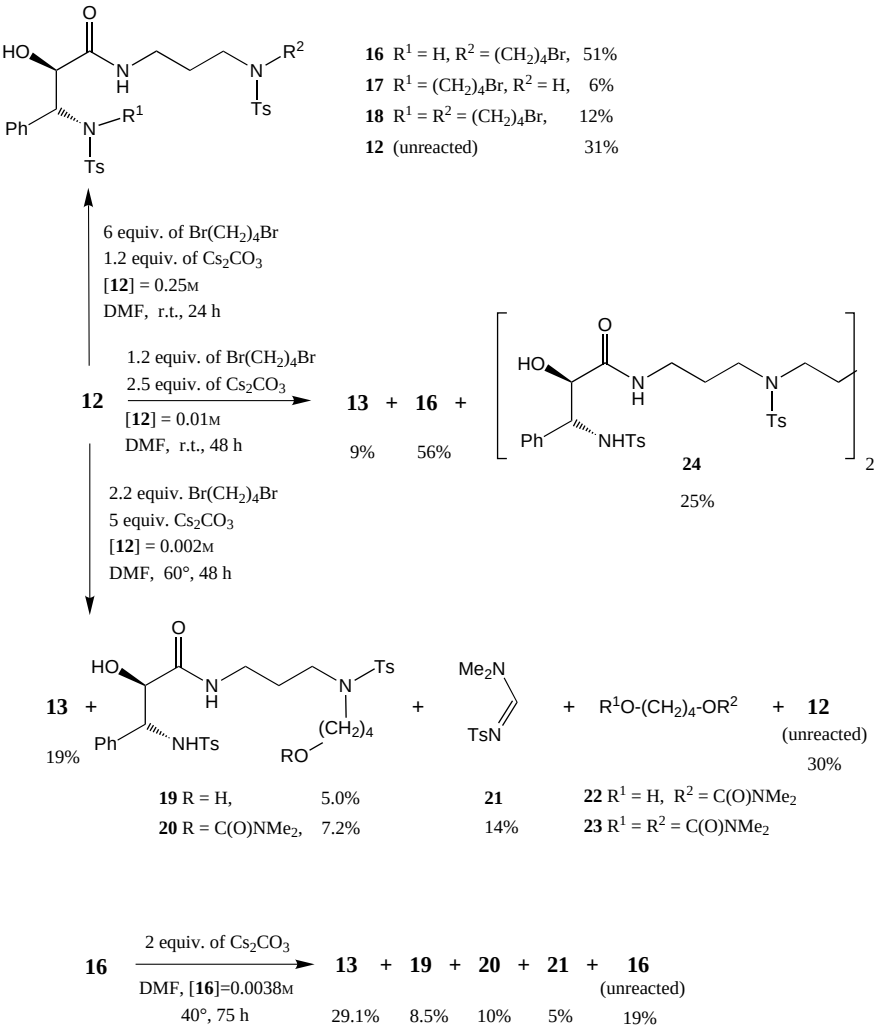
Reaction of **12** with an excess of 1,4-dibromobutane (6 equiv.) and an insufficient amount of Cs_2CO_3 (1.2 equiv.) in the minimum amount of DMF at room temperature (*Entry 2*) showed a *ca.* 10:1 selectivity between the two tosylated N-atoms of **12**

Table 1. *Isolated Yields of* **13** *after* Cs_2CO_3*-Promoted Macrocyclization of* **12** *under Various Conditions*

Entry	Concentration of **12** [M][a])	$X(CH_2)_4X$[b]) [equiv.]	Cs_2CO_3 [equiv.]	*T* [°C], time	**13** [%]
1	0.01	1.2	2.5	r.t., 48 h	9
2[c])	0.2	6	1.2	r.t., 22 h	0
3[c])	[**16**] = 0.0038	–	2.4	40°, 75 h	29
4[c])	0.002	1.1 + 1.1	2.1 + 1.1	60°, 48 h	19
5[c])	0.015	1.1	2.5	50°, 24 h	22
6	0.01	1.2 (X = OTs)	2.5	r.t., 72 h; then 60°, 64 h	15
7	0.075 (DMSO)	1.2	2.5	50°, 24 h; then r.t., 96 h	6.5
8	0.004 (DMSO)	2	2.5	40°, 72 h	< 10[d])
9	0.004 (MeCN)	2	2.5	40°, 72 h; then 60°, 72 h	22

[a]) Solvent = DMF, unless noted otherwise. [b]) X = Br, unless noted otherwise. [c]) See text and *Exper. Part* for the detailed procedure and product distribution. [d]) Only traces of **13** were observed by TLC after workup, and the yield was estimated without separation.

Scheme 3. *Product Distribution after Cs_2CO_3-Promoted Alkylation of* **12** *under Various Conditions*

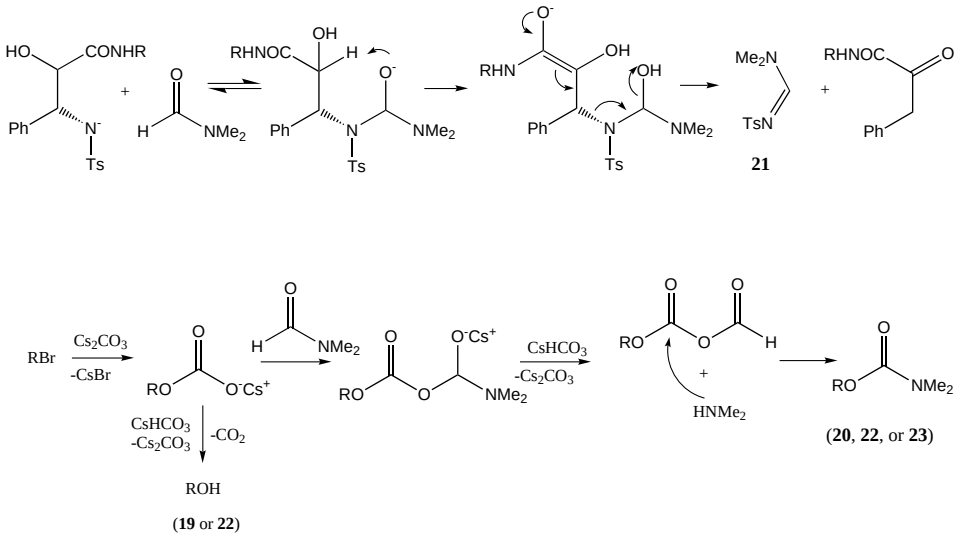


towards alkylation. Thus, the less hindered monoadduct **16** was again the major product (51%) accompanied by only 6% of the more hindered **17**, dialkylated **18** (12%), and unreacted **12** (31%). The isolated monoadduct **16** was then allowed to react with Cs_2CO_3 at moderate dilution ([**16**] = 0.0038M, *Entry 3*). No intramolecular macrocyclization was observed at room temperature. However, a very slow macrocyclization took place at 40°. After 75 h, lactam **13** was obtained in 29% yield along with unreacted **16** (19%), hydroxy compound **19** (8.5%), carbamate **20** (10%), formimidamide **21** [23] (5%), and several other unidentified products, presumably formed by β-elimination of tosylamide and elimination of bromide according to NMR analysis of the crude fractions obtained after column-chromatography separation.

At higher dilution ([**12**] = 0.002M, *Entry 4*), intermolecular monoalkylation of **12** by 1,4-dibromobutane occurred very slowly. Thus, a higher temperature (60°) and an excess of 1,4-dibromobutane (2.2 equiv.) were used to accelerate the reaction. However, several by-products were isolated (*Scheme 3*), similar to those obtained by macrocyclization of **16** after 48 h. The desired lactam **13** was isolated in only 19% yield, along with unreacted **12** (30%), hydroxy compound **19** (5%), carbamate **20** (7%), formimidamide **21** (14%), and carbamates **22** and **23**.

Thus, intramolecular macrocyclization of intermediate **16** involving the more hindered N-atoms proceeded slowly, with a rate comparable to the rates of side reactions, including DMF-assisted β-elimination of tosylamide with the formation of formimidamide **21** (*Scheme 4*), and solvolysis of the monobromo compound **16** to the hydroxy compound **19** and carbamate **20**. Carbamate **20** was presumably formed from **16** according to the mechanism depicted in *Scheme 4*. Although an excess (2.2 equiv.) of 1,4-dibromobutane was used, no dialkylated **18** was detected under high-dilution conditions, and no **24** was observed. The best yield of 13 (22%, *Entry 5*) in the bimolecular macrocyclization was achieved under moderate dilution conditions (0.015M) at 50° in DMF with 1.1 equiv. of 1,4-dibromobutane.

Scheme 4. *Proposed Mechanisms of Side Reactions during Macrocyclization*



The same by-products were isolated when ditosylated 1,4-butanediol was used in the macrocyclization instead of 1,4-dibromobutane, but no yield improvement was achieved (*Entry 6*). To avoid DMF-assisted side reactions, the macrocyclization was also investigated in DMSO and MeCN. In DMSO (*Entries* 7 and *8*), the yields of **13** were even smaller, with a significant amount of hydroxy compound **19** being formed. Reaction in MeCN (*Entry 9*) with an excess of 1,4-dibromobutane (2 equiv.) at 40° proceeded slower than in DMF, with the formation of **16** as the major product, a small amount of the desired **13**, and a significant amount of the unreacted **12**. Temperature

increase to 60° led to only 22% yield of **13** after 72 h, due to the side reactions including, presumably, β-elimination of NHTs, elimination of bromide, and lactam cleavage.

Thus, we were unable to increase the yield of the macrocyclization step above 22%, and alternative routes to **1** were investigated [24]. According to the above-mentioned experimental data, the moderate yields in this step are best explained by the low reactivity of the more hindered tosylated N-atom towards alkylation, which allows slow side reactions to compete with the macrocyclization. With the less hindered ditosylated diamines studied by us, macrocyclization proceeded with somewhat better yields. In particular, with a substrate similar to **12** (with the β-phenyl group, but without the OH group), the optimized yield of the macrocyclization step was 45% [21]. With primary-alkyl moieties in the β-position, the macrocyclization proceeded with the highest yields [22]: the best yield (90%) was observed in the case of the unprotected hydroxymethyl substituent.

Finally, **13** was electrochemically detosylated at -2.25 V to give hydroxylactame **14** according to the procedure of *Guggisberg et al.* [25], followed by selective monoacylation with cinnamoyl chloride at the less hindered N-atom of the macrocycle [26] to give **1**.

NMR Data Analysis. – Complete ^{1}H- and ^{13}C-NMR signal assignments for the macrocyclic **1** and **13** were unambiguously obtained from the 2D NMR data (COSY, HMBC, and HSQC) and summarized in *Tables 2* and *3*. Due to the restricted rotation in the cinnamamide and very small differences in the chemical shifts of two rotamers, several ^{1}H- and ^{13}C-NMR signals of **1** gave broad lines at room temperature in both $CDCl_3$ and (D_6)DMSO. Thus, 2D NMR characterization of **1** was performed at the highest possible temperature before decomposition (70°, (D_6)DMSO) and also at low temperature (−40°, $CDCl_3/CD_3OD$ 30:1). However, even at 70°, the ^{13}C-NMR resonances of the four methylene C-atoms in the vicinity of the *N*-cinnamoyl group still appeared as broad doubled *s*. Also at low temperature, full resolution of all signals was not achieved, due to the very small chemical-shift difference between some resonances of two rotamers.

Unexpectedly, both H- and C-atoms of the β-amino-α-hydroxylactam fragment in ditosylated **13** gave broad signals at room temperature due, perhaps, to the restricted rotation around the crowded endocyclic TsN(1)–C(2)Ph bond. Thus, 2D NMR characterization of **13** was performed at 60° in (D_6)DMSO. Synthesized **1**, **13**, and **14** showed large coupling constants ($J(2,3) = 9.0–9.5$ Hz) for the two vicinal protons at C(2) and C(3), which were almost independent of solvent ((D_6)DMSO, $CDCl_3$) and temperature. Moreover, ^{1}H-NMR chemical shifts and proton coupling of the CH(2)–CH(3) moiety of the synthesized **1** and **14** were identical with those of **15** (*Table 3*) synthesized by a different route [24], but completely different from those of the natural 3-hydroxycelacinnine [3][4]. Based on these observations and the similarity of the rest of their ^{1}H-NMR spectra as well as on the general similarity of their ^{13}C-NMR spectra, we conclude that the natural 3-hydroxycelacinnine should have the reverse relative configuration at the two stereocenters as **1**. The natural alkaloids with the proposed [3][4] structures **1**–**3** gave also almost identical NMR data for the C(2)–C(3) fragment [3][4]; thus, the same correction of the relative configuration at this fragment should be applied to all three natural alkaloids. We are currently working

Table 2. *Comparison of ^1H- and ^{13}C-NMR Data of Natural 3-Hydroxycelacinnine* [3][4] *(2*R**,3*S**)-***1***[a]), and Synthesized (2*R**,3*R**)-3-Hydroxycelacinnine* (**1**)

	(2*R**,3*S**)-**1** [3][a])		**1** (this work)[b])		**1** (this work)[c])	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
CH(2)	4.27 (*d*, *J*(2,3) = 1.2)	64.01, 64.38	3.62 (*d*, *J*(2,3) = 9.1)	65.79	3.64 (br. *d*, *J*(2,3) = 8.9)	66.08
CH(3)	4.16 (*d*, *J*(2,3) = 1.2)	76.07, 76.16	3.90 (*d*, *J*(2,3) = 9.0)	75.62	4.04 (br. *d*, *J*(2,3) = 8.9), 4.07 (br. *d*, *J*(2,3) = 10)	74.77, 74.41
C(4)		172.50, 172.34		173.13	–	174.11, 174.19
NH(5)	7.00 (*t*)		7.87 (br. *t*)		8.06, 8.27 (2 br. *s*)	–
CH_2(6)	3.80 (*m*), 3.00 (*m*)	36.72, 36.16	3.24 (*m*), 3.16 (*m*)	35.45	3.35 (*m*, 1 H), 3.39 (*m*, 1 H)	36.39, 35.95
CH_2(7)	2.25 (*m*), 1.70 (*m*)	27.92, 30.39	1.75–1.93 (*m*)	29.6 (br.), 27.8 (br.)	1.9–2.6 (br. *m*, 2 H)	27.17, 29.72
CH_2(8)	3.75 (*m*), 3.43 (*m*)	43.03, 44.59[d])	3.63 (*m*), 3.28 (*m*)	44.1 (br.), 46.0 (br.)	3.68 + 3.58[g]), 3.72 + 3.33[g])	44.03, 47.08
CH_2(10)	3.57 (*m*), 3.38 (*m*)	44.01, 46.80[d])	3.45–3.65 (*m*)	42.7 (br.), 43.2 (br.)	3.90 + 3.03[g]), 3.54 + 3.59[g])	44.8
43.38						
CH_2(11)	1.92 (*m*), 1.62 (*m*)	24.88[c]), 25.12	1.76 (*m*), 1.56 (*m*)	25.8 (br.), 23.8 (br.)	1.66 + 1.78[g]), 1.70 + 1.90[g])	22.74, 25.27
CH_2(12)	1.65 (*m*), 1.45 (*m*)	24.22[e]), 26.06	1.43 (*m*), 1.32 (*m*)	23.80	1.38 – 1.58 (2 br. *m*, 2 H)	23.75
CH_2(13)	2.86 (*m*), 2.31 (*m*)	46.55, 46.46	2.51 (*m*), 2.28 (*m*)	44.87	2.60 + 2.42[g]), 2.64 + 2.40[g])	44.62, 44.91
HO–C(3)			4.87 (br. *s*)		–	–
Phenyl:						
C(1′)		142.35, 142.44		141.87	–	140.15, 139.92
CH(2′,6′)	7.35 (*m*)	127.76[f])	7.34–7.37 (*m*)	127.45[e])	7.38–7.49[d])	128.48, 128.45[d])
CH(3′,5′)	7.35 (*m*)	126.99[f])	7.34–7.37 (*m*)	127.62[e])	7.33–7.37[d])	127.36[d])
CH(4′)	7.35 (*m*)	127.56[f])	7.34–7.37 (*m*)	128.87	7.31–7.38	127.60, 127.53
Cinnamoyl:						
C=O	165.16, 165.82		164.56	–	166.12, 166.28	
CH=*CH*CO	6.30 (*d*, *J*(2,3) = 15.4)	117.53	7.05 (br. *d*, *J*(2,3) = 15.6)	118.80	6.83 (*d*, *J* = 15.4), 6.87 (*d*, *J* = 15.4)	116.30
CH=CHCO	7.66 (*d*, *J*(2,3) = 15.4)	170.79	7.48 (*d*, *J*(2,3) = 15.4)	140.34	7.69 (*d*, *J* = 15.4), 7.71 (*d*, *J* = 15.4)	142.80, 143.04
C(1″)		135.41	135.41	135.08	–	134.46
HC(2″,6″)	7.52 (*m*)	128.78	7.66 (br. *d*, *J* = 7)	127.45	7.57 (br. *d*), 7.59 (br. *d*)	127.75, 127.72
HC(3″,5″)	7.35 (*m*)	128.78	7.30–7.42 (*m*)	128.32	7.40–7.49	128.70, 128.68
HC(4″)	7.35 (*m*)	129.49	7.22 (*m*)	126.23	7.38–7.46	129.82, 129.76

[a]) Configuration tentative. Spectra in $CDCl_3$ at r.t. with $SiMe_4$ as internal reference; ^1H and ^{13}C at 270 and 67.5 MHz, respectively. [b]) 18 mg in 0.6 ml of (D_6)DMSO, +70°, δ(DMSO) 2.50 (^1H, 300 MHz), and 39.51 (^{13}C, 75 MHz). [c]) 16 mg in 0.6 ml of $CDCl_3$/CD_3OD 30 : 1, −40°, δ($SiMe_4$) = 0.00 (^1H, 500 MHz), δ($CDCl_3$) 77.00 (^{13}C, 125 MHz). [d])[e])[f])Interchangeable values each. [g])(2 br. *m*, 0.5 + 0.5 H).

Table 3. *^{1}H- and ^{13}C-NMR Data of Macrocyclic* **13**–**15**

	13[a])		**14**[b])		**15**[c])	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
CH(2)	5.19 (*d*, *J*(2,3) = 9.5)	63.62	3.56 (*d*, *J*(2,3) = 9.0)	66.62	3.47 (*d*, *J*(2,3) = 10.1)	66.06
CH(3)	4.72 (*d*, *J*(2,3) = 9.6)	70.97	3.98 (*d*, *J*(2,3) = 9.0	73.78	3.99 (*d*, *J*(2,3) = 10.1)	72.61
C(4)		171.13		173.31		173.61
NH(5)	7.82 (br. *t*, *J* = 5)		7.13–7.28		8.51 (br. *t*, *J* = 5)	
CH_2(6)	3.38 (*m*), 3.08 (*m*)	36.29	3.43 (*m*), 3.28 (*m*)	39.84	3.53 (*m*), 3.25 (*m*)	37.36
CH_2(7)	1.84 (*m*), 1.74 (*m*)	27.79	1.68 (*m*, 2 H)	28.04[d])	1.90–1.98 (*m*, 2 H)	29.08
CH_2(8)	3.10 (*m*), 2.91 (*m*)	45.25	2.68–2.80[d]) (*m*, 2 H)	49.69[e])	3.28 (*m*), 3.16 (*m*)	46.59
CH_2(10)	2.90 (*m*), 2.80 (*m*)	48.70	2.43[d]) (*m*), 2.26[d]) (*m*)	49.00[e])	3.39 (*ddd*), 2.88 (*ddd*)	48.55
CH_2(11)	1.27 (*m*, 2 H)	24.43	1.53–1.68[e]) (*m*, 3 H)	27.99[d])	1.83 (*m*), 1.69 (*m*)	24.20
CH_2(12)	1.45 (*m*, 2 H)	25.51	1.53–1.68[e]), 1.36[e]) (*m*, 1 H)	27.71[d])	1.48 (*m*), 1.41 (*m*)	25.29
CH_2(13)	3.05 (*m*), 2.96 (*m*)	46.11	2.58 (*m*, 2 H)[d])	45.97[e])	2.60 (*ddd*), 2.35 (*ddd*)	43.96
HO–C(3)	–				3.70 (br. *s*)	
Phenyl:						
C(1″)		137.15		138.51		140.46
CH(2″,6″)	7.36 (*m*)	128.89	7.13–7.28	128.39[f])	7.23 (*d*, *J*(2,3) = 7.26, 2 H)	127.56
CH(3″, 5″)	7.26 (*m*)	127.39	7.13–7.28	127.89[f])	7.37 (*t*, *J* = 7.55, 2 H)	128.91
CH(4″)	7.27 (*m*)	126.81	7.13–7.28	128.89	7.29 (*t*, *J* = 7.4, 1 H)	128.00
1-Tosyl[g]):						
C(1′)	–	137.55				
CH(2′,6′)	7.52 (*d*, *J*(2,3) = 8.2)	127.29				
CH(3′,5′)	7.18 (*d*, *J*(2,3) = 8.2)	128.59				
C(4′)		142.40				
Me	2.31 (*s*)	20.55				
9-Tosyl[g]):						
C(1′)	–	134.89			–	136.32
CH(2′,6′)	7.63 (*d*, *J*(2,3) = 8.2)	126.73			7.68 (*d*, *J*(2,3) = 8.2)	127.40
CH(3′,5′)	7.41 (*d*, *J*(2,3) = 8.2)	129.40			7.32 (*d*, *J*(2,3) = 8.3)	129.95
C(4′)	–	142.73			–	143.60
Me	2.40 (*s*)	20.55			2.43 (*s*)	21.69

[a]) (D_6)DMSO, 60°, δ(DMSO) 2.50 ppm (^{1}H, 300 MHz), and 39.51 (^{13}C, 75 MHz). [b]) $CDCl_3$, 23°, ^{1}H at 300 MHz, ^{13}C at 75 MHz, $SiMe_4$ as internal reference. No 2D NMR analysis was performed for this compound. [c]) $CDCl_3$, 27°, ^{1}H at 600 MHz, ^{13}C at 150 MHz, $SiMe_4$ as internal reference. [d])[e])[f]) Interchangeable values each. [g]) Aromatic protons of the tosyl group at N(1) gave 2 *d* (br.) in ^{1}H-NMR at r.t., which allowed unambiguous signal assignments for both Ts groups.

on the synthesis of 3-hydroxycelacinnine with the (2*R*,3*S*) absolute configuration which is most probably correct for the natural 3-hydroxycelacinnine. This assumption is based on the observation that all the macrocyclic spermine and spermidine alkaloids with known absolute configuration have the same relative configuration of the three substituents at C(2) (N-atom, phenyl or alkyl group, and substituted or unsubstituted acetamide moiety) [27].

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Experimental Part

General. All solvents were of anal.-grade quality and were used without further purification. DMF was stored under flame-dried molecular sieves 4 Å. DMSO and MeCN were dried and stored over CaH_2. Anh. MeOH under molecular sieves was purchased from *Fluka*. Ultrasound: *Branson B-220*-125-W ultrasonic cleaner. Flash chromatography (FC): silica gel *Merck 60* (40–63 μm, 230–400 mesh). TLC: *Merck* precoated silica-gel *60 F_{254}* plates; detection by UV at 254 nm, by 0.05% *Fluram* (*Fluka*) in acetone at 366 nm for primary amines, *Schlittler* reagent (H_2PtCl_6/HCl/KI) for amines and polyamines [28], Ce/Mo reagent ($Ce(SO_4)_2 \cdot 4\ H_2O$ (10 g), aq. $H_3[P(Mo_3O_{10})_4]$ (25 g), H_2SO_4 (60 ml), H_2O (940 ml)) for epoxides and alcohols. M.p.: *Mettler FP-5/FP-52*. FT-IR: *Perkin-Elmer Spectrum One*, KBr pellets or neat/NaCl; in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker ARX-300*, *DRX-500*, or *AMX-600*, ^1H at 300, 500, or 600 MHz and ^{13}C at 75, 125, or 150 MHz, resp; ^{13}C {^1H}, DEPT-135, and DEPT-90 were recorded for all compounds; chemical shifts δ in ppm rel. to internal $SiMe_4$ ($CDCl_3$), unless noted otherwise, *J* values in Hz, nonobvious signal assignments by comparison with the spectra of the described similar compounds or by 2D NMR data; COSY, HMBC, and HSQC for macrocyclic products; all new compounds were at least 95% pure as judged by careful integration and peak analysis of ^1H-NMR spectra. EI-MS (70 eV) and CI-MS (NH_3 as reactant gas): *Finnigan-MAT 90*. ESI-MS (NaI/MeOH/CH_2Cl_2): *Finnigan TSQ-700* mass spectrometer; in *m/z* (% of base peak). Elemental analyses were performed by the Microanalytical Laboratory, Institute of Organic Chemistry, University of Zurich.

trans-*3-Phenyloxiranecarbonyl Chloride* (**6**) [7]. Oxalyl chloride (4.2 ml, 48.9 mmol) was added dropwise to a cold (ice/water bath) stirred suspension of potassium *trans*-phenylglycidate (**5**; 6.20 g, 30.69 mmol) in THF (90 ml) within 2 min. The cold bath was removed and stirring continued at 23° for 40 min until gas evolution ceased. The mixture was evaporated at r.t. to give a pale yellow oil, which solidified after 1 h under h.v.: 8.01 g of white solid as an equimolar mixture **6**/KCl, which was used in the next step without purification. M.p. 29–32°. FT-IR (KBr): 3050*w*, 3036*w*, 1778*s* (C=O), 1600*w*, 1497*w*, 1458*m*, 1408*m*, 1289*w*, 1237*w*, 1196*w*, 1117*m*, 1085*m*, 1058*w*, 1012*m*, 897*m*, 852*w*, 807*w*, 751*s*, 697*s*, 663*w*, 611*m*, 583*w*. ^1H-NMR (30 mg in 0.6 ml of $CDCl_3$, 300 MHz): 7.37–7.42 (*m*, 3 H); 7.28–7.33 (*m*, 2 H); 4.21 (*d*, *J* = 1.6, H–C(3)); 3.80 (*d*, *J* = 1.6, H–C(2)). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) = 76.91$): 171.01 (COCl); 133.3 (C_{ipso}); 129.57 (C_p); 128.79 (C_m); 125.82 (C_o); 61.90 (C(2)); 59.13 (C(3)). ESI-MS: 201 (45, $[RCO_2Me + Na]^+$), 233 (100, $[PhCH(OMe) - CH(OH) - CO_2Me + Na]^+$); EI-MS: 147 (2, $[M - Cl]^+$), 91 (100), 77 (40).

trans-N-*(3-Bromopropyl)-3-phenyl-oxiranecarboxamide* (**7**). Et_3N (12.8 ml, 92.1 mmol) in CH_2Cl_2 (60 ml) was added dropwise to a cold (ice/water bath) stirred suspension of freshly prepared **6** (7.966 g, 30.18 mmol) and 3-bromopropanamine hydrobromide (8.734 g, 39.9 mmol) in CH_2Cl_2 (60 ml) within 10 min. The mixture was stirred at 10° for 2 h and quenched with 100 ml of 5% aq. citric acid. The org. phase was washed with 5% citric acid (50 ml), H_2O (50 ml), and sat. aq. $NaHCO_3$ soln. (2 × 30 ml). Each aq. phase during these extractions was shaken with a small amount of CH_2Cl_2 and the obtained org. layer combined with the main org. soln. before the following extraction. The final org. phase was dried (Na_2CO_3) and evaporated to give a pale brown oil, which solidified under h.v. (9 h): pure **7** (8.55 g, 98.1% from **5**). Pale yellow solid. M.p. 83.5–85.5°. R_f (5% MeOH/$CHCl_3$) 0.8. FT-IR (KBr): 3271*s* (NH), 3080*m*, 2993*w*, 2965*w*, 2908*w*, 2879*w*, 2856*w*, 1965*w*, 1951*w*, 1895*w*, 1880*w*, 1806*w*, 1650*s* (C=O), 1560*s*, 1497*w*, 1480*w*, 1457*w*, 1439*w*, 1426*w*, 1353*w*, 1311*w*, 1251*m*, 1230*w*, 1110*w*, 1092*w*, 1071*w*, 1044*w*, 1027*w*, 997*w*, 959*w*, 884*m*, 848*w*, 823*w*, 788*w*, 769*w*, 741*m*, 720*w*, 695*m*, 673*m*. ^1H-NMR (300 MHz, 30 mg in 0.7 ml of $CDCl_3$): 7.32–7.40 (*m*, 3 H); 7.23–7.29 (*m*, 2 H); 6.45 (br. *s*, NHCO); 3.88 (*d*, *J* = 2.0, H–C(3)); 3.52 (*d*, *J* = 2.0, H–C(2)); 3.37–3.51 (*m*, CH_2Br, CH_2N); 2.12 (*quint.*, *J* = 6.6, CH_2). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) = 76.93$): 167.64 (CONH); 134.67 (C_{ipso}); 128.98 (C_p); 128.56 (C_m); 125.68 (C_o); 59.03 (C(2)); 58.83 (C(3)); 37.48 (CH_2NH); 31.98 (CH_2); 30.31 (CH_2Br). ESI-MS: 306, 308 (99, 100, $[M + Na]^+$), 589, 591, 593 (4, 8, 4, $[2M + Na]^+$). EI-MS: 283, 285 (2, 2, $M^{+\cdot}$), 204 (3, $[M - Br]^+$), 120 (30), 91 (100), 77 (38). Anal. calc. for $C_{12}H_{14}BrNO_2$ (284.15): H 4.97, C 50.72, N 4.93; found: H 4.98, C 50.68, N 4.76.

Reaction of **7** *with NaN_3 in (D_6)DMSO:* trans-N-*(3-Azidopropyl)-3-phenyl-oxiranecarboxamide* (**8**). The soln. prepared from **7** (52 mg, 0.183 mmol), (D_6)DMSO (0.7 ml), D_2O (0.05 ml), and NaN_3 (35.7 mg, 0.549 mmol) was kept at r.t. in the NMR tube and monitored by ^1H- and ^{13}C-NMR. After 2 h, no starting **7** could be detected; the main product was **8** besides traces of diazidoamide **10** (*ca.* 3%; see below). After 3 days, **8**/**10** 2:1 and *ca.* 10% of by-products were observed after 6 days, **8**/**10** 2:3 and *ca.* 15% of by-products.

Data of **8**: ^1H-NMR (300 MHz, $\delta((D_5)DMSO) = 2.55$): 7.3–7.42 (*m*, 5 arom. H); 4.06 (*d*, *J* = 1.9, H–C(3)); 3.63 (*d*, *J* = 1.95, H–C(2)); 3.38 (*t*, *J* = 6.8, CH_2N_3); 3.21 (*t*, *J* = 6.8, CH_2NH); 1.72 (*quint.*, *J* = 7.8, CH_2). ^{13}C-NMR (75 MHz, $\delta((D_6)DMSO) = 38.98$): 166.78 (CONH); 135.38 (C_{ipso}); 128.61 (C_p); 128.43 (C_m); 125.84 (C_o); 57.71 (C(2)); 56.65 (C(3)); 48.25 (CH_2N_3); 35.75 (CH_2NH); 27.92 (CH_2).

(±)-(2R,3R*)-3-Azido-*N*-(3-bromopropyl)-2-hydroxy-3-phenylpropanamide* (**9**). Commercial anh. $MgSO_4$ (5.07 g, 42.25 mmol) was flame-dried and allowed to cool under N_2. Anh. MeOH (40 ml) and NaN_3 (2.75 g, 42.25 mmol) were introduced and sonicated for 5 min. A soln. of **7** (4.00 g, 14.08 mmol) in anh. MeOH (40 ml) was added at 0° and stirred under N_2. The reaction proceeded very slowly at 0°, but, at 23°, only traces of starting **7** were detectable after 60 min by TLC (SiO_2, 2.5% MeOH/$CHCl_3$). The mixture was stirred for a total of 2 h at 23° and quenched with H_2O (500 ml). The solid was filtered, washed with H_2O (4 × 50 ml), and briefly dried *in vacuo* to give *ca.* 4 g of wet product. The supernatant was extracted with $CHCl_3$ (4 × 100 ml), the extract combined with the solid fraction, dried (Na_2CO_3), and evaporated, and then the residue dried under h.v.: 4.313 g of **9** (93.6%), which contained less than 5% of impurities according to ^{1}H-NMR. The product was recrystallized from $CHCl_3$/hexane (10 ml of $CHCl_3$ for 1 g of **9**, followed by 20 ml of hexane): 3.8 g of pure **9** in two crops. White solid. M.p. 87–89°. FT-IR (KBr); 3300*s*, 3250*s* (NH, OH), 3033*m*, 3062*m*, 2966*m*, 2950*m*, 2921*m*, 2892*m*, 2851*m*, 2738*w*, 2494*w*, 2360*w*, 2220*w*, 2112*s* (N_3), 1957*w*, 1886*w*, 1807*w*, 1744*w*, 1634*s* (C=O), 1540*s*, 1494*m*, 1453*m*, 1426*m*, 1382*w*, 1372*w*, 1355*m*, 1305*m*, 1257*s*, 1196*m*, 1106*s*, 1086*m*, 1058*w*, 1028*w*, 991*w*, 964*w*, 949*w*, 935*w*, 913*w*, 871*w*, 838*w*, 813*w*, 788*w*, 741*m*, 725*m*, 696*s*, 658*m*, 639*m*. ^{1}H-NMR (300 MHz, 43 mg in 0.6 ml of $CDCl_3$): 7.37 (*s*, 5 arom. H); 6.48 (br. *t*, NHCO); 5.08 (*d*, J = 3.8, H–C(3)); 4.47 (br. *d*, J = 3.8, H–C(2)); 3.76 (br. *s*, OH); 3.37 (*sext.* (*ddd*), J = 6.7, 1 H, CH_2NH); 3.16 (*q* (*ddt*), 1 H, CH_2NH); 3.09 (*dt*, ^3J = 6.4, ^2J = 10.3, 1 H, CH_2Br); 2.94 (*dt*, ^3J = 6.7, ^2J = 10.3, 1 H, CH_2Br); 1.79 (*quint.*, J = 6.5, CH_2). ^{13}C-NMR (75 MHz, δ($CDCl_3$) = 76.93): 169.95 (CONH); 133.99 (C_{ipso}); 128.86 (C_p); 128.45 (C_m); 128.28 (C_o); 73.95 (C(2)); 67.13 (C(3)); 37.23 (CH_2NH); 31.67 (CH_2); 30.15 (CH_2Br). CI-MS: 327, 329 (10, 10, $[M+H]^+$), 247 (100, $[M-Br]^+$), 204 (25, $[M-Br-HN_3]^+$). Anal. calc. for $C_{12}H_{15}BrN_4O_2$ (327.18): H 4.62, C 44.05, N 17.12; found: H 4.92, C 44.11, N 17.51.

(±)-(2R,3R*)-3-Azido-*N*-(3-azidopropyl)-2-hydroxy-3-phenylpropanamide* (**10**). The mixture of **9** (2.00 g, 6.12 mmol) and NaN_3 (796 mg, 12.24 mmol) in DMSO (20 ml) was stirred at 23° for 4 h. The obtained pale yellow soln. was quenched carefully with H_2O (70 ml, exothermic), allowed to cool, and shaken with Et_2O (50 ml). The aq. layer was extracted with Et_2O (2 × 50 ml), the combined org. soln. washed with H_2O (4 × 15 ml) and sat. aq. NaCl soln. (15 ml), dried (Na_2CO_3), and evaporated, and the residue dried under h.v. (60 min): 1.690 g (95.6%) of pure **10**, White crystalline solid. M.p. 54–64° (dec.). FT-IR (KBr): 3307*s*, 3240*s* (NH, OH), 3035*m*, 2974*m*, 2926*m*, 2879*m*, 2500*w*, 2100*s* (N_3), 1961*w*, 1887*w*, 1814*w*, 1643*s* (C=O), 1633*s*, 1539*s*, 1496*m*, 1455*m*, 1447*m*, 1377*w*, 1353*m*, 1309*s*, 1254*s*, 1194*m*, 1111*s*, 1030*w*, 1003*w*, 985*w*, 962*w*, 948*w*, 930*w*, 917*w*, 841*w*, 817*w*, 786*w*, 732*m*, 698*m*, 672*w*, 651*w*, 636*w*, 554*m*. ^{1}H-NMR (300 MHz, 20 mg in 0.6 ml of $CDCl_3$): 7.38 (*s*, 5 arom. H); 6.41 (br. *t*, NHCO); 5.08 (*d*, J = 4.0, H–C(3)); 4.46 (br. *d*, J = 4.0, H–C(2)); 3.49 (br. *s*, OH); 3.30 (*m* (*ddt*), J = 6.8, 1 H, CH_2NH); 3.09 (*q* (*ddt*), 1 H, CH_2NH); 3.05 (*dt*, ^3J = 6.7, ^2J = 12.5, 1 H, CH_2N_3); 2.93 (*dt*, ^3J = 6.7, ^2J = 12.5, 1 H, CH_2N_3); 1.52 (unres. *dquint.*, J = 0.7, ^3J = 6.8, CH_2). ^{13}C-NMR (75 MHz, δ($CDCl_3$) = 76.91): 169.64 (CONH); 134.06 (C_{ipso}); 128.85 (C_p); 128.47 (C_m); 128.27 (C_o); 73.96 (C(2)); 67.16 (C(3)); 48.54 (CH_2N_3); 36.24 (CH_2NH); 28.26 (CH_2). CI-MS: 290 (100, $[M+H]^+$), 129 (12), 106 (35). Anal. calc. for $C_{12}H_{15}N_7O_2$ (289.30): H 5.23, C 49.82, N 33.89; found: H 5.53, C 49.75, N 34.12.

(±)-(2R,3R*)-3-Amino-*N*-(3-aminopropyl)-2-hydroxy-3-phenylpropanamide* (**11**). To a soln. of **10** (1.457 g, 5.042 mmol) in MeOH (50 ml), H_2O (5 ml) and Ph_3P (3.97 g, 15.1 mmol) were added. The obtained suspension was flushed with N_2 and sonicated for 2 h with a gradual temperature increase from 23 to 46°. Evolution of N_2 started at 30° and completely ceased after 60 min to give the expected amount of N_2 (252 ml, 10.8 mmol; no further gas evolution). The clear and colorless soln. was evaporated and the residue partitioned between H_2O (50 ml) and $CHCl_3$ (50 ml). The aq. layer was extracted with $CHCl_3$ (5 × 25 ml) and the combined org. soln. extracted with H_2O (25 ml), which was washed with $CHCl_3$ (5 × 10 ml). The combined org. soln. contained no product. The combined aq. soln. was evaporated at 40° and the residue dried under h.v. at r.t. and then at 60° for 4 h until constant weight: 1.171 g (98%) of pure **11**. Colorless solid. R_f ($CHCl_3$/MeOH/25% aq. NH_3 soln. 10 : 4 : 1, UV and *Fluram* detection) 0.2. M.p. 104–107°. FT-IR (KBr) 3700–2100 (br.), 3348*s*, 3300*s*, 3085*s*, 3063*s*, 3033*s*, 2920*s*, 2869*s*, 2714*s* (br.), 2036*w*, 1950*w*, 1882*w*, 1804*w*, 1647*s* (C=O), 1583*s*, 1526*s*, 1493*m*, 1455*m*, 1383*w*, 1370*w*, 1350*w*, 1327*m*, 1294*w*, 1270*w*, 1248*w*, 1204*w*, 1185*w*, 1168*w*, 1158*w*, 1120*m*, 1074*m*, 1051*m*, 1013*m*, 995*m*, 932*m*, 913*m*, 888*m*, 836*w*, 816*w*, 752*m*, 703*s*, 619*w*, 558*m*. ^{1}H-NMR (300 MHz, 20 mg in 0.6 ml of (D_6)DMSO, δ(D_5)DMSO) = 2.66): 7.66 (*t*, J = 5.7, NHCO); 7.3–7.45 (*m*, 5 arom. H); 4.23 (*d*, J = 4.6, H–C(2)); 4.16 (*d*, J = 4.6, H–C(3)); 3.21 (*sext.*, J = 6.6, 1 H, CH_2NH); 3.11 (*sext.*, J = 6.6, 1 H, CH_2NH); 2.48 (unres. *td*, J = 6.6, J = 1.2, CH_2NH_2); 1.5–2.5 (very br., OH, NH_2, H_2O); 1.39–1.53 (*m*, CH_2). ^{13}C-NMR (75 MHz, δ((D_6)DMSO) = 39.41): 171.85 (CONH); 142.73 (C_{ipso}); 127.56, 127.15 (C_m, C_o); 126.17 (C_p); 75.81 (C(2)); 57.66 (C(3)); 38.72 (CH_2NH); 35.56 (CH_2NH_2); 32.55 (CH_2). CI-MS: 238 ($[M+H]^+$), ESI-MS: 238 (100, $[M+H]^+$), 260 (65, $[M+Na]^+$). Anal. calc. for $C_{12}H_{19}N_3O_2$ (237.30): H 8.07, C 60.74, N 17.71; found: H 8.36, C 60.75, N 17.79.

(±)-(2R,3R*)-2-Hydroxy-3-[[(4-methylphenyl)sulfonyl]amino]-*N*-{3-[[(4-methylphenyl)sulfonyl]amino}propyl}-3-phenylpropanamide* (**12**). A soln. of **11** (1.146 g, 4.835 mmol) in H_2O (15 ml) was diluted with dioxane (30 ml), Na_2CO_3 (1.025 g, 9.67 mmol) added, and the mixture allowed to cool in an ice/water bath. TsCl (1.90 g, 9.92 mmol) was added by portions and the mixture stirred at 0°, then slowly warming to 20° until no primary amine could be detected by TLC (SiO_2, $CHCl_3$/MeOH/25% aq. NH_3 soln. 10:4:1; *Fluram*). After 7 h, the mixture was evaporated to a small volume (23°/25 mbar) and quenched with H_2O (70 ml). The crude product was separated by filtration (1.97 g) and crystallized from MeOH/H_2O (75 and 100 ml, resp.): 1.657 g (62.9%) of **12** as white crystalline solid, after washing with H_2O and drying *in vacuo* for 9 h. The product was hardly soluble in all org. solvents, except DMSO and DMF. The combined supernatants were extracted with $CHCl_3$ to give 560 mg of a residue, which contained no **12** according to TLC and NMR. **12**: R_f (5% MeOH/$CHCl_3$) 0.1. M.p. 150° (dec.) FT-IR (KBr): 3432*s*, 3331*s*, 3303*s*, 3256*m*, 3065*w*, 3038*w*, 2923*m*, 2872*w*, 1910*w*, 1807*w*, 1756*w*, 1658*s* (C=O), 1599*w*, 1533*m*, 1495*w*, 1457*m*, 1419*m*, 1322*s*, 1251*w*, 1210*w*, 1184*w*, 1158*s*, 1091*s*, 1065*w*, 1034*w*, 1020*w*, 937*w*, 809*m*, 776*w*, 750*w*, 703*s*, 661*s*, 565*s*, 550*s*. ^{1}H-NMR (300 MHz, 10 mg in 0.6 ml of (D_6)DMSO, δ((D_5)DMSO) = 2.69): 8.27 (*d*, *J* = 9.2, TsN*H*CH); 7.80 (*d*, *J* = 8.2, 2 H of Ts); 7.67 (*d*, *J* = 8.3, 2 H of Ts); 7.58 (overlapping *d*, *J* = 7.9, 2 H of Ts); 7.55 (overlapping *t*, *J* = 6.6, NHCO); 7.50 (*t*, *J* = 6.1, TsN*H*CH_2); 7.34 (*d*, *J* = 8.0, 2 H of Ts); 7.15–7.25 (unres. *m*, Ph); 6.11 (*d*, *J* = 5.8, OH); 4.79 (*dd*, *J*(CH,CH) = 3.5, *J*(CH,NH) = 9.2, H–C(3)); 4.22 (*dd*, *J*(CH,CH) = 3.6, *J*(CH,OH) = 5.8, H–C(2)); 3.08, 2.92 (2 *sext.* (*ddt*), *J* = 6.5, CH_2NHCO); 2.58, 2.47 (2 overlapping *s*, 2 Me); 2.58, 2.47 (2 overlapping *m*, OH_2NHTs); 1.38 (*oct.*, *J* = 6.8, CH_2CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO, δ((D_6)DMSO) = 39.41): 170.57 (CONH); 142.36, 141.90, 138.32, 137.57, 136.60 (5 C); 129.44, 128.92, 128.02, 126.92 (4 arom. CH); 126.57 (of Ph); 126.28 (2 overlapping arom. CH); 74.56 (C(2)); 59.14 (C(3)); 39.56 (*C*H_2NHCO); 35.12 (*C*H_2NHTs); 28.70 (CH_2); 20.72 (2 Me). ESI-MS (MeCN/CH_2Cl_2): 584 (10, $[M+K]^+$), 568 (50, $[M+Na]^+$), 546 (100, $[M+H]^+$), 375 (53, $[M-TsNH]^+$), 255 (24, $[OCNH(CH_2)_3NHTs]^+$), 229 (15, $[H_3N(CH_2)_3NHTs]^+$). Anal. calc. for $C_{26}H_{31}N_3O_6S_2$ (545.67): H 5.73, C 57.23, N 7.70, S 11.75; found: H 5.56, C 57.01, N 7.59, S 11.59.

Reaction of **12** *with an Excess of 1,4-Dibromobutane* (*Table 1*, *Entry 2*). A suspension of Cs_2CO_3 (144 mg, 0.44 mmol, 1.2 equiv.) and **12** (200 mg, 0.367 mmol) in anh. DMF (1 ml) was stirred under N_2 for 20 min. Then 1,4-dibromobutane (313 µl, 570 mg, 2.64 mmol, 6 equiv.) was added. After 22 h at 23°, the mixture was partitioned between H_2O (10 ml) and CH_2Cl_2 (3 × 10 ml), dried (Na_2SO_4), and evaporated under h.v. FC (silica gel (25 ml), gradient $CHCl_3$ → 4% MeOH/$CHCl_3$) gave disubstituted **18** (39 mg, 12.3%; with 1% MeOH), monosubstituted **16** (81 mg; with 1–2% MeOH), **16**/**17** 3:1 (63 mg; with 2% MeOH), and unreacted **12** (62 mg, 31%; with 4% MeOH). Yields of **16**, 128 mg (51.3 %) and of **17**, 15.7 mg (6.3%).

Data of (±)-(2R,3R*)-*N*-{3-[(4-Bromobutyl)[(4-methylphenyl)sulfonyl]amino}propyl}-2-hydroxy-3-[[(4-methylphenyl)sulfonyl]amino}-3-phenylpropanamide* (**16**): White foam. R_f (5% MeOH/$CHCl_3$) 0.26. M.p. 57–59°. FT-IR (KBr): 3000–3700 (br.), 3385*s*, 3299*s*, 3064*w*, 3028*w*, 2927*m*, 2870*w*, 1648*s* (C=O), 1599*m*, 1540*s*, 1495*m*, 1456*s*, 1437*m*, 1331*s*, 1307*m*, 1255*w*, 1185*w*, 1159*s*, 1091*s*, 1063*w*, 1019*w*, 973*w*, 935*w*, 814*m*, 703*s*, 655*s*, 563*s*, 549*s*. ^{1}H-NMR (300 MHz, 81 mg in 1.3 ml of $CDCl_3$): 7.59 (overlapping *d*, *J* = 8.1, 2 H of Ts); 7.56 (overlapping *d*, *J* = 8.1, 2 H of Ts); 7.29 (*d*, *J* = 8.1, 2 H of Ts); 7.11–7.18 (*m*, 2 H of Ph); 7.00–7.11 (*m*, 2 H of Ts, 3 H of Ph, NHCO); 6.32 (br. *d*, *J* = 8.1, TsN*H*CH); 4.82 (unres. *dd*, H–C(3)); 4.55 (*d*, *J*(CH,CH) = 3.6, H–C(2)); 4.4 (very br. *s*, OH); 3.34 (*t*, *J* = 6.5, CH_2Br); 3.24 (*quint.*, 1 H, CH_2NHCO); 2.9–3.1 (*m*, 3 H, CH_2NHCO, CH_2NTs); 2.71 (br. *t*, *J* = 6.5, Br(CH_2)$_3$CH_2NTs); 2.41, 2.29 (2 *s*, 2 Me); 1.76 (*quint.*, *J* = 6.7, CH_2); 1.5–1.6 (overlapping *m*, CH_2); 1.42–1.55, 1.3–1.42 (2 *m*, CH_2). ^{13}C-NMR (75 MHz, δ($CDCl_3$) = 76.92): 170.79 (CONH); 143.37, 143.00 (2 C_p of 2 Ts); 136.98 (C_{ipso} of Ph); 136.06, 135.77 (2 C_{ipso} of 2 Ts); 129.66, 129.23, 128.17, 127.76 (C_o and C_m of Ph, C_m of 2 Ts); 127.45 (C_p of Ph); 127.0 (overlapping, C_o of 2 Ts); 74.51 (C(2)); 59.67 (C(3)), 47.92, 45.53, 35.31, 32.85, 29.51, 28.01, 27.06 (7 CH_2), 21.36, 21.27 (2 Me). ESI-MS: 702, 704 (98, 100, $[M+Na]^+$), 680, 682 (17, 17, $[M+H]^+$).

Data of (±)-(2R,3R*)-3-[(4-bromobutyl)[(4-methylphenyl)sulfonyl]amino}-2-hydroxy-*N*-{3-[[(4-methylphenyl)sulfonyl]amino}propyl}-3-phenylpropanamide* (**17**): R_f (5% MeOH/$CHCl_3$) 0.23. ^{1}H-NMR (300 MHz, $CDCl_3$; data from **16**/**17**, selected resonances): 7.69 (*d*, *J* = 8.3, 2 H of Ts); 7.64 (*d*, *J* = 8.4, 2 H of Ts); 5.55 (br. *t*, TsN*H*); 5.16 (*d*, *J*(CH,CH) = 3.9, H–C(3)); 4.93 (d, *J*(CH,CH) = 3.8, H–C(2)). ^{13}C-NMR (75 MHz, δ($CDCl_3$) = 76.90; selected resonances): 172.22 (CONH); 75.13 (C(2)); 63.68 (C(3)).

Data of (±)-(2R,3R*)-3-[(4-Bromobutyl)[(4-methylphenyl)sulfonyl]amino}-*N*-{3-[(4-bromobutyl)[(4-methylphenyl)sulfonyl]amino}propyl}-2-hydroxy-3-phenylpropanamide* (**18**): R_f (5% MeOH/$CHCl_3$) 0.49. ^{1}H-NMR (300 MHz, 37 mg in 1.0 ml of $CDCl_3$): 7.66 (overlapping *d*, *J* = 8.3, 2 H of Ts); 7.64 (overlapping *d*, *J* = 8.4, 2 H of Ts); 7.31 (*d*, *J* = 8.0, 2 H of Ts); 7.15–7.29 (*m*, Ph, NHCO, 2 H of Ts); 5.14 (*d*, *J*(CH,CH) = 3.8, C*H*NTs); 4.84 (*d*, *J*(CH,CH) = 3.8, H–C(2)); 3.2–3.4 (overlapping *m*, 4 CH_2: 3.37 (*t*, *J* = 6.5, CH_2Br); 3.29 (*t*, *J* = 6.5, CH_2); 3.22 (*t*, *J* = 6.5, CH_2); 3.07 (*t*, *J* = 7.3, CH_2); 2.96 (*t*, *J* = 6.6, CH_2); 2.43, 2.40 (2 *s*, 2 Me); 1.76–1.86

(*m*, 2 H); 1.4–1.75 (*m*, 8 H). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) = 76.90$): 171.04 (CONH); 143.37 (2 C_p of 2 Ts); 137.33 (C_{ipso} of Ph); 136.18, 135.08 (2 C_{ipso} of 2 Ts); 129.69, 129.60, 129.41, 128.16 (C_o and C_m of Ph, C_m of 2 Ts); 128.06 (C_p of Ph); 127.15, 127.00 (C_o of 2 Ts); 74.58 (C(2)); 64.42 (C(3)); 48.06, 47.37, 45.78, 35.78 (4 CH_2); 32.81 (br. *s*, 2 overlapping CH_2); 29.85, 29.52 (2 CH_2); 28.24 (br. *s*, 2 overlapping CH_2); 27.13 (CH_2); 21.37 (br. *s*, 2 overlapping Me). ESI-MS: 836, 838, 840 (50, 100, 50, $[M+Na]^+$), 814, 816, 818 (5, 10, 5, $[M+H]^+$).

Macrocyclization of **12** *with 1,4-Dibromobutane under High Dilution* (*Table 1*, *Entry 4*). A soln. of **12** (801 mg, 1.470 mmol) and 1,4-dibromobutane (192 µl, 1.635 mmol) in DMF (250 ml) was added dropwise to a stirred suspension of Cs_2CO_3 (1.006 g, 3.087 mmol) in DMF (500 ml) at 60° under N_2 within 8 h. After 24 h at 60°, additional 1,4-dibromobutane (192 µl, 1.635 mmol) and Cs_2CO_3 (513 mg) were added, and stirring was continued for another 24 h. The mixture was quenched with H_2O (24 ml) and AcOH (0.5 ml, pH 7) and evaporated at 45°/12 mbar. The crude brown oil was partitioned between CH_2Cl_2 (4 × 50 ml) and H_2O (100 ml), and the combined org. soln. dried (Na_2SO_4) and evaporated to give 1.182 g of brown oil. FC (silica gel (100 ml), $CHCl_3 \rightarrow$ 5% MeOH/$CHCl_3$) gave dicarbamate **23** (83 mg; with $CHCl_3$), formimidamide **21** (46 mg, 13.8%; with $CHCl_3$ and 1% MeOH), macrocyclic **13** (167 mg, 19%; with 1% MeOH), carbamate **22** (132 mg; with 2% MeOH); carbamate **20** (73 mg, 7.2%; with 2% MeOH), starting **12** (247 mg, 30%; with 3% MeOH), and finally hydroxy compound **19** (45 mg, 5%; with 5% MeOH).

*Data of (±)-(2*R**,3*R**)-3-Hydroxy-1,9-bis[(4-methylphenyl)sulfonyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one* (**13**): White solid. M.p. 176–187° (dec.). R_f (5% MeOH/$CHCl_3$) 0.32. Complete ^{1}H- and ^{13}C-NMR assignments from 2D NMR at 60° (at r.t. many ^{1}H- and ^{13}C-NMR signals were broad), see *Table 3*. ^{1}H-NMR (300 MHz, 60 mg in 0.7 ml of $CDCl_3$, 23°): 7.69 (*d*, *J* = 8.0, 2 H of Ts–N(9)); 7.40 (br. *d*, *J* = 6.4, 2 H of Ts–N(1)); 7.32 (*d*, *J* = 8.0, 2 H of Ts-N(9)); 7.10–7.20 (*m*, Ph, NHCO); 6.96 (br. *d*, *J* = 6.7, 2 H of Ts-N(1)); 4.94 (br. *d*, H–C(2)); 4.73 (br. *s*, H–C(3)); 3.76 (*m*, 1 H, CH_2N); 2.95–3.50 (overlapping br. *m*, 7 H, CH_2N); 2.43, 2.36 (2 *s*, 2 Me); 1.5–1.69, 1.69–1.87, 1.87–2.02, 2.02–2.2 (overlapping br. *m*, 3 CH_2). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) = 76.97, 23°$): 171.68 (br. *s*, CONH); 143.54, 143.35 (2 C_p of 2 Ts); 136.74 (br. *s*, C_{ipso} of Ph); 134.91 (br. *s*, C_{ipso} of Ts–N(1)); 134.61 (C_{ipso} of Ts–N(9)); 129.70, 129.29, 128.89, 128.17 (C_o and C_m of Ph, C_m of 2 Ts); 127.89 (C_p of Ph); 127.35 (overlapping C_o of 2 Ts); 71.16 (br. *s*, C(3)); 65.11 (br. *s*, C(2)); 50.66, 46.56, 39.06, 28.13, 27.2, 25.80 (6 br. *s*, 7 CH_2); 21.39 (br. s, 2 Me). ESI-MS: 622 (100, $[M+Na]^+$).

*Data of (±)-(2*R**,3*R**)-2-Hydroxy-*N*-{3-[(4-hydroxybutyl)[(4-methylphenyl)sulfonyl]amino}propyl}-3-{[(4-methylphenyl)sulfonyl]amino}-3-phenylpropanamide* (**19**): R_f (5% MeOH/$CHCl_3$) 0.07. ^{1}H-NMR (300 MHz, 6 mg in 0.5 ml of $CDCl_3$): 7.61 (*d*, *J* = 8.3, 2 H of Ts); 7.55 (*d*, *J* = 8.3, 2 H of Ts); 7.30 (*d*, *J* = 8.0, 2 H of Ts); 7.05–7.15 (*m*, 7 arom. H); 7.00 (br. *t*, *J* = 6.3, NHCO); 6.05 (br. *s*, NHTs); 4.72 (unres. *dd*, H–C(3)); 4.47 (*d*, *J*(CH,CH) = 4.32, H–C(2)); 3.62 (*t*, *J* = 5.7, CH_2OH); 3.10–3.22 (*m*, CH_2NHCO); 2.92–3.12 (*m*, CH_2NTs); 2.76–2.84 (unres. *m*, CH_2NTs); 2.42, 2.32 (2 *s*, 2 Me); 1.35–1.65 (*m*, 3 CH_2). ^{13}C-NMR (75 MHz, 45 mg in 0.6 ml $CDCl_3$, $\delta(CDCl_3) = 76.93$): 171.15 (CONH); 143.26, 142.90 (2 C_p of 2 Ts); 137.06, 135.93, 135.70 (C_{ipso} of Ph, C_{ipso} of 2 Ts); 129.62, 129.17, 128.17, 127.67 (4 arom. CH); 127.35 (C_p of Ph); 127.01 (2 overlapping arom. CH); 74.60 (C(2)); 61.88 (CH_2OH); 59.52 (C(3)); 49.01 (CH_2NTs); 45.79 (CH_2NTs); 35.57 (CH_2NHCO); 29.39 (CH_2); 28.23 (CH_2); 25.28 (CH_2); 21.36, 21.26 (2 Me). ESI-MS: 618 (7, $[M+H]^+$), 640 (100, $[M+Na]^+$).

*Data of (±)-4-{{3-{(2*R**,3*R**)-2-Hydroxy-3-{[(4-methylphenyl)sulfonyl]amino}-1-oxo-3-phenylpropyl}-amino}propyl][(4-methylphenyl)sulfonyl]amino}butyl Dimethylcarbamate* (**20**): R_f (5% MeOH/$CHCl_3$) 0.2. ^{1}H-NMR (300 MHz, 74 mg in 0.8 ml of $CDCl_3$): 7.56 (*d*, *J* = 7.9, 2 H of Ts); 7.52 (*d*, *J* = 8.0, 2 H of Ts); 7.26 (*d*, *J* = 7.7, 2 H of Ts); 6.95–7.15 (*m*, 7 arom. H, NHCO); 6.38 (br. *d*, NHTs); 4.80 (br. *s* (unres. *dd*) *CH*NHTs); 4.48 (br. *d*, *J* = 3, *CH*OH); 3.95–4.01 (unres. *m*, CH_2OCON); 3.15–3.28 (br. *m*, 1 H); 2.9–3.1 (br. *m*, 3 H); 2.85 (*s*, Me_2N); 2.6–2.7 (br. *s* (unres. *m*), CH_2NTs); 2.39, 2.27 (2 *s*, 2 Me); 1.4–1.6 (br. *m*, 5 H, CH_2); 1.25–1.35 (br. *m*, 1 H, CH_2). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) = 76.97$): 170.80 (CONH); 156.63 ($Me_2NC(O)OR$); 143.23, 142.83 (2 C_p of 2 Ts); 137.19, 136.14, 135.91 (C_{ipso} of Ph, C_{ipso} of 2 Ts); 129.60, 129.16, 128.22, 127.62 (4 arom. CH); 127.30 (C_p of Ph); 126.97 (2 overlapping arom. CH); 74.53 (CHOH); 64.58 (CH_2OCON); 59.55 (*C*HNHTs); 48.61 (CH_2); 45.50 (CH_2); 36.26, 35.80 (2 br. *s*, Me_2N); 35.17 (CH_2); 28.13 (CH_2); 26.22 (CH_2); 25.23 (CH_2); 21.36, 21.26 (2 Me of 2 Ts). ESI-MS: 711 (100, $[M+Na]^+$), 689 (5, $[M+H]^+$).

Data of N*-[(Dimethylamino)methylene]-4-methylbenzenesulfonamide* (**21**) [23]: R_f (5% MeOH/$CHCl_3$) 0.5. ^{1}H-NMR (300 MHz, $CDCl_3$): identical with [23]; 8.13 (*s*, NH); 7.77 (*d*, *J* = 8, 2 H of Ts); 7.25 (*d*, *J* = 8, 2 H of Ts); 3.12, 3.01 (2 *s*, Me_2N); 2.40 (*s*, Me of Ts). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) = 76.97$): 159.04 (*HC*=NTs); 142.30, 139.53 (C_p and C_{ipso},, resp., of Ts); 129.19 (2 H_m of Ts); 126.39 (2 H_o of Ts); 41.39, 35.41 (Me_2N); 21.33 (Me of Ts).

Data of 4-Hydroxybutyl Dimethylcarbamate (**22**): R_f (5% MeOH/$CHCl_3$) 0.23. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.10 (*t*, *J* = 6.3, CH_2OCON); 3.67 (*t*, *J* = 6.2, CH_2OH); 2.90 (*s*, Me_2N); 1.6–1.8 (*m*, CH_2CH_2). ^{13}C-NMR

(75 MHz, $\delta(CDCl_3) = 76.92$): 156.70 ($Me_2NC(O)OR$); 65.02 (CH_2OCON); 62.25 (CH_2OH); 36.17 (br. *s*, Me_2N); 28.99, 25.48 (CH_2CH_2).

Data of 1,4-Butanediyl Dimethylcarbamate (**23**): R_f (5% MeOH/$CHCl_3$) 0.6. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.07–4.13 (unres. *m*, 2 CH_2O); 2.90 (*s*, 2 Me_2N); 1.70–1.88 (unres. *m*, 4 H). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) =$ 76.94): 156.54 ($Me_2NC(O)OR$); 64.82 (CH_2O); 35.73, 35.36 (2 br. *s*, Me_2N); 25.70 (CH_2).

Reaction of **12** *with 1,4-Dibromobutane under Moderate Dilution* (*Table 1*, *Entry 1*): A mixture of **12** (30.2 mg, 0.0554 mmol), 1,4-dibromobutane (14.4 mg, 0.0665 mmol), and Cs_2CO_3 (45.1 mg, 0.139 mmol) in anh. DMF (5 ml) was stirred at 23° under N_2 for 44 h. The resulting mixture was partitioned between $CHCl_3$ (30 ml) and 5% aq. citric acid (2 ml) and the org. phase washed with H_2O (5 × 5 ml), dried (Na_2SO_4), and evaporated under h.v.: 41 mg of white solid. FC/silica gel (10 ml, $CHCl_3 \rightarrow$ 5% MeOH/$CHCl_3$) gave **13** (3 mg, 9%), **16** (21 mg, 56%), and **24** (*ca.* 1:1 mixture of 2 diastereoisomers; 8 mg, 25.2%, with 3% MeOH).

*Data of (±)-(2*R*,3*R*)-*N,N′*-{1,4-Butanediylbis{{[(4-methylphenyl)sulfonyl]imino}-3,1-propanediyl}}-bis[2-hydroxy-3-{[(4-methylphenyl)sulfonyl]amino}-3-phenylpropanamide]* (**24**): ^{1}H-NMR (300 MHz, 8 mg in 0.6 ml of $CDCl_3$): 7.60 (*d*, *J* = 8.3, 4 H of Ts); 7.53 (*d*, *J* = 7.85, 4 H of Ts); 7.29 (*d*, *J* = 7.7, 4 H of Ts); 6.95–7.12 (*m*, 12 H, Ph, Ts, 2 NHCO); 6.25–6.42 (2 very br. *s*, 2 H, disappeared after D_2O exchange, 2 TsN*H*CH); 4.80 (br. *s*, 2 H, became 2 *d* at 4.81 (*J*(CH,CH) = 4.2) and 4.78 (*J*(CH,CH) = 4.3) after D_2O exchange, 2 PhC*H*NHTs); 4.56 (*d*, *J* = 4.15, 1 H, 2 C*H*OH of one diastereoisomer); 4.51 (*d*, *J* = 4.25, 1 H, 2 C*H*OH of the other diastereoisomer); 2.85–3.15 (*m*, 12 H); 2.78 (*m*, 4 H); 2.42 (*s*, 6 H, Me); 2.30, 2.29 (2 *s*, 6 H, 2 Me); 1.34–1.65 (*m*, 12 H). ESI-MS: 595 (100, $[M + 2Na]^{2+}$).

Intramolecular Macrocyclization of **16**. A soln. of **16** (78 mg, 0.115 mmol) in DMF (30 ml) was stirred in the presence of Cs_2CO_3 (90 mg, 0.276 mmol) under N_2 for 75 h at 40° and then evaporated. The residue was separated by FC as described above to give **13** (20 mg, 29.1%), **21** (2 mg, 7.7%), unreacted **16** (15 mg, 19%), **20** (10 mg, 10.2%), and **21** (6 mg, 8.5%).

Macrocyclization of **12** *with 1,4-Dibromobutane at Moderate Dilution* (*Table 1*, *Entry 5*). A soln. of **12** (42 mg, 0.0771 mmol) and 1,4-dibromobutane (18.3 mg, 0.0848 mmol) in anh. DMF (5 ml) was stirred in the presence of Cs_2CO_3 for 24 h at 50° under N_2. The mixture was quenched with a small amount of AcOH, evaporated under h.v., and partitioned between $CHCl_3$ and H_2O. Macrocyclic **13** (10.0 mg, 21.7%) was isolated after FC (silica gel, 1% MeOH/$CHCl_3$).

Electrochemical Deprotection of Tosyl Groups [25]: *(±)-(2*R*,3*R*)-3-Hydroxy-2-phenyl-1,5,9-triazacyclotridecan-4-one* (**14**). Controlled-potential electrolysis was carried out in a cylindrical, three electrode, divided cell with an electronic potentiostat and a stirred mercury pool (area: 44 cm^2) as cathode, graphite rod as anode, and SCE as reference electrode. First, 100 ml of 0.1M $(Me_4N)Cl$ in 94% EtOH (used as catholyte and anolyte) were electrolized at −2.25 V under Ar at +5° until the background current remained constant (10 mA). Then **13** (100 mg, 0.167 mmol) in a minimum amount of DMF was added to the cathodic chamber. The electrolysis was carried at −2.25 V until current depletion to the background level was observed in the recorded *I*/*t* curve. Approximately 400% of the necessary number of coulombs were used. The cathodic soln. was then evaporated, the solid residue dissolved in H_2O (5 ml), saturated with K_2CO_3, and extracted with CH_2Cl_2 (5 × 10 ml). The combined org. phase was dried (Na_2CO_3) and evaporated to yield 75 mg of crude **14** contaminated with traces of electrolyte $(Me_4N)Cl$, potassium toluenesulfinate, and DMF. The substance was used in the next step without further purification. R_f ($CHCl_3$/MeOH/25% aq. NH_3 soln. 78:19:3) 0.23. CI-MS: 292 (100, $[M + H]^+$). ^{1}H-NMR (300 MHz, 75 mg in 0.8 ml of $CDCl_3$, see also *Table 3*): 7.13–7.28 (*m*, Ph, NHCO); 3.98 (*d*, *J* = 9.1, H–C(3)); 3.56 (*d*, *J* = 9.0, H–C(2)); 3.37–3.49 (*m*, 1 H, CH_2NH); 3.22–3.34 (*m*, 1 H, CH_2NH); 2.68–2.80 (*m*, 2 H); 2.55–2.60 (*m*, 2 H); 2.38–2.48 (*m*, 1 H); 2.21–2.31 (*m*, 1 H); 1.63–1.73 (*m*, 2 H); 1.53–1.68 (*m*, 3 H); 1.30–1.42 (*m*, 1 H). ^{13}C-NMR (75 MHz, $\delta(CDCl_3) = 77.05$, see also *Table 3*): 173.13 (CONH); 141.00 (C_{ipso} of Ph); 128.71, 128.21, 127.71 (C_o, C_m, and C_p of Ph); 73.6 (C(3)); 66.44 (CHNH); 49.50, 48.82, 45.78, 39.60 (4 CH_2N); 27.86, 27.81, 27.52 (3 CH_2).

*(±)-(2*R*,3*R*)-3-Hydroxy-9-[(2*E*)-1-oxo-3-phenylprop-2-enyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one* (= *3-Hydroxycelacinnine;* **1**). According to the procedure of *Yamamoto* and *Maruoka* described for celacinnine (Et_3N/DMAP, (*N*,*N*-dimethylpyridin-4-amine); −78°) [26], **14** was monoacylated. The product was purified by two FC (silica gel, first 2% MeOH/$CHCl_3$ (**1** eluted together with DMAP), then 8% MeOH/$CHCl_3$): 20 mg (33% from **13**, not optimized) of **1**. R_f (10% MeOH/$CHCl_3$) 0.35. White solid. M.p. 146–150° (dec.). FT-IR (KBr): 3296*s* (br., OH, NH), 3060*w*, 3026*w*, 2927*s*, 2855*m*, 1758*w*, 1731*w*, 1647*s* (C=O), 1595*s*, 1542*m*, 1496*m*, 1496*m*, 1452*m*, 1435*s*, 1377*w*, 1359*w*, 1328*m*, 1310*m*, 1245*w*, 1203*m*, 1121*m*, 1084*w*, 1054*w*, 985*w*, 911*w*, 854*w*, 762*m*, 702*s*. NMR: see *Table 2* for complete signal assignments from 2D NMR data at +70° and −40°. ^{1}H-NMR (300 MHz, 16 mg in 0.6 ml of $CDCl_3$, 23°): 8.36–8.48 (br. *s*, 0.5 H, NHCO); 7.93–8.05 (br. *s*, 0.5 H, NHCO); 7.70 (*d*, J_{trans} = 15.4, PhC*H*=CH); 7.48–7.56 (*m*, 2 H of *Ph*CH=CH); 7.28–7.43 (*m*, 8 arom. H); 6.80 (*d*, J_{trans} = 15.4,

1 H, PhCH=*CH*); 4.08 (*d*, *J*(CH,CH) = 9.6, 1 H, *CH*OH); 3.90–4.05 (br. *m*, 0.5 H); 3.42–3.75 (overlapping *m*, 4 H): 3.61 (*d*, *J*(CH,CH) = 9.60, Ph*CH*NH); 3.22–3.42 (br. *m*, 2 H); 3.05–3.25 (br. *s*, 0.5 H); 2.62–2.72 (*m*, 1 H); 2.42–2.52 (*m*, 1 H); 2.0–2.2 (br. *m*, 1 H); 1.85–2.1 (br. *m*, 2 H); 1.65–1.85 (br. *m*, 2 H); 1.4–1.65 (br. *m*, 3 H). CI-MS: 422 (100, $[M+H]^+$).

(±)-(2R,3R*)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one* (**15**). The procedure and data will be provided in a separate publication [24]. For the NMR data, see *Table 3*.

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